2019

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Favorable Cardiovascular Health at Young and Middle Ages and Dementia in Older Age—The CHA Study

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Background—Data are sparse on the association of cardiovascular health (CVH) in younger/middle age with the incidence of dementia later in life.

Methods and Results—We linked the CHA (Chicago Heart Association Detection Project in Industry) study data, assessed in 1967 to 1973, with 1991 to 2010 Medicare and National Death Index data. Favorable CVH was defined as untreated systolic blood pressure/diastolic blood pressure ≤120/≤80 mm Hg, untreated serum total cholesterol <5.18 mmol/L, not smoking, bone mass index <25 kg/m^2, and no diabetes mellitus. *International Classification of Diseases, Ninth Revision (ICD-9)* codes and claims dates were used to identify the first dementia diagnosis. Cox models were used to estimate hazard ratios of incident dementia after age 65 years by baseline CVH status. Among 10 119 participants baseline aged 23 to 47 years, 32.4% were women, 9.2% were black, and 7.3% had favorable baseline CVH. The incidence rate of dementia during follow-up after age 65 was 13.9%. After adjustment, the hazard ratio for incident dementia was lowest in those with favorable baseline CVH and increased with higher risk factor burden (*P*-trend<0.001). The hazards of dementia in those with baseline favorable, moderate, and 1-only high-risk factor were lower by 31%, 26%, and 20%, respectively, compared with those with ≥2 high-risk factors. The association was attenuated but remained significant (*P*-trend<0.01) when the model was further adjusted for competing risk of death. Patterns of associations were similar for men and women, and for those with a higher and lower baseline education level.

Conclusions—In this large population-based study, a favorable CVH profile at younger age is associated with a lower risk of dementia in older age. (*J Am Heart Assoc*. 2019;8:e009730. DOI: 10.1161/JAHA.118.009730)

Key Words: aging • Alzheimer's disease • cardiovascular disease risk factors • dementia • epidemiology

D ementia, a major neurocognitive disorder commonly caused by Alzheimer disease and vascular disease, is highly prevalent in the elderly. In the United States, it is estimated that ≈11% of individuals aged ≥65 years, and 32% of people aged ≥85 years, suffered from dementia in 2016.[1] Because of the decline in memory and other cognitive functions, dementia significantly diminishes an individual's quality of life and places a heavy burden on family and healthcare systems.[2] Therefore, preventing

dementia is critical to improving the health of the population.

Numerous epidemiological studies have focused on identifying individual risk factors for dementia. Previous research suggests that major cardiovascular disease (CVD) risk factors are associated with a higher risk of dementia, including hypertension,[3–7] hypercholesterolemia,[8,9] diabetes mellitus,[5,7,10] overweight/obesity,[11,12] and smoking.[7,13] However, the association of favorable cardiovascular health (CVH),

Clinical Perspective

What Is New?

- This study reinforces previous findings on the association of favorable cardiovascular health in younger age and neurocognitive disorder in older age with more comprehensive analyses using data from a large population-based cohort of both men and women with decades-long follow-up.
- It suggests that cardiovascular disease-related health outcomes and brain health may share some common causes and may be responsive to the same preventive strategies.

What Are the Clinical Implications?

- The finding allays a common fear that a longer lifespan may translate into a greater vulnerability for dementia, and thus a lower quality of life in later years, by suggesting delayed onset of dementia for those with a low risk profile.
- The finding reinforces the argument for primordial prevention (ie, preventing the development of risk factors).

a measure of overall risk factor burden defined by favorable levels of all major CVD risk factors, ie, low-risk in young/middle ages, and the incidence of dementia later in life has not been thoroughly investigated. Moreover, previous studies examining the association between CVD risk profile and dementia did not account for the competing risk of death before dementia diagnosis, a critical issue in studies of the elderly whose death rate is high and affected by CVD risk factors.[14–16]

We linked baseline data from the CHA (Chicago Heart Association Detection Project in Industry) study assessed in 1967 to 1973 (for participants ages ≤65 years in 1991 and ≥67 years in 2010) with fee-for-service Medicare claims and National Death Index data from 1991 to 2010 to examine the association between favorable CVH profile in young/middle ages and the incidence of dementia ≥40 years of follow-up.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Participants

The CHA Study is a prospective epidemiologic investigation of 39 665 men and women ages 18 to 74 at baseline in 1967 to 1973. The details of the CHA study have been published.[17] Briefly, baseline examination involved collection of demographics, smoking history, medical history, and medical treatment data by questionnaires; measurement of height, weight, supine blood pressure, resting ECG; and blood collection for measurement of serum total cholesterol and plasma glucose.

The CHA cohort has been followed through personal contacts, National Death Index data, and linked Medicare data for all Medicare eligible participants starting from 1991 through 2010. The study has received periodic institutional review board approval and a waiver of consent.

To obtain data on incidence of dementia, we included newly Medicare-eligible participants during 1991 to 2010 participants therefore had to be ≤65 years in 1991. To increase the likelihood that participants would have incurred Medicare claims so that we can approximate incident dementia, we included a 2-year washout period; ie, they had to be aged ≥67 years in 2010.

There were 15 407 age-eligible CHA participants. We excluded those who died before 1991 or before aged 65 years (n=1731), had missing data on baseline CVD risk factors (n=1093), were not found in the Medicare Denominator files (n=510), were unmatched by sex, year of birth, or social security number (n=1379), or were enrolled in Health Maintenance Organization plans after aged 65 (n=404). We also excluded those who had Medicare before age 65 (n=49), as they had a special disability or end-stage renal disease to be eligible for Medicare. In addition, to decrease the likelihood that the participants would have been diagnosed with dementia before age 65 years, those who had any claims for dementia before age 67 were excluded (n=122). The final study sample included 10 119 participants (6839 men and 3280 women), representing 65.7% of the original age-eligible CHA cohort (Figure S1).

Exposure and Covariates

CVH status was defined based on 5 established CVD risk factors assessed at baseline. The definition of the CVH profile is published.[18,19] Briefly, it included 4 categories: 1) Favorable, defined as favorable levels of all major CVD risk factors including untreated blood pressure, untreated serum cholesterol, bone mass index (BMI), diabetes mellitus, and smoking; 2) Elevated (moderate-risk), defined as having 0 high-risk factors but ≥1 unfavorable/borderline values for untreated blood pressure, untreated cholesterol, and BMI; 3) 1 high-risk factor; or 4) ≥2 high-risk factors (Table S1). Covariates included baseline age, race (black, non-black), sex, educational attainment (years in school), and the annual number of medical care visits from age 65 years to the time dementia was first diagnosed or to the censored time.

Outcome Variables

The Medicare (fee-for service) claims data contain *International Classification of Diseases, Ninth Revision (ICD-9)*

diagnosis codes in all claim files from 1991 to 2010; they include the Medicare Provider Analysis and Review, outpatient, carrier, durable medical equipment, home health, and hospice files. As in prior studies, we used *ICD-9* codes of 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, and 331.9 to define all types of dementia, then subtypes of dementia.[20,21] Our primary event of interest was the first diagnosis of dementia in any Medicare claim, regardless of whether it was the primary reason for the medical visit, and the outcome variable was years from aged 65 to the first event. It is worth noting that, in about 50% of the cases, dementia was the primary reason for the medical visit; and about 90% of dementia cases were established from *ICD-9* diagnoses codes in outpatient claims. Individuals who died without a dementia diagnosis were censored, or all-cause death, instead of being censored, remained in the population at risk (ie, a competing event). Individuals who survived dementia-free were censored on December 31, 2010. Information on deaths was obtained from National Death Index data.

Statistical Analysis

Baseline characteristics were compared across baseline CVD risk profile categories using F tests for continuous variables and Chi-square tests for binary variables. The cumulative incidence of dementia with death treated as a competing risk was plotted using cumulative incidence function for each CVD risk category.

For the main analyses, we used the procedure regression analysis of survival data (PHREG) to fit a Cox proportional hazards model to estimate the association between CVH profile and the risk of developing dementia where individuals who died before dementia were censored (model 1). Because death may occur before the diagnosis of dementia in individuals who would have developed dementia (had they lived longer), death may be considered a competing event. Therefore, in model 2, we take into account the potential impact of death using Fine and Gray's extension of the Cox regression model.[22] All hazard ratios with 95% CIs were compared between CVH groups with the high-risk group as the reference. Models were adjusted for baseline age, race, sex, years of education, and the annual number of medical care visits before dementia diagnosis or until the censored time. We adjusted for the annual number of medical care visits to account for potential differences in the likelihood of dementia diagnosis because individuals with more visits may be more likely to be diagnosed. Linear trend across the CVH strata was also tested, with CVH status as an ordinal variable.

Proportional hazard assumptions were checked using Martingale residuals and the Kolmogorov-type supremum test. Standard error estimates robust to misspecification of the Cox was also used. We also conducted sensitivity analyses, using interaction terms between covariates, such as CVH status and age, race, sex, or education; age and sex, race, or education; sex and race or education; and race and education; and splines effects of baseline age to inquire more flexible fits to the data for covariates.

Previous studies suggest that the prevalence and incidence of Alzheimer disease vary by sex.[23] Therefore, analyses were further stratified by sex. Moreover, because the level of education is strongly associated with dementia,[24] we stratified models by level of education at baseline (≤12 years at school versus otherwise). Furthermore, because stroke is considered an important cause of cognitive impairment,[25] we used an exploratory analysis, adding into the models any interim stroke occurring from aged 65 years to the time dementia was first diagnosed (or to the censored time) to examine if having a stroke before dementia may be on the causal pathway of the association of interest.

Finally, models substituting individual risk factors for the combined CVH profile groups were used to examine the association of each risk factor separately with the incidence of dementia.

The analyses used SAS statistical software (version 9.4 with SAS/STAT 14.1, SAS Institute Inc, Cary, NC); a $P<0.05$ was considered statistically significant.

Results

Of 10 119 CHA participants aged 23 to 47 years at baseline, 32.4% were women, 9.2% were black, and 7.3% had a favorable baseline profile. Hypertension and smoking were the most prevalent risk factors, while diabetes mellitus was less common at baseline (41.3%, 40.7%, and 1.3%, respectively) (Table 1). People in the favorable group tended to be younger, female, better educated, and with the lowest average annual number of medical care visits from age 65 years to the first dementia diagnosis or the censored time.

After up to 43 years of follow-up since baseline examination (up to 19 years of follow-up in Medicare after reaching age 65 years), 13.9% of the participants developed at least 1 type of dementia. The percent of those who survived without any dementia was highest in the favorable group (84.4%), and lowest in the ≥2 high-risk factors group (60.3%). Conversely, the outcomes of dementia and all-cause mortality were lowest in the favorable group (9.6% and 6.1%, respectively), and highest in the ≥2 high-risk factors group (16.8% and 23.0%, respectively) ($P<0.001$) (Figure 1).

Figure 2 shows the unadjusted cumulative incidence of dementia taking into account the competing risk of death. There was a significant difference in the dementia-free survival rate ($P<0.001$) across baseline CVH groups. The cumulative incidence of dementia was lowest in the favorable

Table 1. Characteristics of the Study Sample for All and by Baseline Cardiovascular Health Status

| Characteristics* | All | Baseline Cardiovascular Health Status | | | | P Value‖ |
		Favorable†	Moderate-Risk‡	1 High-Risk Factor§	≥2 High-Risk Factor§	
People, n	10 119	742	2238	4220	2919	
Baseline characteristics (1967–1973)						
Age, y	35.3 (5.5)	33.9 (5.4)	35.2 (5.4)	35.2 (5.6)	35.9 (5.5)	<0.001
Female, %	32.4	59.6	32.5	33.8	23.5	<0.001
Black, %	9.2	8.4	7.2	9.6	10.4	<0.001
Education, y	13.6 (2.6)	14.1 (2.5)	14.1 (2.7)	13.6 (2.6)	13.1 (2.6)	<0.001
Smoking status, %						…
Never smoker	33.1	63.3	57.9	28.5	12.9	
Former smoker	25.7	36.7	42.1	23.6	13.9	
Current smoker	41.3	0.0	0.0	47.9	74.0	
BMI, kg/m^2	25.6 (3.9)	22.1 (2.0)	25.0 (2.7)	25.0 (3.4)	27.8 (4.5)	…
BMI ≥30 kg/m^2, %	11.4	0	0	5.5	31.5	…
SBP, mm Hg	131.8 (15.9)	114.4 (6.2)	124.0 (8.2)	131.2 (15.3)	142.9 (15.0)	…
DBP, mm Hg	78.3 (10.6)	69.8 (7.4)	74.2 (7.4)	77.8 (10.3)	84.3 (10.6)	…
Hypertension,§ %	40.7	0	0	40.4	82.8	…
Serum cholesterol, mmol/L¶	196.7 (35.5)	168.5 (19.9)	190.6 (27.1)	192.5 (31.5)	214.6 (41.3)	…
Hypercholesterolemia,§ %	11.5	0	0	5.5	31.9	…
Diabetes mellitus, %	1.3	0	0	0.8	3.3	…
Annual medical care visits#	13.2 (12.4)	11.4 (10.9)	11.9 (10.8)	13.0 (12.1)	15.0 (14.0)	<0.001

BMI indicates body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*Numbers are mean (SD) unless otherwise indicated.

†Favorable level of all major CVD risk factors (BP ≤120/≤80 mm Hg and no antihypertensive medication, serum cholesterol <5.18 mmol/L and no lipid-lowering medication, not smoking, BMI <25 kg/m^2, no diabetes mellitus).

‡One or more unfavorable/borderline levels of untreated systolic blood pressure 121 to 139 mm Hg or diastolic blood pressure 81 to 89 mm Hg, or untreated serum total cholesterol 5.18 to 6.21 mmol/L, or BMI 25.0 to 29.9 kg/m^2, not smoking, no diabetes mellitus.

§High-risk factors: hypertension (systolic blood pressure/diastolic blood pressure (≥140/90) or using antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥6.22 mmol/L or using lipid-lowering medication), smoking, BMI ≥30.0 kg/m^2, diabetes mellitus.

‖P values for overall group comparisons based on Chi-square or F-test except for cardiovascular health components.

¶Divide by 0.0259 to convert to mg/dL.

#Annual number of medical care visits from age 65 years to the first time that dementia was diagnosed or to the censored time.

group and increased with risk factor burden. Specifically, the hazards of dementia in those with baseline favorable, moderate, and 1 only high-risk factor were lower by 28%, 22%, and 17%, respectively, compared with those with ≥2 high-risk factors.

Model 1 of Table 2 shows that a more favorable baseline risk profile was associated with a lower hazard of dementia after adjusting for covariates. Compared with the ≥2 high-risk factors group, the hazards for dementia in the 1-only high-risk factor, moderate-risk, and favorable groups were much lower —the hazards (95% CIs) of dementia were 0.80 (0.71–0.91), 0.74 (0.64–0.86), and 0.69 (0.54–0.89), respectively (P-trend<0.001). The associations were attenuated when the competing risk of death was considered (model 2) but remained significant with P-trends <0.01. There was no evidence that the proportional hazards assumption was

violated as the Kolmogorov-type supremum test results based on 1000 simulations for all the covariates were not significant at alpha level=0.05 (all P>0.05). The standard error estimates robust to misspecification of the Cox model were similar to the model-based counterparts, ie, the main model—the ratios of the robust estimates of the standard error relative to the corresponding model-based estimates for all variables ranged from 0.98 to 1.

In the sensitivity analyses, using interaction terms between covariates did not improve the fit of the model (P=0.916 for the likelihood ratio test). Moreover, the parameter estimates from the model with spline effects of baseline age were similar with the estimates from the model with baseline age as continuous variable and spline effects were not significant; and the Akaike information criterion of the model with spline effects (Akaike information criterion =23 123.627) was
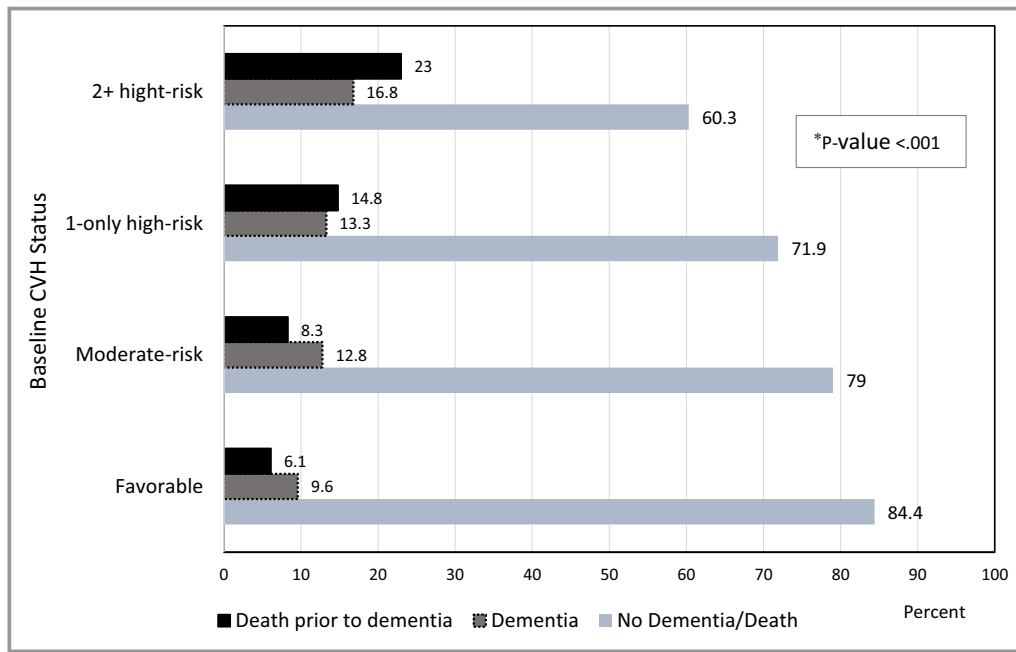
Figure 1. Dementia status and death before dementia during 1991 to 2010 by baseline cardiovascular health status. Death before dementia: all-cause death before the first diagnosis of any type of dementia. Favorable level of all major cardiovascular disease risk factors (blood pressure ≤120/≤80 mm Hg and no antihypertensive medication, serum cholesterol <5.18 mmol/L and no lipid-lowering medication, not smoking, bone mass index <25 kg/m^2, no diabetes mellitus); Moderate-risk: One or more unfavorable/ borderline levels of untreated systolic blood pressure 121 to 139 mm Hg or diastolic blood pressure 81 to 89 mm Hg, or untreated serum total cholesterol 5.18 to 6.21 mmol/L, or BMI 25.0 to 29.9 kg/m^2, not smoking, no diabetes mellitus; High-Risk: High systolic blood pressure/diastolic blood pressure (≥140/90) or using antihypertensive medication, serum total cholesterol ≥6.22 mmol/L or using lipid-lowering medication, smoking, bone mass index ≥30.0 kg/m^2, diabetes mellitus. CVH indicates cardiovascular health. *P value for group comparison based on Chi-square tests.

slightly bigger than the Akaike information criterion obtained in the model without spline function of age (Akaike information criterion =23 120.359).

In analyses of individual risk factors (Table S2), in model 1, baseline blood pressure and smoking status were important predictors of the hazards of dementia. For example, compared with current smokers, the hazards (95% CI) for dementia in those who were not smokers and former smokers were 0.88 (0.78–0.99) and 0.82 (0.71–0.93), respectively. When death before dementia was considered as a competing risk (model 2), the associations of baseline smoking status to dementia were no longer significant. The association of baseline blood pressure with dementia was slightly attenuated but remained significant; eg, in model 1, the hazards (95% CI) of dementia in those with a favorable blood pressure level was 0.85 (0.75, 0.98), compared with those with a high-risk level, and it was 0.87 (0.76–0.99) in model 2.

In sex-specific analyses, results in men and women were similar to the results in the main analyses, especially for model 1. For example, in men, compared with the ≥2 high-risk factors group, the hazards (95% CIs) of dementia in the baseline low-risk, moderate-risk, and 1-only high-risk factor groups were 0.62 (0.40–0.97), 0.80 (0.67–0.96), and 0.83 (0.72–0.97), respectively; and, in women, they were 0.68 (0.49–0.94), 0.63 (0.49–0.82), and 0.74 (0.60–0.92), respectively (Table S3). The interaction terms for sex and CVH profile in both models, were not statistically significant (P>0.05).

In the analysis stratified by education level, results were also similar in both the low (≤12 years of schooling) and high (>12 years of schooling) baseline education groups, especially in model 1, in that the better the CVH status at younger age, the lower the likelihood of having dementia later in life with P-trends <0.05 (Table S4). The interaction terms for the dichotomized education level and CVH profile in both models were not statistically significant (P>0.05).

In the analysis with an additional adjustment for any interim stroke before dementia, the association of CVH status and dementia remained strong, although the interim stroke slightly attenuated the association for vascular dementia. For example: in model 1 without adjustment for an interim stroke, the hazards for all types of dementia (95% CI) in the favorable group was 0.69 (0.54–0.89) versus the ≥2 high-risk factors
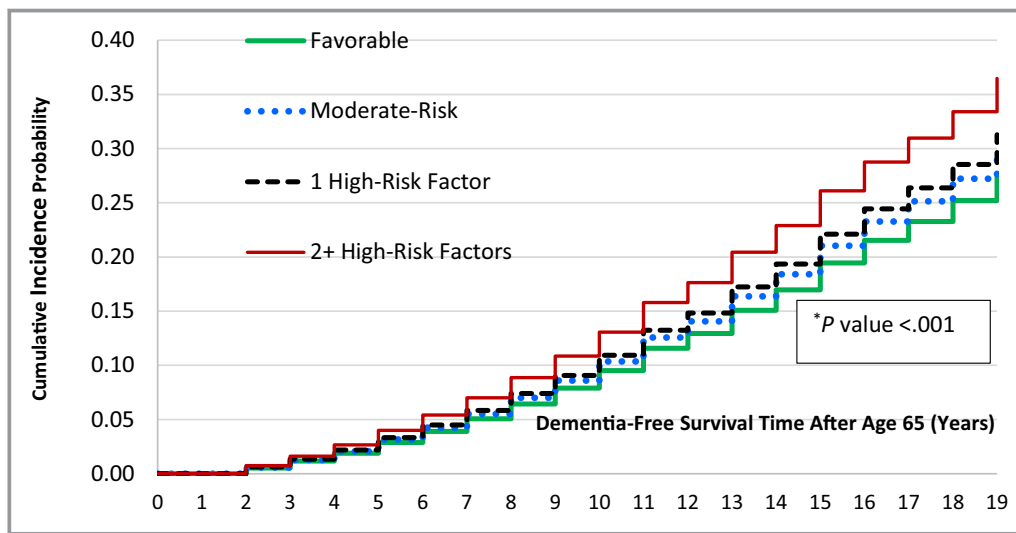
Figure 2. Cumulative incidence of dementia after aged 65 years during 1991 to 2010 by baseline cardiovascular health status. First diagnosis of any type of dementia. Favorable level of all major cardiovascular disease risk factors (blood pressure ≤120/≤80 mm Hg and no antihypertensive medication, serum cholesterol <5.18 mmol/L and no lipid-lowering medication, not smoking, bone mass index <25 kg/m^2, no diabetes mellitus); Moderate-risk: One or more unfavorable/borderline levels of untreated systolic blood pressure 121 to 139 mm Hg or diastolic blood pressure 81 to 89 mm Hg, or untreated serum total cholesterol 5.18 to 6.21 mmol/L, or bone mass index 25.0 to 29.9 kg/m^2, not smoking, no diabetes mellitus; High-risk: high systolic blood pressure/diastolic blood pressure (≥140/90) or using antihypertensive medication, serum total cholesterol ≥6.22 mmol/L or using lipid-lowering medication, smoking, bone mass index ≥30.0 kg/m^2, diabetes mellitus. *P value for the Wald test.

group, and with additional adjustment for interim stroke, it was 0.70 (0.54–0.90). The hazards for vascular dementia (95% CI) without adjustment for the interim stroke was 0.46 (0.31–0.69), and it was 0.51 (0.34–0.76) with adjustment for the interim stroke (Table S5).

Discussion

In this study of 6839 men and 3280 women aged 23 to 47 years at baseline, we found that after up to 43 years of follow-up since baseline examination (with 19 years follow-up in Medicare after reaching age 65 years), a favorable CVH profile at young/middle ages was associated with ≈30% lower risk of developing dementia later in life compared with those with ≥2 high-risk factors. This lower risk was independent of baseline age, sex, race, education, and annual medical care visits before dementia diagnosis, and it increased in a graded fashion with burden of cardiovascular risk factors. With death free of dementia as a competing risk, the association was attenuated but remained significant. The associations were similar for men and women, and for those with a higher and lower baseline education level; they were mainly driven by baseline smoking and blood pressure levels.

Previous epidemiological studies have highlighted strong associations of the combined effects of favorable levels of

all major CVD factors in young adulthood and middle age on subsequent health outcomes including CVD mortality and morbidity,[26–29] subclinical atherosclerosis and markers of inflammation.[30–32] The benefits of favorable CVH have been seen for non-CVD outcomes including lower risk of cancer[33] and general functional disability,[18] better quality of life,[19,34] and lower healthcare costs.[29] Few longitudinal studies have addressed the association of the combined effect of CVD risk factors on cognitive function[35,36] and dementia;[37–40] our findings are consistent with results of these studies. For example, the Northern Manhattan Study found that among 1033 middle-aged participants, those with a higher number of ideal CVH metrics at baseline (including the 5 factors considered here plus diet and physical activity) experienced smaller decline in cognitive performance during 6-year follow-up in older age (mean age at initial cognitive measurement 72 years).[35] This study focused on a subgroup of survivors of the original study, hence the results may not be generalizable to the full study population.

The Young Finns Study, which followed children aged 3 to 18 years at baseline for 31 years, found that the number of CVD risk factors measured in childhood was inversely associated with midlife cognitive performance.[36] The Three-City study in France, which focused on CVH at older age

Table 2. Hazard Ratios (95% CIs) for Any Dementia* After Age 65 Years During 1991 to 2010 by Baseline CVH Status (1967–1973)

| | Baseline CVH Status | | | | |
	Favorable† (n=742)	Moderate Risk‡ (n=2238)	1-Only High-Risk Factor‡ (n=4220)	≥2 High-Risk Factors§ (n=2919)	P-Trend‖
Model 1¶	0.69 (0.54–0.89)	0.74 (0.64–0.86)	0.80 (0.71–0.91)	1.0	<0.001
Model 2#	0.78 (0.61–0.99)	0.85 (0.73–0.98)	0.87 (0.77–0.98)	1.0	0.009

CVH indicates cardiovascular health; *ICD-9, International Classification of Diseases, Ninth Revision*.

*Dementia was defined as any dementia-related diagnoses with *ICD-9*: 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, 331.9. Medicare claims during 1991 to 2010 (including fee-for-service, for inpatient, outpatient [institutional and non-institutional], skilled nursing, durable medical equipment, home health, and hospice claims).

†Ideal levels of all major cardiovascular disease RFs (systolic blood pressure /diastolic blood pressure ≤120/≤80 mm Hg and no antihypertensive medication, serum total cholesterol <5.18 mmol/L and no cholesterol-lowering medication, not smoking, bone mass index <25 kg/m², and no diabetes mellitus).

‡Borderline levels of systolic blood pressure /diastolic blood pressure or serum total cholesterol, not smoking, bone mass index 25.0 to 29.9 kg/m², and no diabetes mellitus.

§High-risk factors: hypertension (systolic blood pressure /diastolic blood pressure [≥140/90] or using antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥6.22 mmol/L or using lipid-lowering medication), smoking, bone mass index ≥30.0 kg/m², diabetes mellitus.

‖P value for graded association across 4 baseline risk factor groups with risk factor status as an ordinal variable.

¶Model 1: Adjusted for baseline age, sex, race, education attainment, and average number of claims per years before dementia diagnosis.

#Model 2: Adjusted for baseline age, sex, race, education attainment, annual average number of claims before dementia diagnosis and death before dementia diagnoses.

(mean age at baseline 74 years) among survivors who participated in the follow-up test, found a lower hazard for dementia was associated with an increased number of optimal CVH factors.[40] Other studies focused on dementia as the outcome but did not examine the combined effects of favorable levels of all risk factors earlier in life, examining instead only the effects of individual risk factors[7] and/or using only standard Cox regression models.[37–39] These other studies also focused only on men of the same age[39] or measured risk factors at older age.[38]

To our knowledge, this study is the first American population-based study to report that having a favorable CVH profile earlier in life is associated with lower incidence of dementia later in life, considering death before dementia as a competing risk in the analyses. Because of our large sample size and rich information on diagnoses from Medicare claims, we were able to examine the association not only for the whole cohort, but also in men and women, and for high and low education levels separately.

Our results on the associations of CVD risk factors assessed singly with the risk of dementia were also consistent with data previously published. We found baseline smoking status and blood pressure levels were all significantly associated with the risk of dementia.[5,6,8–10,12,13] We also found an association between smoking status and dementia was affected by the competing risk of death;[7] these are probably because of the high competing outcome of death in smokers and deaths (eg, by stroke) in hypertensive people is high.[14,41]

Our study benefited from the use of data from a large population-based cohort of >10 000 individuals, including both men and women. Also, all CVD risk factors were measured objectively >40 years ago when all the participants were at young/middle ages. Furthermore, the combination of CVD risk data with data from the National Death Index and 19 years of Medicare claims allowed us to assess the 4-decade-long association of baseline CVD risk profile and the cumulative incidence of dementia during older ages, considering the competing risk of death before dementia diagnosis.

Despite the strengths, the study has limitations. First, early and sustained drug therapy and changes in lifestyle may modify decades-long CVD risks, thereby influencing the association of early CVD risk profile and dementia later in life—an issue we are unable to address in this study. Nonetheless, just a single ascertainment of the favorable CVD risk status at younger age highlights its important role not only for CVD but also non-CVD related outcomes in this and other population-based studies.[18,26,27,29,42] Second, our analyses included only participants who enrolled in fee-for-service Medicare. However, CVH was not related to fee-for-service versus HMO enrollment. Third, the use of *ICD-9* diagnosis codes in Medicare claims only may lead to an imprecise estimate of actual dementia cases. However, administrative data generally are concordant with patient chart data in recording comorbidity (agreement >85%).[43] Administrative data were found to be sensitive and specific for identifying older adults with Alzheimer and related dementias.[44] Using Medicare claims to identify all types of dementia had a sensitivity of 85% and specificity of 89% compared with in-home dementia assessment by clinicians.[20] Medicare data have been used to estimate national prevalence of all types of dementia and the subtypes.[45] Moreover, any possible misclassification on identifying dementia using Medicare data would be similar across CVD risk strata (non-differential), ie, it would underestimate the association. Fifth, information on cognitive function at baseline was not available. However, CHA participants were all employed at baseline in 1967 to 1973, thus the proportion of poor cognitive performance at baseline was likely low. Finally, apart from modifiable risk factors, dementia also has genetic risk factors not assessed here.

Conclusion

Our findings highlight and extend the importance of having favorable levels of all major CVD heath factors in young adulthood and early middle age for preventing or delaying neuro-cognitive disorder in older age. Our findings support an understanding that CVD-related health outcomes and brain health share common underlying protective mechanisms.[46] Our study therefore not only supports the goal of improving cardiovascular health,[47] but also supports the national effort of attaining high-quality, longer lives free of disability for individuals and reducing burdens on families and society.[48]

Findings from this study also have implications on the clinical perspective. In previous publications, we have shown that low risk or higher CVH profile is associated with longer lifespan[26,29] and delaying the onset of all-cause and CVD morbidity.[29] Yet there is a common fear that a longer lifespan may translate into a greater vulnerability for dementia, and thus a lower quality of life in later years. But our findings— that at any time during follow-up, the hazard of dementia in the low risk people is lower than in the high risk people— together with our previous findings suggest delayed onset of dementia for those with a low risk profile, allaying some of the fear commonly associated with a longer lifespan and bolstering the argument for primordial prevention (ie, preventing the development of risk factors).

Acknowledgments

Sources of Funding

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Definitions of Favorable, Elevated and High Levels of Cardiovascular Health Factors.

Definitions of Favorable, Elevated and High Levels of CV Health Factors					
	Smoking	**Diabetes**	**BMI (kg/m²)**	**Blood Pressure (mm Hg)**	**Total Serum Cholesterol (mmol/L)[§]**
Low-Risk (Favorable)	Non-smoker	No diabetes	< 25	Untreated SBP/DBP ≤ 120/80	Untreated cholesterol < 5.18 mmol/L or 200 mg/dl[*]
Moderate-Risk (Elevated)	-	-	25.0-29.9	Untreated SBP/DBP 121-139/81-89	Untreated cholesterol 5.18-6.21mmol/L or 200-239 mg/dl
High-Risk	Smoker	Diabetes	≥ 30	SBP/DBP ≥ 140/90 or taking antihypertensive medications	Cholesterol level ≥ 6.22 mmol/l or 240 mg/dl, or taking cholesterol-lowering medication

[*]Divide by 0.0259 to convert to mg/dl

Table S2. Hazard Ratios (95%Confidence Intervals) for Dementia[*] by Baseline Individual Risk Factors (1967-73).

Baseline Individual Risk Factors		Model 1[†]	Model 2[‡]
Smoking Status	Not smokers	**0.88 (0.78-0.99)**	0.99 (0.88-1.12)
	Ever smokers	**0.82 (0.71-0.93)**	0.92 (0.80-1.05)
	Current smokers	**1.00**	1.00
BMI(kg/m^2)	< 25	0.92 (0.77-1.09)	0.99 (0.83-1.17)
	≥25 and <30	0.89 (0.76-1.05)	0.94 (0.79-1.10)
	≥30	1.00	1.00
BP Level/Med. Use	≤120/80 mmHg, no meds	**0.85 (0.75-0.98)**	**0.87 (0.76-0.99)**
	>120/80, ≤140/90, no meds	0.89 (0.79-1.02)	0.94 (0.83-1.07)
	≥ 140/90 or on meds	1.00	1.00
Cholesterol Level/Meds Use: <5.18 mmol/l[§], no meds		0.86 (0.74-1.01)	0.86 (0.74-1.00)
	≥5.18 and <6.22, no meds	0.96 (0.82-1.12)	0.95 (0.80-1.11)
	≥6.22 or on meds	1.00	1.00
Diabetes		1.32 (0.90-1.95)	1.21 (0.82-1.80)

*Dementia were defined as any dementia-related diagnoses with ICD-9: 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, 331.9. Medicare claims during 1991-2010 [including fee-for-service, for inpatient, outpatient (institutional and non-institutional), skilled nursing, durable medical equipment, home health, and hospice claims].

[†] Model 1: Adjusted for baseline age, sex, race, education attainment, and annual number of medical care visits prior to dementia diagnosis. Deaths prior to dementia were treated as censored observations.

[‡] Model 2: Adjusted for baseline age, sex, race, education attainment, and annual number of medical care visits prior to dementia diagnosis, taking into account the impact of deaths prior to dementia diagnosis on the association of interest.

[§] Divide by 0.0259 to convert to mg/dl

Table S3. Hazard Ratios (95%Confidence Intervals) for Dementia[#] Age 65 During 1991-2010 by Baseline CVH Status (1967-73), Stratified by Sex.

	Baseline CVH Status				
	Favorable[*] (n=742)	Moderate Risk[†] (n=2,238)	1-Only High-Risk Factor[‡] (n=4,220)	2+ High-Risk Factors[‡] (n=2,919)	P-Trend[**]
MEN					
Model 1[§]	**0.62 (0.40-0.97)**	**0.80 (0.67-0.96)**	**0.83 (0.71-0.97)**	**1.0**	**0.002**
Model 2[∥]	0.69 (0.45-1.07)	0.92 (0.76-1.10)	0.89 (0.76-1.03)	1.0	0.096
WOMEN					
Model 1[§]	**0.68 (0.49-0.94)**	**0.63 (0.49-0.82)**	**0.74 (0.60-0.92)**	**1.0**	**0.001**
Model 2[∥]	0.78 (0.56-1.09)	**0.73 (0.57-0.94)**	0.83 (0.67-1.03)	1.0	0.037

*Ideal levels of all major CVD RFs (SBP/DBP ≤120/≤80 mmHg and no antihypertensive medication, serum total cholesterol <5.18 mmol/L and no cholesterol-lowering medication, not smoking, BMI < 25 kg/m2, and no diabetes).

†Borderline levels of SBP/DBP or serum total cholesterol, not smoking, BMI 25.0-29.9 kg/m2, and no diabetes

‡ High-risk factors: hypertension (SBP/DBP (≥ 140/90) or using antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥ 6.22 mmol/L or using lipid-lowering medication), smoking, BMI ≥30.0 kg/m2, diabetes.

§Model 1: Adjusted for baseline age, race, education attainment, and average number of claims per years prior to dementia diagnosis.

ǁModel 2: Adjusted for baseline age, race, education attainment, annual average number of claims prior to dementia diagnosis and death prior to dementia diagnoses.

#Dementia were defined as any dementia-related diagnoses with ICD-9: 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, 331.9. Medicare claims during 1991-2010 [including fee-for-service, for inpatient, outpatient (institutional and non-institutional), skilled nursing, durable medical equipment, home health, and hospice claims].

**P value for graded association across baseline risk factor groups with risk factor status as an ordinal variable.

Table S4. Hazard Ratios (95%Confidence Intervals) for Dementia[#] After Age 65 During 1991-2010 by Baseline CVH Status (1967-73), Stratified by Education Levels.

	Baseline CVH Status				
	Favorable[*] (n=742)	Moderate Risk[†] (n=2,238)	1-Only High-Risk Factor[‡] (n=4,220)	2+ High-Risk Factors[‡] (n=2,919)	P-Trend[**]
>12 years of schooling at baseline					
Model 1[§]	**0.62 (0.43-0.90)**	**0.72 (0.58-0.89)**	0.84 (0.69-1.01)	**1.0**	**<0.001**
Model 2[‖]	**0.68 (0.47-0.99)**	**0.79 (0.64-0.99)**	0.89 (0.74-1.07)	1.0	**0.011**
≤12 years of schooling at baseline					
Model 1[§]	0.76 (0.54-1.08)	**0.76 (0.62-0.93)**	**0.78 (0.66-0.91)**	**1.0**	**0.004**
Model 2[‖]	**0.58 (0.36-0.94)**	0.79 (0.60-1.04)	0.86 (0.68-1.10)	**1.0**	**0.016**

*Ideal levels of all major CVD RFs (SBP/DBP ≤120/≤80 mmHg and no antihypertensive medication, serum total cholesterol <5.18 mmol/L and no cholesterol-lowering medication, not smoking, BMI < 25 kg/m2, and no diabetes).

†Borderline levels of SBP/DBP or serum total cholesterol, not smoking, BMI 25.0-29.9 kg/m2, and no diabetes

‡ High-risk factors: hypertension (SBP/DBP (≥ 140/90) or using antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥ 6.22 mmol/L or using lipid-lowering medication), smoking, BMI ≥30.0 kg/m2, diabetes.

§Model 1: Adjusted for baseline age, race, sex, and average number of claims per years prior to dementia diagnosis.

‖Model 2: Adjusted for baseline age, race, sex, annual average number of claims prior to dementia diagnosis and death prior to dementia diagnoses.

#Dementia were defined as any dementia-related diagnoses with ICD-9: 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, 331.9. Medicare claims during 1991-2010 [including fee-for-service, for inpatient, outpatient (institutional and non-institutional), skilled nursing, durable medical equipment, home health, and hospice claims].

**P value for graded association across baseline risk factor groups with risk factor status as an ordinal variable.

Table S5. Hazard Ratios (95%Confidence Intervals) for Dementia[#] After Age 65 During 1991-2010 by Baseline CVH Status (1967-73), Further Adjusted for Interim Stroke.

	Baseline CVH Status				
	Favorable[*] (n=742)	Moderate Risk[†] (n=2,238)	1-Only High-Risk Factor[‡] (n=4,220)	2+ High-Risk Factors[‡] (n=2,919)	P-Trend[**]
Model 1[§]	0.70 (0.54-0.90)	0.75 (0.65-0.87)	0.81 (0.72-0.92)	1.0	<.001
Model 2[∥]	0.79 (0.62-1.02)	0.87 (0.77-1.00)	0.88 (0.78-0.99)	1.0	0.020

*Ideal levels of all major CVD RFs (SBP/DBP ≤120/≤80 mmHg and no antihypertensive medication, serum total cholesterol <5.18 mmol/L and no cholesterol-lowering medication, not smoking, BMI < 25 kg/m2, and no diabetes).

†Borderline levels of SBP/DBP or serum total cholesterol, not smoking, BMI 25.0-29.9 kg/m2, and no diabetes

‡ High-risk factors: hypertension (SBP/DBP (≥ 140/90) or using antihypertensive medication), hypercholesterolemia (serum total cholesterol ≥ 6.22 mmol/L or using lipid-lowering medication), smoking, BMI ≥30.0 kg/m2, diabetes.
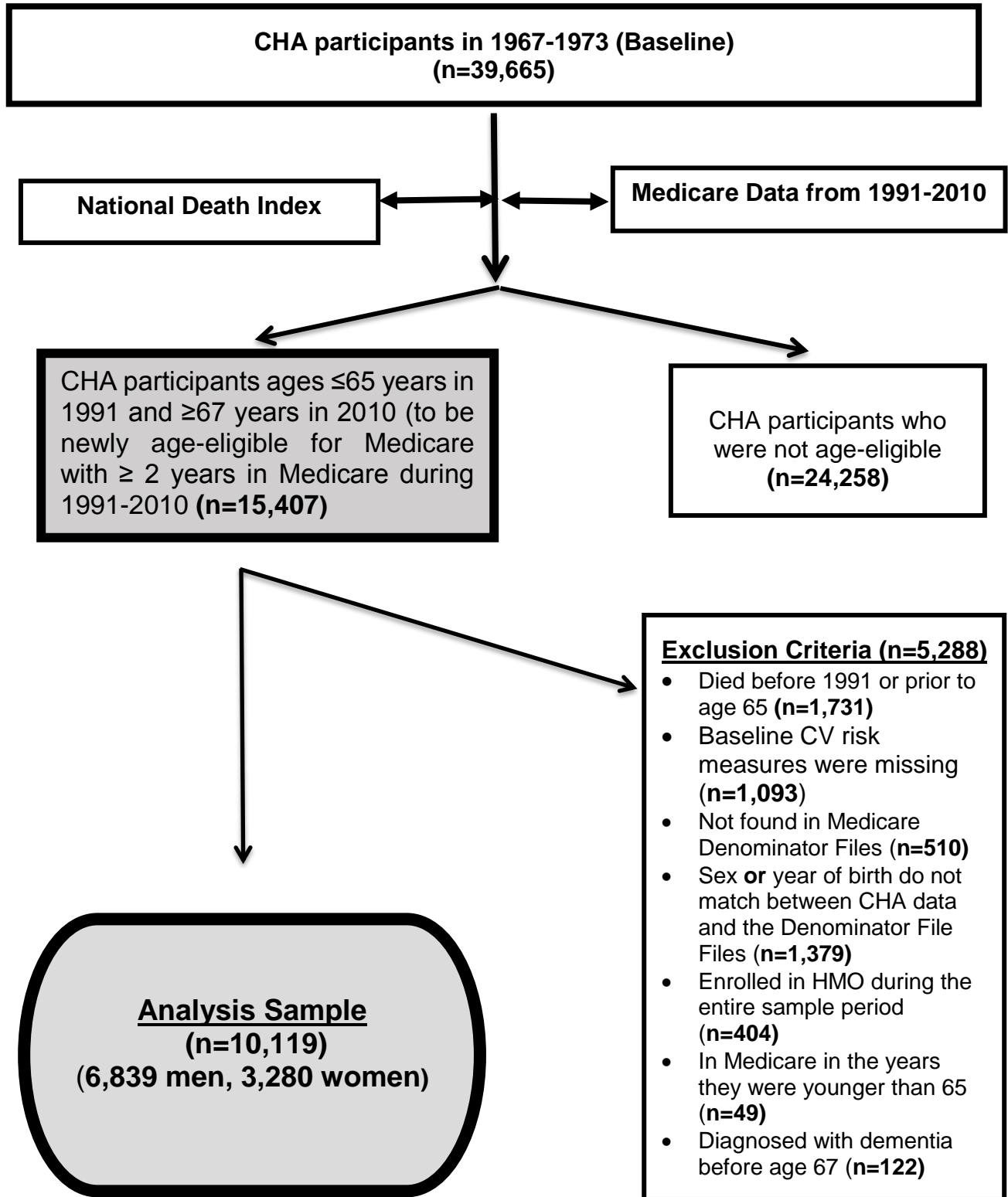
§Model 1: Adjusted for baseline age, sex, race, education attainment, average number of claims per years prior to dementia diagnosis, and any interim stroke occurring from age 65 to the time dementia was first diagnosed (or to the censored time).

ᴵᴵModel 2: Adjusted for baseline age, sex, race, education attainment, annual average number of claims prior to dementia diagnosis, and any interim stroke occurring from age 65 to the time dementia was first diagnosed (or to the censored time), and death prior to dementia diagnoses.

#Dementia were defined as any dementia-related diagnoses with ICD-9: 290, 290.0–4, 290.8–9, 294.1, 331, 331.0–2, 331.9. Medicare claims during 1991-2010 [including fee-for-service, for inpatient, outpatient (institutional and non-institutional), skilled nursing, durable medical equipment, home health, and hospice claims].

**P value for graded association across 4 baseline risk factor groups with risk factor status as an ordinal variable.

Figure S1. Flow Chart Depicting CHA-MEDICARE* Analysis Sample.

CHA participants in 1967-1973 (Baseline)
(n=39,665)

National Death Index

Medicare Data from 1991-2010

CHA participants ages ≤65 years in 1991 and ≥67 years in 2010 (to be newly age-eligible for Medicare with ≥ 2 years in Medicare during 1991-2010 (n=15,407)

CHA participants who were not age-eligible (n=24,258)

Exclusion Criteria (n=5,288)
- Died before 1991 or prior to age 65 (n=1,731)
- Baseline CV risk measures were missing (n=1,093)
- Not found in Medicare Denominator Files (n=510)
- Sex or year of birth do not match between CHA data and the Denominator File Files (n=1,379)
- Enrolled in HMO during the entire sample period (n=404)
- In Medicare in the years they were younger than 65 (n=49)
- Diagnosed with dementia before age 67 (n=122)

Analysis Sample
(n=10,119)
(6,839 men, 3,280 women)

*CHA, Chicago Heart Association Detection Project in Industry Study