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Cardiovascular Damage Phenotypes and All-Cause and CVD Mortality in Older Adults

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Abstract

Purpose: The association between CVD risk factors and mortality is well established, however, current tools for addressing subgroups have focused on the overall burden of disease. The identification of risky combinations of characteristics may lead to a better understanding of physiologic pathways that underlie morbidity and mortality in older adults.

Methods: Participants included 5,067 older adults from the Cardiovascular Health Study, followed for up to 6 years. Using latent class analysis (LCA), we created CV damage phenotypes based on probabilities of abnormal brain infarctions, major echocardiogram abnormalities, N-terminal pro-brain natriuretic peptide, troponin T, interleukin-6, c reactive-protein, galectin-3, cystatin C. We assigned class descriptions based on the probability of having an abnormality among risk factors, such that a healthy phenotype would have low probabilities in all risk factors. Participants were assigned to phenotypes based on the maximum probability of membership. We used Cox-proportional hazards regression to evaluate the association between the categorical CV damage phenotype and all-cause and CVD-mortality.

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Results: The analysis yielded 5 CV damage phenotypes consistent with the following descriptions: healthy (59%), cardio-renal (11%), cardiac (15%), multisystem morbidity (6%), and inflammatory (9%). All four phenotypes were statistically associated with a greater risk of all-cause mortality when compared with the healthy phenotype. The multisystem morbidity phenotype had the greatest risk of all-cause death (HR: 4.02; 95% CI: 3.44, 4.70), and CVD-mortality (HR: 4.90, 95% CI: 3.95, 6.06).

Conclusion: Five CV damage phenotypes emerged from CVD risk factor measures. CV damage across multiple systems confers a greater mortality risk compared to damage in any single domain.

Keywords

Risk Factors; Cardiovascular Disease; Latent Class Analysis

Introduction

The association between cardiovascular disease risk factors, and adverse outcomes including frailty, dementia, and all-cause mortality, is well established.[1–4] Yet, despite evidence of heterogeneity of CVD risk factors in older adults,[4–6] many studies have evaluated these relationships using independent associations or composite scores. For example, Chaves et al. evaluated a preexisting composite score of subclinical cardiovascular disease (SCVD) in the Cardiovascular Health Study (CHS), defined as present (yes or no) if participants had an abnormal measure in at least one variable. The authors found that the presence of any SCVD increased the risk for incident CVD, stroke, mortality, frailty, as well as physical and cognitive decline.[2,7]

While these studies have been critical in our understanding of CVD risk profiles, there are some limitations to these measures. First, individual risk factors likely do not capture the full spectrum of cardiovascular damage and may only measure high risk. Secondly, composite measures are useful at capturing the overall burden of disease for people in high or low risk categories; however, risk may vary across the heterogeneous types of CVD risk profiles. For instance, participants with the same composite score may have the same burden of disease, yet the risk for different components may differ. Furthermore, composite measures lack the ability to evaluate how risk-factors co-occur on the pathophysiology of disease. This may provide additional information regarding etiology from a common source, and whether these risky combinations have differential effects on adverse outcomes such as mortality.

The present study extends prior work on CVD risk factors to evaluate the morbidity patterns that are most strongly associated with mortality. By using methods that cluster observations into groups, we can provide a clearer picture of the riskiest combinations of CVD risk factor measures and ignite areas of further research that may provide clinicians with the ability to improve targeted interventions for persons with specific cardiovascular profiles. Thus, the objective of the present study was to cluster older adults from the CHS into cardiovascular damage phenotypes, and to evaluate these phenotypes with all-cause and CVD mortality.

Materials and Methods

Study Design

This research included participants in the Cardiovascular Health Study (CHS), a population-based prospective study initiated by the National Heart, Lung and Blood Institute (NHLBI) in 1989 with the objective of examining risk factors for cardiovascular disease in older adults. At entry, the study enrolled 5,201 adults 65 years of age and older from four field centers: University of California, Davis in Sacramento County, California; Johns Hopkins University in Washington County, Maryland; Wake Forest University School of Medicine in Forsyth County, North Carolina; University of Pittsburgh in Pittsburgh, Pennsylvania. Six hundred and eighty-seven African American participants were recruited from the same study sites after the initial baseline survey using similar methods in 1992–1993.

Participants were recruited from Medicare eligibility lists in each of the four areas. Eligibility criteria included all persons living in the household of the individual sampled from the Health Care Financing Administration (HCFA), were non-institutionalized, aged 65 or older, expected to remain in the area for the following three years, and had the ability to give informed consent without the need for a proxy at baseline. Exclusion criteria included participants on hospice treatment, wheelchair bound in the home at baseline, or receiving radiation or chemotherapy for cancer.

At baseline and annually during the first 10 years, participants completed home visits, physical examinations, health questionnaires, and donation of blood specimens. At 16 years of follow-up, participants were invited to participate in a follow-up exam consisting of the same elements. Telephone interviews were conducted every 6 months beginning in 1989 to obtain information on outcomes, and potential events were both self-reported and obtained from hospital records.[8] The study was approved by the institutional review boards at all institutions involved in the study, and informed consent was obtained from all participants.

Due to availability of the subclinical measures, the 3rd follow-up visit (1992/93) was used as baseline for this study.

Exposure

To create cardiovascular damage phenotypes, we first tested 14 indicator variables available in the CHS at the third follow-up visit representing different types of morbidity, including vascular markers (internal intima-media thickness [IMT], white matter grade [WMG], cortical brain infarctions, intermittent claudication, and ankle arm index [AAI]), cardiac markers (major echocardiogram abnormalities [ECG], N-terminal pro-brain natriuretic peptide [NTproBNP], angina, troponin-T, and ST2), inflammatory markers (interleukin-6 [IL-6], C-reactive protein [CRP], and galectin-3 [Gal3]), in addition to cystatin C, a marker of renal function. Two of these variables were excluded due to low prevalence (<5% of observations) of abnormalities (intermittent claudication, and angina).

Indicator variables were evaluated at baseline and dichotomized into normal/abnormal based on clinical cut-points or cut-points found in the literature. *Internal carotid intima-media thickness (IMT)* was measured from carotid ultrasound. The maximum wall thickness for

the internal carotid artery was defined as a mean of the maximum wall thickness for the near and far wall on all three longitudinal views.[9] An abnormal IMT was defined as ≥ 75th percentile.[10,11] *White matter disease* was measured by MRI scans using a grade from 0–9, where 0 is no changes, and 9 is most pronounced changes. Abnormal was defined as a grade of ≥ 5.[12] *Cortical brain infarctions* were measured using an MRI scan and defined as a presence or absence of lesions ≥ 3 mm.[13] *Ankle arm index (AAI)* was measured by trained technicians under standard protocol. Participants underwent duplicate readings after a brief 50-minute rest in the supine position. Duplicate blood pressure readings were taken by a mercury sphygmomanometer and a Doppler stethoscope in the right arm and right ankle. The ratio represented an average of the duplicate readings. The cut-off of ≤0.9 was used to define abnormal.[14] *Major ECG abnormalities* was defined according to the Minnesota code as left ventricular conduction defects, atrial fibrillation, major Q or QS abnormalities, minor Q or QS with ST-T wave abnormalities, left ventricular hypertrophy, isolated major ST-T wave changes, and first-degree atrioventricular block. Major ECG abnormalities was dichotomized as abnormal or normal.[15] All blood samples were stored in a central laboratory at −70C or colder. *Serum N-terminal pro-brain natriuretic peptide (NTproBNP) pg/mL* was measured in serum; the coefficient of variation was 2% to 5, and the analytical measurement range was 5–35,000 pg/ml.[16] The highest quintile of NTproBNP was defined as abnormal (> 356 ng/L).[17(p201)] *Serum troponin-T pg/mL* was stored in serum at −70°C to −80°C with a coefficient of variation 2%−5%; analytical measurement range for troponin T is 3–10,000 pg/ml.[18] Troponin T was dichotomized was dichotomized at 5 ng/L with ≥ 5 defined as abnormal.[19,20] *Serum ST2 ng/mL* was measured by the Presage ST2 assay (Critical Diagnostics, San Diego, CA). The highest tertile of ST2 (39.5 ng/mL) was used to define abnormal.[21] *Serum interleukin-6 (IL-6) pg/mL* was stored in serum and measured by high sensitivity in-house ELISA; the analytic coefficient of variation was 6.3%.The upper tertile of IL-6 in this population was used to define abnormal. *C-reactive protein (CRP), mg/L* was measured in plasma by high sensitivity in-house ELISA; the analytic coefficient of variation of 8.9%. A level of >3 was considered abnormal.[1] *Serum Galectin-3 (gal3), ng/mL* was measured using an optimized ELISA (BG Medicine, Waltham, MA, USA).[22] A level of > 17.7 ng/mL was defined as abnormal.[23] *Cystatin C mg/L* was measured by a BNII nephelometer (Dade Behring Inc., Deerfield, IL) in serum, and the highest quartile (values ≥ 1.29 mg/L) were considered abnormal.[24] Both intermittent claudication and angina were dichotomized into rarely/none of the time, and some or a little of the time, where some or a little of the time was considered abnormal. Cortical brain infarctions and WMG were only available in a subset of participants that underwent an MRI (n=3660).[12]

Outcome

The outcomes of interest were all-cause mortality and CVD-mortality occurring before July 16, 2015. Deaths were identified by an adjudication committee that reviewed obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services files.[8,25] CVD mortality was defined as death due to atherosclerotic coronary heart disease (CHD), cerebrovascular disease, other atherosclerotic disease, and other cardiovascular disease.

Covariates

Covariates were chosen *a priori* and were measured at baseline. Age (in years), sex, race (white, African American/other), years of education, and clinic site (University of California, Davis, Johns Hopkins University, Wake Forest University, University of Pittsburgh). Smoking status (never, former, current user), alcohol use defined as none (0 drinks per week), low (1–7 drinks per week for women, or 1–14 drinks for men) or high (> 7 drinks per week for women, or > 14 drinks per week for men). Body mass index calculated as weight(kg)/height(m)^2, and activities of daily living (ADL) categorized as none and 1 or more. Diabetes (fasting glucose level greater than 125 mg/dL or the use of glucose-lowering medications), and high blood pressure (seated systolic blood pressure ≥ 140 mmHg, seated diastolic blood pressure of ≥ 90 mmHg). Low-density lipoprotein (LDL) cholesterol (mg/dl). Medications were transcribed by technicians based on prescription bottles brought in by participants during clinic visits.[26] Medication use included anti-hypertensive medication (indication of high blood pressure and use of any of the following: beta-blockers, calcium-channel blockers, diuretics, vasodilators, etc.). Measurement methods for apolipoprotein e4 allele (APOE) have been published elsewhere.[27] APOE was dichotomized as having at least one ε4 allele (yes, no), and analyses were limited to those with available DNA who consented to genetic studies.

Statistical Analysis

We used latent class analysis (LCA) to create phenotypes of cardiovascular damage. LCA is a subset of structural equation modeling that uses the posterior distribution of the data to predict membership into each mutually exclusive latent class. In LCA, the user choses the number of classes to be estimated by the data, where the size of each class and the probability of a response to each variable given class membership is also included.[28] The LCA model provides the user with likelihood probabilities of the presence of an abnormality to each indicator, however, it does not provide the degree of likelihood. Goodness of fit (GOF) statistics (likelihood ratio G^2, degrees of freedom, Akaike information criterion (AIC), Bayesian information criterion (BIC), adjusted BIC, entropy) are used to help provide an empirical method for choosing the number of classes that best fits the data, however, a theoretical understanding is also suggested.[28] In our analysis, we chose to model 2 through 7 classes to allow both empirical and theoretical reasoning in model selection. In addition to GOF statistics, the optimal number of classes was chosen based on physiologic interpretability of classes, and class size to ensure there was enough power to detect statistical differences between classes.[29] The maximum probability assignment rule, which places the participant into the latent class where they have the highest posterior probability of membership, was used to extract latent classes and to create the categorical exposure variable. We labeled each of the classes as phenotypes, based on the clinical knowledge of the variables contributing to each class.

Baseline characteristics were compared between phenotypes using one-way analysis of variance for continuous variables and pairwise chi-squared (χ^2) tests for categorical variables. We used Cox-proportional hazards regression to evaluate the association between phenotype with all-cause mortality and CVD-mortality. We used SAS 9.4 (Cary, NC) for

LCA, and Stata 14 (Stata Corp., College Station, TX) for descriptive statistics and time-to-event analyses.

Results

In 5,067 participants with data available on the biomarkers of interest, we compared models ranging from 2 to 7 classes, and found that the 5-class solution was the best fit for the data while excluding WMG, AAI, and IMT for not meaningfully contributing to the model. Specifically, the 5-class model had the smallest BIC and adjusted BIC, as well as the most clinically meaningful classes that were large enough to maintain adequate power (Supplemental Table 1). We characterized the 5 classes into a healthy phenotype (59%) due to low probabilities of having abnormalities for every indicator variable and was the most common phenotype, a cardio-renal phenotype (11%) because of high probabilities of abnormalities in NTproBNP, Troponin T, Gal3 and Cystatin C, and low probabilities in all other indicator variables. Similarly, we characterized the third class as a cardiac phenotype (15%) due to high probabilities of ECG abnormalities, NTproBNP and Troponin T, the fourth class as a multisystem morbidity phenotype (6%) because of high probabilities of abnormalities among all of the indicator variables that span multiple systems, and finally the 5^{th} class as an inflammatory phenotype (9%) because of high probabilities of having abnormalities in CRP and IL-18. The item-response probabilities, for these 5 phenotypes are displayed in Table 1. The healthy phenotype, or absence of risk phenotype, was the most common phenotype (59% of participants), while the cardiac phenotype was the most common disease phenotype (15% participants).

Descriptive statistics for participants stratified by phenotype suggested that the participants in the healthy phenotype tended to be younger, female, have more education, have lower systolic blood pressure, were less likely to have hypertension and diabetes. (Table 2) On the contrary, the multisystem morbidity phenotypes tended to be older, male, have less education, have hypertension and diabetes, and have lower cholesterol. African-Americans were more likely to have higher presence of the inflammatory phenotype.

Participants were followed for an average of 9.35 years. We observed 2,919 deaths from all-causes with an incident rate of 59 (per 1000 person-years). All phenotypes were associated with a greater risk of death from all causes compared with the healthy phenotype, and these associations remained significant when adjusted for covariates. In adjusted models, the multisystem morbidity phenotype had the greatest risk of all-cause mortality with an HR of 4.02 (95% CI: 3.44, 4.70) compared with the healthy phenotype, followed by the cardio-renal phenotype (HR: 2.31, 95% CI: 2.02, 2.64), the cardiac phenotype (HR: 1.76; 95% CI: 1.55, 1.99), and finally the inflammatory phenotype (HR: 1.50, 95% CI: 1.28, 1.76; Table 3). Kaplan-Meier failure estimates show clear differences between the healthy phenotype and others, showing the multisystem morbidity phenotype with the highest cumulative probability of mortality over follow-up (Figure 1).

There were 1,525 deaths attributed to CVD with an incident rate of 31 (per 1,000 person-years). In the unadjusted model, all phenotypes were associated with a greater risk of CVD-mortality, and all reached statistical significance in adjusted models. The multisystem

morbidity phenotype had the greatest risk of CVD related deaths with a HR of 4.90 (95% CI: 3.95, 6.06) followed by the cardiac-renal phenotype (HR: 2.29, 95% CI: 1.89, 2.77), the cardio phenotype (HR: 2.22 (1.88, 2.62) and finally the inflammatory phenotype (HR: 1.46, 95% CI: 1.17, 1.81, Table 3).

Discussion

The current study aimed to identify cardiovascular damage phenotypes and their association with all-cause and CVD-mortality in a large population based prospective cohort study of community-dwelling older adults. We found 5 classes consistent with the following descriptions: healthy, cardio-renal, cardiac, multisystem morbidity and inflammatory. We also found that all cardiovascular damage phenotypes were significantly associated with a greater risk of death from all causes compared with the healthy phenotype, as well as with CVD related mortality. These findings highlight the heterogeneity of CVD risk factors and suggest that some cardiovascular profiles are riskier than others for mortality, particularly those with abnormalities spanning multiple domains.

Our study adds to the literature on CVD risk factors by identifying groups of participants using an innovative clustering technique. In another study conducted in the CHS, Inzitari et al. created an index of subclinical vascular disease by summing abnormalities on ankle-arm index, electrocardiogram, and common carotid intima-media thickness (no, mild, severe). Authors found a dose-response association, where those with higher disease severity had a greater risk of CVD and mortality, and those with a lower burden had longer survival.[4,30] Similarly, a physiologic index of comorbidity was created in the CHS that measured CV, pulmonary, and kidney function, glucose tolerance and brain MRI, with scores ranging from 0 (health) to 10 (unhealth). Authors found a similar relationship where higher scores were associated with higher mortality, mobility limitation and ADL difficulty.[31,32] While this is not the first study to use clustering techniques to create phenotypes in CHS,[33] we extended this research by examining the patterning and variations of risk factors from multiple domains using LCA, which has not been done previously. By combining markers into phenotypes, instead of examining risk factors one at a time, we are able to account for correlations between risk factors while reducing type 1 error, making this an ideal method for distinguishing clinically important phenotypes.[34]

Although all disease phenotypes were significantly associated with all-cause mortality compared with the healthy phenotype, in this elderly population, the risk associated with the multisystem morbidity phenotype was approximately double other 3 groups. This is consistent with other studies demonstrating that pathology across multiple domains confers greater risk than pathology in a single domain.[35,36] Unlike the cardio-renal and cardiac groups, the inflammatory phenotype was the least risky group compared with healthy phenotype in all models. This would suggest that older adults with abnormal concentrations of inflammatory biomarkers without other CVD risk factor abnormalities may be at lower risk or have less advanced disease progression compared to other subtypes in our population. For instance, a previous study in CHS found that CRP only increased the risk of stroke in the presence of carotid disease.[37] This is also supported by studies that have found both inflammation and cerebrovascular disease such as WMG to be a precursor for CVD.[38–40]

Strengths of this study include the large, cohort study of community dwelling older adults, and the prospective design. Furthermore, this is the first study to our knowledge that has used an innovative approach to cluster participants into phenotypes based on their interrelationship of CVD risk factor markers. There are some limitations that should be noted. It could be argued that the inherent need for dichotomized variables in LCA makes this method unfavorable (as opposed to using latent profile analysis and continuous variables), however, using specific cut-offs that are clinically meaningful, may help ease the translation from research to clinical practice.[41] We are also assuming that these risk factors remain the same over time, which is likely not the case. However, due to the small number of indicator variables with measurements at multiple time points, we were unable to evaluate the change in phenotype class over time using latent transition analysis. Furthermore, because MRI variables were only available in a subset of the cohort (n=3660), only those with data on cortical brain infarcts and WMG were able to have likelihood probabilities for those indicators. Moreover, recruiting participants from Medicare eligibility lists may not include persons with a social security number such as undocumented immigrants. Finally, results may not apply to younger populations where interventions to reduce risk might result in more years of healthy life gained, so confirmation is required.

Conclusions

In summary, the present study provides evidence of heterogeneity among CVD risk factors. Clinically, older adults with decrements across multiple systems, specifically cardio-renal and multisystem, may indicate a high mortality risk group when compared to older adults in the mild to moderate risk groups. Due to the exploratory nature of this study, future work should focus on validating these findings in other population-based studies, and should evaluate with other clinically important outcomes and improving interventions to target specific phenotypes. If confirmed, our work could lead to more tailored risk assessments among older adults with risk factors for CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

Abbreviations:

CVD	Cardiovascular Disease
SCVD	Subclinical Cardiovascular Disease

CHS	Cardiovascular Health Study
IMT	internal intima-media thickness
WMG	white matter grade
AAI	ankle arm index
ECG	major echocardiogram abnormalities
NTproBNP	N-terminal pro-brain natriuretic peptide
IL-6	interleukin-6
CRP	C-reactive protein
Gal3	galectin-3
ADL	Activities of Daily Living
LDL cholesterol	Low-density Lipoprotein Cholesterol
APOE	Apolipoprotein e4
LCA	Latent Class Analysis
GOF	Goodness of Fit
BIC	Bayesian Information Criterion
AIC	Akaike Information Criterion
HR	Hazard Ratio

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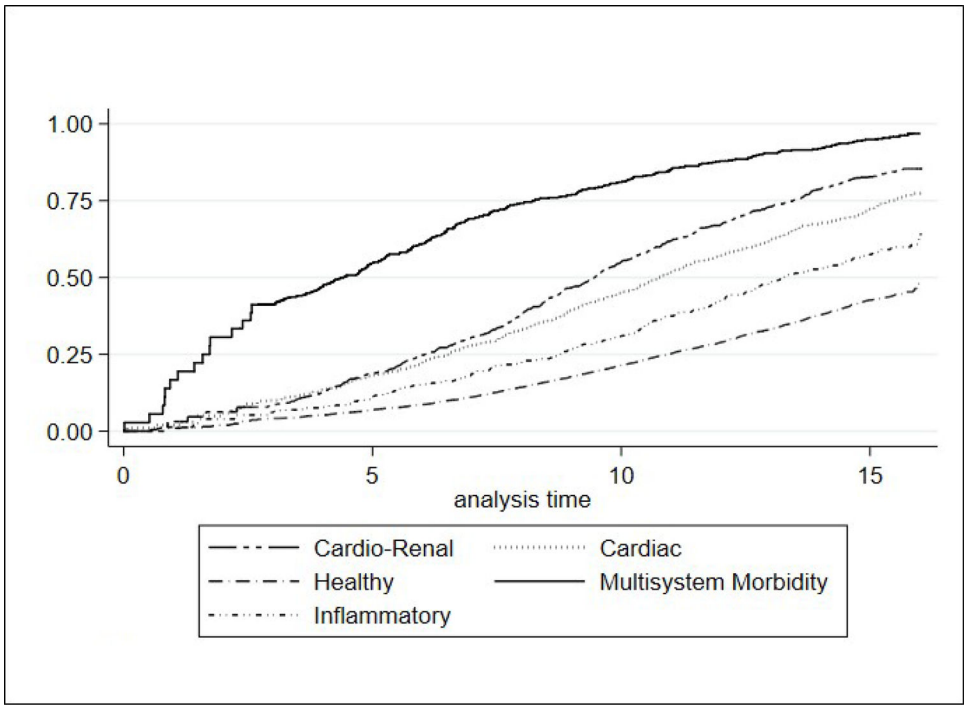

Figure 1.
Kaplan-Meier failure estimates by phenotype.

Table 1:

Item-response Probability for the 5-class model: Probabilities of having an Abnormality given Latent Class.

Number of Classes and Suggested Phenotypes for 5 class model					
	Class 1	**Class 2**	**Class 3**	**Class 4**	**Class 5**
	Cardio-Renal	**Cardiac**	**Healthy**	**Multisystem**	**Inflammatory**
Membership Probability	0.11	0.18	0.53	0.07	0.11
Cortical Brain Infarct	0.45	0.40	0.23	**0.51**	0.32
ECG	0.46	**0.73**	0.20	**0.89**	0.23
NTproBNP	**0.60**	**0.55**	0.11	**0.99**	0.14
Troponin T	**0.91**	**0.81**	0.33	**0.98**	0.45
ST2	0.37	0.43	0.24	**0.64**	0.39
CRP	0.11	0.05	0.05	**0.55**	**0.52**
IL-6	0.41	0.26	0.13	**0.99**	**0.98**
Gal3	**0.69**	0.15	0.16	**0.56**	0.33
Cystatin C	**0.96**	0.10	0.04	**0.58**	0.18

Note. IMT=internal intima-media thickness; WMG=white matter grade; ECG=major echocardiogram abnormalities; NTproBNP= N-terminal pro-brain natriuretic peptide; IL-6= interleukin-6; Gal3= galectin-3

Table 2.

Characteristics of 5067 Participants from the Cardiovascular Health Study stratified by Phenotype

Characteristics	Healthy	Cardio-Renal	Cardiac	Multisystem Morbidity	Inflammatory	P-value
	n=2987	n=571	n=757	n=306	n=446	
	Mean (SD) or N(%)					
Age, years	73.8 (4.7)	78.3 (6.1)	76.8 (5.7)	77.9 (6.1)	73.6 (4.5)	<0.001
Women	1994 (65%)	290 (51%)	336 (44%)	126 (41%)	266 (60%)	<0.001
African American (vs. white/other)	522 (17%)	74 (13%)	135 (18%)	47 (15%)	97 (22%)	0.005
Grade (no. years)	14.2 (4.7)	13.3 (4.9)	13.6 (4.9)	13.6 (4.9)	13.4 (4.5)	<0.001
Alcohol use (frequent)	324 (11%)	36 (7%)	55 (8%)	28 (10%)	40 (10%)	<0.001
Current Smokers	270 (9%)	50 (9%)	58 (8%)	39 (13%)	68 (16%)	<0.001
Systolic BP, mmHg	134.4 (19.9)	140.0 (23.9)	141.1 (24.3)	140.2 (23.4)	135.9 (21.4)	<0.001
Diastolic BP, mmHg	71.3 (10.9)	70.3 (12.3)	72.1 (12.9)	70.2 (13.2)	71.5 (11.1)	0.02
Hypertension	1036 (36%)	322 (56%)	382 (51%)	154 (50%)	211 (47%)	<0.001
LDL Cholesterol	129.6 (32.9)	123.9 (34.9)	123.5 (33.5)	122.03 (39.7)	126.0 (34.8)	<0.001
Diabetes	343 (13%)	101 (18%)	140 (20%)	78 (26%)	109 (25%)	<0.001
APOE	701 (26%)	129 (25%)	173 (25%)	64 (22%)	89 (22%)	0.35

Note. Frequent alcohol use was defined as > 7 drinks per week for women, or > 14 drinks per week for men.

Note. APOE= apolipoprotein E ε4 allele

Table 3:

The Association between Cardiovascular Damage Phenotype with All-cause and CVD Mortality.

	Unadjusted	Adjusted[a]
All-Cause Mortality 2919 deaths	**HR (95% CI)**	
Phenotype		
Healthy (ref)	-	-
Cardio-Renal	3.30 (2.96, 3.67) ***	2.31 (2.02, 2.64) ***
Cardiac	2.39 (2.16, 2.65) ***	1.76 (1.55, 1.99) ***
Multisystem Morbidity	5.59 (4.91, 6.37) ***	4.02 (3.44, 4.70) ***
Inflammatory	1.58 (1.38, 1.81) ***	1.50 (1.28, 1.76) ***
CVD-Mortality 1525 deaths	**HR (95% CI)**	
Phenotype		
Healthy (ref)	-	-
Cardio-Renal	3.33 (2.85, 3.89) ***	2.29 (1.89, 2.77) ***
Cardiac	3.22 (2.82, 3.68) ***	2.22 (1.88, 2.62) ***
Multisystem Morbidity	6.80 (5.66, 8.17) ***	4.90 (3.95, 6.06) ***
Inflammatory	1.58 (1.30, 1.91) ***	1.46 (1.17, 1.81) **

*** P<0.001

** P<0.01

[a]Adjusted for clinic site, age, sex, race, alcohol use, smoking status, body mass index, years of education, diabetes, LDL cholesterol, hypertension, antihypertensive medication, limitations in activities of daily living, and apolipoprotein e ε4 allele.