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Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objectives: This study investigated the sex differences in the associations between ideal cardiovascular health (CVH), measured by the American Heart Association's Life's Simple 7 and cardiovascular disease (CVD)-related biomarkers among an ethnically diverse cohort of men and women free of clinical CVD at baseline.

Setting: We analyzed data from the Multi-Ethnic Study of Atherosclerosis conducted in 6 centers across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN).

Participants: This is a cross-sectional study of 5,379 men and women, aged 45 to 84 years old. Mean age (SD) was 62 (10), 52% were women, 38% White, 11% Chinese American, 28% Black and 23% Hispanic.

Primary measures: The 7 metrics (smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and blood glucose) were each scored as 0 points (poor), 1 point (intermediate) and 2 points (ideal). The total CVH score ranged from 0-14. The CVD-related biomarkers studied were high-sensitivity C-reactive protein, D-dimer, fibrinogen, homocysteine, high-sensitivity cardiac troponin T, and NT-proBNP. We examined the association between the CVH score and each biomarker using multivariable linear regression, adjusting for age, race/ethnicity, education, income, and health insurance status.

Results: Higher CVH scores were associated with lower concentrations of all biomarkers, except for NT-proBNP where there was a positive association. There were statistically significant interactions by sex for all biomarkers ($p<0.001$), but results were qualitatively similar between women and men.

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Conclusion: A more favorable CVH score was associated with lower levels of multiple CVD-related biomarkers for women and men, except for NT-proBNP. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of CVD risk for both women and men.

Keywords: Biomarkers, cardiovascular disease, ideal cardiovascular health metrics, Life's Simple 7, sex, gender

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Strengths and limitations of this study

- Use of a large and diverse study sample that enabled for stratification by sex, race/ethnicity and age.
- Use of validated survey instruments and standardized methods for data collection allows for comparison with other studies.
- Study population included adults between the ages of 45 and 84 years which limits the generalizability of our findings to a younger age group.

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Introduction

The ideal cardiovascular health (CVH) construct, defined as meeting specific criteria for 7 risk factors called the Life's Simple 7 (LS7) metrics, was introduced by the American Heart Association (AHA) to decrease the burden of CVD[1]. This was a shift towards primordial prevention – focusing on wellness rather than disease[2]. Biomarkers, which are often used in conjunction with traditional risk factors, are subclinical indicators of physiological and pathological processes[3] and serve as useful tools in facilitating early detection and prognostication of CVD[4]. Although prior studies have examined the relationship of biomarkers with incident CVD, few have focused on biomarkers and measures of cardiovascular wellness. Not surprisingly, the studies that have examined the association between ideal CVH and subclinical biomarkers of disease have shown an inverse relationship[5]. For example, in a prior analysis from the Multi-Ethnic Study of Atherosclerosis (MESA), poor CVH was found to be associated with higher levels of GlycA (a novel inflammatory marker) and higher levels of traditional inflammatory markers [high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL6), fibrinogen, and D-dimer][6]. However, research on the sex differences of the relationship of CVH with CVD-related biomarkers is sparse[7].

There are known sex differences in the levels of CVD-related biomarkers. Women are known to have higher levels of hsCRP[8, 9] and N-terminal pro B-type natriuretic peptide (NT-proBNP)[10] than men even after accounting for cardiometabolic risk factors, while troponin levels[11, 12] are higher in men than women. Thus, understanding sex differences in the relationship of ideal CVH measures with

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biomarkers is an important intermediate step in explaining sex differences in clinical CVD.

This study aimed to examine the sex differences in the associations between ideal CVH and CVD-related biomarkers among men and women free of clinical CVD in an ethnically diverse cohort. We hypothesized that better CVH would be associated with lower concentrations of CVD-related biomarkers especially in women.

Methods

Study population

As previously described, MESA is a longitudinal study of 6,814 adult women and men between the ages of 45 and 84 years. The study participants, with no previous history of clinical CVD at baseline, were enrolled from 6 centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN) in the United States between July 2000 and August 2002[13]. Among participants, 38% were White, 11% Chinese American, 28% Black, and the remaining 23% were Hispanic. The MESA protocol was approved by the institutional review boards of all the recruitment centers. Informed consent was provided by all participants. Baseline information was collected using standardized questionnaires, physical examinations and fasting laboratory blood draw. For the current analyses, we included 5,379 participants from the MESA baseline exam after excluding participants with missing information for the CVD biomarkers and LS7 metrics.

Assessment of biomarkers

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We examined biomarkers that were measured at baseline. Fasting blood samples were drawn, processed and stored using standardized procedures[14]. HsCRP, D-dimer, fibrinogen and homocysteine levels were analyzed at the laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Serum levels of hsCRP (mg/L) were measured using the BNII nephelometer (Dade Behring, Deerfield, IL). Analytical intra-assay coefficients of variation (CV) of hsCRP ranged from 2.3% to 4.4%, and inter-assay CV ranged from 2.1% to 5.7%[6, 15]. D-dimer (µg/mL) was measured with an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) which was used on a Sta-R analyzer (Diagnostica Stago, Parsippany, NJ). The lower detection limit of D-dimer assay was 0.01 µg/mL[6]. Serum fibrinogen (mg/dL) was measured by immunoprecipitation of fibrinogen antigen using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The intra-assay and inter-assay CV were 2.7% and 2.6%, respectively[6, 15].

Plasma homocysteine (µmol/L) was measured using a fluorescence polarization immunoassay with the IMx analyzer (Abbott Diagnostics, Abbott Park, IL). The CV was 4.5%[16]. High-sensitivity cardiac troponin T (hs-cTnT, ng/L) and N-terminal Pro-B-Type Natriuretic Peptide (NT-proBNP, pg/mL) were measured in serum using the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN). All analyses were performed at a core lab (Veteran's Affairs San Diego Healthcare System, La Jolla, CA). For hs-cTnT, the inter-assay CV observed for the MESA cohort measurements were 3.6% at 28 ng/L and 2.0% at 2154 ng/L[17]. For NT-proBNP, the intra-and inter-assay CV were as follows: at 175 pg/mL, 2.7% and 3.2%; at 355 pg/mL, 2.4% and 2.9%; at 1068 pg/mL, 1.9% and 2.6%; and at 4962 pg/mL, 1.8% and 2.3%, respectively[10] .

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Assessment of cardiovascular health

Cardiovascular health was assessed at baseline using the LS7 metrics based on AHA criteria[1]. A detailed assessment can be found in the supplementary material.

Assessment of covariates

Sociodemographic factors included as covariates are age, sex, race/ethnicity education income and health insurance. Age was categorized as <65 and ≥65 years. Race/ethnicity had 4 groups: White, Chinese-American, Black and Hispanic. We had 9 categories for education and 13 categories for income. “Yes” or “No” responses were given for health insurance status.

Statistical Analyses

The characteristics of the study participants were reported for the overall population and by sex. Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means with standard deviation (SD). We compared the baseline characteristics of participants by sex, using ANOVA and chi-square tests as appropriate. The CVD-related biomarkers were natural logarithmically transformed for the analyses because distribution was skewed. The LS7 metrics were defined as ideal, intermediate, and poor[1], and their distribution was reported by sex, as shown in **Supplementary Tables 1 & 2**. Points were awarded to each category of the LS7 metrics with 0 indicating poor; 1, intermediate; and 2, ideal. The points were summed, yielding a total CVH score ranging from 0 to 14[18]. As previously reported, total CVH scores of 0 to 8, 9 to 10, and 11 to 14 were considered as inadequate, average, and optimal CVH respectively[19-21].

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Using linear regression models, we estimated the crude beta coefficients and corresponding 95% confidence intervals (CI) for the associations between the CVH score (assessed continuously) and CVD-related biomarkers (log-transformed, assessed continuously) in the overall cohort and by sex (model 1). We adjusted for sociodemographic factors [age (continuous), sex (for overall cohort), race/ethnicity (4 categories), education (9 categories), income (13 categories), and health insurance status (yes/no)] in model 2 and reported the adjusted beta coefficients. We examined the interaction of the CVH score categories with sex for all 6 biomarkers using the Wald test, by including interaction terms in model 2.

The associations between the LS7 metrics and CVD-related biomarkers were examined by comparing the intermediate and ideal categories of the metrics to the poor category. We reported only the adjusted model for women and men. In supplementary analyses, we examined the association between the CVH score and CVD-related biomarkers stratified by race/ethnicity and age (<65 and ≥65 years) within each sex, using multivariable linear regression models. For statistical analyses, STATA version 15.0 was used (StataCorp LP, College Station, TX) and an alpha level of <.05 was considered statistically significant.

Patient involvement

No patients were involved in this study.

Results

Baseline characteristics of participants are shown in **Table 1**. Over half of the participants were women (52%), and the mean age (SD) was 62 (10) years. Women

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had higher hsCRP, D-dimer, fibrinogen and NT-proBNP levels, while men had higher hs-cTnT and homocysteine levels. Women were less likely to be physically active and were more likely to have higher systolic blood pressure as well as higher healthy diet score and total cholesterol levels **(Table 1 and Supplementary Table 2)**.

Table 1- Characteristics of Study Participants

	Total (N= 5,379)	Women (n=2,775)	Men (n=2,604)	P value
Age, mean (SD), y	62 (10)	62 (10)	62 (10)	0.67
Age, y				
<65 n (%)	3,013 (56)	1,559 (56)	1,454 (56)	0.80
≥65 n (%)	2,366 (44)	1,216 (44)	1,150 (44)	
Race/Ethnicity				
White n (%)	2,150 (40)	1092 (39)	1058 (41)	
Chinese American n (%)	733 (14)	372 (13)	361 (14)	0.17
Black n (%)	1,253 (23)	681 (25)	572 (22)	
Hispanic n (%)	1,243 (23)	630 (23)	613 (24)	
Education				<0.001
≥ Bachelor's degree n (%)	1,929 (36)	824 (30)	1,105 (42)	
< Bachelor's degree n (%)	3,450 (64)	1,951 (70)	1,499 (58)	
Income				<0.001
≥$40,000 n (%)	2,648 (49)	1,162 (42)	1,486 (57)	
<$40,000 n (%)	2,731 (51)	1,613 (58)	1,118 (43)	
Health insurance				

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Yes n (%)	4,871 (91)	2,511 (90)	2,360 (90)	0.86
No n (%)	508 (9)	264 (10)	244 (10)	
Biomarkers, Mean (95% CI)				
hsCRP (mg/L)	3.7 (3.5, 3.8)	4.5 (4.2, 4.7)	2.8 (2.6, 3.0)	<0.001
D-dimer (µg/mL)	0.37 (0.34, 0.39)	0.38 (0.35, 0.41)	0.35 (0.32, 0.39)	0.29
Fibrinogen, mg/dL	345.2 (343.2, 347.1)	358.0 (355.2,360.8)	331.5 (328.8, 334.1)	<0.001
Homocysteine (µmol/L)	9.3 (9.2, 9.4)	8.7 (8.6, 8.8)	10.0 (9.9, 10.1)	<0.001
hs-cardiac Troponin T (ng/L)	6.6 (6.4, 6.8)	5.2 (5.0, 5.4)	8.1 (7.7, 8.5)	<0.001
NT-proBNP (pg/mL)	100.8 (94.2, 107.4)	114.0 (108.1, 119.8)	86.8 (74.8, 98.9)	0.0001
LS7 metrics				
Current smoking n (%)	671 (12)	303 (11)	368 (14)	<0.001
Body mass index (kg/m2)	28 (5)	29 (6)	28 (4)	<0.001
Physical activity (MET-min/week)	401 (589)	338 (490)	468 (672)	<0.001
Healthy diet score (0-5)	1.6 (0.9)	1.7 (0.9)	1.4 (0.9)	<0.001
Total cholesterol (mg/dL)	194 (36)	200 (36)	189 (35)	<0.001
Systolic blood pressure (mmHg)	126 (21)	127 (23)	125 (19)	0.03
Diastolic blood pressure (mmHg)	72 (10)	69 (10)	75 (9)	<0.001
Fasting blood glucose (mg/dL)	97 (31)	95 (29)	100 (32)	<0.001
CVH score				
Inadequate	2,509 (47)	1,284 (46)	1,225 (47)	
Average	1,772 (33)	915 (33)	857 (33)	0.78
Optimal	1,098 (20)	576 (21)	522 (20)	

Abbreviations: SD, standard deviation; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; LS7, Life's Simple 7; CVH, Cardiovascular health

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The associations between the total CVH score and the CVD-related biomarkers are reported in **Table 2**. After adjusting for sociodemographic factors (model 2), higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers except for NT-proBNP, where CVH was associated with a higher concentration. For example, in the overall cohort, a 1-unit increment in the CVH score corresponded to a 0.13 mg/L lower log (hsCRP) concentration and a 0.04 ng/L lower log (hs-cTnT) concentration, but a 0.02 pg/mL higher log (NT-proBNP) concentration.

Table 2- The associations between CVH score and CVD-related biomarkers

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)
Total, N= 5,379						
Model 1	**-0.16 (-0.17, -0.14)**	**-0.06 (-0.07, -0.05)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.06, -0.05)**	0.00004 (-0.01, 0.01)
Model 2	**-0.13 (-0.14, -0.12)**	**-0.03 (-0.04, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.01, -0.01)**	**-0.04 (-0.05, -0.03)**	**0.02 (0.01,0.03)**
Women, n= 2,775						
Model 1	**-0.18 (-0.20, -0.16)**	**-0.07 (-0.09, -0.06)**	**-0.03 (-0.03, -0.03)**	**-0.02 (-0.03, -0.02)**	**-0.04 (-0.05, -0.04)**	0.01 (-0.01,0.03)
Model 2	**-0.16 (-0.18, -0.14)**	**-0.03 (-0.05, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**0.03 (0.01,0.04)**
Men, n= 2,604						
Model 1	**-0.13 (-0.15, -0.11)**	**-0.04 (-0.05, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.07 (-0.08, -0.06)**	-0.01 (-0.03,0.01)
Model 2	**-0.10**	**-0.02**	**-0.02**	**-0.01**	**-0.06**	0.005

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	(-0.12, -0.08)	**(-0.03, -0.001)**	**(-0.02, -0.01)**	**(-0.01, -0.004)**	**(-0.07, -0.05)**	(-0.01,0.02)

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 for total population was adjusted for age, sex, race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score corresponds to a 0.16mg/L lower log (hsCRP) concentration. Interactions by sex for all 6 biomarkers was significant at p <0.001. Results in bold font were statistically significant (p<0.05)

For all CVD-related biomarkers, there was a significant interaction for CVH with sex at p<0.001. For a unit increase in CVH score, the magnitude of concentrations were marginally lower for hsCRP and D-dimer in women compared to men, while for hs-cTnT, the magnitude of concentration was lower in men compared to women. No difference in magnitude of concentration was observed for fibrinogen and homocysteine for both sexes (**Table 2**). The **Figure** illustrates the sex-stratified mean biomarker concentrations by categories of the total CVH score. For all the biomarkers, participants with optimal scores had the smallest mean values.

The associations between the LS7 metrics and CVD-related biomarkers (log-transformed) in women and men are reported in **Tables 3 & 4.** For the ideal category of smoking, lower concentrations of D-dimer, fibrinogen, homocysteine and NT-proBNP were found in men but only lower concentration of homocysteine was found in women. For ideal smoking status, the magnitude of concentration of homocysteine was marginally lower in women than men. For the ideal category of BMI, lower concentrations of all biomarkers except for NT-proBNP were found in women; whereas

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in men, lower concentrations of hsCRP, D-Dimer, fibrinogen and hs-cTnT were found. Both sexes had higher concentrations of NT-proBNP for ideal BMI. Additionally, for ideal BMI, the magnitudes of concentration of hsCRP, D-Dimer and fibrinogen were lower in women than men but hs-cTnT was lower in men. For the ideal category of physical activity, lower concentrations of hsCRP, fibrinogen and hs-cTnT were found in women while lower concentrations of fibrinogen, homocysteine and hs-cTnT were found in men. For ideal physical activity, the magnitude of concentration of fibrinogen and hs-cTnT were marginally similar in women and men. An ideal diet score was associated with lower concentration of hsCRP in women. For the ideal category of total cholesterol, lower concentrations of hs-cTnT were found in men while lower concentrations of fibrinogen and higher concentration of NT-proBNP were found in women and men. For total cholesterol, the magnitude of concentration of fibrinogen was marginally lower in women than men while the magnitude of concentration of NT-proBNP was higher in women than men, although confidence intervals between women and men overlapped.

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Table 3- The associations between LS7 metrics and CVD-related biomarkers in women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)
Smoking						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.07 (-0.51, 0.38)	0.11 (-0.22, 0.44)	0.03 (-0.05, 0.11)	0.03 (-0.08, 0.14)	0.005 (-0.17, 0.18)	0.003 (-0.35, 0.36)
Ideal	0.02 (-0.12, 0.16)	0.03 (-0.07, 0.13)	-0.01 (-0.03, 0.02)	**-0.08 (-0.11, -0.04)**	-0.01 (-0.07, 0.04)	0.07 (-0.04, 0.18)
Body mass index						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.61 (-0.71, -0.51)**	**-0.17 (-0.25, -0.10)**	**-0.08 (-0.10, -0.07)**	**-0.04 (-0.07, -0.02)**	**-0.07 (-0.11, -0.03)**	0.06 (-0.03, 0.14)
Ideal	**-1.15 (-1.25, -1.04)**	**-0.32 (-0.40, -0.23)**	**-0.14 (-0.16, -0.12)**	**-0.06 (-0.08, -0.03)**	**-0.09 (-0.14, -0.05)**	**0.26 (0.17, 0.35)**
Physical activity						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.06 (-0.19, 0.07)	0.05 (-0.05, 0.15)	0.01 (-0.02, 0.03)	**-0.03 (-0.07, -0.00)**	-0.02 (-0.07, 0.03)	0.01 (-0.09, 0.12)
Ideal	**-0.16 (-0.27, -0.06)**	-0.04 (-0.11, 0.04)	**-0.03 (-0.05, -0.02)**	-0.02 (-0.05, 0.00)	**-0.05 (-0.09, -0.005)**	0.04 (-0.05, 0.12)
Diet						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.16 (-0.25, -0.07)**	-0.02 (-0.09, 0.04)	-0.01 (-0.02, 0.01)	-0.002 (-0.02, 0.02)	-0.01 (-0.05, 0.02)	-0.01 (-0.09, 0.06)

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Ideal	**-0.40 (-0.74, -0.07)**	-0.09 (-0.33, 0.16)	-0.02 (-0.07, 0.04)	-0.07 (-0.16, 0.01)	-0.11 (-0.24, 0.02)	-0.05 (-0.32, 0.21)
Total Cholesterol						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.02 (-0.11, 0.14)	-0.04 (-0.13, 0.05)	-0.02 (-0.04, 0.00)	-0.0001 (-0.03, 0.03)	-0.01 (-0.06, 0.04)	**0.12 (0.02, 0.21)**
Ideal	-0.08 (-0.21, 0.04)	-0.02 (-0.11, 0.08)	**-0.06 (-0.08, -0.04)**	0.01 (-0.02, 0.04)	-0.006 (-0.04, 0.06)	**0.24 (0.14, 0.34)**
Blood pressure						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.13 (-0.24, -0.03)**	-0.05 (-0.13, 0.03)	-0.003 (-0.02, 0.02)	-0.005 (-0.03, 0.02)	**-0.09 (-0.13, -0.04)**	**-0.28 (-0.37, -0.20)**
Ideal	**-0.45 (-0.56, -0.35)**	**-0.11 (-0.19, -0.03)**	**-0.02 (-0.04, -0.002)**	**-0.04 (-0.07, -0.01)**	**-0.12 (-0.16, -0.08)**	**-0.30 (-0.39, -0.21)**
Blood glucose						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.04 (-0.22, 0.14)	0.01 (-0.13, 0.14)	-0.01 (-0.04, 0.02)	0.04 (-0.01, 0.08)	**-0.16 (-0.23, -0.09)**	0.10 (-0.04, 0.25)
Ideal	**-0.43 (-0.57, -0.28)**	-0.03 (-0.14, 0.08)	**-0.07 (-0.09, -0.04)**	0.002 (-0.03, 0.04)	**-0.19 (-0.25, -0.13)**	**0.29 (0.17, 0.40)**

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model was adjusted for age, race/ethnicity, education, income, and health insurance status.

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Table 4- The associations between LS7 metrics and CVD-related biomarkers in Men

	hsCRP	D-dimer	Fibrinogen	Homocysteine	hs-cTnT	NT-ProBNP
Smoking						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.16 (-0.50, 0.17)	-0.17 (-0.45, 0.11)	-0.04 (-0.10, 0.02)	**-0.16 (-0.25, -0.07)**	-0.07 (-0.28, 0.12)	**-0.52 (-0.86, -0.19)**
Ideal	-0.27 (-0.39, 0.15)	**-0.17 (-0.27, -0.07)**	**-0.05 (-0.07, -0.03)**	**-0.05 (-0.08, -0.02)**	0.02 (-0.04, 0.08)	**-0.15 (-0.27, -0.03)**
Body mass index						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.50 (-0.59, -0.40)**	**-0.11 (-0.20, -0.03)**	**-0.06 (-0.08, -0.05)**	-0.01 (-0.04, 0.01)	**-0.17 (-0.22, -0.12)**	0.07 (-0.02, 0.17)
Ideal	**-0.80 (-0.92, -0.69)**	**-0.17 (-0.26, -0.07)**	**-0.08 (-0.10, -0.06)**	-0.02 (-0.05, 0.01)	**-0.29 (-0.35, -0.23)**	**0.25 (0.14, 0.36)**
Physical activity						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.09 (-0.04, 0.23)	-0.06 (-0.17, 0.06)	-0.002 (-0.03, 0.02)	-0.01 (-0.05, 0.02)	-0.07 (-0.14, 0.01)	0.03 (-0.10, 0.17)
Ideal	-0.03 (-0.14, 0.07)	-0.05 (-0.13, 0.04)	**-0.02 (-0.04, -0.004)**	**-0.02 (-0.05, -0.00)**	**-0.07 (-0.13, -0.02)**	0.05 (-0.05, 0.15)
Diet						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.11 (-0.19, -0.02)**	0.002 (-0.07, 0.07)	-0.01 (-0.03, 0.00)	-0.003 (-0.02, 0.02)	-0.02 (-0.07, 0.02)	0.04 (-0.04, 0.12)
Ideal	-0.57 (-1.25, 0.11)	-0.50 (-1.07, 0.07)	0.01 (-0.12, 0.14)	0.06 (-0.11, 0.24)	-0.17 (-0.37, 0.20)	0.31 (-0.36, 0.98)

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Total Cholesterol						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.03 (-0.17, 0.11)	0.01 (-0.11, 0.12)	**-0.04 (-0.06, -0.01)**	-0.003 (-0.04, 0.03)	**-0.10 (-0.18, -0.02)**	-0.09 (-0.22, 0.05)
Ideal	-0.01 (-0.15,0.13)	0.05 (-0.06, 0.17)	**-0.05 (-0.08, -0.03)**	-0.006 (-0.04, 0.03)	**-0.10 (-0.17, -0.02)**	**0.19 (0.05, 0.32)**
Blood pressure						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.10 (-0.20, 0.01)	-0.06 (-0.14, 0.03)	-0.01 (-0.03, 0.004)	**-0.03 (-0.06, -0.005)**	**-0.12 (-0.18, -0.07)**	**-0.37 (-0.47, -0.27)**
Ideal	**-0.23 (-0.34, -0.13)**	-0.01 (-0.10, 0.08)	**-0.03 (-0.05, -0.01)**	**-0.04 (-0.07, -0.02)**	**-0.22 (-0.27, -0.16)**	**-0.40 (-0.50, -0.30)**
Blood glucose						
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.07 (-0.08, 0.22)	0.03 (-0.09, 0.16)	-0.01 (-0.04, 0.02)	0.04 (-0.003, 0.08)	**-0.23 (-0.31, -0.15)**	-0.06 (-0.21, 0.09)
Ideal	**-0.17 (-0.30, -0.04)**	0.04 (-0.07, 0.15)	**-0.03 (-0.06, -0.01)**	0.01 (-0.02, 0.05)	**-0.36 (-0.43, -0.29)**	0.04 (-0.09, 0.17)

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model adjusted for age, race/ethnicity, education, income, and health insurance status.

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For ideal blood pressure, a lower concentration of all biomarkers was found in women; whereas in men a lower concentration was observed for all biomarkers except D-dimer. Additionally, for ideal blood pressure, the magnitudes of concentration of fibrinogen, hs-cTnT and NT-proBNP were lower in men than women. For ideal blood glucose levels, a higher concentration of NT-proBNP was found in women while a lower concentration of hsCRP, fibrinogen and hs-cTnT was observed in both sexes. For ideal blood glucose, the magnitudes of concentration of hsCRP and fibrinogen were lower in women than men.

The supplementary analyses show the associations between CVH and CVD-related biomarkers stratified by race/ethnicity and age for women and men. The results were similar for both sexes and mostly showed a statistically significant lower concentration of CVD-related biomarkers for a unit increment in CVH score. Among White and Chinese-American Women as well as women <65 years old, a unit increment in CVH score was associated with higher concentrations of NT-proBNP **(Supplementary Tables S3-S6)**.

Discussion

In this cross-sectional analysis of 5,379 adult women and men free of clinical CVD at baseline, after adjusting for sociodemographic factors, we found an inverse association between the CVH score and most of the CVD-related biomarkers. Higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers in women and men, except for NT-proBNP which showed a positive relationship. A similarly inverse relationship was found between the LS7 metrics and CVD-related biomarkers except for NT-proBNP where the associations were both direct

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and inverse. In the stratified analyses by race/ethnicity and age, the associations observed were similar for both sexes.

Our results are similar to a study conducted to investigate the association between CVH metrics and biomarkers (hsCRP and homocysteine) among 3,009 Chinese adults between the ages of 24 and 85 years, without a history of CVD[7]. In their study, after adjusting for age, sex and education, a unit increment in CVH score was inversely related to biomarker concentration [CRP: -0.182 (-0.652, -0.457); and homocysteine: -0.092, (-0.930, -0.426)]. A similar association was found in women and men, although the association was stronger in women.

A cross-sectional study of 2,680 participants from the Framingham Heart Study also examined the association between CVH and CVD-related biomarkers (BNP, CRP, D-dimer, fibrinogen and homocysteine)[22]. Similar to our findings in MESA, the Framingham researchers found that the CVH score had a direct association with higher circulating concentrations of natriuretic peptides but was inversely related to blood concentrations of the other biomarkers examined, after adjusting for age and sex[22]. For a unit increase in CVH score, the beta coefficients for the biomarkers are as follows: BNP, 0.057 pg/mL (0.035, 0.080); CRP, -0.248 mg/L (-0.279, -0.217); D-dimer, -0.030 ng/mL (-0.046, -0.014); fibrinogen, -0.028 mg/dL (-0.033,-0.023) and homocysteine, -0.021 mmol/L (-0.029,-0.012). The authors concluded that the inverse association of CVH with incident CVD events was at least partly attributable to the favorable relationship of CVH and subclinical biomarkers of risk[22]. Notably, none of the aforementioned studies examined for effect modification by sex in the association of CVH with subclinical biomarkers, as we newly present here.

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Our main finding showed a better CVH score was associated with lower concentrations of all CVD-related biomarkers (except NT-proBNP) in both women and men. Despite statistically significant interactions by sex for the total CVH score, qualitatively the magnitude of lower concentrations for these biomarkers per 1 unit increment in CVH were generally similar among women and men. However, for the metric of ideal BMI, the magnitude of lower concentrations hsCRP, D-Dimer, and fibrinogen per unit of CVH was greater in women than men. In the univariate analysis, women in this study had slightly higher BMI than men. Studies have shown that estrogen and adipose tissue may increase the circulating levels of inflammatory biomarkers[9, 23], and thus a more favorable BMI might have greater impact on these biomarker concentrations in women than men.

In the univariate analyses, homocysteine concentrations were higher in men which may be attributable to a higher prevalence of smoking and poorer healthy diet score[24]. In the adjusted regression analyses a unit increment in CVH score corresponded to a slightly lower concentration of homocysteine in women. In addition, the higher prevalence of smoking found in men in this study may be responsible for their higher baseline hs-cTnT concentrations[25]. Although in adjusted regression analysis, the magnitude of concentration of hs-cTnT per 1-unit increment in CVH score was lower in men.

Interestingly, a better CVH score was associated with higher concentrations of NT-proBNP, particularly in women. At first this may seem paradoxical, as in the setting of disease states, BNP levels are frequently elevated. However, in normal states, NT-proBNP actually plays a favorable cardioprotective role by inhibiting cardiac hypertrophy

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and fibrosis and promoting vasodilation and natriuresis. In patients with heart failure, there is relative BNP deficiency and BNP resistance, resulting in a compensatory increase in NT-proBNP concentrations to restore homeostasis[26]. We found that baseline concentrations of NT-proBNP were higher in women than men, as had been previously reported in MESA[10], though average concentrations for both sexes were within normal limits in this cohort free of clinical heart failure at baseline. Other previous studies have also reported higher NT-proBNP concentrations in women[22, 27], as well as a prior analysis in the MESA cohort that showed a more androgenic ("male-like") sex hormone profile was associated with lower NT-proBNP concentrations[10].

The sex-specific differences observed in the association of CVH and CVD-related biomarkers may reflect different pathways of CVD risk. Additional research that explain the potential sex-specific mechanisms underlying the association between CVH and CVD-related biomarkers may improve our knowledge of the development of CVD in women and men[28]. An understanding of these pathways may also help clinicians tailor interventions specific to the prevention and treatment of CVD risk factors in women and men[28]. Our study emphasizes the importance of promoting ideal CVH, which may be more beneficial in women, particularly with research showing that women have poorer cardiovascular outcomes compared to men. Encouraging the attainment of ideal CVH may reverse this trend and lead to a decrease in CVD burden.

In the interpretation of our findings, some limitations should be noted. First, neither temporality nor causal inferences between the association of CVH and CVD-related biomarkers can be determined because of the cross-sectional observational study design. Second, we cannot rule out recall bias from the use of self-administered

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questionnaires to collect data on smoking, diet, and physical activity. Third, the findings of this study may not be generalizable to younger people because our participants were between 45 and 84 years old. Fourth, multiple statistical tests were performed and some findings might be expected to occur by chance; however, our findings were generally consistent between women and men and across age and race/ethnic subgroups. Lastly, CVH was assessed once at baseline and may not be representative of the future CVH status of study participants.

We found that more favorable CVH scores were associated with lower concentrations of CVD-related biomarkers in both women and men, except for NT-proBNP which showed a direct relationship. These favorable associations of CVH with biomarkers of risk may be an intermediary step in the prevention of clinical CVD events. Overall, our findings were qualitatively similar between the sexes. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of risk among women and men. However, long-term outcome studies are needed to improve our understanding of the underlying sex-specific mechanisms and the clinical implications of these findings.

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Author contributions

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Study conception and design: OO, OO and EDM; Acquisition of data and analysis: OO and OO; Interpretation of data: OO, OO, MT, EB and EDM; Drafting of manuscript: OO, OO and EDM; Critical revision and approval of final version submitted: OO, OO, MT, EB and EDM.

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Conflicts of interest:

None of the authors report any conflicts of interest with this work.

Ethics approval:

The MESA protocol was approved by the institutional review boards of all the recruitment centers.

Data sharing statement:

The MESA study participates in data sharing through the National Heart, Lung, Blood Institute (NHLBI) Biologic Specimen and Data Repository Coordinating Center

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(BioLINCC). Requests for access to the data can be made through their website: https://biolincc.nhlbi.nih.gov/studies/mesa/.

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Figure Legend

Sex-stratified mean biomarker levels by cardiovascular health score categories (inadequate (0-8), average (9-10) and optimal (11-14). Lighter color=Women; Darker color=Men. hsCRP=high-sensitivity C-reactive protein; hs-cTnT=high-sensitivity cardiac troponin T; NT-proBNP= N-terminal pro B-type natriuretic peptide. Mean values for biomarkers were not log transformed

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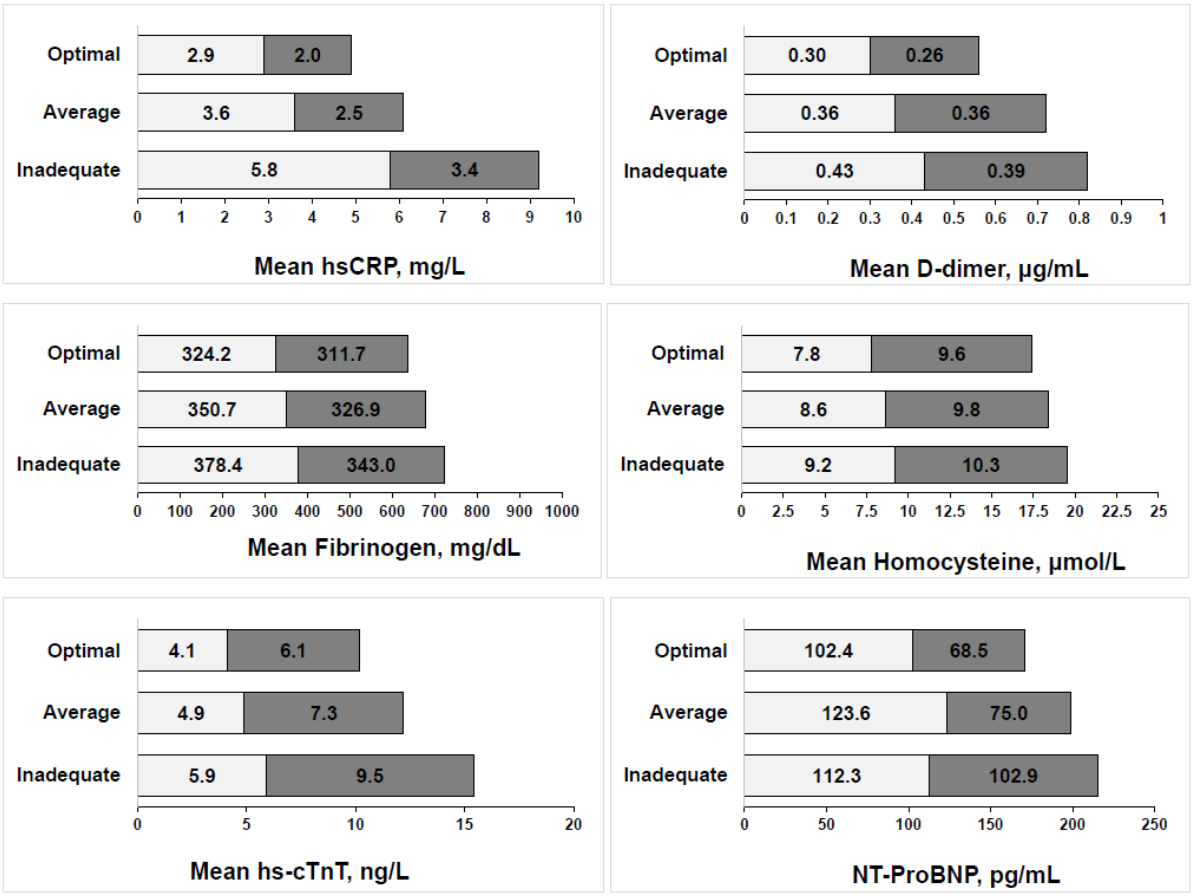

Figure Legend

Sex-stratified mean biomarker levels by cardiovascular health score categories (inadequate (0-8), average (9-10) and optimal (11-14). Lighter color, Women; Darker color, Men. hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide. Mean values for biomarkers were not log transformed.

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SUPPLEMENTARY MATERIAL

Assessment of cardiovascular health

Table S1: Definition of Life's Simple 7 Metrics

Table S2: Distribution of Life's Simple 7 Metrics by Sex

Table S2: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

Table S3: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

Table S4: The associations between CVH score and CVD-related biomarkers by Age for Women

Table S5: The associations between CVH score and CVD-related biomarkers by Age for Men

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Assessment of cardiovascular health

Information on the LS7 metrics were collected from study participants at baseline. Based on AHA guidelines, ideal CVH is achieved if the following criteria are met for the LS7 metrics: non-smoking, physical activity at goal levels, BMI <25kg/m^2 and a healthy diet consistent with guidelines, total cholesterol <200mg/dL (not on lipid lowering medications), blood pressure <120/<80mmHg (not on anti-hypertensive medications), and fasting blood glucose <100mg/dL (not on diabetes medications) [1]. Smoking status was assessed by self-report and categorized as; 1) participants who never smoked or quit more than 12 months (non-smokers), 2) participants who quit within 12 months (former smokers) and 3) current smokers [1]. Physical activity was evaluated using a self-report survey instrument adapted from the Cross-Cultural Activity Participation Study [2] containing 28 questions on time and frequency of activities during a week in the previous month. The total minutes of moderate and vigorous exercise in metabolic equivalents of task (MET/min) were estimated and used for our analyses [3].

BMI (kg/m^2) was calculated using the weight and height measurements. Dietary habits were evaluated using a 120-item validated food frequency questionnaire modified from the Insulin Resistance Atherosclerosis Study instrument [4, 5]. Based on recommended dietary guidelines, a healthy diet was made up of fruits and vegetables, fish, whole grains and intake of sodium <1500mg per day and sugar-sweetened beverages ≤450 kcal (36 oz.) per week [1]. For blood pressure, with participants in a seated position, 3 measurements were obtained after resting for 5 minutes and the average values of the last two readings were recorded. For total cholesterol (mg/dL)

and blood glucose (mg/dL) measurements, blood samples were collected following a 12 hour fast.

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Table S1 – Definition of the Life's Simple 7 metrics

LS7 Metrics	Score	Definition
Smoking	0	Current smoker
	1	Former smoker, quit ≤12 months ago
	2	Never smoker or quit >12 months ago
Body Mass Index	0	≥30 kg/m^2
	1	25.0–29.99 kg/m^2
	2	<25.0 kg/m^2
Physical Activity	0	No exercise
	1	1–149 min of moderate exercise or 1–74 min of vigorous exercise/week
	2	150+ min of moderate exercise or 75+ min of vigorous exercise/week
Diet	0	0–1 components of healthy diet
	1	2–3 components of healthy diet
	2	4–5 components of healthy diet
Total Cholesterol	0	≥240 mg/dL
	1	200–239 mg/dL or treated to <200mg/dL
	2	<200 mg/dL, unmedicated
Blood Pressure	0	SBP ≥140 mmHg or DBP ≥90 mmHg
	1	SBP 120–139 mmHg or DBP 80–89 mmHg or treated to <120/80 mm Hg
	2	<120/80 mm Hg, unmedicated
Blood Glucose	0	≥126 mg/dL fasting
	1	100–125 mg/dL fasting or treated to <100 mg/dL
	2	<100 mg/dL fasting, unmedicated

Adapted from Lloyd Jones et al[1] and Unger et al[3], LS7 indicates Life's Simple 7; DBP, diastolic blood pressure, and SBP, systolic blood pressure. Poor=0 points; Intermediate=1 point; ideal =2 points. *When combining vigorous and moderate exercise, vigorous exercise was weighted double.

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Table S2 - Distribution of Life's Simple 7 Metrics by Sex

	Total (N=5,379)	Women (n= 2,775)	Men (n= 2,604)	P value
Total CVH score, mean (SD)	8.6 (2.2)	8.6 (2.3)	8.6 (2.1)	0.85
LS7 metrics, n (%)				
Smoking				
Poor	671 (12)	303 (11)	368 (14)	
Intermediate	68 (1)	27 (1)	41 (2)	<0.001
Ideal	4640 (86)	2445 (88)	2195 (84)	
Body mass index				
Poor	1657 (31)	958 (35)	699 (27)	
Intermediate	2127 (40)	936 (34)	1191 (46)	<0.001
Ideal	1595 (30)	881 (32)	714 (28)	
Physical activity				
Poor	1231 (23)	684 (25)	547 (21)	
Intermediate	909 (17)	529 (19)	380 (15)	<0.001
Ideal	3239 (60)	1562 (56)	1677 (64)	
Diet				
Poor	2425 (45)	1029 (37)	1396 (54)	
Intermediate	2898 (54)	1699 (61)	1199 (46)	<0.001
Ideal	56 (1)	47 (2)	9 (0.4)	
Total Cholesterol				
Poor	729 (14)	466 (17)	263 (10)	
Intermediate	2107 (39)	1143 (41)	964 (37)	<0.001
Ideal	2543 (47)	1166 (42)	1377 (53)	
Blood pressure				
Poor	1996 (37)	1085 (39)	911 (35)	
Intermediate	1505 (28)	695 (25)	810 (31)	<0.001
Ideal	1878 (35)	995 (36)	883 (34)	
Blood glucose				
Poor	572 (11)	275 (10)	297 (11)	
Intermediate	846 (16)	359 (13)	487 (19)	<0.001
Ideal	3961 (74)	2141 (77)	1820 (70)	

Abbreviations: CVH indicates cardiovascular health; SD, standard deviation; LS7, Life's Simple 7; percentages were rounded up to whole numbers

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Table S3 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

	hsCRP (mg/L)	D-dimer (μg/mL)	Fibrinogen (mg/dL)	Homocysteine (μmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)
White, n=1,092						
Model 1	**-0.18 (-0.21, -0.15)**	**-0.06 (-0.08, -0.04)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.03, -0.01)**	**-0.05 (-0.06, -0.04)**	0.01 (-0.01, 0.04)
Model 2	**-0.19 (-0.23,-0.16)**	**-0.04 (-0.07, -0.02)**	**-0.03 (-0.04, -0.02)**	**-0.01 (-0.02, -0.002)**	**-0.03 (-0.04, -0.02)**	**0.05 (0.03, 0.07)**
Chinese-American, n=372						
Model 1	**-0.11 (-0.17, -0.06)**	**-0.08 (-0.13, -0.04)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**-0.05 (-0.07, -0.03)**	-0.01 (-0.06, 0.05)
Model 2	**-0.13 (-0.18, -0.07)**	-0.04 (-0.09, 0.01)	**-0.01 (-0.02, -0.004)**	**-0.01 (-0.03, -0.00)**	**-0.03 (-0.005, -0.01)**	**0.07 (0.02, 0.12)**
Black, n=681						
Model 1	**-0.15 (-0.19, -0.11)**	**-0.06 (-0.09, -0.03)**	**-0.03 (-0.03, -0.02)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.06, -0.02)**	-0.02 (-0.06, 0.02)
Model 2	**-0.15 (-0.19, -0.10)**	**-0.05 (-0.08, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.004)**	**-0.03 (-0.05, -0.01)**	0.005 (-0.03, 0.04)
Hispanic, n= 630						
Model 1	**-0.13 (-0.17, -0.10)**	**-0.03 (-0.07, -0.003)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.05, -0.02)**	**-0.04 (-0.07, -0.003)**
Model 2	**-0.14 (-0.18, -0.10)**	-0.004 (-0.04, 0.03)	**-0.01 (-0.02, -0.005)**	**-0.01 (-0.02, -0.002)**	**-0.02 (-0.04, -0.005)**	0.01 (-0.03, 0.04)

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-ProBNP, N-terminal pro B-type natriuretic peptide.
*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White women corresponds to a 0.18mg/L lower logCRP concentration.

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Table S4 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)
White, n=1,058						
Model 1	**-0.15 (-0.18, -0.12)**	-0.02 (-0.05, 0.004)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.02)**	0.002 (-0.03,0.03)
Model 2	**-0.14 (-0.17, -0.11)**	-0.02 (-0.05, 0.005)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.03)**	0.01 (-0.02, 0.04)
Chinese-American, n= 361						
Model 1	**-0.09 (-0.15, -0.04)**	-0.01 (-0.06, 0.04)	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.001)**	**-0.06 (-0.08, -0.03)**	0.04 (-0.02, 0.11)
Model 2	**-0.11 (-0.17, -0.05)**	0.001 (-0.05, 0.05)	**-0.02 (-0.03, -0.01)**	**-0.02 (-0.03, -0.002)**	**-0.06 (-0.09, -0.04)**	0.02 (-0.03, 0.07)
Black, n= 572						
Model 1	**-0.07 (-0.12, -0.03)**	**-0.05 (-0.09, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.01 (-0.02, -0.001)**	**-0.09 (-0.11, -0.06)**	-0.03 (-0.08, 0.02)
Model 2	**-0.06 (-0.11, -0.02)**	-0.02 (-0.06, 0.01)	**-0.01 (-0.02, -0.01)**	-0.01 (-0.02, 0.003)	**-0.07 (-0.09, -0.05)**	0.02 (-0.03, 0.06)
Hispanic, n=613						
Model 1	**-0.08 (-0.12, -0.04)**	-0.03 (-0.06, 0.01)	**-0.02 (-0.03, -0.01)**	-0.001 (-0.01, 0.01)	**-0.08 (-0.11, -0.06)**	**-0.06 (-0.11, -0.01)**
Model 2	**-0.08 (-0.12, -0.04)**	-0.01 (-0.04, 0.02)	**-0.02 (-0.02, -0.01)**	0.003 (-0.01, 0.01)	**-0.08 (-0.10, -0.05)**	-0.03 (-0.07, 0.02)

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White men corresponds to a 0.15mg/L lower logCRP concentration.

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Table S5 - The associations between CVH score and CVD-related biomarkers by Age for Women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)
Age <65 years, n=1,559						
Model 1	**-0.22 (0.24, -0.19)**	**-0.07 (-0.09, -0.05)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.03, -0.02)**	**0.03 (0.01, 0.06)**
Model 2	**-0.19 (-0.21, -0.16)**	**-0.04 (-0.06, -0.02)**	**-0.03 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**0.03 (0.004, 0.05)**
Age ≥ 65 years, n= 1,216						
Model 1	**-0.14 (-0.17, -0.11)**	**-0.06 (-0.08, -0.04)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.04)**	0.02 (-0.01, 0.04)
Model 2	**-0.12 (-0.15, -0.09)**	**-0.03 (-0.06, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.02, -0.01)**	**-0.05 (-0.06, -0.03)**	0.01 (-0.02, 0.03)

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.
*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in women <65 years corresponds to a 0.22mg/L lower logCRP concentration.

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Table S6 - The associations between CVH score and CVD-related biomarkers by Age for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)
Age <65 years, n= 1,454						
Model 1	**-0.14 (-0.17, -0.12)**	**-0.02 (-0.05, -0.003)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.01, -0.001)**	**-0.07 (-0.08, -0.06)**	-0.02 (-0.04, 0.01)
Model 2	**-0.12 (-0.15, -0.10)**	-0.02 (-0.04, 0.007)	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.01, -0.00)**	**-0.07 (-0.08, -0.06)**	-0.01 (-0.04, 0.02)
Age ≥ 65 years, n= 1,150						
Model 1	**-0.11 (-0.14, -0.08)**	**-0.05 (-0.07, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.06 (-0.08, -0.04)**	0.01 (-0.02, 0.04)
Model 2	**-0.07 (-0.10, -0.04)**	**-0.03 (-0.05, -0.001)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.03)**	0.01 (-0.02, 0.05)

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in men <65 years corresponds to a 0.14mg/L lower logCRP concentration.

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Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: A cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis

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Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: A cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objectives: This study investigated the sex differences in the associations between ideal cardiovascular health (CVH), measured by the American Heart Association's Life's Simple 7 and cardiovascular disease (CVD)-related biomarkers among an ethnically diverse cohort of men and women free of clinical CVD at baseline.

Setting: We analyzed data from the Multi-Ethnic Study of Atherosclerosis conducted in 6 centers across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN).

Participants: This is a cross-sectional study of 5,379 men and women, aged 45 to 84 years old. Mean age (SD) was 62 (10), 52% were women, 38% White, 11% Chinese American, 28% Black and 23% Hispanic.

Primary measures: The 7 metrics (smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and blood glucose) were each scored as 0 points (poor), 1 point (intermediate) or 2 points (ideal). The total CVH score ranged from 0-14. The CVD-related biomarkers studied were high-sensitivity C-reactive protein, D-dimer, fibrinogen, homocysteine, high-sensitivity cardiac troponin T, NT-proBNP and IL-6. We examined the association between the CVH score and each biomarker using multivariable linear regression, adjusting for age, race/ethnicity, education, income, and health insurance status.

Results: Higher CVH scores were associated with lower concentrations of all biomarkers, except for NT-proBNP where there was a positive association. There were statistically significant interactions by sex for all biomarkers ($p<0.001$), but results were qualitatively similar between women and men.

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Conclusion: A more favorable CVH score was associated with lower levels of multiple CVD-related biomarkers for women and men, except for NT-proBNP. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of CVD risk for both women and men.

Keywords: Biomarkers, cardiovascular disease, ideal cardiovascular health metrics, Life's Simple 7, sex, gender

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Strengths and limitations of this study

- Use of a large and diverse study sample that enabled stratification by sex, race/ethnicity and age.
- Use of validated survey instruments and standardized methods for data collection allowed for comparison with other studies.
- Study population included adults between the ages of 45 and 84 years, which limited the generalizability of our findings to younger or older age groups.
- Cross-sectional observational design cannot establish temporality or causation.

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Introduction

The ideal cardiovascular health (CVH) construct, defined as meeting specific criteria for 7 health behaviors and health factors called the Life's Simple 7 (LS7) metrics, was introduced by the American Heart Association (AHA) to decrease the burden of CVD[1]. This was a shift towards primordial prevention – focusing on wellness rather than disease[2]. Biomarkers, which are often used in conjunction with traditional risk factors, are subclinical indicators of physiological and pathological processes[3] and serve as useful tools in facilitating early detection and prognostication of CVD[4]. Although prior studies have examined the relationship of biomarkers with incident CVD, few have focused on biomarkers and measures of cardiovascular wellness. Not surprisingly, the studies that have examined the association between ideal CVH and subclinical biomarkers of disease have shown an inverse relationship[5]. For example, in a prior analysis from the Multi-Ethnic Study of Atherosclerosis (MESA), poor CVH was found to be associated with higher levels of GlycA (a novel inflammatory marker) and higher levels of traditional inflammatory markers [high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), fibrinogen, and D-dimer][6]. However, research on the sex differences of the relationship of CVH with CVD-related biomarkers is sparse[7].

There are known sex differences in the levels of CVD-related biomarkers. Women are known to have higher levels of hsCRP[8, 9] and N-terminal pro B-type natriuretic peptide (NT-proBNP)[10] than men even after accounting for cardiometabolic risk factors, while troponin levels[11, 12] are higher in men than women. Thus, understanding sex differences in the relationship of ideal CVH measures with

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biomarkers is an important intermediate step in explaining sex differences in clinical CVD.

This study aimed to examine the sex differences in the associations between ideal CVH and CVD-related biomarkers among men and women free of clinical CVD in an ethnically diverse cohort. We hypothesized that better CVH would be associated with lower concentrations of CVD-related biomarkers especially in women.

Methods

Study population

As previously described, MESA is a longitudinal study of 6,814 adult women and men between the ages of 45 and 84 years. The study participants, with no previous history of clinical CVD at baseline, were recruited from 6 centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN) in the United States between July 2000 and August 2002[13]. Among participants, 38% were White, 11% Chinese American, 28% Black, and the remaining 23% were Hispanic. Informed consent was provided by all participants. The MESA protocol was approved by the institutional review boards (IRB) of all the recruitment centers. At the Johns Hopkins field center where this analysis was conducted, the IRB approval number was NA_00030361.

Baseline information was collected using standardized questionnaires, physical examinations and fasting laboratory blood draw. For the current analyses, we included 5,379 participants from the MESA baseline exam after excluding participants with missing information for the CVD biomarkers and LS7 metrics.

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Assessment of biomarkers

We examined biomarkers that were measured at baseline. Fasting blood samples were drawn, processed and stored using standardized procedures[14]. HsCRP, D-dimer, fibrinogen, IL-6, and homocysteine levels were analyzed at the laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Serum levels of hsCRP (mg/L) were measured using the BNII nephelometer (Dade Behring, Deerfield, IL). Analytical intra-assay coefficients of variation (CV) of hsCRP ranged from 2.3% to 4.4%, and inter-assay CV ranged from 2.1% to 5.7%[6, 15]. D-dimer (µg/mL) was measured with an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) which was used on a Sta-R analyzer (Diagnostica Stago, Parsippany, NJ). The lower detection limit of D-dimer assay was 0.01 µg/mL[6]. Serum fibrinogen (mg/dL) was measured by immunoprecipitation of fibrinogen antigen using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The intra-assay and inter-assay CV were 2.7% and 2.6%, respectively[6, 15]. Serum IL-6 (pg/mL) was measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). The analytical CV was 6.3%[15]. Plasma homocysteine (µmol/L) was measured using a fluorescence polarization immunoassay with the IMx analyzer (Abbott Diagnostics, Abbott Park, IL). The CV was 4.5%[16].

The assays for high-sensitivity cardiac troponin T (hs-cTnT, ng/L) and NT-proBNP (pg/mL) were performed at the Veteran's Affairs San Diego Healthcare System (La Jolla, CA) and measured in serum using the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN). For hs-cTnT, the inter-assay CV observed for the MESA

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cohort measurements were 3.6% at 28 ng/L and 2.0% at 2154 ng/L[17]. For NT-proBNP, the intra-and inter-assay CV were as follows: at 175 pg/mL, 2.7% and 3.2%; at 355 pg/mL, 2.4% and 2.9%; at 1068 pg/mL, 1.9% and 2.6%; and at 4962 pg/mL, 1.8% and 2.3%, respectively[10].

Assessment of cardiovascular health

Cardiovascular health was assessed at baseline using the LS7 metrics based on AHA criteria[1]. A detailed assessment can be found in the supplementary material (**Supplementary Methods**).

Assessment of covariates

Sociodemographic factors included as covariates are age, sex, race/ethnicity education income and health insurance. Age was examined continuously in the multivariable models but dichotomized as <65 and ≥65 years for subgroup testing. Race/ethnicity had 4 groups: White, Chinese-American, Black and Hispanic. We had 9 categories for education and 13 categories for income (**Supplementary Table 1**), which were used in our multivariable models; however, they were dichotomized as ≥ bachelor's degree and < bachelor's degree; ≥$40,000 and < $40,000 respectively, for descriptive statistics. Yes" or "No" responses were given for health insurance status.

Statistical analyses

The characteristics of the study participants were reported for the overall population and by sex. Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means with standard deviation (SD). We compared the baseline characteristics of participants by sex, using

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ANOVA and chi-square tests as appropriate. The CVD-related biomarkers were natural logarithmically transformed for the analyses because distribution was skewed. The LS7 metrics were each defined as ideal, intermediate, and poor[1], and their distribution was reported by sex, as shown in **Supplementary Tables 2 & 3**. Points were awarded to each category of the LS7 metrics with 0 indicating poor; 1, intermediate; and 2, ideal. The points were summed, yielding a total CVH score ranging from 0 to 14[18]. As previously reported, total CVH scores of 0 to 8, 9 to 10, and 11 to 14 were considered as inadequate, average, and optimal CVH respectively[19-21].

Using linear regression models, we estimated the crude beta coefficients and corresponding 95% confidence intervals (CI) for the associations between the CVH score (assessed continuously) and CVD-related biomarkers (log-transformed, assessed continuously) in the overall cohort and by sex (model 1). We adjusted for sociodemographic factors [age (continuous), sex (for overall cohort), race/ethnicity (4 categories), education (9 categories), income (13 categories), and health insurance status (yes/no)] in model 2 and reported the adjusted beta coefficients. We examined the interaction of the CVH score categories with sex for all 6 biomarkers using the Wald test, by including interaction terms in model 2.

The associations between the LS7 metrics and CVD-related biomarkers were examined by comparing the intermediate and ideal categories of the metrics to the poor category. We reported only the adjusted model for women and men. In supplementary analyses, we examined the association between the CVH score and CVD-related biomarkers stratified by race/ethnicity and age (<65 and ≥65 years) within each sex, using multivariable linear regression models. For statistical analyses, STATA version

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15.0 was used (StataCorp LP, College Station, TX) and an alpha level of <.05 was considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the conduct of this research. We did not invite patients to comment on the study design nor did we consult them to develop patient related outcomes or interpret the results of this study. We did not invite patients to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline characteristics of participants are shown in **Table 1**. Over half of the participants were women (52%), and the mean age (SD) was 62 (10) years. Women had higher hsCRP, D-dimer, fibrinogen, NT-proBNP and IL-6 levels, while men had higher hs-cTnT and homocysteine levels. Women were less likely to be physically active and were more likely to have higher systolic blood pressure as well as higher healthy diet score and total cholesterol levels **(Table 1 and Supplementary Table 3)**.

Table 1- Characteristics of Study Participants

	Total (N= 5,379)	Women (n=2,775)	Men (n=2,604)	P value
Age, mean (SD), y	62 (10)	62 (10)	62 (10)	0.67
Age, y				
<65 n (%)	3,013 (56)	1,559 (56)	1,454 (56)	0.80

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≥65 n (%)	2,366 (44)	1,216 (44)	1,150 (44)	
Race/Ethnicity				
White n (%)	2,150 (40)	1092 (39)	1058 (41)	
Chinese American n (%)	733 (14)	372 (13)	361 (14)	0.17
Black n (%)	1,253 (23)	681 (25)	572 (22)	
Hispanic n (%)	1,243 (23)	630 (23)	613 (24)	
Education				<0.001
≥ Bachelor's degree n (%)	1,929 (36)	824 (30)	1,105 (42)	
< Bachelor's degree n (%)	3,450 (64)	1,951 (70)	1,499 (58)	
Income				<0.001
≥$40,000 n (%)	2,648 (49)	1,162 (42)	1,486 (57)	
<$40,000 n (%)	2,731 (51)	1,613 (58)	1,118 (43)	
Health insurance				
Yes n (%)	4,871 (91)	2,511 (90)	2,360 (90)	0.86
No n (%)	508 (9)	264 (10)	244 (10)	
Biomarkers, Mean (95% CI)				
hsCRP (mg/L)	3.7 (3.5, 3.8)	4.5 (4.2, 4.7)	2.8 (2.6, 3.0)	<0.001
D-dimer (µg/mL)	0.37 (0.34, 0.39)	0.38 (0.35, 0.41)	0.35 (0.32, 0.39)	0.29
Fibrinogen, mg/dL	345.2 (343.2, 347.1)	358.0 (355.2,360.8)	331.5 (328.8, 334.1)	<0.001
Homocysteine (µmol/L)	9.3 (9.2, 9.4)	8.7 (8.6, 8.8)	10.0 (9.9, 10.1)	<0.001
hs-cardiac Troponin T (ng/L)	6.6 (6.4, 6.8)	5.2 (5.0, 5.4)	8.1 (7.7, 8.5)	<0.001
NT-proBNP (pg/mL)	100.8 (94.2, 107.4)	114.0 (108.1, 119.8)	86.8 (74.8, 98.9)	<0.001
*IL-6 (pg/mL)	1.5 (1.5, 1.6)	1.6 (1.5, 1.6)	1.5 (1.4, 1.5)	0.002
LS7 metrics				
Current smoking n (%)	671 (12)	303 (11)	368 (14)	<0.001

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Body mass index (kg/m2)	28 (5)	29 (6)	28 (4)	<0.001
Physical activity (MET-min/week)	401 (589)	338 (490)	468 (672)	<0.001
Healthy diet score (0-5)	1.6 (0.9)	1.7 (0.9)	1.4 (0.9)	<0.001
Total cholesterol (mg/dL)	194 (36)	200 (36)	189 (35)	<0.001
Systolic blood pressure (mmHg)	126 (21)	127 (23)	125 (19)	0.03
Diastolic blood pressure (mmHg)	72 (10)	69 (10)	75 (9)	<0.001
Fasting blood glucose (mg/dL)	97 (31)	95 (29)	100 (32)	<0.001
CVH score				
Inadequate	2,509 (47)	1,284 (46)	1,225 (47)	
Average	1,772 (33)	915 (33)	857 (33)	0.78
Optimal	1,098 (20)	576 (21)	522 (20)	

Abbreviations: SD, standard deviation; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6; LS7, Life's Simple 7; CVH, Cardiovascular health; For IL-6, total sample size = 5,279; women, n = 2,733; men, n = 2,546

The associations between the total CVH score and the CVD-related biomarkers are reported in **Table 2**. After adjusting for sociodemographic factors (model 2), higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers except for NT-proBNP, where CVH was associated with a higher concentration. For example, in the overall cohort, a 1-unit increment in the CVH score corresponded to a 0.13 mg/L lower log (hsCRP) concentration and a 0.04 ng/L lower log(hs-cTnT) concentration, but a 0.02 pg/mL higher log (NT-proBNP) concentration

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Table 2- The associations between CVH score and CVD-related biomarkers

	hsCRP (mg/L)	D-dimer (μg/mL)	Fibrinogen (mg/dL)	Homocysteine (μmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Total, N= 5,379							
Model 1	**-0.16 (-0.17, -0.14)**	**-0.06 (-0.07, -0.05)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.06, -0.05)**	0.004 (-0.01, 0.01)	**-0.09 (-0.10, -0.08)**
Model 2	**-0.13 (-0.14, -0.12)**	**-0.03 (-0.04, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.01, -0.01)**	**-0.04 (-0.05, -0.03)**	**0.02 (0.01, 0.03)**	**-0.07 (-0.08, -0.06)**
Women, n= 2,775							
Model 1	**-0.18 (-0.20, -0.16)**	**-0.07 (-0.09, -0.06)**	**-0.03 (-0.03, -0.03)**	**-0.02 (-0.03, -0.02)**	**-0.04 (-0.05, -0.04)**	0.01 (0.01,0.03)	**-0.11 (-0.12, -0.10)**
Model 2	**-0.16 (-0.18, -0.14)**	**-0.03 (-0.05, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**0.03 (0.01, 0.04)**	**-0.08 (-0.09, -0.07)**
Men, n= 2,604							
Model 1	**-0.13 (-0.15, -0.11)**	**-0.04 (-0.05, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.07 (-0.08, -0.06)**	-0.01 (-0.03, 0.01)	**-0.07 (-0.08, -0.06)**
Model 2	**-0.10 (-0.12, -0.08)**	**-0.02 (-0.03, -0.001)**	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.01, -0.004)**	**-0.06 (-0.07, -0.05)**	0.005 (-0.01, 0.02)	**-0.05 (-0.06, -0.04)**

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Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 for total population was adjusted for age, sex, race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score corresponds to a 0.16 mg/L lower log (hsCRP) concentration. Interactions by sex for all 7 biomarkers was significant at p <0.001. Results in bold font were statistically significant (p<0.05); †For IL-6, total sample size = 5,279.

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For all CVD-related biomarkers, there was a significant interaction for CVH with sex at p<0.001. For a unit increase in CVH score, the magnitude of concentrations were marginally lower for hsCRP, D-dimer and IL-6 in women compared to men, while for hs-cTnT, the magnitude of concentration was lower in men compared to women. No difference in magnitude of concentration was observed for fibrinogen and homocysteine for both sexes (**Table 2**). The **Figure** illustrates the sex-stratified mean biomarker concentrations by categories of the total CVH score. For all the biomarkers, participants with optimal scores had the smallest mean values.

The associations between the LS7 metrics and CVD-related biomarkers (log-transformed) in women and men are reported in **Tables 3 & 4.** For the ideal category of smoking, lower concentrations of D-dimer, fibrinogen, homocysteine, NT-proBNP and IL-6 were found in men but only lower concentration of homocysteine and IL-6 were found in women. For ideal smoking status, the magnitude of concentration of homocysteine was marginally lower in women than men, while the magnitude of concentration of IL-6 was marginally lower in men than women. For the ideal category of BMI, lower concentrations of all biomarkers except for NT-proBNP were found in women; whereas in men, lower concentrations of hsCRP, D-Dimer, fibrinogen, hs-cTnT and IL-6 were found. Both sexes had higher concentrations of NT-proBNP for ideal BMI. Additionally, for ideal BMI, the magnitudes of concentration of hsCRP, D-Dimer, fibrinogen and IL-6 were lower in women than men but hs-cTnT was lower in men. For the ideal category of physical activity, lower concentrations of hsCRP, fibrinogen, hs-cTnT and IL-6 were found in women while lower concentrations of fibrinogen, homocysteine, hs-cTnT and IL-6 were found in men. For ideal physical activity, the

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magnitudes of concentration of fibrinogen and hs-cTnT were marginally similar in women and men. The magnitude of concentration of IL-6 was marginally lower in men. An ideal diet score was associated with lower concentrations of hsCRP and IL-6 in women. For the ideal category of total cholesterol, lower concentrations of hs-cTnT were found in men while lower concentrations of fibrinogen and higher concentrations of NT-proBNP and IL-6 were found in women and men. For total cholesterol, the magnitudes of concentration of fibrinogen and IL-6 were marginally lower in women than men while the magnitude of concentration of NT-proBNP was higher in women than men, although confidence intervals between women and men overlapped.

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Table 3- The associations between LS7 metrics and CVD-related biomarkers in women, N=2,775

	hsCRP (mg/L)	D-dimer (μg/mL)	Fibrinogen (mg/dL)	Homocysteine (μmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
Smoking							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	-0.07	0.11	0.03	0.03	0.005	0.003	0.03
	(-0.51, 0.38)	(-0.22, 0.44)	(-0.05, 0.11)	(-0.08, 0.14)	(-0.17, 0.18)	0.35, 0.36)	(-0.22, 0.29)
Ideal	0.02	0.03	-0.01	**-0.08**	-0.01	0.07	**-0.10**
	(-0.12, 0.16)	(-0.07, 0.13)	(-0.03, 0.02)	**(-0.11, -0.04)**	(-0.07, 0.04)	0.04, 0.18)	**(-0.18, -0.02)**
Body mass index							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	**-0.61**	**-0.17**	**-0.08**	**-0.04**	**-0.07**	0.06	**-0.34**
	(-0.71, -0.51)	**(-0.25, -0.10)**	**(-0.10, -0.07)**	**(-0.07, -0.02)**	**(-0.11, -0.03)**	-0.03, 0.14)	**(-0.40, -0.29)**
Ideal	**-1.15**	**-0.32**	**-0.14**	**-0.06**	**-0.09**	**0.26**	**-0.61**
	(-1.25, -1.04)	**(-0.40, -0.23)**	**(-0.16, -0.12)**	**(-0.08, -0.03)**	**(-0.14, -0.05)**	**0.17, 0.35)**	**(-0.67, -0.55)**
Physical activity							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	-0.06	0.05	0.01	**-0.03**	-0.02	0.01	0.01

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	(-0.19, 0.07)	(-0.05, 0.15)	(-0.02, 0.03)	**(-0.07, -0.00)**	(-0.07, 0.03)	(-0.09, 0.12)	(-0.07, 0.08)
Ideal	**-0.16**	-0.04	**-0.03**	-0.02	**-0.05**	0.04	**-0.10**
	(-0.27, -0.06)	(-0.11, 0.04)	**(-0.05, -0.02)**	(-0.05, 0.00)	**(-0.09, -0.005)**	(-0.05, 0.12)	**(-0.16, -0.04)**
Diet							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	**-0.16**	-0.02	-0.01	-0.002	-0.01	-0.01	**-0.10**
	(-0.25, -0.07)	(-0.09, 0.04)	(-0.02, 0.01)	(-0.02, 0.02)	(-0.05, 0.02)	(-0.09, 0.06)	**(-0.15, -0.05)**
Ideal	**-0.40**	-0.09	-0.02	-0.07	-0.11	-0.05	**-0.24**
	(-0.74, -0.07)	(-0.33, 0.16)	(-0.07, 0.04)	(-0.16, 0.01)	(-0.24, 0.02)	(-0.32, 0.21)	**(-0.43, -0.06)**
Total Cholesterol							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	0.02	-0.04	-0.02	-0.0001	-0.01	**0.12**	**0.09**
	(-0.11, 0.14)	(-0.13, 0.05)	(-0.04, 0.00)	(-0.03, 0.03)	(-0.06, 0.04)	**(0.02, 0.21)**	**(0.02, 0.16)**
Ideal	-0.08	-0.02	**-0.06**	0.01	-0.006	**0.24**	**0.13**
	(-0.21, 0.04)	(-0.11, 0.08)	**(-0.08, -0.04)**	(-0.02, 0.04)	(-0.04, 0.06)	**(0.14, 0.34)**	**(0.06, 0.20)**
Blood pressure							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	**-0.13**	-0.05	-0.003	-0.005	**-0.09**	**-0.28**	**-0.07**

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	(-0.24, -0.03)	(-0.13, 0.03)	(-0.02, 0.02)	(-0.03, 0.02)	**(-0.13, -0.04)**	**(-0.37, -0.20)**	**(-0.13, -0.01)**
Ideal	**-0.45**	**-0.11**	**-0.02**	**-0.04**	**-0.12**	**-0.30**	**-0.21**
	(-0.56, -0.35)	**(-0.19, -0.03)**	**(-0.04, -0.002)**	**(-0.07, -0.01)**	**(-0.16, -0.08)**	**(-0.39, -0.21)**	**(-0.27, -0.15)**
Blood glucose							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	-0.04	0.01	-0.01	0.04	**-0.16**	0.10	-0.0002
	(-0.22, 0.14)	(-0.13, 0.14)	(-0.04, 0.02)	(-0.01, 0.08)	**(-0.23, -0.09)**	-0.04, 0.25)	(-0.10, 0.10)
Ideal	**-0.43**	-0.03	**-0.07**	0.002	**-0.19**	**0.29**	**-0.28**
	(-0.57, -0.28)	(-0.14, 0.08)	**(-0.09, -0.04)**	(-0.03, 0.04)	**(-0.25, -0.13)**	**(0.17, 0.40)**	**(-0.36, -0.20)**

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model was adjusted for age, race/ethnicity, education, income, and health insurance status. †For IL-6, sample size = 2,733

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Table 4- The associations between LS7 metrics and CVD-related biomarkers in Men, N=2,604

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
Smoking							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.16	-0.17	-0.04	**-0.16**	-0.07	**-0.52**	**-0.21**
	(-0.50, 0.17)	(-0.45, 0.11)	(-0.10, 0.02)	**(-0.25, -0.07)**	(-0.25, 0.12)	**(-0.86, -0.19)**	**(-0.42, -0.005)**
Ideal	-0.27	**-0.17**	**-0.05**	**-0.05**	0.02	**-0.15**	**-0.19**
	(-0.39, 0.15)	**(-0.27, -0.07)**	**(-0.07, -0.03)**	**(-0.08, -0.02)**	(-0.04, 0.08)	**(-0.27, -0.03)**	**(-0.27, -0.12)**
Body mass index							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.50**	**-0.11**	**-0.06**	-0.01	**-0.17**	0.07	**-0.30**
	(-0.59, -0.40)	**(-0.20, -0.03)**	**(-0.08, -0.05)**	(-0.04, 0.01)	**(-0.23, -0.12)**	(-0.02, 0.17)	**(-0.36, -0.24)**
Ideal	**-0.80**	**-0.17**	**-0.08**	-0.02	**-0.29**	**0.25**	**-0.37**
	(-0.92, -0.69)	**(-0.26, -0.07)**	**(-0.10, -0.06)**	(-0.05, 0.01)	**(-0.35, -0.23)**	**(0.14, 0.36)**	**(-0.43, -0.30)**
Physical activity							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.09	-0.06	-0.002	-0.01	-0.07	0.03	-0.02

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	(-0.04, 0.23)	(-0.17, 0.06)	(-0.03, 0.02)	(-0.05, 0.02)	(-0.14, 0.01)	(-0.10, 0.17)	(-0.10, 0.07)
Ideal	-0.03	-0.05	**-0.02**	**-0.02**	**-0.07**	0.05	**-0.14**
	(-0.14, 0.07)	(-0.13, 0.04)	**(-0.04, -0.004)**	**(-0.05, -0.00)**	**(-0.13, -0.02)**	(-0.05, 0.15)	**(-0.20, -0.07)**
Diet							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.11**	0.002	-0.01	-0.003	-0.02	0.04	**-0.05**
	(-0.19, -0.02)	(-0.07, 0.07)	(-0.03, 0.00)	(-0.02, 0.02)	(-0.07, 0.02)	(-0.04, 0.12)	**(-0.10, -0.003)**
Ideal	-0.57	-0.50	0.01	0.06	-0.17	0.31	-0.14
	(-1.25, 0.11)	(-1.07, 0.07)	(-0.12, 0.14)	(-0.11, 0.24)	(-0.54, 0.20)	(-0.36, 0.98)	(-0.56, 0.27)
Total Cholesterol							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.03	0.01	**-0.04**	-0.003	**-0.10**	-0.09	0.08
	(-0.17, 0.11)	(-0.11, 0.12)	**(-0.06, -0.01)**	(-0.04, 0.03)	**(-0.18, -0.02)**	(-0.22, 0.05)	(-0.01, 0.16)
Ideal	-0.01	0.05	**-0.05**	-0.006	**-0.10**	**0.19**	**0.17**
	(-0.15,0.13)	(-0.06, 0.17)	**(-0.08, -0.03)**	(-0.04, 0.03)	**(-0.17, -0.02)**	**(0.05, 0.32)**	**(0.08, 0.25)**
Blood pressure							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.10	-0.06	-0.01	**-0.03**	**-0.12**	**-0.37**	**-0.07**

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	(-0.20, 0.01)	(-0.14, 0.03)	(-0.03, 0.004)	**(-0.06, -0.005)**	**(-0.18, -0.07)**	**(-0.47, -0.27)**	**(-0.13, -0.01)**
Ideal	**-0.23**	-0.01	**-0.03**	**-0.04**	**-0.22**	**-0.40**	**-0.09**
	(-0.34, -0.13)	(-0.10, 0.08)	**(-0.05, -0.01)**	**(-0.07, -0.02)**	**(-0.27, -0.16)**	**(-0.50, -0.30)**	**(-0.16, -0.03)**
Blood glucose							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.07	0.03	-0.01	0.04	**-0.23**	-0.06	-0.04
	(-0.08, 0.22)	(-0.09, 0.16)	(-0.04, 0.02)	(-0.003, 0.08)	**(-0.31, -0.15)**	(-0.21, 0.09)	(-0.14, 0.05)
Ideal	**-0.17**	0.04	**-0.03**	0.01	**-0.36**	0.04	**-0.15**
	(-0.30, -0.04)	(-0.07, 0.15)	**(-0.06, -0.01)**	(-0.02, 0.05)	**(-0.43, -0.29)**	(-0.09, 0.17)	**(-0.23, -0.07)**

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model adjusted for age, race/ethnicity, education, income, and health insurance status. For IL-6, n = 2,545.

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For ideal blood pressure, a lower concentration of all biomarkers was found in women; whereas in men a lower concentration was observed for all biomarkers except D-dimer. Additionally, for ideal blood pressure, the magnitudes of concentration of fibrinogen, hs-cTnT and NT-proBNP were lower in men than women while the magnitude of concentration of IL-6 was lower in women than men. For ideal blood glucose levels, a higher concentration of NT-proBNP was found in women while a lower concentration of hsCRP, fibrinogen, hs-cTnT and IL-6 was observed in both sexes. For ideal blood glucose, the magnitudes of concentration of hsCRP, fibrinogen and IL-6 were lower in women than men.

The supplementary analyses show the associations between CVH and CVD-related biomarkers stratified by race/ethnicity and age for women and men. The results were similar for both sexes and mostly showed a statistically significant lower concentration of CVD-related biomarkers for a unit increment in CVH score. Among White and Chinese-American Women as well as women <65 years old, a unit increment in CVH score was associated with higher concentrations of NT-proBNP **(Supplementary Tables S4-S7)**.

Discussion

In this cross-sectional analysis of 5,379 adult women and men free of clinical CVD at baseline, after adjusting for sociodemographic factors, we found an inverse association between the CVH score and most of the CVD-related biomarkers. Higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers in women and men, except for NT-proBNP that showed a positive relationship. We found a similarly inverse relationship between the LS7 metrics and

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CVD-related biomarkers except for NT-proBNP where the associations were both direct and inverse. Additionally, we observed a direct association between ideal cholesterol and IL-6 in both sexes. In the stratified analyses by race/ethnicity and age, the associations observed were similar for both sexes.

Our results are similar to a study conducted to investigate the association between CVH metrics and biomarkers (hsCRP and homocysteine) among 3,009 Chinese adults between the ages of 24 and 85 years, without a history of CVD[7]. In their study, after adjusting for age, sex and education, a unit increment in CVH score was inversely related to biomarker concentration [CRP: -0.182 (-0.652, -0.457); and homocysteine: -0.092, (-0.930, -0.426)]. A similar association was found in women and men, although the association was stronger in women.

A cross-sectional study of 2,680 participants from the Framingham Heart Study also examined the association between CVH and CVD-related biomarkers (BNP, CRP, D-dimer, fibrinogen and homocysteine)[22]. Similar to our findings in MESA, the Framingham researchers found that the CVH score had a direct association with higher circulating concentrations of natriuretic peptides but was inversely related to blood concentrations of the other biomarkers examined, after adjusting for age and sex[22]. For a unit increase in CVH score, the beta coefficients for the biomarkers are as follows: BNP, 0.057 pg/mL (0.035, 0.080); CRP, -0.248 mg/L (-0.279, -0.217); D-dimer, -0.030 ng/mL (-0.046, -0.014); fibrinogen, -0.028 mg/dL (-0.033,-0.023) and homocysteine, -0.021 mmol/L (-0.029,-0.012). The authors concluded that the inverse association of CVH with incident CVD events was at least partly attributable to the favorable relationship of CVH and subclinical biomarkers of risk[22]. Notably, none of the

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aforementioned studies examined for effect modification by sex in the association of CVH with subclinical biomarkers, as we newly present here. One prior study conducted in a Chinese population[7] did stratify the association between CVH and biomarkers by sex; however, they did not test for effect modification. In contrast to our study, that study did not include D-dimer, fibrinogen, hs-cTnT, NT-proBNP and IL-6 in their analysis[7].

Our main finding showed a better CVH score was associated with lower concentrations of all CVD-related biomarkers (except NT-proBNP) in both women and men. Despite statistically significant interactions by sex for the total CVH score, qualitatively the magnitude of lower concentrations for these biomarkers per 1 unit increment in CVH were generally similar among women and men. However, for the metric of ideal BMI, the magnitude of lower concentrations hsCRP, D-Dimer, fibrinogen and IL-6 per unit of CVH was greater in women than men. In the univariate analysis, women in this study had slightly higher BMI than men. Studies have shown that estrogen and adipose tissue may increase the circulating levels of inflammatory biomarkers[9, 23], and thus a more favorable BMI might have greater impact on these biomarker concentrations in women than men.

Additionally we note that, in women, ideal BMI, a health behavior, was associated with a greater magnitude of reduction in hsCRP, D-dimer, fibrinogen and IL-6 compared to ideal blood pressure, ideal blood glucose (health factors) while in men, the same association was observed for hsCRP and IL-6. This may suggest that attaining ideal health behaviors such as ideal BMI may lead to more reductions in the biomarkers of CVD risk compared to ideal health factors. However, more elaborate

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studies would be needed to explore these findings so definite conclusions can be reached.

In the univariate analyses, homocysteine concentrations were higher in men which may be attributable to a higher prevalence of smoking and poorer healthy diet score[24]. In the adjusted regression analyses a unit increment in CVH score corresponded to a slightly lower concentration of homocysteine in women. In addition, the higher prevalence of smoking found in men in this study may be responsible for their higher baseline hs-cTnT concentrations[25]. Although in adjusted regression analysis, the magnitude of concentration of hs-cTnT per 1-unit increment in CVH score was lower in men. Moreover, we found that ideal cholesterol was directly associated with IL-6 in both sexes. Although this finding has been previously documented among healthy individuals, other studies have reported an inverse association in pathological conditions, which according to prior research may suggest polymorphism in the IL-6 gene differentially affects lipid metabolism[26].

Interestingly, a better CVH score was associated with higher concentrations of NT-proBNP, particularly in women. At first this may seem paradoxical, as in the setting of disease states, BNP levels are frequently elevated. However, in normal states, NT-proBNP actually plays a favorable cardioprotective role by inhibiting cardiac hypertrophy and fibrosis and promoting vasodilation and natriuresis. In patients with heart failure, there is relative BNP deficiency and BNP resistance, resulting in a compensatory increase in NT-proBNP concentrations to restore homeostasis[27]. We found that baseline concentrations of NT-proBNP were higher in women than men, as had been previously reported in MESA[10], though average concentrations for both sexes were within normal

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limits in this cohort free of clinical heart failure at baseline. Other previous studies have also reported higher NT-proBNP concentrations in women[22, 28], as well as a prior analysis in the MESA cohort that showed a more androgenic ("male-like") sex hormone profile was associated with lower NT-proBNP concentrations[10].

The sex-specific differences observed in the association of CVH and CVD-related biomarkers may reflect different pathways of CVD risk. Additional research that explain the potential sex-specific mechanisms underlying the association between CVH and CVD-related biomarkers may improve our knowledge of the development of CVD in women and men[29]. An understanding of these pathways may also help clinicians tailor interventions specific to the prevention and treatment of CVD risk factors in women and men[29]. Our study emphasizes the importance of promoting ideal CVH, which may be more beneficial in women, particularly with research showing that women have poorer cardiovascular outcomes compared to men. Encouraging the attainment of ideal CVH may reverse this trend and lead to a decrease in CVD burden.

In the interpretation of our findings, some limitations should be noted. First, neither temporality nor causal inferences between the association of CVH and CVD-related biomarkers can be determined because of the cross-sectional observational study design. Second, we cannot rule out recall bias from the use of self-administered questionnaires to collect data on smoking, diet, and physical activity. Third, the findings of this study may not be generalizable to younger people or adults of very advanced age because our participants were between ages of 45 and 84 years old. Fourth, multiple statistical tests were performed and some findings might be expected to occur by chance; however, our findings were generally consistent between women and men

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and across age and race/ethnic subgroups. Lastly, CVH was assessed once at baseline and may not be representative of the future CVH status of study participants.

Conclusions

We found that more favorable CVH scores were associated with lower concentrations of CVD-related biomarkers in both women and men, except for NT-proBNP which showed a direct relationship. These favorable associations of CVH with biomarkers of risk may be an intermediary step in the prevention of clinical CVD events. Overall, our findings were qualitatively similar between the sexes. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of risk among women and men. However, long-term outcome studies are needed to improve our understanding of the underlying sex-specific mechanisms and the clinical implications of these findings.

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Author contributions

Study conception and design: OO, OO and EDM; Acquisition of data and analysis: OO and OO; Interpretation of data: OO, OO, MT, EB and EDM; Drafting of

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Conflicts of interest:

None of the authors report any conflicts of interest with this work.

Ethics approval:

The MESA protocol was approved by the institutional review boards of all the recruitment centers.

Data sharing statement:

The MESA study participates in data sharing through the National Heart, Lung, Blood Institute (NHLBI) Biologic Specimen and Data Repository Coordinating Center (BioLINCC). Requests for access to the data can be made through their website: https://biolincc.nhlbi.nih.gov/studies/mesa/.

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Figure Legend

Sex-stratified mean biomarker levels by cardiovascular health score categories (inadequate (0-8), average (9-10) and optimal (11-14). Lighter color=Women; Darker color=Men. hsCRP=high-sensitivity C-reactive protein; hs-cTnT=high-sensitivity cardiac troponin T; NT-proBNP= N-terminal pro B-type natriuretic peptide; IL-6, interleukin-6. Mean values for biomarkers were not log transformed

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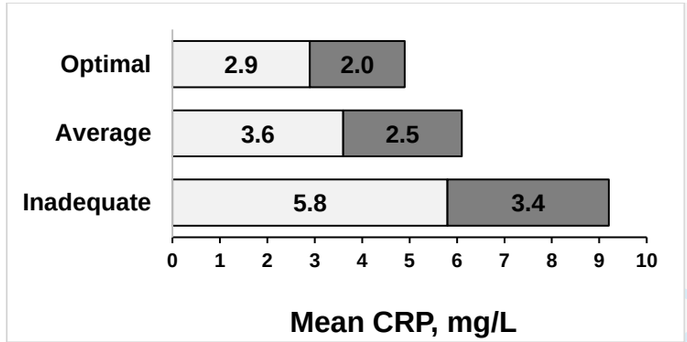

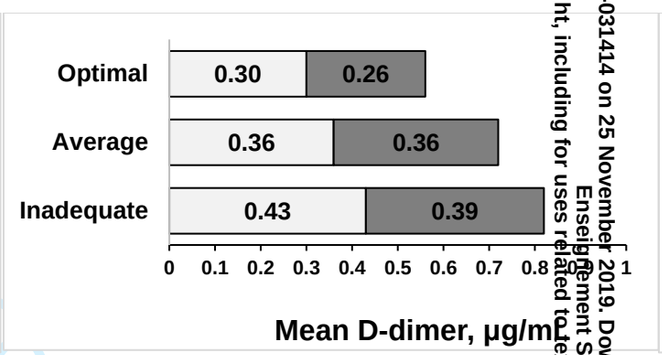

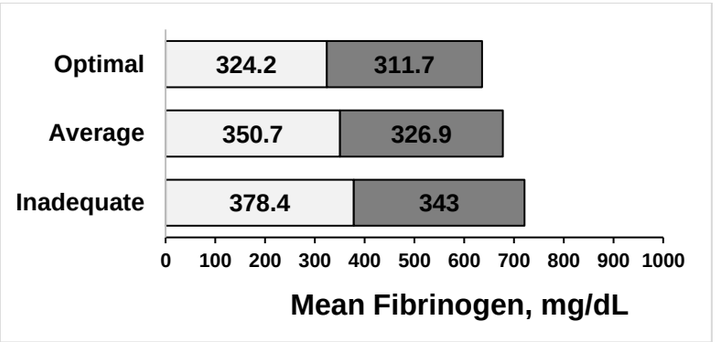

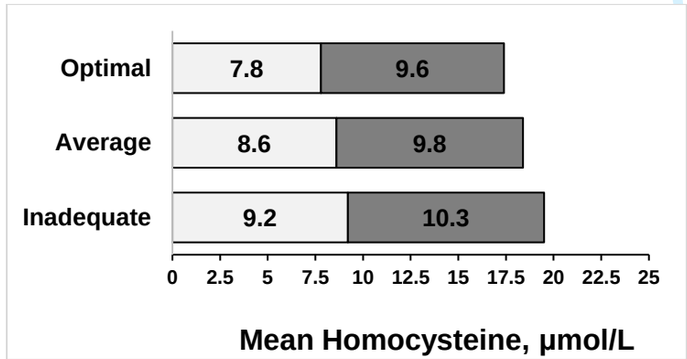

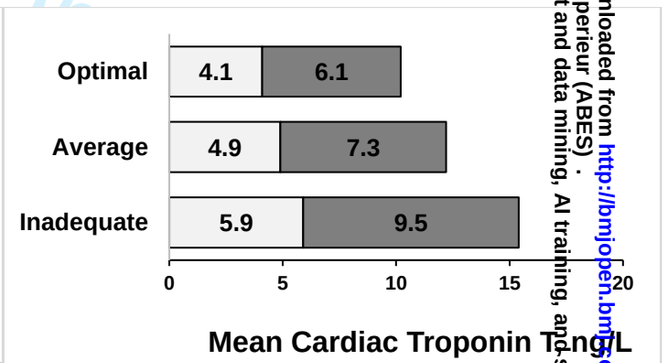

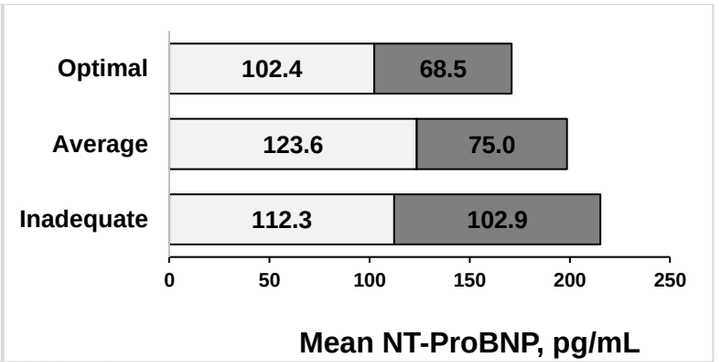

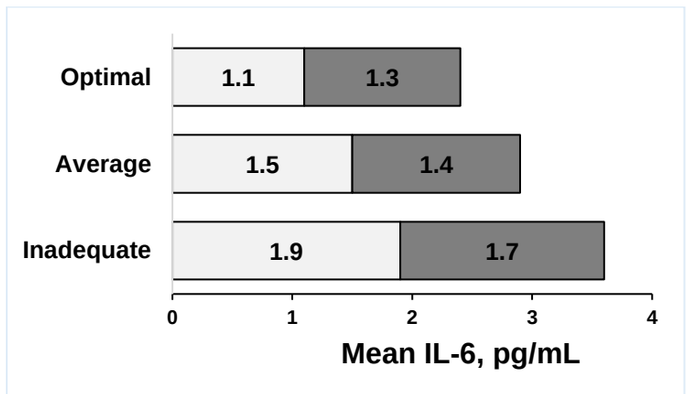

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SUPPLEMENTARY MATERIAL

Supplementary Methods: Assessment of cardiovascular health

Table S1: Baseline categories of income and education

Table S2: Definition of Life's Simple 7 Metrics

Table S3: Distribution of Life's Simple 7 Metrics by Sex

Table S4: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

Table S5: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

Table S6: The associations between CVH score and CVD-related biomarkers by Age for Women

Table S7: The associations between CVH score and CVD-related biomarkers by Age for Men

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Supplementary Methods: Assessment of cardiovascular health

Information on the LS7 metrics were collected from study participants at baseline. Based on AHA guidelines, ideal CVH is achieved if the following criteria are met for the LS7 metrics: non-smoking, physical activity at goal levels, BMI <25kg/m^2 and a healthy diet consistent with guidelines, total cholesterol <200mg/dL (not on lipid lowering medications), blood pressure <120/<80mmHg (not on anti-hypertensive medications), and fasting blood glucose <100mg/dL (not on diabetes medications) [1]. Smoking status was assessed by self-report and categorized as; 1) participants who never smoked or quit more than 12 months (non-smokers), 2) participants who quit within 12 months (former smokers) and 3) current smokers [1]. Physical activity was evaluated using a self-report survey instrument adapted from the Cross-Cultural Activity Participation Study [2] containing 28 questions on time and frequency of activities during a week in the previous month. The total minutes of moderate and vigorous exercise in metabolic equivalents of task (MET/min) were estimated and used for our analyses [3].

BMI (kg/m^2) was calculated using the weight and height measurements. Dietary habits were evaluated using a 120-item validated food frequency questionnaire modified from the Insulin Resistance Atherosclerosis Study instrument [4, 5]. Based on recommended dietary guidelines, a healthy diet was made up of fruits and vegetables, fish, whole grains and intake of sodium <1500mg per day and sugar-sweetened beverages ≤450 kcal (36 oz.) per week [1]. For blood pressure, with participants in a seated position, 3 measurements were obtained after resting for 5 minutes and the average values of the last two readings were recorded. For total cholesterol (mg/dL)

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and blood glucose (mg/dL) measurements, blood samples were collected following a 12 hour fast.

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Table S1 - Baseline categories of income and education, N=5,379

Income			Education		
1	< $5,000	131 (2%)	1	NO SCHOOLING	60 (1%)
2	$5,000-$7,999	214 (4%)	2	GRADES 1-8	558 (10%)
3	$8,000-$11,999	310 (6%)	3	GRADES 9-11	367 (7%)
4	$12,000-$15,999	399 (7%)	4	COMPLETED HIGH SCHOOL/GED	950 (18%)
5	$16,000-$19,999	275 (5%)	5	SOME COLLEGE BUT NO DEGREE	855 (16%)
6	$20,000-$24,999	404 (8%)	6	TECHNICAL SCHOOL CERTIFICATE	385 (7%)
7	$25,000-$29,999	311 (6%)	7	ASSOCIATE DEGREE	275 (5%)
8	$30,000-$34,999	374 (7%)	8	BACHELOR'S DEGREE	951 (18%)
9	$35,000-$39,999	313 (6%)	9	GRADUATE OR PROFESSIONAL SCHOOL	978 (18%)
10	$40,000-$49,999	517 (10%)			
11	$50,000-$74,999	883 (16%)			
12	$75,000-$99,999	483 (9%)			
13	$100,000+	765 (14%)			

% are rounded to whole numbers

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Table S2 – Definition of the Life's Simple 7 metrics

LS7 Metrics	Score	Definition
Smoking	0	Current smoker
	1	Former smoker, quit ≤12 months ago
	2	Never smoker or quit >12 months ago
Body Mass Index	0	≥30 kg/m^2
	1	25.0–29.99 kg/m^2
	2	<25.0 kg/m^2
Physical Activity	0	No exercise
	1	1–149 min of moderate exercise or 1–74 min of vigorous exercise/week
	2	150+ min of moderate exercise or 75+ min of vigorous exercise/week
Diet	0	0–1 components of healthy diet
	1	2–3 components of healthy diet
	2	4–5 components of healthy diet
Total Cholesterol	0	≥240 mg/dL
	1	200–239 mg/dL or treated to <200mg/dL
	2	<200 mg/dL, unmedicated
Blood Pressure	0	SBP ≥140 mmHg or DBP ≥90 mmHg
	1	SBP 120–139 mmHg or DBP 80–89 mmHg or treated to <120/80 mm Hg
	2	<120/80 mm Hg, unmedicated
Blood Glucose	0	≥126 mg/dL fasting
	1	100–125 mg/dL fasting or treated to <100 mg/dL
	2	<100 mg/dL fasting, unmedicated

Adapted from Lloyd Jones et al[1] and Unger et al[3], LS7 indicates Life's Simple 7; DBP, diastolic blood pressure, and SBP, systolic blood pressure. Poor=0 points; Intermediate=1 point; ideal =2 points. *When combining vigorous and moderate exercise, vigorous exercise was weighted double.

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Table S3 - Distribution of Life's Simple 7 Metrics by Sex

	Total (N=5,379)	Women (n= 2,775)	Men (n= 2,604)	P value
Total CVH score, mean (SD)	8.6 (2.2)	8.6 (2.3)	8.6 (2.1)	0.85
LS7 metrics, n (%)				
Smoking				
Poor	671 (12)	303 (11)	368 (14)	
Intermediate	68 (1)	27 (1)	41 (2)	<0.001
Ideal	4640 (86)	2445 (88)	2195 (84)	
Body mass index				
Poor	1657 (31)	958 (35)	699 (27)	
Intermediate	2127 (40)	936 (34)	1191 (46)	<0.001
Ideal	1595 (30)	881 (32)	714 (28)	
Physical activity				
Poor	1231 (23)	684 (25)	547 (21)	
Intermediate	909 (17)	529 (19)	380 (15)	<0.001
Ideal	3239 (60)	1562 (56)	1677 (64)	
Diet				
Poor	2425 (45)	1029 (37)	1396 (54)	
Intermediate	2898 (54)	1699 (61)	1199 (46)	<0.001
Ideal	56 (1)	47 (2)	9 (0.4)	
Total Cholesterol				
Poor	729 (14)	466 (17)	263 (10)	
Intermediate	2107 (39)	1143 (41)	964 (37)	<0.001
Ideal	2543 (47)	1166 (42)	1377 (53)	
Blood pressure				
Poor	1996 (37)	1085 (39)	911 (35)	
Intermediate	1505 (28)	695 (25)	810 (31)	<0.001
Ideal	1878 (35)	995 (36)	883 (34)	
Blood glucose				
Poor	572 (11)	275 (10)	297 (11)	
Intermediate	846 (16)	359 (13)	487 (19)	<0.001
Ideal	3961 (74)	2141 (77)	1820 (70)	

Abbreviations: CVH indicates cardiovascular health; SD, standard deviation; LS7, Life's Simple 7; percentages were rounded up to whole numbers

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Table S4 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
White, n=1,092							
Model 1	**-0.18 (-0.21, -0.15)**	**-0.06 (-0.08, -0.04)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.03, -0.01)**	**-0.05 (-0.06, -0.04)**	-0.01 (-0.03, 0.04)	**-0.10 (-0.12, -0.08)**
Model 2	**-0.19 (-0.23,-0.16)**	**-0.04 (-0.07, -0.02)**	**-0.03 (-0.04, -0.02)**	**-0.01 (-0.02, -0.002)**	**-0.03 (-0.04, -0.02)**	**0.025 (0.003, 0.047)**	**-0.09 (-0.11, -0.07)**
Chinese-American, n=372							
Model 1	**-0.11 (-0.17, -0.06)**	**-0.08 (-0.13, -0.04)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**-0.05 (-0.07, -0.03)**	-0.01 (-0.06, 0.05)	**-0.07 (-0.10, -0.04)**
Model 2	**-0.13 (-0.18, -0.07)**	-0.04 (-0.09, 0.01)	**-0.01 (-0.02, -0.004)**	**-0.01 (-0.03, -0.00)**	**-0.03 (-0.005, -0.01)**	**0.047 (0.003, 0.12)**	**-0.06 (-0.10, -0.03)**
Black, n=681							
Model 1	**-0.15 (-0.19, -0.11)**	**-0.06 (-0.09, -0.03)**	**-0.03 (-0.03, -0.02)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.06, -0.02)**	-0.02 (-0.06, 0.02)	**-0.09 (-0.11, -0.07)**
Model 2	**-0.15 (-0.19, -0.10)**	**-0.05 (-0.08, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.004)**	**-0.03 (-0.05, -0.01)**	0.005 (-0.03, 0.04)	**-0.08 (-0.11, -0.06)**
Hispanic, n= 630							
Model 1	**-0.13 (-0.17, -0.10)**	**-0.03 (-0.07, -0.003)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.05, -0.02)**	**-0.04 (-0.07, -0.003)**	**-0.09 (-0.11, -0.07)**
Model 2	**-0.14 (-0.18, -0.10)**	-0.004 (-0.04, 0.03)	**-0.01 (-0.02, -0.005)**	**-0.01 (-0.02, -0.002)**	**-0.02 (-0.04, -0.005)**	0.011 (-0.03, 0.04)	**-0.08 (-0.10, -0.06)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-ProBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White women corresponds to a 0.18 mg/L lower logCRP concentration. † For IL-6, Women: White, n=1,080; Chinese-American, n=371; Black, n=664; Hispanic, n=618

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Table S5 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
White, n=1,058							
Model 1	**-0.15 (-0.18, -0.12)**	-0.02 (-0.05, 0.004)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.02)**	0.0 (-0.03, 0.0)	**-0.08 (-0.10,-0.06)**
Model 2	**-0.14 (-0.17, -0.11)**	-0.02 (-0.05, 0.005)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.03)**	0.0 (-0.02, 0.0)	**-0.07 (-0.09, -0.05)**
Chinese-American, n= 361							
Model 1	**-0.09 (-0.15, -0.04)**	-0.01 (-0.06, 0.04)	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.001)**	**-0.06 (-0.08, -0.03)**	0.0 (-0.02, 0.0)	-0.04 (-0.07, 0.0002)
Model 2	**-0.11 (-0.17, -0.05)**	0.001 (-0.05, 0.05)	**-0.02 (-0.03, -0.01)**	**-0.02 (-0.03, -0.002)**	**-0.06 (-0.09, -0.04)**	0.0 (-0.03, 0.0)	-0.03 (-0.07, 0.004)
Black, n= 572							
Model 1	**-0.07 (-0.12, -0.03)**	**-0.05 (-0.09, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.01 (-0.02, -0.001)**	**-0.09 (-0.11, -0.06)**	-0.03 (-0.08, 0.0)	**-0.04 (-0.07, -0.02)**
Model 2	**-0.06 (-0.11, -0.02)**	-0.02 (-0.06, 0.01)	**-0.01 (-0.02, -0.01)**	-0.01 (-0.02, 0.003)	**-0.07 (-0.09, -0.05)**	0.02 (-0.03, 0.0)	**-0.03 (-0.06, -0.01)**
Hispanic, n=613							
Model 1	**-0.08 (-0.12, -0.04)**	-0.03 (-0.06, 0.01)	**-0.02 (-0.03, -0.01)**	-0.001 (-0.01, 0.01)	**-0.08 (-0.11, -0.06)**	**-0.06 (-0.11, -0.01)**	**-0.06 (-0.08, -0.03)**
Model 2	**-0.08 (-0.12, -0.04)**	-0.01 (-0.04, 0.02)	**-0.02 (-0.02, -0.01)**	0.003 (-0.01, 0.01)	**-0.08 (-0.10, -0.05)**	-0.03 (-0.07, 0.01)	**-0.05 (-0.07, -0.02)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White men corresponds to a 0.15mg/L lower logCRP concentration.

† For IL-6, Men: White, n=1,042; Chinese American, n=355; Black, n=554; Hispanic, n=595

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Table S6 - The associations between CVH score and CVD-related biomarkers by Age for Women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Age <65 years, n=1,559							
Model 1	**-0.22 (0.24, -0.19)**	**-0.07 (-0.09, -0.05)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.03, -0.02)**	**-0.03 (-0.06, 0.06)**	**-0.11 (-0.13, -0.10)**
Model 2	**-0.19 (-0.21, -0.16)**	**-0.04 (-0.06, -0.02)**	**-0.03 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.03 (-0.04, 0.05)**	**-0.09 (-0.10, -0.07)**
Age ≥ 65 years, n= 1,216							
Model 1	**-0.14 (-0.17, -0.11)**	**-0.06 (-0.08, -0.04)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.04)**	-0.02 (-0.12, 0.04)	**-0.09 (-0.11, -0.07)**
Model 2	**-0.12 (-0.15, -0.09)**	**-0.03 (-0.06, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.02, -0.01)**	**-0.05 (-0.06, -0.03)**	-0.01 (-0.11, 0.03)	**-0.07 (-0.09, -0.06)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in women <65 years corresponds to a 0.22mg/L lower logCRP concentration. † For IL-6, Women: Age <65, n=1,539 Age ≥ 65 years, n=1,194

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Table S7 - The associations between CVH score and CVD-related biomarkers by Age for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Age <65 years, n= 1,454							
Model 1	**-0.14 (-0.17, -0.12)**	**-0.02 (-0.05, -0.003)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.01, -0.001)**	**-0.07 (-0.08, -0.06)**	-0.02 (-0.04, 0.01)	**-0.07 (-0.09, -0.06)**
Model 2	**-0.12 (-0.15, -0.10)**	-0.02 (-0.04, 0.007)	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.01, -0.00)**	**-0.07 (-0.08, -0.05)**	-0.01 (-0.04, 0.02)	**-0.06 (-0.08, -0.04)**
Age ≥ 65 years, n= 1,150							
Model 1	**-0.11 (-0.14, -0.08)**	**-0.05 (-0.07, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.06 (-0.08, -0.04)**	0.01 (-0.02, 0.04)	**-0.06 (-0.08, -0.04)**
Model 2	**-0.07 (-0.10, -0.04)**	**-0.03 (-0.05, -0.001)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.03)**	0.01 (-0.02, 0.05)	**-0.04 (-0.06, -0.02)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.
*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in men <65 years corresponds to a 0.14mg/L lower logCRP concentration. † For IL-6, Men: Age <65, n=1,425; Age ≥ 65 years, n=1,121

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10-23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

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		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-23
Discussion			
Key results	18	Summarise key results with reference to study objectives	23-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27-28
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24-28
Generalisability	21	Discuss the generalisability (external validity) of the study results	27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: A cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis

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Keywords:	Biomarkers, Cardiovascular disease, Ideal cardiovascular health metrics, Life's Simple 7, Sex, Gender

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Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: A cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objectives: This study investigated the sex differences in the associations between ideal cardiovascular health (CVH), measured by the American Heart Association's Life's Simple 7 and cardiovascular disease (CVD)-related biomarkers among an ethnically diverse cohort of men and women free of clinical CVD at baseline.

Setting: We analyzed data from the Multi-Ethnic Study of Atherosclerosis conducted in 6 centers across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN).

Participants: This is a cross-sectional study of 5,379 men and women, aged 45 to 84 years old. Mean age (SD) was 62 (10), 52% were women, 38% White, 11% Chinese American, 28% Black and 23% Hispanic.

Primary measures: The 7 metrics (smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and blood glucose) were each scored as 0 points (poor), 1 point (intermediate) or 2 points (ideal). The total CVH score ranged from 0-14. The CVD-related biomarkers studied were high-sensitivity C-reactive protein, D-dimer, fibrinogen, homocysteine, high-sensitivity cardiac troponin T, NT-proBNP and IL-6. We examined the association between the CVH score and each biomarker using multivariable linear regression, adjusting for age, race/ethnicity, education, income, and health insurance status.

Results: Higher CVH scores were associated with lower concentrations of all biomarkers, except for NT-proBNP where there was a positive association. There were statistically significant interactions by sex for all biomarkers ($p<0.001$), but results were qualitatively similar between women and men.

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Conclusion: A more favorable CVH score was associated with lower levels of multiple CVD-related biomarkers for women and men, except for NT-proBNP. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of CVD risk for both women and men.

Keywords: Biomarkers, cardiovascular disease, ideal cardiovascular health metrics, Life's Simple 7, sex, gender

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Strengths and limitations of this study

- Use of a large and diverse study sample that enabled stratification by sex, race/ethnicity and age.
- Use of validated survey instruments and standardized methods for data collection allowed for comparison with other studies.
- Study population included adults between the ages of 45 and 84 years, which limited the generalizability of our findings to younger or older age groups.
- Cross-sectional observational design cannot establish temporality or causation.

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Introduction

The ideal cardiovascular health (CVH) construct, defined as meeting specific criteria for 7 health behaviors and health factors called the Life's Simple 7 (LS7) metrics, was introduced by the American Heart Association (AHA) to decrease the burden of CVD[1]. This was a shift towards primordial prevention – focusing on wellness rather than disease[2]. Biomarkers, which are often used in conjunction with traditional risk factors, are subclinical indicators of physiological and pathological processes[3] and serve as useful tools in facilitating early detection and prognostication of CVD[4]. Although prior studies have examined the relationship of biomarkers with incident CVD, few have focused on biomarkers and measures of cardiovascular wellness. Not surprisingly, the studies that have examined the association between ideal CVH and subclinical biomarkers of disease have shown an inverse relationship[5]. For example, in a prior analysis from the Multi-Ethnic Study of Atherosclerosis (MESA), poor CVH was found to be associated with higher levels of GlycA (a novel inflammatory marker) and higher levels of traditional inflammatory markers [high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), fibrinogen, and D-dimer][6]. However, research on the sex differences of the relationship of CVH with CVD-related biomarkers is sparse[7].

There are known sex differences in the levels of CVD-related biomarkers. Women are known to have higher levels of hsCRP[8, 9] and N-terminal pro B-type natriuretic peptide (NT-proBNP)[10] than men even after accounting for cardiometabolic risk factors, while troponin levels[11, 12] are higher in men than women. Thus, understanding sex differences in the relationship of ideal CVH measures with

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biomarkers is an important intermediate step in explaining sex differences in clinical CVD.

This study aimed to examine the sex differences in the associations between ideal CVH and CVD-related biomarkers among men and women free of clinical CVD in an ethnically diverse cohort. We hypothesized that better CVH would be associated with lower concentrations of CVD-related biomarkers especially in women.

Methods

Study population

As previously described, MESA is a longitudinal study of 6,814 adult women and men between the ages of 45 and 84 years. The study participants, with no previous history of clinical CVD at baseline, were recruited from 6 centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY and St Paul, MN) in the United States between July 2000 and August 2002[13]. Among participants, 38% were White, 11% Chinese American, 28% Black, and the remaining 23% were Hispanic. Informed consent was provided by all participants. The MESA protocol was approved by the institutional review boards (IRB) of all the recruitment centers. At the Johns Hopkins field center where this analysis was conducted, the IRB approval number was NA_00030361.

Baseline information was collected using standardized questionnaires, physical examinations and fasting laboratory blood draw. For the current analyses, we included 5,379 participants from the MESA baseline exam after excluding participants with missing information for the CVD biomarkers and LS7 metrics.

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Assessment of biomarkers

We examined biomarkers that were measured at baseline. Fasting blood samples were drawn, processed and stored using standardized procedures[14]. HsCRP, D-dimer, fibrinogen, IL-6, and homocysteine levels were analyzed at the laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont). Serum levels of hsCRP (mg/L) were measured using the BNII nephelometer (Dade Behring, Deerfield, IL). Analytical intra-assay coefficients of variation (CV) of hsCRP ranged from 2.3% to 4.4%, and inter-assay CV ranged from 2.1% to 5.7%[6, 15]. D-dimer (µg/mL) was measured with an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) which was used on a Sta-R analyzer (Diagnostica Stago, Parsippany, NJ). The lower detection limit of D-dimer assay was 0.01 µg/mL[6]. Serum fibrinogen (mg/dL) was measured by immunoprecipitation of fibrinogen antigen using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The intra-assay and inter-assay CV were 2.7% and 2.6%, respectively[6, 15]. Serum IL-6 (pg/mL) was measured by ultrasensitive enzyme-linked immunosorbent assay (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). The analytical CV was 6.3%[15]. Plasma homocysteine (µmol/L) was measured using a fluorescence polarization immunoassay with the IMx analyzer (Abbott Diagnostics, Abbott Park, IL). The CV was 4.5%[16].

The assays for high-sensitivity cardiac troponin T (hs-cTnT, ng/L) and NT-proBNP (pg/mL) were performed at the Veteran's Affairs San Diego Healthcare System (La Jolla, CA) and measured in serum using the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN). For hs-cTnT, the inter-assay CV observed for the MESA

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cohort measurements were 3.6% at 28 ng/L and 2.0% at 2154 ng/L[17]. For NT-proBNP, the intra-and inter-assay CV were as follows: at 175 pg/mL, 2.7% and 3.2%; at 355 pg/mL, 2.4% and 2.9%; at 1068 pg/mL, 1.9% and 2.6%; and at 4962 pg/mL, 1.8% and 2.3%, respectively[10].

Assessment of cardiovascular health

Cardiovascular health was assessed at baseline using the LS7 metrics based on AHA criteria[1]. A detailed assessment can be found in the supplementary material (**Supplementary Methods**).

Assessment of covariates

Sociodemographic factors included as covariates are age, sex, race/ethnicity education income and health insurance. Age was examined continuously in the multivariable models but dichotomized as <65 and ≥65 years for subgroup testing. Race/ethnicity had 4 groups: White, Chinese-American, Black and Hispanic. We had 9 categories for education and 13 categories for income (**Supplementary Table 1**), which were used in our multivariable models; however they were dichotomized as ≥ bachelor's degree and < bachelor's degree; ≥$40,000 and < $40,000 respectively, for descriptive statistics. Yes" or "No" responses were given for health insurance status.

Statistical analyses

The characteristics of the study participants were reported for the overall population and by sex. Categorical variables were presented as frequencies with percentages, and continuous variables were presented as means with standard deviation (SD). We compared the baseline characteristics of participants by sex, using

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ANOVA and chi-square tests as appropriate. The CVD-related biomarkers were natural logarithmically transformed for the analyses because distribution was skewed. The LS7 metrics were each defined as ideal, intermediate, and poor[1], and their distribution was reported by sex, as shown in **Supplementary Tables 2 & 3**. Points were awarded to each category of the LS7 metrics with 0 indicating poor; 1, intermediate; and 2, ideal. The points were summed, yielding a total CVH score ranging from 0 to 14[18]. As previously reported, total CVH scores of 0 to 8, 9 to 10, and 11 to 14 were considered as inadequate, average, and optimal CVH respectively[19-21].

Using linear regression models, we estimated the crude beta coefficients and corresponding 95% confidence intervals (CI) for the associations between the CVH score (assessed continuously) and CVD-related biomarkers (log-transformed, assessed continuously) in the overall cohort and by sex (model 1). We adjusted for sociodemographic factors [age (continuous), sex (for overall cohort), race/ethnicity (4 categories), education (9 categories), income (13 categories), and health insurance status (yes/no)] in model 2 and reported the adjusted beta coefficients. We examined the interaction of the CVH score categories with sex for all 6 biomarkers using the Wald test, by including interaction terms in model 2.

The associations between the LS7 metrics and CVD-related biomarkers were examined by comparing the intermediate and ideal categories of the metrics to the poor category. We reported only the adjusted model for women and men. In supplementary analyses, we examined the association between the CVH score and CVD-related biomarkers stratified by race/ethnicity and age (<65 and ≥65 years) within each sex, using multivariable linear regression models. For statistical analyses, STATA version

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15.0 was used (StataCorp LP, College Station, TX) and an alpha level of <.05 was considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the conduct of this research. We did not invite patients to comment on the study design nor did we consult them to develop patient related outcomes or interpret the results of this study. We did not invite patients to contribute to the writing or editing of this document for readability or accuracy.

Results

Baseline characteristics of participants are shown in **Table 1**. Over half of the participants were women (52%), and the mean age (SD) was 62 (10) years. Women had higher hsCRP, D-dimer, fibrinogen, NT-proBNP and IL-6 levels, while men had higher hs-cTnT and homocysteine levels. Women were less likely to be physically active and were more likely to have higher systolic blood pressure as well as higher healthy diet score and total cholesterol levels **(Table 1 and Supplementary Table 3)**.

Table 1- Characteristics of Study Participants

	Total (N= 5,379)	Women (n=2,775)	Men (n=2,604)	P value
Age, mean (SD), y	62 (10)	62 (10)	62 (10)	0.67
Age, y				
<65 n (%)	3,013 (56)	1,559 (56)	1,454 (56)	0.80

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≥65 n (%)	2,366 (44)	1,216 (44)	1,150 (44)	
Race/Ethnicity				
White n (%)	2,150 (40)	1092 (39)	1058 (41)	
Chinese American n (%)	733 (14)	372 (13)	361 (14)	0.17
Black n (%)	1,253 (23)	681 (25)	572 (22)	
Hispanic n (%)	1,243 (23)	630 (23)	613 (24)	
Education				<0.001
≥ Bachelor's degree n (%)	1,929 (36)	824 (30)	1,105 (42)	
< Bachelor's degree n (%)	3,450 (64)	1,951 (70)	1,499 (58)	
Income				<0.001
≥$40,000 n (%)	2,648 (49)	1,162 (42)	1,486 (57)	
<$40,000 n (%)	2,731 (51)	1,613 (58)	1,118 (43)	
Health insurance				
Yes n (%)	4,871 (91)	2,511 (90)	2,360 (90)	0.86
No n (%)	508 (9)	264 (10)	244 (10)	
Biomarkers, Mean (95% CI)				
hsCRP (mg/L)	3.7 (3.5, 3.8)	4.5 (4.2, 4.7)	2.8 (2.6, 3.0)	<0.001
D-dimer (µg/mL)	0.37 (0.34, 0.39)	0.38 (0.35, 0.41)	0.35 (0.32, 0.39)	0.29
Fibrinogen, mg/dL	345.2 (343.2, 347.1)	358.0 (355.2,360.8)	331.5 (328.8, 334.1)	<0.001
Homocysteine (µmol/L)	9.3 (9.2, 9.4)	8.7 (8.6, 8.8)	10.0 (9.9, 10.1)	<0.001
hs-cardiac Troponin T (ng/L)	6.6 (6.4, 6.8)	5.2 (5.0, 5.4)	8.1 (7.7, 8.5)	<0.001
NT-proBNP (pg/mL)	100.8 (94.2, 107.4)	114.0 (108.1, 119.8)	86.8 (74.8, 98.9)	<0.001
*IL-6 (pg/mL)	1.5 (1.5, 1.6)	1.6 (1.5, 1.6)	1.5 (1.4, 1.5)	0.002
LS7 metrics				
Current smoking n (%)	671 (12)	303 (11)	368 (14)	<0.001

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Body mass index (kg/m2)	28 (5)	29 (6)	28 (4)	<0.001
Physical activity (MET-min/week)	401 (589)	338 (490)	468 (672)	<0.001
Healthy diet score (0-5)	1.6 (0.9)	1.7 (0.9)	1.4 (0.9)	<0.001
Total cholesterol (mg/dL)	194 (36)	200 (36)	189 (35)	<0.001
Systolic blood pressure (mmHg)	126 (21)	127 (23)	125 (19)	0.03
Diastolic blood pressure (mmHg)	72 (10)	69 (10)	75 (9)	<0.001
Fasting blood glucose (mg/dL)	97 (31)	95 (29)	100 (32)	<0.001
CVH score				
Inadequate	2,509 (47)	1,284 (46)	1,225 (47)	
Average	1,772 (33)	915 (33)	857 (33)	0.78
Optimal	1,098 (20)	576 (21)	522 (20)	

Abbreviations: SD, standard deviation; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6; LS7, Life's Simple 7; CVH, Cardiovascular health; For IL-6, total sample size = 5,279; women, n = 2,733; men, n = 2,546

The associations between the total CVH score and the CVD-related biomarkers are reported in **Table 2**. After adjusting for sociodemographic factors (model 2), higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers except for NT-proBNP, where CVH was associated with a higher concentration. For example, in the overall cohort, a 1-unit increment in the CVH score corresponded to a 0.13 mg/L lower log (hsCRP) concentration and a 0.04 ng/L lower log(hs-cTnT) concentration, but a 0.02 pg/mL higher log (NT-proBNP) concentration

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Table 2- The associations between CVH score and CVD-related biomarkers

	hsCRP (mg/L)	D-dimer (μg/mL)	Fibrinogen (mg/dL)	Homocysteine (μmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Total, N= 5,379							
Model 1	**-0.16 (-0.17, -0.14)**	**-0.06 (-0.07, -0.05)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.06, -0.05)**	0.004 (-0.01, 0.01)	**-0.09 (-0.10, -0.08)**
Model 2	**-0.13 (-0.14, -0.12)**	**-0.03 (-0.04, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.01, -0.01)**	**-0.04 (-0.05, -0.03)**	**0.02 (0.01, 0.03)**	**-0.07 (-0.08, -0.06)**
Women, n= 2,775							
Model 1	**-0.18 (-0.20, -0.16)**	**-0.07 (-0.09, -0.06)**	**-0.03 (-0.03, -0.03)**	**-0.02 (-0.03, -0.02)**	**-0.04 (-0.05, -0.04)**	0.01 (0.01,0.03)	**-0.11 (-0.12, -0.10)**
Model 2	**-0.16 (-0.18, -0.14)**	**-0.03 (-0.05, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**0.03 (0.01, 0.04)**	**-0.08 (-0.09, -0.07)**
Men, n= 2,604							
Model 1	**-0.13 (-0.15, -0.11)**	**-0.04 (-0.05, -0.02)**	**-0.02 (-0.02, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.07 (-0.08, -0.06)**	-0.01 (-0.03, 0.01)	**-0.07 (-0.08, -0.06)**
Model 2	**-0.10 (-0.12, -0.08)**	**-0.02 (-0.03, -0.001)**	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.01, -0.004)**	**-0.06 (-0.07, -0.05)**	0.005 (-0.01, 0.02)	**-0.05 (-0.06, -0.04)**

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Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 for total population was adjusted for age, sex, race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score corresponds to a 0.16 mg/L lower log (hsCRP) concentration. Interactions by sex for all 7 biomarkers was significant at p <0.001. Results in bold font were statistically significant (p<0.05); †For IL-6, total sample size = 5,279.

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For all CVD-related biomarkers, there was a significant interaction for CVH with sex at p<0.001. For a unit increase in CVH score, the magnitude of concentrations were marginally lower for hsCRP, D-dimer and IL-6 in women compared to men, while for hs-cTnT, the magnitude of concentration was lower in men compared to women. No difference in magnitude of concentration was observed for fibrinogen and homocysteine for both sexes (**Table 2**). The **Figure** illustrates the sex-stratified mean biomarker concentrations by categories of the total CVH score. For all the biomarkers, participants with optimal scores had the smallest mean values.

The associations between the LS7 metrics and CVD-related biomarkers (log-transformed) in women and men are reported in **Tables 3 & 4.** For the ideal category of smoking, lower concentrations of D-dimer, fibrinogen, homocysteine, NT-proBNP and IL-6 were found in men but only lower concentration of homocysteine and IL-6 were found in women. For ideal smoking status, the magnitude of concentration of homocysteine was marginally lower in women than men, while the magnitude of concentration of IL-6 was marginally lower in men than women. For the ideal category of BMI, lower concentrations of all biomarkers except for NT-proBNP were found in women; whereas in men, lower concentrations of hsCRP, D-Dimer, fibrinogen, hs-cTnT and IL-6 were found. Both sexes had higher concentrations of NT-proBNP for ideal BMI. Additionally, for ideal BMI, the magnitudes of concentration of hsCRP, D-Dimer, fibrinogen and IL-6 were lower in women than men but hs-cTnT was lower in men. For the ideal category of physical activity, lower concentrations of hsCRP, fibrinogen, hs-cTnT and IL-6 were found in women while lower concentrations of fibrinogen, homocysteine, hs-cTnT and IL-6 were found in men. For ideal physical activity, the

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magnitudes of concentration of fibrinogen and hs-cTnT were marginally similar in women and men. The magnitude of concentration of IL-6 was marginally lower in men. An ideal diet score was associated with lower concentrations of hsCRP and IL-6 in women. For the ideal category of total cholesterol, lower concentrations of hs-cTnT were found in men while lower concentrations of fibrinogen and higher concentrations of NT-proBNP and IL-6 were found in women and men. For total cholesterol, the magnitudes of concentration of fibrinogen and IL-6 were marginally lower in women than men while the magnitude of concentration of NT-proBNP was higher in women than men, although confidence intervals between women and men overlapped.

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Table 3- The associations between LS7 metrics and CVD-related biomarkers in women, N=2,775

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
Smoking							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.07	0.11	0.03	0.03	0.005	0.003	0.03
	(-0.51, 0.38)	(-0.22, 0.44)	(-0.05, 0.11)	(-0.08, 0.14)	(-0.17, 0.18)	(-0.35, 0.36)	(-0.22, 0.29)
Ideal	0.02	0.03	-0.01	**-0.08**	-0.01	0.07	**-0.10**
	(-0.12, 0.16)	(-0.07, 0.13)	(-0.03, 0.02)	**(-0.11, -0.04)**	(-0.07, 0.04)	(-0.04, 0.18)	**(-0.18, -0.02)**
Body mass index							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.61**	**-0.17**	**-0.08**	**-0.04**	**-0.07**	0.06	**-0.34**
	(-0.71, -0.51)	**(-0.25, -0.10)**	**(-0.10, -0.07)**	**(-0.07, -0.02)**	**(-0.11, -0.03)**	(-0.03, 0.14)	**(-0.40, -0.29)**
Ideal	**-1.15**	**-0.32**	**-0.14**	**-0.06**	**-0.09**	**0.26**	**-0.61**
	(-1.25, -1.04)	**(-0.40, -0.23)**	**(-0.16, -0.12)**	**(-0.08, -0.03)**	**(-0.14, -0.05)**	**(0.17, 0.35)**	**(-0.67, -0.55)**
Physical activity							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.06	0.05	0.01	**-0.03**	-0.02	0.01	0.01

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	(-0.19, 0.07)	(-0.05, 0.15)	(-0.02, 0.03)	**(-0.07, -0.00)**	(-0.07, 0.03)	(-0.09, 0.12)	(-0.07, 0.08)
Ideal	**-0.16**	-0.04	**-0.03**	-0.02	**-0.05**	0.04	**-0.10**
	(-0.27, -0.06)	(-0.11, 0.04)	**(-0.05, -0.02)**	(-0.05, 0.00)	**(-0.09, -0.005)**	(-0.05, 0.12)	**(-0.16, -0.04)**
Diet							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	**-0.16**	-0.02	-0.01	-0.002	-0.01	-0.01	**-0.10**
	(-0.25, -0.07)	(-0.09, 0.04)	(-0.02, 0.01)	(-0.02, 0.02)	(-0.05, 0.02)	(-0.09, 0.06)	**(-0.15, -0.05)**
Ideal	**-0.40**	-0.09	-0.02	-0.07	-0.11	-0.05	**-0.24**
	(-0.74, -0.07)	(-0.33, 0.16)	(-0.07, 0.04)	(-0.16, 0.01)	(-0.24, 0.02)	(-0.32, 0.21)	**-0.43, -0.06)**
Total Cholesterol							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	0.02	-0.04	-0.02	-0.0001	-0.01	**0.12**	**0.09**
	(-0.11, 0.14)	(-0.13, 0.05)	(-0.04, 0.00)	(-0.03, 0.03)	(-0.06, 0.04)	**(0.02, 0.21)**	**(0.02, 0.16)**
Ideal	-0.08	-0.02	**-0.06**	0.01	-0.006	**0.24**	**0.13**
	(-0.21, 0.04)	(-0.11, 0.08)	**(-0.08, -0.04)**	(-0.02, 0.04)	(-0.04, 0.06)	**(0.14, 0.34)**	**(0.06, 0.20)**
Blood pressure							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	**-0.13**	-0.05	-0.003	-0.005	**-0.09**	**-0.28**	**-0.07**

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	(-0.24, -0.03)	(-0.13, 0.03)	(-0.02, 0.02)	(-0.03, 0.02)	**(-0.13, -0.04)**	**(-0.37, -0.20)**	**(-0.13, -0.01)**
Ideal	**-0.45**	**-0.11**	**-0.02**	**-0.04**	**-0.12**	**-0.30**	**-0.21**
	(-0.56, -0.35)	**(-0.19, -0.03)**	**(-0.04, -0.002)**	**(-0.07, -0.01)**	**(-0.16, -0.08)**	**(-0.39, -0.21)**	**(-0.27, -0.15)**
Blood glucose							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	(reference)	1 (reference)
Intermediate	-0.04	0.01	-0.01	0.04	**-0.16**	0.10	-0.0002
	(-0.22, 0.14)	(-0.13, 0.14)	(-0.04, 0.02)	(-0.01, 0.08)	**(-0.23, -0.09)**	-0.04, 0.25)	(-0.10, 0.10)
Ideal	**-0.43**	-0.03	**-0.07**	0.002	**-0.19**	**0.29**	**-0.28**
	(-0.57, -0.28)	(-0.14, 0.08)	**(-0.09, -0.04)**	(-0.03, 0.04)	**(-0.25, -0.13)**	**(0.17, 0.40)**	**(-0.36, -0.20)**

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model was adjusted for age, race/ethnicity, education, income, and health insurance status. †For IL-6, sample size = 2,733

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Table 4- The associations between LS7 metrics and CVD-related biomarkers in Men, N=2,604

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
Smoking							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.16	-0.17	-0.04	**-0.16**	-0.07	**-0.52**	**-0.21**
	(-0.50, 0.17)	(-0.45, 0.11)	(-0.10, 0.02)	**(-0.25, -0.07)**	(-0.25, 0.12)	**(-0.86, -0.19)**	**(-0.42, -0.005)**
Ideal	-0.27	**-0.17**	**-0.05**	**-0.05**	0.02	**-0.15**	**-0.19**
	(-0.39, 0.15)	**(-0.27, -0.07)**	**(-0.07, -0.03)**	**(-0.08, -0.02)**	(-0.04, 0.08)	**(-0.27, -0.03)**	**(-0.27, -0.12)**
Body mass index							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.50**	**-0.11**	**-0.06**	-0.01	**-0.17**	0.07	**-0.30**
	(-0.59, -0.40)	**(-0.20, -0.03)**	**(-0.08, -0.05)**	(-0.04, 0.01)	**(-0.23, -0.12)**	(-0.02, 0.17)	**(-0.36, -0.24)**
Ideal	**-0.80**	**-0.17**	**-0.08**	-0.02	**-0.29**	**0.25**	**-0.37**
	(-0.92, -0.69)	**(-0.26, -0.07)**	**(-0.10, -0.06)**	(-0.05, 0.01)	**(-0.35, -0.23)**	**(0.14, 0.36)**	**(-0.43, -0.30)**
Physical activity							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.09	-0.06	-0.002	-0.01	-0.07	0.03	-0.02

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	(-0.04, 0.23)	(-0.17, 0.06)	(-0.03, 0.02)	(-0.05, 0.02)	(-0.14, 0.01)	(-0.10, 0.17)	(-0.10, 0.07)
Ideal	-0.03	-0.05	**-0.02**	**-0.02**	**-0.07**	0.05	**-0.14**
	(-0.14, 0.07)	(-0.13, 0.04)	**(-0.04, -0.004)**	**(-0.05, -0.00)**	**(-0.13, -0.02)**	(-0.05, 0.15)	**(-0.20, -0.07)**
Diet							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	**-0.11**	0.002	-0.01	-0.003	-0.02	0.04	**-0.05**
	(-0.19, -0.02)	(-0.07, 0.07)	(-0.03, 0.00)	(-0.02, 0.02)	(-0.07, 0.02)	(-0.04, 0.12)	**(-0.10, -0.003)**
Ideal	-0.57	-0.50	0.01	0.06	-0.17	0.31	-0.14
	(-1.25, 0.11)	(-1.07, 0.07)	(-0.12, 0.14)	(-0.11, 0.24)	(-0.54, 0.20)	(-0.36, 0.98)	(-0.56, 0.27)
Total Cholesterol							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.03	0.01	**-0.04**	-0.003	**-0.10**	-0.09	0.08
	(-0.17, 0.11)	(-0.11, 0.12)	**(-0.06, -0.01)**	(-0.04, 0.03)	**(-0.18, -0.02)**	(-0.22, 0.05)	(-0.01, 0.16)
Ideal	-0.01	0.05	**-0.05**	-0.006	**-0.10**	**0.19**	**0.17**
	(-0.15,0.13)	(-0.06, 0.17)	**(-0.08, -0.03)**	(-0.04, 0.03)	**(-0.17, -0.02)**	**(0.05, 0.32)**	**(0.08, 0.25)**
Blood pressure							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	-0.10	-0.06	-0.01	**-0.03**	**-0.12**	**-0.37**	**-0.07**

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	(-0.20, 0.01)	(-0.14, 0.03)	(-0.03, 0.004)	**(-0.06, -0.005)**	**(-0.18, -0.07)**	**(-0.47, -0.27)**	**(-0.13, -0.01)**
Ideal	**-0.23**	-0.01	**-0.03**	**-0.04**	**-0.22**	**-0.40**	**-0.09**
	(-0.34, -0.13)	(-0.10, 0.08)	**(-0.05, -0.01)**	**(-0.07, -0.02)**	**(-0.27, -0.16)**	**(-0.50, -0.30)**	**(-0.16, -0.03)**
Blood glucose							
Poor	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	0.07	0.03	-0.01	0.04	**-0.23**	-0.06	-0.04
	(-0.08, 0.22)	(-0.09, 0.16)	(-0.04, 0.02)	(-0.003, 0.08)	**(-0.31, -0.15)**	(-0.21, 0.09)	(-0.14, 0.05)
Ideal	**-0.17**	0.04	**-0.03**	0.01	**-0.36**	0.04	**-0.15**
	(-0.30, -0.04)	(-0.07, 0.15)	**(-0.06, -0.01)**	(-0.02, 0.05)	**(-0.43, -0.29)**	(-0.09, 0.17)	**(-0.23, -0.07)**

Abbreviations: LS7, Life's Simple 7; CVD, cardiovascular disease; hsCRP; high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6. *All biomarkers were log-transformed. LS7 metrics were compared as categories to their respective reference group. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model adjusted for age, race/ethnicity, education, income, and health insurance status. For IL-6, n = 2,545.

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For ideal blood pressure, a lower concentration of all biomarkers was found in women; whereas in men a lower concentration was observed for all biomarkers except D-dimer. Additionally, for ideal blood pressure, the magnitudes of concentration of fibrinogen, hs-cTnT and NT-proBNP were lower in men than women while the magnitude of concentration of IL-6 was lower in women than men. For ideal blood glucose levels, a higher concentration of NT-proBNP was found in women while a lower concentration of hsCRP, fibrinogen, hs-cTnT and IL-6 was observed in both sexes. For ideal blood glucose, the magnitudes of concentration of hsCRP, fibrinogen and IL-6 were lower in women than men.

The supplementary analyses show the associations between CVH and CVD-related biomarkers stratified by race/ethnicity and age for women and men. The results were similar for both sexes and mostly showed a statistically significant lower concentration of CVD-related biomarkers for a unit increment in CVH score. Among White and Chinese-American Women as well as women <65 years old, a unit increment in CVH score was associated with higher concentrations of NT-proBNP. **(Supplementary Tables S4-S7)**.

Discussion

In this cross-sectional analysis of 5,379 adult women and men free of clinical CVD at baseline, after adjusting for sociodemographic factors, we found an inverse association between the CVH score and most of the CVD-related biomarkers. Higher CVH scores were associated with lower concentrations of all of the CVD-related biomarkers in women and men, except for NT-proBNP that showed a positive relationship. We found a similarly inverse relationship between the LS7 metrics and

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CVD-related biomarkers except for NT-proBNP where the associations were both direct and inverse. Additionally, we observed a direct association between ideal cholesterol and IL-6 in both sexes. In the stratified analyses by race/ethnicity and age, the associations observed were similar for both sexes.

Our results are similar to a study conducted to investigate the association between CVH metrics and biomarkers (hsCRP and homocysteine) among 3,009 Chinese adults between the ages of 24 and 85 years, without a history of CVD[7]. In their study, after adjusting for age, sex and education, a unit increment in CVH score was inversely related to biomarker concentration [CRP: -0.182 (-0.652, -0.457); and homocysteine: -0.092, (-0.930, -0.426)]. A similar association was found in women and men, although the association was stronger in women.

A cross-sectional study of 2,680 participants from the Framingham Heart Study also examined the association between CVH and CVD-related biomarkers (BNP, CRP, D-dimer, fibrinogen and homocysteine)[22]. Similar to our findings in MESA, the Framingham researchers found that the CVH score had a direct association with higher circulating concentrations of natriuretic peptides but was inversely related to blood concentrations of the other biomarkers examined, after adjusting for age and sex[22]. For a unit increase in CVH score, the beta coefficients for the biomarkers are as follows: BNP, 0.057 pg/mL (0.035, 0.080); CRP, -0.248 mg/L (-0.279, -0.217); D-dimer, -0.030 ng/mL (-0.046, -0.014); fibrinogen, -0.028 mg/dL (-0.033,-0.023) and homocysteine, -0.021 mmol/L (-0.029,-0.012). The authors concluded that the inverse association of CVH with incident CVD events was at least partly attributable to the favorable relationship of CVH and subclinical biomarkers of risk[22]. Notably, none of the

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aforementioned studies examined for effect modification by sex in the association of CVH with subclinical biomarkers, as we newly present here. One prior study conducted in a Chinese population[7] did stratify the association between CVH and biomarkers by sex; however, they did not test for effect modification. In contrast to our study, that study did not include D-dimer, fibrinogen, hs-cTnT, NT-proBNP and IL-6 in their analysis[7].

Our main finding showed a better CVH score was associated with lower concentrations of all CVD-related biomarkers (except NT-proBNP) in both women and men. Despite statistically significant interactions by sex for the total CVH score, qualitatively the magnitude of lower concentrations for these biomarkers per 1 unit increment in CVH were generally similar among women and men. However, for the metric of ideal BMI, the magnitude of lower concentrations hsCRP, D-Dimer, fibrinogen and IL-6 per unit of CVH was greater in women than men. In the univariate analysis, women in this study had slightly higher BMI than men. Studies have shown that estrogen and adipose tissue may increase the circulating levels of inflammatory biomarkers[9, 23], and thus a more favorable BMI might have greater impact on these biomarker concentrations in women than men.

Additionally we note that, in women, ideal BMI, a health behavior, was associated with a greater magnitude of reduction in hsCRP, D-dimer, fibrinogen and IL-6 compared to ideal blood pressure, ideal blood glucose (health factors) while in men, the same association was observed for hsCRP and IL-6. This may suggest that attaining ideal health behaviors such as ideal BMI may lead to more reductions in the biomarkers of CVD risk compared to ideal health factors. However, more elaborate studies would be needed to explore these findings so definite conclusions can be

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reached because of the importance of biomarkers such as hsCRP, fibrinogen and IL-6 in mediating the relationship between CVH and CVD[24]. For example, in a prior study of over 9300 men followed for 10-years, individuals with ideal CVH had lower risk for all CVD subtypes examined and the lower risk of coronary heart disease was mediated in part through lower inflammatory and hemostatic factors[24].

In the univariate analyses, homocysteine concentrations were higher in men which may be attributable to a higher prevalence of smoking and poorer healthy diet score[25]. In the adjusted regression analyses a unit increment in CVH score corresponded to a slightly lower concentration of homocysteine in women. In addition, the higher prevalence of smoking found in men in this study may be responsible for their higher baseline hs-cTnT concentrations[26]. Although in adjusted regression analysis, the magnitude of concentration of hs-cTnT per 1-unit increment in CVH score was lower in men. Moreover, we found that ideal cholesterol was directly associated with IL-6 in both sexes. Although this finding has been previously documented among healthy individuals, other studies have reported an inverse association in pathological conditions, which according to prior research may suggest polymorphism in the IL-6 gene differentially affects lipid metabolism[27].

Interestingly, a better CVH score was associated with higher concentrations of NT-proBNP, particularly in women. At first this may seem paradoxical, as in the setting of disease states, BNP levels are frequently elevated. However, in normal states, NT-proBNP actually plays a favorable cardioprotective role by inhibiting cardiac hypertrophy and fibrosis and promoting vasodilation and natriuresis. In patients with heart failure, there is relative BNP deficiency and BNP resistance, resulting in a compensatory

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increase in NT-proBNP concentrations to restore homeostasis[28]. We found that baseline concentrations of NT-proBNP were higher in women than men, as had been previously reported in MESA[10], though average concentrations for both sexes were within normal limits in this cohort free of clinical heart failure at baseline. Other previous studies have also reported higher NT-proBNP concentrations in women[22, 29], as well as a prior analysis in the MESA cohort that showed a more androgenic ("male-like") sex hormone profile was associated with lower NT-proBNP concentrations[10].

The sex-specific differences observed in the association of CVH and CVD-related biomarkers may reflect different pathways of CVD risk. Additional research that explain the potential sex-specific mechanisms underlying the association between CVH and CVD-related biomarkers may improve our knowledge of the development of CVD in women and men[30]. An understanding of these pathways may also help clinicians tailor interventions specific to the prevention and treatment of CVD risk factors in women and men[30]. Our study emphasizes the importance of promoting ideal CVH, which may be more beneficial in women, particularly with research showing that women have poorer cardiovascular outcomes compared to men. Encouraging the attainment of ideal CVH may reverse this trend and lead to a decrease in CVD burden.

In the interpretation of our findings, some limitations should be noted. First, neither temporality nor causal inferences between the association of CVH and CVD-related biomarkers can be determined because of the cross-sectional observational study design. Second, we cannot rule out recall bias from the use of self-administered questionnaires to collect data on smoking, diet, and physical activity. Third, the findings of this study may not be generalizable to younger people or adults of very advanced

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age because our participants were between ages of 45 and 84 years old. Fourth, multiple statistical tests were performed and some findings might be expected to occur by chance; however, our findings were generally consistent between women and men and across age and race/ethnic subgroups. Lastly, CVH was assessed once at baseline and may not be representative of the future CVH status of study participants.

Conclusions

We found that more favorable CVH scores were associated with lower concentrations of CVD-related biomarkers in both women and men, except for NT-proBNP which showed a direct relationship. These favorable associations of CVH with biomarkers of risk may be an intermediary step in the prevention of clinical CVD events. Overall, our findings were qualitatively similar between the sexes. These data suggest that promotion of ideal CVH would have similarly favorable impact on the reduction of biomarkers of risk among women and men. However, long-term outcome studies are needed to improve our understanding of the underlying sex-specific mechanisms and the clinical implications of these findings.

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Author contributions

Study conception and design: OO, OO and EDM; Acquisition of data and analysis: OO and OO; Interpretation of data: OO, OO, MT, EB and EDM; Drafting of manuscript: OO, OO and EDM; Critical revision and approval of final version submitted: OO, OO, MT, EB and EDM.

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Conflicts of interest:

None of the authors report any conflicts of interest with this work.

Ethics approval:

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The MESA protocol was approved by the institutional review boards of all the recruitment centers.

Data sharing statement:

The MESA study participates in data sharing through the National Heart, Lung, Blood Institute (NHLBI) Biologic Specimen and Data Repository Coordinating Center (BioLINCC). Requests for access to the data can be made through their website: https://biolincc.nhlbi.nih.gov/studies/mesa/.

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Figure Legend

Sex-stratified mean biomarker levels by cardiovascular health score categories (inadequate (0-8), average (9-10) and optimal (11-14). Lighter color=Women; Darker color=Men. hsCRP=high-sensitivity C-reactive protein; hs-cTnT=high-sensitivity cardiac troponin T; NT-proBNP= N-terminal pro B-type natriuretic peptide; IL-6, interleukin-6. Mean values for biomarkers were not log transformed

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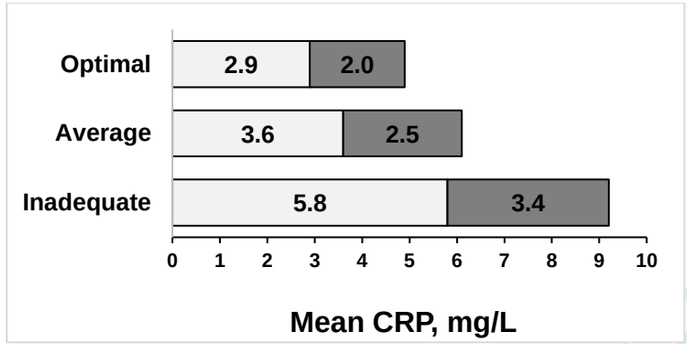

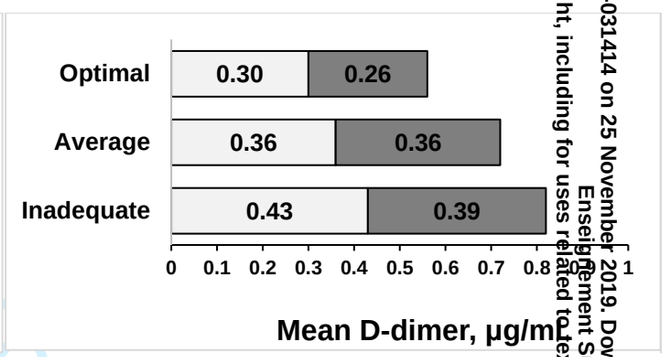

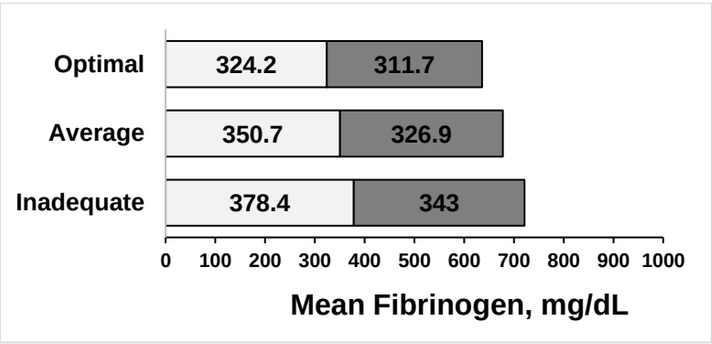

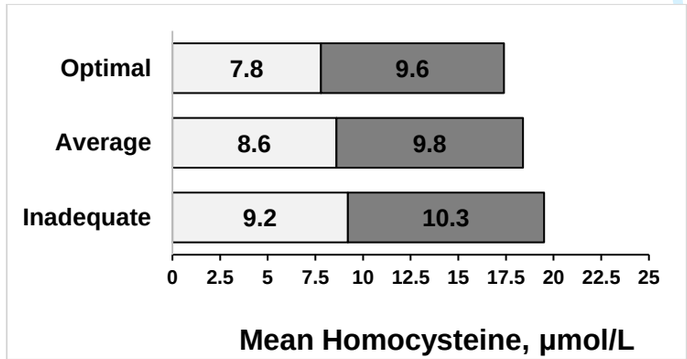

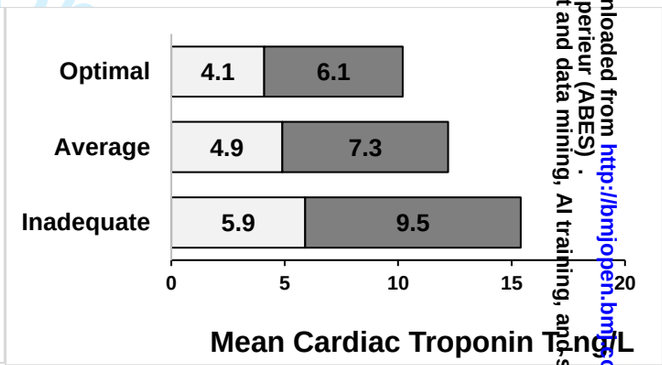

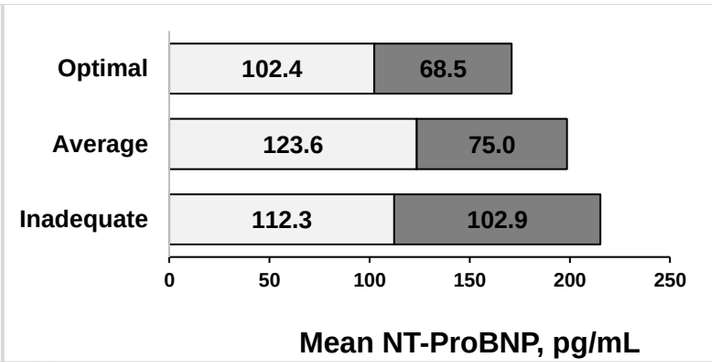

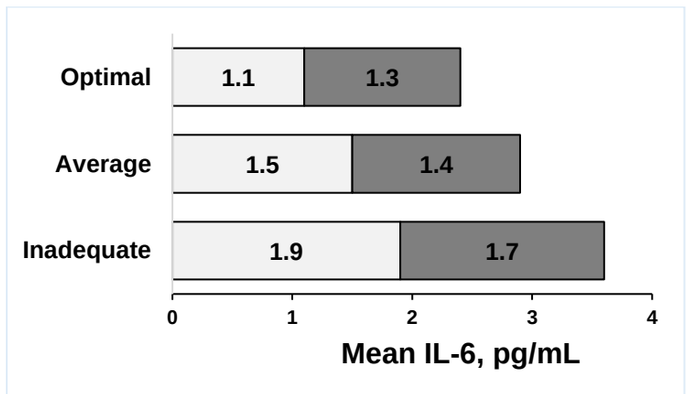

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SUPPLEMENTARY MATERIAL

Supplementary Methods: Assessment of cardiovascular health

Table S1: Baseline categories of income and education

Table S2: Definition of Life's Simple 7 Metrics

Table S3: Distribution of Life's Simple 7 Metrics by Sex

Table S4: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

Table S5: The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

Table S6: The associations between CVH score and CVD-related biomarkers by Age for Women

Table S7: The associations between CVH score and CVD-related biomarkers by Age for Men

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Supplementary Methods: Assessment of cardiovascular health

Information on the LS7 metrics were collected from study participants at baseline. Based on AHA guidelines, ideal CVH is achieved if the following criteria are met for the LS7 metrics: non-smoking, physical activity at goal levels, BMI <25kg/m^2 and a healthy diet consistent with guidelines, total cholesterol <200mg/dL (not on lipid lowering medications), blood pressure <120/<80mmHg (not on anti-hypertensive medications), and fasting blood glucose <100mg/dL (not on diabetes medications) [1]. Smoking status was assessed by self-report and categorized as; 1) participants who never smoked or quit more than 12 months (non-smokers), 2) participants who quit within 12 months (former smokers) and 3) current smokers [1]. Physical activity was evaluated using a self-report survey instrument adapted from the Cross-Cultural Activity Participation Study [2] containing 28 questions on time and frequency of activities during a week in the previous month. The total minutes of moderate and vigorous exercise in metabolic equivalents of task (MET/min) were estimated and used for our analyses [3].

BMI (kg/m^2) was calculated using the weight and height measurements. Dietary habits were evaluated using a 120-item validated food frequency questionnaire modified from the Insulin Resistance Atherosclerosis Study instrument [4, 5]. Based on recommended dietary guidelines, a healthy diet was made up of fruits and vegetables, fish, whole grains and intake of sodium <1500mg per day and sugar-sweetened beverages ≤450 kcal (36 oz.) per week [1]. For blood pressure, with participants in a seated position, 3 measurements were obtained after resting for 5 minutes and the average values of the last two readings were recorded. For total cholesterol (mg/dL)

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and blood glucose (mg/dL) measurements, blood samples were collected following a 12 hour fast.

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Table S1 - Baseline categories of income and education, N=5,379

Income			Education		
1	< $5,000	131 (2%)	1	NO SCHOOLING	60 (1%)
2	$5,000-$7,999	214 (4%)	2	GRADES 1-8	558 (10%)
3	$8,000-$11,999	310 (6%)	3	GRADES 9-11	367 (7%)
4	$12,000-$15,999	399 (7%)	4	COMPLETED HIGH SCHOOL/GED	950 (18%)
5	$16,000-$19,999	275 (5%)	5	SOME COLLEGE BUT NO DEGREE	855 (16%)
6	$20,000-$24,999	404 (8%)	6	TECHNICAL SCHOOL CERTIFICATE	385 (7%)
7	$25,000-$29,999	311 (6%)	7	ASSOCIATE DEGREE	275 (5%)
8	$30,000-$34,999	374 (7%)	8	BACHELOR'S DEGREE	951 (18%)
9	$35,000-$39,999	313 (6%)	9	GRADUATE OR PROFESSIONAL SCHOOL	978 (18%)
10	$40,000-$49,999	517 (10%)			
11	$50,000-$74,999	883 (16%)			
12	$75,000-$99,999	483 (9%)			
13	$100,000+	765 (14%)			

% are rounded to whole numbers

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Table S2 – Definition of the Life's Simple 7 metrics

LS7 Metrics	Score	Definition
Smoking	0	Current smoker
	1	Former smoker, quit ≤12 months ago
	2	Never smoker or quit >12 months ago
Body Mass Index	0	≥30 kg/m^2
	1	25.0–29.99 kg/m^2
	2	<25.0 kg/m^2
Physical Activity	0	No exercise
	1	1–149 min of moderate exercise or 1–74 min of vigorous exercise/week
	2	150+ min of moderate exercise or 75+ min of vigorous exercise/week
Diet	0	0–1 components of healthy diet
	1	2–3 components of healthy diet
	2	4–5 components of healthy diet
Total Cholesterol	0	≥240 mg/dL
	1	200–239 mg/dL or treated to <200mg/dL
	2	<200 mg/dL, unmedicated
Blood Pressure	0	SBP ≥140 mmHg or DBP ≥90 mmHg
	1	SBP 120–139 mmHg or DBP 80–89 mmHg or treated to <120/80 mm Hg
	2	<120/80 mm Hg, unmedicated
Blood Glucose	0	≥126 mg/dL fasting
	1	100–125 mg/dL fasting or treated to <100 mg/dL
	2	<100 mg/dL fasting, unmedicated

Adapted from Lloyd Jones et al[1] and Unger et al[3], LS7 indicates Life's Simple 7; DBP, diastolic blood pressure, and SBP, systolic blood pressure. Poor=0 points; Intermediate=1 point; ideal =2 points. *When combining vigorous and moderate exercise, vigorous exercise was weighted double.

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Table S3 - Distribution of Life's Simple 7 Metrics by Sex

	Total (N=5,379)	Women (n= 2,775)	Men (n= 2,604)	P value
Total CVH score, mean (SD)	8.6 (2.2)	8.6 (2.3)	8.6 (2.1)	0.85
LS7 metrics, n (%)				
Smoking				
Poor	671 (12)	303 (11)	368 (14)	
Intermediate	68 (1)	27 (1)	41 (2)	<0.001
Ideal	4640 (86)	2445 (88)	2195 (84)	
Body mass index				
Poor	1657 (31)	958 (35)	699 (27)	
Intermediate	2127 (40)	936 (34)	1191 (46)	<0.001
Ideal	1595 (30)	881 (32)	714 (28)	
Physical activity				
Poor	1231 (23)	684 (25)	547 (21)	
Intermediate	909 (17)	529 (19)	380 (15)	<0.001
Ideal	3239 (60)	1562 (56)	1677 (64)	
Diet				
Poor	2425 (45)	1029 (37)	1396 (54)	
Intermediate	2898 (54)	1699 (61)	1199 (46)	<0.001
Ideal	56 (1)	47 (2)	9 (0.4)	
Total Cholesterol				
Poor	729 (14)	466 (17)	263 (10)	
Intermediate	2107 (39)	1143 (41)	964 (37)	<0.001
Ideal	2543 (47)	1166 (42)	1377 (53)	
Blood pressure				
Poor	1996 (37)	1085 (39)	911 (35)	
Intermediate	1505 (28)	695 (25)	810 (31)	<0.001
Ideal	1878 (35)	995 (36)	883 (34)	
Blood glucose				
Poor	572 (11)	275 (10)	297 (11)	
Intermediate	846 (16)	359 (13)	487 (19)	<0.001
Ideal	3961 (74)	2141 (77)	1820 (70)	

Abbreviations: CVH indicates cardiovascular health; SD, standard deviation; LS7, Life's Simple 7; percentages were rounded up to whole numbers

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Table S4 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
White, n=1,092							
Model 1	**-0.18 (-0.21, -0.15)**	**-0.06 (-0.08, -0.04)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.03, -0.01)**	**-0.05 (-0.06, -0.04)**	-0.01 (-0.01, 0.04)	**-0.10 (-0.12, -0.08)**
Model 2	**-0.19 (-0.23,-0.16)**	**-0.04 (-0.07, -0.02)**	**-0.03 (-0.04, -0.02)**	**-0.01 (-0.02, -0.002)**	**-0.03 (-0.04, -0.02)**	**-0.05 (0.03, 0.07)**	**-0.09 (-0.11, -0.07)**
Chinese-American, n=372							
Model 1	**-0.11 (-0.17, -0.06)**	**-0.08 (-0.13, -0.04)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.04, -0.02)**	**-0.05 (-0.07, -0.03)**	-0.01 (-0.06, 0.05)	**-0.07 (-0.10, -0.04)**
Model 2	**-0.13 (-0.18, -0.07)**	-0.04 (-0.09, 0.01)	**-0.01 (-0.02, -0.004)**	**-0.01 (-0.03, -0.00)**	**-0.03 (-0.005, -0.01)**	**-0.07 (0.02, 0.12)**	**-0.06 (-0.10, -0.03)**
Black, n=681							
Model 1	**-0.15 (-0.19, -0.11)**	**-0.06 (-0.09, -0.03)**	**-0.03 (-0.03, -0.02)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.06, -0.02)**	-0.02 (-0.06, 0.02)	**-0.09 (-0.11, -0.07)**
Model 2	**-0.15 (-0.19, -0.10)**	**-0.05 (-0.08, -0.02)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.02, -0.004)**	**-0.03 (-0.05, -0.01)**	-0.005 (-0.03, 0.04)	**-0.08 (-0.11, -0.06)**
Hispanic, n= 630							
Model 1	**-0.13 (-0.17, -0.10)**	**-0.03 (-0.07, -0.003)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.04 (-0.05, -0.02)**	**-0.04 (-0.07, -0.003)**	**-0.09 (-0.11, -0.07)**
Model 2	**-0.14 (-0.18, -0.10)**	-0.004 (-0.04, 0.03)	**-0.01 (-0.02, -0.005)**	**-0.01 (-0.02, -0.002)**	**-0.02 (-0.04, -0.005)**	-0.01 (-0.03, 0.04)	**-0.08 (-0.10, -0.06)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-ProBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.
*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White women corresponds to a 0.18 mg/L lower logCRP concentration. † For IL-6, Women: White, n=1,080; Chinese-American, n=371; Black, n=664; Hispanic, n=618

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Table S5 - The associations between CVH score and CVD-related biomarkers by Race/Ethnicity for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-ProBNP (pg/mL)	IL-6† (pg/mL)
White, n=1,058							
Model 1	**-0.15 (-0.18, -0.12)**	-0.02 (-0.05, 0.004)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.02)**	0.0 (-0.03, 0)	**-0.08 (-0.10,-0.06)**
Model 2	**-0.14 (-0.17, -0.11)**	-0.02 (-0.05, 0.005)	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.04 (-0.06, -0.03)**	0.0 (-0.02, 0.0)	**-0.07 (-0.09, -0.05)**
Chinese-American, n= 361							
Model 1	**-0.09 (-0.15, -0.04)**	-0.01 (-0.06, 0.04)	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.001)**	**-0.06 (-0.08, -0.03)**	0.0 (-0.02, 0.0)	-0.04 (-0.07, 0.0002)
Model 2	**-0.11 (-0.17, -0.05)**	0.001 (-0.05, 0.05)	**-0.02 (-0.03, -0.01)**	**-0.02 (-0.03, -0.002)**	**-0.06 (-0.09, -0.04)**	0.0 (-0.03, 0.0)	-0.03 (-0.07, 0.004)
Black, n= 572							
Model 1	**-0.07 (-0.12, -0.03)**	**-0.05 (-0.09, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.01 (-0.02, -0.001)**	**-0.09 (-0.11, -0.06)**	-0.03 (-0.08, 0.01)	**-0.04 (-0.07, -0.02)**
Model 2	**-0.06 (-0.11, -0.02)**	-0.02 (-0.06, 0.01)	**-0.01 (-0.02, -0.01)**	-0.01 (-0.02, 0.003)	**-0.07 (-0.09, -0.05)**	0.02 (-0.03, 0.07)	**-0.03 (-0.06, -0.01)**
Hispanic, n=613							
Model 1	**-0.08 (-0.12, -0.04)**	-0.03 (-0.06, 0.01)	**-0.02 (-0.03, -0.01)**	-0.001 (-0.01, 0.01)	**-0.08 (-0.11, -0.06)**	**-0.06 (-0.11, -0.01)**	**-0.06 (-0.08, -0.03)**
Model 2	**-0.08 (-0.12, -0.04)**	-0.01 (-0.04, 0.02)	**-0.02 (-0.02, -0.01)**	0.003 (-0.01, 0.01)	**-0.08 (-0.10, -0.05)**	-0.03 (-0.07, 0.01)	**-0.05 (-0.07, -0.02)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for age, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in White men corresponds to a 0.15mg/L lower logCRP concentration.

† For IL-6, Men: White, n=1,042; Chinese American, n=355; Black, n=554; Hispanic, n=595

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Table S6 - The associations between CVH score and CVD-related biomarkers by Age for Women

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Age <65 years, n=1,559							
Model 1	**-0.22 (0.24, -0.19)**	**-0.07 (-0.09, -0.05)**	**-0.03 (-0.04, -0.03)**	**-0.02 (-0.02, -0.01)**	**-0.03 (-0.03, -0.02)**	**-0.03 (-0.06, 0.06)**	**-0.11 (-0.13, -0.10)**
Model 2	**-0.19 (-0.21, -0.16)**	**-0.04 (-0.06, -0.02)**	**-0.03 (-0.03, -0.02)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.03, -0.01)**	**-0.03 (-0.04, 0.05)**	**-0.09 (-0.10, -0.07)**
Age ≥ 65 years, n= 1,216							
Model 1	**-0.14 (-0.17, -0.11)**	**-0.06 (-0.08, -0.04)**	**-0.02 (-0.03, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.04)**	0.02 (-0.01, 0.04)	**-0.09 (-0.11, -0.07)**
Model 2	**-0.12 (-0.15, -0.09)**	**-0.03 (-0.06, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.02, -0.01)**	**-0.05 (-0.06, -0.03)**	0.01 (-0.01, 0.03)	**-0.07 (-0.09, -0.06)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.

*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in women <65 years corresponds to a 0.22mg/L lower logCRP concentration. † For IL-6, Women: Age <65, n=1,539 Age ≥ 65 years, n=1,194

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Table S7 - The associations between CVH score and CVD-related biomarkers by Age for Men

	hsCRP (mg/L)	D-dimer (µg/mL)	Fibrinogen (mg/dL)	Homocysteine (µmol/L)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)	IL-6† (pg/mL)
Age <65 years, n= 1,454							
Model 1	**-0.14 (-0.17, -0.12)**	**-0.02 (-0.05, -0.003)**	**-0.02 (-0.03, -0.02)**	**-0.01 (-0.01, -0.001)**	**-0.07 (-0.08, -0.06)**	-0.02 (-0.04, 0.01)	**-0.07 (-0.09, -0.06)**
Model 2	**-0.12 (-0.15, -0.10)**	-0.02 (-0.04, 0.007)	**-0.02 (-0.02, -0.01)**	**-0.01 (-0.01, -0.00)**	**-0.07 (-0.08, -0.05)**	-0.01 (-0.04, 0.02)	**-0.06 (-0.08, -0.04)**
Age ≥ 65 years, n= 1,150							
Model 1	**-0.11 (-0.14, -0.08)**	**-0.05 (-0.07, -0.02)**	**-0.02 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.06 (-0.08, -0.04)**	0.01 (-0.02, 0.04)	**-0.06 (-0.08, -0.04)**
Model 2	**-0.07 (-0.10, -0.04)**	**-0.03 (-0.05, -0.001)**	**-0.01 (-0.02, -0.01)**	**-0.02 (-0.02, -0.01)**	**-0.05 (-0.07, -0.03)**	0.01 (-0.02, 0.05)	**-0.04 (-0.06, -0.02)**

Abbreviations: CVH, cardiovascular health; CVD, cardiovascular disease; hsCRP; High-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; IL-6, interleukin 6.
*All biomarkers were log-transformed; CVH was assessed as a continuous variable. Results are presented as beta-coefficients (95% CI) from multivariable adjusted linear regression. Model 1 was unadjusted; Model 2 was adjusted for race/ethnicity, education, income, and health insurance status. Interpretation: For example, a 1-unit increment in the CVH score in men <65 years corresponds to a 0.14mg/L lower logCRP concentration. † For IL-6, Men: Age <65, n=1,425; Age ≥ 65 years, n=1,121

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10-23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

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		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-23
Discussion			
Key results	18	Summarise key results with reference to study objectives	23-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	27-28
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24-28
Generalisability	21	Discuss the generalisability (external validity) of the study results	27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	29

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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