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## Life's Essential 8, genetic susceptibility, and incident cardiovascular disease: a prospective study

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### Abstract

**Background:** The American Heart Association recently released a new cardiovascular health (CVH) metric, Life's Essential 8 (LE8) for health promotion. However, the association between levels of LE8 and the risk of CVD outcomes is not known from a large prospective cohort. We aim to analyze the relationship between CVH, indicated by LE8, and risks of coronary heart disease (CHD), stroke, and cardiovascular disease (CVD). Moreover, we sought to test whether the genetic susceptibility to CHD or stroke could be modified by LE8.

**Methods:** A total of 137,794 participants free of CVD from the UK Biobank were included. CVH was scored using LE8 and categorized as low, moderate, and high.

**Results:** During a median of 10 years, 8,595 CVD cases (6,968 CHD and 1,948 strokes) were documented. A higher LE8 score was associated with remarkably lower risks of CHD, stroke, and CVD ( $p < 0.001$  for all). Comparing the high CVH to the low CVH, the HRs (95% CI) were 0.34 (0.30, 0.38) for CHD, 0.45 (0.37, 0.54) for stroke, and 0.36 (0.33, 0.40) for CVD. Moreover, the model with LE8 achieved higher accuracy and outperformed the model with Life's Simple 7 for CHD, stroke, and CVD ( $p < 0.001$  for all). The protective associations of the LE8 score with CVD outcomes were more pronounced among women ( $p$ -interaction  $< 0.001$  for CHD and 0.0013 for CVD, respectively), and among younger adults ( $p$ -interaction  $< 0.001$ , 0.007, and  $< 0.001$  for CHD, stroke, and CVD, respectively). In addition, a significant interaction was found between the genetic risk of CHD and the LE8 score ( $p$ -interaction  $< 0.001$ ). The inverse association was stronger among those with a lower genetic risk of CHD.

**Conclusions:** High level of CVH, defined by LE8, was associated with significantly lower risks of CHD, stroke, and CVD.

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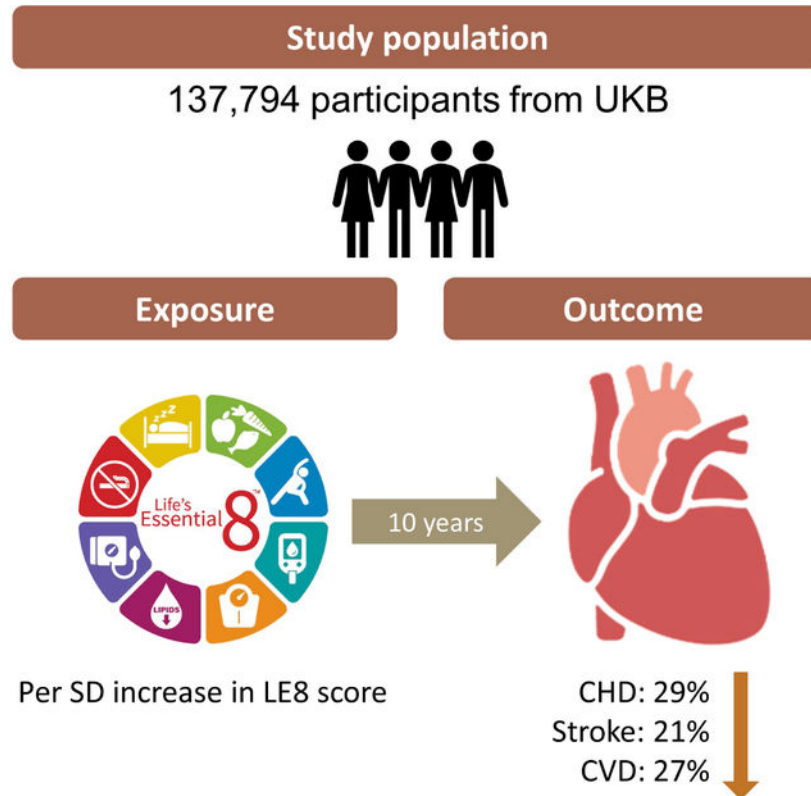
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Supplemental Material

Tables S1–S5

Figures S1–S4

**Graphical Abstract:****Keywords**

Cardiovascular health; Gene-Lifestyle interaction; Cohort study

**Introduction**

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity in the U.S. and worldwide.<sup>1,2</sup> Reducing the burden of CVD continues to be a pivotal public health focus. Of note, the risk of CVD is largely driven by unhealthy lifestyles, such as an unhealthy diet, physical inactivity,<sup>3,4</sup> and unhealthy sleep habits.<sup>5,6</sup> To improve cardiovascular health (CVH), the American Heart Association (AHA) formulated a novel construct of CVH.<sup>7</sup> Recently, the AHA released an enhanced approach to assess CVH: Life's essential 8 (LE8).<sup>8</sup> Sleep health, indicated by optimal habitual sleep duration, is incorporated as a new metrics component, on basis of the accumulating studies that consistently link sleep duration with cardiometabolic health and health outcomes.<sup>5,6</sup> Moreover, sleep duration is closely related to each of the original 7 components of CVH and adds independent value to the overall CVH.<sup>9-11</sup> Therefore, with sleep health being adopted, the LE8 metrics may hold great potential for better improving CVH among the general population. However, supportive data is still lacking.

In addition, it is well-recognized that both genetic and lifestyle factors contribute to the risk of CVD.<sup>12</sup> Genome-wide association studies have successfully identified genetic variants that are associated with CVD outcomes.<sup>13,14</sup> Previous studies have shown that genetic susceptibility to CVD could be attenuated by adhering to a healthy lifestyle, though the results were not entirely consistent.<sup>12,15–17</sup> We hypothesized that CVH defined by LE8 might interact with genetic susceptibility in relation to CVD risk.

In the current study, we sought to evaluate the association between the level of CVH, as defined using the LE8 score, and the incident CVD outcomes among adult participants from the UK Biobank. We also tested the interaction between genetic predisposition to CHD or stroke and LE8, as well as the joint association of LE8 and genetic factors on the risk of CVD.

## Materials and Methods

All data and materials that support the findings of this study are available at the UK biobank. Qualified researchers who have been trained in human subject confidentiality protocols may request the access to the UK Biobank (<https://www.ukbiobank.ac.uk/researchers/>).

### Study design and population

The UK biobank is a large, prospective cohort study in the United Kingdom, which provides in-depth genetic and health information.<sup>18,19</sup> The details of the study design have been reported previously.<sup>19</sup> Briefly, over 500,000 middle-aged (age range: 37–73) participants were recruited between 2006 and 2010 from 22 assessment centers across England, Scotland, and Wales. Participants provided a wide range of health-related information through touchscreen questionnaires, physical examinations, and biological samples. The 24-hour dietary recall questionnaire was distributed to participants who provided email addresses at the initial visit. A total of 210,962 participants completed at least one 24-hour dietary recall of the previous day between 2009 and 2012. The study was approved by both the National Health Service (NHS) National Research Service (ref: 11/NW/0382) and the Institutional Review Board of Tulane University (study number: 2018–1872). All participants provided written informed consent.

In the current study, we defined the time when the first 24-hour diet recall was completed as the baseline. Among participants with at least one typical 24-hour diet recall, we excluded participants with CHD or stroke at baseline, and those with missing information on one or more components of LE8, leaving a total of 137,794 participants for the analyses. Compared to the entire UK biobank participants, those who provided 24-hour dietary recall data were with high socioeconomic status and less likely to have concurrent diseases (Table S1). When analyzing genetic data, we only included 136,659 participants with complete genetic data for the analyses.

### Cardiovascular health metrics (CVH) assessment with Life's Essential 8 (LE8)

LE8 is a mix of behavioral (healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep, and healthy weight) and biological (healthy levels of blood lipids, blood glucose, and blood pressure) targets.<sup>8</sup> Healthy diet was evaluated by the Dietary

Approaches to Stop Hypertension (DASH) diet score using the information collected from the 24-hour dietary recall.<sup>20</sup> Frequency and duration of moderate and vigorous physical activity, nicotine exposure, sleep duration, and medication use were assessed by touchscreen questionnaires at baseline. Height and body weight were measured during the initial assessment center visit; body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters ( $\text{kg}/\text{m}^2$ ). Total cholesterol was measured by CHO-POD analysis and high-density cholesterol was measured by enzyme immunoassay on a Beckman Coulter AU5800. Glycated hemoglobin (HbA1c) was measured by HPLC analysis on a Bio-Rad VARIANT II Turbo. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice by an Omron device, and averaged values were used for analyses. The details of the scoring algorithm according to AHA are shown in Table S2. Each component ranges from 0 to 100 points; the aggregate score is also scaled from 0 to 100 points. We categorized the CVH scores according to the AHA advisory as follows: high CVH (80–100); moderate CVH (50–79); and low CVH (0–49).<sup>8</sup> We also calculated a behavior subscale based on the behavioral metrics (diet, physical activity, nicotine exposure, sleep health, and BMI) and a biological subscale based on the biological metrics (blood lipids, blood glucose, and blood pressure).

### Assessment of the outcomes

The diagnosis of CVD, including CHD and stroke, was defined by information from the International Statistical Classification of Diseases and Related Health Problems 9<sup>th</sup> (ICD-9) and 10<sup>th</sup> (ICD-10) revisions (through hospital admissions), self-report, and death registries. Incident CHD was defined by ICD-10 code I20-I25; incident stroke was defined by ICD-10 code I60–64. Incident CVD was defined as the composite outcomes of CHD and stroke.

### Covariates assessment

Age, sex, and ethnicity were obtained from baseline. Townsend deprivation index (based on participant's postcode, a higher score indicates higher degree of deprivation) was obtained from local NHS Primary Care Trust registries and the name of the recruitment center. Alcohol intake was self-reported as never, special occasions only, 1–3 times/month, once or twice/week, 3–4 times/week, and daily or almost daily. Education, average household income, and use of medications were assessed by the touchscreen questionnaire during the initial assessment center visit. Sedentary behavior time was calculated as the sum of time spent on television watching, computer use (not at work), and driving.<sup>21</sup>

### Calculation of genetic risk score

Genotyping was performed by the UK biobank team by two similar arrays: UK BiLEVE Axiom array and UK Biobank Axiom array. Detailed information is available elsewhere (<http://www.ukbiobank.ac.uk/scientists-3/genetic-data/>).<sup>22</sup> We created a weighted genetic risk score (GRS) for CHD using 64 single-nucleotide polymorphisms (SNPs) identified to be associated with CHD from genome-wide association study (GWAS).<sup>13</sup> Each SNP is coded as 0, 1, or 2 according to the number of risk alleles. The weight GRS was calculated by the widely used equation:  $\text{GRS} = (\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \dots + \beta_{64} \times \text{SNP}_{64}) \times (\text{total number of SNPs} / \text{sum of the } \beta \text{ coefficient})$ . Similarly, a GRS for stroke was created using 30 SNPs identified from stroke GRS.<sup>14</sup> A higher GRS indicates a higher genetic predisposition to

CHD or stroke. We also categorized the GRS into low (Q1), medium (Q2-Q4), and high (Q5) based on quintile distributions of the GRS, according to previous studies.<sup>12</sup>

### Statistical analysis

Baseline characteristics were presented as mean (SD) or median [interquartile range (IQR)] for continuous variables and N (%) for categorical variables according to the categories of CVH. Follow-up time was calculated from the baseline to the date of first diagnosis of CHD or stroke, or end of the follow-up (May 2021), whichever came first. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between LE8 and risk of CHD, stroke, and CVD. Proportional hazard assumption was tested by adding an interaction term of LE8 and log of the time variable in the model; we did not find violation of the assumption. Model 1 was adjusted for age, ethnicity, and sex. Model 2 was further controlled for assessment center, Townsend deprivation index, alcohol intake, sedentary behavior, average household income, and education levels. We repeated the analyses for behavior and biological subscale scores, with mutual adjustment for each other in the model. We also analyzed the association between each individual component of the LE8 and incidence of CVD outcomes, with all the 8 metrics simultaneously included in the model. Moreover, we compared the performance of LE8 with the previous assessment tool for CVH, Life's simple 7 (LS7). The different survival model was assessed by the Harrell's C-statistics.<sup>23</sup> The methods proposed by Uno et al was further applied to examine the c-index difference between model with LE8 and model with LS7.<sup>24</sup> We also conducted a sensitivity analysis by excluding sleep health from the LE8 score. To investigate whether the genetic predisposition could be offset by CVH, an interaction between LE8 and genetic factor was tested by adding a cross-product of LE8 and GRS into the model. Sex difference and age modification were also tested by adding an interaction term between LE8 and age or sex in the model. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc). All the statistical tests were 2-sided and  $p < 0.05$  was considered as statistically significant.

### Results

Among the 137,794 participants with complete information on LE8 and no previous CVD, 52% were female, and the mean age was 56 years. Of all the study participants, 18.9% (N=26,071) met the high CVH criteria, and 74.3% (N=102,364) of the study participants were in the moderate CVH category, 6.8% (N=9,359) were in the low CVH category. Baseline characteristics of the participants according to low, moderate, and high cardiovascular health metrics (CVH) are shown in Table 1. Participants with a high CVH were younger, more likely to be women, had lower levels of deprivation, higher education, and higher average household income. Distribution of the overall LE8 score and each component of LE8 among the study participants are shown in Figure S1. The distribution of ideal status varied widely across LE8 metrics, ranging from 16% of participants having ideal status of blood pressure, to 85% of participants having ideal status of blood glucose. Fifty percent of participants had a poor status of healthy diet and more than 50% had a poor status of blood lipids.

During a median follow-up of 10 years, a total of 8,595 CVD cases (6,968 CHD and 1,948 stroke) were documented. The cumulative incidence showed graded relationships according to the levels of CVH categories during follow-up, particularly for CHD and CVD (Figure 1, Log-rank tests  $<0.001$  for all). After adjustment for age, race, sex, a better CVH, indicated by a higher LE8 score, was associated with significantly lower risks of CHD, stroke, and CVD (Table 2, Model 1). The HR (95% CI) for each SD increment in LE8 score was 0.69 (0.67, 0.70) for CHD, 0.77 (0.73, 0.80) for stroke, and 0.71 (0.69, 0.72) for CVD. Further adjustment for assessment center, Townsend deprivation index, alcohol intake, sedentary behavior, average household income, and education did not appreciably attenuate the relationship (Table 2, Model 2). Compared to those with a low CVH category, participants with a moderate CVH had a 42% lower risk of developing CHD (HR: 0.58, 95% CI: 0.54, 0.62), a 35% lower risk of developing stroke (HR: 0.65, 95% CI: 0.57, 0.74), and a 40% lower risk of developing CVD (HR: 0.60, 95% CI: 0.56, 0.64). More strikingly, high CVH was associated with a 66% lower risk of CHD (HR: 0.34, 95% CI: 0.30, 0.38), a 55% lower risk of stroke (HR: 0.45, 95% CI: 0.37, 0.54), a 64% lower risk of CVD (HR: 0.36, 95% CI: 0.33, 0.40). In addition, both behavior and biological subscale scores were associated with lower risks of CHD, stroke, and CVD, similar to the overall LE8 score, but with attenuated magnitudes (Table 2). Models with each individual component of LE8 showed higher C-indexes compared to the base model (Table S5). Furthermore, the model with LE8 achieved higher accuracy and outperformed the model with LS7 (C-index: 0.7417 vs. 0.7345,  $p<0.001$  for CHD, 0.7208 vs. 0.7165,  $p<0.001$  for stroke, and 0.7339 vs. 0.7276,  $p<0.001$  for CVD).

When we analyzed the individual component of LE8 and simultaneously included all the metrics in the model, high sleep health was associated with significant lower risks of CHD (HR: 0.73, 95% CI: 0.67, 0.80), stroke (HR: 0.81, 95% CI: 0.68, 0.96), and CVD (HR: 0.74, 95% CI: 0.69, 0.81), independent of the other 7 components (Table S3). Moreover, excluding sleep health in the LE8 showed an attenuated association with the risks of CHD, stroke, and CVD, compared with the full LE8 score. The differences in Uno's concordance statistics compared to the full LE8 score indicated that excluding sleep from the LE8 had a lower model fit, particularly for CHD and CVD (Table S4).

We observed significant sex difference in the association of LE8 with risks of CHD and CVD (Table 3,  $p$ -interaction  $<0.001$  for CHD, and  $p=0.0013$  for CVD). Compared with men, women had greater benefit by having a high CVH defined by LE8. Among women, each SD increment in LE8 score was associated with an HR of 0.68 (95% CI: 0.65, 0.71) for CHD and 0.70 (95% CI: 0.68, 0.73) for CVD after adjustment for covariates, while among men, the HR was 0.73 (0.71, 0.76) for CHD and 0.75 (0.73, 0.77) for CVD. The associations between LE8 score and risk of stroke were similar among men and women. In addition, significant effect modification with age was detected such that the beneficial association between LE8 and the CVD outcomes were stronger when LE8 was measured at age  $\leq 55$  years versus age  $> 55$  years (Figure S2,  $p$ -interaction  $<0.001$ , 0.007, and  $<0.001$  for CHD, stroke, and CVD, respectively). The protective association appeared to be stronger among participants aged 55 and younger. The adjusted HR was 0.62 (0.59, 0.65) for CHD, 0.76 (0.69, 0.83) for stroke, and 0.64 (0.61, 0.67) for CVD. Among participants  $>55$  years old,

the adjusted HR was 0.75 (0.73, 0.77) for CHD, 0.80 (0.76, 0.84) for stroke, and 0.76 (0.74, 0.78) for CVD.

Intriguingly, we found that the genetic predisposition to CHD significantly modified the association between the LE8 score and the risk of CHD (Table 4, p-interaction <0.001). The inverse association between LE8 and CHD risk appeared to be stronger among those with a lower genetic risk of CHD (HRs in ascending GRS stratum: 0.68 (0.64, 0.72), 0.70 (0.67, 0.72), and 0.77 (0.73, 0.81), respectively). We did not find significant interaction between GRS for stroke and LE8 (p-interaction=0.43). The joint association of the LE8 score and CHD-GRS is shown in Figure S3. Compared with participants with a high genetic risk of CHD and low CVH profile, those with a low genetic risk of CHD and a high CVH had a 78% lower risk of developing CHD (HR: 0.22, 95% CI: 0.17, 0.28). A similar pattern was also observed for the joint categories of stroke GRS and categories of CVH for stroke incidence (Figure S4). Compared with participants with a high genetic risk of stroke and low CVH, those with a low genetic risk of stroke and a high CVH had a 64% lower risk of developing stroke (HR: 0.36, 95% CI: 0.24, 0.53).

## Discussion

In this large prospective cohort, we found that better CVH, defined by higher LE8 score, was associated with significantly lower risks of CHD, stroke, and CVD. Compared with participants with a low CVH, those with a high CVH had a 66%, 55%, and 64% lower risk of developing CHD, stroke, and CVD, respectively. The protective association was more evident among women and younger participants. In addition, the genetic predisposition to CHD significantly modified the association between LE8 score and risk of CHD. Participants with a lower genetic risk of CHD appeared to benefit more from a high LE8 score.

To our knowledge, this is the first study to examine the association of the new CVH metrics, defined by LE8, and the risk of CVD outcomes. Our results are consistent with previous reports using LS7 as the assessment for CVH.<sup>25–28</sup> For example, in the Atherosclerosis Risk in Communities Study (ARIC) cohort (aged 45 to 64 years), there was a strong gradient of cumulative CVD incidence according to the number of ideal health metrics met.<sup>25</sup> Such associations were also observed across ethnic background. In the Northern Manhattan Study, participants with 5 ideal CVH metrics had significantly lower risks of myocardial infarction, stroke, and CVD, compared with those with 0 or 1 ideal CVH metrics, across whites, blacks, and Caribbean Hispanics.<sup>26</sup> Of note, the previous algorithm defined by LS7 was less sensitive to interindividual difference, due to its very simplified categories of ideal, intermediate, and ideal classification for each component. For example, individuals with 1 minute/week moderate to vigorous activity and individuals with 149 minutes/week vigorous activity would be categorized into the same intermediate group.<sup>8</sup> The LE8 score, a more continuous scale (each component varies from 0–100), is designed to be more sensitive to interindividual differences.<sup>8</sup> The improved performance of LE8 in predicting CVD risks could be explained by the more sophisticated scoring algorithm, as well as the inclusion of more relative factor that contribute the diseases risk, i.e., sleep health. Moreover, our sensitivity analysis showed that excluding sleep health from the CVH score, the association

with CVD outcomes were all attenuated, indicating the newly included component, sleep health, indeed added independent values to the overall CVH.

Our stratified analyses showed that the protective associations were more pronounced among women. Such observation is consistent with previous studies, where women appeared to have a healthier lifestyle compared to men.<sup>29,30</sup> The sex difference in CVD has long been noted.<sup>31,32</sup> In line with our findings, previous study found that women presented with a more favorable CVH profile than do man, particularly at a younger age.<sup>33</sup> In the Jackson Heart Study, it was also reported that the men had a higher CVD incidence rate across the number of ideal CVH metrics evaluated by LS7, compared to women.<sup>29</sup> Similarly, in Kailuan community cohort (>100,000 participants, mean age 51 years old), the cumulative incidence rates of CVD were higher among men than women, regardless of the number of the ideal LS7 met.<sup>30</sup> The reasons underpinning the sex differences in CVD outcomes are not fully understood. Factors, such as stress,<sup>34</sup> hormones,<sup>35,36</sup> and psychosocial factors,<sup>37–39</sup> may contribute additionally to higher CVD incidence among men. This implies that women could benefit to a greater extent in having a higher level of CVH defined by AHA LE8 than men; more efforts are needed to improve the CVH profile among men.

Several prior studies have reported significant age effects whereby the CVD protections associated with attaining more healthy CVD metrics were more pronounced among younger compared with older middle age adults.<sup>40,41</sup> In accordance with our results, Ramírez-Vélez et al. conducted a meta-regression of 12 prospective studies with 210,443 adults and showed a significant age effect on the association between CVH defined by LS7 and overall CVD incidence.<sup>40</sup> The association was significantly stronger among younger participants.<sup>40</sup> Another study conducted among 4,638 young adults (mean age 25) from Coronary Artery Risk Development in Young Adults Study (CARDIA) also reported a strong inverse association between CVH assessed by LS7 at late adolescent/young adult with CVD outcomes.<sup>42</sup> Our results showed that a high level of healthy CVH, defined by LE8, may have greater impact particularly among young adults. This finding is of special importance because data suggest that young adults have experienced frustrating small decreases in CVD incidence.<sup>4,43</sup>

Intriguingly, for the first time, we found a significant interaction between the LE8 and genetic susceptibility to CHD. The observed protective association was more evident among participants with a lower genetic risk of CHD. The result is in line with previous studies on gene-environment interactions,<sup>16</sup> suggesting that genetic factors and lifestyle factors jointly influence the risk of disease.<sup>44</sup> Even though the magnitude of risk reduction is relatively low in high genetic risk group compared to low genetic risk group, our results demonstrated that the risk of developing CHD conferred by high genetic predisposition could still be largely offset by healthy lifestyle.

Our study also has limitations. First, the assessments of behavioral factors are mainly obtained by self-report. Information bias and misclassification are inevitable. Second, same as any population-based cohort study, the disease prevalence and incidence rates are generally lower due to the healthy volunteer bias.<sup>45,46</sup> However, this would not affect the internal validity of our analyses. Third, most of the study participants were whites. Further



investigations in other racial/ethnic groups are warranted. Fourth, LE8 was only calculated at one-time point. We could not account for potential lifestyle changes during the follow-up to the current analysis. The strengths of this study include the application of the new LE8 score to assess CVH, the large study sample, and a prospective ascertainment of CVD outcomes.

In conclusion, our findings in a large prospective cohort study indicate a strong graded inverse association between the LE8 defined CVH and risks of CHD, stroke, and CVD. Such associations are particularly pronounced among women, younger participants, and those with lower genetic risk. These findings highlight the importance of improving cardiovascular health by adopting the AHA LE8.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments:

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## Non-standard Abbreviations and Acronyms (alphabetic order)

<b>AHA</b>	American Heart Association
<b>CHD</b>	coronary heart disease
<b>CVD</b>	cardiovascular disease
<b>CVH</b>	cardiovascular health
<b>DBP</b>	diastolic blood pressure
<b>GRS</b>	genetic risk score
<b>LE8</b>	Life's Essential 8
<b>SBP</b>	systolic blood pressure
<b>SNP</b>	single nucleotide polymorphism

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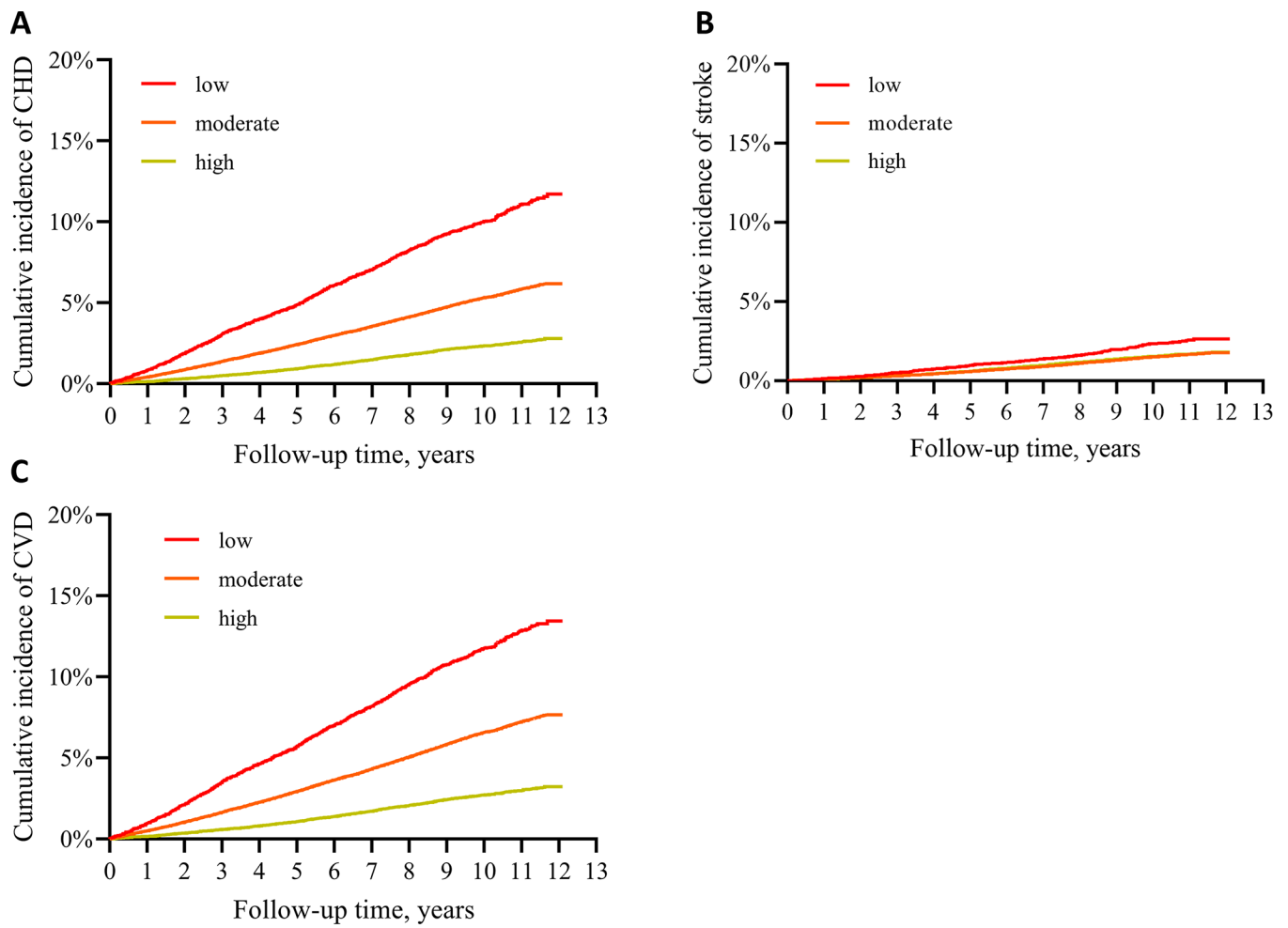
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### Highlights

- The American Heart Association recently released a new cardiovascular health (CVH) metric, Life's Essential 8 (LE8) for health promotion and preservation. However, supportive data is lacking on the association between CVH defined by LE8 and cardiovascular disease (CVD) risk.
- We found that higher cardiovascular health, indicated by a higher LE8 score, was associated with significantly lower risks of coronary heart disease (CHD), stroke, and CVD.
- Moreover, the new LE8 score outperformed the previous cardiovascular health metrics, Life's Simple 7.
- In addition, we found genetic predisposition to CHD significantly modified the association between LE8 and the risk of CHD.



**Figure 1.** Cumulative incidence of CHD, stroke, and CVD according to CVH categories defined by LE8. CHD: coronary heart disease; CVD: cardiovascular disease. Panel A: CHD; B: stroke, C: CVD. Log-rank tests  $p < 0.001$  for all.

**Table 1.**

Baseline characteristics according to the categories of LE8

	Life's Essential 8		
	Low	Moderate	High
Age, years	56.2 (7.4)	56.6 (7.8)	53.7 (8.1)
Female, Y	3,924 (41.9)	52,758 (51.5)	19,418 (74.5)
White, Y	8,499 (91.3)	93,428 (91.6)	23,623 (90.8)
BMI, kg/m <sup>2</sup>	32.5 (5.6)	27.1 (4.2)	23.3 (2.5)
Townsend deprivation index	-1.6 [4.6]	-2.4 [3.6]	-2.4 [3.6]
College/University degree, Y	2,665 (28.5)	42,040 (41.1)	14,293 (54.8)
Non-HDL, mg/dL	183.6 (44.7)	168.7 (39.6)	140.5 (30.9)
Glucose, mg/dL	99.5 (33.3)	91.4 (17.0)	87.7 (11.9)
HbA1c, %	5.8 (3.0)	5.4 (2.6)	5.2 (2.5)
Dash diet score	20.8 (4.0)	24.7 (4.5)	28.7 (3.9)
Sleep duration, h/day	6.8 (1.4)	7.2 (1.0)	7.3 (0.8)
Moderate physical activity, min/week	0.0 [30.0]	90.0 [220.0]	175.0 [280.0]
Vigorous physical activity, min/week	0.0 [0.0]	20.0 [100.0]	60.0 [130.0]
Sedentary behavior time, h/day	5.6 (2.6)	4.4 (2.3)	3.5 (2.1)
SBP, mmHg	145.9 (16.9)	138.9 (17.7)	124.7 (15.6)
DBP, mmHg	88.3 (10.0)	82.9 (9.6)	75.2 (8.3)
Alcohol intake			
Daily or almost daily	2,2255 (24.1)	24,713 (24.2)	4,972 (19.1)
Three or four times a week	1,794 (19.2)	25,637 (25.1)	7,258 (27.8)
Once or twice a week	2,077 (22.2)	25,164 (24.6)	6,980 (26.8)
One to three times a month	1,179 (12.6)	11,041 (10.8)	2,928 (11.2)
Special occasions only	1,304 (13.9)	9,710 (9.5)	2,362 (9.1)
Never	744 (8.0)	6,065 (5.9)	1,566 (6.0)
Household income			
Less than £18,000	1,893 (22.8)	14,181 (15.4)	2,599 (11.0)
£18,000 to £30,999	2,071 (24.9)	22,913 (24.9)	5,000 (21.1)
£31,000 to £51,999	2,307 (27.7)	26,539 (28.9)	6,879 (29.0)
£52,000 to £100,000	1,646 (19.8)	22,104 (24.0)	6,783 (28.6)
Greater than £100,000	401 (4.8)	6,220 (6.8)	2,472 (10.4)
Medication use			
Cholesterol-lowering	2,504 (26.9)	14,266 (14.0)	1,312 (5.1)
Antihypertensive	3,452 (37.0)	18,199 (17.9)	1,023 (3.9)
Insulin treatment	247 (2.7)	728 (0.7)	36 (0.1)

Data are mean (SD), median [IQR], or N (%).

IQR: interquartile range; BMI: body mass index; Non-HDL: non-high-density-lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 2.**

Life's essential 8 and incidence of CVD outcomes

	Model 1		Model 2	
	HR (95%)	p	HR (95%)	p
<b>CHD</b>				
<b>Cardiovascular health metrics</b>				
Low	ref		ref	
Moderate	0.52 (0.49, 0.56)	<0.001	0.58 (0.54, 0.62)	<0.001
High	0.29 (0.26, 0.32)	<0.001	0.34 (0.30, 0.38)	<0.001
Per SD increment in LE8	0.69 (0.67, 0.70)	<0.001	0.71 (0.69, 0.73)	<0.001
<b>Subscale</b>				
Per SD increment in behavior scale	0.80 (0.78, 0.82)	<0.001	0.83 (0.81, 0.85)	<0.001
Per SD increment in biological scale	0.75 (0.73, 0.77)	<0.001	0.75 (0.73, 0.77)	<0.001
<b>Stroke</b>				
<b>Cardiovascular health metrics</b>				
Low	ref		ref	
Moderate	0.61 (0.53, 0.69)	<0.001	0.65 (0.57, 0.75)	<0.001
High	0.40 (0.33, 0.48)	<0.001	0.45 (0.37, 0.54)	<0.001
Per SD increment in LE8	0.77 (0.73, 0.80)	<0.001	0.79 (0.75, 0.82)	<0.001
<b>Subscale</b>				
Per SD increment in behavior scale	0.85 (0.81, 0.89)	<0.001	0.87 (0.83, 0.91)	<0.001
Per SD increment in biological scale	0.82 (0.78, 0.86)	<0.001	0.82 (0.78, 0.86)	<0.001
<b>CVD</b>				
<b>Cardiovascular health metrics</b>				
Low	ref		ref	
Moderate	0.55 (0.51, 0.58)	<0.001	0.60 (0.56, 0.64)	<0.001
High	0.31 (0.29, 0.35)	<0.001	0.36 (0.33, 0.40)	<0.001
Per SD increment in LE8	0.71 (0.69, 0.72)	<0.001	0.73 (0.72, 0.75)	<0.001
<b>Subscale</b>				
Per SD increment in behavior scale	0.82 (0.80, 0.83)	<0.001	0.85 (0.83, 0.87)	<0.001
Per SD increment in biological scale	0.76 (0.74, 0.78)	<0.001	0.76 (0.74, 0.78)	<0.001

CHD: coronary heart disease; CVD: cardiovascular heart disease.

Model 1 was adjusted for age, race, and sex.

Model 2: Model 1 + assessment center, Townsend deprivation index, alcohol intake, sedentary behavior, average household income, and education.

Behavior scale and biological scale were mutually adjusted for subscale analyses.



**Table 3.**

Hazard ratios of CVD outcomes according to LE8 in women and men

	Women		Men		p-int
	HR (95%)	p	HR (95%)	p	
<b>CHD</b>					<b>&lt;0.001</b>
<b>Cardiovascular health metrics</b>					
Low	ref		ref		
Moderate	0.53 (0.46, 0.60)	<0.001	0.60 (0.55, 0.65)	<0.001	
High	0.29 (0.24, 0.34)	<0.001	0.39 (0.34, 0.45)	<0.001	
Per SD increment in LE8	0.68 (0.65, 0.71)	<0.001	0.73 (0.71, 0.76)	<0.001	
<b>Subscale</b>					
Per SD increment in behavior scale	0.78 (0.75, 0.82)	<0.001	0.85 (0.83, 0.88)	<0.001	
Per SD increment in biological scale	0.76 (0.73, 0.80)	<0.001	0.75 (0.73, 0.78)	<0.001	
<b>Stroke</b>					<b>0.44</b>
<b>Cardiovascular health metrics</b>					
Low	ref		ref		
Moderate	0.69 (0.54, 0.89)	<0.001	0.63 (0.54, 0.75)	<0.001	
High	0.43 (0.32, 0.58)	<0.001	0.50 (0.39, 0.65)	<0.001	
Per SD increment in LE8	0.77 (0.72, 0.83)	<0.001	0.80 (0.75, 0.85)	<0.001	
<b>Subscale</b>					
Per SD increment in behavior scale	0.86 (0.80, 0.92)	<0.001	0.88 (0.83, 0.93)	<0.001	
Per SD increment in biological scale	0.82 (0.76, 0.88)	<0.001	0.83 (0.78, 0.89)	<0.001	
<b>CVD</b>					<b>0.0013</b>
<b>Cardiovascular health metrics</b>					
Low	ref		ref		
Moderate	0.56 (0.49, 0.63)	<0.001	0.61 (0.57, 0.66)	<0.001	
High	0.32 (0.27, 0.37)	<0.001	0.41 (0.36, 0.47)	<0.001	
Per SD increment in LE8	0.70 (0.68, 0.73)	<0.001	0.75 (0.73, 0.77)	<0.001	
<b>Subscale</b>					
Per SD increment in behavior scale	0.80 (0.77, 0.83)	<0.001	0.87 (0.85, 0.90)	<0.001	
Per SD increment in biological scale	0.77 (0.74, 0.81)	<0.001	0.76 (0.74, 0.79)	<0.001	

CHD: coronary heart disease; CVD: cardiovascular heart disease.

Model was adjusted for age, race, assessment center, Townsend deprivation index, alcohol intake, sedentary behavior, average household income, and education.

Behavior scale and biological scale were mutually adjusted for subscale analyses.

**Table 4.**

Association between LE8 and incident CHD and stroke by stratum of the genetic risk scores

GRS	CHD			Stroke		
	HR (95% CI)	P	p-interaction	HR (95% CI)	P	p-interaction
Q1	0.68 (0.64, 0.72)	<0.001		0.84 (0.75, 0.93)	<0.001	
Q2-Q4	0.70 (0.67, 0.72)	<0.001	<0.001	0.79 (0.74, 0.84)	<0.001	0.43
Q5	0.77 (0.73, 0.81)	<0.001		0.73 (0.66, 0.80)	<0.001	

HR: hazard ratio; GRS: genetic risk score; Q1 is the lowest quintile.

HR were estimated per SD increment of the LE8.

Models were adjusted for age, race, sex, assessment center, Townsend deprivation index, alcohol intake, sedentary behavior, average household income, and education.

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