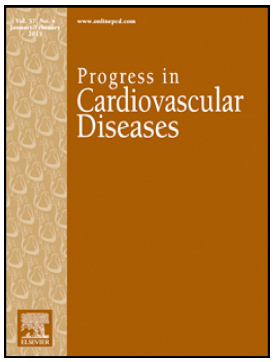


Dose-response associations of the American Heart Association's new "Life's essential 8" metrics with all-cause and cardiovascular mortality in a nationally representative sample from the United States

Rubén López-Bueno, Joaquín Calatayud, Jesús del Pozo Cruz, Lin Yang, Borja del Pozo Cruz

PII: S0033-0620(24)00090-2

DOI: https://doi.org/10.1016/j.pcad.2024.06.001

Reference: YPCAD 1474

To appear in: *Progress in Cardiovascular Diseases*

Please cite this article as: R. López-Bueno, J. Calatayud, J. del Pozo Cruz, et al., Dose-response associations of the American Heart Association's new "Life's essential 8" metrics with all-cause and cardiovascular mortality in a nationally representative sample from the United States, *Progress in Cardiovascular Diseases* (2023), https://doi.org/10.1016/j.pcad.2024.06.001

Dose-Response Associations of the American Heart Association's New "Life's Essential 8" Metrics with All-Cause and Cardiovascular Mortality in a Nationally Representative Sample from the United States

Rubén López-Bueno[1,2,3*], Joaquín Calatayud[2,3], Jesús del Pozo Cruz[4,5], Lin Yang[6,7], Borja del Pozo Cruz[8,9,10]

[1]Department of Physical Medicine and Nursing, University of Zaragoza, Zaragoza, Spain

[2]Exercise Intervention for Health Research Group (EXINH-RG), Department of Physiotherapy, University of Valencia, Valencia, Spain

[3]National Research Centre for the Working Environment, Copenhagen, Denmark

[4]Physical Education and Sports Department, Faculty of Education, University of Seville, Seville, Spain

[5]Epidemiology of Physical Activity and Fitness Across the Lifespan Research Group (EPAFit), University of Seville, Seville, Spain

[6]Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Canada

[7]Departments of Oncology and Community Health Sciences, University of Calgary, Calgary, Canada

[8]Faculty of Education, University of Cádiz, Cádiz, Spain

[9]Biomedical Research and Innovation Institute of Cádiz (INiBICA) Research Unit, Puerta del Mar University Hospital, University of Cádiz, Spain

[10]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark

COI/Disclosures: None

Corresponding author:

Dr. Rubén López-Bueno. Department of Physical Medicine and Nursing, University of Zaragoza, Domingo Miral, 50009 Zaragoza, Spain. Email: rlopezbu@unizar.es Mobile phone: +34 661416735

Abstract

Background

Our aim was to examine the prospective dose-response associations of American Heart Association´s (AHA) LIFE´s Essential 8 (LE8) score and number of cardiovascular health (CVH) factors with high score with all-cause and cardiovascular disease (CVD) related mortality.

Methods

We pooled 6 consecutive waves of the National Health and Nutrition Examination Survey (NHANES) comprising rounds between 2007-2008 and 2017-2018. We calculated hazard ratios (HRs) and conducted restricted cubic splines models to assess the dose-response association of LE8 score and CVH factors with all-cause and CVD mortality.

Results

Analyses included 23 531 adults aged 18 years and over (mean [SD] age, 43.6 [16.7] years; 11 979 [51%] female; 8960 [38.1%] non-Hispanic white individuals) with a median follow-up of 7.3 years (IQR 4.3-10.1), corresponding to 168 033 person-years.

The dose-response analyses showed a significant inverse curvilinear trend for the association between LE8 score with all-cause and CVD mortality. The optimal risk reduction for all-cause mortality was found at 100 points of the LE8 Score (HR, 0.50; 95% CI, 0.27-0.93) compared to the reference (median LE8 score [62.5 points]). Moreover, the dose-response association between LE8 and CVD mortality also exhibited a significant inverse curvilinear association up to 90 points (HR, 0.41; 95% CI, 0.17-0.99). Optimal levels of LE8 score may

be able to avert around 40% of the annual all-cause and CVD deaths among the US adult population.

Conclusions

Best-case scenario of CVH may reduce around 40% of the all-cause and CVD annual mortality among adults in the United States.

Keywords: preventive medicine; epidemiology; public health; risk factors; lifestyle

Abbreviations

AHA American Heart Association; BMI Body mass index; BP Blood pressure; CDC Centers for Disease Control and Prevention; CV Cardiovascular; CVD Cardiovascular disease; CVH Cardiovascular health; FBG Fasting blood glucose; HDL High-density lipoprotein; HEI 2015 Healthy Eating Index 2015; HR Hazard ratio; ICD-10 International Statistical Classification of Diseases and Related Health Problems; LE8; Life´s Essential 8; LS7 Life's Simple 7; NCHS National Center for Health Statistics; NHANES National Health and Nutrition Examination Survey; PA Physical activity; PAF Population attributable fraction; PAQ-K Physical Activity Questionnaire; STROBE Strengthening the Reporting of Observational Studies in Epidemiology; US United States

Introduction

Cardiovascular (CV) disease (CVD) remains the leading cause of morbidity and mortality both in the United States (US) and worldwide, representing a significant disease and economic burden, especially in high-income countries.[1] In 2016, the estimated average annual cost associated with CVD was 320 billion dollars,[1,2] a concerning economic cost that may rise since CVD mortality has increased among middle-aged US citizens over the last decade,[3] a trend that has also been observed in other Western countries.[4]

To address the burden associated with CVD, the American Heart Association (AHA) introduced the concept of optimal CV health (CVH) in 2010 and developed the Life's Simple 7 (LS7) score for measuring and monitoring CVH.[5] In 2022, the AHA updated the LS7 score to the Life's Essential 8 (LE8) score, which includes sleep as a new CVH factor, grades the extent of CVH achieved on a continuous scale from 0 to 100, and provides more detailed criteria for measurement.[6] The LE8 score has been used to estimate CVH and has demonstrated inverse associations with adverse outcomes, such as CVD, diabetes, cancer, dementia, and all-cause and CVD mortality in adults.[7–12] However, most of the existing research to date use a categorized LE8 score as proxy for CVH, and only one study has examined the dose-response association of LE8 with all-cause and CVD mortality.[8,9,12] The only existing study on the dose-response association of LE8 score and CVD mortality failed to identify possible thresholds of either minimal or optimal LE8 points for risk reduction of all-cause and CVD mortality.[9] Furthermore, the referred study did not use the recommended AHA cut-off points for this purpose,[9] which may hamper interpretations of the results within AHA´s framework.

It is crucial to examine this dose-response relationship as it can provide valuable information on the incremental LE8 scores that contribute to reducing the risk of all-cause and CVD mortality. Moreover, dose-response analyses may reveal specific thresholds for minimum, optimal and maximal risk reductions in the population. Additionally, individual CVH factors as defined in LE8 have received, to date, much less attention, even though determining the optimal number of CVH factors necessary to reduce the risk of all-cause and CVD mortality may be relevant for public health. Although meeting a greater number of CVH metrics has been previously associated with a lower risk of total and CVD mortality,[13] this association has not yet been examined under the framework of the LE8 score.

Capitalizing on a large representative sample of US adults, the present study aimed to examine the dose-response relationship between global and individual LE8 CVH factors and the risk of all-cause and CVD mortality. Furthermore, we assessed the number of absolute annual deaths averted in the US associated with incremental LE8 scores.

Methods

Study Design and Sample

This prospective cohort study retrieved deidentified data from 6 consecutive waves of the National Health and Nutrition Examination Survey (NHANES) conducted between 2007-2008 and 2017-2018 by the National Center for Health Statistics (NCHS) and Center for Disease Control and Prevention (CDC). Previous NHANES waves were excluded due to missing information in one or more LE8 components. The NHANES is conducted in 2-year cycles using a complex, multistage probability sampling design to select a representative sample of the civilian, noninstitutionalized population of the US.[14] Briefly, participants from NHANES were interviewed at home and physically examined in a mobile examination center; examinations included anthropometric measurements, physiological explorations, and blood

tests. Written informed consent was obtained from all participants or their guardians before the home interview and the physical examination. The NHANES received approval from the National Center for Health Statistics Research Ethics Review Board. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[15]

From an initial pooled sample of 32 600 adults (≥18 years), we excluded pregnant females (n=372), and individuals self-reporting any history of congestive heart failure, coronary heart disease, angina, heart attack, stroke, emphysema or cancer (n=3217).[10,16] Participants with missing values in any of the LE8 components or study covariates were also removed from the analytic sample (n=3673). Overall, the study cohort consisted of 23 531 participants.

Life's Essential 8 Components

The LE8 score comprises four health behaviors (nicotine exposure, physical activity/PA, diet, and sleep) and four health factors (body mass index, blood glucose levels, blood lipid levels, and blood pressure). The LE8 score is calculated as the average value of the eight components, each of which is assessed on a scale of 0 to 100 using established cut-points.[6] We used the CVH metrics for adults as reference. Further information on LE8 and its individual components can be found in the seminal article.[6]

Diet

Information on diet was obtained by accessing self-reported information from questionnaires through adherence to the Healthy Eating Index (HEI-2015). The resulting score was used to classify participants in relation to the HEI-2015 population levels (1st–24th, 25th–49th, 50th–74th, 75th–94th, and ≥ 95th percentile values) corresponding to 0, 25, 50, 80, and 100 points, respectively.

PA

PA was assessed using the Physical Activity Questionnaire (PAQ-K) which measured moderate to vigorous weekly PA in the domains of recreation, commuting to work and workplace. The total minutes of PA in these domains was categorized as 0, 1–29, 30–59, 60–89, 90–119, 120–149, and ≥ 150 min per week, corresponding to 0, 20, 40, 60, 80, 90, and 100 points, respectively.

Nicotine Exposure

Self-reported information on nicotine exposure from NHANES interviews was used. We retrieved data on questions concerning current or prior combustible tobacco use, inhaled nicotine-delivery systems use or second-hand exposure at home. Current smoking, prior smoking habit (quit <1 year) or current use of inhaled nicotine delivery systems, prior smoking habit (quit 1 to <5 years), prior smoking habit (quit ≥5 years), and never smoker, corresponded to 0, 25, 50, 80, and 100 points, respectively. Additionally, twenty points were subtracted for adults living with current indoor smokers.

Sleep Health

Sleep was assessed based on self-reported average sleep hours in NHANES survey. According to LE8 score, we categorized sleep hours as <4, 4 to <5, 5 to <6 or ≥10, 6 to <7, 9 to < 10, and 7 to <9 h, which respectively corresponded to 0, 20, 40, 70, 90, and 100 points.

Body mass index

Weight and height were objectively measured and served to calculate body mass index (BMI; i.e., weight in kilograms divided by height in meters squared). Categorization of BMI levels were ≥40.0, 35.0–39.9, 30.0–34.9, 25.0–29.9, and <25.0 kg/m2, which respectively corresponded to 0, 15, 30, 70, and 100 points.

Blood Lipids

Data retrieved from NHANES were both the total and high-density lipoprotein (HDL) cholesterol (mg/dL) using blood samples. Non-HDL cholesterol levels were calculated by subtracting HDL cholesterol from total cholesterol. The non-HDL cholesterol levels were categorized as follows: ≥220, 190–219, 160–189, 130–159, and <130 mg/dL, corresponding to 0, 20, 40, 60, and 100 points, respectively.

Blood Glucose

Fasting blood glucose (FBG) was measured through fasting blood samples, while HbA1c levels were measured using both fasting and non-fasting blood samples. Blood glucose levels were categorized as diabetes with HbA1c ≥10.0%, diabetes with HbA1c of 9.0–9.9%, diabetes with HbA1c of 8.0–8.9%, diabetes with HbA1c of 7.0–7.9%, diabetes with HbA1c <7.0%, no diabetes and FBG of 100–125 mg/dL or HbA1c of 5.7–6.4%, and no history of diabetes and FBG < 100 mg/dL or HbA1c <5.7%. These categories corresponded to 0, 10, 20, 30, 40, 60, and 100 points, respectively.

Blood Pressure(BP)

BP was measured after a 5-minute rest in a seated position using a properly sized cuff; BP levels were classified as systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg, 140–159 or 90–99 mmHg, 130–139 or 80–89 mmHg, 120–129/ <80 mmHg, and < 120/80 mmHg, which respectively corresponded to 0, 25, 50, 75, and 100 points. If blood pressure was treated, 20 points were subtracted from the score.

According to AHA procedures,[6] total LE8 score for measurement and quantitative assessment of CVH was obtained by calculating the average of the eight individual CV metric scores (range 0-100). In agreement with the AHA's recommendations, we categorized overall and individual CVH into low (LE8 score <50), moderate (LE8 score ≥50 and <80), and high (LE8 score ≥80) levels.[6]

All-Cause and CVD Mortality

To ascertain the vital status of the participants, we conducted a probabilistic record matching method through the National Death Index records[17] until December 31, 2019. The accuracy of information of the National Death Index records has been previously validated.[18] All-cause mortality was defined based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10). We identified specific CVD mortality by using the I00-I09, I11, I13, I20-I51, and I60-I69 codes of the ICD-10.[19] Further information on the linkage of NHANES data with National Death Index records are publicly available elsewhere.[17]

Covariates

Study covariates comprised sex (male and female), age (years), race/ethnicity (Mexican-American, other-Hispanic, non-Hispanic White, non-Hispanic Black, and others), educational level ($< 9^{th}$ grade, $9\text{-}11^{th}$ grade, high school or equivalent, some college or associate degree, and college graduate or above), and the ratio of family income to poverty (0-5).

Statistical Analysis

Statistical analysis was conducted using Stata, version 16.1 software (StataCorp LLC), in March, 2022. We used restricted cubic splines to assess the dose-response associations of LE8 score and number of individual CVH factors with all-cause and CVD mortality, allowing for potential non-linearity. Pre-specified knots were placed at the 10th, 50th, and 90th percentiles of the exposure distribution. Non-linearity was assessed through a Wald test evaluating the null hypothesis that the coefficient of the second spline was equal to zero. Time-on-study in months was used as the time scale, and participants were censored when they died due to any cause, CVD as the leading cause, or at the end of follow-up (December 31, 2019), whichever came first. Analyses accounted for weights, primary sampling units, and strata from the complex multistage sampling design of NHANES to estimate Hazard Ratios (HRs) and

adjusted Population Attributable Fractions (PAF) with their corresponding 95% CIs. An adjusted Wald test found no evidence of any interaction of any covariate with either LE8 score or the number of individual CVH factors ($p>0.10$); thus, the results are presented combined for all participants.

The punaf postestimation command served to calculate PAFs.[20] This procedure estimated the adjusted proportion of preventable deaths attributable to two hypothetical scenarios by estimating the log of the mean rate ratio in all-cause and CVD mortality. Exposure was set to specific values and the rest of covariates in the model remained standardized. We compared the actual LE8 scores with different counterfactual scenarios in which the entire study population obtained 0,10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 points in LE8 score. Thereupon, we multiplied the proportion of preventable deaths obtained from each comparison of hypothetical scenarios by the number of all-cause and CVD deaths registered in the US in 2019 (i.e., 2 854 838 and 809 046 respectively),[21] which resulted in the final annual number of estimated preventable deaths for the two outcomes.

Additionally, we conducted dose-response analyses of each individual CVH factor score (range 0-100) with all-cause and CVD mortality. Moreover, we estimated the number of deaths potentially averted in the study cohort in the hypothetical scenario that participants at higher CVH risk (i.e., those with less than 50 points in LE8 score) increased up to a medium level of cardiovascular health (i.e., 60 points in LE8 score). We used a two-tailed test with a significance level of 0.05 to determine statistical significance.

Sensitivity analyses

We conducted several sensitivity analyses to ensure the robustness of our findings. First, to circumvent the potential reverse causation bias, we repeated the analyses for the main outcome after left censoring the first two years of deaths due to all-cause and CVD. Second,

to minimize the possibility of survivorship bias, we restricted the study cohort to those participants aged 79 years or younger.[9]

Results

The final study sample included 23 531 adults with a mean (SD) age of 43.6 (16.7) years, of which 11 979 (50.9%) were female and 8 960 (38.1%) were non-Hispanic white individuals. The median follow-up was 7.3 (IQR 4.3-10.1) years, corresponding to 168 033 person-years. A total of 1292 participants died during follow-up, of which 357 died due to CVD. A total of 130 (0.6%) participants achieved a high score (i.e., ≥80 points) in the eight individual LE8 CVH factors.

Table 1 shows the baseline characteristics of the study cohort by levels of CVH (low, moderate or high). Around 65% of the study cohort showed moderate levels of CVH. Participants with higher levels of CVH were younger, female, non-Hispanic white, had higher education level, had higher ratio of family income to poverty, and achieved a higher score (≥80 points) in more individual CVH factors.

Table 1. Study cohort characteristics at baseline by levels of Cardiovascular Health (CVH) (N=23 531)

	No.(%)		
Characteristics	**Low CVH (<50 LE8 points)**	**Moderate CVH (≥50-<80 LE8 points)**	**High CVH (≥80 LE8 points)**
Participants	5064(21.5)	15 363(65.3)	3104(13.2)
Age, mean (SD), y	48.4(16.5)	43.4(16.6)	36.7(14.6)
Sex			

Male	2665(52.6)	7772(50.6)	1115(35.9)
Female	2399(47.4)	7591(49.4)	1989(64.1)
Race/Ethnicity			
Mexican-American	818(16.2)	2568(16.7)	442(14.2)
Other-Hispanic	528(10.4)	1670(10.9)	325(10.5)
Non-Hispanic White	1932(38.2)	5798(37.7)	1230(39.6)
Non-Hispanic Black	1364(26.9)	3225(21.0)	377(12.2)
Others	422(8.3)	2102(13.7)	730(23.5)
Education			
< 9^{th} grade	578(11.4)	1399(8.7)	178(5.7)
9-11^{th} grade	973(19.2)	2161(14.1)	257(8.3)
High school or equivalent	1381(27.3)	3641(23.7)	473(15.2)
College or associate degree	1462(28.9)	4702(30.6)	820(26.4)
College graduate or above	670(13.2)	3520(22.9)	1376(44.3)
Ratio of family income to poverty (0-5), mean(SD)	2.2(1.5)	2.5(1.6)	2.9(1.7)
Life's essential 8 score, mean (SD)			
Total CVH Score	40.7(7.2)	64.1(8.2)	85.8(4.8)
Diet score	38.1(36.8)	45.8(33.8)	66.0(30.0)
Physical activity score	44.7(47.0)	77.8(38.7)	95.2(17.2)
Nicotine exposure score	29.0(44.1)	59.7(47.9)	93.4(23.3)
Sleep health score	70.3(29.7)	82.6(24.2)	92.2(15.7)

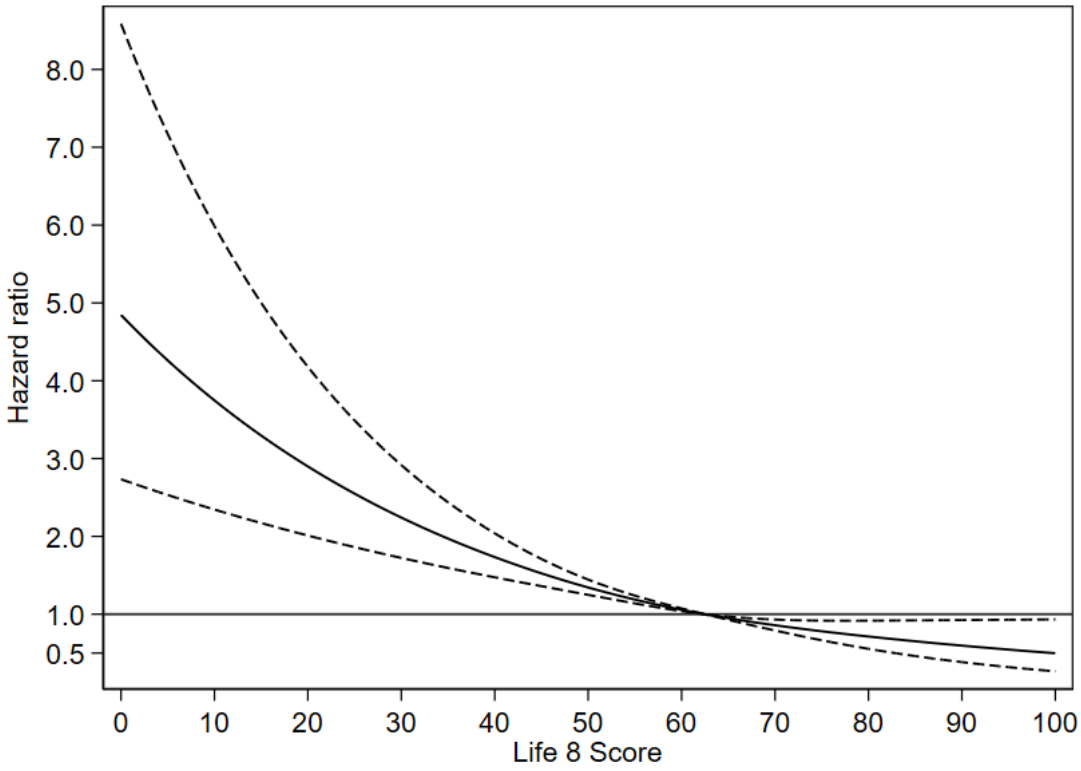
Body mass index score	34.7(33.2)	61.8(33.3)	87.9(20.1)
Blood lipid score	36.2(33.5)	65.2(32.7)	87.7(21.6)
Blood glucose score	34.6(25.2)	53.2(25.9)	73.2(27.8)
Blood pressure score	38.0(35.3)	66.8(34.7)	91.2(20.1)
Number of CVH factors with high score (≥80points), mean (SD)	1.8(0.9)	3.6(1.1)	6.0(0.9)

LE8: Life Essential 8

All-Cause mortality

The dose-response analyses showed a significant inverse curvilinear trend for the association between LE8 score and all-cause mortality (*p* for nonlinearity<0.05) (Figure 1). The highest risk reduction for all-cause mortality was observed at an LE8 score of 100 points (HR, 0.50; 95% CI, 0.27-0.93) compared to the reference (median LE8 score [62.5 points]). A minimum significant dose for reducing all-cause mortality was observed at 63 points (HR, 0.99; 95% CI, 0.99-0.99). Similarly, a higher number of individual CVH factors with a high score (≥80 points) was inversely associated with risk for all-cause mortality in a close-to linear dose-response fashion (Figure 2; reference: 4 cardiovascular health factors). Significant risk reductions were observed from 5 CVH factors (HR, 0.87; 95% CI, 0.82-0.91). We observed the highest risk reduction for 8 CVH factors with high score (HR, 0.56; 95% CI, 0.45-0.70).

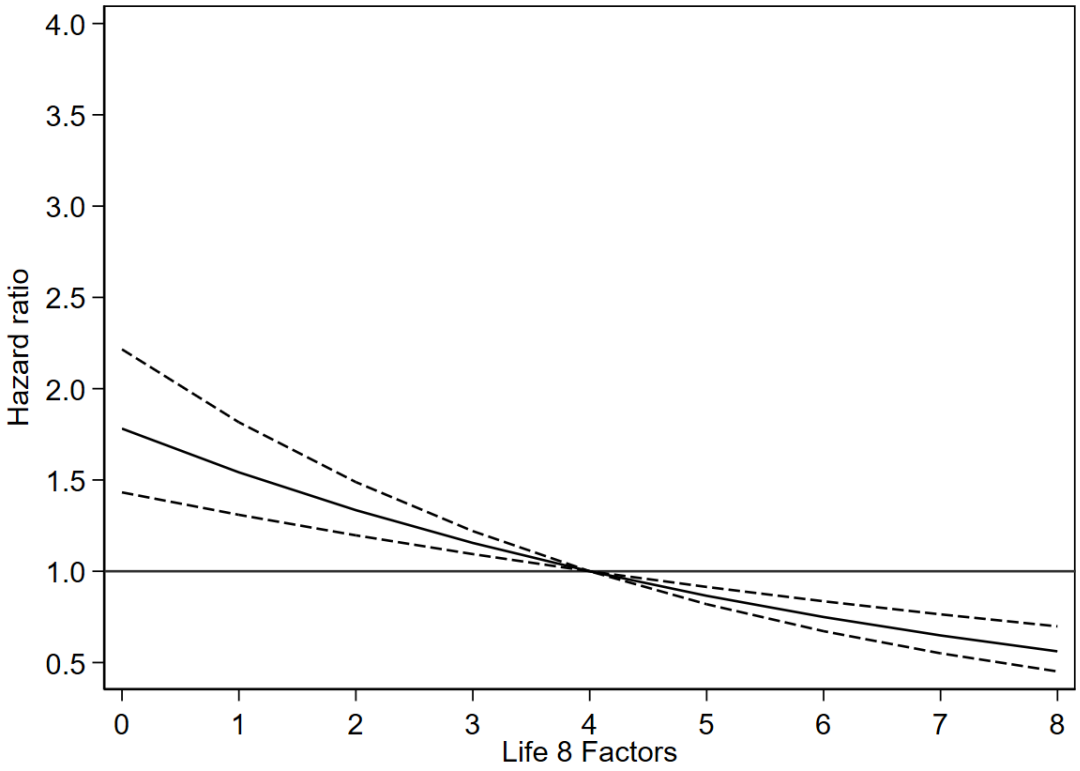
Figure 1. Dose-response association of Life 8 Essential score with all-cause mortality



Hazard ratios from restricted cubic splines were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and weights.

Note: dotted lines correspond to 95% Confidence Interval lower and upper boundaries. Reference: median value of Life Essential 8 in the study cohort (62.5 points). Reference line set at y=1.

Figure 2. Dose-response association of number of individual cardiovascular health factors with all-cause mortality



Hazard ratios from restricted cubic splines were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and weights.

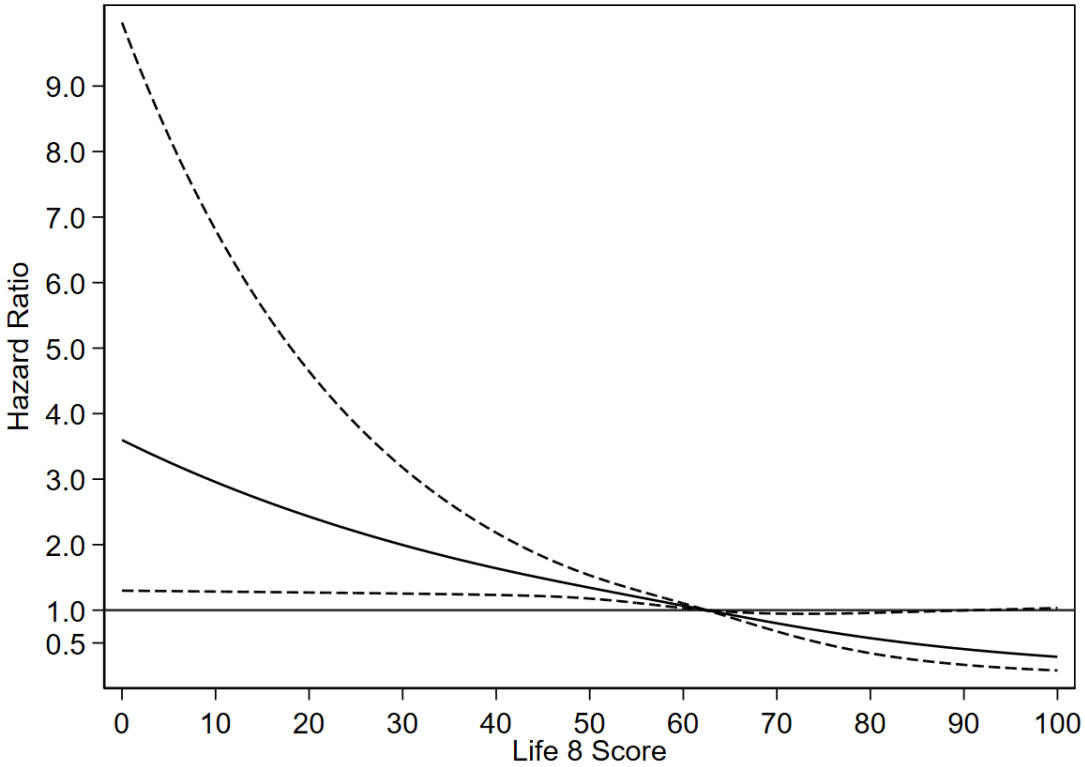
Note: dotted lines correspond to 95% Confidence Interval lower and upper boundaries. Reference: median number of cardiovascular health factors (4). Reference line set at y=1.

CVD Mortality

Figure 3 displays the dose-response association between CVH and CVD mortality, which exhibited a significant inverse curvilinear association up to an LE8 score of 90 points (p for nonlinearity<0.05) (HR, 0.41; 95% CI, 0.17-0.99) compared to the reference (median LE8 score [62.5 points]). A minimum significant dose for reducing CVD mortality was observed at 63 points (HR, 0.99; 95% CI, 0.98-0.99). Moreover, a higher number of individual CVH

factors with a high score (≥80 points) was inversely associated with risk of CVD mortality in a close-to linear dose-response fashion (Figure 4) (reference: 4 CVH factors). We identified the highest risk reduction at 8 CVH factors with high score (HR, 0.54; 95% CI, 0.37-0.79), although significant risk reductions were observed from 5 individual CVD factors (HR, 0.86; 95% CI, 0.78-0.94).

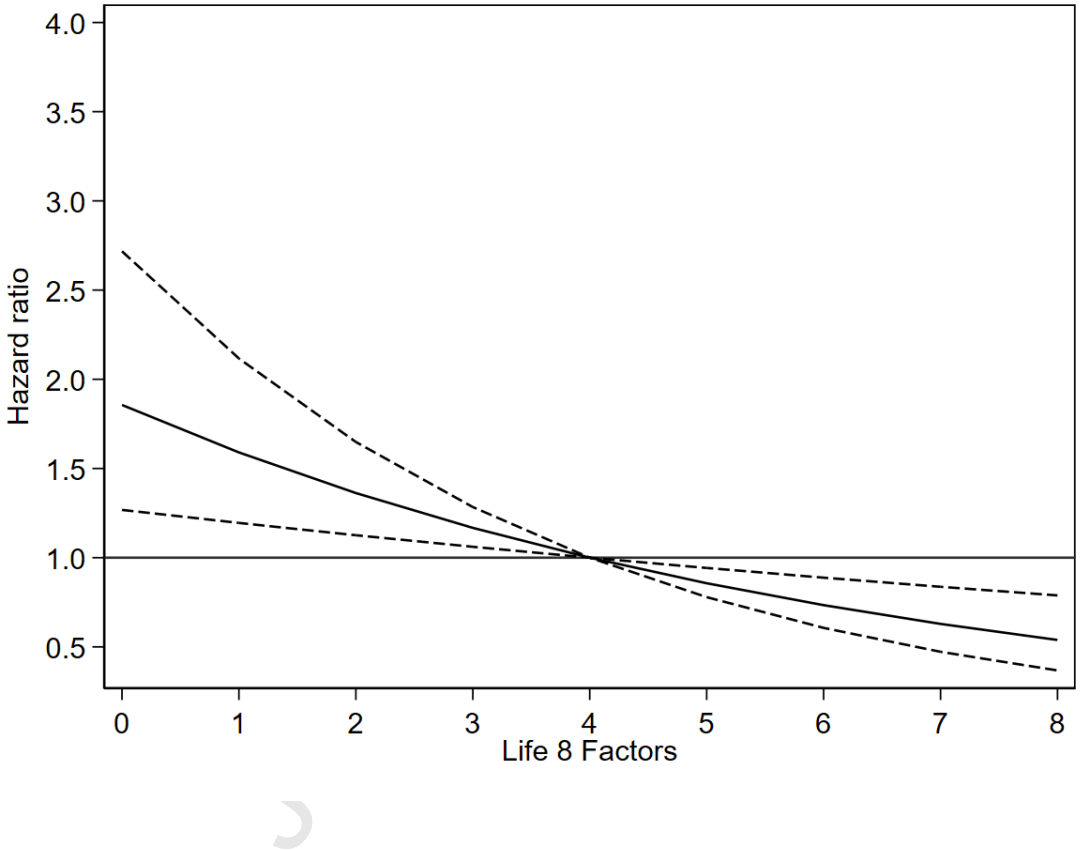
Figure 3. Dose-response association of Life 8 Essential score with CVD mortality



Hazard ratios from restricted cubic splines were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and weights.

Note: dotted lines correspond to 95% Confidence Interval lower and upper boundaries. Reference: median value of Life Essential 8 in the study cohort (62.5 points). Reference line set at y=1.

Figure 4. Dose-response association of number of individual cardiovascular health factors with CVD mortality



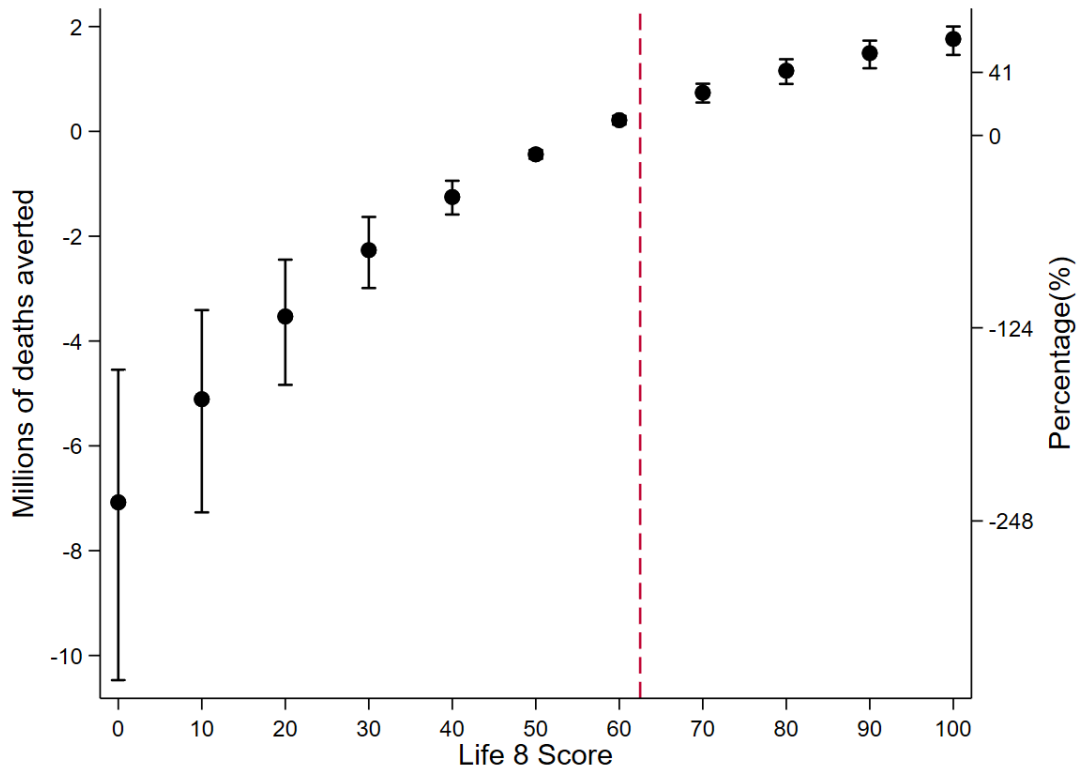
Hazard ratios from restricted cubic splines were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and weights.

Note: dotted lines correspond to 95% Confidence Interval lower and upper boundaries. Reference: median number of cardiovascular health factors (4). Reference line set at y=1.

Number of Averted Deaths

Estimated number of absolute adjusted number of annual all-cause averted deaths is shown in Figure 5. When compared to the actual LE8 score in the study cohort (median: 62.5), we estimated that a whole population achieving 100 points in the LE8 score would avert 1 763 389 annual deaths in the US (95% UI, 1 458 500-2 001 706). With regards to CVD mortality (Figure 6), a whole population achieving 100 points in the LE8 would avert 504 528 annual deaths in the US (95% UI, 333 833-613 910). We observed a significant number of averted deaths from 60 to 100 LE8 points for both mortality outcomes.

Figure 5. Number of annual averted deaths due to all-cause in the US population in relation to LIFE 8 score

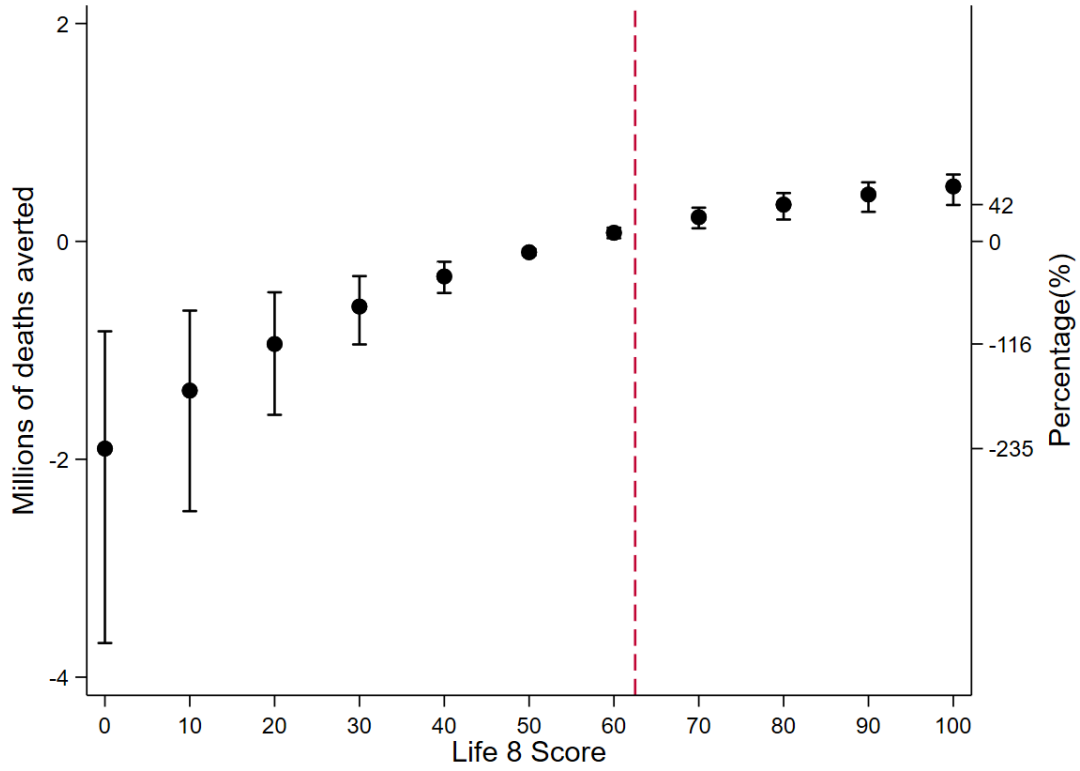


Counterfactual scenario using a study population with median value of Life Essential 8 in the study cohort (62.5 points) as reference. Models were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and

weights. Total preventable deaths and percentages derived from adjusted Population Attributable Fractions (95% CIs) of previously estimated Hazard Ratios (95% CIs). Final values were obtained computing the number of deaths due to all-cause in the US in 2019 (2 854 838). Points represent the estimation of deaths due to all-cause averted and whiskers represent 95% CIs.

Note: dotted line corresponds to reference value of Life Essential 8.

Figure 6. Number of annual averted deaths due to CVD in the US population in relation to LIFE 8 score



Counterfactual scenario using a study population with median value of Life Essential 8 in the study cohort (62.5 points) as reference. Models were adjusted for age, sex, race, educational attainment, and ratio of family income to poverty. Models accounted for National Health and Nutrition Examination Survey complex design and weights. Total preventable deaths and percentages derived from adjusted Population Attributable Fractions (95% CIs) of previously estimated Hazard Ratios (95% CIs). Final values were obtained computing the number of

deaths due to cardiovascular diseases in the US in 2019 (809 046). Points represent the estimation of deaths due to all-cause averted and whiskers represent 95% CIs.

Note: dotted line corresponds to reference value of Life Essential 8.

Additional analyses also observed a significant number of deaths averted within the study cohort if participants classified in the first LE8 quartile (≤50points) had achieved 60 points in the LE8 score (Figure S1, Figure S2).

Individual CVH Factors

Additional dose-response associations of each individual CVH factor with all-cause showed significant non-linear associations, including a flattened U-shape for blood lipids and body mass index scores, a L-shape for blood pressure and blood glucose scores, and a close to inverse linear shape for sleep and PA scores (Figure S3, Figure S4, Figure S5, Figure S6, Figure S7, Figure S8, Figure S9, Figure S10) (reference: factor-specific median value). Similar associations were observed for CVD mortality (Figure S11, Figure S12, Figure S13, Figure S14, Figure S15, Figure S16, Figure S17, Figure S18).

Sensitivity Analyses

Left-censoring the first two years of mortality outcomes showed similar pattern of associations for overall CVH and incremental number of individual CVH factors with all-cause mortality (Figure S19, Figure S20). Greater variations for pattern associations were observed for CVD mortality (Figure S21, Figure S22). Similarly, analyses removing older participants (>79 years) also showed resembling patterns of associations for all-cause mortality (Figure S23, Figure S24) and somewhat different patterns of associations for CVD mortality (Figure S25, Figure S26).

Discussion

This study examines the dose-response association of LE8 score with all-cause and CVD mortality in a nationally representative sample of US adults and estimated the number of absolute annual averted deaths in relation to the LE8 score achieved by the US population. We also provide novel estimates on the dose-response association between the number of individual CVH factors with a high score and all-cause and CVD mortality. The results show a significant inverse curvilinear association of LE8 score and all-cause and CVD mortality, with the latter limited to 90 points. Moreover, we observed a close to linear association between the number of individual CVH factors with high score and all-cause and CVD mortality. The estimation of absolute annual number of deaths averted showed potential reductions of more than 40% for all-cause and CVD mortality in the most optimal scenario (i.e., 100 points of LE8). Furthermore, small improvements of CVH among the population in the first quartile of LE8 score may provide a reduction of 36% in all-cause and CVD mortality. Additionally, individual CVH factors such as blood lipids, BMI, BP, blood glucose, sleep and physical activity scores showed a significant independent contribution to reduce all-cause mortality, whereas BMI and BP scores showed significant independent reduction of CVD mortality. All these associations showed different dose-response associations shapes.

Comparison with Other Studies

Our main results support the findings from a previous study, which showed close to linear dose–response associations of continuous CVH scores with all-cause and CVD-specific mortality.[9] However, the latter study failed to identify possible thresholds of either minimal or optimal LE8 points for risk reduction of all-cause and CVD mortality. Moreover, the authors categorized the LE8 score in low, medium and high in accordance with ad-hoc analyses, but they did not use the recommended AHA cut-off points for this purpose (i.e., ≥75 points or ≥85 points instead of AHA´s ≥80 points for high level of CVH) which may hamper comparisons

with other studies. By contrast, our study provides LE8 scores thresholds that might be used as public health guidelines for the general adult US population and used original AHA´s cut-off points to determine adequate CVH levels in the population. Another difference is that we found that a higher total LE8 score up to 90 points was associated with a reduced risk of all-cause and CVD-specific mortality in a dose–response manner. This issue is probably due to the different reference value that the two studies took for their analyses since we used the median value of the LE8 score in the study sample instead of the mean value of the LE8 score (i.e.,62.5 vs 50.0 points respectively).

The present study also adds novel knowledge on the association between the number of individual CVH factors with a high score (i.e., ≥80 points) and all-cause and CVD mortality risk. Although prior research has observed the existence of such inverse association for both outcomes,[13] our study confirms the robustness of this association also with the new LE8 score. The fact that our risk reduction estimates were greater than those observed in the study by Yang et al.[13] may indicate the contribution of the sleep CVH factor to the reduction of all-cause and CVD mortality.

Concerning the number of deaths averted, our estimates showed a slightly higher percentage for averted all-cause deaths and similar percentage for averted CVD deaths than those reported in prior research.[9] Differences in percentage for averted all-cause deaths between the two studies may be to methodological differences whereby our study, compared with previous studies, relied on fully adjusted models and accounted for the complex NHANES survey design and weights to obtain PAFs. A different study estimated an average of 43% of the gained life expectancy at age 50 years from adhering to high CVH (i.e., ≥80 points in the LE8 score) attributable to reduced risk of CVD death,[22] which endorses our estimates concerning averted CVD mortality.

Additionally, we analyzed the dose-response association of each individual CVH factor with all-cause and CVD mortality. We observed consistent inverse associations for sleep and PA with all-cause mortality, whereas BMI and BP showed a clear L-shape association with CVD mortality. Prior research has also added other CVH factors such as nicotine exposure and diet as important contributors to all-cause mortality, and PA and blood glucose as important contributors to CVD mortality.[9] The different nature of the analyses (continuous vs categorized exposure) and the use of different reference values (i.e., our study used a higher LE8 score as reference value) may explain the observed differences in the contribution of individual CVH factors to all-cause and CVD mortality.

Remarkably, we estimated that small improvements in participants in the first quartile of the LE8 score may lead to substantial reductions in all-cause and CVD mortality. Similar all-cause and CVD mortality reductions have also been estimated for small improvements in CVH among individuals with low LE8 score in prior research.[9,23] Thus, identifying determinants that define individuals with low LE8 score is a priority to develop preventive strategies aimed at high-risk groups. In our study, the low CVH category was featured by male participants, older, non-Hispanic black, and with both lower educational achievement and ratio of family income to poverty. An early attempt to disentangle the influence of social determinants such as race and socioeconomic status with cardiovascular status was conducted by He et al., who observed clear racial disparities between white and black individuals, only attenuated by education, income, home ownership, employment, health insurance, and access to health care[24]. This point has critical public health implications and deserves further investigation under the framework of the LE8 tool, which may provide more accurate information.

Clinical Implications

Together, these findings indicate the existence of a robust dose-response association between the LE8 score and all-cause and CVD mortality. Optimal all-cause and CVD mortality risk reductions were achieved with high levels of CVH, and the inclusion of the sleep CVH factor in the LE8 contributes to higher risk reductions than previously observed.[13] Thus, recommendations on the number of sleep hours are also critical when designing strategies for preventive public health recommendations among the general population. Moreover, low education, low income, and unemployed status among other socioeconomic factors have previously been associated with frequent insomnia-related symptoms and short and long sleep duration, thus preventive strategies may target these specific populations, which are also characterized by having other poor CVH factors.[24,25] Even small improvements in overall CVH among those with poorer CVH could prevent a substantial amount of related annual deaths among the US population. Meeting a high score in a single CVH factor such as sleep, PA, BMI or BP could also contribute to lower risks of all-cause and CVD mortality. Together, these observations on high-risk groups and improvements in individual CVH factors may point out feasible targets when providing individual medical counselling.

Strengths and Limitations

The present study focuses on the dose-response association of LE8 score with all-cause and CVD by strictly following the updated AHA´s guidelines that define each of the considered eight critical CVH factors. We used a large representative sample of US adults. In contrast to previous research,[9] we accounted for the complexity of the NHANES survey design in all our estimations. Nevertheless, there are limitations to this observational study, including potential recall bias due to self-reported data of the four CVH behavioral factors and covariates. Also, there is still a chance for a certain degree of residual confounding bias. Moreover, the possibility of residual reverse causation exists even despite sensitivity analyses performed showing consistent results. Additionally, the present study cohort has shown sparse

confidence intervals at the higher ends of the LE8 and individual CVH scores factors, which may have attenuated the dose-response associations of LE8 with all-cause and CVD mortality and could partially explain several non-statistically significant associations for individual CVH factors. Finally, the nature design of NHANES does not allow for controlling time-varying oscillations of either exposures or covariates, which may contribute to increase the risk for biased estimates.

Conclusions

We identified optimal thresholds for the inverse association of the LE8 score and individual CVH factors with all-cause and CVD mortality in the US adult population. Meeting optimal LE8 scores in the population may be able to prevent approximately 40% of all-cause and CVD annual deaths among US adults. Substantial reductions of the CVD burden may be addressed through small improvements in the LE8 score by targeting specific groups with poorer CVH or meeting high scores in individual CVH factors.

Funding

RLB is supported by the European Union – Next Generation EU. BdPC is supported by the Government of Andalusia, Research Talent Recruitment Programme (EMERGIA 2020/00158).

Data availability statement

The data used in this study is publicly available at https://www.cdc.gov/nchs/nhanes/index.htm

References

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a

systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 2018;392:1736–1788. doi:10.1016/S0140-6736(18)32203-7.

2. Birger M, Kaldjian AS, Roth GA, Moran AE, Dieleman JL, Bellows BK. Spending on Cardiovascular Disease and Cardiovascular Risk Factors in the United States: 1996 to 2016. Circulation 2021;144:271–282. doi:10.1161/CIRCULATIONAHA.120.053216.
3. Shah NS, Lloyd-Jones DM, O'Flaherty M, Capewell S, Kershaw KN, Carnethon M, et al. Trends in Cardiometabolic Mortality in the United States, 1999-2017. JAMA 2019;322:780–782. doi:10.1001/jama.2019.9161.
4. Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. Int J Epidemiol 2019;48:1815–1823. doi:10.1093/ije/dyz143.
5. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction. Circulation 2010;121:586–613. doi:10.1161/CIRCULATIONAHA.109.192703.
6. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory from the American Heart Association. Circulation 2022;146:E18–E43. doi:10.1161/CIR.0000000000001078.
7. Shetty NS, Parcha V, Patel N, Yadav I, Basetty C, Li C, et al. AHA Life's essential 8 and ideal cardiovascular health among young adults. Am J Prev Cardiol 2023;13:100452. doi:10.1016/j.ajpc.2022.100452.
8. Yi J, Wang L, Guo X, Ren X. Association of Life's Essential 8 with all-cause and cardiovascular mortality among US adults: A prospective cohort study from the NHANES 2005–2014. Nutr Metab Cardiovasc Dis 2023;33:1134–1143.

doi:10.1016/j.numecd.2023.01.021.

9. Sun J, Li Y, Zhao M, Yu X, Zhang C, Magnussen CG, et al. Association of the American Heart Association's new "Life's Essential 8" with all-cause and cardiovascular disease-specific mortality: prospective cohort study. BMC Med 2023;21:116. doi:10.1186/s12916-023-02824-8.
10. Lloyd-Jones DM, Ning H, Labarthe D, Brewer LP, Sharma G, Rosamond W, et al. Status of Cardiovascular Health in US Adults and Children Using the American Heart Association's New "Life's Essential 8" Metrics: Prevalence Estimates From the National Health and Nutrition Examination Survey (NHANES), 2013 Through 2018. Circulation 2022;146:822–835. doi:10.1161/CIRCULATIONAHA.122.060911.
11. Ma H, Wang X, Xue Q, Li X, Liang Z, Heianza Y, et al. Cardiovascular Health and Life Expectancy Among Adults in the United States. Circulation 2023;147:1137–1146. doi:10.1161/CIRCULATIONAHA.122.062457.
12. Isiozor NM, Kunutsor SK, Voutilainen A, Laukkanen JA. Life's Essential 8 and the risk of cardiovascular disease death and all-cause mortality in Finnish men. Eur J Prev Cardiol 2023;30:658–667. doi:10.1093/eurjpc/zwad040.
13. Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. JAMA 2012;307:1273–1283. doi:10.1001/jama.2012.339.
14. Centers for Disease Control and Prevention; National Center for Health Statistics.National Health and Nutrition Examination Survey. Accessed May 2, 2023. https://www.cdc.gov/nchs/nhanes/index.htm
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Epidemiology 2007;18:800–

804. doi:10.1016/j.ijsu.2014.07.013.

16. Dos Santos M, Ferrari G, Lee DH, Rey-López JP, Aune D, Liao B, et al. Association of the “weekend Warrior” and Other Leisure-time Physical Activity Patterns with All-Cause and Cause-Specific Mortality: A Nationwide Cohort Study. JAMA Intern Med 2022;182:840–848. doi:10.1001/jamainternmed.2022.2488.
17. National Center for Health Statistics. Centers for Disease Control and Prevention. The Linkage of National Center for Health Statistics Survey Data to the National Death Index-2015 Linked Mortality File (LMF): Methodology Overview and Analytic Considerations. n.d.
18. Lochner K, Hummer RA, Bartee S, Wheatcroft G, Cox C. The public-use national health interview survey linked mortality files: Methods of reidentification risk avoidance and comparative analysis. Am J Epidemiol 2008;168:336–344. doi:10.1093/aje/kwn123.
19. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final Data for 2013. Natl Vital Stat Rep 2016;64:1–119.
20. Newson RB. Attributable and unattributable risks and fractions and other scenario comparisons. Stata J 2013;13:672–698. doi:10.1177/1536867x1301300402.
21. Alzheimer´s association report. 2021 Alzheimer’s disease facts and figures. Alzheimer’s Dement 2021;17:327–406. doi:10.1002/alz.12328.
22. Wang X, Ma H, Li X, Heianza Y, Manson JE, Franco OH, et al. Association of Cardiovascular Health With Life Expectancy Free of Cardiovascular Disease, Diabetes, Cancer, and Dementia in UK Adults. JAMA Intern Med 2023;183:340–349. doi:10.1001/jamainternmed.2023.0015.
23. Petermann-Rocha F, Deo S, Celis-Morales C, Ho FK, Bahuguna P, McAllister D, et al. An Opportunity for Prevention: Associations Between the Life’s Essential 8 Score and

Cardiovascular Incidence Using Prospective Data from UK Biobank. Curr Probl Cardiol 2023;48:101540. doi:10.1016/j.cpcardiol.2022.101540.

24. He J, Zhu Z, Bundy JD, Dorans KS, Chen J, Hamm LL. Trends in Cardiovascular Risk Factors in US Adults by Race and Ethnicity and Socioeconomic Status, 1999-2018. JAMA 2021;326:1286. doi:10.1001/jama.2021.15187.

25. Lallukka T, Sares-Jäske L, Kronholm E, Sääksjärvi K, Lundqvist A, Partonen T, et al. Sociodemographic and socioeconomic differences in sleep duration and insomnia-related symptoms in Finnish adults. BMC Public Health 2012;12. doi:10.1186/1471-2458-12-565.

Conflict of interest: None.