Curr Probl Cardiol 49 (2024) 102176

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Invited Review Article

Dose-response association between cardiovascular health and mortality in cancer survivors

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ARTICLE INFO

Keywords:
Life expectancy
Lifestyle
Oncology
Cardiology
Preventive medicine
Public health

ABSTRACT

Background: There is little knowledge on the dose-response association between cardiovascular health (CVH) and risk of all-cause, cardiovascular disease (CVD) and cancer deaths among cancer survivors.

Aims: We aimed to examine the dose-response association of CVH with all-cause, CVD, and cancer mortality.

Methods: A total of 1701 US adult cancer survivors were followed-up during a median of 7.3 (IQR 4.0-10.2) years from 2007 to 2018 through the National Health and Nutrition Examination Survey (NHANES). We used the American Heart Association's (AHA) Life's Essential 8 (LE8) as a proxy for CVH.

Results: Restricted cubic spline models indicated a close to inverse linear shape for the dose-response association between LE8 score and all-cause mortality with significant risk reductions within the range between 61.25 (Hazard ratio [HR]: 0.76, 95% CI, 0.59-0.98) and 100 points (HR: 0.28, 95%CI, 0.12-0.62), and a curvilinear shape for the dose-response association between LE8 score and CVD deaths with significant risk reductions within the range between 50.25 (HR: 0.72, 95% CI, 0.52-0.99) and 90.25 points (HR: 0.15, 95%CI, 0.02-0.98). No significant dose-response association was observed between LE8 and cancer deaths.

Conclusions: Our study showed a close to inverse relationship between higher LE8 and risk of death from all cause, an inverse curvilinear relationship between higher LE8 and the risk for CVD death, and a non-significant association between higher LE8 and the risk of cancer death among US adult cancer survivors, which may translate to a substantial number of annual averted deaths and thus important public health implications.

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https://doi.org/10.1016/j.cpcardiol.2023.102176

Available online 3 November 2023

Introduction

Global aging is driving the increasing number of cancer cases.[1] Meanwhile, cancer survival has significantly improved owning to advancements in early detection and treatment, particularly in high-income countries.[2] In the US, the number of cancer survivors is projected to reach 26 million by 2040.[3] Cancer treatment can exacerbate the existing comorbidities and increase the risk of new comorbidities in cancer survivors,[4,5] posing unique late effects in the cancer survivorship.[6,7] As such, non-cancer deaths, particularly cardiovascular disease (CVD), has outweighed cancer-related deaths in certain cancers.[8,9] The cancer survivor population is expected to continue to rise over the next 50 years[10], which is likely to bring about substantial CVD burden in the population[11].

Beside age, CVD and cancer has several shared risk factors, such as smoking, obesity, diabetes mellites, suggesting their shared biology.[12] Shared risk factors and cancer treatment induced toxicities (i.e., cardiotoxicity) have put cancer survivors now at risk of developing CVD.[11,12] A recent US population-based study found increased short-, medium- and long-term risk of CVD death in cancer survivors of many types[8]. Other studies also suggested that the excessive CVD burden among cancer survivors were observed in all population subgroups,[11] but notably different by racial and ethnic groups in the US.[13] Recognizing this significant association between cancer and CVD, it is imperative to develop clinical tools to monitor cardiovascular health (CVH) in cancer survivors to inform risk-stratification.[14] More importantly, preventive measures are required beyond clinical management to improve CVH in cancer survivors to reduce the burden from the survivors and the healthcare system.[15]

Recently, the American Heart Association (AHA) updated the Life's Essential 8 (LE8) score, which captures modifiable risk factors, including smoking, body mass index, physical activity, sleep, dietary habits, blood pressure, fasting glucose, and total cholesterol levels, to assess CVH. Previous studies have demonstrated a robust association between LE8 and CVD and all-cause mortality in the general population. This study aims to investigate the dose-response associations of LE8 with all-cause, CVD and cancer mortality among cancer survivors. Furthermore, it seeks to estimate the potential number of prevented deaths in the US through incremental improvements in LE8 scores.

Methods

Study design and sample

This prospective cohort study analysed deidentified data from 6 consecutive waves of the National Health and Nutrition Examination Survey (NHANES; 2007-2018). NHANES, conducted and approved by the National Center for Health Statistics and Center for Disease Control and Prevention, is a biannual survey employing a complex, multistage probability sampling design to represent the US civilian, noninstitutionalized population.[16] The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[17]

From an initial sample of 8412 adults (≥18 years) self-reporting a cancer diagnosis and free from history of specific conditions (congestive heart failure, coronary heart disease, angina, heart attack, stroke, or emphysema) ,[18,19] we excluded pregnant women (n=10), and participants with missing values in LE8 components or study covariates (n=6701). Overall, the study cohort comprised 1701 participants.

Life's Essential 8 components

The LE8 score covers 4 health behaviours (nicotine exposure, physical activity, diet, and sleep) and 4 health factors (body mass index, blood glucose levels, blood lipid levels, and blood pressure). The LE8 score is calculated as the mean value of these 8 components graded on a scale 0 to 100.[18] The overall CVH score was categorized into low (<50), moderate (≥50-<80) and high (≥80) in accordance with standard cut-offs. More information on the LE8 score is provided in the seminal study.[20]

All-cause, cardiovascular and cancer deaths

Vital status was ascertained using a probabilistic record matching method with the National Death Index records[21] until December 31, 2019. All-cause mortality was based on the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Specific CVD mortality was identified through I00-I09, I11, I13, I20-I51, and I60-I69 codes, whereas cancer mortality was ascertained through C00-C97 ICD-10 codes.[22]

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 (< 9th grade, 9-11th grade, high school or equivalent, some college or associate degree, and college graduate or above), ratio of family income to poverty (0-5), number of cancers experienced, and age at the last cancer diagnosis.

Statistical analysis

We used restricted cubic splines to assess the dose-response associations between LE8 score and all-cause, CVD and cancer mortality

among cancer survivors. Knots were pre-specified at the 10th, 50th, and 90th percentiles of the exposure distribution. Non-linearity and interactions between LE8 and sex, age, and race were assessed using Wald tests. No significant result was found for neither of the latter ($p>0.10$). Time-on-study in months served as the time scale, and participants were censored at the time of death (any cause, CVD or cancer as the leading cause) or the end of follow-up (December 31, 2019). Analyses accounted for weights, primary sampling units, and strata from the NHANES complex sampling design to estimate Hazard Ratios (HRs) and adjusted Population Attributable Fractions (PAFs) with corresponding 95% CIs. The punaf postestimation command was used to calculate PAFs,[23] estimating the adjusted proportion of preventable deaths. Hypothetical scenarios were created by setting the exposure (LE8 score) to specific values (10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 points in the LE8 score) and keeping other covariates standardized. The proportion of preventable deaths was multiplied by the annual rates per million to determine annual rates of adverted deaths per million. All the used models were fully adjusted. To mitigate reverse causation bias, the analyses were repeated after left censoring the first two years of deaths due to all-cause, CVD, and cancer. All analyses were conducted in Stata version 16.1. Statistical significance was determined using a two-tailed test with a significance level of 0.05.

Results

The final study sample included 1701 cancer survivors with a mean (SD) age of 62.0 (15.0) years, of which 952 (56.0%) were female and 1113 (65.4%) were non-Hispanic white individuals. The median follow-up was 7.3 (IQR 4.0-10.2) years, corresponding to 11 884 person-years. Overall, 353 participants died during follow-up, of which 65 died due to CVD and 146 due to cancer.

Table 1 show the baseline characteristics of the study population by levels of CVH defined by LE8 (low, moderate or high). Overall, the vast majority cancer survivors had low (24.9%) and moderate (66.1%) CVH. Cancer survivors with higher CVH were younger, male, non-Hispanic white, had higher education level, had higher ratio of family income to poverty, and were younger when the last cancer was diagnosed.

The restricted cubic splines indicated a close to inverse linear shape (p for non-linearity: 0.0025) for the dose-response association between LE8 score and all-cause deaths (Fig. 1). There was a statistically significant risk reduction of death from all-cause associated with higher LE8 score within the range between 61.25 (HR: 0.76, 95% CI, 0.59-0.98) and 100 points (HR: 0.28, 95%CI, 0.12-0.62).

Specific to CVD death among cancer survivors, the restricted cubic splines indicated an inverse curvilinear shape (p for non-linearity: 0.0035) for the dose-response association between LE8 score and CVD mortality (Fig. 1). There was a statistically significant CVD death risk reduction associated with higher LE8 score within the range between 50.25 (HR: 0.72, 95% CI, 0.52-0.99) and 90.25 points (HR: 0.15, 95%CI, 0.02-0.98).

With respect to cancer death, we found an inverse statistically non-significant curvilinear relationship between LE8 and cancer specific death among cancer survivors (p for non-linearity: 0.4097) (Fig. 1).

Annual rates of averted all-cause deaths per million in cancer survivors showed a maximal reduction for a LE8 score of 95 (22 801; 95% CI, 12 626- 29 598) compared with a hypothetical scenario in which the entire population of cancer survivors met the 10th percentile (39.4 points) of the LE8 score (Fig. 2). Similarly, a LE8 score of 95 represented the maximal number of averted deaths due to CVD per million (4198; 95% CI, 2023-6261) when compared with the same reference (Fig. 2).

Sensitivity analyses by excluding cancer survivors who died during the first two years of follow-up retrained similar findings for the

Table 1
Study cohort characteristics at baseline by levels of cardiovascular health (CVH) (N=1701).

	No.(%)		
Characteristics	Low CVH (<50 LE8 points)	Moderate CVH (≥50-<80 LE8 points)	High CVH (≥80 LE8 points)
Participants	423(24.9)	1125(66.1)	153(9.0)
Age, mean (SD), y	63.4(14.0)	62.3(15.1)	56.7(16.0)
Sex			
Male	179(42.3)	524(46.6)	46(30.1)
Female	244(57.7)	601(53.4)	107(29.9)
Race/Ethnicity			
Mexican-American	37(8.8)	81(7.2)	11(7.2)
Other-Hispanic	25(5.9)	94(8.4)	11(7.2)
Non-Hispanic White	261(61.7)	743(66.0)	109(71.2)
Non-Hispanic Black	82(19.4)	143(12.7)	11(7.2)
Others	18(4.3)	64(5.6)	11(7.2)
Education			
< 9th grade	56(13.2)	80(7.1)	2(1.3)
9-11th grade	70(16.6)	117(10.4)	8(5.2)
High school or equivalent	83(19.6)	243(21.6)	19(12.4)
College or associate degree	143(33.8)	328(29.2)	36(23.5)
College graduate or above	71(16.8)	357(31.7)	88(57.5)
Ratio of family income to poverty (0-5), mean(SD)	2.4(1.6)	3.0(1.7)	3.7(1.6)
Number of cancers, mean(SD)	1.1(0.4)	1.1(0.3)	1.1(0.3)
Age when last cancer was diagnosed, mean(SD), y.	52.6(16.8)	52.5(16.5)	48.2(15.3)
LE 8 score, mean (SD)	39.8(7.8)	63.3(8.1)	85.2(4.7)

LE8: Lifeś Essential 8.

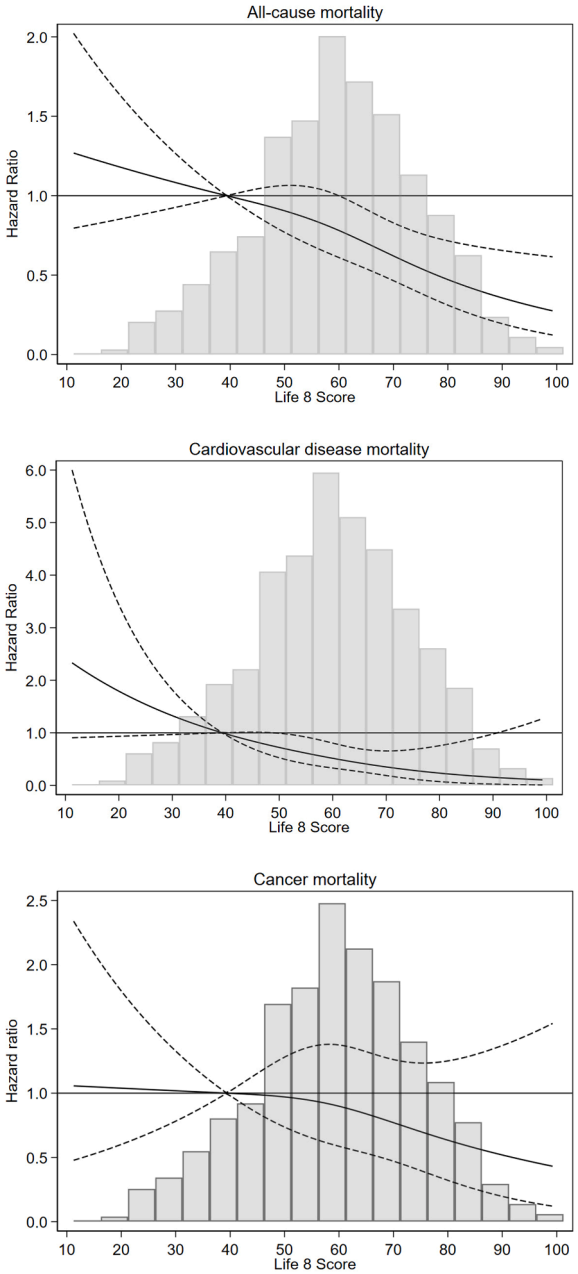

Fig. 1. Dose-response association of Life 8 Essential score with all-cause and CVD mortality in cancer survivors.
Hazard ratios from restricted cubic splines were adjusted for age, sex, race, educational attainment, ratio of family income to poverty, number of diagnosed cancers, and age when the last cancer was diagnosed. 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: 10th percentile value of Life Essential 8 in the study cohort (39.4 points). Reference line set at y=1. Vertical blue bars correspond to a histogram of Life 8 score distribution.

dose-response association between the LE8 score and all-cause, CVD, and cancer death (Supplementary Figs. 1-3).

Discussion

In a US nationally representative sample of cancer survivors, this study examined the dose-response association of LE8 score with all cause, CVD, and cancer deaths. In addition, we estimated the expected number of annual averted deaths per million in relation to the LE8 score achieved in US cancer survivors. Findings from this study demonstrated a close to inverse relationship between higher

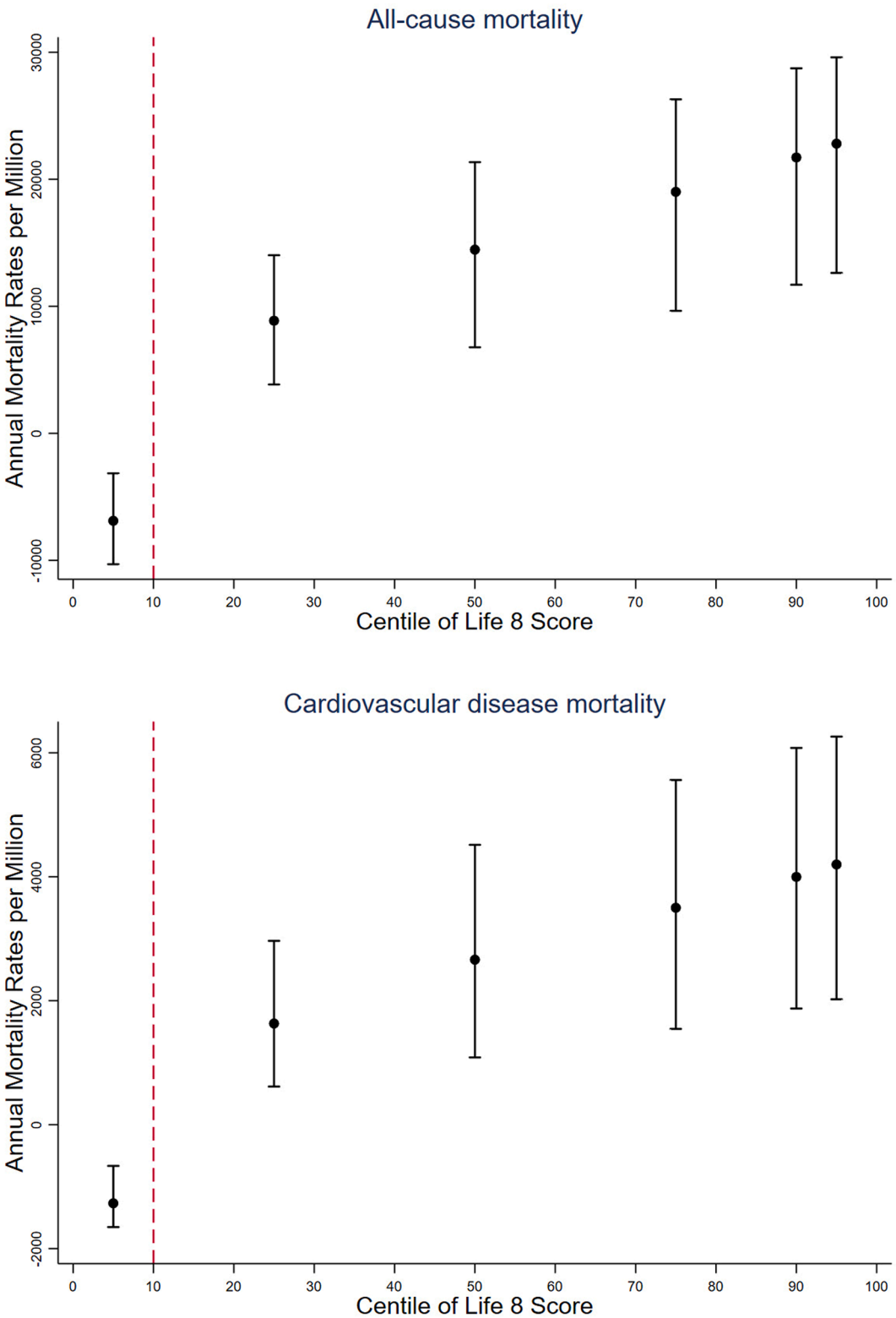

Fig. 2. Annual rates of averted deaths per million in cancer survivors.
Counterfactual scenarios using a study population with 10th percentile cut-point value of Life Essential 8 in the study cohort (39.4 points) as reference. Models were adjusted for age, sex, race, educational attainment, ratio of family income to poverty, number of diagnosed cancers, and age when the last cancer was diagnosed. Models accounted for National Health and Nutrition Examination Survey complex design and weights. Total

annual averted death rates derived from adjusted Population Attributable Fractions (95% CIs) of previously estimated Hazard Ratios (95% CIs). Points represent the estimation of deaths due to all-cause averted and whiskers represent 95% CIs.
Note: dotted lines correspond to reference value of Life Essential 8.

LE8 and the reduced risk of death from all cause, an inverse curvilinear relationship between higher LE8 and the reduced risk of death from CVD, and a non-significant association between higher LE8 and the risk of cancer death among US adult cancer survivors. Moreover, we observed a concerning low percentage of cancer survivors achieving high LE8 scores.

The mortality risk reduction from all-cause, CVD, and cancer associated with either LE8 or CVH has been previously investigated in the general population.[24,25] A prospective cohort study of 1662 Finnish men identified a strong inverse association between LE8 being and CVD and all-cause mortality in a linear dose-response relationship.[24] Similarly, LE8 was investigated in 23 110 US adults and revealed a 40% and 54% risk reduction associated with high CVH (LE8 $\geq$80) as compared to low CVH (LE8 $<$50) for all-cause and CVD mortality, respectively.[25]

It is widely recognized that multiple risk factors contributing to CVD aetiology and progression and that a comprehensive approach is required to assess and promote CVH.[20] Hence, the AHA developed the "Life's Simple 7″ metrics comprising the presence of both ideal health behavior and ideal health factors to comprehensively characterize CVH.[26] Ten years since the "Life's Simple 7″ was initially developed, sleep health was added as a crucial factor for CHV and updated the new metrics to LE8.[20] Better CVH as assessed by Life's Simple 7 had been linked with lower overall cancer incidence in a large cohort of 13 253 adults.[27] Nevertheless, we found no association between LE8 and cancer specific death after cancer. Our findings suggest a potential complex interplay between CVH, cancer and cancer treatment. It is possible that the potential protective effect of CVH on cancer development is diminished due to treatment side-effects. Moreover, current cancer care focuses on cancer control with no routine practice to monitor CVD risk. Hence, there is a lack of adequate CVD risk management in cancer survivors leading to early death despite durable cancer control.

To the best of our knowledge, the present study is the first to investigate the association between LE8 and long-term outcomes in cancer survivors. Cardiotoxic drugs, most notably arrhythmia, and chest radiation are known to damage the cardiovascular system of individuals undergoing cancer treatment, i.e., cardiotoxicity.[28] However, the importance of CVH is not limited to cancer survivors with cardiotoxicity as a result of treatment complications. In support, our analyses suggested that less than 10% of the US cancer survivor population is achieving high CVH. Some studies suggested that survivors of prostate cancer do not experience higher risk of CVD comparing to non-prostate cancer men,[9] but CVD remains the leading cause of death in prostate cancer survivors.[29] Hence, it is imperative to develop tools to monitor and optimize CVH in cancer survivors.

Nicotine exposure and obesity have been associated with increased risk of death from both CVD and cancer among cancer survivors.[30,31] Evidence on the lack of physical activity and unhealthy diet was strong for cancer specific death after cancer and is emerging for CVD specific death among cancer survivors.[32,33] Evidence is limited for sleep health but initial research suggest that sleep health plays a role for both CVD and cancer outcomes among cancer survivors.[34] Likewise, although limited, recent evidence on the negative impact of elevated blood pressure, fasting glucose and total cholesterol level on increased CVD risk among cancer survivors is emerging.[35,36] Altogether, our findings suggested that despite cancer and its treatment may impair the cardiovascular system and increase CVD risk, there is a range of modifiable factors could be intervened upon to improve CVD outcomes during the long-term cancer survivorship.

Our findings provide valuable insights for developing evidence-based management strategies to optimize cardiovascular outcomes and reduce mortality in the rapidly growing survivor population. Currently, CVH assessment is not yet a part of the standard cancer care. Given the increased short-, medium- and long-term risk of CVD death in cancer survivors of many types,[8] recent studies began to develop and test the usability of digital tools to assess CVH for cancer survivors,[37] Our does-response analyses provide critical data to inform the LE8 score cut-off specifics to cancer survivors. Notably, our analyses found no interaction of age, sex and race on the association between LE8 and mortality outcomes among cancer survivors. Although our study population is a sizable cohort of cancer survivors, it may be under powered to investigate subgroup differences such as social determinants of health and specific cancer types. Beyond assessment and monitoring, using metrics such as LE8 owns the unique advantage to identify modifiable risk factors and refers cancer survivors for targeted interventions to manage their CVD risk. Future research in larger study samples is needed to investigate whether the optimal CVH defined by LE8 may differed in population subgroups and implement and evaluate CVH promotion interventions in the high-risk cancer survivor population.

Strengths and limitations

The present study focuses on the dose-response association of LE8 score with all-cause, CVD and cancer deaths by adhering the updated AHAś guidelines to determine each of the considered CVH factors, and 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 and misclassification bias due to self-reported data of four out of five CVH behavioral factors as well as used covariates. Furthermore, there might still be a chance for residual confounding bias due to potential confounders not included in our models. Also, the possibility of residual reverse causation exists despite sensitivity analyses. Finally, the design of NHANES does not permit controlling time-varying variations of either LE8 score or covariates, which might lead to less accurate estimates.

Conclusions

The present study observed a close to inverse relationship between higher LE8 and risk of death from all cause, an inverse curvilinear relationship between higher LE8 and the risk for CVD death, and a non-significant association between higher LE8 and the risk of cancer death among US adult cancer survivors. Achieving a higher CVH score among US adult cancer survivors may prevent a substantial number of annual deaths due to all-cause and CVD. These figures illustrate to what extent improving CVH in cancer survivors may impact in terms of public health among the population.

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).

Availability of data and materials

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cpcardiol.2023.102176.

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