Association between Life's Essential 8 and all-cause or cardiovascular-specific mortality in patients with rheumatoid arthritis

X. Kong[1], W. Wang[2]

[1]Department of Rheumatology, Zhongshan Hospital, Fudan University, Shanghai, China;
[2]Department of Nephrology, Shanghai Tenth People's Hospital, Shanghai, China.

Abstract

Objective

Patients with rheumatoid arthritis (RA) have been found to have a higher cardiovascular disease (CVD) burden. We aimed to examine the associations between Life's Essential 8 (LE8), a metric of cardiovascular health (CVH) recently proposed by the American Heart Association, and all-cause and CVD mortality in RA patients.

Methods

This prospective cohort study analysed RA patients from the National Health and Nutrition Examination Survey 2005–2018 with linked mortality data through December 31, 2019. Total LE8 scores were calculated and divided into the high- (LE8 80–100), moderate- (LE8 50–79), and low-CVH (LE8 0–49) groups. Weighted multivariable Cox regression, logistic regression and restricted cubic spline models were applied to explore the association between LE8 and outcomes.

Results

A total of 1424 RA patients were enrolled with a weighted mean age of 57.87 years and female proportion of 58.94%. During a median follow-up of 82 months, 270 all-cause (85 CVD) deaths were recorded. Compared with the high-CVH group, participants in the moderate- and low-CVH groups had an 85.8% and 129.5% increased risk of all-cause mortality, respectively. After adjustment for potential confounders, each 1 point decrease in LE8 score was associated with a 2.6% increased risk of CVD mortality. Subgroup analyses showed significant interactions between LE8 score and non-Hispanic white population with risk of all-cause mortality. The results were robust for all-cause mortality, but not for CVD mortality in the sensitivity analysis.

Conclusion

CVH measured by the LE8 score is a robust and independent predictor of all-cause mortality among U.S. RA patients.

Key words

cardiovascular health, Life's Essential 8, mortality, NHANES, rheumatoid arthritis

Xiufang Kong, MD, PhD
Wei Wang, MD, PhD

Please address correspondence to:
Wei Wang
Department of Nephrology,
Shanghai Tenth People's Hospital,
Middle Yanchang Road 301,
Shanghai 200032, China.
E-mail: 13211010060@fudan.edu.cn

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Introduction

Rheumatoid arthritis (RA) is a chronic and debilitating systemic inflammatory disease that progressively compromises joint function, leading to irreversible functional loss and permanent disability. Prior studies have shown that in addition to bone erosion and joint deformity, RA patients are also susceptible to a higher burden of cardiovascular disease (CVD) (1). For instance, earlier studies have shown that RA patients had 68% and 41% increased risk for myocardial infarction and cerebrovascular accidents, respectively, as compared with the general population (2). Despite significant advances in RA treatment, epidemiologic studies still indicate an increased risk of premature mortality and health decline in this patient population (3). Therefore, there remains an unfulfilled need to identify potentially modifiable risk factors to screen high-risk patients for early intervention and reduce patient mortality.

Adhering to a healthy lifestyle to promote cardiovascular health (CVH) has been recommended by several rheumatology society guidelines to promote health outcomes in RA patients (4). However, the beneficial effects of a healthy lifestyle on RA outcomes have been rarely evaluated in real-world settings. Recognising that much of the CVD burden is attributable to a limited number of health and behavioural factors, the American Heart Association recently updated its assessment of CVH by introducing a novel metric called Life's Essential 8 (LE8), which comprises 4 health-related quantitative measures (blood pressure, blood glucose, blood lipids and body mass index [BMI]) and 4 health-related behaviour measures (physical activity, diet, nicotine exposure and sleep health) (5). Earlier studies have suggested that LE8 is positively associated with life expectancy and risk of all-cause mortality in the general U.S. population (6). However, given the increased all-cause and CVD-specific mortality in RA patients, the impact of a healthy lifestyle as assessed by LE8 on patient outcomes remains unknown.

To bridge this gap, the current study aimed to explore the associations between cardiovascular fitness, as defined by LE8, and all-cause and CVD-specific mortality in RA by leveraging nationally representative data from the National Health and Nutrition Examination Survey (NHANES).

Materials and methods

Study population

The study utilised data from the NHANES, a serial biennial cross-sectional survey that aimed to evaluate the health and nutritional status of non-institutionalised U.S. civilians by employing complex, multistage probability sampling design (7). Since the NHANES protocol has already received approval from the National Center for Health Statistics Institutional Review Board, and all adult participants have provided written informed consent, no further ethic approval is necessary.

We combined data from a total of 7 cycles of NHANES from 2005 to 2018, since components of LE8 were unavailable in cycles preceding 2005. The study flow chart was presented in Figure 1. Eligible participants were aged ≥20 years with self-reported RA in the personal interview. The questions used to assess whether a participant has arthritis and the specific type of arthritis were "Has a doctor or other health professional ever told you that you had arthritis?" (MCQ160A) and "Which type of arthritis was it?" (MCQ 190). Participants were excluded for pregnancy or breastfeeding at the time of the interview (n=3), missing data on LE8 or its components (n=602), and missing outcome data (n=3). The final analytic sample for the current report consisted of 1424 RA patients.

Ascertainment of LE8

The ascertainment of LE8 aligned with the algorithm outlined by the American Heart Association, in which each of the 8 components of LE8 was scored on a scale of 0 to 100 points. The scores of each component were summed up for each individual and the LE8 was calculated by dividing the total score by 8. Consistent with previous research, the LE8 scores were classified as high CVH, moderate CVH and low CVH based on respective scores of 80–100, 50–79, and <50 points (8).

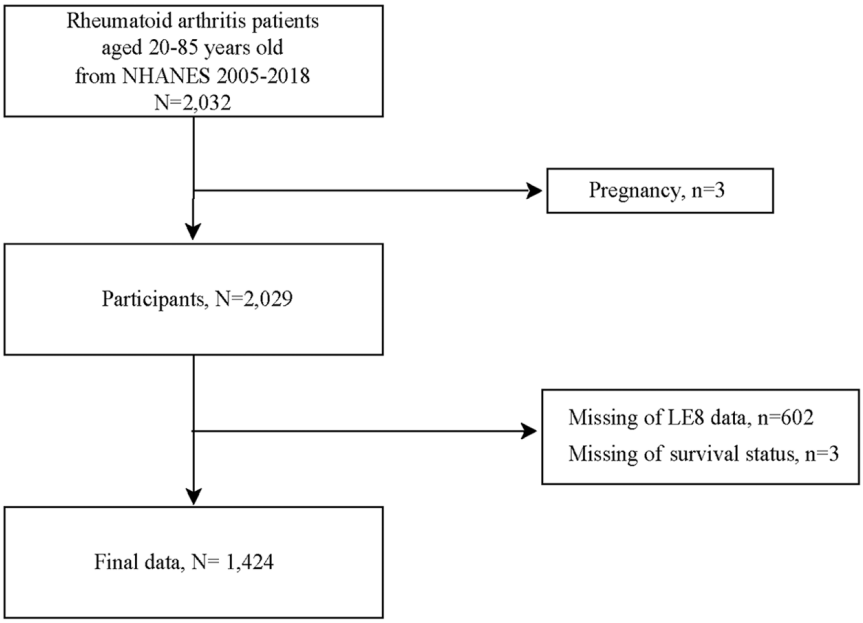

Fig. 1. Study flowchart.

Individual component scores for LE-8 were calculated as previously reported (9). In brief, a score of 0, 25, 50, 75 and 100 was assigned for an individual if the systolic blood pressure (SBP) ≥160 mmHg or diastolic blood pressure (DBP) ≥100 mmHg, SBP 140–159/DBP 90–99 mmHg, SBP 130–139/DBP 80–89 mmHg, SBP 120–129/DBP <80 mmHg, and SBP<120/DBP<80 mmHg, respectively. Furthermore, 20 points were subtracted from the final score of participants who were taking antihypertensives at the time of the interviews (5). Blood glucose scores were assessed primarily with glycated haemoglobin (HbA1C) levels, in which a HbA1C ≥10.0%, 9.0–9.9%, 8.0–8.9%, 7.0–7.9%, and diabetes with HbA1C<7.0% were allocated with a score of 0, 10, 20, 30 and 40 points, respectively. Participants with a fasting blood glucose of 100–125mg/dl or HbA1C of 5.7–6.4% were assigned a score of 60. For participants without diabetes and a fasting blood glucose <100 mg/dl or HbA1C<5.7%, a score of 100 was assigned. Participants with non-HDL cholesterol ≥220, 190–219, 160–189, 130–159, and <130 mg/dL were assigned 0, 20, 40, 60, and 100 points, respectively. Participants with a body mass index of ≥40.0, 35.0–39.9, 30.0-34.9, 25.0–29.9, and <25.0 kg/m^2 were assigned scores of 0, 15, 30, 70, and 100 points, respectively.

Participants who reported different levels of physical activity per week were assigned corresponding scores of 0, 20, 40, 60, 80, 90, and 100 for 0, 1–29, 30-59, 60–89, 90-119, 120–149, and ≥150 minutes, respectively. Similarly, participants who reported sleep duration of <4, 4 to <5, 5 to <6 or ≥10, 6 to<7, 9 to <10, and 7 to <9 h were assigned with a score of 0, 20, 40, 70, 90, and 100 points, respectively. For the dietary score, a numeric conformity to the Healthy Eating Index 2015 within the 1st-24th, 25th-49th, 50th-74th, 75th-94th, and ≥95th percentile ranges resulted in 0, 25, 50, 80, and 100 points, respectively. Nicotine exposure scores were evaluated based on smoking status: current smoker, former smoker (quit <1 year), former smoker (quit 1 to <5 years), former smoker (quit ≥5 years), and never smoker were equivalent to 0, 25, 50, 80, and 100 points, respectively (10).

Study outcomes

Mortality status and follow-up data were collected by linking the 2005-2018 NHANES to the National Death Index death certificate records until December 31, 2019. CVD-specific mortality was defined as causes of death determined by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes I00–I09, I11, I13, I20–I51, and I60–I69 (11).

Study covariates

Demographic and socioeconomic variables, including patient age, sex, race/ethnicity, education level and family poverty-to-income ratio, as well as marital status were acquired through standardised questionnaires conducted during household interviews. The race/ethnicity was categorised into non-Hispanic White, non-Hispanic Black, Mexican Americans and other race. The education level was divided into less than 9th grade, high school, some college or AA degree, and college graduate or above.

Statistical analysis

Statistical analyses were performed according to the Centers for Disease Control and Prevention guidelines and included appropriate weighting to obtain nationally representative estimates of the U.S. population. Baseline characteristics were presented as weighted means (standard errors) for continuous variables and actual sample sizes (weighted percentages) for categorical variables. One-way analysis of variance or the Rao-Scott χ^2 test was used to test for differences in baseline characteristics within different CVH groups, as appropriate.

Kaplan-Meier curves for all-cause and CVD-specific mortality were plotted for follow-up time and compared using the log-rank test. Survey-weighted multivariable Cox proportional hazard regression models were used to calculate the hazard ratios (HR) with 95% confidence intervals (CI) for the associations of CVH categories with risks of all-cause and CVD mortality. In addition, the weighted logistic regression models were also constructed with LE8 score as a continuous variable. Three models were generated: Model 1, the crude unadjusted model; Model 2, adjusted for age and sex; and Model 3, adjusted for age, sex, race/ethnicity, education level, family poverty-to-income ratio, and marital status. The fully adjusted restricted cubic spline model was fitted to examine the dose-response association of LE8 score with all-cause and CVD-specific mortality. Subgroup analyses were performed to examine the association of total LE8

Table I. Patient characteristics according to the titres of Life's Essential 8 score.

	Total	High-CVH	Moderate-CVH	Low-CVH	*p*-value
Age (years, SE)	57.87 (0.45)	56.66 (1.27)	58.24 (0.59)	57.72 (0.79)	0.525
Age (n, %)					0.727
< 60 years	591 (52.49)	83 (56.00)	366 (51.66)	142 (52.29)	
≥ 60 years	833 (47.51)	99 (44.00)	530 (48.34)	204 (47.71)	
Sex (n, %)					0.13
Male	599 (41.06)	71 (41.50)	410 (43.72)	118 (32.95)	
Female	825 (58.94)	111 (58.50)	486 (56.29)	228 (67.05)	
Race (n, %)					0.015
Non-Hispanic White	592 (67.59)	82 (69.08)	385 (69.65)	125 (60.41)	
Non-Hispanic Black	429 (16.10)	36 (8.68)	267 (16.09)	126 (21.71)	
Mexican Americans	136 (4.82)	22 (5.36)	75 (4.13)	39 (6.46)	
Other	267 (11.49)	42 (16.88)	169 (10.13)	56 (11.42)	
Marital status (n, %)					0.002
Single	636 (37.98)	66 (27.62)	384 (37.47)	186 (47.24)	
Non-single	788 (62.02)	116 (72.38)	512 (62.53)	160 (52.76)	
Poverty to income ratio (SE)	2.58 (0.07)	3.02 (0.24)	2.66 (0.08)	2.02 (0.13)	<0.0001
Poverty to income ratio (n, %)					0.006
0.00-1.00	350 (18.59)	37 (15.76)	205 (17.97)	108 (27.71)	
1.00-3.00	606 (39.34)	62 (36.04)	384 (41.31)	160 (47.26)	
≥3.00	364 (36.17)	65 (48.20)	240 (40.72)	59 (25.023)	
Education level					0.002
Less than 9th grade	195 (7.98)	16 (4.38)	116 (7.11)	63 (13.26)	
High School	589 (40.57)	63 (30.81)	376 (41.83)	150 (44.32)	
Some college or AA degree	464 (35.85)	63 (38.13)	294 (35.94)	107 (33.96)	
College graduate or above	174 (15.54)	39 (26.68)	109 (15.12)	26 (8.46)	
LE8 Total score	61.14 (0.67)	82.14 (0.68)	62.50 (0.34)	41.35 (0.64)	< 0.0001
Healthy eating index score	37.71 (1.33)	61.68 (2.84)	38.09 (1.42)	18.57 (1.80)	< 0.0001
Physical activity score	61.35 (1.72)	95.03 (1.41)	64.10 (1.99)	27.95 (2.45)	< 0.0001
Nicotine exposure score	64.03 (1.62)	81.14 (4.02)	66.94 (1.93)	42.60 (3.16)	< 0.0001
Sleep score	75.04 (1.15)	90.46 (1.80)	76.59 (1.33)	58.90 (2.63)	< 0.0001
BMI score	53.37 (1.35)	78.11 (2.26)	54.47 (1.66)	31.54 (2.62)	< 0.0001
Non-HDL score	60.92 (1.11)	76.49 (2.95)	61.40 (1.34)	47.78 (1.86)	< 0.0001
Glucose score	78.40 (0.99)	94.37 (1.73)	80.94 (1.14)	58.94 (2.14)	< 0.0001
Blood pressure score	58.29 (1.24)	79.87 (2.53)	57.45 (1.49)	44.49 (2.05)	< 0.0001

score with all-cause and CVD-specific mortality stratified by age, sex, race/ethnicity, education level, poverty-to-income ratio, and marital status. A two-tailed *p*-value <0.05 indicated statistical significance.

Results

Baseline patient characteristics

A total of 1424 subjects were enrolled with a weighted mean age of 57.87±0.45 years and a weighted female proportion of 58.94%. The majority were non-Hispanic Whites (67.59%). As displayed in Table I, there were 182, 896 and 346 subjects categorised into the high-, moderate- and low-CVH group, respectively. For the weighted demographic sociology, participants in the low CVH group were more likely to be non-Hispanic Black, single, less educated and have a lower poverty-to-income ratio.

Associations between LE-8 and all-cause or CVD mortality

During a median of 82 (interquartile range 43–125) months of follow-up, 270 all-cause and 85 CVD-specific deaths have been recorded. The Kaplan-Meier survival curves (Fig. 2) based on LE-8 categories showed that the overall survival was significantly different among the 3 groups. Compared with the high CVH group, patients in the moderate- and low-CVH groups had an 85.8% (HR= 1.858, 95% CI 1.049–3.289) and 129.5% (HR = 2.297, 95% CI 1.168–4.515) increased risk of all-cause mortality, respectively, after adjustment for all potential covariates (Table II). A similar trend was observed in the fully adjusted model with LE8 as a continuous variable. Additional analyses showed that the scores of physical activity, body mass index, glucose and blood pressure levels were significantly associated with all-cause mortality (Fig. 3).

After adjustment for potential confounders, each 1 point decrease in LE8 score was associated with a 2.6% (HR=0.974, 95% CI 0.952–0.996) increased risk of CVD mortality (Table II). However, a similar trend toward increased risk of CVD mortality was not observed when LE8 score was categorised into groups (Table II). When evaluating the individual measures of LE8, only the physical activity score and the blood pressure score were significantly associated with CVD mortality (Fig. 3).

Restricted cubic spline analysis

To flexibly model the association between LE8 score and all-cause or CVD mortality, we applied the restricted cubic spline model (Fig. 4), which suggested that a higher LE score was pro-

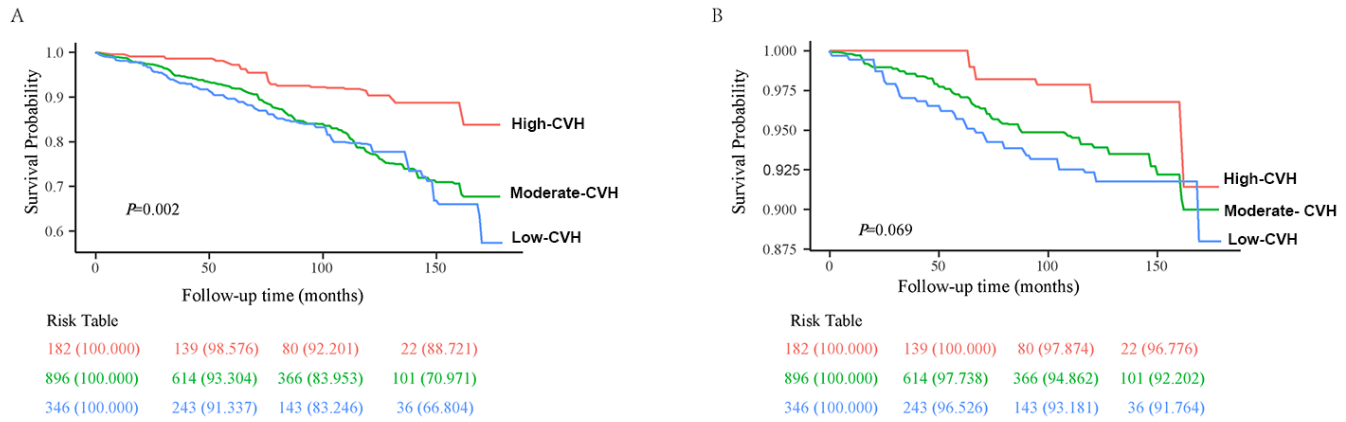

Fig. 2. Kaplan-Meier curves showing the associations of different cardiovascular health as assessed by the Life's Essential 8 with all-cause (**A**) and cardiovascular mortality (**B**) in patients with rheumatoid arthritis.

Table II. Survey-weighted association of Life's Essential 8 score with all-cause and cardiovascular mortality.

	Deaths (n)	Weighted death (n)	Univariable model		Multivariable model 1		Multivariable model 2	
			HR	*p*	HR	P	HR	*p*
All-cause mortality								
LE8	270	1,027,663	0.978 (0.969, 0.987)	**<0.0001**	0.969 (0.959, 0.979)	**<0.0001**	0.976 (0.963, 0.988)	**<0.001**
Categories								
High-CVH	20	71,622	Reference	–	Reference	–	Reference	–
Moderate-CVH	176	705,942	2.423 (1.372, 4.279)	**0.002**	2.701 (1.547, 4.715)	**<0.001**	1.858 (1.049, 3.289)	**0.034**
Low-CVH	74	250,099	2.719 (1.388, 5.325)	**0.004**	3.697 (1.948, 7.016)	**<0.0001**	2.297 (1.168, 4.515)	**0.016**
Cardiovascular mortality								
LE8	85	292,249	0.979 (0.960, 0.999)	**0.041**	0.966 (0.948, 0.985)	**<0.001**	0.974 (0.952, 0.996)	**0.021**
Categories								
High-CVH	5	21,130	Reference	–	Reference	–	Reference	–
Moderate-CVH	55	191,038	2.296 (0.747, 7.057)	0.147	2.603 (0.920, 7.370)	0.072	1.656 (0.569,4.820)	0.354
Low-CVH	25	80,081	3.069 (0.877, 10.741)	0.079	4.680 (1.506, 14.539)	**0.008**	2.789 (0.851,9.138)	0.090

The multivariable model 1 was adjusted for age and sex; the multivariable model 2 was adjusted for patient age, sex, race/ethnicity, poverty-to-income ratio, education levels, and marital status.

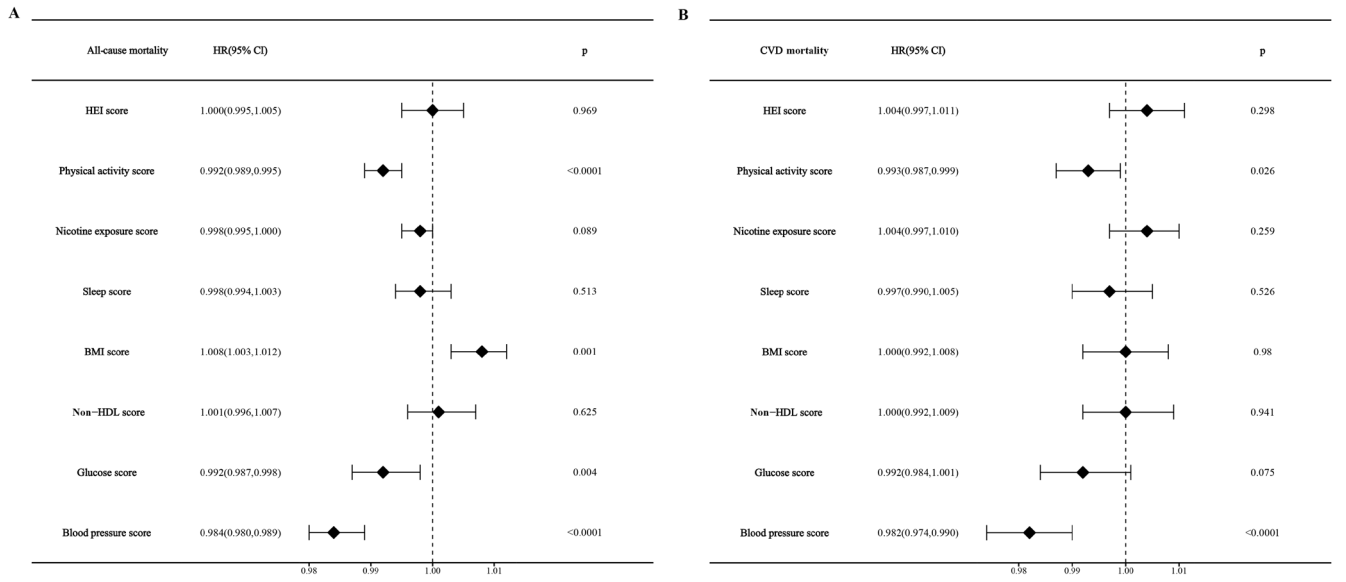

Fig. 3. Hazard ratios with 95% confidence interval of individual metrics of Life's Essential 8 for all-cause (**A**) and cardiovascular mortality (**B**) in patients with rheumatoid arthritis.

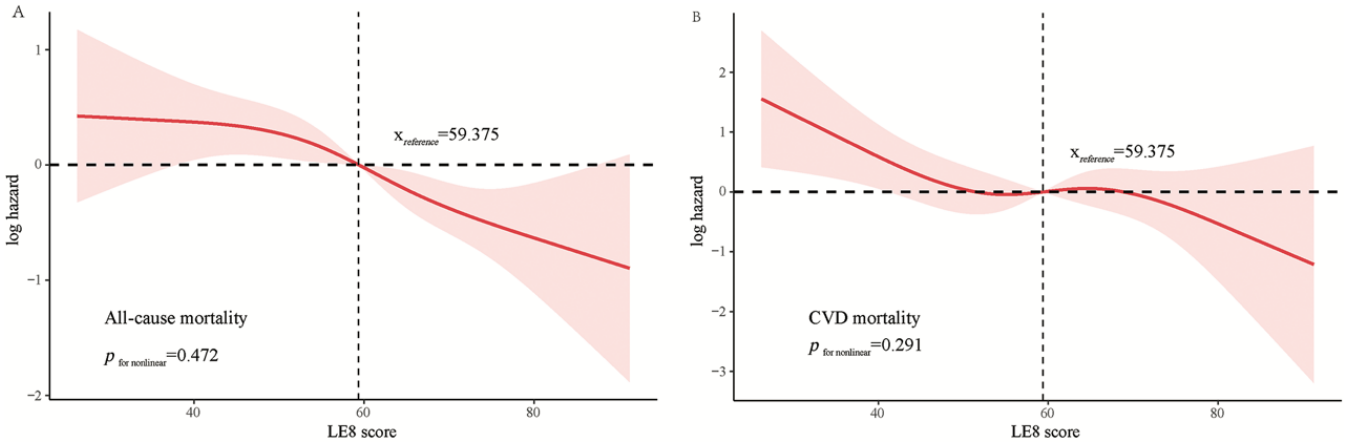

Fig. 4. Restricted cubic spline analysis showing the dose-response relationships between Life's Essential 8 score and mortality from all-cause (**A**) and cardiovascular disease (**B**).

tective against all-cause and CVD mortality (all *p* for non-linearity >0.05). The minimum thresholds for the beneficial association between LE8 score and all-cause and CVD mortality were both at approximately 59 points.

Subgroup analysis

Subgroup analyses (Fig. 5) based on age, sex, race, marital status, PIR, and education level showed significant interactions between LE8 score and non-Hispanic white population with risk of all-cause mortality. None of the variables modified the association between LE8 score and CVD mortality.

Sensitivity analysis

The results were generally robust for all-cause mortality in the sensitivity analysis that excluded participants who died within 48 months of follow-up. As shown in the Supplementary Table, the fully adjusted HR was 1.933 for the moderate-CVH group and 2.377 for the low-CVH group, with the high-CVH group as the reference. However, the LE8 score as a continuous or categorical variable was not significantly associated with CVD death.

Discussion

In this study, we evaluated the predictive value of cardiovascular fitness as assessed by LE8 for RA patient outcomes in a nationally representative sample and found that a lower LE8 score was independently associated with higher all-cause mortality. In addition, there was an approximately linear dose-response association of higher LE8 scores with reduced risk of all-cause mortality. The association between LE8 as a continuous variable and CVD mortality in this study was not robust. Subgroup analysis showed that the beneficial effect of higher LE8 was more pronounced in non-Hispanic white Americans. The results suggest that interventions to promote CVH by increasing LE8 would likely result in a substantial reduction in mortality among RA patients in the U.S. population.

The LE8 is a novel quantitative measure of CVH designed to increase the sensitivity of scoring to inter-individual differences and to changes over time in both individuals and populations (12). A multitude of investigators have examined its cross-sectional correlates, upstream determinants and the associations with the all-cause and CVD mortality in the general U.S. and UK population. For instance, the studies by Zhang *et al*. and Yi *et al*. both demonstrated that a higher LE8 score was independently associated with a reduced all-cause and CVD mortality (13, 14). However, RA patients present with disparate demographics and have an approximately 1.45 times higher all-cause mortality risk and 50% increased CVD-specific mortality than the general population (15).

This is the first study, to the best of our knowledge, to interrogate the associations of LE8 metrics with long-term prognosis in RA patients. Growing evidence suggest that adherence to a healthy lifestyle is beneficial for RA and thus recommended by several society guidelines in the management of this patient population (4, 16). An expert consensus statement for RA suggested investigation of risk factors that may be potentially preventable and correcting modifiable lifestyles for improving cardiovascular health (17). The results of the current study are largely compatible with this endorsement as demonstrated by the finding that the LE8 metrics are generally linearly associated with the all-cause of mortality in RA patients.

This study also suggested that not all the individual metrics of LE8 contributed equally to the reduction in mortality risk. Specifically, physical activity, body mass index, glucose and blood pressure levels were found to be the major determinants. Contrary to the traditional belief that physical activity impairs joint function, a large body of evidence has shown that increased physical activity is beneficial in reducing RA disease activity and systemic inflammation (18). Although the exact mechanisms underlying the association between physical activity and all-cause or CVD mortality remain largely undefined, available research suggests that improved blood pressure control and sensitivity to insulin resistance may be of particular importance (19). In addition, physical activity would also improve muscle mass and effectively prevent cachexia in RA patients by blocking the expression of tumour necrosis factor α, a cytokine that has been found to be associated with premature

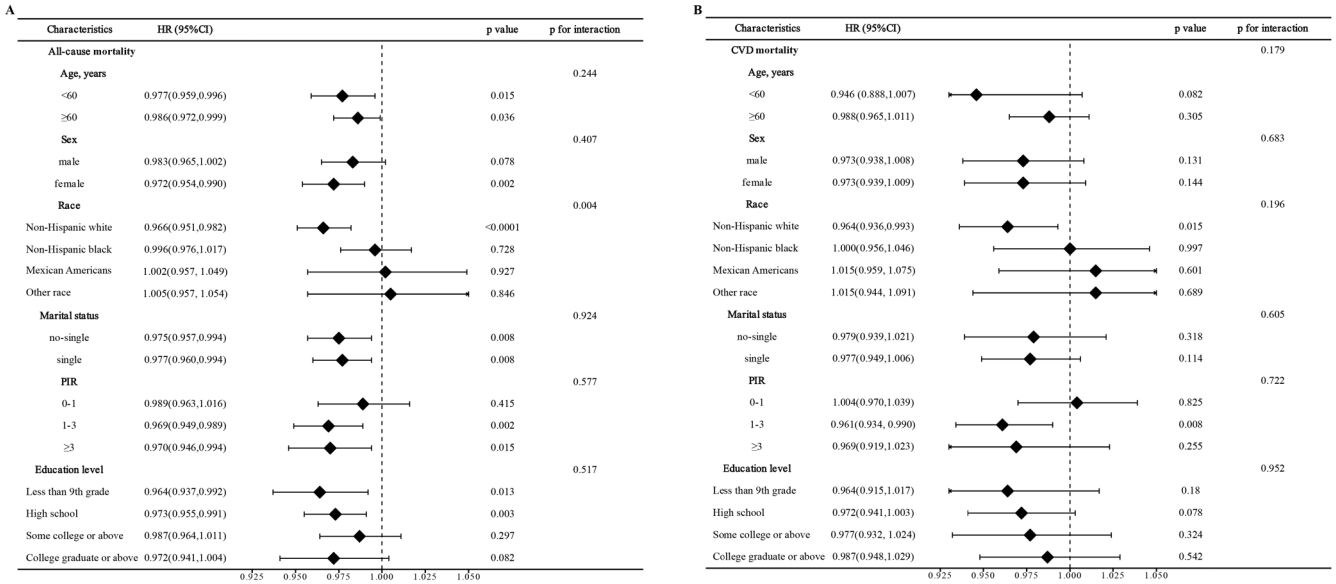

Fig. 5. The forest map showing the hazard ratios with 95% confidence interval of benefits with LE8 for all-cause (**A**) and cardiovascular-specific (**B**) mortality stratified by different subgroups.

mortality in RA (20). A prior multi-centre study found that only 13.8% of RA patients reported at least 30 minutes of physical activity 3 times per week (21), which is significantly less than the recommended amount.

We found that blood pressure control metrics of LE8 was independently associated with both all-cause and CVD mortality. Although prior studies have established that uncontrolled high blood pressure is prevalent and linked to target organ damages in RA patients (22), its role in patient outcomes remain scarcely explored. The present study suggest that vigorous control of blood pressure is a potentially modifiable risk factor for reducing RA mortality. According to a study from England, hypertension is highly prevalent in patients with RA and aggressive monitoring and treatment strategies are required for those with any cardiovascular comorbidity (23). However, currently, the blood pressure goals have not been specifically made in RA management. The management of blood pressure in patients with RA still adopted CVD preventive guidelines for the general population (24).

The study documented that a higher BMI is associated with more optimal all-cause outcomes in RA, which is consistent with the so-called "obesity paradox". Although obesity has been associated with a host of adverse complications, RA patients with higher BMI tend to have reduced risk of premature death, and rapid weight loss would rather increase the mortality rate (25).

Blood glucose metrics of LE8 also appeared to predict all-cause mortality in RA patients in this study. An increased prevalence or risk of impaired fasting glucose or diabetes mellitus has been reported RA patients (26). Consistently, a systematic review demonstrated a twofold increase in CVD risk in RA patients with diabetes mellitus compared with those who do not have diabetes mellitus (27). Similar to hypertension, the treatment of diabetes in patients with RA was similar to those in the general population. However, patients with RA and diabetes are more likely to have unfavourable outcomes and require particularly attentive management via lifestyle and medication intervention (24).

In the stratified analyses, the benefits of higher LE8 in RA patients were more apparent in non-Hispanic whites. The exact cause of these racial/ethnic differences remains unknown, but the study by Greenberg *et al*. showed significantly lower RA disease activity and higher remission rate in RA patients in non-Hispanic whites compared to other ethnic groups (28).

To the best of our knowledge, this is the first large-scale, nationally representative cohort study to evaluate the association of individual and total CVH measures with mortality risk in RA patients. Nevertheless, the inherent limitations of the study should be acknowledged and warrant further consideration. First, the inclusion of RA patients was based on self-report, which may introduce recall bias. Notably, the associations of LE8 score with CVD outcomes disappeared in the sensitivity analysis, which we speculate may be related to the relatively small sample size for CVD-specific mortality. Another plausible explanation would be that this study did not assess RA disease activity, as prior studies have shown different CVD outcomes in RA patients with different disease activity control (29). In addition, all health-related behaviours were collected from self-reported questionnaires, which may be subject to recall bias and measurement error. Finally, we evaluated the LE8 score at only a single visit, and the dynamic changes of LE8 may be more meaningful for predicting outcomes.

In conclusion, higher CVH as measured by LE8 was independently associated with a lower risk of all-cause mortality in US RA patients. Physical activity, body mass index, glucose, and blood pressure were the top 4 individual contributors to all-cause mortality. This finding highlights that interventional measures to promote CVH using the LE8 as a primary tool are promising to reduce mortality in RA patients.

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