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Association of Life's Essential 8 with incidence of heart failure modified by depressive symptoms: a prospective cohort study from UK Biobank

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Abstract

Background The Life's Essential 8 (LE8) proposed by the American Heart Association for assessing cardiovascular health (CVH) has been demonstrated to be associated with cardiovascular disease, but rarely includes heart failure (HF), and the role of psychological factors has not been considered. We aimed to prospectively investigate the independent, joint, and interactive associations of LE8 and depressive symptoms with HF incidence.

Methods A total of 336,939 participants recruited from UK Biobank without HF, coronary heart disease, and stroke were included in the cohort study. The LE8 score consisted of four behavioral (diet, physical activity, nicotine exposure, and sleep) and four biological factors (glucose, blood lipids, blood pressure, and body mass index) and was classified into three levels: low, moderate, and high CVH. Depressive symptoms at baseline were identified by self-report and linkage to medical records. Incident HF cases during follow-up were extracted through primary care, hospital admissions, self-reports, and death registrations. Cox proportional hazard models were conducted to examine the associations of LE8 and depressive symptoms with HF incidence, with findings presented as hazard ratios (HRs) (95% confidence interval, CI).

Results A total of 9379 (2.8%) participants developed HF during a median follow-up of 13.6 years. Compared with low-CVH individuals, the multivariate-adjusted HRs with 95% CI for incident HF were 0.596 (0.565–0.629) and 0.458 (0.408–0.514) in those with moderate and high CVH, respectively. Per standard deviation increment in LE8 was associated with a 25.5% (HR = 0.745; 95% CI: 0.729–0.762) lower risk of HF. The stratification analysis indicated that the detrimental effect of low CVH on HF was more pronounced in participants with depressive symptoms compared to those without, with a significant multiplicative interaction (*P* for multiplicative interaction = 0.016). The joint test showed that the lowest risk of HF was observed in participants with high CVH and no depressive symptoms (HR = 0.344; 95% CI: 0.295–0.401), which may be attributed to a significant additive interaction observed.

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Conclusions The cohort study revealed that LE8-defined CVH not only could predict the incidence of HF, but also mitigate the increased risk of HF attributable to depressive symptoms. Achieving the high LE8 scores recommended by the AHA to improve CVH will be beneficial in reducing the population burden of HF, especially among patients with depressive symptoms.

Keywords Incident heart failure, Life's Essential 8, Cardiovascular health, Depressive symptoms, Interaction

Background

Heart failure (HF) is a chronic progressive condition where the heart fails to supply sufficient blood to meet the demands of the body, caused by impaired cardiac output, such as reduced ejection fraction (EF), or other underlying mechanisms, and is a major contributor to mortality worldwide [1, 2]. The global prevalence of HF increased by 106.3% from 1990 to 2019, reaching 56.2 million cases worldwide in 2019 [3], posing a significant challenge to global public health. Epidemiologic studies have suggested that the incidence of HF can be reduced by controlling modifiable factors, such as smoking cessation, regular physical activity (PA), high-quality diets, weight control, and the regulation of blood pressure (BP), lipids, and glucose levels [4–6]. Yet, most previous studies have predominantly concentrated on the association between individual or subsets of risk factors and HF [4, 6], thereby overlooking the interrelated nature of these factors and their potential synergistic effect on HF incidence.

Significantly, these factors constitute Life's Simple 7 (LS7), a comprehensive metric for evaluating cardiovascular health (CVH) first introduced by the American Heart Association (AHA) in 2010 [7]. Although the association of LS7 with HF has been widely reported [8–11], some limitations remain, such as the contribution of sleep health not considered by LS7 [12]. Meanwhile, there is consistent evidence linking sleep health to HF risk [13, 14]. Recently, the AHA updated the assessment of CVH by incorporating sleep duration into LS7, thereby introducing the concept of Life's Essential 8 (LE8) [12]. The LE8 score has been reported to be significantly and negatively associated with the risk of all-cause and cause-specific mortality [15]. While no study has directly compared LS7 and LE8 in predicting HF risk, existing evidence has indicated that LE8 has significantly higher predictive power than LS7 for adverse outcomes [16, 17]. For example, Li et al. observed that LE8 exhibited higher predictive accuracy for CHD, stroke, and cardiovascular disease (CVD) compared to LS7 using data from UK Biobank [16]. Therefore, clarifying the association between LE8 and the incidence of HF could contribute to HF prevention. Several extant studies have examined the association between LE8 and HF incidence [18–22], but many remain limited by small sample sizes [18], short follow-up periods [20], and special populations [22]. For example, Cai et al. found that ideal CVH was associated with a 62% reduction in the risk of HF in a cohort study with 4-year follow-up [20]. Huo et al. observed that CVH as defined by LE8 was associated with HF risk in patients with chronic kidney disease (CKD) [22]. Although two large prospective studies based on UK Biobank demonstrated an association between LE8 and the risk of HF, HF was not the primary study outcome in either study [19, 21], which might have restricted the depth and focus of their analyses. For instance, Petermann-Rocha et al. found a significant association with HF when investigating LE8 and adverse cardiovascular events [19]. More importantly, none of these studies considered the crucial role of psychological factors [18–22], such as depressive symptoms, despite the growing interest in the interplay between physical and psychological health.

Depressive symptoms, the most prevalent psychological health condition, as a remarkable risk factor for the incidence of HF have been widely recognized [23, 24]. Moreover, Gaffey et al. first introduced the concept of the "Life's Critical 9" (LC9) in the journal *Circulation*, affirming the significance of psychological health (e.g., depressive symptoms) in improving CVH, albeit evidence from empirical studies is still absent [25]. Notably, mounting epidemiologic evidence has indicated that lifestyle factors may interact with depressive symptoms to affect health outcomes [26–29]. For example, a prospective cohort study found that depressive symptoms and unhealthy diet may interact to increase the risk of the composite outcome of CVD incidence and all-cause mortality [27]. Nevertheless, no studies have been conducted on the joint or interactive effects of depressive symptoms and LE8, which may provide additional health benefits for preventing HF.

To illustrate the above research gaps, we performed a prospective study leveraging data from the UK Biobank to examine the independent, joint, and interactive association of LE8-defined CVH and depressive symptoms with the risk of incident HF.

Methods

Study participants

The study leveraged data derived from the UK Biobank, a large prospective cohort with ongoing follow-up that

recruited more than a half-million participants aged 37–73 years who completed touchscreen questionnaires, underwent physical examinations, and provided biological information at baseline (2006–2010) in England, Scotland, and Wales. A comprehensive description of the cohort can be found in previously published research [30]. In short, participants in the cohort provided information on the sociodemographic, lifestyle, environmental, and genetic determinants of a range of complex conditions. The UK Biobank project received ethical approval from the Northwest Multi-center Research Ethics Committee. Informed consent was obtained from all participants before recruitment. The study was conducted under the UK Biobank project application number 91536.

In the current study, we first excluded participants who were withdrawn or lost to follow-up ($n=1,297$). Second, we excluded participants missing information on LE8 components ($n=134,499$), and those with HF, coronary heart disease (CHD) (including angina, myocardial infarction, and ischemic heart disease), or stroke ($n=25,629$) at baseline. Also, participants with missing covariates were excluded ($n=3,174$). Finally, a total of 336,939 eligible participants were included in the formal analysis (Additional file 1: Fig. S1).

Assessment of LE8

As defined by the AHA [12], the LE8 was a composite of eight elements, including four behavioral elements (diet, PA, nicotine exposure, and sleep duration) and four biological elements [body mass index (BMI), BP, blood glucose, and blood lipids]. A detailed description of the LE8 was available elsewhere [12]. Briefly, each element of LE8 was assigned a score from 0 to 100, where higher scores denote better health status. The total LE8 scores were the sum of the eight element scores divided by eight, and ranged from 0 to 100, with higher scores implying superior CVH. Similarly, we calculated behavioral and biological subscale scores. Consistent with the AHA recommendations [12], high CVH was defined as LE8 scores within the range of 80 to 100, moderate CVH was within the range of 50 to 79, and low CVH was within the range of 0 to 49. Of note, a more recent definition of the dietary scores assessing CVH was utilized to accommodate the availability of data from the UK Biobank, which is consistent with previous studies [31, 32]. Detailed definitions of dietary and LE8 scores were available in Additional file 1: Tables S1 and S2, respectively.

Assessment of depressive symptoms

Similar to previous studies [26, 33], multiple sources were used to identify depressive status at baseline. First, depressive disorders were diagnosed at baseline based on the International Classification of Diseases, Tenth Revision (ICD-10) codes F32 and F33 among the "First occurrence fields" of health-related outcomes from the UK Biobank (Data category: 2405). Moreover, the Patient Health Questionnaire-2 (PHQ-2) was used to assess the depressive symptoms by inquiring "How often have you felt down, depressed or hopeless?" and "How often have you had little interest or pleasure in doing things?" over the past 2 weeks. Response options for each question ranged from "not at all" to "nearly every day" (score range: 0 to 3). The PHQ-2 is therefore scored on a scale of 0–6, with scores of 3 or more suggesting possible depressive symptoms [26, 33]. Hence, depressive symptoms were recognized by a positive response from any of the aforementioned sources in the study.

Definition of incident HF

Consistent with the approach used in previous studies to define outcomes [16, 21, 34, 35], participants diagnosed with HF during follow-up were confirmed by the ICD-10 code I50 according to the "First occurrence fields" of health-related outcomes in the UK Biobank, which were obtained by linkage to self-reported, primary care, hospital admission, and death registries (Data category: 2409). The inpatient hospital information was detected from Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. The date of death for participants from England and Wales was obtained from National Health Service Digital, whereas participants from Scotland were sourced from the National Health Service Central Register. Less than 1% of HF cases were identified through self-reporting and subsequently verified by nurses to confirm the accuracy of these reports [34]. The follow-up time was computed as the time interval from the recruitment date to the diagnosis date of HF, date of death, or the censoring data (31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales), whichever occurred first. The same approach was performed to define CHD (I20–I25) and stroke (I60–I64) at baseline.

Assessment of covariates

Covariates associated with LE8 and HF were selected [6, 16, 32], including sociodemographic characteristics [age (continuous), sex, ethnicity (White vs. others), educational level (college or university vs. others), and Townsend Deprivation Index (TDI, continuous)], lifestyle factors [alcohol consumption status (daily or almost daily vs. others) and sedentary behavior time], and medical histories (hypertension, diabetes, and cancer). The TDI covered information on social class, employment and housing, and reflected area-level deprivation, with

higher scores indicating higher deprivation [6]. In the UK Biobank, alcohol intake frequency is categorized into six groups: daily or almost daily, three or four times a week, once or twice a week, one to three times a month, special occasions only, and never. Based on previous literature [36], we further dichotomized alcohol intake frequency into alcohol consumption status (daily or almost daily vs. others). Time spent in sedentary behavior is calculated as the total time spent watching television, using computers outside of work hours, and driving [16]. Medical histories regarding hypertension (I10–I15) and diabetes (E10–E14) were identified primarily by ICD-10 codes in the "First occurrence fields." Furthermore, systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, and the use of antihypertensive medications were used to assist in confirming the history of hypertension. Similarly, glycated hemoglobin (HbA1c) ≥ 6.5% and the use of insulin were employed to aid in ascertaining the history of diabetes. History of cancer was identified through linkage to the National Cancer Registry based on the "Cancer registry fields" (ICD-10 codes: C00–C97) in the health-related outcomes from the UK Biobank. Missing information on covariates was summarized in Additional file 1: Fig. S1.

Statistical analyses

ANOVA or Wilcoxon rank-sum tests were performed for continuous variables [expressed as mean (standard deviation, SD) or median (interquartile range, IQR)] and chi-square tests were utilized for categorical variables [presented as frequency (%)], to describe baseline characteristics by CVH or incident HF status.

After the proportional hazards assumption was not violated according to the Schoenfeld residual test, multivariable Cox proportional hazards models with the follow-up time as the time scale were utilized to explore the associations of LE8 and depressive symptoms with risk of incident HF, with results reported as hazard ratios (HR) and 95% confidence intervals (CI). Three Cox models with stepwise adjustments for covariates were conducted: model 1 adjusted for sociodemographic characteristics; model 2 accounted for lifestyle factors plus model 1; model 3 incorporated medical histories and depressive symptoms (or LE8) in addition to those in model 2. First, to estimate the risk of incident HF ascribed to low CVH, we analyzed LE8 as categorical variables, considering the low CVH as the reference group. Also, the association between depressive symptoms and incident HF was examined. Second, the continuous LE8 scores as well as the behavioral and biological subscale scores (mutually adjusted in the model) were standardized (z-scores) to calculate HR per SD increment. To compare the contribution of each element of the LE8 to the risk of incident HF, we repeated the analysis by simultaneously including all eight elements in the model. Third, the cumulative incidence of HF in the CVH subgroups defined by LE8 was plotted using the Kaplan–Meier method ("survminer" package in R software). Fourth, the restricted cubic spline (RCS) model ("rcssci" package in R software) with 5 knots was employed to examine the dose–response relationship between LE8 scores and the incidence of HF among all individuals as well as those grouped by depressive status while adjusting for covariates in model 3. The RCS analyses were repeated for behavioral and biological subscale scores, and they were adjusted for each other. Moreover, to examine the percentage of incident HF in the study population that theoretically would not have occurred if all individuals had adhered to an ideal CVH, the population attributable risk (PAR) for the total LE8 score and each component of the LE8 was calculated under the assumption of causality. The PAR was calculated using the following formula: $PAR = [p(RR-1)]/[p(RR-1)+1]$. In this formula, p represents the proportion of the population exposed to suboptimal CVH, and RR is the relative risk of HF associated with suboptimal CVH compared to ideal CVH. The RR values were derived from the HRs obtained using the Cox proportional hazards model. Ideal CVH was defined as a LE8 score ranging from 80 to 100, while suboptimal CVH encompassed all scores below this threshold. The computation of PAR estimates was conducted using the "AF" package in R software [37]. The PAR (95% CI) was reported according to the median follow-up duration of the study.

The joint effect of LE8-defined CVH and depressive symptoms on the risk of HF was evaluated by creating six distinct combinations using participants with depressive symptoms and low CVH as the reference group. The relationship between LE8-defined CVH and HF incidence was also assessed stratified by the presence or absence of depressive symptoms, with high CVH as the reference group. An interaction term combining LE8 score and depressive symptoms was introduced to model 3 to examine their multiplicative interaction impact on the risk of incident HF. The likelihood test was applied to test the significance of the interaction term. An additive interaction model was constructed to assess whether depressive symptoms modify the association of LE8 with HF incidence using a series of indexes including the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI). An additive interaction was indicated if the 95% CI for RERI and AP excluded zero or the 95% CI for SI did not include one [38]. The details of the calculation procedure for additive interaction were described in Additional file 1: Supplementary Method.

To augment the reliability of our findings, multiple additional analyses were conducted. First, we reran the main analyses with LE8 scores divided into quartiles. Second, to reduce the potential for reverse causation bias, participants diagnosed with HF within the initial 2 years of follow-up were eliminated. Third, sensitivity analyses were conducted using multiple imputations by chained equations to address missing data ("mice" package in R software). Initially, only missing values in covariates were imputed. Additionally, we performed an extended analysis in which missing values for both LE8 components and covariates were imputed. Fourth, in light of the potential impact of deaths, we reassessed the LE8-HF associations employing the competitive hazard model proposed by Fine and Grey and presented the findings as subdistribution hazard ratios (SHRs) with 95% CIs. Fifth, to assess the individual contributions of each element comprising LE8 to the incidence of HF, we recalculated LE8 scores for reanalysis by omitting one element at a time. Sixth, we additionally adjusted for incident CHD as a time-varying covariate. Seventh, genetic susceptibility to HF as quantified by a polygenic risk score was further considered (Additional file 1: Supplementary Method and Table S3) [39, 40]. Eighth, sensitivity analyses were conducted after excluding participants with cancer at baseline. Ninth, the associations of LE8 with HF incidence were re-examined after excluding patients with atrial fibrillation (AF) at baseline. Tenth, to further address potential residual confounders from baseline cardiovascular comorbidities, the associations were reassessed after excluding participants with any documented cardiovascular events (classified under ICD-10 codes I00–I99) at baseline. Finally, stratification analyses were conducted by sex (male, female), age (<60 years, ≥ 60 years), education (college or university, others), TDI (median), drinking status (daily or almost daily, others), sedentary behavior duration (median), and genetic susceptibility to HF (low, high) to assess potential effect modification. We incorporated product terms of LE8 and the stratification factors into model 3 to test the modification effect's significance with likelihood ratio tests.

All analyses were conducted by SAS 9.4 (SAS Institute, Cary, NC, USA) and R Statistical Software (version 4.0.2). A two-tailed *P* value lower than 0.05 was regarded as statistically significant.

Results

Baseline characteristics

The study sample comprised 336,939 participants [mean age (SD), 56.1 (8.1) years; 45.1% were male], with a total of 9379 cases of HF documented during a median follow-up of 13.588 years (IQR, 12.909–14.256 years; 95% CI, 13.582–13.593 years). In comparison to individuals with low or moderate CVH, those exhibiting high CVH (11.0%) were younger, more likely to be female and White, had higher education, faced less deprivation, and adhered to healthier lifestyles (including less smoking, alcohol consumption, and sedentary time; more PA and normal sleep duration). Furthermore, they had lower BMI, HbA1c, BP, and cholesterol levels, and lower prevalence of hypertension, diabetes, and cancer (Table 1). Similar findings were observed when describing baseline characteristics according to incident HF (Additional file 1: Table S4).

Associations of LE8 and depressive symptoms with HF incidence

The follow-up period revealed a significantly different cumulative incidence of HF based on CVH classification, with the lowest cumulative incidence in high-CVH individuals (Additional file 1: Fig. S2). RCS analysis revealed a nonlinear relationship between LE8 scores and HF incidence, characterized by a steeper slope at lower scores and a plateau at higher scores (nonlinear $P<0.001$) (Fig. 1). The consistent nonlinear associations in behavioral and biological subscale scores also were found (Additional file 1: Figs. S3 and S4). When stratified by depressive symptoms, we observed this nonlinear association only in individuals without depressive symptoms (Additional file 1: Fig. S5), but not in individuals with depressive symptoms (Additional file 1: Fig. S6). After adjustment for covariates in model 3, compared with low-CVH individuals, those with moderate and high CVH were associated with 40.4% (HR = 0.596; 95% CI: 0.565–0.629) and 54.2% (HR = 0.458; 95% CI: 0.408, 0.514) reduced risk of incident HF, respectively. Adherence to ideal CVH could have potentially prevented 20.2% (95% CI: 8.3–32.1%) of incident HF cases. Compared to individuals without depressive symptoms, those with depressive symptoms exhibited a 30.9% (HR = 1.309, 95% CI: 1.232–1.391) elevated risk of HF. Furthermore, the HR for per SD increment in LE8 score, and behavioral and biological subscale scores were 0.745 (95% CI: 0.729–0.762), 0.826 (0.810–0.842), and 0.815 (0.795–0.836) for the incidence of HF, respectively (Table 2). When all eight elements were simultaneously included in model 3, it was observed that all except for diet and lipids significantly reduced the risk of developing HF. Of these factors, the ideal BMI score demonstrated the most substantial protective effect, with a PAR% of 19.3% (95% CI: 15.6–22.9%) (Additional file 1: Table S5).

Joint and interaction analyses of LE8 and depressive symptoms on the incidence of HF

Table 3 presents the joint and interaction effects of LE8 and depressive symptoms on the incidence of HF.

Table 1 Descriptive statistics of participants by cardiovascular health defined by Life's Essential 8 score

Characteristics	Overall (*N* = 336,939)	Cardiovascular health defined by LE8 score[a]			*P* value
		Low (*N* = 30,257)	Moderate (*N* = 269,488)	High (*N* = 37,194)	
Age	56.1 (8.1)	56.9 (7.6)	56.5 (8.0)	52.1 (8.1)	< 0.001
Male, *n* (%)	151,941 (45.1)	15,429 (51.0)	125,591 (46.6)	10,921 (29.4)	< 0.001
College or university degree, *n* (%)	116,950 (34.7)	6818 (22.5)	92,042 (34.2)	18,090 (48.6)	< 0.001
White, *n* (%)	322,620 (95.8)	28,837 (95.3)	258,104 (95.8)	35,679 (95.9)	< 0.001
Townsend Deprivation Index[b]	−2.3 (−3.7, 0.2)	−1.5 (−3.3, 1.6)	−2.3 (−3.7, 0.1)	−2.4 (−3.8, −0.2)	< 0.001
Alcohol consumed daily or almost daily, *n* (%)	70,948 (21.1)	6516 (21.5)	58,271 (21.6)	6161 (16.6)	< 0.001
Sedentary behavior time, hours/day	4.8 (2.4)	5.7 (2.9)	4.8 (2.3)	3.9 (2.0)	< 0.001
Healthy diet score (0–10)[b]	3 (2, 4)	3 (2, 3)	3 (2, 4)	4 (3, 5)	< 0.001
Moderate activity[b], min/week	120 (30, 300)	0 (0, 60)	120 (40, 300)	180 (90, 360)	< 0.001
Vigorous activity[b], min/week	30 (0, 120)	0 (0, 0)	30 (0, 120)	90 (30, 180)	< 0.001
Current smokers, *n* (%)	33,787 (10.0)	10,349 (34.2)	23,284 (8.6)	154 (0.4)	< 0.001
Secondary smoking exposure, *n* (%)	30,912 (9.9)	4120 (18.5)	24,847 (9.8)	1945 (5.2)	< 0.001
Sleep duration (7–9 h), *n* (%)	232,632 (69.0)	13,670 (45.2)	187,331 (69.5)	31,631 (85.0)	< 0.001
BMI, kg/m^2	27.2 (4.6)	32.0 (5.6)	27.2 (4.2)	23.3 (2.5)	< 0.001
SBP, mm Hg	137.9 (18.5)	147.9 (17.6)	139.2 (17.9)	120.6 (12.3)	< 0.001
DBP, mm Hg	82.7 (10.1)	88.8 (9.7)	83.2 (9.6)	73.6 (7.5)	< 0.001
Total cholesterol, mg/dL	223.1 (42.8)	239.3 (46.8)	225.0 (42.1)	196.4 (32.4)	< 0.001
HDL cholesterol, mg/dL	56.7 (14.7)	50.3 (12.5)	56.6 (14.6)	62.4 (14.7)	< 0.001
Non-HDL cholesterol, mg/dL	166.5 (40.8)	188.9 (43.5)	168.4 (39.3)	134.0 (28.5)	< 0.001
Glucose, mg/dL	91.4 (20.4)	100.2 (36.9)	91.1 (18.3)	86.4 (12.2)	< 0.001
HbA1c, %	5.4 (0.6)	5.8 (0.9)	5.4 (0.5)	5.2 (0.3)	< 0.001
Prevalent hypertension, *n* (%)	125,976 (37.4)	19,435 (64.2)	103,903 (38.6)	2638 (7.1)	< 0.001
Prevalent diabetes, *n* (%)	14,538 (4.3)	3626 (12.0)	10,614 (3.9)	298 (0.8)	< 0.001
Prevalent cancer, *n* (%)	29,850 (8.9)	2910 (9.6)	24,042 (8.9)	2898 (7.8)	< 0.001
Prevalent depressive symptoms, *n* (%)	38,592 (11.5)	5490 (18.1)	29,610 (11.0)	3492 (9.4)	< 0.001
LE8 scores[b]					
Total LE8 score	66.2 (58.1, 73.8)	45.0 (41.3, 47.5)	66.3 (60.0, 71.9)	83.8 (81.3, 86.3)	< 0.001
Behavior subscale score	81.3 (71.3, 87.5)	45.0 (36.3, 53.8)	71.3 (60.0, 80.0)	81.3 (77.5, 87.5)	< 0.001
Biological subscale score	62.5 (52.5, 73.8)	42.5 (35.0, 50.0)	61.3 (53.8, 71.3)	87.5 (81.3, 92.5)	< 0.001
Diet score	25 (25, 50)	25 (25, 25)	25 (25, 50)	50 (25, 50)	< 0.001
Physical activity score	100 (40, 100)	0 (0, 40)	100 (60, 100)	100 (100, 100)	< 0.001
Tobacco/nicotine exposure score	100 (55, 100)	50 (0, 80)	100 (55, 100)	100 (100, 100)	< 0.001
Sleep health score	100 (70, 100)	90 (70, 100)	100 (90, 100)	100 (100, 100)	< 0.001
BMI score	100 (70, 100)	30 (30, 70)	70 (70, 100)	100 (100, 100)	< 0.001
Blood lipids score	40 (20, 60)	20 (0, 40)	40 (20, 60)	80 (60, 100)	< 0.001
Blood pressure score	50 (25, 70)	25 (0, 30)	30 (25, 50)	100 (50, 100)	< 0.001
Blood glucose score	100 (100, 100)	100 (60, 100)	100 (100, 100)	100 (100, 100)	< 0.001

Abbreviations: *BMI*, body mass index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *HDL*, high-density lipoprotein; *LE8*, Life's Essential 8; *IQR*, interquartile range; *SD*, standard deviation

[a] Continuous variables are presented as mean (SD); categorical variables are presented as *N* (%)

[b] Those characteristics were presented as median (IQR)

High-CVH individuals without depressive symptoms had the lowest risk of HF (HR = 0.344; 95% CI, 0.295–0.401). Notably, the results of the multiplicative interaction revealed that depressive symptoms significantly modified the association between the LE8 score and the risk of HF (*P* for interaction = 0.016). In terms of additive interactions, for high-CVH individuals without depressive symptoms, the RERI, AP, and SI were 0.229 (95% CI: 0.070–0.388), 0.658 (0.168–1.149), and 0.740 (0.619–0.884), respectively, suggesting the existence of a significant additive interaction. The reduced risk of HF in these individuals could be explained by 65.8% by the additive

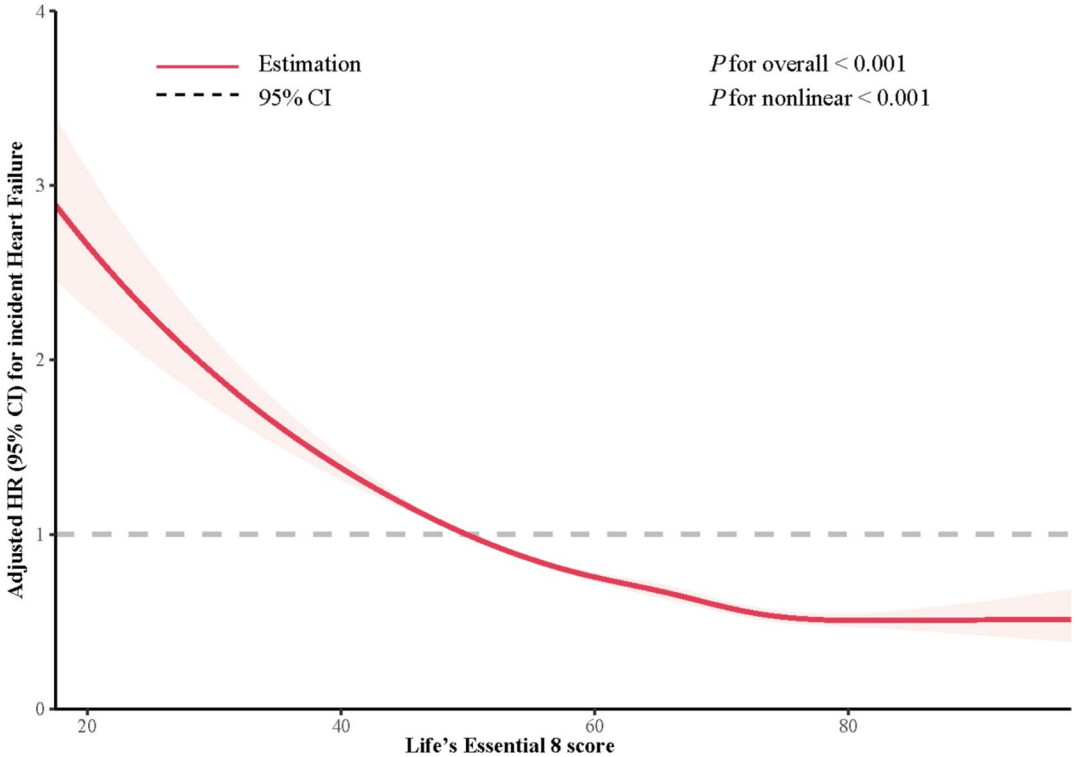

Fig. 1 Dose–response relationships between Life's Essential 8 score and incidence risk of HF among all individuals. Note: the solid line represents the point estimate and the shaded area formed by the dashed line represents the corresponding 95% CI. Adjusted for age, sex, education, ethnicity, Townsend Deprivation Index, alcohol drinking status, total sedentary time, hypertension, diabetes, cancer, and depressive symptoms. Abbreviations: HR, hazard ratio; CI, confidence interval; HF, Heart failure

Table 2 Associations of Life's Essential 8 and depressive symptoms with the incidence of HF

Variables	Cases (%)	Risk of incident HF					
		Model 1		Model 2		Model 3	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LE8 score (CVH status[a])							
Low CVH	1760 (5.82)	1 (reference)		1 (reference)		1 (reference)	
Moderate CVH	7241 (2.69)	0.485 (0.461–0.512)	< 0.001	0.508 (0.481–0.536)	< 0.001	0.596 (0.565–0.629)	< 0.001
High CVH	378 (1.02)	0.304 (0.271–0.340)	< 0.001	0.325 (0.290–0.364)	< 0.001	0.458 (0.408–0.514)	< 0.001
PAR[b], %		38.1 (31.5–44.6)		36.9 (29.8–44.0)		20.2 (8.3–32.1)	
Per SD increment in LE8 score							
Total score	9379 (2.78)	0.673 (0.659–0.688)	< 0.001	0.685 (0.671–0.700)	< 0.001	0.745 (0.729–0.762)	< 0.001
Behavior subscale[c] score	9379 (2.78)	0.812 (0.797–0.828)	< 0.001	0.820 (0.804–0.836)	< 0.001	0.826 (0.810–0.842)	< 0.001
Biological subscale[c] score	9379 (2.78)	0.714 (0.698–0.730)	< 0.001	0.724 (0.708–0.741)	< 0.001	0.815 (0.795–0.836)	< 0.001
Depressive symptoms							
No	8133 (2.73)	1 (reference)		1 (reference)		1 (reference)	
Yes	1246 (3.23)	1.450 (1.365–1.540)	< 0.001	1.389 (1.307–1.475)	< 0.001	1.309 (1.232–1.391)	< 0.001

Note: [a]The CVH status was categorized based on total LE8 score as follows: low CVH (< 50), moderate CVH (50–79), and high CVH (≥ 80). [b]The percentage of HF theoretically attributable to non-adherence to ideal CVH (≥ 80 points); population attributable risk at the median follow-up time (13.6 years) of the study population was reported. [c]LE8 subscales are mutually adjusted in the model

Model 1 adjusted for age, sex, education, ethnicity, and Townsend Deprivation Index

Model 2 adjusted for model 1 plus alcohol drinking status and total sedentary time

Model 3 adjusted for model 2 plus hypertension, diabetes, cancer, and depressive symptoms/CVH status

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval; *SD*, standard deviation; *LE8*, Life's Essential 8; *CVH*, cardiovascular health; *HF*, heart failure; *PAR*, population attributable risk

Table 3 Joint and interactive effects of LE8-defined CVH and depressive symptoms on the incidence of HF

CVH status	Joint effect		Additive interaction			Multiplicative interaction
	Depressive symptoms (HR, 95% CI)[a]		No depressive symptoms			*P* for interaction[c]
	Yes	No	RERI (95% CI)[b]	AP (95% CI)[b]	SI (95% CI)[b]	
Low CVH	1 (Reference)	0.731 (0.650, 0.822)				0.016
Moderate CVH	0.571 (0.504, 0.648)	0.440 (0.394, 0.491)	0.136 (0.030, 0.242)	0.308 (0.039, 0.576)	0.804 (0.699, 0.925)	
High CVH	0.375 (0.263, 0.534)	0.344 (0.295, 0.401)	0.229 (0.070, 0.388)	0.658 (0.168, 1.149)	0.740 (0.619, 0.884)	

Note: [a]All results were calculated adjusted by age, sex, education, ethnicity, Townsend Deprivation Index, alcohol drinking status, total sedentary time, hypertension, diabetes, and cancer. [b]The estimates of RERI, AP, and SI were calculated based on the reference group with depressive symptoms and low CVH; an additive interaction was indicated if neither the 95% CI for RERI nor the 95% CI for AP contained zero or the 95% CI of the SI did not contain one. [c]Likelihood tests were applied to test the significance of interaction term by comparing the model with and without the interaction term

Abbreviations: *LE8*, Life's Essential 8; *HF*, heart failure; *CVH*, cardiovascular health; *AP*, attributable proportion due to interaction; *RERI*, relative excess risk due to interaction; *SI*, synergy index; *HR*, hazard ratio; *CI*, confidence interval

interaction. Additionally, in analyses stratified by depressive symptoms, we found that the adverse effect of low CVH was stronger in individuals with depressive symptoms compared to those without depressive symptoms [HR (95% CI): 2.520 (1.752–3.626) vs. 2.143 (1.896–2.423)] (Fig. 2).

Sensitivity and subgroup analyses

The associations of LE8 with the risk of incident HF were generally consistent with the primary analysis in the following analyses: (1) using the quartiles of LE8 scores (Additional file 1: Table S6); (2) excluding participants who had experienced HF in the first 2 years of follow-up (Additional file 1: Table S7); (3) utilizing multiple imputations for missing covariates (Additional file 1: Table S8); (4) imputing miss data for LE8 components and covariates (Additional file 1: Table S9); (5) using the competitive hazard model (Additional file 1: Table S10); (6) omitting one element of LE8 at a time (Additional file 1: Table S11); (7) adjusting for incident CHD as a time-varying covariate (Additional file 1: Table S12); (8) adjusting for genetic susceptibility to HF (Additional file 1: Table S13); (9) excluding cancer cases at baseline (Additional file 1: Table S14); (10) excluding patients with AF at baseline (Additional file 1: Table S15); and (11) excluding patients with any cardiovascular events at baseline (Additional file 1: Table S16). Stratified analyses indicated that the association was similar across subgroups stratified by education, TDI, alcohol consumption, sedentary time, and genetic susceptibility to HF, and no significant moderation role was detected between LE8 and these stratified factors (all *P* for interaction > 0.05, Table S16). However, the protective role of high LE8 scores on the risk of incident HF was more pronounced in younger and female participants (all *P* for interaction < 0.001) (Additional file 1: Table S17).

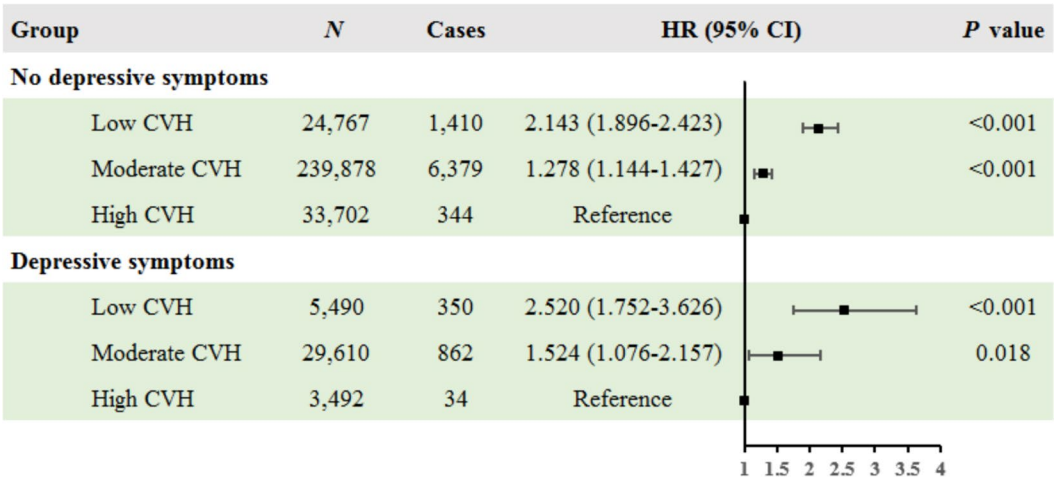

Fig. 2 Stratified analysis of the association between LE8-defined CVH and risk of incident HF by depressive symptoms. Note: Adjusted for age, sex, education, ethnicity, Townsend Deprivation Index, alcohol drinking status, total sedentary time, hypertension, diabetes, and cancer. Abbreviations: CI, confidence interval; HR, hazard ratio; LE8, Life's Essential 8; CVH, cardiovascular health; HF, heart failure

Discussion

Taking advantage of a large prospective cohort study with a median follow-up of over 13 years, the study observed that higher LE8-defined CVH was significantly associated with a decreased risk of incident HF. Furthermore, the significant multiplicative interaction observed in the study suggested that depressive symptoms significantly modified the association. In other words, achieving an ideal CVH could mitigate the increased risk of HF attributable to depressive symptoms. As well, we identified a significant additive interaction between depressive symptoms and CVH in the incidence of HF. Specifically, the lowest risk of HF was observed among participants without depressive symptoms with high CVH.

Although the relationship between CVH and HF has been documented by previous studies [8–11], CVH was defined using the scoring algorithm of LS7 in these studies. Contrary to LE8, LS7 simplified each element to three levels (poor, intermediate, and ideal), potentially causing misclassification bias and rendering it unsuitable for exploring dose–response associations with outcomes [12]. Concurrently, LE8 has been indicated greater predictive ability for adverse outcomes, which might be explained by its additional inclusion of sleep health [16, 17]. To substantiate this, CVH was redefined in our study by excluding sleep from the components of LE8, resulting in a diminished association with HF (Additional file 1: Table S10). According to our knowledge, this is one of the few and largest prospective studies investigating the association between LE8-defined novel CVH metrics and HF risk. The findings of this study align with previous studies [19–22]. Taking an example, in a prospective cohort investigation with 38,571 participants from 2016 to 2020, Cai et al. evidenced that ideal CVH is associated with a 62% (HR = 0.38; 95% CI: 0.26–0.57) reduction in the risk of HF [20]. Yet, this study had a relatively short follow-up and did not utilize the AHA-recommended refined LE8 scoring algorithm but rather roughly tri-categorized each element [20]. Consequently, this study's findings are limited in depicting the long-term association between well-recognized LE8 and HF [20]. Similarly, the LE8-HF association has been observed in CKD patients, but the findings could not be extrapolated to the general population [22]. Although two other studies based on the UK Biobank investigated the association between LE8 and HF [19, 21], HF was not the primary outcome in either study, potentially reducing the comprehensiveness and focus of their analyses. In contrast, our study systematically and comprehensively evaluated the association between LE8 and HF incidence in a large prospective cohort with a median follow-up of 13.6 years, incorporating a series of sensitivity and subgroup analyses to ensure the robustness of the findings. More importantly, our study demonstrated the interaction between LE8-defined CVH and depressive symptoms in the incidence of HF, providing a novel perspective on the interplay between physical and psychological health. This innovative finding was not considered in any of the aforementioned studies [19–22], underscoring the unique contribution of our research.

In line with a previous review and findings from a large cohort study [23, 24], our findings showed that depressive symptoms markedly elevated the risk of HF incidence. Significantly, this study was the first to uncover a multiplicative interaction between CVH and depressive symptoms, contributing to the incidence of HF. Put simply, maintaining ideal CVH as defined by LE8 could significantly mitigate the increased risk of HF due to depressive symptoms. The findings provided the first empirical evidence from a population-based perspective that emphasized the essential role of psychological health in CVH enhancement, potentially supporting the view of Gaffey et al. [25]. Similar to the present study, prior studies have demonstrated that lifestyles can interact with depressive symptoms to influence CVD outcomes. For example, Jin et al. observed a significant multiplicative interaction between short sleep duration and depressive symptoms on CVD risk [28]. Bai and Guo found that higher LE8 scores may moderate the associations of depressive symptoms with all-cause and CVD mortality [29]. Notably, we identified a significant additive interaction between CVH and depressive symptoms, suggesting the synergistic effect of combined exposure to low CVH and depressive symptoms surpassed the sum of their respective effects. The observed additive interaction was similar to previous studies exploring the interaction of lifestyle factors and depressive symptoms on health outcomes. For instance, a longitudinal study from Amsterdam found a significant additive interaction between physical activity and depressive symptoms on CVD risk [41]. An earlier study by our team observed a significant additive effect of low levels of physical activity and depressive symptoms on the increased risk of all-cause mortality [26]. While the exact mechanism of the interaction between depressive symptoms and CVH remains unclear, both are associated with inflammation and vascular endothelial dysfunction [23, 42], which have been implicated in the pathogenesis of HF [43]. Therefore, it is reasonable to speculate that inflammatory disorders and vascular endothelial dysfunction might be one of the potential mechanisms for the interactions identified in the present study, and well-designed studies will be warranted in the future to further confirm this speculation. As expected, we observed a linear trend in the dose–response relationship between LE8 and HF incidence only among participants with depressive symptoms, implying that the

protective effect of high LE8 levels against the risk of HF incidence in these participants is not bottlenecked. Gender-stratified analyses further reinforced the robustness of the linear relationship observed only in these participants (Additional file 1: Figs. S7 and S8). These findings emphasized that improving CVH should be a priority in the treatment of patients with depressive symptoms, given their potential to achieve greater health benefits. However, patients with depressive symptoms often face barriers such as low motivation and reduced adherence to behavioral changes, which may undermine the effectiveness of generalized CVH promotion strategies for HF prevention [44]. Therefore, combining treatment of depressive symptoms (e.g., cognitive behavioral therapy or pharmacological interventions) with structured lifestyle interventions (e.g., supervised exercise programs) might not only enhance adherence but also provide significant benefits in reducing the risk of HF [45]. Additionally, leveraging digital health tools, such as mobile applications that provide personalized reminders and progress tracking, might further facilitate engagement and ensure the long-term sustainability of these interventions [46]. By addressing depressive symptoms alongside CVH improvement, these integrated approaches might offer a more practical and impactful strategy for HF prevention in this high-risk population.

In alignment with prior research [16, 31], our findings demonstrated a more pronounced protective effect of high CVH on HF risk among females and young adults. For instance, Li et al. noted in their prospective study that a higher LE8 score significantly reduced the risk of CVD, particularly in females and young adults [16]. Also, Zhang et al. obtained consistent findings when exploring the association between LE8 and atrial fibrillation [31]. One plausible reason is that males are more frequently associated with unhealthy lifestyle choices, such as smoking and drinking alcohol, which are significant risk factors for HF. Additionally, sex-specific genetic and biological differences in HF may contribute to this [43, 47]. The stronger protective effect of high CVH in younger individuals might be explained by their lower baseline risk compared to older adults and the longer duration of cumulative protection associated with maintaining high CVH [31, 48]. These findings stressed the public health imperative of embedding LE8 interventions in early HF prevention efforts, particularly for females and young people. In the study, we found that adherence to ideal CVH could theoretically avert over 20% of HF cases, with the largest contributions from BMI, which supported and expanded upon findings from previous studies [25, 31]. Undoubtedly, BMI stands as a significant and changeable risk factor for HF. A comprehensive meta-analysis encompassing 12 Mendelian randomization studies supported a causal relationship between high BMI and an increased risk of incident HF [49]. Active mediators secreted by adipose tissue could influence changes in coagulation and inflammation, potentially causing arteriosclerosis and subsequently increasing the risk of HF [50]. Consequently, sustaining an ideal body weight could be a crucial strategy in lowering the risk of HF.

Strengths and limitations

The current study was strengthened by its prospective design, substantial sample size with extensive follow-up, and adequate adjustment for confounders. The first combination of depressive symptoms and novel CVH evaluation metrics was used to assess the associations of physical and psychological health interactions with the incidence of HF. The identified interaction could facilitate the precision prevention of targeted at-risk populations. Certain limitations of our study warranted attention. First, information regarding behavioral factors comprising LE8 and some covariates was obtained through self-reports, which may be susceptible to information bias. Second, while the study made sufficient adjustments for common confounders, the potential for unmeasured or residual confounders cannot be entirely dismissed. Third, since this study utilized an observational design, the identified associations should not be interpreted as causality. Fourth, the predominance of White participants (95.9%) in our study necessitated the replication of the findings among diverse ethnic populations. Fifth, although "healthy volunteer" bias in the UK Biobank may compromise the representativeness of the findings [51], the external validity of these risk factor associations has been established in prior research [52]. Sixth, approximately one-third of the participants were excluded due to missing data on LE8 and covariates. Although the discrepancies between the included and excluded participants in terms of sociodemographic and lifestyle characteristics were modest (Additional file 1: Table S18), the possibility of selection bias cannot be disregarded. Seventh, temporal variations in LE8 were not considered in the study due to the availability of data, despite existing evidence of the relative stable of CVH scores [53]. Nonetheless, additional studies are still warranted to investigate the impact of LE8 changes over time on the risk of HF. Furthermore, the current study lacked sufficient EF data to consider the different subtypes of HF. Future research with more comprehensive EF data could be used to better explore the associations between LE8 and HF subtypes. Another limitation of this study is the absence of fasting glucose measurements in the UK Biobank dataset, as blood samples were collected under non-fasting conditions [54]. Although the combination of medical records, HbA1c, and insulin use provided robust measures for identifying

diabetes [55], the lack of fasting glucose data might have limited our ability to capture all diabetes cases.

Conclusions

The large prospective cohort study suggested that LE8-defined CVH was negatively associated with the incidence of HF. Achieving higher LE8 scores can substantially mitigate the risk of HF associated with depressive symptoms. Additionally, participants with both depressive symptoms and low CVH not only were at the highest risk of incident HF but also exhibited a synergistic effect on the incidence of HF. These findings underscored the critical importance of following the AHA-recommended LE8 to improve CVH for HF prevention, especially in patients with depressive symptoms.

Abbreviations

HF	Heart failure
PA	Physical activity
BP	Blood pressure
LS7	Life's Simple 7
AHA	American Heart Association
CVH	Cardiovascular health
LE8	Life's Essential 8
CVD	Cardiovascular disease
CKD	Chronic kidney disease
LC9	Life's Critical 9
CHD	Coronary heart disease
BMI	Body mass index
ICD-10	International Classification of Diseases, Tenth Revision
PHQ-2	Patient Health Questionnaire-2
TDI	Townsend Deprivation Index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HbA1c	Glycated hemoglobin
SD	Standard deviation
IQR	Interquartile range
HR	Hazard ratio
CI	Confidence interval
RCS	Restricted cubic spline
PAR	Population attributable risk
RERI	Relative excess risk due to interaction
AP	Attributable proportion due to interaction
SI	Synergy index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04011-3.

Additional file 1: Supplementary Method, Tables S1–S18, and Figures S1–S8. Table S1 Components of more recent dietary recommendations for cardiovascular health used in the UK Biobank. Table S2 Detailed description of the 8 components of Life's Essential 8. Table S3 Information of single-nucleotide polymorphisms associated with heart failure in the UK Biobank. Table S4 Descriptive statistics of participants by incident heart failure. Table S5 Associations of 8 metrics of LE8 with the incidence of heart failure. Table S6 Associations of quartiles of LE8 score with the incidence of heart failure ($n = 336,939$). Table S7 Associations of LE8 with the incidence of heart failure after excluding participants with events that occurred in the first 2 years' follow-up ($n = 335,334$). Table S8 Associations of LE8 with the incidence of heart failure using multiple imputations for missing covariates ($n = 340,876$). Table S9 Comparison of associations between LE8 and incident HF after excluding or imputing miss values for LE8 and covariates. Table S10 Associations of LE8 with the incidence of heart failure using competing risk models ($n = 336,939$). Table S11 Associations of LE8 consisting of 7 components with the incidence of heart failure ($n = 336,939$). Table S12 Association between LE8 and incident HF after additional adjustment for incident CHD as a time-varying covariate ($n = 336,939$). Table S13 Association between LE8 and incident HF after additional adjustment genetic susceptibility for HF ($n = 334,433$). Table S14 Association between LE8 and incident HF after excluding individuals with cancer at baseline ($n = 307,089$). Table S15 Association between LE8 and incident HF after excluding individuals with atrial fibrillation at baseline ($n = 333,319$). Table S16 Association between LE8 and incident HF after excluding individuals with any cardiovascular events at baseline ($n = 294,068$). Table S17 Stratified analysis for the association of LE8 with the incidence of heart failure. Table S18 Comparison analysis of baseline characteristics of the included and excluded participants. Fig. S1 Participant flow chart: selection process of included participants from the UK Biobank. Fig. S2 The Kaplan–Meier plot according to LE8 categories. Fig. S3 Dose–response relationships between continuous behavior subscale score and risk of incident HF. Fig. S4 Dose–response relationships between continuous biological subscale score and risk of incident HF. Fig. S5 Dose–response relationships between LE8 score and incidence risk of incident HF among individuals without depressive symptoms. Fig. S6 Dose–response relationships between LE8 score and risk of incident HF among individuals with depressive symptoms. Fig. S7 Dose–response relationships between LE8 score and the risk of HF among males with and without depressive symptoms. Fig. S8 Dose–response relationships between LE8 score and the risk of HF among females with and without depressive symptoms.

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Authors' contributions

YQH, BPL, and CXJ are corresponding authors and senior authors who contributed equally to this study. WH and CHZ are joint first authors with equal contributions. BPL and CXJ had full access to all the data in this study and took full responsibility for the integrity of the data and the accuracy of the data analysis. YQH, BPL, and CXJ conceived and designed the study. WH, CHZ, JNW, ZZS, and GT undertook the statistical analysis. WH and CHZ drafted the manuscript. YQH, BPL, and CXJ are the guarantors. All authors provided critical input to the analyses, interpreted the data, revised the manuscript critically, and approved the final manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Northwest Multi-center Research Ethics Committee (MREC reference: 21/NW/0157) provided ethical approval for the UK Biobank project. All participants gave informed consent before being recruited.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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