Mediation analysis of adiposity and inflammation in the associations of Life's Crucial 9 and Life's Essential 8 with mortality among postmenopausal women

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Abstract

Objective: Life's Essential 8 (LE8) and Life's Crucial 9 (LC9) summarize overall cardiovascular health. This study investigated the associations between LC9 and LE8 with all-cause and cardiovascular mortality in postmenopausal women and further assessed whether adiposity-related and inflammation-related indicators statistically mediated these associations.

Methods: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2005-2018, with mortality follow-up through December 31, 2019. The primary outcome was all-cause mortality, and the secondary outcome was cardiovascular mortality. Survey-weighted Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality. Nonlinear dose-response relationships were assessed using generalized additive models with penalized splines, and survival differences were visualized by Kaplan-Meier curves with log-rank tests. Stratified analyses were performed across demographic and clinical subgroups. Mediation analyses further quantified the indirect effects of adiposity-related indices (a body shape index [ABSI], weight–waist index [WWI]) and inflammation-related indicators (systemic inflammation response index [SIRI], red cell distribution width [RDW]).

Results: Among 7,842 postmenopausal women, there were 1,313 all-cause deaths and 395 cardiovascular deaths during follow-up. In Cox models, higher cardiovascular health scores were associated with lower mortality. For LE8, each 1-SD increase (14.4 points) was associated with lower all-cause mortality (HR = 0.72, 95% CI = 0.68-0.77) and cardiovascular mortality (HR = 0.67, 95% CI = 0.60-0.75). LC9 analyses were restricted to participants with nonmissing LC9 (n = 7,496). For LC9, each 1-SD increase (14.0 points) was associated with lower all-cause mortality (HR = 0.70, 95% CI = 0.65-0.75) and cardiovascular mortality (HR = 0.62, 95% CI = 0.55-0.70). Categorized analyses showed graded associations, with lower mortality at higher score levels. In mediation analyses, adiposity-related and inflammation-related indicators explained a small proportion of these associations. For LE8, the proportion mediated was ~5.4% (ABSI), 6.6% (WWI), 8.7% (SIRI), and 10.5% (RDW). For LC9, SIRI, and RDW–mediated ~8.7% and 10.3%, respectively (all indirect effects $P < 0.001$).

Conclusions: We observed inverse associations between LE8 and LC9 scores and both all-cause and cardiovascular mortality in postmenopausal women. Indicators of adiposity and systemic inflammation showed partial statistical mediation of these observed associations.

Key Words: Adiposity, All-cause mortality, Cardiovascular mortality, Inflammation, LC9, LE8, Mediation analysis, Postmenopausal women.

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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among women worldwide, and the risk markedly increases after menopause due to hormonal changes, metabolic alterations,

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Data were derived from the following resources available in the public domain: https://www.cdc.gov/nchs/nhanes/index.htm. The survival data were obtained from the NCHS: https://www.cdc.gov/nchs/data-linkage/mortality.htm.

This study is based on publicly available data from the National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health Statistics (NCHS). All procedures involving human participants were approved by the NCHS Research Ethics Review Board, under Protocol #2005-06 and Protocol #2011-17. Written informed consent was obtained from all participants at the time of original data collection.

J.W.: formal analysis, data curation, and conceptualization. Y.L.: validation, software, methodology, conceptualization.

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and vascular aging. Comprehensive assessment of cardiovascular health (CVH) is therefore essential for identifying high-risk populations and guiding prevention strategies in postmenopausal women.[1–4]

In 2022, the American Heart Association (AHA) updated its construct of ideal CVH from Life's Simple 7 to Life's Essential 8 (LE8), incorporating sleep health and refining behavioral and clinical metrics to provide a more complete assessment of cardiovascular status.[5] Building on these principles, Life's Crucial 9 (LC9) has been proposed as an extension of LE8, adding additional cardiometabolic components such as psychosocial health. Although LC9 has not been codified by the AHA, it offers a further refinement of the multidimensional CVH concept, and both LE8 and LC9 serve as quantitative tools for capturing CVH profiles in population studies.[6,7]

Although higher LE8 or LC9 scores have been associated with reduced risks of cardiovascular events and mortality,[8,9] the potential mechanisms underlying these associations remain incompletely characterized. Postmenopausal women undergo substantial shifts in body composition and fat redistribution (eg, increased central and visceral adiposity) that elevate cardiometabolic risk.[10,11] Moreover, in this population, higher adiposity is frequently associated with upregulation of inflammatory markers and metabolic dysregulation.[12] Therefore, it is important to examine whether adiposity-related and inflammation-related indicators might statistically mediate the associations of global cardiovascular health scores with mortality in this specific group.

Accordingly, we conducted an association analysis using a nationally representative sample of postmenopausal women to examine the relationships between LE8 and LC9 and all-cause and cardiovascular mortality, and to evaluate whether adiposity-related and inflammation-related indicators statistically mediate these associations.

METHODS

Data source and population

Flow diagram showing participant selection for the analytic baseline from the National Health and Nutrition Examination Survey (NHANES) 2005-2018 (Fig. 1). Participants included adults aged 20 years and older. Women aged 45 years and older were retained after excluding men and younger participants. Postmenopausal women were defined as those with natural or surgical menopause. Participants with missing LC9 or LE8 metrics or missing all-cause mortality data were excluded from the final analytic cohort (n = 7,842). The NHANES survey is cross-sectional, meaning that each participant is sampled once without repeated visits. Data were derived from the following resources available in the public domain: https://www.cdc.gov/nchs/nhanes/. The survival data were obtained from the NCHS: https://www.cdc.gov/nchs/data-linkage/mortality.htm. NHANES protocols were approved by the National Center for Health Statistics Institutional Review Board, and written informed consent was obtained from all participants before data collection.

Assessment of LE8 and LC9 scores

The LE8 score is an index developed to assess cardiovascular health, encompassing eight critical components: diet quality, blood pressure, blood glucose, non-HDL cholesterol, body mass index (BMI), sleep quality, physical activity, and smoking status.[13] These components are evaluated through clinical measurements as well as participant self-reports. Each component is assigned a score on a scale from 0 to 100, with higher values indicating better health outcomes. The overall LE8 score is computed as the average of the scores for each component.[5]

Blood pressure, blood glucose, and BMI are determined through standard clinical evaluations. Sleep quality is gauged using a self-reported questionnaire, which considers sleep duration, disturbances, and overall satisfaction. Physical activity is measured by self-reported data on exercise frequency and intensity, and smoking status is categorized as current, former, or nonsmoker. Non-HDL cholesterol is measured via laboratory blood tests. The LE8 score provides a comprehensive view of cardiovascular health by integrating clinical measures and behavioral factors, including sleep and activity levels.[14] For this analysis, the LE8 total scores were categorized into three groups: low CVH (<50), moderate CVH (50–79), and high CVH (≥ 80).[8,15,16]

LC9 builds upon the LE8 framework by adding psychosocial health. This was assessed using the Patient Health Questionnaire-9 (PHQ-9), a validated self-report tool used to screen for depression and assess its severity.[17,18] The PHQ-9 includes 9 items, each corresponding to one of the diagnostic criteria for major depressive disorder as outlined in DSM-IV. Participants rated the frequency of their depressive symptoms over the preceding 2 weeks on a scale from 0 ("Not at all") to 3 ("Nearly every day"). The total score ranges from 0 to 27, with higher scores indicating greater severity of depression. Depression scores were categorized as mild (5-9), moderate (10-14), moderately severe (15-19), or severe (20-27). This tool contributes to the psychosocial health component of the LC9 score, as detailed in Supplemental Table S1, Supplemental Digital Content 1, http://links.lww.com/MENO/B493.

In this study, LC9 was employed as a sensitivity analysis to examine whether the inclusion of psychosocial health and additional cardiometabolic components influences the observed associations with LE8. Both LE8 and LC9 scores are derived using a similar methodology, where each individual component is rated on a scale from 0 to 100, and the overall score is the average of these component scores.[19]

Assessment of all-cause and cardiovascular mortality

Vital status and causes of death were obtained by linking NHANES participants to the National Death Index via the NHANES public-use mortality linkage, with follow-up available through December 31, 2019. The primary endpoint was all-cause mortality, defined as death from any cause. The secondary endpoint was

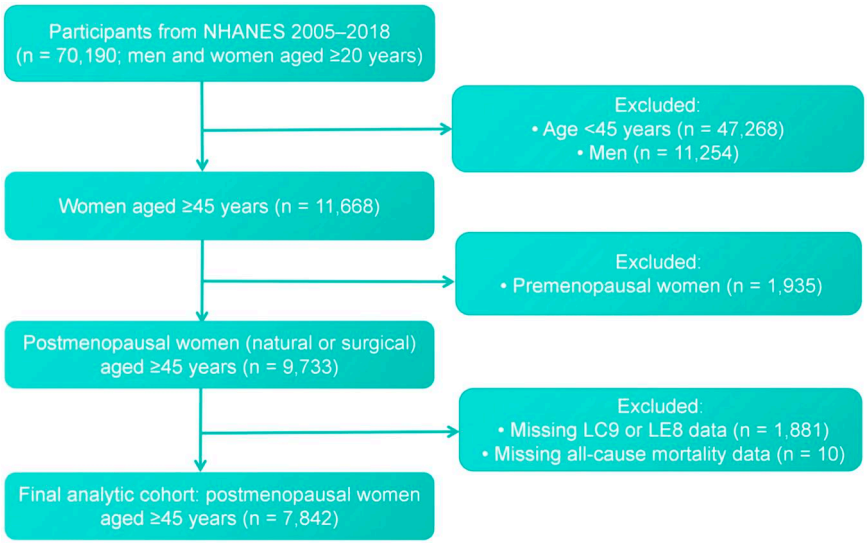

FIG. 1. Flow diagram of participant selection from the NHANES 2005-2018. NHANES, National Health and Nutrition Examination Survey.

cardiovascular mortality, determined from the underlying cause of death coded using ICD-10 and restricted to deaths due to heart disease or cerebrovascular disease. Person-time was accrued from the participant's baseline interview date until death or censoring at the end of follow-up (December 31, 2019).[20]

Determination of postmenopausal status

Postmenopausal status was determined using responses from the NHANES reproductive health questionnaire.[21] Female participants were first asked whether they had regular menstrual periods during the preceding 12 months; those who reported no regular periods were further asked to indicate the reason, with prespecified options of menopause/change of life, pregnancy, breast-feeding, medical conditions/treatments, or other. Women who selected menopause/change of life on these items were considered postmenopausal in the present analysis, and menopausal status was defined based on self-reported questionnaire data.

Evaluation and calculation of mediators

Two categories of potential mediators were evaluated in this study: (1) obesity-related indices, including a body shape index (ABSI) and weight-waist index (WWI), and (2) inflammation-related indices, including the systemic inflammation response index (SIRI) and red cell distribution width (RDW). All variables were obtained from the baseline National Health and Nutrition Examination Survey (NHANES) examination and laboratory data. Measurements were performed by trained technicians following standardized protocols at the Mobile Examination Centers (MEC).[22]

(1) Obesity-related indices.

ABSI was calculated using waist circumference (WC), height, and BMI according to the following formula:

$$\mathrm{ABSI} = \frac{\mathrm{WC(m)}}{\mathrm{BMI}^{2/3} \times \mathrm{height}^{1/2}\mathrm{(m)}}.$$

Waist circumference and height were converted to meters (m), and BMI was expressed in kg/m^2. ABSI reflects central body shape characteristics independent of overall body mass.[23]

WWI was calculated as:

$$\mathrm{WWI} = \frac{\mathrm{WC\ (cm)}}{\sqrt{\mathrm{Weight\ (kg)}}}.$$

WWI quantifies abdominal adiposity adjusted for body weight and is a simple indicator of body fat distribution.[24]

(2) Inflammation-related indices.

SIRI was derived from complete blood count data as follows:

$$\mathrm{SIRI} = \frac{\mathrm{neutrophil\ count} \times \mathrm{monocyte\ \ count}}{\mathrm{lymphocyte\ \ count}}.$$

Neutrophil, monocyte, and lymphocyte counts (10^9/L) were obtained from whole blood analyses using automated hematology analyzers at the MEC. SIRI reflects the balance between innate and adaptive immune responses.[25]

RDW was obtained directly from NHANES laboratory data, measured as the coefficient of variation (RDW-CV, %) of red blood cell volume distribution using standardized automated hematology analyzers. RDW indicates erythrocyte size heterogeneity and has been associated with systemic inflammation and adverse outcomes.[26]

TABLE 1. Baseline characteristics of participants by survival status

All-cause mortality	Mean ± SD	Survival	Deceased participants	*P*
N		6,529	1,313	
Age (y)	64.93 ± 9.85	63.40 ± 9.24	72.53 ± 9.22	< 0.001
BMI (kg/m^2)	30.17 ± 7.28	30.38 ± 7.20	29.11 ± 7.56	< 0.001
A body shape index	0.08 ± 0.00	0.08 ± 0.00	0.08 ± 0.01	< 0.001
Weight-waist index	11.55 ± 0.78	11.52 ± 0.78	11.70 ± 0.81	< 0.001
Red cell distribution width	13.46 ± 1.33	13.41 ± 1.21	13.74 ± 1.82	< 0.001
Systemic inflammation response index	1.15 ± 0.83	1.08 ± 0.72	1.52 ± 1.20	< 0.001
Diastolic blood pressure	68.92 ± 12.50	69.72 ± 11.97	64.87 ± 14.27	< 0.001
Systolic blood pressure	131.42 ± 20.99	130.33 ± 19.96	136.93 ± 24.83	< 0.001
White blood cell count	7.11 ± 5.06	7.07 ± 5.40	7.34 ± 2.72	< 0.001
Platelet	252.95 ± 67.15	253.06 ± 63.63	252.34 ± 83.00	0.135
LE8	61.51 ± 14.47	62.37 ± 14.39	57.25 ± 14.10	< 0.001
LC9	63.66 ± 14.02	64.48 ± 13.91	59.34 ± 13.81	< 0.001
Ethnicity				< 0.001
Non-Hispanic White	3,761 (47.96%)	2,932 (44.91%)	829 (63.14%)	
Non-Hispanic Black	1,744 (22.24%)	1,466 (22.45%)	278 (21.17%)	
Mexican American	986 (12.57%)	890 (13.63%)	96 (7.31%)	
Other Hispanic	786 (10.02%)	722 (11.06%)	64 (4.87%)	
Other race	565 (7.20%)	519 (7.95%)	46 (3.50%)	
Poverty income ratio				< 0.001
Poor	1,325 (16.90%)	1,060 (16.24%)	265 (20.18%)	
Nearly poor	2,008 (25.61%)	1,553 (23.79%)	455 (34.65%)	
Middle income	1,962 (25.02%)	1,653 (25.32%)	309 (23.53%)	
High income	1,798 (22.93%)	1,633 (25.01%)	165 (12.57%)	
Missing	749 (9.55%)	630 (9.65%)	119 (9.06%)	
Education level, n (%)				< 0.001
Below high school	950 (12.11%)	761 (11.66%)	189 (14.39%)	
High school	3,035 (38.70%)	2,401 (36.77%)	634 (48.29%)	
Above high school	3,849 (49.08%)	3,361 (51.48%)	488 (37.17%)	
Missing	8 (0.10%)	6 (0.09%)	2 (0.15%)	
Smoking status				< 0.001
Never	4,712 (60.09%)	4,028 (61.69%)	684 (52.09%)	
Former	2,051 (26.15%)	1,623 (24.86%)	428 (32.60%)	
Now	1,074 (13.70%)	874 (13.39%)	200 (15.23%)	
Missing	5 (0.06%)	4 (0.06%)	1 (0.08%)	
Alcohol use, n (%)				< 0.001
Never	1,667 (21.26%)	1,343 (20.57%)	324 (24.68%)	
Former	1,616 (20.61%)	1,180 (18.07%)	436 (33.21%)	
Mild	2,358 (30.07%)	2,049 (31.38%)	309 (23.53%)	
Moderate	1,057 (13.48%)	949 (14.54%)	108 (8.23%)	
Heavy	559 (7.13%)	499 (7.64%)	60 (4.57%)	
Missing	585 (7.46%)	509 (7.80%)	76 (5.79%)	
Hypertension				< 0.001
No	2,607 (33.25%)	2,339 (35.83%)	268 (20.43%)	
Yes	5,233 (66.75%)	4,189 (64.17%)	1,044 (79.57%)	
Marital status, n (%)				< 0.001
Married/living with partner	3,894 (49.66%)	3,450 (52.84%)	444 (33.82%)	
Widowed/divorced/separated	3,407 (43.45%)	2,599 (39.81%)	808 (61.54%)	
Never married	537 (6.85%)	476 (7.29%)	61 (4.65%)	
Missing	4 (0.05%)	4 (0.06%)	0 (0.00%)	
Diabetes mellitus				< 0.001
No	4,820 (61.46%)	4,149 (63.55%)	671 (51.10%)	
Yes	2,261 (28.83%)	1,752 (26.83%)	509 (38.77%)	
IFG	367 (4.68%)	312 (4.78%)	55 (4.19%)	
IGT	394 (5.02%)	316 (4.84%)	78 (5.94%)	
Hyperlipidemia				0.290
No	1,261 (16.08%)	1,037 (15.89%)	224 (17.06%)	
Yes	6,580 (83.92%)	5,491 (84.11%)	1,089 (82.94%)	
Hysterectomy or BSO				0.013
No	4,613 (58.8%)	3,881 (59.4%)	732 (55.8%)	
Yes	3,229 (41.2%)	2,648 (40.6%)	581 (44.2%)	

TABLE 1. (*continued*)

All-cause mortality	Mean ± SD	Survival	Deceased participants	*P*
Natural menopause/menopause-related				0.002
No	3,618 (46.1%)	2,960 (45.3%)	658 (50.1%)	
Yes	4,224 (53.9%)	3,569 (54.7%)	655 (49.9%)	
≥ 55 y				0.098
No	7,453 (95.0%)	6,217 (95.2%)	1,236 (94.1%)	
Yes	389 (5.0%)	312 (4.8%)	77 (5.9%)	
Oral estrogen				0.002
No	4,820 (63.97%)	3,983 (63.20%)	837 (67.88%)	
Yes	2,715 (36.03%)	2,319 (36.80%)	396 (32.12%)	

BMI, body mass index; BSO, bilateral oophorectomy; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; LC9, Life's Crucial 9; LE8, Life's Essential 8; NHANES, National Health and Nutrition Examination Survey; SD, standard deviation.

Data are presented as mean ± standard deviation (SD) for continuous variables or number (percentage) for categorical variables. Ethnicity categories follow NHANES coding. "Other Hispanic" refers to Hispanic participants who are not of Mexican American descent. "Other Race" includes participants not classified as non-Hispanic White, non-Hispanic Black, Mexican American, or Other Hispanic and may include non-Hispanic Asian, multiracial, and other race groups.

Covariates

Covariates included age, ethnicity, education level, marital status, and poverty income ratio. Health behaviors included smoking status and alcohol use. Clinical factors included BMI (kg/m^2), systolic blood pressure, diastolic blood pressure, hypertension, diabetes status, and hyperlipidemia. Laboratory covariates included white blood cell count and platelet count. Reproductive and hormone-related variables included hysterectomy or bilateral oophorectomy, natural menopause status, age 55 years or older, and current oral estrogen use.[27]

Statistical analyses

All analyses adhered to NHANES analytic recommendations and incorporated the complex survey design by applying sampling weights together with strata and primary sampling units. Continuous variables are presented as weighted means with standard deviations, and categorical variables as weighted percentages. Between-group comparisons used weighted linear regression for continuous variables and the Rao-Scott χ^2 test for categorical variables. Associations of LE8 and LC9 with all cause and cardiovascular mortality were evaluated with survey weighted Cox proportional hazards models, reporting hazard ratios with 95% confidence intervals.[28] LE8 and LC9 were assessed in separate models and were examined both per 1 standard deviation increase and by tertiles. Model 1 adjusted for age, race or ethnicity, and education, and Model 2 additionally adjusted for marital status, poverty income ratio, white blood cell count, and platelet count. To check collinearity among predictors, variance inflation factors were examined, and LE8 and LC9 were not entered simultaneously in the same model (Supplemental Table S4, Supplemental Digital Content 1, http://links.lww.com/MENO/B493). Possible nonlinear patterns were explored using generalized additive models with smoothing splines.[29] Kaplan-Meier curves were used to describe survival across tertiles, with log-rank tests for group differences. Prespecified subgroup analyses were conducted, and effect modification was evaluated by including multiplicative interaction terms. Mediation analyses estimated total, direct, and indirect effects through ABSI and WWI as adiposity-related indices and SIRI and RDW as inflammation-related indicators, and the proportion mediated was reported when the effects were directionally consistent.[30] Two-sided *P*-values below 0.05 were considered statistically significant. Analyses were performed using R software, version 4.2.2 (R Core Team, Vienna, Austria) and EmpowerStats, version 5.2 (X&Y Solutions Inc., Boston, MA).

RESULTS

Baseline characteristics

Among 7,842 participants, 6,529 were survival participants, and 1,313 were deceased participants during follow-up (Table 1). The distribution of follow-up duration and the corresponding mortality counts by follow-up time quartiles are shown in Supplemental Table S6, Supplemental Digital Content 1, http://links.lww.com/MENO/B493. Deceased participants were older (72.53 ± 9.22 vs. 63.40 ± 9.24 y, $P < 0.001$) and had lower BMI (29.11 ± 7.56 vs. 30.38 ± 7.20 kg/m^2, $P < 0.001$) but higher WWI, ABSI, RDW, SIRI, systolic blood pressure (SBP), and white blood cell counts (all $P < 0.001$). Diastolic blood pressure (DBP) was lower in deceased participants (64.87 ± 13.48 vs. 69.72 ± 11.72 mm Hg, $P < 0.001$), while platelet count showed no significant difference ($P = 0.135$). Scores for LE8 and LC9 were lower among deceased participants (LE8: 57.25 ± 10.82 vs. 62.37 ± 10.01; LC9: 59.34 ± 10.63 vs. 64.48 ± 9.66; both $P < 0.001$). Deceased participants were more likely to be non-Hispanic White (63.14% vs. 44.91%), live below the poverty threshold (20.18% vs. 16.24%), and have lower education levels (high school or below: 14.39% vs. 11.66%) (all $P < 0.001$).

They were more often current or former smokers and had higher prevalences of hypertension and diabetes (all $P < 0.001$). In contrast, current alcohol consumption was less frequent, while past or never drinking was more common ($P < 0.001$). A greater proportion were widowed, divorced, or separated ($P < 0.001$). The prevalence of hyperlipidemia did not differ significantly between groups ($P = 0.290$).

TABLE 2. Associations of Life's Essential 8 and Life's Crucial 9 scores with all-cause and cardiovascular mortality in postmenopausal women

Exposure	Events/Total	Adjust I	Adjust II
All-cause mortality			
LE8 score (per 1-SD increase)	1,313/7,842	0.69 (0.65-0.74) < 0.0001	0.72 (0.68-0.77) < 0.0001
LE8 tertile			
< 50	382/1,645	1.0 (Reference)	1.0 (Reference)
50–79	853/5,333	0.63 (0.56-0.71) < 0.0001	0.73 (0.64-0.83) < 0.0001
≥ 80	78/864	0.40 (0.31-0.52) < 0.0001	0.46 (0.36-0.60) < 0.0001
P for trend		< 0.0001	< 0.0001
LC9 score (per 1-SD increase)		0.67 (0.63-0.71) < 0.0001	0.70 (0.65-0.75) < 0.0001
LC9 tertile			
Low	537/2,472	1.0 (Reference)	1.0 (Reference)
Middle	398/2,524	0.62 (0.55-0.71) < 0.0001	0.67 (0.59-0.77) < 0.0001
High	258/2,500	0.42 (0.36-0.49) < 0.0001	0.47 (0.40-0.55) < 0.0001
P for trend		< 0.0001	< 0.0001
Cardiovascular mortality			
LE8 score (per 1-SD increase)	395/7,842	0.64 (0.58-0.71) < 0.0001	0.67 (0.60-0.75) < 0.0001
LE8 tertile			
< 50	123/1,645	1.0 (Reference)	1.0 (Reference)
50–79	256/5,333	0.58 (0.47-0.73) < 0.0001	0.70 (0.56-0.88) 0.0021
≥ 80	16/864	0.27 (0.16-0.47) < 0.0001	0.30 (0.17-0.52) < 0.0001
P for trend		< 0.0001	< 0.0001
LC9 score (per 1-SD increase)		0.62 (0.55-0.69) < 0.0001	0.62 (0.55-0.70) < 0.0001
LC9 tertile			
Low	165/2,472	1.0 (Reference)	1.0 (Reference)
Middle	125/2,524	0.63 (0.50-0.80) 0.0001	0.65 (0.51-0.83) 0.0005
High	68/2,500	0.37 (0.28-0.50) < 0.0001	0.40 (0.30-0.54) < 0.0001
P for trend		< 0.0001	< 0.0001

LC9, Life's Crucial 9; LE8, Life's Essential 8; SD, standard deviations.

Data are presented as hazard ratios (HR) with 95% confidence intervals (CI) and *P* values. Adjust I model adjusted for age, ethnicity, and education. Adjust II model further adjusted for marital status, poverty income ratio, white blood cell count, and platelet count. Per 1-SD increase represents the hazard ratio associated with each one standard deviation increase in the LE8 or LC9 score. For LE8, Per 1-SD = 14.4; for LC9, Per 1-SD = 14.0. LE8 was the primary exposure, and thus analyses for LE8 included all eligible participants (N = 7,842). LC9 was a secondary exposure; 346 participants with missing LC9 metrics were excluded from LC9-related analyses, yielding a reduced analytic sample (N = 7,496).

Association of LE8 and LC9 scores with all-cause and cardiovascular mortality

Cox proportional hazards analyses indicated that LE8 and LC9 scores were inversely associated with both all-cause and cardiovascular mortality in postmenopausal women.

For all-cause mortality, each 1-standard deviation (SD) increase in LE8 and LC9 scores was associated with a lower risk of mortality (LE8: HR = 0.72, 95% CI = 0.68-0.77; LC9: HR = 0.70, 95% CI = 0.65-0.75; both $P < 0.0001$). Compared with participants in the lowest category of LE8 (low: < 50), those in the middle (50-79) and high (≥ 80) categories had significantly lower risks of all-cause mortality (middle: HR = 0.67, 95% CI = 0.59-0.76; high: HR = 0.50, 95% CI = 0.43-0.58; both $P < 0.0001$). A similar pattern was observed for LC9 (middle: HR = 0.67, 95% CI = 0.59-0.77; high: HR = 0.47, 95% CI = 0.40-0.55; both $P < 0.0001$), with significant linear trends for both indices (*P* for trend < 0.0001) (Table 2).

For cardiovascular mortality, each 1-SD increase in LE8 and LC9 scores was also inversely associated with risk (LE8: HR = 0.67, 95% CI = 0.60-0.75; LC9: HR = 0.62, 95% CI = 0.55-0.70; both $P < 0.0001$). In the LE8 categories, compared with the lowest category (low: < 50), participants in the middle (HR = 0.71, 95% CI = 0.57-0.90, $P = 0.0045$) and high (HR = 0.46, 95% CI = 0.34-0.61, $P < 0.0001$) categories had significantly lower cardiovascular mortality. Similarly, higher LC9 tertiles were associated with lower cardiovascular mortality (middle: HR = 0.65, 95% CI = 0.51-0.83, $P = 0.0005$; high: HR = 0.40, 95% CI = 0.30-0.54, $P < 0.0001$), with significant linear trends for both indices (*P* for trend < 0.0001) (Table 2).

Generalized additive model curves relating LE8 and LC9 scores to all-cause and cardiovascular mortality

The fitted curves showed clear inverse associations between both LE8 and LC9 scores and mortality risks (Fig. 2). As the LE8 and LC9 scores increased, the log-relative risk of all-cause and cardiovascular mortality decreased steadily. The decline appeared approximately linear across the full range of scores.

Kaplan-Meier survival analysis

We used Kaplan-Meier curves to depict all-cause survival by categories of LE8 and tertiles of LC9, with group differences evaluated using the log-rank test (Fig. 3). The survival curves demonstrated a clear gradient of survival probabilities across the categories of LE8 and tertiles of LC9 scores. Specifically, participants in the highest category of LE8 (≥ 80) and the highest tertile of LC9 (high) exhibited the lowest cumulative mortality, while those in

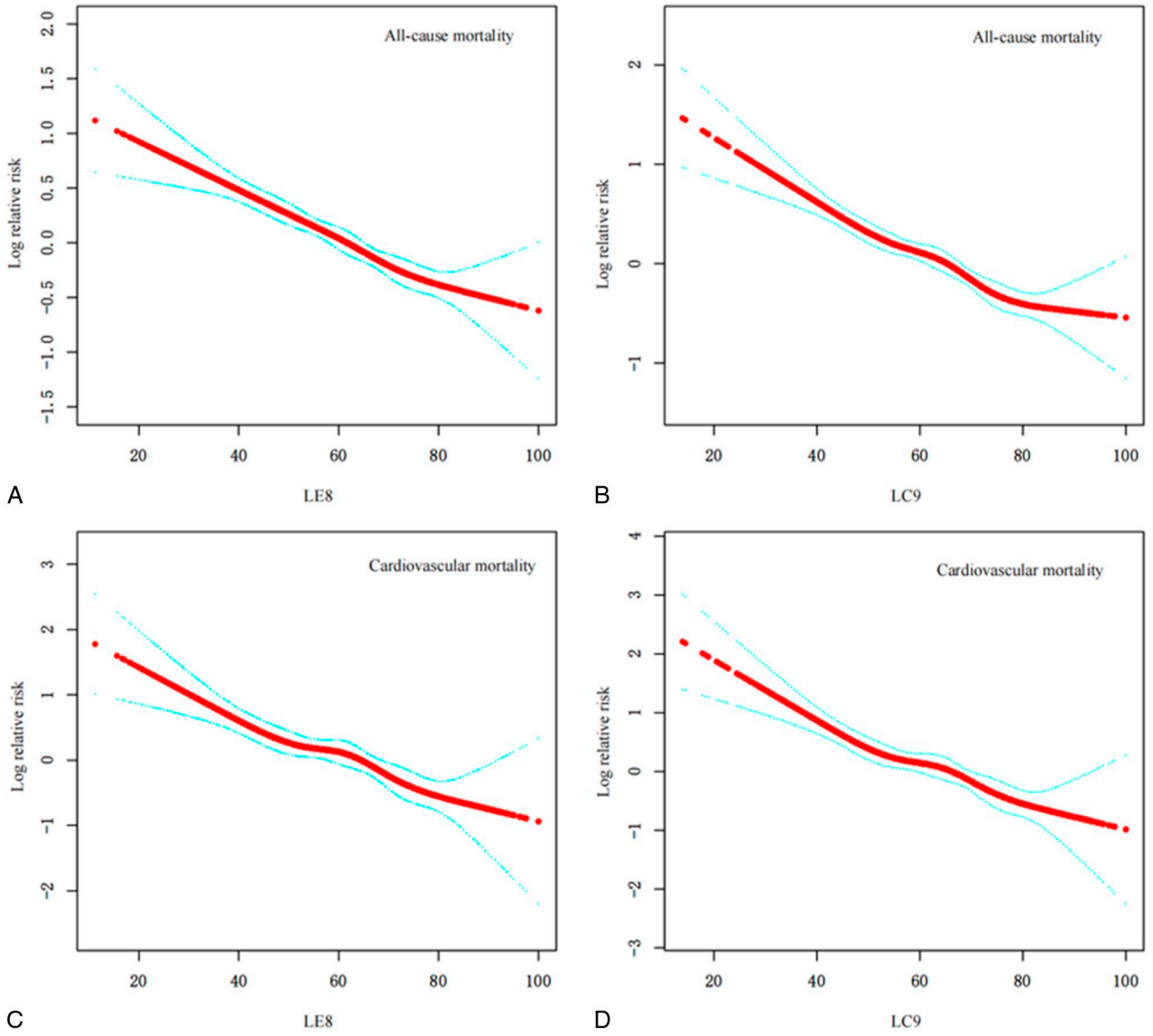

FIG. 2. Smooth curve fitting using generalized additive models was applied to illustrate how LE8 and LC9 scores (as the sum of component averages) relate to mortality outcomes. **(A)** LE8 and all-cause mortality. **(B)** LC9 and all-cause mortality. **(C)** LE8 and cardiovascular mortality. **(D)** LC9 and cardiovascular mortality. Models were adjusted for age, ethnicity, education level, marital status, poverty-income ratio, white blood cell count, and platelet count. The solid red lines represent the estimated log-relative risks, while the dotted lines show the 95% confidence intervals. The *y*-axis represents the log-transformed relative risk, and the *x*-axis shows the continuous covariates (LE8 and LC9 scores). CI, confidence interval; LC9, Life's Crucial 9; LE8, Life's Essential 8.

the lowest category (LE8 < 50) and the lowest tertile (LC9 low) had the highest mortality risk throughout the follow-up period. The survival curves for both LE8 and LC9 were clearly separated across LE8 categories and LC9 tertiles, and the log-rank tests revealed significant differences between groups ($P < 0.0001$ for both LE8 and LC9).

Mediation analyses

In this study, mediation analyses were conducted to explore whether adiposity-related and inflammation-related indices mediated the associations between LE8 and LC9 scores and mortality outcomes, including all-cause and cardiovascular mortality. The adiposity-related indices assessed were ABSI and WWI, while the inflammation-related markers included SIRI and RDW. The results showed that the associations between LE8 and LC9 scores and mortality were partially mediated by these adiposity and inflammation markers. Specifically, ABSI explained 5.4% of the relationship between LE8 and survival (Fig. 4A), and WWI accounted for 6.6% of the

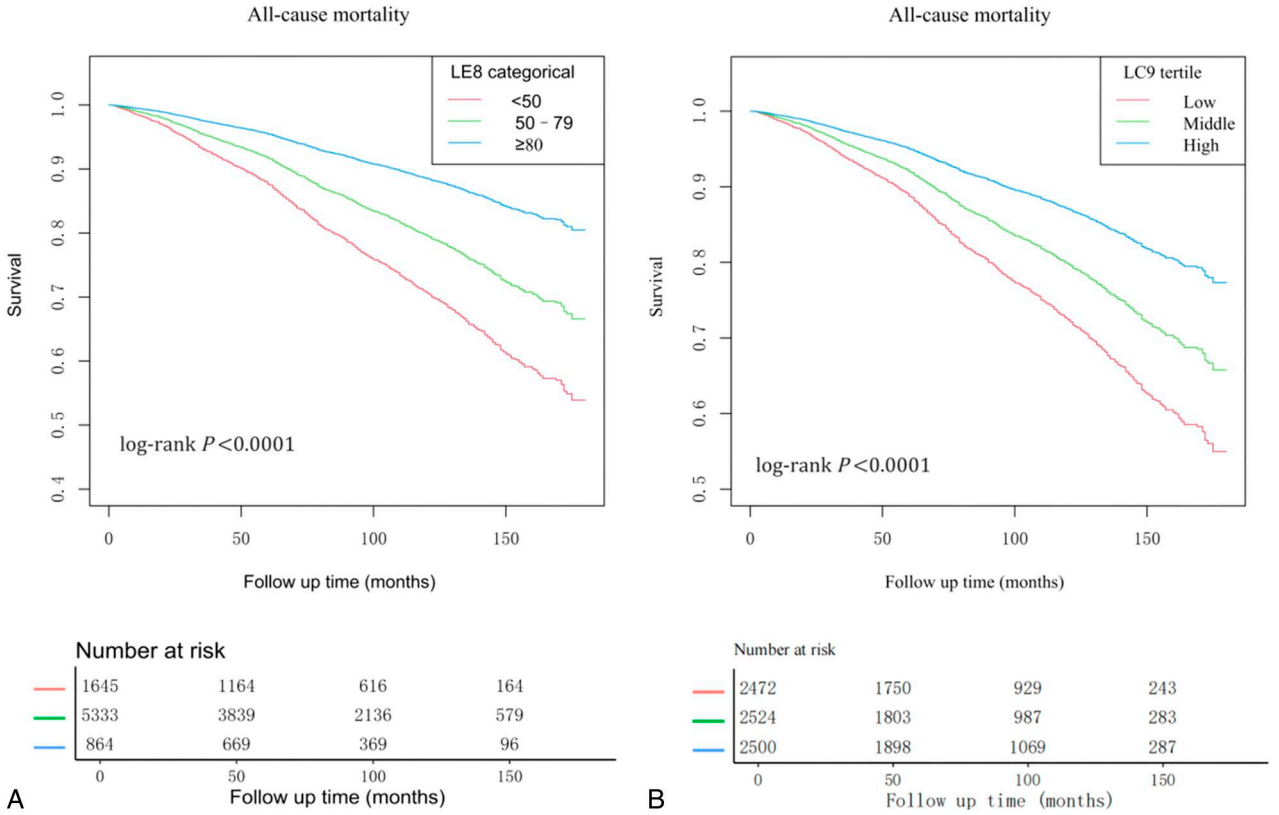

FIG. 3. Kaplan-Meier survival curves for all-cause mortality by tertiles of LE8 and LC9 scores. **(A)** All-cause mortality according to tertiles of Life's Essential 8 (LE8) score. **(B)** All-cause mortality according to tertiles of Life's Crucial 9 (LC9) score. *P* values were derived from log-rank tests. LC9, Life's Crucial 9; LE8, Life's Essential 8.

association (Fig. 4B). For inflammation-related markers, SIRI mediated 8.7% of the association between LE8 and survival (Fig. 4C), while RDW explained 10.5% of the effect (Fig. 4D). Similarly, for LC9, SIRI accounted for 8.7% (Fig. 4G) and RDW explained 10.3% (Fig. 4H) of the mediation. All indirect effects were statistically significant, with *P* values < 0.001 for all variables (Fig. 4). We performed age-stratified causal mediation analyses and assessed the influence of hormone therapy by adjusting for and stratifying by current oral estrogen use, with results shown in Supplemental Tables S3 and S5, Supplemental Digital Content 1, http://links.lww.com/MENO/B493.

Stratified analyses

Subgroup analyses showed that the associations between higher LE8 or LC9 scores and lower all-cause and cardiovascular mortality were broadly similar across the strata examined (Tables 3 and 4). The direction of association remains unchanged within categories defined by age, race or ethnicity, education, and poverty-income ratio, with higher scores generally corresponding to lower mortality. The associations were similar in participants with different marital status, smoking and alcohol consumption patterns, and in those with or without hypertension, diabetes, or hyperlipidemia. Comparable results were also observed across body mass index and blood pressure categories.

Significant interaction effects were observed in several subgroups. For LE8, significant interactions with age groups were found for both all-cause mortality (*P* for interaction = 0.0010) and cardiovascular mortality (*P* for interaction = 0.0027). In addition, a significant interaction with diastolic blood pressure tertiles was found for cardiovascular mortality (*P* for interaction = 0.0036). Similarly, for LC9, significant interactions with age groups were observed for both all-cause (*P* for interaction < 0.0001) and cardiovascular mortality (*P* for interaction = 0.0039), and with diabetes status (*P* for interaction = 0.0481). Significant interactions with diastolic blood pressure tertiles were also found for cardiovascular mortality (*P* for interaction = 0.0092).

Although a few subgroups, including never-married women, heavy drinkers, and participants with impaired glucose tolerance, did not show statistically significant associations, the overall direction of association was consistent. No significant effect modification was detected, indicating that the inverse relationships between

FIG. 4. Mediation analyses of the associations of LE8 and LC9 with all-cause mortality through adiposity- and inflammation-related indicators. **(A–D)** Mediation models for LE8 with **(A)** ABSI, **(B)** WWI, **(C)** SIRI, and **(D)** RDW as mediators. **(E–H)** Mediation models for LC9 with **(E)** ABSI, **(F)** WWI, **(G)** SIRI, and **(H)** RDW as mediators. Each panel presents the estimated total, direct, and indirect effects with 95% confidence intervals and the proportion mediated. ABSI, a body shape index; LC9, Life's Crucial 9; LE8, Life's Essential 8; RDW, red cell distribution width; SIRI, systemic inflammation response index; WWI, weight waist index.

TABLE 3. Stratified analysis of LE8 with all-cause and cardiovascular mortality risk

LE8	N	All-cause mortality HR (95% CI) *P*	*P* for interaction	Cardiovascular mortality HR (95% CI) *P*	*P* for interaction
Age (y) groups			0.0010		0.0027
45-59	2,481	0.61 (0.53-0.71) <0.0001		0.44 (0.32-0.62) <0.0001	
60-69	2,702	0.58 (0.51-0.65) <0.0001		0.50 (0.39-0.64) <0.0001	
70-85	2,659	0.78 (0.73-0.83) <0.0001		0.73 (0.65-0.82) <0.0001	
Ethnicity			0.3924		0.2944
Non-Hispanic White	3,761	0.68 (0.63-0.73) <0.0001		0.63 (0.56-0.71) <0.0001	
Non-Hispanic Black	1,744	0.70 (0.62-0.79) <0.0001		0.65 (0.53-0.80) <0.0001	
Mexican American	986	0.77 (0.62-0.97) 0.0278		1.03 (0.67-1.58) 0.9056	
Other Hispanic	786	0.85 (0.66-1.09) 0.2038		0.76 (0.49-1.17) 0.2112	
Other race	565	0.75 (0.56-1.01) 0.0595		0.55 (0.30-1.02) 0.0560	
Marital status			0.0549		0.3148
Married/living with partner	3,894	0.68 (0.62-0.74) <0.0001		0.62 (0.52-0.73) <0.0001	
Widowed/divorced/separated	3,407	0.77 (0.72-0.83) <0.0001		0.73 (0.65-0.83) <0.0001	
Never married	537	0.96 (0.75-1.22) 0.7226		0.82 (0.50-1.33) 0.4207	
Poverty income ratio			0.6928		0.4624
Poor	1,325	0.81 (0.71-0.92) 0.0009		0.77 (0.62-0.97) 0.0232	
Nearly poor	2,008	0.78 (0.71-0.86) <0.0001		0.78 (0.66-0.93) 0.0047	
Middle income	1,962	0.73 (0.65-0.83) <0.0001		0.60 (0.48-0.75) <0.0001	
High income	1,798	0.70 (0.60-0.82) <0.0001		0.68 (0.51-0.90) 0.0065	
Missing	749	0.79 (0.67-0.94) 0.0082		0.71 (0.51-0.98) 0.0387	
Education level			0.9772		0.3723
Below high school	950	0.74 (0.62-0.88) 0.0005		0.77 (0.57-1.04) 0.0884	
High school	3,035	0.75 (0.69-0.81) <0.0001		0.72 (0.63-0.83) <0.0001	
Above high school	3,849	0.73 (0.67-0.79) <0.0001		0.64 (0.54-0.75) <0.0001	
Alcohol use			0.1951		0.6391
Never	1,667	0.71 (0.63-0.80) <0.0001		0.63 (0.51-0.78) <0.0001	
Former	1,616	0.75 (0.69-0.83) <0.0001		0.70 (0.59-0.83) <0.0001	
Mild	2,358	0.72 (0.65-0.81) <0.0001		0.71 (0.58-0.87) 0.0007	
Moderate	1,054	0.69 (0.57-0.83) 0.0001		0.59 (0.41-0.85) 0.0050	
Heavy	559	0.86 (0.67-1.10) 0.2215		0.65 (0.38-1.14) 0.1329	
Missing	585	0.89 (0.71-1.10) 0.2846		0.84 (0.56-1.27) 0.4151	
Smoking status			0.1919		0.9972
Never	4,712	0.69 (0.64-0.75) <0.0001		0.65 (0.57-0.76) <0.0001	
Former	2,051	0.70 (0.64-0.77) <0.0001		0.62 (0.52-0.73) <0.0001	
Now	1,074	0.83 (0.71-0.96) 0.0131		0.63 (0.46-0.86) 0.0031	
Missing	5	0.65 (0.06-7.13) 0.7270		0.65 (0.06-7.13) 0.7270	
Hypertension			0.9628		0.1392
No	2,607	0.76 (0.68-0.86) <0.0001		0.62 (0.48-0.80) 0.0003	
Yes	5,233	0.77 (0.73-0.83) <0.0001		0.77 (0.69-0.86) <0.0001	
BMI (kg/m^2) groups			0.8548		0.5599
<26.3	2,577	0.59 (0.53-0.64) <0.0001		0.57 (0.48-0.68) <0.0001	
≥26.3 to <31.91	2,578	0.62 (0.55-0.69) <0.0001		0.52 (0.43-0.64) <0.0001	
≥31.91	2,579	0.63 (0.56-0.71) <0.0001		0.60 (0.48-0.74) <0.0001	
Diabetes			0.0701		0.3826
No	4,820	0.72 (0.66-0.77) <0.0001		0.73 (0.63-0.84) <0.0001	
Yes	2,142	0.80 (0.73-0.89) <0.0001		0.72 (0.61-0.85) <0.0001	
IFG	356	0.77 (0.58-1.03) 0.0740		0.55 (0.33-0.92) 0.0240	
IGT	382	0.93 (0.72-1.19) 0.5482		0.95(0.60-1.50) 0.8132	
Diastolic blood pressure tertile groups			0.0905		0.0036
≤63	2,357	0.77 (0.71-0.84) <0.0001		0.78 (0.68-0.90) 0.0006	
64-73	2,559	0.69 (0.62-0.77) <0.0001		0.63 (0.52-0.76) <0.0001	
≥74	2,682	0.65 (0.58-0.73) <0.0001		0.51 (0.41-0.62) <0.0001	
Systolic blood pressure tertile groups			0.2454		0.5578
≤118	2,461	0.71 (0.64, 0.79) <0.0001		0.74 (0.61, 0.91) 0.0039	
119-135	2,527	0.80 (0.71, 0.89) <0.0001		0.63 (0.52, 0.78) <0.0001	
≥136	2,662	0.76 (0.70-0.83) <0.0001		0.72 (0.62-0.84) <0.0001	
Hyperlipidemia			0.9996		0.9528
No	1,261	0.71 (0.62-0.80) <0.0001		0.65 (0.52-0.82) 0.0003	
Yes	6,580	0.71 (0.67-0.75) <0.0001		0.67 (0.60-0.74) <0.0001	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; LE8, Life's Essential 8.

Hazard ratios and 95% confidence intervals were estimated using unadjusted Cox proportional hazards models with LE8 as the exposure. Subgroup analyses were conducted across demographic and clinical strata. *P* values for interaction were obtained by adding multiplicative interaction terms. No covariates were included in these models.

TABLE 4. Stratified analysis of LC9 with all-cause and cardiovascular mortality risk

		All-Cause Mortality		Cardiovascular Mortality	
LC9	**N**	**HR (95% CI) *P***	***P* for Interaction**	**HR (95% CI) *P***	***P* for Interaction**
Age (y) groups			< 0.0001		0.0039
45-59	2,413	0.59 (0.51-0.69) < 0.0001		0.44 (0.32-0.61) < 0.0001	
60-69	2,620	0.54 (0.47-0.61) < 0.0001		0.47 (0.37-0.61) < 0.0001	
70-85	2,463	0.77 (0.72-0.83) < 0.0001		0.71 (0.62-0.80) < 0.0001	
Ethnicity			0.6403		0.3259
Non-Hispanic White	3,617	0.66 (0.58-0.75) < 0.0001		0.62 (0.54-0.70) < 0.0001	
Non-Hispanic Black	1,656	0.72 (0.57-0.90) 0.0051		0.63 (0.51-0.78) < 0.0001	
Mexican American	944	0.72 (0.57-0.90) 0.0051		1.00 (0.64-1.56) 0.9839	
Other Hispanic	753	0.77 (0.60-1.00) 0.0482		0.66 (0.43-1.03) 0.0688	
Other race	526	0.70 (0.50-0.97) 0.0320		0.54 (0.27-1.08) 0.0806	
Marital status			0.0817		0.3122
Married/living with partner	3,761	0.67 (0.61-0.74) < 0.0001		0.61 (0.51-0.73) < 0.0001	
Widowed/divorced/separated	3,218	0.75 (0.70-0.81) < 0.0001		0.71 (0.62-0.81) < 0.0001	
Never married	513	0.94 (0.73-1.20) 0.6010		0.87 (0.54-1.39) 0.5584	
Poverty income ratio			0.8622		0.5060
Poor	1,254	0.79 (0.69-0.89) 0.0002		0.77 (0.61-0.97) 0.0251	
Nearly poor	1,923	0.77 (0.70-0.86) < 0.0001		0.74 (0.62-0.89) 0.0013	
Middle income	1,875	0.71 (0.63-0.81) < 0.0001		0.58 (0.46-0.74) < 0.0001	
High income	1,745	0.72 (0.61-0.85) 0.0001		0.66 (0.49-0.90) 0.0074	
Missing	699	0.79 (0.66-0.95) 0.0110		0.75 (0.52-1.08) 0.1202	
Education level			0.9992		0.5900
Below high school	862	0.71 (0.59-0.85) 0.0003		0.73 (0.52-1.01) 0.0611	
High school	2,903	0.73 (0.67-0.79) < 0.0001		0.70 (0.60-0.81) < 0.0001	
Above high school	3,725	0.72 (0.66-0.79) < 0.0001		0.64 (0.54-0.76) < 0.0001	
Alcohol use			0.3497		0.7751
Never	1,632	0.67 (0.60-0.76) < 0.0001		0.59 (0.48-0.74) < 0.0001	
Former	1,587	0.75 (0.68-0.82) < 0.0001		0.69 (0.58-0.82) < 0.0001	
Mild	2,346	0.73 (0.65-0.82) < 0.0001		0.72 (0.58-0.88) 0.0013	
Moderate	1,054	0.71 (0.58-0.85) 0.0003		0.64 (0.45-0.92) 0.0148	
Heavy	559	0.84 (0.66-1.07) 0.1597		0.64 (0.37-1.09) 0.1013	
Missing	318	1.18 (0.62-2.25) 0.6085		1.88 (0.12-29.24) 0.6537	
Smoking status			0.1409		0.9316
Never	4,485	0.68 (0.63-0.74) < 0.0001		0.64 (0.55-0.74) < 0.0001	
Former	1,964	0.68 (0.62-0.76) < 0.0001		0.61 (0.51-0.74) < 0.0001	
Now	1,042	0.82 (0.70-0.95) 0.0079		0.59 (0.43-0.80) 0.0007	
Missing	5	0.40 (0.02-9.30) 0.5657		0.40 (0.02-9.30) 0.5657	
Hypertension			0.4395		0.4417
No	2,507	0.78 (0.69-0.88) 0.0001		0.65 (0.50-0.86) 0.0027	
Yes	4,987	0.75 (0.70-0.80) < 0.0001		0.74 (0.66-0.83) < 0.0001	
BMI (kg/m^2) groups			0.9849		0.5223
< 26.3	2,455	0.60 (0.54-0.66) < 0.0001		0.59 (0.49-0.71) < 0.0001	
≥ 26.3 to < 31.91	2,462	0.62 (0.55-0.69) < 0.0001		0.53 (0.43-0.65) < 0.0001	
≥ 31.91	2,500	0.62 (0.55-0.70) < 0.0001		0.59 (0.48-0.72) < 0.0001	
Diabetes			0.0481		0.1072
No	4,616	0.70 (0.65-0.76) < 0.0001		0.75 (0.64-0.88) 0.0003	
Yes	2,142	0.80 (0.73-0.89) < 0.0001		0.70 (0.59-0.83) < 0.0001	
IFG	356	0.71 (0.52-0.96) 0.0274		0.41 (0.24-0.73) 0.0022	
IGT	382	0.94 (0.73-1.22) 0.6665		0.91 (0.57-1.47) 0.7037	
Diastolic blood pressure tertile groups			0.0797		0.0092
≤ 63	2,241	0.77 (0.71-0.83) < 0.0001		0.77 (0.67-0.90) 0.0006	
64-73	2,457	0.69 (0.62-0.77) < 0.0001		0.62 (0.50-0.75) < 0.0001	
≥ 74	2,602	0.63 (0.56-0.71) < 0.0001		0.51 (0.41-0.64) < 0.0001	
Systolic blood pressure tertile groups			0.3403		0.5711
≤ 118	2,378	0.70 (0.63-0.79) < 0.0001		0.75 (0.60-0.92) 0.0067	
119-135	2,447	0.77 (0.69-0.87) < 0.0001		0.63 (0.51-0.78) < 0.0001	
≥ 136	2,527	0.75 (0.69-0.82) < 0.0001		0.71 (0.61-0.83) < 0.0001	
Hyperlipidemia			0.9569		0.9316
No	1,189	0.70 (0.62-0.80) < 0.0001		0.66 (0.52-0.84) 0.0007	
Yes	6,307	0.70 (0.66-0.75) < 0.0001		0.65 (0.59-0.73) < 0.0001	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; LC9, Life's Crucial 9.

Hazard ratios and 95% confidence intervals were estimated using unadjusted Cox proportional hazards models with LC9 as the exposure. Subgroup analyses were conducted across demographic and clinical strata. No covariates were included in these models.

cardiovascular health metrics and mortality were robust across all examined strata. We conducted stratified analyses by menopausal characteristics; detailed results are shown in Supplemental Table S2, Supplemental Digital Content 1, http://links.lww.com/MENO/B493.

DISCUSSION

Among postmenopausal women in this nationally representative cohort, higher LE8 and LC9 scores were associated with lower all-cause and cardiovascular mortality. These associations were consistent across demographic and clinical subgroups. Furthermore, adiposity and inflammation–related indicators partially mediated these relationships, suggesting that part of the statistical association between LC9/LE8 and mortality may be explained by these factors.

These results align with earlier work indicating that more favorable overall cardiovascular health profiles are related to lower mortality. Studies evaluating LE8 in both general cohorts and specific patient groups have similarly reported stepwise decreases in all-cause and cardiovascular mortality with increasing cardiovascular health levels.[31,32] Similarly, studies evaluating LC9 have extended these observations by incorporating additional cardiometabolic or psychosocial components.[6,7] The current results extend this evidence to postmenopausal women, a population particularly vulnerable to adverse cardiometabolic changes due to hormonal and metabolic transitions.

In this analysis, adiposity and inflammation-related indicators, namely the ABSI, WWI, SIRI, and RDW, partially mediated the statistical associations between cardiovascular health scores and mortality. These findings suggest that body composition and systemic inflammatory status may play a role in the observed relationships between LC9/LE8 and mortality at the statistical level. Together, these parameters represent intermediate physiological states that are closely linked to cardiometabolic health. Adiposity and inflammation are both biologically plausible and statistically intertwined with cardiovascular health.[33] Anthropometric indices, such as the ABSI and WWI, reflect central adiposity and body composition,[34,35] while blood-based markers such as RDW and the SIRI represent hematologic and inflammatory status.[36,37] The partial mediation by these indicators suggests that a portion of the statistical associations between higher LE8/LC9 scores and lower mortality may operate through pathways involving adiposity and systemic inflammation.

Beyond the statistical associations, these findings may have implications for cardiovascular health assessment in postmenopausal women. The LC9 score, which integrates cardiovascular and psychological health components, may provide a broader framework for evaluating overall health status in this population.[6] The associations observed emphasize the importance of maintaining favorable levels of traditional risk factors,[38] such as blood pressure, glucose, and lipid profiles, together with healthy lifestyle behaviors including physical activity, adequate sleep, and a balanced diet.[39–41] The inclusion of psychological well-being in LC9 also highlights the potential relevance of mental health assessment in comprehensive cardiovascular evaluation. However, these results represent statistical associations rather than causal effects, and interventional studies are needed to determine whether improving cardiovascular and psychological health metrics can lead to better long-term outcomes.

The strengths of this study include the use of a large, nationally representative dataset with standardized data collection, validated mortality linkage, and comprehensive assessment of cardiovascular health using both LE8 and LC9 constructs. Moreover, the application of mediation analysis provides insight into potential intermediate pathways in an at-risk population.

Several limitations should be noted. LE8 and LC9 were measured only at baseline, so the analyses reflect a cross-sectional exposure assessment and do not support a causal interpretation, even though the mortality follow-up was prospective. Psychological well-being relied on self-report, which may introduce measurement error. While we adjusted for multiple demographic and clinical factors, residual confounding remains possible, and medication use, such as lipid-lowering or antihypertensive therapy, could have attenuated the observed associations. Because participants were postmenopausal women in the United States, extrapolation to other settings or age groups should be done cautiously. In addition, menopausal status was based on self-reported questionnaire data and may have been misclassified; such misclassification is likely nondifferential and would tend to bias associations toward the null. Information on hormone therapy in NHANES was limited to current self-reported oral estrogen use, without details on dose, duration, route, or formulation. As a result, we could only account for oral estrogen use and could not evaluate whether associations varied across different hormone therapy regimens.

CONCLUSIONS

In summary, higher LC9 and LE8 scores were associated with lower risks of all-cause and cardiovascular mortality among postmenopausal women. Adiposity-related and inflammation-related indicators partially mediated these associations. These findings underscore the importance of comprehensive cardiovascular health assessment and suggest that maintaining favorable cardiometabolic profiles may be beneficial for longevity in this population. Future prospective and mechanistic studies are needed to further clarify the pathways linking cardiovascular health metrics to mortality outcomes.

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