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ORIGINAL ARTICLE

Life's Simple 7, depressive symptoms, cognitive performance, and their associations with all-cause mortality among middle-aged urban adults

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Abstract Cardiovascular health, depressive symptoms, and cognitive performance are closely interconnected and jointly influence all-cause mortality. We investigated the independent associations of Life's Simple 7 (LS7), depressive symptom trajectories, and cognitive performance with all-cause mortality and conducted exploratory four-way decomposition analyses to evaluate complementary mechanistic hypotheses linking these factors. We analyzed data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study ($N=1466$; mean age = 56 years; 41.7% men; 60.6% African American). Cox proportional hazards models, group-based trajectory analyses, and four-way decomposition models were used. Higher LS7 scores were associated with lower mortality, particularly among White adults, whereas persistently elevated depressive symptom trajectories were associated with higher mortality, especially among women. Poorer cognitive performance was independently associated with increased mortality (HR = 1.20, 95% CI 1.02–1.41; $P=0.035$). In fully adjusted four-way decomposition

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Michael F. Georgescu and May A. Beydoun had full access to the data used in this manuscript and completed all the statistical analyses.

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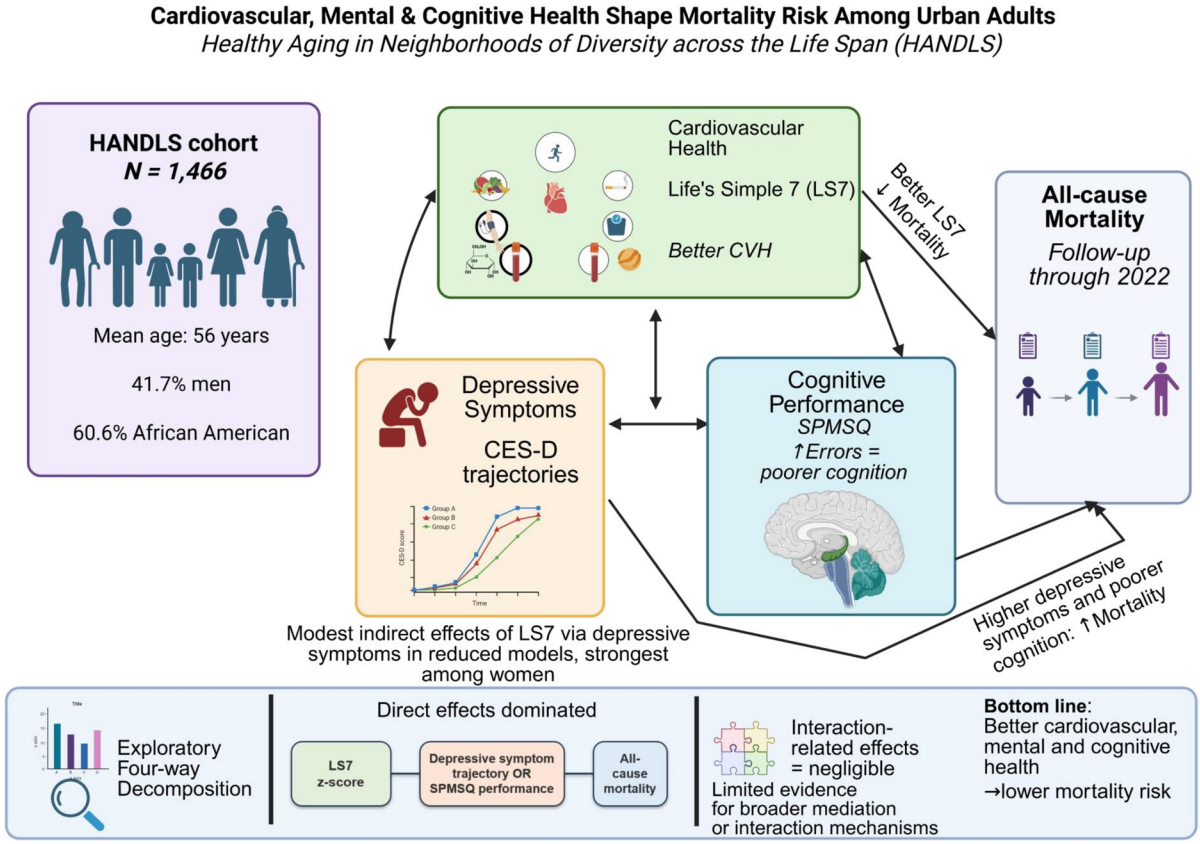
analyses, little evidence supported indirect or interaction-related effects. In reduced models, depressive symptom trajectory showed a significant indirect effect in the association between LS7 and mortality in the overall sample (PIE = −0.04 ± 0.01, $q = 0.030$) and among women (PIE = −0.09 ± 0.03, $q = 0.001$) after false discovery rate correction, whereas all other indirect effects were attenuated after multiple-testing correction. Better cardiovascular health, fewer depressive symptoms, and preserved cognitive performance were independently associated with lower mortality risk. Exploratory decomposition analyses suggest that depressive symptoms may contribute modestly to the association between cardiovascular health and mortality, although evidence for broader mediation or interaction mechanisms was limited.

Graphical Abstract



Keywords Life's Simple 7 · Depressive symptoms · Cognitive performance · Adults

Abbreviations

CVD	Cardiovascular diseases
AHA	American Heart Association
CVH	Cardiovascular health
LS7	Life's Simple 7
BMI	Body mass index
MVR	Mobile research vehicles
HANDLS	Healthy Aging in Neighborhoods of Diversity across the Life Span study
SPMSQ	Short Portable Mental Status Questionnaire
SPMSQtot	SPMSQ total score
CES-D	Center of Epidemiologic Studies Depression Scale

BQ	Baecke Questionnaire
GBTM	Group-based trajectory models
TE	Total effect
PIE	Pure indirect effect
CDE	Controlled direct effect
SE	Standard error
Ln	Log
HR	Hazard ratio
CI	Confidence interval
INTREF	Reference interaction
INTMED	Mediated interaction
AMPM	Automated multiple pass method
USDA	United States Department of Agriculture
FNDDS	Food and Nutrient Database for Dietary Studies
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BPAQ	Buss-Perry Aggression Questionnaire

Introduction

Cardiovascular diseases (CVDs) are leading causes of death globally and in the USA [1, 2]. Despite declining CVD morbidity in previous decades [3], cardiovascular mortality reversed its long-term downward trend beginning in 2020 and has remained elevated in subsequent years [2]. To address and prevent CVD-related deaths and disability, the American Heart Association (AHA) introduced seven key health components titled "Life's Simple 7" (LS7) for improving cardiovascular health (CVH) [4].

These seven interconnected cardiovascular health components include blood pressure, cholesterol, fasting blood glucose, body mass index (BMI), physical activity, diet, and smoking [4]. The LS7 metric is a well-established measure of cardiovascular health (CVH) that facilitates the identification and quantification of disparities in cardiovascular disease risk [5]. Although the American Heart Association has since replaced LS7 with Life's Essential 8, the present study retained LS7 because it was designed and analyzed before the newer framework was introduced and widely adopted.

Given that CVDs are a leading cause of mortality, it is critically important to identify factors related to CVH and understand how they work together influence mortality. Prior research has implicated two key correlates of CVH, depressive symptoms and cognitive performance. Depressive symptoms are associated with CVD incidence and premature mortality [6–11]. Additionally, CVD incidence varies across depression subgroups, such that major depressive disorder and nonatypical major depressive disorder have varying relationships with CVD (major depressive disorder having greater risk of CVD) [12]; reinforcing that depressive symptoms are associated with increased CVD risk [12] and CVD risk factors are associated with depressive symptoms [13–15]. Depressive symptoms and CVD have differential effects by sex [16, 17] and race [18, 19], where women have lower CVD risk but elevated depressive symptoms [16, 17] and White adults having lower CVD and depressive symptoms [18, 19].

Prior research has also shown that adults' cognitive performance is related to both depressive symptoms and CVH [4, 14, 20–23]. As populations age worldwide, age-associated cognitive decline has become a major public health concern [21]. Several studies have identified bidirectional effects between depressive symptoms and cognitive performance. Some studies have shown depressive symptoms precede cognitive decline [24–26], while others suggest CVH is associated with cognitive decline [23, 27]. CVH is also associated with later depression [28–30], but depression is also associated with CVH [28, 31]. Capturing the bidirectional relationships of CVH, depressive symptoms, and cognitive performance is necessary for understanding how each interacts and relates to one another. Prior studies have identified the mediating role of depression in associations between CVH and cognition [22, 32]. However, despite consistent evidence of associations between CVH, depressive symptoms, and cognitive performance, it remains unclear how these relate to each other in influencing CVD-related mortality. To our knowledge, no studies have directly investigated mediating and moderating effects of CVH between depressive symptoms and cognitive performance to all-cause mortality, while also measuring depressive symptoms and cognitive performance as alternative exposures to all-cause mortality in middle-aged urban adults.

Therefore, given the interrelationships among cardiovascular health (CVH), depressive symptoms, and cognitive performance, we examined their independent associations with all-cause mortality in a middle-aged urban cohort while adjusting for demographic, socioeconomic, and health-related covariates, overall

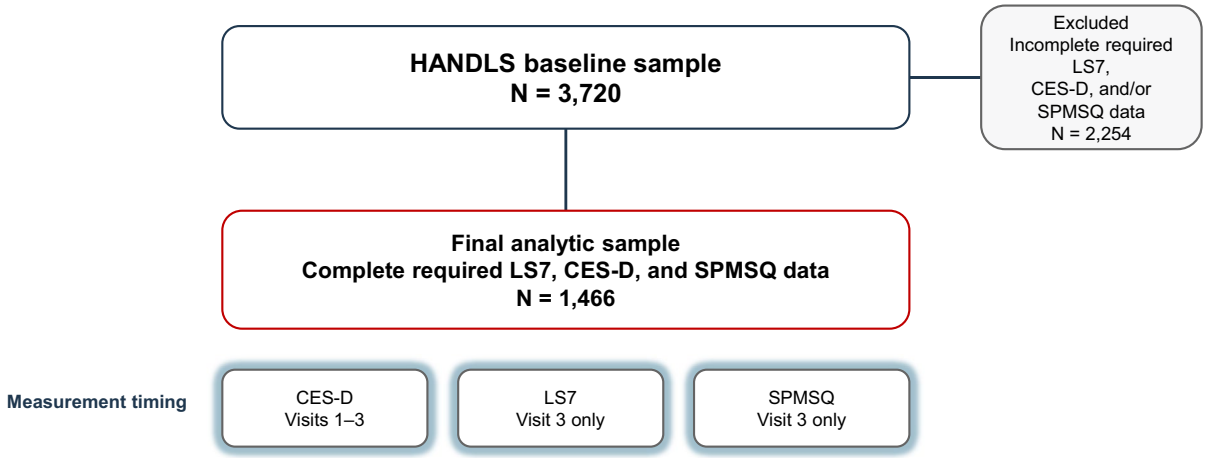


Fig. 1 Participant flow diagram for the HANDLS analytic sample. The HANDLS baseline sample included 3720 participants. Participants with incomplete data required for the present analyses, including depressive symptoms assessed using the CES-D, cardiovascular health assessed using Life's Simple 7 (LS7), and cognitive screening performance assessed using the SPMSQ, were excluded ($n = 2254$), resulting in a final analytic sample of 1466 participants. CES-D was assessed across visits 1–3, LS7 components were assessed at visit 3 only, and SPMSQ was available at visit 3 only. HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; CES-D, Center for Epidemiologic Studies Depression Scale; LS7, Life's Simple 7; SPMSQ, Short Portable Mental Status Questionnaire

and by sex and race. We also conducted exploratory four-way decomposition analyses to evaluate complementary mechanistic hypotheses linking LS7, depressive symptoms, cognitive performance, and mortality. Because these factors exhibit bidirectional relationships, the alternative models were intended to examine distinct biologically plausible mechanisms rather than interchangeable causal pathways. Interaction-related components were assessed through the reference interaction (INTREF) and mediated interaction (INTMED) components of the four-way decomposition models.

Material and methods

Database

In 2004, the National Institute on Aging initiated the Healthy Aging in Neighborhoods of Diversity across the Life Span study (HANDLS), a prospective cohort study designed to investigate health differences in a socioeconomically diverse sample of working-age white and African American adults [33]. Written informed consent was given by every subject. Approval of HANDLS was given by the National Institutes of Health Institutional Review Board.

The current study analyzed data from visit 1 (v1, 2004–2009), visit 2 (v2, 2009–2013), and visit 3 (v3, 2013–2017). Data on depressive symptoms were collected on all 3 visits, with several measures assessing LS7 at v3. Data on cognitive performance were collected only at v3. HANDLS metadata can be viewed at https://handls.nih.gov/06Coll-w00dataDocR. Data are shared upon approval of a project and following an institutional data use agreement.

Study sample

The study reached its final sample sequentially. Of 3720 participants available at the baseline home visit, we excluded 2254 participants with incomplete data required for the present analyses, resulting in a final analytic sample of 1466 participants (Fig. 1).

Study measures

Cognitive assessment

Cognitive performance was operationalized with the Short Portable Mental Status Questionnaire (SPMSQ) [34]. SPMSQ was collected at v3 of the HANDLS project and included 10 items identifying cognitive

performance. Clinical staff utilized the SPMSQ [34] as part of the physical exam of the HANDLS project. Each SPMSQ item is explained in detail in Supplemental Methods 1. Many studies have found SPMSQ as a useful tool for cognitive impairment [35–39]. However, SPMSQ is only a brief screening instrument for cognitive performance [36]. The domains of the SPMSQ are global mental state, memory, orientation, and recall. SPMSQ total score (SPMSQtot) included the total errors across all 10 items, where 0–2 indicates normal cognitive performance, 3–4 mild cognitive impairment, 5–7 moderate cognitive impairment, and 8 or more indicates severe cognitive impairment [34].

Depressive symptoms

The study measured depressive symptoms, which are divided into affective, interpersonal issues, somatic complaints, and positive affect, using the 20-item Center of Epidemiologic Studies Depression Scale (CES-D). Each CES-D item is explained in detail in Supplemental Methods 1. A total score of ≥ 16 signifies increased depressive symptoms. The domains of CES-D included somatic complaints, depressed affect, interpersonal problems, and well-being. CES-D scores were measured at visits 1, 2, and 3. Each domain of CES-D and the CES-D total scores were estimated using the STATA plugin (mi estimate), well-established with SAS [40].

Life's Simple 7

In accordance with AHA standards, the LS7 measurements are specified in Supplemental Methods 2 and Table S1A. Food and nutrient intake was assessed using two 24-h recalls from HANDLS v3, as previously documented [41]. In v3, participants reported the duration of their engagement in moderate-to-vigorous physical activity utilizing the validated Baecke questionnaire (BQ) [42]. Health technicians evaluated body weight and height to calculate BMI metrics. At Quest, glucose and cholesterol levels were assessed utilizing standard laboratory automation methods. The arithmetic means of systolic and diastolic blood pressure readings from left and right sitting positions were collected with mercury sphygmomanometer. Participants were requested to self-report their smoking behaviors, excluding exposure to secondhand smoke. The final LS7 score was calculated by assigning values of two, one, and zero points to excellent, intermediate, and poor scores, respectively. The overall score ranged from 0 to 14 points, with higher values indicating superior cardiovascular health. The component estimates for the LS7 were detailed in the supplement (Table S1A).

Mortality

In the HANDLS study, mortality status was collected prospectively through data linkages to the National Death Index (NDI), maintained by the National Center for Health Statistics. This process enabled the accurate determination of participants' vital status, with complete data available for all participants through December 31, 2022 (https://www.cdc.gov/nchs/data/ndi/ndi_users_guide.pdf). The NDI linkage provides verified information on date and underlying cause of death, coded using the International Classification of Diseases (ICD) system, and is conducted under strict confidentiality protocols. Mortality follow-up began at HANDLS visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the visit 3 examination until age at death or censoring. During follow-up period, 1466 participants were used in our final sample. Among those who died from any cause with a known date of death, 207 were counted. Time-to-death or censoring was assessed by age of follow-up (measured in years) between age at v1 and date of death.

Covariates

Potentially confounding covariates were evaluated or established at the v1 baseline. Covariates included v1 age (continuous, in years), self-identified race (White, African American), sex at birth, v1 educational attainment (less than high school, high school, more than high school), v1 employment status (employed vs. unemployed), v1 marital status (married vs. unmarried), v1 poverty status ($<125\%$ vs. $\geq 125\%$ of the federal poverty threshold), v1 current drug use (opiates, cocaine, or marijuana, yes vs. no), self-rated health (poor/fair, good, very good/excellent), and v1 comorbidity index. Comorbidity burden was summarized using a composite comorbidity index, calculated as the sum of five physician-reported chronic disease categories: hypertension,

diabetes, dyslipidemia, cardiovascular disease, and inflammatory disorders. Each category contributed one point if present and zero otherwise, yielding a total score ranging from 0 to 5, with higher scores indicating a greater burden of chronic disease. Cardiovascular disease included atrial fibrillation, coronary artery disease, angina, congestive heart failure, and myocardial infarction. Inflammatory disorders included multiple sclerosis, lupus, gout, rheumatoid arthritis, psoriasis, and thyroid disorders. The 2004 US Census Bureau poverty level was utilized to define poverty according to total family size and household income [43]. There was < 5% missingness in basic sociodemographic covariates at visit 1 before multiple imputation. A directed acyclic graph (DAG) is presented in Figure S1.

Statistical methods

The analyses were completed using Stata version 18.0 (StataCorp, College Station, TX, USA).

Missing covariate data were multiply imputed using chained equations with five imputations and 10 iterations [44, 45]. Among the Stata commands used were mi register, *mi stset*, *mi impute*, *mi passive*, followed by *mi estimate*. Sex and race differences were evaluated using linear, logistic, and multinomial logistic regression models, as appropriate for continuous, binary, and categorical outcomes. Sample characteristics were summarized using means and percentages overall and by sex and race. Those models were subsequently modified in multivariable-adjusted models employing other sociodemographic components like age, race, sex, and poverty status in order to determine sex and racial disparities. To derive CES-D trajectories for total and domain scores between v1, v2, and v3, a zero-inflated Poisson model [46], group-based trajectory models (GBTM) were utilized (Supplementary methods 3). LS7 total and individual scores respectively across race and sex and their interactions were associated with the CES-D total score trajectory at follow-up v3 using Cox PH. The proportional hazards assumption was evaluated for all Cox proportional hazards models using Schoenfeld residuals (global and covariate-specific tests). No meaningful violations of the proportional hazards assumption were detected (all $P > 0.05$).

Sequentially, Model 1 included age, sex, and race; Model 2 included Model 1+ poverty status, educational attainment, marital status, and job status; and Model 3 included Model 2+ comorbidity, self-rated health, and current drug use. All models were corrected for potential sample selectivity by age, sex, race, and poverty level using the inverse mills ratio utilizing two-stage Heckman selection technique done in earlier studies [15, 47]. These models tested the associations of CES-D total score trajectory, SPMSQ total score, and LS7 independent relationships with mortality risk while adjusting for each of these exposures simultaneously along with the set of covariates in Models 1, 2, and 3. In addition, interactions between LS7 and each of CES-D total score trajectory and SPMSQ total score were tested for each of these 3 models.

We used four-way decomposition models to partition the total effect (TE) into the controlled direct effect (CDE), reference interaction (INTREF), mediated interaction (INTMED), and pure indirect effect (PIE) (Supplemental Methods 4). Analyses were performed using the Stata *med4way* command [48]. Because cardiovascular health, depressive symptoms, and cognitive performance are biologically interconnected and may influence one another bidirectionally, no single causal ordering was assumed. Instead, we specified complementary four-way decomposition models to evaluate distinct mechanistic hypotheses rather than interchangeable causal pathways. In the first framework, depressive symptom trajectory (CES-D; low vs. high) or cognitive performance (SPMSQ *z*-score) was specified as the exposure, LS7 (*z*-score) as the intermediate variable, and time to all-cause mortality as the outcome. The outcome model consisted of a Cox proportional hazards regression, whereas the mediator model was a linear regression with LS7 as the dependent variable. Both models were adjusted for the same set of exogenous covariates. Fully adjusted models included all covariates from Model 3, whereas reduced models included age, sex, race, and poverty status. In a complementary framework, LS7 was specified as the primary exposure, whereas depressive symptom trajectory or SPMSQ score was specified as the alternative intermediate variable to evaluate whether these factors contributed to the association between cardiovascular health and mortality. The mediator model for CES-D trajectory was fitted using logistic regression because of its binary classification. Type I error was set at 0.05 for all analyses, with Benjamini–Hochberg false discovery rates (FDR) applied to both reduced and fully adjusted four-way decomposition models for multiple testing correction. Because depressive symptoms, LS7, and cognitive

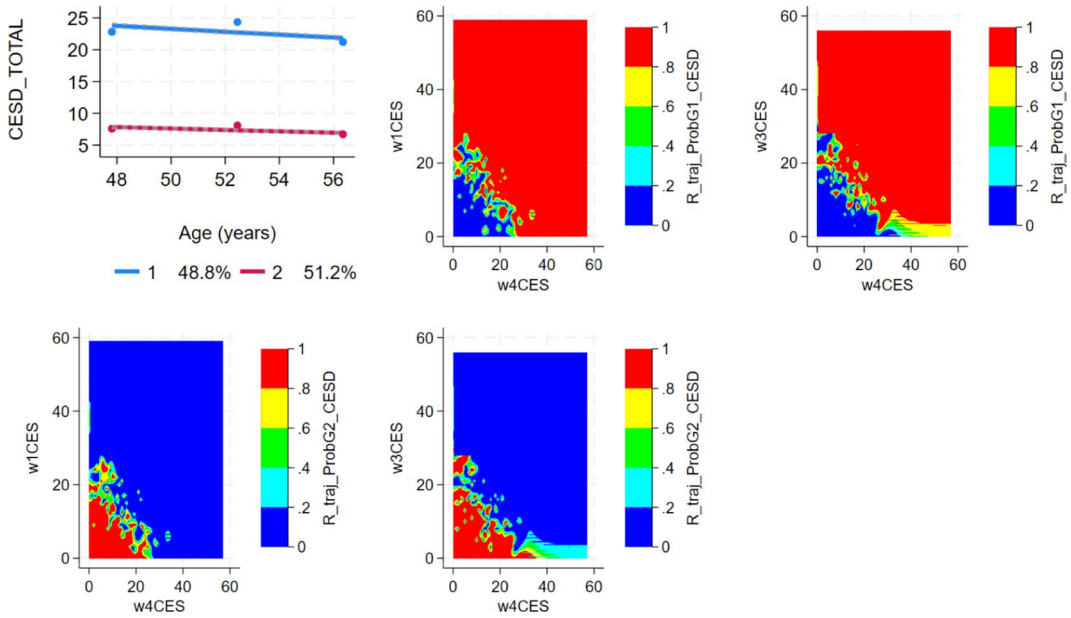


Fig. 2 Group-based trajectories of depressive symptoms across HANDLS visits and posterior probabilities of trajectory-group membership. Depressive symptom trajectories were estimated from total Center for Epidemiologic Studies Depression Scale (CES-D) scores measured across HANDLS visits 1, 2, and 3 using group-based trajectory modeling (GBTM). A two-group zero-inflated Poisson model with linear age terms was fitted among the 1466 participants in the analytic sample. The upper-left panel displays the estimated CES-D trajectories as a function of age, identifying a lower-symptom declining trajectory (Group 1; 51.2%) and a higher-symptom declining trajectory (Group 2; 48.8%). Both groups showed modest decreases in estimated CES-D scores with increasing age while remaining clearly separated throughout the observed age range. The remaining panels display contour plots of posterior probabilities of membership in Group 1 and Group 2 according to observed CES-D scores at pairs of study visits; colors represent posterior probabilities ranging from 0 to 1. The fitted model had high classification certainty (entropy = 0.936). CES-D, Center for Epidemiologic Studies Depression Scale; GBTM, group-based trajectory modeling; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span

screening performance were measured during overlapping periods, the temporal ordering required for causal mediation cannot be definitively established. Accordingly, the four-way decomposition analyses were considered exploratory and were used to characterize statistical decomposition under alternative prespecified directional frameworks rather than to establish causal mediation. The complementary models should therefore be interpreted as hypothesis-generating analyses of potentially interrelated pathways.

Results

Group-based trajectory model for CES-D findings

Group-based trajectory modeling identified two distinct trajectories of total CES-D scores across the three HANDLS visits (Fig. 2). The two-class zero-inflated Poisson model classified 51.2% of participants into a lower-symptom declining trajectory and 48.8% into a higher-symptom declining trajectory. Both trajectories declined modestly with age, but substantial separation between the groups was maintained across the observation period. Among participants assigned to the lower-symptom group, mean CES-D scores were 7.56, 7.98, and 6.66 at visits 1, 2, and 3, respectively, compared with 22.81, 24.40, and 21.24 among those assigned to the higher-symptom group. Classification certainty was high (entropy = 0.936), and posterior probability of membership in the higher-symptom trajectory was strongly positively correlated with observed CES-D scores at visits 1, 2, and 3 ($r = 0.689$, 0.708, and 0.685, respectively). Conversely, probabilities of membership in the lower-symptom trajectory were inversely correlated with CES-D scores ($r = -0.689, -0.708$, and -0.685). The

posterior-probability contour plots further demonstrated clear differentiation of participants with persistently lower versus higher CES-D scores (Fig. 2).

Descriptives of analytic sample by sex and race

Of the 1466 individuals sampled, 855 were women and 611 men; 577 identified as White, and 889 identified as African American. The average age was 56.35 years. In Table 1, women compared to men in multivariable models were more likely to have a lower LS7 total score (7.38 vs. 7.78, $P<0.001$), higher depressed affect (4.17 vs. 3.54, $P=0.023$) and higher SPMSQ total score (0.78 vs. 0.62, $P=0.001$). The higher-symptom declining total CES-D trajectory comprised 48.9% of the analytic sample and was more common among women than men (51.1% vs. 45.8%; bivariate $P=0.046$) and among White than African American adults (51.7% vs. 47.1%; bivariate $P=0.011$), although these differences were attenuated in multivariable analyses. Domain-specific trajectory analyses showed that women were more likely than men to belong to the higher depressive-affect trajectory (49% vs. 40%; multivariable $P=0.005$), whereas African American adults were less likely than White adults to belong to this trajectory (43% vs. 49%; multivariable $P=0.004$). No significant multivariable sex or race differences were observed for interpersonal-problem or somatic-complaint trajectories (Table S4).

Sample selectivity analyses (Table S1B in Appendices) indicated modest differences between participants included in the final analytic sample ($n=1466$) and those excluded ($n=2254$). Included participants were slightly younger than excluded participants (47.8 vs. 48.6 years, $P=0.008$, at visit 1 2004–2009) and were more likely to be women (58.3% vs. 52.4%, $P<0.001$). In contrast, the distribution of race ($P=0.120$) and poverty status ($P=0.135$) did not differ significantly by analytic sample inclusion, suggesting limited evidence of substantial sociodemographic selectivity.

Cox PH models of Life's Simple 7, depressive symptom trajectories, and cognitive performance with all-cause mortality

Tables 2 and 3 examine the associations between Life's Simple 7 (LS7) total score, depressive symptom trajectories, and total cognitive performance score (SPMSQ) with all-cause mortality, using a series of Cox PH models that were incrementally adjusted for various sets of covariates while stratifying by sex and race. The results in these models generally show that a higher LS7 total score is consistently associated with a lower hazard of mortality, with stronger associations observed among White adults (Table 2). High depressive symptom trajectories were associated with increased mortality risk, with a stronger association detected among women (Table 2). Lower cognitive performance (or more errors on the SPMSQ) was associated with an increased mortality risk, particularly among women. The association was somewhat weaker but remained significant among Whites and African Americans (Table 2). Adjusting for additional sociodemographic and health-related covariates (Models 2 and 3 in Table 2) attenuated these associations, but the patterns remained similar. Overall, higher LS7 scores were inversely related with mortality, while worse depressive symptom trajectories and lower cognitive performance increased mortality risk. These associations were stronger in women and among Whites but persisted across models with varying adjustments. Adjusting for both LS7 and depressive symptoms trajectory as well as other covariates (Model 3), lower cognitive performance remained independently associated with higher mortality status in the overall sample (Table 3).

Four-way decomposition models where cognitive performance and depressive symptoms are alterative exposures and Life's Simple 7 is also a mediator/moderator

Table 4 presents the fully adjusted four-way decomposition analyses for the conceptual framework in which cognitive performance (SPMSQ total score) and depressive symptom trajectory (CES-D) were specified as alternative exposures, LS7 as the intermediate variable, and all-cause mortality as the outcome. The total effect (TE) of poorer cognitive performance on mortality was significant in the overall sample (TE $= +0.15 \pm 0.07$, $P=0.048$). Among women, the TE of cognitive performance was marginally significant (TE $= +0.21 \pm 0.11$, $P=0.053$), whereas higher depressive symptom trajectory was associated with greater mortality risk (TE $= +1.29 \pm 0.59$, $P=0.028$). Within this

Table 1 Study sample characteristics for sociodemographic, lifestyle, and health[a,b,c]

	Overall	Women	Men	White adults	African American adults	$P_{\text{sex, multivariate}}$	$P_{\text{sex, bivariate}}$	$P_{\text{race, multivariate}}$	$P_{\text{race, bivariate}}$
	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE				
	N = 1466	*N* = 855	*N* = 611	*N* = 577	*N* = 889				
Socio-demographic, visit 1, 2004–2009									
Sex									
Women	58.32 ± 1.29	100	0	58.93 ± 0.02	57.93 ± 1.66	--	--	--	--
Men	41.68 ± 1.29	0	100	41.07 ± 0.02	42.07 ± 1.66	--	--	0.470	0.706
Age, years, v3									
Continuous	56.35 ± 0.23	56.41 ± 0.31	56.26 ± 0.35	56.29 ± 0.35	56.38 ± 0.31	0.607	0.742	0.653	0.845
Race									
White	39.36 ± 1.28	39.77 ± 1.67	38.79 ± 2.00	100	0	0.706	0.706	--	--
African American	60.64 ± 1.28	60.23 ± 1.67	61.21 ± 2.00	0	100	--	--	--	--
Poverty status									
Above	60.23 ± 1.28	56.96 ± 1.69	64.81 ± 1.93	66.90 ± 1.96	55.91 ± 2.00	--	--	--	--
Below	39.77 ± 1.28	43.04 ± 1.69	35.19 ± 1.93	33.10 ± 1.96	44.09 ± 2.00	0.002	0.002	0.000	0.000
Marital status									
Never married	68.19 ± 1.22	72.89 ± 1.52	61.60 ± 1.97	58.61 ± 2.06	74.40 ± 1.47	--	--	--	--
Married/partnered	31.81 ± 1.22	27.11 ± 1.52	38.40 ± 1.97	41.39 ± 2.06	25.60 ± 1.47	0.000	0.000	0.000	0.000
Employment status									
Unemployed	57.94 ± 1.31	61.15 ± 1.68	53.45 ± 2.08	57.78 ± 2.11	58.04 ± 1.70	--	--	--	--
Employed	42.06 ± 1.31	38.85 ± 1.68	46.55 ± 2.08	42.22 ± 2.11	41.96 ± 1.70	0.021	0.004	0.426	0.924
Education									
< High school	6.70 ± 0.66	6.39 ± 0.84	7.14 ± 1.05	9.39 ± 1.22	04.95 ± 0.73	0.354	0.562	0.000	0.000
High school	60.34 ± 1.30	60.70 ± 1.70	59.84 ± 1.99	55.91 ± 2.14	63.22 ± 1.62	--	--	--	--
> High school	32.96 ± 1.25	32.91 ± 1.64	33.03 ± 1.91	34.70 ± 2.06	31.83 ± 1.56	0.670	0.877	0.358	0.078
Lifestyle and health, visit 1, 2004–2009									
Current drug use									
No	72.65 ± 1.16	75.79 ± 1.46	68.25 ± 1.88	78.68 ± 1.70	68.73 ± 1.55	--	--	--	--
Yes	16.85 ± 0.98	13.45 ± 1.17	21.60 ± 1.66	12.48 ± 1.38	19.69 ± 1.33	0.000	0.000	0.000	0.000
Missing	10.50 ± 0.80	10.76 ± 1.06	10.14 ± 1.22	8.80 ± 1.20	11.6 ± 1.1	0.55	0.79	0.063	0.026
Self-rated health									
Poor/average	26.40 ± 1.15	27.02 ± 1.52	25.53 ± 1.76	27.56 ± 1.86	25.65 ± 1.46	0.385	0.499	0.387	0.572
Good	42.70 ± 1.29	45.26 ± 1.70	39.12 ± 1.97	42.63 ± 2.06	42.74 ± 1.66	--	--	--	--
Very good/excellent	30.90 ± 1.21	27.72 ± 1.53	35.35 ± 1.93	29.81 ± 1.90	31.61 ± 1.56	0.004	0.002	0.420	0.659
Comorbidities									
Continuous	2.34 ± 0.03	2.41 ± 0.04	2.25 ± 0.04	2.36 ± 0.05	2.33 ± 0.03	0.012	0.007	0.330	0.524
Hypertension									
No	37.45 ± 1.26	34.85 ± 1.63	41.08 ± 1.99	45.75 ± 2.07	32.06 ± 1.57	0.016	0.015	0.000	0.000
Yes	62.55 ± 1.26	65.15 ± 1.63	58.92 ± 1.99	54.25 ± 2.07	67.94 ± 1.57	--	--	--	--
Diabetes									
Yes	19.51 ± 1.03	21.05 ± 1.39	17.35 ± 1.53	18.20 ± 1.61	20.36 ± 1.35	0.087	0.078	0.335	0.308
No	80.49 ± 1.03	78.95 ± 1.39	82.65 ± 1.53	81.80 ± 1.61	79.64 ± 1.35	--	--	--	--

Table 1 (continued)

	Overall	Women	Men	White adults	African American adults	$P_{\text{sex, multivariate}}$	$P_{\text{sex, bivariate}}$	$P_{\text{race, multivariate}}$	$P_{\text{race, bivariate}}$
	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE	Mean/% ± SE				
	N = 1466	*N* = 855	*N* = 611	*N* = 577	*N* = 889				
High cholesterol									
No	55.42 ± 1.31	54.45 ± 1.72	56.78 ± 2.00	50.18 ± 02.10	58.83 ± 1.67	--	--	--	--
Yes	44.58 ± 1.31	45.55 ± 1.72	43.22 ± 2.00	49.82 ± 02.10	41.17 ± 1.67	0.452	0.380	0.000	0.001
Cardiovascular disease									
No	76.25 ± 1.12	75.44 ± 1.48	77.39 ± 2.00	77.46 ± 1.75	75.46 ± 1.46	--	--	--	--
Yes	23.75 ± 1.12	24.56 ± 1.48	22.61 ± 2.0	22.54 ± 1.75	24.54 ± 1.46	0.564	0.394	0.626	0.382
Inflammatory conditions									
No	77.69 ± 1.09	73.92 ± 1.50	82.98 ± 2.00	72.62 ± 1.86	80.99 ± 1.32	--	--	--	--
Yes	22.31 ± 1.09	26.08 ± 1.50	17.02 ± 2.00	27.38 ± 1.86	19.01 ± 1.32	0.000	0.000	0.000	0.000
LS7 total score, visit 3, 2013–2018	7.55 ± 0.05	7.38 ± 0.07	7.78 ± 0.08	7.56 ± 0.09	7.54 ± 0.06	0.000	0.000	0.816	0.850
Mortality rate; 2018–2022									
#death per 1000 P-Y with 95% CI	20 (18–23)	17 (14–20)	26 (21–31)	21 (17–25)	20 (17–24)	--	--		
Depressive symptoms and domains, visit 3 2013–2018									
Total	13.78 ± 0.29	14.34 ± 0.39	12.99 ± 0.42	14.57 ± 49.71	13.26 ± 34.88	0.059	0.022	0.004	0.026
Depressed affect	3.90 ± 0.12	4.17 ± 0.16	3.54 ± 0.17	4.39 ± 0.20	3.59 ± 0.15	0.023	0.009	0.000	0.001
Interpersonal problems	0.83 ± 0.03	0.83 ± 0.04	0.84 ± 0.05	0.80 ± 0.05	0.85 ± 0.04	0.652	0.863	0.746	0.480
Somatic complaints	5.84 ± 0.11	6.04 ± 0.15	5.55 ± 0.17	6.16 ± 0.19	5.62 ± 0.14	0.065	0.029	0.005	0.020
Well-being	8.80 ± 0.08	8.70 ± 0.11	8.93 ± 0.13	8.79 ± 0.13	8.81 ± 0.11	0.343	0.173	0.481	0.897
Total CES-D trajectory: 2004–2018									
Low declining	51.09 ± 1.31	48.89 ± 1.71	54.17 ± 2.02	48.35 ± 2.08	52.87 ± 1.67	--	--	--	--
High declining	48.91 ± 1.31	51.11 ± 1.71	45.83 ± 2.02	51.65 ± 2.08	47.13 ± 1.67	0.162	0.046	0.011	0.091
Cognitive performance									
SPMSQ total score	0.71 ± 0.02	0.78 ± 0.03	0.62 ± 0.03	0.65 ± 0.03	0.75 ± 0.03	0.001	0.000	0.001	0.019

Abbreviations: *LS7*, Life's Simple 7; *CES-D*, Center for Epidemiologic Studies Depression Scale; *SPMSQ*, Short Portable Mental Status Questionnaire; *SE*, standard error; v1, visit 1 (2004–2009); v2, visit 2 (2009–2013); v3, visit 3 (2013–2018)

[a]Values are means ± SE column percentages for overall and fixed sample characteristics, across sex and race/ethnicity groups, accounting for sampling design complexity. [b]Based on linear or multinomial logit models using sex or race as main predictors for both continuous and categorical variables, accounting for sampling design complexity. [c]Results are from multivariate models

complementary mechanistic framework, there was no evidence that LS7 contributed meaningful indirect effects linking cognitive performance or depressive symptom trajectory with mortality, as the pure indirect effect (PIE) was not statistically significant in any subgroup ($P > 0.05$). The interaction-related components (INTREF and INTMED) were consistently small and non-significant, indicating little evidence that interaction materially contributed to the observed total effects.

Table 5 presents the fully adjusted four-way decomposition analyses for the complementary

Table 2 Cox models for all-cause mortality risk (2018–2022) with depressive symptom trajectory (visits 1–3), total cognitive performance scores (visit 3, 2013–2018), and LS7 (visit 3, 2013–2018), stratified by sex and race and by their interactions

	Overall LnHR ± SE *N* = 1466	Women LnHR ± SE *N* = 855	Men LnHR ± SE *N* = 611	Whites LnHR ± SE *N* = 577	African American LnHR ± SE *N* = 889
Model 1A					
LS7 total score, v3	**−0.092 ± 0.038***	***−0.092 ± 0.053***	***−0.089 ± 0.053***	**−0.123 ± 0.058***	−0.073 ± 0.050
CES-D trajectory, v1–v3	**+0.571 ± 0.148****	**+1.104 ± 0.238***[a]**	+0.197 ± 0.197	**+0.582 ± 0.237***	**+0.538 ± 0.191****
Model 1B					
LS7 total score, v3	**−0.112 ± 0.037****	**−0.133 ± 0.052***	***−0.095 ± 0.053***	**−0.136 ± 0.057***	***−0.094 ± 0.050***
SPMSQ total score, v3	**+0.286 ± 0.079*****	**+0.349 ± 0.111****	**+0.228 ± 0.116***	**+0.322 ± 0.116****	**+0.249 ± 0.109***
Model 2A					
LS7 total score, v3	***−0.070 ± 0.039***	−0.071 ± 0.055	−0.063 ± 0.056	−0.089 ± 0.061	−0.057 ± 0.051
CES-D trajectory, v1–v3	***+0.304 ± 0.155***	**+0.920 ± 0.248***[a]**	−0.118 ± 0.207	+0.342 ± 0.249	+0.268 ± 0.201
Model 2B					
LS7 total score, v3	**−0.080 ± 0.039***	***−0.102 ± 0.054***	−0.065 ± 0.056	−0.098 ± 0.061	−0.066 ± 0.051
SPMSQ total score, v3	**+0.175 ± 0.082***	**+0.255 ± 0.117***	+0.117 ± 0.120	+0.199 ± 0.126	+0.150 ± 0.110
Model 3A					
LS7 total score, v3	−0.051 ± 0.040	**−0.054 ± 0.057**	−0.056 ± 0.056	−0.072 ± 0.062	−0.038 ± 0.053
CES-D trajectory, v1–v3	+0.217 ± 0.160	**+0.823 ± 0.253**[a]**	−0.236 ± 0.214	−0.153 ± 0.255	+0.233 ± 0.207
Model 3B					
LS7 total score, v3	−0.057 ± 0.040	−0.068 ± 0.056	−0.057 ± 0.056	−0.076 ± 0.061	−0.042 ± 0.053
SPMSQ total score, v3	**+0.187 ± 0.082***	**+0.283 ± 0.117***	+0.115 ± 0.121	***+0.208 ± 0.126***	+0.174 ± 0.110

Abbreviations: *LS7* Life's Simple 7, *CES-D* Center for Epidemiologic Studies Depression Scale, *SPMSQ* Short Portable Mental Status Questionnaire, *Ln* log, *HR* hazard ratio, *SE* standard error, v1 visit 1 (2004–2009), v2 visit 2 (2009–2013), v3 visit 3 (2013–2018)

Models A and B included CES-D trajectory or SPMSQ total score alternatively in addition to LS7 total score. Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for poverty status, education level, marital status, and employment status. Model 3 is the full model, and it adjusted for current drug use, comorbidities, and self-rated health, in addition to covariates included in Model 2. Mortality follow-up began at HANDLS visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the visit 3 examination until age at death or censoring

P-value: * < 0.05, ** ≤ 0.01, *** ≤ 0.001

[a] $P < 0.05$ for null hypothesis that interaction between CES-D trajectory or SPMSQ total score and sex is = 0

[b] $P < 0.05$ for null hypothesis that interaction between CES-D trajectory or SPMSQ total score and race is = 0

conceptual framework in which LS7 was specified as the primary exposure, cognitive performance (SPMSQ total score) or depressive symptom trajectory (CES-D) as the intermediate variable, and all-cause mortality as the outcome. Among women, although the total effect (TE) of LS7 was not statistically significant (TE = −0.12 ± 0.10, $P = 0.22$), the pure indirect effect (PIE) through depressive symptom trajectory was significant (PIE = −0.04 ± 0.02, $P = 0.03$), suggesting that depressive symptoms contributed to the indirect component of the association. Similarly, among White adults, LS7 showed a marginal inverse association with mortality (TE = −0.18 ± 0.10, $P = 0.075$), while the controlled direct effect strengthened after accounting for cognitive performance (CDE = −0.20 ± 0.10, $P = 0.048$). Across analyses, the interaction-related components (INTREF and INTMED) remained small and non-significant, indicating that the observed decomposition was driven primarily by direct effects and, where present, indirect effects rather than interaction.

When cognitive performance and depressive symptom trajectory were exposures in the reduced four-way decomposition models adjusted only for age, sex and race (Table S2), the higher depressive symptoms trajectory and the poorer cognitive performance were associated with higher mortality risk, overall and among women (TE > 0, $P < 0.05$). Partial mediation

Table 3 Cox models for all-cause mortality risk (2018–2022), with LS7 (visit 3, 2013–2018), depressive symptom trajectory (visits 1–3), total cognitive performance scores, and all-cause mortality

	Ln(HR) ± SE	*P*	HR	95% CI
Model 1				
LS7, v3	**−0.090 ± 0.038**	**0.017**	**0.91**	**0.85, 0.98**
CES-D trajectory, v1–v3	**+0.498 ± 0.150**	**0.001**	**1.64**	**1.23, 2.21**
SPMSQ total score, v3	**+0.233 ± 0.081**	**0.004**	**1.26**	**1.08, 1.48**
Model 2				
LS7, v3	***−0.072 ± 0.039***	***0.063***	***0.93***	***0.86, 1.00***
CES-D trajectory, v1–v3	***+0.271 ± 0.157***	***0.084***	***1.31***	***0.96, 1.78***
SPMSQ total score, v3	***+0.158 ± 0.083***	***0.057***	***1.17***	***0.99, 1.38***
Model 3				
LS7, v3	−0.055 ± 0.039	0.17	0.95	0.88, 1.02
CES-D trajectory, v1–v3	+0.172 ± 0.161	0.29	1.19	0.87, 1.63
SPMSQ total score, v3	**+0.179 ± 0.083**	**0.035**	**1.20**	**1.02, 1.41**

Abbreviations: *LS7* Life's Simple 7, *CES-D* Center for Epidemiologic Studies Depression Scale, *SPMSQ* Short Portable Mental Status Questionnaire, *Ln* log, *HR* hazard ratio, *SE* standard error, *CI* confidence interval, v1 visit 1 (2004–2009), v2 visit 2 (2009–2013), v3 visit 3 (2013–2018)

Values from Cox PH regression models were exponentiated from their log-values to obtain the hazard ratio. Lower and upper CI were obtained using exp[Ln(HR) ± 1.96*SE(LnHR)]. Model 1 adjusted for age, sex, and race. Model 2 additionally adjusted for poverty status, education level, marital status, and employment status. Model 3 is the full model and it adjusted for current drug use, comorbidities, and self-rated health, in addition to covariates included in Model 2. Mortality follow-up began at HANDLS visit 3 (Wave 4; 2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the visit 3 examination until age at death or censoring

P-value: * < 0.05, ** ≤ 0.01, *** ≤ 0.001

through LS7 was only marginally detectable in the overall sample (% PIE of TE > 10% for the CES-D trajectory exposure, $P = 0.097$, %PIE of TE ~ 5% for the SPMSQ total score exposure, $P = 0.098$). None of the pure indirect effects (PIEs) remained statistically significant after Benjamini–Hochberg false-discovery-rate correction, although nominal evidence of indirect effects was observed in the overall sample for SPMSQ ($P = 0.097$) and CES-D trajectory ($P = 0.098$), and among White adults for SPMSQ ($P = 0.101$).

Importantly, in reduced four-way decomposition models adjusted only for age, sex and race (Table S3), LS7 showed an inverse association with mortality risk, with an especially strong mediation through depressive symptoms trajectory among women (TE = −0.24 ± 0.08. $P = 0.004$, PIE = −0.09 ± 0.03, $P = 0.005$), with PIE accounting for 37.5% of TE. A similar proportion mediated with PIE of the TE was observed in the overall sample and among White adults. The CDE of LS7 on mortality remained significant, even after accounting for SPMSQ and CES-D trajectory in the overall sample, among women and in White adults. After Benjamini–Hochberg false-discovery-rate correction for the ten PIE tests, only the indirect effects through depressive symptom trajectory remained significant in the overall sample (PIE = −0.04 ± 0.01, $q = 0.030$) and among women (PIE = −0.09 ± 0.03, $q \approx 0.001$), whereas all other indirect effects were attenuated and no longer reached statistical significance.

Discussion

This study examined the relationships among cardiovascular health, depressive symptoms, cognitive performance, and all-cause mortality in a diverse cohort of middle-aged adults. To our knowledge, it is the first to apply four-way decomposition models to evaluate complementary mechanistic hypotheses linking these factors by quantifying direct, indirect, and interaction-related components. Higher LS7 scores were associated with lower mortality, particularly among White adults, whereas persistently elevated depressive symptom trajectories

Table 4 Depressive symptom trajectory (v1–v3) and poorer cognitive performance measured at visit 3 (Exposure X) and their association with all-cause mortality: four-way decomposition models through LS7 measured at visit 3 (alternative mediators M, with interaction assessed through the INTREF and INTMED components), overall, by sex and by race, fully adjusted

	TE		CDE		INTREF		INTMED		PIE	
Y = All-cause mortality, 2018–2022; M = LS7 total score, 2013–2018	>$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*
Overall										
SPMSQ total score (v3)	**0.15 ± 0.07**	**0.048**	**0.15 ± 0.07**	**0.044**	−0.00 ± 0.01	0.455	−0.00 ± 0.00	0.733	0.00 ± 0.00	0.694
CES-D trajectory (v1–v3)	0.26 ± 0.20	0.199	0.25 ± 0.20	0.222	−0.00 ± 0.01	0.781	−0.00 ± 0.02	0.899	0.02 ± 0.02	0.350
Men										
SPMSQ total score (v3)	0.09 ± 0.11	0.388	0.09 ± 0.11	0.384	−0.00 ± 0.00	0.778	−0.00 ± 0.00	0.960	−0.00 ± 0.00	0.957
CES-D trajectory (v1–v3)	−0.21 ± 0.17	0.226	−0.22 ± 0.17	0.209	0.01 ± 0.01	0.614	−0.00 ± 0.01	0.720	0.01 ± 0.02	0.650
Women										
SPMSQ total score (v3)	***0.21 ± 0.11***	***0.053***	**0.23 ± 0.11**	**0.033**	−0.02 ± 0.02	0.221	−0.00 ± 0.00	0.561	0.00 ± 0.01	0.558
CES-D trajectory (v1–v3)	**1.29 ± 0.59**	**0.028**	**1.25 ± 0.59**	**0.034**	0.00 ± 0.02	0.984	0.02 ± 0.07	0.824	0.02 ± 0.04	0.626
White										
SPMSQ total score (v3)	0.15 ± 0.11	0.169	0.17 ± 0.11	0.120	−0.02 ± 0.02	0.306	0.00 ± 0.01	0.657	−0.00 ± 0.01	0.653
CES-D trajectory (v1–v3)	0.20 ± 0.31	0.517	0.20 ± 0.31	0.530	−0.02 ± 0.03	0.655	−0.02 ± 0.04	0.588	0.04 ± 0.04	0.314
African American										
SPMSQ total score (v3)	0.12 ± 0.10	0.220	0.11 ± 0.10	0.276	0.01 ± 0.02	0.503	0.00 ± 0.00	0.772	0.00 ± 0.00	0.794
CES-D trajectory (v1–v3)	0.28 ± 0.27	0.289	0.27 ± 0.27	0.310	0.00 ± 0.01	0.935	0.01 ± 0.02	0.774	0.01 ± 0.02	0.758

Abbreviations: *LS7* Life's Simple 7, *TE* total effect, *CDE* controlled direct effect, *INTREF* reference interaction, *INTMED* mediated interaction, *PIE* pure indirect effect, *SPMSQ* Short Portable Mental Status Questionnaire, *CES-D* Center for Epidemiologic Studies Depression Scale, *SE* standard error

Four-way decomposition model where Depressive symptom trajectory and poorer cognitive performance are alternative mortality predictors and LS7 *z*-score is the main mediator/moderator assessed, and all-cause mortality is the outcome of interest. Exogenous variables included age, sex, race, poverty status, education level, marital status, employment status, comorbidities, self-rated health, and current drug use. See the "Covariates" section for details. Mortality follow-up began at HANDLS visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the visit 3 examination until age at death or censoring

Table 5 LS7 (Exposure X) and its association with all-cause mortality: four-way decomposition models through poorer cognitive performance measured at visit 3 and depressive symptoms trajectory measured at visits 1–3 (alternative mediators M, with interaction assessed through the INTREF and INTMED components), overall, by sex and by race, fully adjusted

		TE	CDE		INTREF		INTMED		PIE	
Y = All-cause mortality X = LS7 total score	**β ± SE**	***P***	**β ± SE**	***P***	**β ± SE**	***P***	**β ± SE**	***P***	**β ± SE**	***P***
Overall										
SPMSQ total score (v3)	−0.11 ± 0.07	0.107	−0.12 ± 0.07	0.093	0.01 ± 0.01	0.519	−0.00 ± 0.00	0.739	−0.00 ± 0.00	0.688
CES-D trajectory (v1–v3)	−0.11 ± 0.07	0.128	−0.11 ± 0.10	0.266	0.01 ± 0.07	0.907	−0.00 ± 0.00	0.907	−0.01 ± 0.01	0.245
Men										
SPMSQ total score (v3)	−0.12 ± 0.10	0.256	−0.12 ± 0.10	0.245	0.00 ± 0.01	0.726	−0.00 ± 0.00	0.960	0.00 ± 0.00	0.959
CES-D trajectory (v1–v3)	−0.13 ± 0.10	0.222	−0.18 ± 0.16	0.262	0.05 ± 0.09	0.597	−0.00 ± 0.00	0.714	0.00 ± 0.01	0.643
Women										
SPMSQ total score (v3)	−0.12 ± 0.10	0.212	−0.15 ± 0.10	0.123	0.03 ± 0.03	0.229	−0.00 ± 0.00	0.568	−0.00 ± 0.01	0.532
CES-D trajectory (v1–v3)	−0.12 ± 0.10	0.223	−0.06 ± 0.11	0.593	−0.02 ± 0.10	0.809	0.00 ± 0.01	0.810	**−0.04 ± 0.02**	**0.033**
White										
SPMSQ total score (v3)	***−0.18 ± 0.10***	***0.075***	**−0.20 ± 0.10**	**0.048**	0.02 ± 0.01	0.259	0.00 ± 0.00	0.667	0.00 ± 0.01	0.656
CES-D trajectory (v1–v3)	−0.17 ± 0.11	0.108	−0.22 ± 0.14	0.115	0.06 ± 0.10	0.566	−0.00 ± 0.01	0.592	−0.01 ± 0.01	0.531
African American										
SPMSQ total score (v3)	−0.07 ± 0.10	0.472	−0.06 ± 0.10	0.536	−0.01 ± 0.01	0.292	0.00 ± 0.00	0.772	−0.00 ± 0.00	0.776
CES-D trajectory (v1–v3)	−0.08 ± 0.10	0.445	−0.04 ± 0.14	0.746	−0.03 ± 0.09	0.767	0.00 ± 0.01	0.772	−0.01 ± 0.01	0.371

Abbreviations: *LS7* Life's Simple 7, *TE* total effect, *CDE* controlled direct effect, *INTREF* reference interaction, *INTMED* mediated interaction, *PIE* pure indirect effect, *CES-D* Center for Epidemiologic Studies Depression Scale, *SPMSQ* Short Portable Mental Status Questionnaire, *SE* standard error

Four-way decomposition model where depressive symptom trajectory and poorer cognitive performance are alternative mediators/moderators and LS7 z-score is the main exposure and all-cause mortality is the outcome of interest. Exogenous variables included age, sex, race, poverty status, education level, marital status, employment status, comorbidities, self-rated health, and current drug use. See the "Covariates" section for details. Mortality follow-up began at HANDLS visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the visit 3 examination until age at death or censoring

were associated with greater mortality risk, especially among women. Poorer cognitive performance remained independently associated with higher mortality after adjustment for LS7, depressive symptoms, and other covariates. Although exploratory four-way decomposition analyses suggested modest indirect effects of depressive symptoms on the association between LS7 and mortality in reduced models, most mediation findings were attenuated after false-discovery-rate correction, and interaction-related components were consistently small and non-significant. Overall, these findings indicate that the observed associations were driven primarily by direct effects rather than interaction or widespread mediation.

Cognitive decline [49, 50], by reducing LS7 guideline adherence, may affect the ability to make informed health decisions needed for essential lifestyle changes for better CVH. Cognitive impairments hinder essential health-promoting behaviors like diet, exercise, and chronic disease management, which require planning, organization, and problem-solving skills [51, 52]. Some notable implications of such impairments include reduced motivation and executive functioning for adherence to LS7 guidelines due to lack of self-care activities [52, 53]. Depressive symptoms and cognitive decline often occur together, worsening low motivation and adherence to LS7 guidelines through lifestyle changes [54, 55]. Considering the link between emotional well-being and cognitive performance, it is important to address both cognitive and mental health to enhance adherence to health-promoting behaviors [52, 56].

Our study identified a stronger correlation between poor cognitive performance, depression, and adherence to LS7 in women. This result may be attributed to biological, psychosocial, and cultural factors. During menopause, women experience increased rates of depression, which involve hormonal fluctuations that affect mood and cognition [57, 58]. Additionally, mental strategies such as rumination (also linked to exacerbating depression and cognitive decline) may further complicate LS7 adherence among women [59, 60]. Social pressures and cultural norms can also play a role, as women frequently encounter caregiving responsibilities that elevate stress levels and may adversely impact their health behaviors [61].

Researchers have reported an inverse relationship between CVH (assessed by LS7) and poorer cognitive performance across sexes in studies from the USA [27], French [62], and China [63]. This study found that African American adults had poorer cognitive performance, as indicated by higher SPMSQ scores, and lower CVH based on LS7 scores in diet, fasting glucose, and blood cholesterol compared to White adults. These results align with research on the connection between cognitive performance and CVH assessed using Life's Essential 8 from the American Heart Association [64]. Unlike other research, we did not find significant associations between smoking and physical activity with cognitive performance [65].

Depressive symptoms and cognitive impairments are common among older adults. Studies have shown that depression and low global cognition increase the risk of all-cause mortality [66–68]. These factors may be additive to mortality [68]. Imaging studies reveal volumetric reductions in brain regions in individuals with major depressive disorder and mild cognitive impairments [69] highlighting the bidirectional relationship between depression and cognition [24–26, 70–72]. Depression often accompanies cognitive impairment [73] increasing mortality risk [68].

Our research supports previous findings that show how depressive symptoms can be related to cognition, cardiovascular health, and mortality in older adults. Long-lasting depressive symptoms can lead to quicker cognitive decline and increased risks of adverse health events such as hospitalization and death [74]. In patients with heart disease, physical symptoms of depression are strongly associated with poor cardiac outcomes and physical health after a heart attack or heart failure [75]. Despite its significant impact, depression is often underdiagnosed and inadequately treated in these cases [76]. The cumulative physiological stress, known as allostatic load, may partly explain the connection between depression and negative health outcomes [77]. These associations become more severe with the presence of multiple health conditions, including mental health issues, which leads to higher risks of death [78]. This evidence emphasizes the importance of integrated screening and management of depressive symptoms, particularly in the contexts of aging, multimorbidity, and cardiovascular health.

Nevertheless, in our present study, associations and indirect effects were generally attenuated after

adjustment for clinical and health-related characteristics. Although these covariates may reduce confounding, some, including comorbidity and self-rated health, could also lie downstream of cardiovascular health or share consequences with the exposures examined. Consequently, the fully adjusted models may represent conservative estimates and could potentially involve overadjustment. We therefore present reduced and fully adjusted decomposition models as complementary analyses rather than interpreting either specification as uniquely causal.

Strengths and limitations

This study has several important strengths. First, to our knowledge, it is among the first studies to jointly examine cardiovascular health, longitudinal depressive symptom patterns, cognitive screening performance, and subsequent all-cause mortality in a socioeconomically and racially diverse urban sample of middle-aged adults. The HANDLS cohort is particularly well suited to this question because of its substantial representation of African American adults and individuals across socioeconomic strata, permitting examination of potential differences in associations by sex and race. Second, the prospective design incorporated repeated assessments of depressive symptoms across multiple study visits, enabling depressive symptom patterns to be characterized using group-based trajectory modeling rather than relying on a single cross-sectional measurement. Cardiovascular health was assessed using the multidimensional LS7 metric, while cognitive performance was evaluated using a standardized screening instrument. Third, mortality was ascertained prospectively through linkage with the National Death Index, providing objectively determined vital status and extended follow-up after the analytic index visit. Fourth, the study employed complementary statistical approaches, including group-based trajectory modeling, multivariable Cox proportional hazards regression, interaction analyses, and four-way decomposition models that distinguished direct, indirect, and interaction-related components under alternative prespecified mechanistic frameworks. Finally, analyses considered potential sample selectivity and missing covariate data and examined associations overall and separately by sex and race. Together, these features allowed the study to evaluate the interrelationships among cardiovascular, psychological, and cognitive health and mortality from several complementary perspectives while appropriately recognizing the exploratory nature of the mechanistic analyses.

The study has several limitations. First, cognitive performance was assessed using the Short Portable Mental Status Questionnaire (SPMSQ), which was administered only at visit 3. Consequently, we were unable to evaluate longitudinal changes in cognitive performance or determine the temporal relationship between cognitive decline and mortality. In addition, the SPMSQ is a brief global cognitive screening instrument rather than a comprehensive neuropsychological assessment. Although it has been validated for identifying cognitive impairment, it provides limited assessment of specific cognitive domains such as executive function, attention, processing speed, language, and visuospatial abilities and may be less sensitive to subtle or early cognitive impairment. As a result, some participants may have been misclassified, potentially attenuating the observed associations. Future studies incorporating repeated, comprehensive cognitive assessments (e.g., the Montreal Cognitive Assessment or detailed neuropsychological batteries) would help better characterize longitudinal cognitive trajectories and their relationships with cardiovascular health, depressive symptoms, and mortality. Second, many exposures, outcomes, and covariates were self-reported, which could introduce measurement errors and impact associations. Third, high missingness in dietary data for LS7 may have impacted the final sample size. Fourth, the observational design of HANDLS does not allow for establishing causality.

Conclusions

In conclusion, better cardiovascular health, fewer depressive symptoms, and preserved cognitive performance were independently associated with lower all-cause mortality among middle-aged urban adults. Exploratory four-way decomposition analyses provided limited evidence that depressive symptoms contributed indirectly to the association between LS7 and mortality, with significant indirect effects remaining only in the overall sample and among women after false-discovery-rate correction in reduced models. Interaction-related relationships were consistently negligible. These findings support integrated approaches targeting

cardiovascular, mental, and cognitive health while highlighting the need for longitudinal studies with repeated cognitive assessments to further clarify the temporal and mechanistic relationships among these factors.

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Data availability Data from the HANDLS study are available to qualified investigators upon approval of a research proposal and completion of the required institutional data-use agreement. Additional information regarding HANDLS data and procedures for requesting access is available through the HANDLS study website.

Declarations

Ethics approval The HANDLS study was approved by the Institutional Review Board of the National Institutes of Health. The study was conducted in accordance with applicable institutional and ethical standards for research involving human participants.

Consent to participate Written informed consent was obtained from all HANDLS participants.

Consent for publication Not applicable. The manuscript does not contain identifiable individual participant information requiring consent for publication.

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ONLINE SUPPLEMENTARY MATERIALS

Life's simple 7, depressive symptoms, cognitive performance and their associations with all-cause mortality among middle-aged urban adults

Georgescu M. F. et. Al.

Supplementary Methods 1: Cognitive performance and depressive symptoms

SHORT PORTABLE MENTAL STATUS QUESTIONNAIRE ITEMS

Physical Exam-SPMSQ	How old are you?
Physical Exam-SPMSQ	When were you born?
Physical Exam-SPMSQ	Count down from 20 by 3s
Physical Exam-SPMSQ	What is the date?
Physical Exam-SPMSQ	What is the day of the week?
Physical Exam-SPMSQ	What is your mother's maiden name?
Physical Exam-SPMSQ	Who was the previous president?
Physical Exam-SPMSQ	What is your phone number?
Physical Exam-SPMSQ	What is the name of this place?
Physical Exam-SPMSQ	Who is the current president?
Physical Exam-SPMSQ	Total errors

Buss-Perry Aggression Questionnaire Items

	Variable Label	**Value Label/Factor Levels**
BPAQsport1	Do you play sports or are you physically active in your leisure time or time away from work?	No|Yes
BPAQsport2	What sport or physical activity do you do most frequently?	Low intensity activities (e.g., walking at a slow pace, bowling, golf) |Moderate intensity activities (e.g., bicycling, dancing, swimming, tennis, walking at a fast pace) |High intensity activities (e.g., basketball, football, rowing or paddling, boxing)
BPAQsport3	How many hours a week do you play or do your most frequent activity?	<1 hour|1-2 hours|2-3 hours|3-4 hours|>4 hours

BPAQsport4	How many months in the year do you play or do your most frequent activity?	<1 month|1-3 months|4-6 months|7-9 months|>9 months
BPAQsport5	What sport or physical activity do you do next most frequently?	Low intensity activities (e.g., walking at a slow pace, bowling, golf) |Moderate intensity activities (e.g., bicycling, dancing, swimming, tennis, walking at a fast pace) |High intensity activities (e.g., basketball, football, rowing or paddling, boxing)
BPAQsport6	How many hours a week do you play or do your next most frequent activity?	<1 hour|1-2 hours|2-3 hours|3-4 hours|>4 hours
BPAQsport7	How many months in the year do you play or do your next most frequent activity?	<1 month|1-3 months|4-6 months|7-9 months|>9 months
BPAQleisure1	During leisure time I watch television	Never|Seldom|Sometimes|Often|vOften
BPAQleisure2	During leisure time I walk	Never|Seldom|Sometimes|Often|vOften
BPAQleisure3	During leisure time I cycle	Never|Seldom|Sometimes|Often|vOften
BPAQleisure4	How many minutes per day do you walk or cycle to and from work or shopping?	<5 minutes|5-15 minutes|15-30 minutes|30-45 minutes|>45 minutes

Center for Epidemiologic Studies Depression Scale (CES-D)

CES01	CES-Depression: Bothered by things	Rarely|Sometimes|Occasionally|Mostly
CES02	CES-Depression: Not feel like eating, poor appetite	Rarely|Sometimes|Occasionally|Mostly

CES03	CES-Depression: Could not shake off blues	Rarely|Sometimes|Occasionally|Mostly
CES04	CES-Depression: Felt just as good as other people	Rarely|Sometimes|Occasionally|Mostly
CES05	CES-Depression: Trouble keeping mind on task	Rarely|Sometimes|Occasionally|Mostly
CES06	CES-Depression: Felt depressed	Rarely|Sometimes|Occasionally|Mostly
CES07	CES-Depression: Everything was an effort	Rarely|Sometimes|Occasionally|Mostly
CES08	CES-Depression: Hopeful about the future	Rarely|Sometimes|Occasionally|Mostly
CES09	CES-Depression: Life had been a failure	Rarely|Sometimes|Occasionally|Mostly
CES10	CES-Depression: Felt fearful	Rarely|Sometimes|Occasionally|Mostly
CES11	CES-Depression: Sleep was restless	Rarely|Sometimes|Occasionally|Mostly
CES12	CES-Depression: Happy	Rarely|Sometimes|Occasionally|Mostly
CES13	CES-Depression: Talked less than usual	Rarely|Sometimes|Occasionally|Mostly
CES14	CES-Depression: Felt lonely	Rarely|Sometimes|Occasionally|Mostly
CES15	CES-Depression: People unfriendly	Rarely|Sometimes|Occasionally|Mostly
CES16	CES-Depression: Enjoyed life	Rarely|Sometimes|Occasionally|Mostly
CES17	CES-Depression: Had crying spells	Rarely|Sometimes|Occasionally|Mostly
CES18	CES-Depression: Felt sad	Rarely|Sometimes|Occasionally|Mostly
CES19	CES-Depression: Felt people disliked me	Rarely|Sometimes|Occasionally|Mostly

CES20	CES-Depression: Could not get going	Rarely|Sometimes|Occasionally|Mostly

Supplementary Methods 2: LIFE'S SIMPLE 7 DESCRIPTION

1.1 Life's simple 7 body mass index, total cholesterol, fasting glucose, smoking and blood pressure

BMI was categorized as the following: <25 kg/m^2 as "ideal"(1, 2), "intermediate" as ≥ 25 kg/m^2 and <30 kg/m^2, and "poor" ≥ 30 kg/m^2, from measures of weight and height. Total cholesterol was categorized as "ideal" <200mg/dL, "intermediate" ≥200 and <240 mg/dL, and "poor" ≥240 mg/dL (1, 2). Fasting glucose was categorized as "ideal" <100mg/dL, "intermediate" ≥100 and <126 mg/dL, and "poor" ≥126 mg/dL (1, 2). Smoking status was defined in three groups: "ideal" never tried or tried but never used regularly, "intermediate" former user, and "poor" as current user (1, 2). Finally, blood pressure was categorized as "ideal" <120 mm Hg systolic and <80 mm Hg diastolic, "intermediate" systolic ≥120 & <140 mm Hg and diastolic≥80 & <90 mm Hg, and "poor" as systolic≥140 mm Hg with >=90 mm Hg diastolic (1, 2).

1.2 Dietary assessment in HANDLS, v_3 (2013-2017)

At v3, HANDLS participants recorded their food intake over the course of two days, using Automated Multiple Pass Method (AMPM), a dietary data collecting tool from the United States Department of Agriculture (USDA) (3, 4). Four to ten days elapsed between 24-hour recalls. The first recall was conducted in-person while the second was done over the phone. A pamphlet with illustrations of food models and other aids to help with portion estimation were given to participants. USDA Survey Net, a computer-assisted food code processing system, was used to input data on food and beverage quantities consumed, collected by AMPM. 2013-2014,the USDA Food and Nutrient Database for Dietary Studies (FNDDS), provided an 8-digit

number for each food and beverage that was recorded (5). Survey Net or nutritionists with dietary coding training assigned these codes.

Intake values for sodium, fiber, and carbohydrates was calculated by FNDDS, as well as to convert the food and drinks participants in the HANDLS study consumed into gram quantities. Computed for each recall day, two dietary components for Life Simple 7 were determined by averaging these nutrient levels. Food and beverages from FNDDS were converted to food groups using the USDA Food Patterns Equivalents Database 2013–14 [66]. The creation of the dietary measure used once equivalents for cereals and fish and cup equivalents for fruits and vegetables. Added sugars to non-sweetened beverages were calculated by in a two-step process for energy from sugar-sweetened beverages.

Coffee, tea, and other beverages with added sugar were assigned a combination code in AMPM. A food category for sugar-sweetened beverages by combining additions to main beverages were done by trained coders. The sugar-sweetened beverages included soft drinks, fruit-flavored beverages, fruitades, nonalcoholic beer, wine, cocktails, energy drinks, coffee substitutes, and tea.

1.3. Life's simple 7 dietary component

The AHA LS7 variables were used to define dietary component of CVH metrics (6). The optimal metric, in terms of diet, was based on five nutrition components: fruit and vegetables (≥ 4.5 Cup equivalents/day), fish (≥ two 3.5 oz servings/week), whole grains high in fiber (≥ 3-oz equivalent servings/day or ≥ 1.1 gm fiber per 10 gm carbohydrate/day, the equivalent of a fiber to carbohydrate ratio ≥ 0.11 gm/day), sodium (<1500 mg/day), and sugar-sweetened beverages (≤ 450 kcal/week) (6). The optimal metric for consumption is 2,000 kcal (6). Actual

consumption amounts for individuals were scaled to match optimal target intake (6). One point was given for individuals who reach this target. “Ideal” included a total sum of 4-5 points, “intermediate” as 2-3, and “poor” as 0-1 (6).

1.4. Life’s simple 7 physical activity component:

Baecke questionnaire for physical activity (BQ)(7), HANDLS v3:

In the Baecke questionnaire there are three domains (work, sports, and non-sport leisure activity) with sixteen total items, on a five-point Likert scale, ranging from never to very often for each question. The work domain was evaluated as unreliable. The remaining domains had scores ranged from one to five points, with an overall score can vary from three (minimum) to ten (maximum). For each domain, we used the original scoring methodology: “sport” was defined as the mean score of four questions on sports, “non-leisure activity” was defined as the mean score of four habitual physical activities. Two of the most often reported sports activities, specific questions on among of hours per week and months per year of engagement were asked. To evaluate test-retest reliability, the first questionnaire was administered in-person. The last step included scoring and adding up each participant’s scores in two domains “sports” and “non-sports leisure.”

The two domains we had for physical activity were sports and leisure, constructed from the HANDLS Life’s Simple 7 score. The following self-reported questions (from BPAQ) were part of the physical activity criteria’s sport component:

- Do you play sports or are you physically active in your leisure time or time awake? (yes/no)
- What sport of physical activity do you do most frequently? (low intensity e.g. walking, moderate intensity, e.g. biking, high intensity, e.g. basketball)

- How many hours a week do you play or do your most frequent activity? (<1 hour, 1-2 hours, 2-3 hours, 3-4 hours, >4 hours)
- What sport or physical activity do you do next most frequently? (low intensity e.g. walking, moderate intensity, e.g. biking, high intensity, e.g. basketball)

An analogous set of questions were supplied for the leisure component and code is available upon request. The LS7 PA component was scored by total minutes per week spent on each activity, considering intensity of PA. The primary criterion, for the ideal level of physical activity was ≥150 minutes per week at a moderate intensity, >75 minutes per week at vigorous intensity, or a combination. A score of 2 was generated from meeting this criterion, no active scored 0, and any activity generated a score of 1 (Supplementary Table 1). The variables used to generate LS7 PA are listed in Supplemental Table 2. On request, the detailed code can be provided.

1.5. Life's Simple 7 Total Score

Each criterion for HANDLS LS7 was given 2 points for excellent, 1 point for intermediate, and 0 points for poor to calculate a total LS7 score. The range was from 0 to 14 with 0 indicating worst and 14 as best. Other studies have classified scores as either optimal (10–14), moderate (5–9), or poor (0–4) cardiovascular health [62]. Poor health was defined by current smoking, along with one of five dietary guidelines, not exercising, and high BMI (≥30 kg/m2), blood pressure (SBP ≥140 mm Hg or DBP ≥90 mm Hg), total cholesterol (≥6.22 mmol/L), and fasting glucose (≥6.99 mmol/L). Additional information regarding poor and intermediate levels of each component are provided in Supplemental Table 1 [67].

TABLE S1.A. Life's Simple 7 components and levels

Component	Ideal (2 Points)	Intermediate (1 Point)
Smoking	Never or former = >1 year	Former = ≤1 year
Healthy diet score*	4-5 points	2-3 points
Physical activity*	≥4 sessions/wk of intense physical activity enough to work a sweat; adjusted to ≥150 min/wk moderate intensity or ≥75 min/wk vigorous intensity or combination	1 to 3 sessions/wk of intense physical activity enough to work a sweat; adjusted to "Intense activity below criterion"
Body mass index	<25 kg/m^2	25-29.9 kg/m^2
Blood pressure	<120/<80 mm Hg untreated	SBP 120-139 or DBP 80-89 mm Hg or treated t ideal level
Total cholesterol	<5.18 mmol/L (<200 mg/dL) untreated	5.18-6.19 mmol/L (200 to 239 mg/dL) or treate to ideal level
Fasting glucose	<5.55 mmol/L (<100 mg/dL) untreated	5.55-6.94 mmol/L (100-125 mg/dL) or treated t ideal level

***** The original measures were adjusted according to data available in HANDLS.
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4309046/

TABLE S1.B. Study sample selectivity according to inclusion in final analytic sample

Characteristic	Not included in final sample (n = 2,254)	Included in final sample (n = 1,466)	P value
Age, years, mean (SD), visit 1 (2004-2009)	48.60 (9.71)	47.76 (8.77)	0.008
Race, n (%)			0.120
White	945 (41.93)	577 (39.36)	
African American	1,309 (58.07)	889 (60.64)	
Poverty status, n (%)			0.135
Above poverty threshold	1,302 (57.76)	883 (60.23)	
Below poverty threshold	952 (42.24)	583 (39.77)	
Sex, n (%)			<0.001
Women	1,180 (52.35)	855 (58.32)	
Men	1,074 (47.65)	611 (41.68)	

Note: Values are n (%) unless otherwise indicated. Percentages for categorical variables are column percentages.

The baseline HANDLS sample included 3,720 participants. Of these, 1,466 (39.41%) were included in the final analytic sample and 2,254 (60.59%) were not included.

Differences between participants included and not included in the final analytic sample were assessed using a two-sample t test for age and Pearson χ^2 tests for categorical variables.

For age, the mean difference (not included minus included) was 0.83 years (t = 2.66, df = 3,718; P = 0.0079). P values are shown to three decimal places; P < 0.001 is reported for sex.

TABLE S2. Cognitive performance score, depressive symptom trajectory, and all-cause mortality: four-way decomposition models through LS7, overall, by sex and by race, adjusting for socio-demographics only

Y=All-cause mortality; **M**= LS7	**TE** **β±SE**	**P**	**CDE** **β±SE**	**P**	**INTREF** **β±SE**	**P**	**INTMED** **β±SE**	**P**	**PIE** **β±SE**	**P**
Overall										
SPMSQ total score, v3	**0.20±0.07**	**0.008**	**0.20±0.07**	**0.007**	-0.01±0.01	0.385	-0.00±0.00	***0.590***	***0.01±0.01***	***0.097***
CES-D trajectory, v1-v3	**0.65±0.25**	**0.008**	**0.59±0.24**	**0.016**	-0.01±0.01	0.287	-0.00±0.06	***0.990***	***0.07±0.04***	***0.098***
MEN										
SPMSQ total score, v3	0.15±0.11	0.160	0.14±0.11	0.181	0.00±0.01	0.975	0.00±0.00	0.709	0.01±0.01	0.475
CES-D trajectory, v1-v3	0.12±0.22	0.588	0.09±0.22	0.691	0.01±0.02	0.714	-0.03±0.05	0.580	0.05±0.04	0.201
Women										
SPMSQ total score, v3	**0.25±0.11**	**0.019**	**0.26±0.10**	**0.007**	-0.03±0.03	0.243	-0.01±0.01	0.419	0.02±0.01	0.114
CES-D trajectory, v1-v3	**1.89±0.69**	**0.006**	**1.75±0.68**	**0.010**	-0.02±0.03	0.526	0.06±0.16	0.704	0.10±0.09	0.261
White										
SPMSQ total score, v3	0.18±0.11	0.084	**0.21±0.10**	**0.034**	-0.04±0.02	0.124	-0.02±0.01	0.169	0.03±0.02	0.101
CES-D trajectory, v1-v3	0.78±0.42	0.067	0.68±0.42	0.105	-0.02±0.03	0.465	-0.03±0.14	0.827	0.15±0.10	0.134
African American										
SPMSQ total score, v3	0.17±0.10	0.098	0.14±0.10	0.156	0.02±0.02	0.432	0.00±0.00	0.577	0.00±0.01	0.556
CES-D trajectory, v1-v3	0.57±0.30	0.060	0.52±0.30	0.081	-0.00±0.00	0.301	0.01±0.06	0.816	0.03±0.04	0.410

Abbreviations: LS7: Life's Simple 7; TE: Total Effect; CDE: Controlled Direct Effect; INTREF: Reference Interaction; INTMED: Mediated Interaction; PIE: Pure Indirect Effect; CES-D: Center for Epidemiologic Studies Depression Scale; SPMSQ: Short Portable Mental Status Questionnaire; SE: Standard Error; v1=Visit 1 (2004-2009); v2=Visit 2 (2009-2013); v3=Visit 3 (2013-2018).

Notes: Four-way decomposition model where depressive symptom trajectory and poorer cognitive performance are alternative exposures and LS7 z-score is the main mediator/moderator assessed, while all-cause mortality is the outcome of interest. Exogenous variables included age, sex, race and poverty status. See Covariates section for details.

Mortality follow-up began at HANDLS Visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the Visit 3 examination until age at death or censoring.

TABLE S3. LS7 association with all-cause mortality and four-way decomposition through poorer cognitive performance and depressive symptoms trajectory, overall, by sex and by race, adjusting for socio-demographics only

Y=All-cause mortality; **X**= LS7	**TE** **β±SE**	**P**	**CDE** **β±SE**	**P**	**INTREF** **β±SE**	**P**	**INTMED** **β±SE**	**P**	**PIE** **β±SE**	**P**
Overall										
SPMSQ total score, v3	**-0.19±0.06**	**0.002**	**-0.19±0.06**	**0.002**	0.01±0.01	0.485	-0.00±0.00	0.683	-0.01±0.01	0.088
CES-D trajectory, v1-v3	**-0.19±0.06**	**0.002**	**-0.15±0.08**	**0.046**	-0.00±0.06	0.957	0.00±0.01	0.957	**-0.04±0.01**	**0.006**
MEN										
SPMSQ total score, v3	-0.16±0.09	0.082	-0.16±0.09	0.088	0.00±0.00	0.689	0.00±0.00	0.690	-0.00±0.01	0.482
CES-D trajectory, v1-v3	-0.17±0.09	0.067	-0.21±0.12	0.096	0.05±0.09	0.576	-0.01±0.01	0.583	-0.01±0.01	0.683
Women										
SPMSQ total score, v3	**-0.24±0.08**	**0.003**	**-0.24±0.08**	**0.002**	0.02±0.02	0.343	-0.00±0.00	0.574	-0.02±0.01	0.093
CES-D trajectory, v1-v3	**-0.24±0.08**	**0.004**	-0.12±0.08	0.165	-0.04±0.09	0.620	0.01±0.02	0.622	**-0.09±0.03**	**0.000**
White										
SPMSQ total score, v3	**-0.25±0.09**	**0.004**	**-0.25±0.09**	**0.004**	0.03±0.02	0.121	-0.01±0.01	0.268	-0.02±0.01	0.104
CES-D trajectory, v1-v3	**-0.25±0.09**	**0.005**	**-0.21±0.10**	**0.041**	0.01±0.09	0.906	-0.00±0.02	0.906	**-0.05±0.02**	**0.049**
African American										
SPMSQ total score, v3	-0.15±0.09	0.087	-0.13±0.09	0.120	-0.01±0.01	0.241	0.00±0.00	0.571	-0.00±0.00	0.552
CES-D trajectory, v1-v3	-0.15±0.09	0.082	-0.11±0.11	0.358	-0.02±0.08	0.797	0.00±0.01	0.797	-0.03±0.02	0.058

Abbreviations: LS7: Life's Simple 7; TE: Total Effect; CDE: Controlled Direct Effect; INTREF: Reference Interaction; INTMED: Mediated Interaction; PIE: Pure Indirect Effect; CES-D: Center for Epidemiologic Studies Depression Scale; SPMSQ: Short Portable Mental Status Questionnaire; SE: Standard Error; v1=Visit 1 (2004-2009); v2=Visit 2 (2009-2013); v3=Visit 3 (2013-2018).

Notes: Four-way decomposition model where depressive symptom trajectory and poorer cognitive performance are alternative mediators/moderators and LS7 z-score is the main exposure of interest, while all-cause mortality is the outcome of interest. Exogenous variables included age, sex, race and poverty status. See Covariates section for details. Mortality follow-up began at HANDLS Visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the Visit 3 examination until age at death or censoring.

TABLE S4. Study sample characteristics for sociodemographic, lifestyle and health for CES-D trajectory and LS7 sub-scores [a,b,c]

	Overall	**Women**	**Men**	**White**	**African American**	**Sex Difference** [c]	**Race Difference** [c]	**$P_{sex,\ multivariate}$**	**$P_{sex,\ bivariate}$**	**$P_{race,\ multivariate}$**	**$P_{race,\ bivariate}$**
	Mean/%±SE N=1,466	Mean/%±SE N=855	Mean/%±SE N=611	Mean/%±SE N= 577	Mean/%±SE N= 889	Mean/%±SE N=1,466	Mean/%±SE N=1,466				
CES-D TRAJECTORY SUBSCORES											
Depressive affect trajectory											
Low declining	0.55±0.01	0.51±0.02	0.60±0.02	0.51±0.02	0.57±0.02	--	--	--	--	--	--
High declining	0.45±0.01	0.49±0.02	0.40±0.02	0.49±0.02	0.43±0.02	-0.30±0.11	-0.32±0.11	0.005	0.001	0.004	0.028
Interpersonal problems trajectory											
Low declining	0.57±0.01	0.58±0.02	0.56±0.02	0.58±0.02	0.57±0.02	--	--	--	--	--	--
High declining	0.43±0.01	0.42±0.02	0.44±0.02	0.42±0.02	0.43±0.02	0.16±0.11	-0.02±0.11	0.132	0.322	0.874	0.576
Somatic complaints trajectory											
Low declining	0.42±0.01	0.41±0.02	0.43±0.02	0.41±0.02	0.42±0.02	0.04±0.11	0.13±0.11	0.682	0.361	0.250	0.644
High declining	0.58±0.01	0.59±0.02	0.57±0.02	0.59±0.02	0.58±0.02	--	--	--	--	--	--
LS7 SUBSCORES											
BMI	0.73±0.02	0.62±0.03	0.90±0.03	0.72±0.03	0.74±0.03	0.29±0.04	0.01±0.04	0.000	0.000	0.872	0.609
Blood pressure	1.46±0.02	1.43±0.02	1.50±0.03	1.60±0.03	1.37±0.03	0.06±0.04	-0.21±0.04	0.112	0.071	0.000	0.000
Cholesterol	1.52±0.02	1.43±0.02	1.64±0.03	1.46±0.03	1.56±0.02	0.21±0.04	0.09±0.04	0.000	0.000	0.016	0.008
Cigarette smoking	0.88±0.02	0.93±0.03	0.81±0.03	0.93±0.04	0.85±0.03	-0.15±0.04	-0.04±0.04	0.001	0.004	0.333	0.082
Diet	0.40±0.01	0.42±0.02	0.38±0.02	0.37±0.02	0.42±0.02	-0.04±0.03	0.06±0.03	0.136	0.184	0.032	0.056
Physical activity	1.04±0.01	1.00±0.02	1.08±0.02	1.01±0.02	1.05±0.02	0.07±0.03	0.05±0.03	0.015	0.005	0.080	0.207
Fasting blood glucose	1.52±0.02	1.55±0.02	1.47±0.03	1.47±0.03	1.55±0.02	-0.08±0.04	0.08±0.04	0.030	0.033	0.036	0.035

Abbreviations: CES-D: Center for Epidemiologic Studies Depression Scale; LS7: Life's Simple 7; SE: Standard Error; BMI: Body Mass Index; v1=Visit 1 (2004-2009); v2=Visit 2 (2009-2013); v3=Visit 3 (2013-2018).

Notes: [a] Values are means ± SE column percentages for overall and fixed sample characteristics, across sex and race/ethnicity groups. [b] Based on linear or multinomial logit models using sex or race as main predictors for both continuous and categorical variables. [c] Results are from multivariate models that include age at v3, sex, race, and poverty status. . Mortality follow-up began at HANDLS Visit 3 (2013–2017) and continued through December 31, 2022. Participants contributed person-time from their age at the Visit 3 examination until age at death or censoring.

TABLE S5. Group-based trajectory model parameters and classification diagnostics for total CES-D scores across HANDLS visits 1–3

Parameter	Lower-symptom declining trajectory (Group 1)	Higher-symptom declining trajectory (Group 2)
Participants, %	51.23	48.77
Trajectory intercept, β	2.7756	3.6536
Linear age term, β	−0.0149	−0.0101
P value, linear age term	<0.001	<0.001
Mean CES-D, Visit 1	7.56	22.81
SD, Visit 1	5.45	10.87
Mean CES-D, Visit 2	7.98	24.40
SD, Visit 2	5.44	10.84
Mean CES-D, Visit 3	6.66	21.24
SD, Visit 3	5.33	10.23
Correlation of posterior group probability with CES-D, Visit 1	−0.689	+0.689
Correlation of posterior group probability with CES-D, Visit 2	−0.708	+0.708
Correlation of posterior group probability with CES-D, Visit 3	−0.685	+0.685

Overall model diagnostics

Model characteristic	Value
Analytic N	**1,466**
Number of trajectory groups	**2**
Distribution	**Zero-inflated Poisson**
Trajectory functional form	**Linear age**
Entropy	**0.936**
Log-likelihood	**−19,035.50**

Model characteristic	Value
AIC	**−19,040.50**
BIC, observations	**−19,056.35**
BIC, participants	**−19,053.73**

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CES-D, Center for Epidemiologic Studies Depression Scale; GBTM, group-based trajectory modeling; HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span; SD, standard deviation.

Notes: Group-based trajectory modeling was applied to total CES-D scores assessed across HANDLS visits 1–3. A two-group zero-inflated Poisson model with linear age terms was used to characterize longitudinal depressive symptom patterns. Group 1 represented a lower-symptom declining trajectory and Group 2 a higher-symptom declining trajectory. Group percentages are based on posterior trajectory classification. Posterior probabilities of trajectory membership were estimated for each participant; entropy summarizes overall classification certainty, with values approaching 1 indicating greater separation between trajectory groups. Mean CES-D scores are descriptive observed values within the assigned trajectory groups rather than model-predicted values. **Figure 2** displays the fitted trajectories and posterior-probability contour plots.

Supplemental Methods 3. Group-based trajectory modeling of depressive symptoms

Longitudinal patterns of depressive symptoms were characterized using group-based trajectory modeling (GBTM). Total depressive symptom burden was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) at three HANDLS visits. CES-D scores were modeled as a function of participants' age at each assessment, thereby accounting for differences in age across the repeated observations. The trajectory analysis was restricted to the 1,466 participants included in the final analytic sample. The main manuscript describes CES-D assessment across all three visits.

Because CES-D scores are non-negative count-like measures with a substantial concentration of observations at low values, trajectories were estimated using a zero-inflated Poisson distribution. The final model specified two latent trajectory groups, with a linear age term within each group. Thus, for individual *i* belonging to latent group *j*, the expected CES-D score at age *t* was modeled as a group-specific function of age, while the zero-inflation component accommodated excess observations at zero. Maximum-likelihood estimation was used to simultaneously estimate the trajectory parameters and probability of membership in each latent group.

The fitted model identified two clearly differentiated trajectories. Group 1 comprised 51.23% of participants and was characterized by persistently lower depressive symptom scores that declined modestly with age. The estimated intercept and linear age coefficient for this group were 2.7756 and −0.0149, respectively (both $P<0.001$). Group 2 comprised 48.77% of participants and

was characterized by persistently higher depressive symptom scores with a similarly modest decline with age; its estimated intercept and linear age coefficient were 3.6536 and −0.0101, respectively (both $P<0.001$). The model yielded BIC values of −19,056.35 based on the number of observations and −19,053.73 based on the number of participants, an AIC of −19,040.50, and a log-likelihood of −19,035.50.

For each participant, the fitted GBTM generated posterior probabilities of membership in each trajectory group. Participants were assigned to the trajectory with the highest posterior membership probability for descriptive analyses, while the estimated posterior probability of membership in the higher-symptom group was retained in the analytical dataset.

Classification quality was evaluated using entropy, with values approaching 1 indicating greater separation of the latent classes. Entropy for the final two-group model was 0.936, indicating high classification certainty.

As an additional assessment of construct separation, posterior membership probabilities were compared with observed CES-D scores at each assessment. Probability of membership in the higher-symptom trajectory was positively correlated with observed CES-D scores at visits 1, 2, and 3 ($r=0.689$, 0.708, and 0.685, respectively), whereas probability of membership in the lower-symptom trajectory showed correlations of equal magnitude in the opposite direction. Among participants assigned to the lower-symptom trajectory, mean (SD) CES-D scores were 7.56 (5.45), 7.98 (5.44), and 6.66 (5.33) across the three assessments. Corresponding values among participants assigned to the higher-symptom trajectory were 22.81 (10.87), 24.40

(10.84), and 21.24 (10.23). This is presented in detail in **Table S5**.

Trajectory estimates and posterior probabilities were visualized in **Figure 2**. The primary trajectory panel presents fitted CES-D scores over age for the two latent groups, whereas contour plots display posterior probabilities of membership in each group according to pairs of observed CES-D measurements. Together, these diagnostics were used to characterize separation and classification of the identified depressive symptom trajectories.

Supplemental Methods 4

3.1 Four-Way Decomposition Models

3.1.1 Background

Let Y represent the response, A signify the exposure (specifically, the trajectory of the Center of Epidemiologic Studies Depression Scale (CESD) or the total score of the Short Portable Mental Status Questionnaire z-transformed and reverse coded (zSPMSQtot & CESD; continuous), a its realized value, M the mediator (the LS7 scores–transformed using $\log[\frac{Pr}{1-\Pr}])$, m its realized value, and c the vector of confounders. Assuming no confounding, specifically:

i. $Y_{am} \perp A|C$

ii. $Y_{am} \perp M|(A,C)$

iii. $M_a \perp A|C$

iv. $Y_{am} \perp A * |C$

that the effect of A on Y is unconfounded conditional on C (i), that the effect of M on Y is unconfounded conditional on (A,C), (ii), the effect of A on M is unconfounded conditional on C (iii), and that any confounders of mediator outcomes are unaffected by the exposure (iv), we can decompose the sources of the total effect of the model into four components (Equation 1) (8).

$$TE = CDE + INT_{ref} + INT_{med} + PIE \quad (1)$$

The model indicates the overall impact of exposure A on outcome Y comprises the *controlled direct effect* (CDE), which represents effect A on Y independent of any interaction or mediation; the *reference interaction* (INTREF), which pertains to the effect of interaction only; the *mediated*

interaction (INTMED) encompasses both interaction and mediation; and the *pure indirect effect* (PIE), refers to an indirect effect only. The components are conceptualized in the following:

- *Controlled direct effect*: effect of exposure on the outcome without mediator.

- *Reference interaction*: exposure affects outcome with mediator presence and exposure presence is not required for mediator presence.

- *Mediated interaction*: exposure affects outcome in presence of mediator and exposure presence is required for mediator presence.

- *Pure indirect effect*: mediator causes outcome in absence of exposure, but exposure is required for mediator to be present.

  We refer readers to original publications regarding details on the four-way decomposition model (8, 9).

3.1.2 Four-Way Decomposition Model Implementation

Fitting two regression models and using the parameter estimates for the final component computation are the steps involved in estimating the components of the partitioned model in Equation 1. While we will give a brief overview of how to use and estimate the impacts, we advise reviewers to go to a thorough explanation of the med4way command in STATA (10). We estimate the model's four components at the population level, but not at the individual level, assuming there is no unmeasured confounding (as explained in 1.1 above). The expected value of M given the exposure and confounders (Equation 3) and the expected value of Y given the exposure, mediator, and confounders (Equation 2) are the subject of two regression models:

$$\mathrm{E}[Y|(a,m,c)] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a * m + \theta_c c \quad (2)$$

$$\mathrm{E}[M|(a,\boldsymbol{c})] = \beta_0 + \beta_1 a + \boldsymbol{\beta}_c^T \boldsymbol{c} \quad (3)$$

Therefore, estimates of these parameters make direct computations of estimates of the four component sources of variation for the total effect (TE) directly:

$$\mathrm{E}[CDE|c] = \theta_1(a - a')$$
$$\mathrm{E}[INT_{ref}|c] = \theta_3(\beta_0 + \beta_1 a' + \boldsymbol{\beta}_c^T \boldsymbol{c})(a - a')$$
$$\mathrm{E}[INT_{med}|c] = \theta_3\beta_1(a - a')(a - a')$$
$$\mathrm{E}[PIE|c] = (\theta_2\beta_1 + \theta_3\beta_1 a')(a - a')$$

Where, in the case of a binary exposure, $a = 1$ and $a' = 0$.[11] Med4way can handle outcome variables from a variety of distributions, including binomial, log-binomial, Poisson, negative binomial, Weibull, Cox, and others, and the models we present are generalizable (10). E[Y |(a,m,c)] and E[M|(a,c)] are defined as follows in our analyses:

$$E(y|x, v, \boldsymbol{z}) = \theta_0 + \theta_1 x + \theta_2 v + \theta_3 x * v + \boldsymbol{\theta}_z^T \boldsymbol{z} \quad (4)$$
$$\mathrm{E}[V|(x, \boldsymbol{z})] = \beta_0 + \beta_1 x + \boldsymbol{\beta}_z^T \boldsymbol{z} \quad (5)$$

where, the expectation of y, zLIFE7_TOTALSCORE, as a function of x, zSPMSQtot, v, CESD, and z, the vector of confounders/covariates discussed in the manuscript, are Equation 4. Using ordinary least squares we model the expectation of the mediator, V, as a function of zLIFE7_TOTALSCORE and the other covariates in Equation 5.

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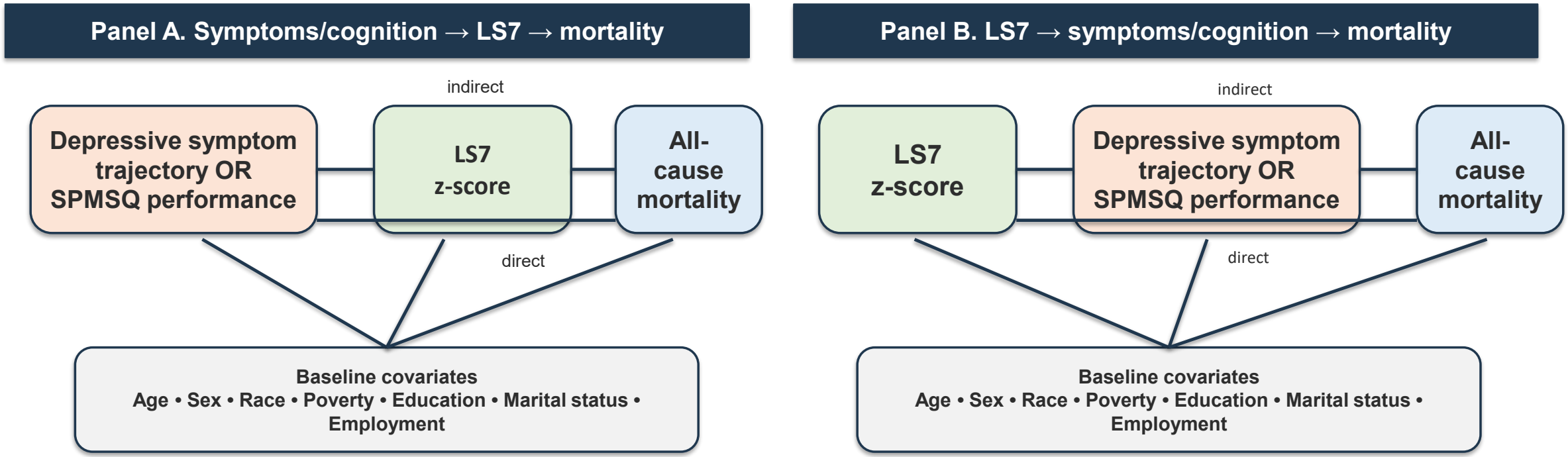
Figure S1. Alternative conceptual frameworks for exploratory four-way decomposition analyses

HANDLS: cardiovascular health, depressive symptoms, cognitive screening performance, and all-cause mortality



Four-way decomposition partitions the total effect into CDE, INTREF, INTMED, and PIE; interaction-related components are assessed within each framework.

Interpretation: These panels represent complementary, prespecified analytical hypotheses. Because LS7, depressive symptoms, and cognitive screening performance were measured during overlapping periods, the diagrams do not establish temporal or causal ordering; the decomposition analyses are exploratory and hypothesis-generating.