The Journal of Prevention of Alzheimer's Disease 12 (2025) 100273

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

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

Original Article

Associations of cardiovascular health assessed by life's crucial 9 with incident cardiovascular disease and dementia: A prospective cohort study

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ARTICLE INFO

Keywords:
Cardiovascular health
Life's crucial 9
Cardiovascular disease
dementia

ABSTRACT

Background: The associations of the renewed cardiovascular health (CVH) assessed by Life's Crucial 9 (LC9), which consisted of Life's Essential 8 (LE8) and psychological health, with incident cardiovascular disease (CVD) and dementia remained unexplored.
Objectives: This study aims to investigate the associations and determine whether LC9 has a higher discrimination ability than LE8 in predicting incident CVD and dementia.
Design, setting, and participants: This study was a prospective population-based cohort study using data from the UK Biobank.
Measurements: LC9 was assessed as American Heart Association recommended. Incident CVD and dementia were based on self-reported data, hospital inpatient records, and death register records.
Results: Of 289,649 included participants, 137,480 (47.5 %) were male, and the mean age was 56.6 ± 8.1 years. Compared with participants having low LC9, those having moderate or high LC9 had lower risks of incident CVD (moderate: 0.46 [0.43–0.48]; high: 0.25 [0.23–0.27]; p for trend <0.001) and dementia (moderate: 0.57 [0.50–0.64]; high: 0.45 [0.39–0.52]; p for trend <0.001) after multivariate adjustment. Both the LE8 and LC9 achieved good discriminative performance for incident CVD (LE8 Harrell C-statistic= 0.7138 vs. LC9 Harrell C-statistic=0.7144, $p = 0.136$); the net reclassification improvement was estimated at 0.07 % ($p = 0.749$), and integrated discrimination improvement was estimated at 0.009 ($p < 0.001$). The results for dementia showed similar patterns.
Conclusions and Relevance: Optimal LC9 was associated with lower risks of incident CVD and dementia. Although psychological health is essential for preventing CVD and dementia, including it into CVH's evaluation criteria did not significantly improve CVH's predictive performance.

1. Introduction

With a continued global shift of population age structures towards older ages, the number of individuals having cardiovascular disease (CVD) and dementia will increase considerably [1,2]. It's estimated that CVD caused 424.5 million disability-adjusted life years (DALYs) in 2022 and will increase to 508.1 million in 2050; DALYs of Alzheimer's disease and other dementia was 113.5 million in 2022 and will also elevate to 191.1 million, both of which have a substantial impact on public health [3]. The 2024 report of the Lancet Commission on Dementia Prevention, Intervention and Care suggests that by eliminating 14 modifiable risk factors, the number of dementia cases could be reduced by as much as 45 % [4]. Growing evidence indicates that CVD and dementia share

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https://doi.org/10.1016/j.tjpad.2025.100273
Received 24 April 2025; Received in revised form 3 July 2025; Accepted 5 July 2025
Available online 11 July 2025

Non-standard Abbreviations and Acronyms

AHA	American Heart Association
ApoE4	Apolipoprotein E4
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
C-statistic	Concordance statistic
CVD	Cardiovascular disease
CVH	Cardiovascular health
DALYs	Disability-adjusted life years
HbA1c	Hemoglobin A1c
HR	Hazard ratio
IDI	Integrated discrimination improvement
IQR	Interquartile range
LC9	Life's Crucial 9
LE8	Life's Essential 8
LS7	Life's Simple 7
MI	Myocardial infarction
NHS	National Health Service
NRI	Net reclassification improvement
PAR	Population-level attributable risk
PHQ-4	4-item Patient Health Questionnaire
SD	Standard deviation
UKB	UK Biobank

common risk factors; incident CVD played a partial role in the association of cardiovascular risk burden with dementia [5,6].

In 2010, the American Heart Association (AHA) proposed "Cardiovascular Health" (CVH), also known as "Life's Simple 7" (LS7), which contained three health behavior metrics (smoking, diet, and physical activity) and four health factor metrics (body mass index [BMI], total cholesterol, blood pressure, and fasting plasma glucose) to define and set goals for CVH promotion and CVD reduction [7]. In 2017, AHA put forward a suggestion to choose LS7 to define optimal brain health [8]. In 2022, AHA updated the LS7 to the "Life's Essential 8" (LE8), which included "sleep" as the fourth health behavior metric for CVH assessment [9]. Subsequently, a large number of studies have shown that optimal CVH, as defined by LS7 or LE8, is not only associated with a lower risk of CVD but also dementia [10–12]. Despite this, it is worth mentioning that neither LS7 nor LE8 has considered the role of psychological health, although the importance of psychological health has been affirmed by the Advisory of LE8 [9]. In 2024, psychological health was brought forward as a crucial component of CVH, hence renewed LE8 to "Life's Crucial 9" (LC9), and the 4-item Patient Health Questionnaire (PHQ-4) was recommended as its assessment tool [13].

To date, no studies have yet explored the longitudinal associations of the newly launched LC9 score with the risk of incident CVD and dementia, and the impact of including a ninth metric for psychological health on the predictive performance of the CVH has yet to be determined. Therefore, this study aims to investigate the associations of CVH assessed by LC9 with risks of incident CVD and dementia, and determine whether LC9 has a higher discrimination ability than LE8 in predicting CVD and dementia.

2. Methods

2.1. Study design and participants

This cohort study used data from the UKB, which is a large-scale biomedical database and research resource. A total of 502,411 participants aged 40–-69 years lived within 25 miles of 1 of 22 assessment centers located throughout England, Wales, and Scotland were recruited from 2006 to 2010 for baseline assessment. The UKB collected extensive phenotypic and genotypic details about its participants' sociodemographic, physical, lifestyle, and health-related information using questionnaires, physical measurements, biological sample assays, and other approaches. More detailed information can be found on the UKB website [14]. The UKB study had received a Research Tissue Bank approval from the National Health Service (NHS) North West Multicenter Research Ethical Committee, and all participants provided written informed consent before baseline data collection. Our study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guideline.

2.2. Ascertainment of LE8 and LC9

LC9 consists of LE8 and psychological health [13]. LE8 were divided into two dimensions (health behaviors and health factors) and created by eight components: diet, physical activity, tobacco/nicotine exposure, sleep, body mass index, blood lipids, blood glucose, and blood pressure [9]. Diet information which included consumption of fruit, vegetables, whole grains, nuts and legumes, low-fat dairy, sweetened beverages, red and processed meat, and sodium was collected from 24-h dietary recalls (1–5 times) conducted using the Oxford WebQ between 2009 and 2012 [15,16]. We excluded 24-h dietary assessments where participants reported that their diet for that day was not typical because of fasting, illness, or other reasons. Besides, sodium intake was estimated using a formula derived from the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) study [17]. Physical activity (minutes of moderate or vigorous physical activity per week), tobacco/nicotine exposure (combustible tobacco use and secondhand smoke exposure), and sleep (sleep duration per night) were collected by touchscreen questionnaires. Height and weight were measured at baseline after participants removed their shoes and heavy outer clothing. BMI was calculated as weight in kilograms divided by height in square meters. The measurement of serum cholesterol and glycated hemoglobin was performed at the central laboratory. Non-high-density lipoprotein cholesterol was calculated by total cholesterol minus high-density lipoprotein cholesterol, both of which were measured using the Beckman Coulter AU5800. Hemoglobin A1c (HbA1c) was measured using HPLC analysis on a Bio-Rad VARIANT II Turbo [18]. Participants were considered to have diabetes if they had any of the following: elevated HbA1c levels ($\geq$6.5 %), use of glucose-lowering medications, and self-reported history of diabetes [19]. Diabetes score was calculated according to both diabetes status and HbA1c levels. Blood pressure was determined by calculating the mean value of two assessments. Drug information was collected by self-reported using cholesterol-lowering or blood pressure medications. Scores of blood lipids and blood pressure would subtract 20 points if measurements were drug-treated levels.

Information about psychological health was collected by the PHQ-4 questionnaire, which consists of two depression items and two anxiety items: "frequency of depressed mood", "frequency of unenthusiasm/disinterest", "frequency of tenseness/restlessness", "frequency of tiredness/lethargy" using a four-point Likert scale from 0 (not at all) to 3 (nearly every day) [20]. The total score ranges from 0 to 12. According to clinical practice, a total score of $\geq$3 on either the depression or anxiety items was considered as presence of that condition, while total scores of $\geq$6 and $\geq$9 trigger "yellow flag (need detailed clinical interview)" and "red flags (presence of a depression and/or anxiety)" respectively [21].

According to the AHA's recommendations, each LE8 component scores ranging from 0 to 100 points [9], hence we assigned the psychological health score on a percentage scale according to the threshold

value of the PHQ-4 questionnaire [21]. The overall LC9 score was the nine metrics' mean value and also ranged from 0 to 100 points. We categorized the overall LC9 score into low (LC9 score <50), moderate (50 ≤ LC9 score <80), and high (LC9 score ≥80) levels [9]. More details and scoring algorithms are presented in Supplementary Tables S1-S3.

2.3. Ascertainment of cardiovascular disease and dementia

In this analysis, the most recent follow-up was conducted on December 31, 2022. Ascertainment of CVD, which included myocardial infarction (MI) and stroke, and dementia were based on self-reported data, hospital inpatient records, and death register records in the UKB cohort study [22]. More information is detailed in Supplementary Table S4.

2.4. Covariates

According to previous literature [23,24], we choose the following indicators as covariates: age, sex(male or female), race/ethnicity (White or other ethnicity), level of education (higher or not according to a college or university degree or other professional qualifications), current drinking (at least once per week or not) all of which were collected by NHS records or touchscreen questionnaires. The status of apolipoprotein E4 (ApoE4) (carrier, non-carrier, or untyped) was defined according to genomic data. Further comprehensive details about the covariates are presented in Supplementary Table S5.

2.5. Statistical analysis

The baseline characteristics of 289,649 participants were presented as the mean with standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. As appropriate, the comparison of baseline characteristics among the three groups was tested via ANOVA or χ^2 test.

The associations of the CVH category (low, moderate, high) with the risk of incident CVD and dementia were investigated by using Cox proportional hazard model. The time scale was defined as years between baseline to outcome, death, or follow-up, whichever came first. A fully adjusted model was constructed to account for possible confounding factors: age, sex, race/ethnicity, educational level, and alcohol consumption; the association with dementia was additionally adjusted for ApoE4 status. To estimate the population-level attributable risk (PAR) to CVH and its components, the adjusted PAR% comparing high (≥80 points) to intermediate or low (<80 points) was calculated to estimate the proportion of cases that could be prevented if all participants achieved high scores. We also performed Cox regression to investigate the association of 10-point increments in CVH score with the risk of incident CVD and dementia. All results were displayed as hazard ratios (HRs) with 95 % confidence intervals (CIs).

The area under the curve (AUC) analysis, which was used to produce Harrell concordance statistic (C-statistic), was calculated to compare the predictive performance of LE8 and LC9 scores. Additionally, as the C-statistic may lack sensitivity to meaningful improvements when the C-statistic of the LE8 score was already high, we applied net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to determine the discriminative performance of the LE8 and LC9 scores for predicting risk of incident CVD and dementia [25,26]. The predicted risk for each participant was calculated by using the significant coefficients from the final Cox model including the LE8 or LC9 category separately [27], we then stratified all participants into three risk groups according to the two predicted risk indexes separately [26].

Subgroup and sensitivity analyses were also conducted. First, we conducted subgroup analyses to examine the associations of LC9 with incident CVD and dementia stratified by sex (female, male), age (<65 years, ≥65 years), ethnicity (white, non-white), higher level of education (yes, no), current drinking (yes, no), ApoE4 carrier (yes, no) to distinguish potential modifying factors. Second, we reperformed the main analysis by treating MI and stroke as separate outcomes. Third, we examined the association of the LC9 category with the risk of incident CVD and dementia, treating death as a competing event. Fourth, we excluded participants who were diagnosed with CVD or dementia within two years since baseline to avoid possible reversal causality.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute). Analysis was two-sided, with a threshold of statistical significance set at 0.05. Data were analyzed from June to November 2024.

3. Results

3.1. General characteristics of participants

Supplementary Figure S1 demonstrates the flowchart of participant selection in our study. A total of 502,411 participants were recruited at baseline; after excluding those having no available data on variables that were used to calculate scores of LC9 ($n = 202,560$), with baseline CVD ($n = 10,128$) or dementia ($n = 74$), we finally included 289,649 participants in the primary analysis and divided them into three groups according to their LC9 score: Low ($n = 10,235$), Moderate ($n = 218,099$), and High ($n = 61,315$) [9].

The mean (SD) age was 56.6 (8.1) years, 137,480 (47.5 %) were male, and 277,273 (95.7 %) were white. The mean (SD) value of the total LC9 score was 70.7 (11.0). Table 1 illustrates the baseline characteristics categorized by levels of CVH assessed by the LC9 score. Participants with higher levels of CVH were more likely to be younger, female, and have a higher level of education.

3.2. Associations of CVH assessed by LE8 or LC9 with incident CVD and dementia

Over a median follow-up of 12.9 years (interquartile range [IQR]: 12.1–13.8 years), a total of 15,879 incident CVD cases, which included 10,008 MI cases and 6533 stroke cases, and 4455 incident dementia cases were observed.

Tables 2 and 3 present the HRs and p values of Cox proportional hazard models. Compared with participants having a low level of LE8, those having moderate or high LE8 had lower risks of incident CVD (moderate: 0.54 [0.52–0.56]; high: 0.30 [0.28–0.32]; p for trend <0.001) and dementia (moderate: 0.69 [0.63–0.76]; high: 0.55 [0.48–0.63]; p for trend <0.001) after multivariate adjustment. Similarly, compared with participants having a low category of LC9, those having moderate or high LC9 had lower risks of incident CVD (moderate: 0.46 [0.43–0.48]; high: 0.25 [0.23–0.27]; p for trend <0.001) and dementia (moderate: 0.57 [0.50–0.64]; high: 0.45 [0.39–0.52]; p for trend <0.001) after full adjustment. The risk of incident CVD decreased by 25 % (24 %−26 %) and 27 % (26 %−28 %), respectively, for a 10-point increase in the LE8 and LC9 score in the fully adjusted Cox regression model, and the risk of incident dementia decreased by 12 % (10 %−15 %) and 15 % (12 %−17 %) respectively. The adjusted PAR % of high versus low or moderate overall LE8 and LC9 scores with CVD were respectively 43.9 % (40.6 %−47.1 %) and 41.2 % (38.3 %−43.9 %), and the adjusted PAR % with dementia were respectively 19.9 % (12.1 %−27.1 %) and 18.8 % (12.4 %−24.8 %).

Supplementary Figures S2-S3 present the associations of CVH components with incident CVD and dementia. Increasing the 10-point score of psychological health can decrease CVD risk by 8 % (7 %−9 %) and dementia risk by 10 % (8 %−12 %) after multivariate adjustment, ranked second after blood glucose among all the nine components. The adjusted PAR % of psychological health for CVD and dementia were 5.3 % (4.6 %−6.0 %) and 7.6 % (6.2 %−9.1 %), ranked sixth and third, respectively.

Table 1
Baseline characteristics of participants according to LC9 category.

	Total	Low (0–49 Points)	Moderate (50–79 Points)	High (80–100 Points)	*P*-for-Difference Value
N (%)	289,649 (100)	10,235 (3.5)	218,099 (75.3)	61,315 (21.2)	
Age (years), mean (SD)	56.6 ± 8.1	56.2 ± 7.6	57.2 ± 7.9	54.3 ± 8.3	<0.001
Sex					<0.001
Male	137,480 (47.5)	6121 (59.8)	112,646 (51.7)	18,713 (30.5)	
Female	152,169 (52.5)	4114 (40.2)	105,453 (48.3)	42,602 (69.5)	
Race/Ethnicity					<0.001
White	277,273 (95.7)	9651 (94.3)	208,626 (95.7)	58,996 (96.2)	
Others	12,376 (4.3)	584 (5.7)	9473 (4.3)	2319 (3.8)	
Higher education					<0.001
Yes	149,468 (51.6)	3373 (33.0)	106,614 (48.9)	39,481 (64.4)	
No	140,181 (48.4)	6862 (67.0)	111,485 (51.1)	21,834 (35.6)	
Current drinking					<0.001
Yes	209,220 (72.2)	6121 (59.8)	157,851 (72.4)	45,248 (73.8)	
No	80,429 (27.8)	4114 (40.2)	60,248 (27.6)	16,067 (26.2)	
ApoE4 carrier					<0.001
Yes	69,156 (23.9)	2388 (23.4)	53,135 (24.4)	13,633 (22.2)	
No	174,332 (60.2)	5725 (55.9)	130,027 (59.6)	38,580 (62.9)	
Untyped	46,161 (15.9)	2122 (20.7)	34,937 (16.0)	9102 (14.8)	
LC9 score, mean (SD)					
Total score	70.7 ± 11.0	44.4 ± 4.9	67.9 ± 7.4	85.2 ± 4.2	<0.001
Health behaviors score	70.7 ± 15.7	38.7 ± 12.4	68.2 ± 13.7	85.0 ± 8.9	<0.001
Diet score	42.6 ± 32.4	14.7 ± 21.6	37.4 ± 30.9	65.7 ± 26.6	<0.001
PA score	76.8 ± 36.1	24.4 ± 36.2	74.5 ± 37.0	93.8 ± 17.4	<0.001
Sleep score	89.9 ± 18.1	70.1 ± 27.6	89.2 ± 18.3	95.6 ± 11.3	<0.001
Nicotine exposure score	73.5 ± 28.2	45.5 ± 36.8	71.7 ± 28.4	84.8 ± 19.3	<0.001
Health factors score	64.8 ± 15.6	43.8 ± 11.9	61.0 ± 12.9	82.1 ± 10.4	<0.001
BMI score	70.1 ± 28.1	35.3 ± 26.7	65.9 ± 27.4	90.8 ± 15.6	<0.001
Blood lipids score	47.4 ± 29.2	28.8 ± 26.3	42.7 ± 27.1	67.4 ± 27.6	<0.001
Blood glucose score	99.1 ± 7.3	93.2 ± 20.7	99.2 ± 6.9	99.9 ± 2.0	<0.001
Blood pressure score	42.5 ± 33.7	17.9 ± 25.8	35.8 ± 30.8	70.5 ± 29.0	<0.001
Psychological health score	94.6 ± 17.2	69.8 ± 36.6	94.7 ± 16.7	98.5 ± 8.0	<0.001

Abbreviations: LC9, life's crucial 9; SD, standard deviation; ApoE4, apolipoprotein E4; PA, physical activity; BMI, body mass index.
Note: ANOVA and $\chi 2$ test were used to test the differences among categories for continuous and categorical variables, respectively.

Table 2
Associations of CVH category with incident cardiovascular disease.

Cardiovascular disease	No. of events / No. of participants (%)	Unadjusted		Full-adjusted*		
		HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	PAR % (95 % CI) ‡
Life's Essential 8						43.9 (40.6–47.1)
Low	2273/20,673 (11.0 %)	Ref	/	Ref	/	
Moderate	12,590/221,570 (5.7 %)	0.49 (0.47–0.52)	<0.001	0.54 (0.52–0.56)	<0.001	
High	1016/47,406 (2.1 %)	0.18 (0.17–0.20)	<0.001	0.30 (0.28–0.32)	<0.001	
P for trend†	/	/	<0.001	/	<0.001	
Per 10-point increase	/	0.69 (0.68–0.70)	<0.001	0.75 (0.74–0.76)	<0.001	
Life's Crucial 9						41.2 (38.3–43.9)
Low	1293/10,235 (12.6 %)	Ref	/	Ref	/	
Moderate	13,125/218,099 (6.0 %)	0.45 (0.43–0.48)	<0.001	0.46 (0.43–0.48)	<0.001	
High	1461/61,315 (2.4 %)	0.17 (0.16–0.19)	<0.001	0.25 (0.23–0.27)	<0.001	
P for trend†	/	/	<0.001	/	<0.001	
Per 10-point increase	/	0.68 (0.67–0.69)	<0.001	0.73 (0.72–0.74)	<0.001	

Abbreviations: HR, hazard ratio; CI, confidence interval; PAR, population-level attributable risk.
* Adjusted for age, sex, race/ethnicity, level of education, alcohol consumption.
† Tests for linear trends were performed by entering the median value of each category as a continuous variable in the models.
‡ The adjusted PAR % was calculated by comparing high (≥80 points) to intermediate or low (<80 points).

3.3. Effect of adding psychological health to LE8 for predicting risk of incident CVD and dementia

AUC analysis indicated that both the LE8 and LC9 score achieved outstanding discriminative performance for predicting the risk of CVD (LE8 Harrell C-statistic= 0.7138 vs. LC9 Harrell C-statistic=0.7144, $p = 0.136$) and dementia (LE8 Harrell C-statistic = 0.8158 vs. LC9 Harrell C-statistic = 0.8161, $p = 0.065$). Reclassification tables are presented in Supplementary Tables S6-S7. The NRI and IDI were 0.07 % ($p = 0.749$) and 0.009 ($p < 0.001$) for predicting incident CVD; and were −0.08 % ($p = 0.692$) and 0.004 ($p = 0.017$) for incident dementia.

3.4. Subgroup and sensitivity analysis

Results of subgroup analysis are displayed in Figs. 1–2. We identified that sex, age, and alcohol consumption modified associations of LC9 with CVD (p for interaction < 0.001); participants who were female, younger than 65 years old, and didn't drink benefited more from an increase of 10 points in their LC9 score. Age (p for interaction = 0.002) and ApoE4 status (p for interaction < 0.001) modified associations of LC9 with dementia, participants of younger ages and non-carrier of ApoE4 benefited more.

When treating MI and stroke as separate outcomes, we found that higher LC9 scores were associated with decreased risks of both MI and

Table 3
Associations of CVH category with incident dementia.

Dementia	No. of events / No. of participants (%)	Unadjusted		Full-adjusted*		
		HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	PAR % (95 % CI) ‡
Life's Essential 8						19.9 (12.1–27.1)
Low	467/20,673 (2.3 %)	Ref	/	Ref	/	
Moderate	3621/221,570 (1.6 %)	0.71 (0.64–0.78)	<0.001	0.69 (0.63–0.76)	<0.001	
High	367/47,406 (0.8 %)	0.33 (0.29–0.38)	<0.001	0.55 (0.48–0.63)	<0.001	
P for trend†	/	/	<0.001	/	<0.001	
Per 10-point increase	/	0.80 (0.78–0.82)	<0.001	0.88 (0.85–0.90)	<0.001	
Life's Crucial 9						18.8 (12.4–24.8)
Low	254/10,235 (2.5 %)	Ref	/	Ref	/	
Moderate	3672/218,099 (1.7 %)	0.66 (0.58–0.75)	<0.001	0.57 (0.50–0.64)	<0.001	
High	529/61,315 (0.9 %)	0.34 (0.29–0.39)	<0.001	0.45 (0.39–0.52)	<0.001	
P for trend†	/	/	<0.001	/	<0.001	
Per 10-point increase	/	0.79 (0.77–0.81)	<0.001	0.85 (0.83–0.88)	<0.001	

Abbreviations: HR, hazard ratio; CI, confidence interval; PAR, population-level attributable risk.
* Adjusted for age, sex, race/ethnicity, level of education, alcohol consumption, ApoE4 status.
† Tests for linear trends were performed by entering the median value of each category as a continuous variable in the models.
‡ The adjusted PAR % was calculated by comparing high (≥80 points) to intermediate or low (<80 points).

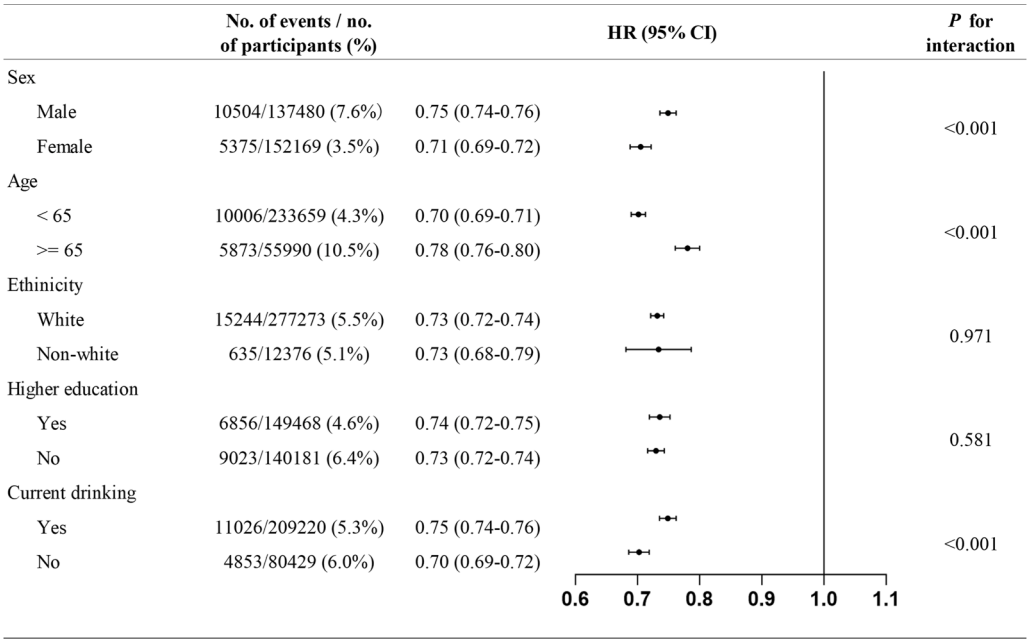

Fig. 1. Subgroup analysis of the association between 10-point increase of LC9 score and incident cardiovascular disease.Abbreviation: ApoE4, apolipoprotein E4; CI: confidence interval; HR: hazard ratio
Forest plots displaying hazard ratios and 95 % confidence intervals for cardiovascular disease with 10-point increase of LC9 score.Analyses were adjusted for age, sex, race/ethnicity, level of education, and alcohol consumption, except where an adjusting variable itself was being tested, by using Cox proportional hazards models.

stroke, and the strength of association with incident MI appeared to be stronger than that of stroke. (*P* values for *Z*-tests are all <0.001) (Supplementary Tables S8-S10). There was still no improvement in the discriminative performance of LC9 for either MI or stroke (Supplementary Tables S11-S12). When treating the death as a competing event, associations of LC9 with incident CVD and dementia remain stable (Supplementary Table S13). After excluding participants who were diagnosed with incident CVD or dementia within two years since baseline, the results were consistent with the primary analysis (Supplementary Tables S14-S15).

4. Discussion

In this large longitudinal cohort study of 289,649 UKB participants, we observed that a higher score of LC9 was associated with lower risks of incident CVD and dementia after multiple adjustments. Participants who were female, younger, and did not drink had a lower risk of CVD; those younger ones and non-carrier of ApoE4 had a lower risk of dementia. Although the inclusion of a ninth metric for psychological health lowered more risks compared with LE8, it did not improve the predictive performance of CVH for predicting incident CVD or dementia.

As far as we know, the present study was the first to explore the association of the newly launched LC9 with the risks of incident CVD and dementia. Our findings were in line with previous findings regarding associations of CVH assessed by LS7 or LE8. A cohort study including 32,896 American adults found that elevating 10 points in LE8 may decrease the risk of incident CVD by 22 %−40 % [28]. A dose-response meta-analysis consisted of fourteen publications with

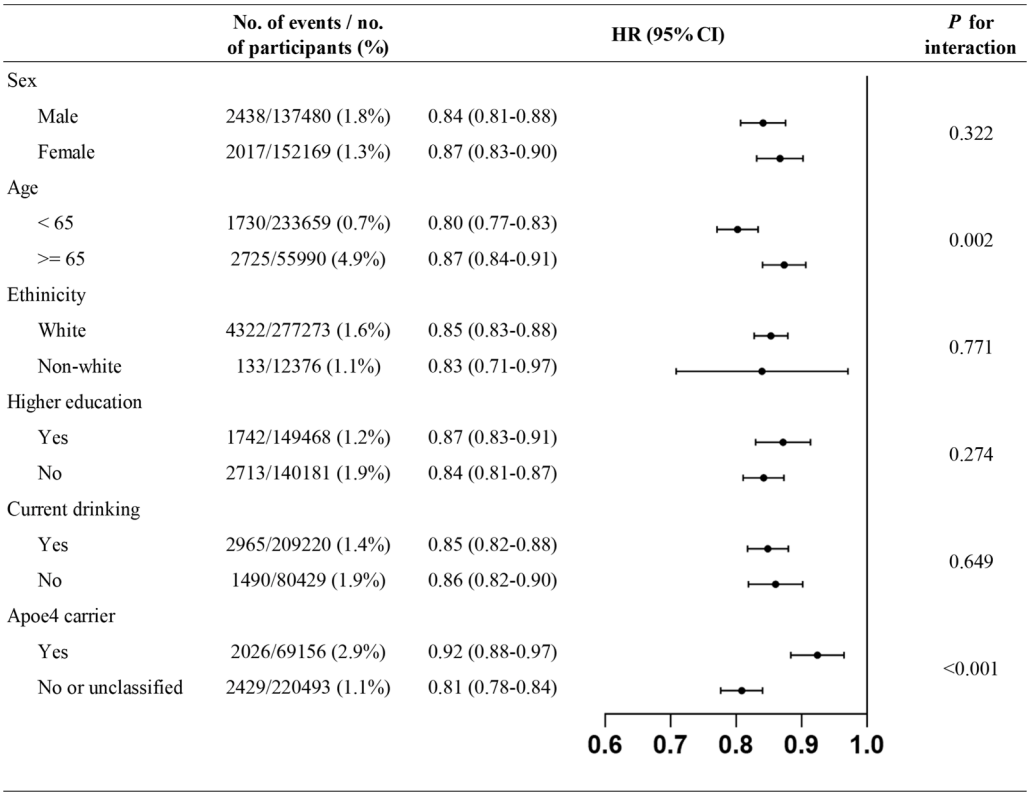

Fig. 2. Subgroup analysis of the association between 10-point increase of LC9 score and incident dementia. Abbreviation: ApoE4, apolipoprotein E4; CI: confidence interval; HR: hazard ratio

Forest plots displaying hazard ratios and 95 % confidence intervals for dementia with 10-point increase of LC9 score.Analyses were adjusted for age, sex, race/ethnicity, level of education, alcohol consumption, and ApoE4 status, except where an adjusting variable itself was being tested, by using Cox proportional hazards models.

longitudinal design from six European and eight North American countries, resulting in a final sample of 311,654 participants with 8006 incident dementia cases, found a considerable effect of favorable LS7 score on reduced risk of incident dementia in older adults [11]. Another study found that higher LE8 scores were associated with lower dementia risk, better cognitive performance, and larger total brain and hippocampal volumes [29]. There were also other potential advantages of LC9 in contexts other than CVD or dementia. A cohort study found that improving the LE8 score could reduce risks of 25 common non-communicable chronic diseases, including those in the digestive system, mental and behavioral disorders, and cancer [30]. Therefore, further studies are warranted to determine whether the LC9 could enhance the prevention of these diseases.

Psychological health is a crucial component of CVH and is equally essential for dementia prevention. When AHA updated its LE8 approach for maintaining CVH in a Presidential Advisory that added sleep as an 8th component to its previous LS7, the writing group also pointed out that psychological health was foundational in achieving optimal and equitable CVH in the population [9]. DALYs of depressive disorders will increase from 502.9 million in 2022 to 681.9 million in 2050; anxiety disorders will increase from 362.4 million to 447.5 million [3]. Prior study found that depression and anxiety were associated with CVH [31]. Depression was included as one of the 14 modifiable risk factors of dementia by the Lancet Commission on Dementia Prevention, Intervention and Care [4]. Studies also found that anxiety was associated with increased risks of cognitive impairment and dementia [32,33]. Our study observed that elevating 10 points in psychological health, which mainly included depression and anxiety as recommended [13], could respectively decrease risks of CVD and dementia by 8 % and 10 %, ranked second, with blood glucose being the first, among all nine components, demonstrating the importance of psychological health in CVH, as already pointed by the AHA Presidential Advisory.

However, the inclusion of psychological health did not improve the CVH's performance in predicting the risk of CVD and dementia. The observed Harrell C-statistic did not increase substantially, which is quite understandable given the initial C-statistic of LE8 is already high [25]. We therefore performed a reclassification analysis and calculated IDI, which were more suitable for evaluating the added predictive ability of a new marker [26]. The NRI was not significant for either CVD or dementia. Although the IDI was statistically significant, the change of magnitude was very slight. Taken together, it seems that, adding psychological health into CVH's evaluation criteria did not substantially escalate its discrimination ability in predicting the risk of CVD or dementia. This may be caused by the fact that participants in our study had overall high scores of psychological health, causing few participants with the low category of psychological health, which could limit estimating the improvement of adding psychological health for prediction.

In compatible with previous studies showing that the associations of LE8 score with incident CVD and dementia were more robust in people younger than 60 years old [34,35], we observed that the associations of a 10-point increase in LC9 score with the risks of incident CVD and dementia were also more significant among younger participants, highlighting the significance of early prevention. Our study was also consistent with prior studies reporting that the inverse association between LE8 score and CVD was more pronounced in female participants [35,36]. Moreover, we found that people who do not regularly drink could benefit more from enhancing their LC9 score against CVD incidence, this may be because alcohol consumption uniformly increases blood pressure and stroke risk [37]. Our study also observed that in both ApoE4 carriers and non-carriers, a higher LC9 score was related to a lower risk of dementia, suggesting that even for people with genetic susceptibility to dementia, maintaining an ideal LC9 could be beneficial

in reducing future risk of dementia [38].

The first strength of our study was the long-term follow-up duration and large sample size, which provided adequate statistical power to examine the association of LC9 with the risk of developing CVD and dementia. Second, we algorithmically defined health outcomes using a standardized approach that included self-reported data, hospital inpatient records, and mortality register data, resulting in a high positive predictive value of CVD and dementia [22]. Third, we compared the predictive performance of LC9 with LE8 by using not only Harrell C-statistic but also NRI and IDI, resulting in a more comprehensive evaluation of the predictive performance of LE8 and LC9.

The present study also has several limitations. First, a causal relationship cannot be confirmed because this is an observational study. Second, although we have adjusted for a range of potential confounders, residual confounding might still exist. For instance, social determinants of health are known to accumulate and interact throughout the life course, influencing the development of dementia [39]. However, due to the unavailability of certain data in the UKB, we were unable to fully account for the potential role of these factors in the prevention of CVD and dementia, and this may bias our results. Third, 95.7 % of the total participants were white ethnicity, therefore, the study sample's representativeness is weakened, and the generalization of our findings should be cautious. Fourth, our study's ascertainment of health behaviors derived from self-reported information may inevitably cause recall bias. Fifth, our study used a baseline score of LC9 to predict the risk of later-life CVD and dementia, which may fail to capture the long-term change of LC9 across the life course and bias the results. Sixth, 202,560 participants with incomplete LC9 data were excluded. Their baseline characteristics were significantly different from the analytical sample (Supplementary Table S16), potentially introducing selection bias that limits both the internal and external validity of the present findings. Therefore, the generalization of the present findings requires caution. Seventh, incorporating self-reported data into algorithmically defined health outcomes might induce reporting bias. Eighth, the follow-up period was not enough to identify dementia cases given that the analytical sample was relatively young. Further studies with longer follow-up periods are warranted. Ninth, although the PHQ-4 scale is an efficient tool to screen for depression and anxiety, its symptom assessment is very brief and limited, which might be subject to the potential for underreporting of symptoms and therefore bias the results. Further studies with more comprehensive psychological health assessment are needed to validate the present findings.

5. Conclusions

In this prospective cohort study of 289,649 UKB participants with a median follow-up of 12.9 years, we observed that a higher LC9 score was significantly associated with lower risks of CVD and dementia. Although psychological health is essential for preventing CVD and dementia, including it assessed with PHQ-4 questionnaire into CVH's evaluation criteria did not substantially improve the discrimination ability of CVH for predicting incident CVD or dementia.

CRediT authorship contribution statement

Yiwen Dai: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuling Liu:** Writing – review & editing. **Yang Pan:** Writing – review & editing. **Jingya Ma:** Writing – review & editing. **Jie Liang:** Writing – review & editing. **Wenya Zhang:** Writing – review & editing. **Xuyang Diao:** Writing – review & editing. **Menghan Zhu:** Writing – review & editing. **Xinqing Yang:** Writing – review & editing. **Darui Gao:** Writing – review & editing. **Yanyu Zhang:** Writing – review & editing. **Mengmeng Ji:** Writing – review & editing. **Yichi Zhang:** Writing – review & editing. **Wuxiang Xie:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Fanfan Zheng:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of interests

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

Acknowledgements

We appreciate efforts made by the original data creators, depositors, copyright holders, the funders of the data collections, and their contributions for access to data from the UK Biobank, approved project number 90492.

Source of funding

This study was supported by grants from the National Natural Science Foundation of China (82373665), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2021-RC330-001), and the 2022 China Medical Board-open competition research grant (22-466).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100273.

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