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Metabolite Signature of Life's Essential 8 and Risk of Coronary Heart Disease among Low-Income Black and White Americans

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Abstract

Background: Life's Essential 8 (LE8) is a comprehensive construct of cardiovascular health. Yet, little is known about the LE8 score, its metabolic correlates, and their predictive implications among Black Americans and low-income individuals.

Methods: In a nested case-control study of coronary heart disease (CHD) among 299 pairs of Black and 298 pairs of White low-income Americans from the Southern Community Cohort Study, we estimated LE8 score and applied untargeted plasma metabolomics and elastic net with leave-one-out cross-validation to identify metabolite signature (MetaSig) of LE8. Associations of LE8 score and MetaSig with incident CHD were examined using conditional logistic regression. Mediation effect of MetaSig on the LE8-CHD association was also examined. The external validity of MetaSig was evaluated in another nested CHD case-control study among 299 pairs of Chinese adults.

Results: Higher LE8 score was associated with lower CHD risk [standardized OR=0.61 (95% CI: 0.53–0.69)]. The MetaSig, consisting of 133 metabolites, showed significant correlation with LE8 score (r=0.61) and inverse association with CHD [OR=0.57 (0.49–0.65)], robust to adjustment for LE8 score and across participants with different sociodemographic and health

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Authors' contributions: D.Y. designed the study. K.D. analyzed the data. K.D. drafted the manuscript, D.K.G., X.-O.S., L.L., W.Z., V.E.T., H.C, Q.C., T.J.W., and D.Y. provided critical revisions of the manuscript for important intellectual content. All authors contributed to the interpretation of the data and approved the final version of the manuscript. D.Y. is the guarantor of the work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures: None

Supplemental Materials:
Supplemental Methods
Supplemental Tables I–VI
Supplemental Figures I–IV
References[49–68]

status (ORs: 0.42–0.69; all $P<0.05$). MetaSig mediated a large portion of the LE8-CHD association: 53% (32%−80%). Significant associations of MetaSig with LE8 score and CHD risk were found in validation cohort [$r=0.49$; OR=0.57 (0.46–0.69)].

Conclusions: Higher LE8 score and its MetaSig were associated with lower CHD risk among low-income Black and White Americans. Metabolomics may offer an objective measure of LE8 and its metabolic phenotype relevant to CHD prevention among diverse populations.

Keywords

Life's Essential 8; Cardiovascular Health; Coronary Heart Disease; Multi-racial Population; Metabolomics

Introduction

Coronary heart disease (CHD) is a leading cause of morbidity and mortality in the United States (US) and worldwide, with significant and persistent sociodemographic disparities[1,2]. To reduce the burden and life lost due to CHD and other cardiovascular diseases (CVD), the American Heart Association (AHA) has recently proposed Life's Essential 8 (LE8) to assess and promote cardiovascular health (CVH) in individuals and populations[3]. LE8 includes 4 health behaviors (healthy diet, participation in physical activity, avoidance of nicotine, and healthy sleep [a new component]) and 4 health factors (weight, blood lipids, glucose, and blood pressure), and has a new scoring system with continuous scale to better reflect inter-individual differences. While a higher LE8 score has been recently associated with lower CVD incidence and mortality[4–7], few studies have evaluated the LE8 score and its association with incident CHD or CVD among Black and White Americans who have low socioeconomic status (SES) and face disproportionate disease burdens. In addition, although some potential mechanisms have been identified (eg, reduced inflammation and atherosclerosis)[8,9], beyond those known CVD risk pathways, mechanisms and inter-individual differences underlying the cardioprotective effects of LE8 and its included health behaviors and health factors are not fully understood.

Metabolite profiling ("metabolomics") comprehensively measures small-molecule metabolites in biological samples and represents a powerful tool for mechanistic investigation, novel biomarker discovery, and precision medicine[10,11]. Metabolite profiling of blood samples may improve assessments of individuals' alignment with LE8, particularly for behavioral factors that are prone to survey and recall biases. In addition, circulating metabolites related to LE8 may capture varied individual metabolic responses to LE8, providing novel mechanistic insights into its cardioprotective effects and informing precision medicine. While previous studies have identified metabolites related to the components of LE8, including diet[12–16], physical activity[17–19], tobacco exposure[20–22], sleep[23–26], and body mass index (BMI)[27,28], to our knowledge, no study has applied untargeted plasma metabolomics to identify a comprehensive metabolite signature (MetaSig) for LE8 to enable studies with incident CHD. Given that those health behaviors and factors often correlate and interact with each other, investigating whether plasma metabolomics could provide a good objective assessment of individuals' alignment with and metabolic responses to overall LE8 and uncovering potential pathways linking LE8 to incident CHD is highly warranted.

Here, leveraging a case-control study of CHD nested within the Southern Community Cohort Study (SCCS) involving 598 Black Americans (299 case-control pairs) and 596 White Americans (298 pairs), we assessed LE8 score and its MetaSig and examined their relations with incident CHD. The results were further replicated in another nested CHD case-control study of racially and geographically different populations: 598 Chinese adults (299 pairs) from the Shanghai Women's Health Study and Shanghai Men's Health Studies (SWMHS). In addition, we identified MetaSigs for the health behaviors and health factors recommended in the LE8 and evaluated their associations with incident CHD.

Methods

An overview of our study design is presented in Fig. I in the Data Supplement. Detailed methods are available in the Data Supplement. The SCCS was approved by the Institutional Review Boards of the Vanderbilt University Medical Center and Meharry Medical College; the SWMHS was approved by the Vanderbilt University Medical Center and Shanghai Cancer Institute. Informed consent was obtained from all enrolled participants. The data and code that support the findings of the present study are available upon request and approval by the Data Use Committees of the Southern Community Cohort Study (https://www.southerncommunitystudy.org/) and Shanghai Women's Health Study & Shanghai Men's Health Study (https://swhs-smhs.app.vumc.org/index.php).

Results

Baseline characteristics of study participants

The mean age at baseline (blood collection) was 55 years in our study participants (Table 1). The mean (SD) of LE8 score was 48.1 (12.3) in Black women, 50.0 (13.6) in Black men, 48.1 (13.4) in White women, and 48.5 (14.4) in White men. The median follow-up time for incident CHD cases was 5 (interquartile range: 3–8) years in SCCS. Incident CHD cases had significantly lower total LE8 score, health behaviors score, and health factors score than controls among subpopulations by race or sex (Fig. 1, Table 1, and Table II in the Data Supplement; all $P<0.05$ except for health behaviors score among male participants). The characteristics of participants in SWMHS (mean age: 61 years; mean LE8 score: 57.2 in women and 50.7 in men) are shown in Table III in the Data Supplement. There were moderate correlations between total LE8 score and individual component scores (r ranged from 0.22 with smoking to 0.47 with BMI and blood pressure scores in SCCS; Fig. II in the Data Supplement).

Metabolite signature of LE8

We identified 133 metabolites related to LE8 in elastic net regression model (top 30 are shown in Fig. 2A; the full list can be found in Table IV in the Data Supplement). We then constructed the MetaSig through a leave-one-out cross-validation approach. The MetaSig was significantly correlated with LE8 score ($r = 0.61$, $P<0.001$; Fig. 2B); meanwhile, variations in MetaSig were observed among individuals with the same LE8 score, demonstrating interindividual differences in metabolic phenotype of LE8. The MetaSig was then externally validated in SWMHS using the elastic net regression coefficients obtained

from the SCCS dataset. MetaSig was also correlated with LE8 score in SWMHS (r = 0.49, P<0.001; Fig. 2C). Stratified analyses showed that correlations between LE8 score and MetaSig were consistent regardless of age, sex, race, fasting status, diabetes status, hypertension status, dyslipidemia status, and incident CHD status (r ranged from 0.54 to 0.64; Table V in the Data Supplement), suggesting the robustness of our identified LE8 metabolite signature across participants with different sociodemographic backgrounds and metabolic disease status.

Associations with incident CHD

Higher LE8 score and its MetaSig were significantly associated with lower risk of CHD in conditional logistic regression models, adjusting for age, education, income, alcohol intake, and family history of CHD: standardized multivariable-adjusted odds ratio (OR) = 0.61 (95% CI: 0.53–0.69) for LE8 score and 0.57 (0.49–0.65) for MetaSig; both P<0.001 (Table 2). Sensitivity analysis showed that the MetaSig-CHD associations did not change after excluding any individual metabolites from the signature (Table VI in the Data Supplement). The MetaSig-CHD association did not change after excluding two drug metabolites (hydrochlorothiazide and metformin) from the MetaSig [OR (95% CI) = 0.55 (0.48–0.64); P<0.001]. Moreover, excluding 29 unknown metabolites (X-) from the MetaSig also did not change the MetaSig-CHD association [OR (95% CI) = 0.58 (0.50–0.66); P<0.001]. The scaled relative levels (Z-scores) of all 133 metabolites included in MetSig and their associations with incident CHD were shown in Table IV in the Data Supplement.

After further adjusting for LE8 score, the MetaSig-CHD association was only slightly attenuated [OR (95% CI) = 0.66 (0.55–0.78); P<0.001; Table 2], suggesting circulating metabolites may complement LE8 assessment and contribute to CHD risk beyond LE8 score. On the other hand, the LE8-CHD association was moderately attenuated after adjusting for MetaSig [OR (95% CI) = 0.78 (0.66–0.92), P=0.003]. Mediation analysis showed that MetaSig mediated a large portion of the LE8-CHD association [53% (32% −80%); $P_{mediation}$<0.001; Fig. 2D].

Both LE8 and its MetaSig were inversely associated with CHD risk in subpopulations by race, age group, education, income, diabetes status, hypertension status, and dyslipidemia status ($P_{interaction}$>0.05; Fig. 3), with stronger associations observed in women than in men [for LE8, OR (95% CI) = 0.53 (0.42–0.66) in women and 0.66 (0.55–0.80) in men, $P_{interaction}$=0.017; for MetaSig, 0.48 (0.38–0.6) in women and 0.65 (0.54–0.78) in men, $P_{interaction}$=0.016].

The association of MetaSig with incident CHD was replicated in SWMHS (Table 2), with OR (95% CI) = 0.57 (0.46–0.69) and 0.69 (0.55–0.86) after further adjusting for LE8 score (both P<0.001). The MetaSig also mediated a considerable portion of the LE8-CHD association in SWMHS [27.4% (10%−47%); $P_{mediation}$<0.001; Fig. 2E].

Metabolite signatures of health behaviors and health factors and associations with CHD

We further identified MetaSigs for health behaviors (Fig. IIIA in the Data Supplement) and health factors in SCCS (Fig. IVA in the Data Supplement; full lists of metabolites and their relative levels and associations with incident CHD are shown in Table IV in

the Data Supplement), which showed significant correlations with health behaviors score (r = 0.59, P<0.001; Fig. IIIB in the Data Supplement) and with health factors score (r = 0.76, P<0.001; Fig. IVB in the Data Supplement). Significant correlations were also found among participant subgroups (Table V in the Data Supplement), suggesting the robustness of identified metabolite signatures for health behaviors and health factors. In addition, there were significant inverse associations of health behaviors score, health factors score, and their related signatures with risk of CHD (all P<0.001; Table 2). Specifically, standardized OR (95% CI) was 0.73 (0.63–0.85) for health behaviors MetaSig and 0.57 (0.49–0.66) for health factors MetaSig. Similarly, metabolites mediated large portions of the health behaviors-CHD association [43.9% (13.9%−101%), P=0.004; Fig. IIID in the Data Supplement] and health factors-CHD association [53.2% (24.8%−89%), $P_{mediation}$<0.001; Fig. IVD in the Data Supplement]. Further, all results on health behaviors MetaSig and health factors MetaSig were replicated in SWMHS (Table 2, Fig. III and Fig. IV in the Data Supplement).

Discussion

Leveraging untargeted plasma metabolites data in a nested case-control study among low-income Black and White Americans, we identified a metabolite signature that could reflect LE8 score and was associated with incident CHD, even after adjusting for LE8 and among participants with varied sociodemographic and metabolic health status, suggesting that circulating metabolite profiling may be used to help assess LE8 alignment across diverse populations and offer additional information on CVH (eg, inter-individual metabolic phenotypes related to LE8). We also identified MetaSigs for health behaviors and health factors and found consistent results showing that circulating metabolites could reflect the alignment with those recommendations and underlying metabolic phenotypes, which were further linked to incident CHD across diverse populations. All the results were further replicated in another nested case-control study of CHD among Chinese adults. Our findings demonstrate the potential utility of blood metabolomics to improve the assessment of LE8 and its underlying metabolic variations that are linked to incident CHD among sociodemographically diverse populations, towards advancing precision medicine and addressing disparities in CVH.

LE8 is the American Heart Association's updated and enhanced guideline to measure and promote CVH for individuals and populations[3]. The beneficial associations of following the LE8 with lower risks of CHD, CVD, and related mortality have been demonstrated in recent studies[4–7]. However, multi-racial/ethnic populations with low SES remain underrepresented in research studies, even though they have persistently experienced worse CVH and CVD outcomes, as well as systemic disadvantages to improve CVH, than White and middle-class Americans[2,29–31]. Leveraging resources from SCCS, a large cohort of predominantly low-income Black and White Americans (in the present study: ~65% with household income <$15,000/y and ~95% with household income <$25,000/y), our study assessed CVH based on LE8 and evaluated the association of LE8 score with incident CHD. We found that a higher LE8 score (per SD increase) was associated with ~40–50% lower risk of CHD among Black Americans and individuals with low SES. While LE8 provides a comprehensive approach to quantify CVH, its assessment involves a series of procedures such as questionnaires, anthropometric and blood pressure measures, and

blood draw. Particularly, health behaviors (diet, physical activity, smoking, and sleep) are usually assessed by questionnaires, which are time-consuming and prone to measurement errors and low compliance (particularly in the clinical setting). Also, the LE8 score cannot capture varied individual metabolic responses to lifestyle exposures. Hence, we incorporated untargeted plasma metabolomics data and for the first time, identified a robust metabolite signature of LE8 and then examined its association with incident CHD.

Metabolomics has been demonstrated as a powerful tool for improving exposure assessment and identifying potential novel biomarkers and mechanistic pathways in population studies, given its high-throughput characterization of thousands of metabolites in a small amount of biological samples[32]. Our study provides new evidence that plasma metabolite profiling may provide objective and comprehensive measures of LE8 and CVH among racially and geographically diverse populations. The identified metabolite signature may complement LE8 scores, improve the precision to stratify individuals with different future CHD risks, and potentially facilitate personalized CHD prevention strategies.

Our identified MetaSig consists of metabolites reflecting participants' alignment with LE8 health behaviors and metabolic health status, majority of which are lipids and amino acids, and many of them have been linked to diet[12–16], physical activity[17–19], smoking[20–22], sleep[23–26], obesity[27,28,33], or composite lifestyles scores[34–37] in previous studies. For example, (2,4 or 2,5)-dimethylphenol sulfate, tartronate, and ethyl beta-glucopyranoside are derived from plant-based foods; cotinine is the major metabolite of nicotine from tobacco smoking; cholesterol, sphingomyelin, cortisol, and 1-palmitoleoylglycerolare are related to blood lipids; mannose, metformin, and fructosyllysine are related to prevalent diabetes and blood glucose. Particularly, drug metabolites, including hydrochlorothiazide and metformin, reflect antihypertensive and antidiabetic medications defined in LE8. Nevertheless, the associations of MetaSig with LE8 score and incident CHD were consistent among participants with or without history of hypertension or diabetes or after excluding those drug metabolites from the MetaSig. Notably, the MetaSig also contains microbial metabolites, eg, maltotetraose, anthranilate, indolebutyrate, and bile acids (taurohyocholate, glycodeoxycholate 3-sulfate, 3b-hydroxy-5-cholenoic acid, and glycohyocholate), suggesting the role of gut microbiome in host's CVH, which cannot be captured by questionnaires or measurements of glucose, cholesterol, or blood pressure. Moreover, several metabolic pathways related to CVH and CVD development were highlighted. For example, anthranilate, indolebutyrate, picolinate, and serotonin are members of tryptophan metabolism pathway[38–40]; taurohyocholate, glycodeoxycholate 3-sulfate, 3b-hydroxy-5-cholenoic acid, and glycohyocholate belong to secondary bile acid metabolism pathway[41,42]; alpha-tocopherol, delta-tocopherol, and gamma-tocopherol/beta-tocopherol are vitamin E derivatives through tocopherol metabolism pathway[43,44].

Importantly, the MetaSig was related to future CHD risk regardless of participants' age, sex, race, SES, metabolic disease history, and even after adjustment for LE8. Further analyses indicated that circulating metabolites could play a substantial mediating role linking LE8 and reduced CHD risk. Moreover, our findings were replicated in a racially and geographically different population, suggesting external validity and potential generalizability of our findings. Taken together, our findings demonstrated that circulating

metabolites could complement LE8 to improve the precision of CVH assessment and predict CHD risk among sociodemographically and geographically diverse populations.

To our knowledge, this is the first study that assessed the LE8 score, constructed its metabolite signature, and associated LE8 score and its MetaSig with incident CHD in Black and White Americans with low SES. Besides its novelty and inclusion of populations facing socioeconomic challenges and health disparities, other strengths of our study include its prospective design, comprehensive profiling of >1500 blood metabolites for a broad coverage and improved ability to construct metabolite signature for LE8, and robustness of results across populations with different sociodemographic and health status. Meanwhile, several limitations of our current study need to be acknowledged. First, as MetaSig of LE8 was identified using cross-sectional data from baseline blood samples, we cannot be certain as to the directionality of LE8-MetaSig association, and mediation analysis assumed that LE8 score preceded MetaSig. Although several population- or animal-based studies have shown the causal effects of LE8 components on blood metabolites[21,26,45–48], given that blood metabolites might precede some LE8 components, the longitudinal association between LE8 adherence and circulating metabolites should be investigated. Second, given the observational nature of our study, the causality is unable to be confirmed. However, the prospective design reduces the concern of reverse causation for the LE8/MetaSig-CHD association. Third, we cannot rule out the influence of residual confounding on the LE8/MetaSig-CHD association, although we have adjusted for and stratified by major CHD risk factors. Fourth, the concentrations of fasting glucose and HbA1c and SBP and DBP were not measured in SSCS; thus, glucose score and blood pressure score were defined based on history of diabetes or hypertension, use of medications, and relative levels of glucose measured in metabolites profiling, which may influence the accuracy of LE8 score. Also, Fig. 2B–C and residual plot suggested some bias of MetaSig at the extreme levels of LE8, i.e., potential overestimation at low LE8 while underestimation at high LE8, which seems to be a common problem of metabolite/biomarker signatures. Finally, the nested case-control design may overestimate the predictive ability of the LE8 score and its MetaSig. Therefore, our results should be further validated in other prospective cohort studies.

In summary, our study assessed the LE8 score and identified MetaSig of LE8 among low-income Black and White Americans. We found that both LE8 score and its MetaSig were inversely associated with risk of CHD, consistently among participants with varied sociodemographic and metabolic health status. Our identified metabolite signature may provide an objective and comprehensive measure of LE8 and its metabolic underpinning, which may help improve the precision of CVH assessment and facilitate more effective and personalized CHD prevention strategies in diverse populations. Further examination of our identified metabolites may improve understanding of biological mechanisms as to how following LE8 benefits CHD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CVD	cardiovascular disease
CVH	cardiovascular health
DASH	Dietary Approaches to Stop Hypertension
FFQ	food frequency questionnaire
LE8	Life's Essential 8
MetaSig	metabolite signature
MS	mass spectrometry
NMR	nuclear magnetic resonance
OR	odds ratio
QC	quality control
SCCS	Southern Community Cohort Study
SD	standard deviation
SES	socioeconomic status
SWMHS	Shanghai Women's and Men's Health Studies
VIF	variance inflation factor

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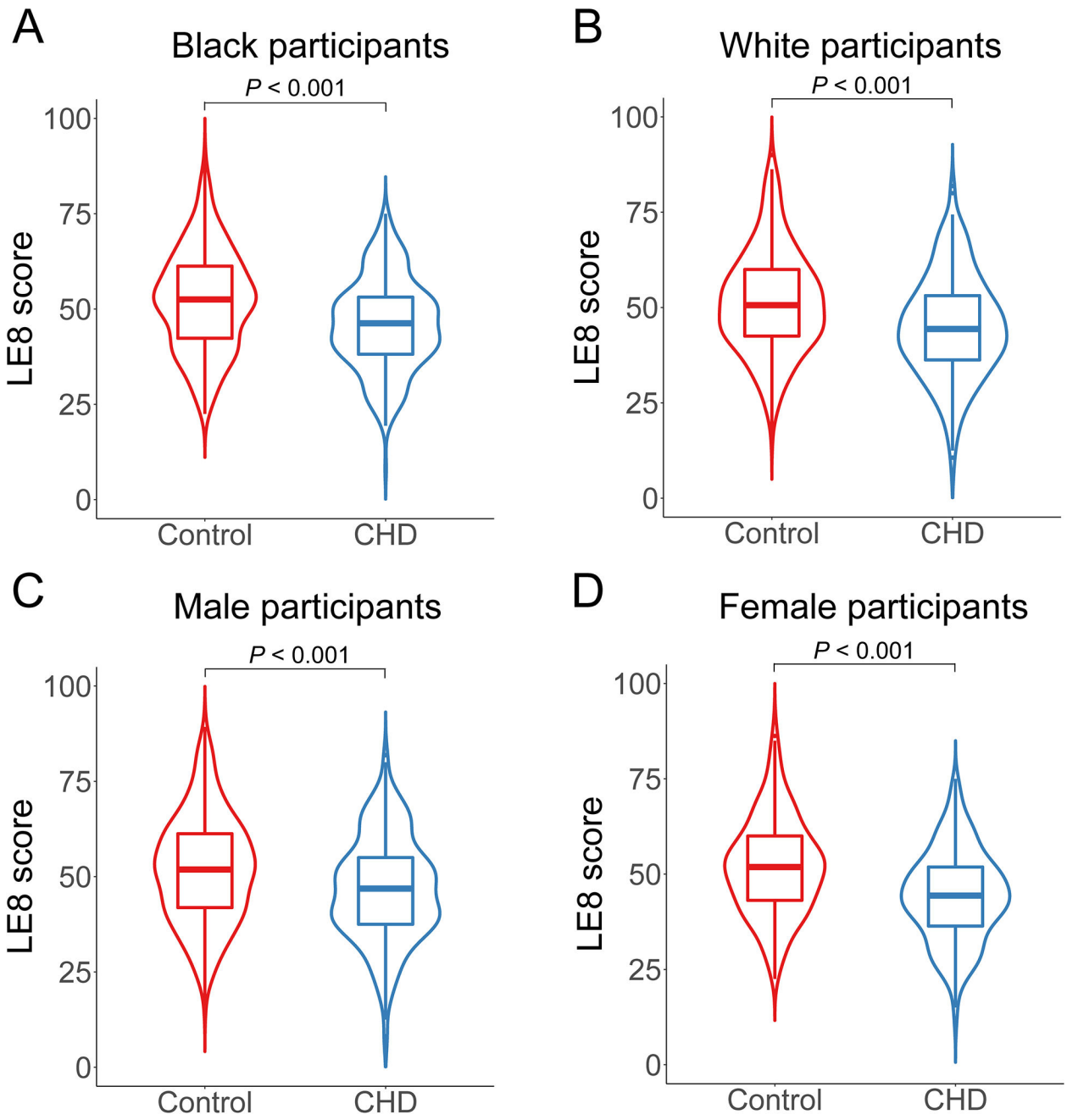

Figure 1.

The Life's Essential 8 score among incident coronary heart disease cases and matched controls by race and sex in the Southern Community Cohort Study. **(A)** The LE8 score among CHD cases and controls in Black participants. **(B)** The LE8 score among CHD cases and controls in White participants. **(C)** The LE8 score among CHD cases and controls in male participants. **(D)** The LE8 score among CHD cases and controls in female participants. LE8, Life's Essential 8; CHD, coronary heart disease. *P* value was calculated by the Wilcoxon signed-rank test.

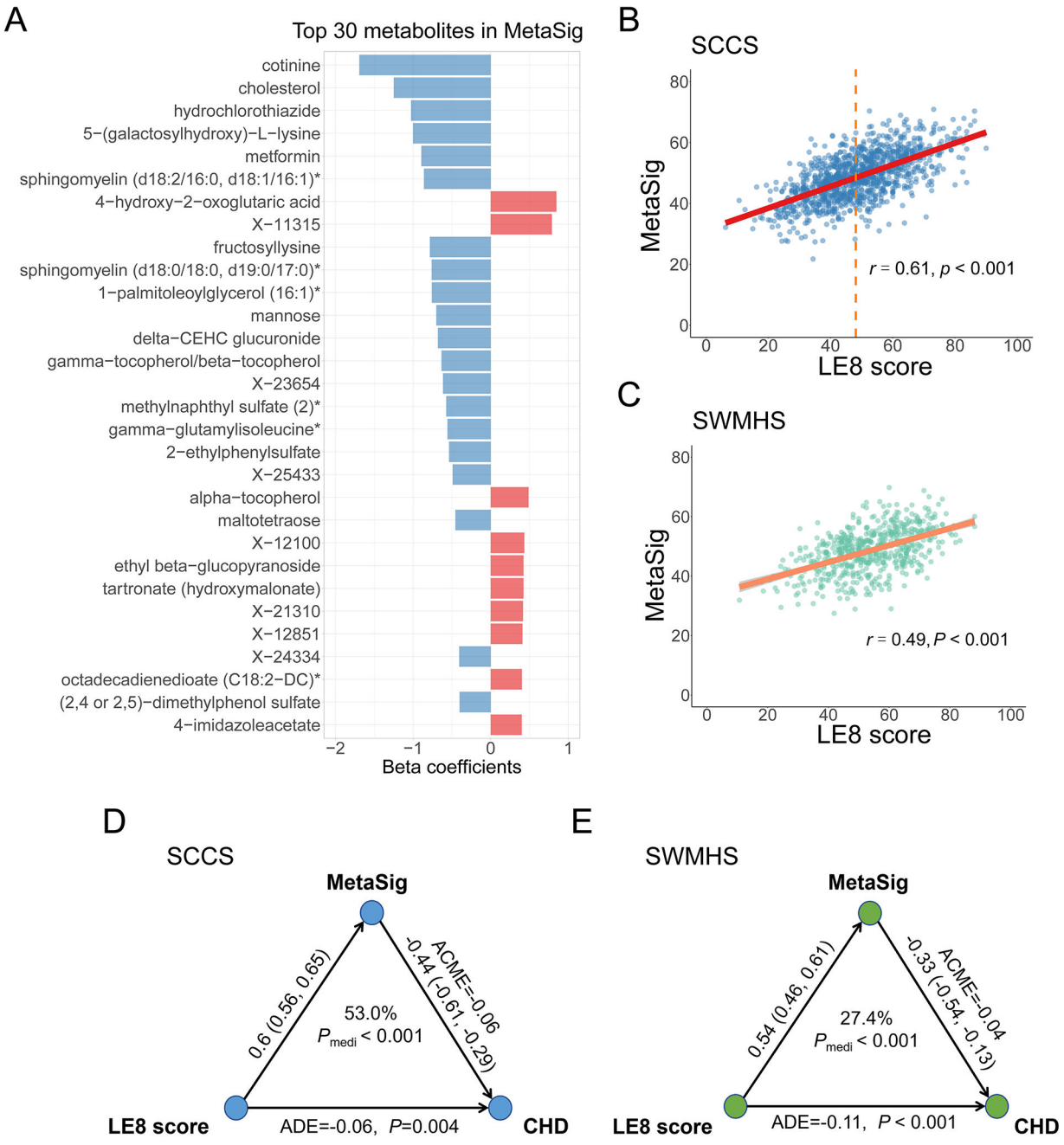

Figure 2.

The metabolite signature of Life's Essential 8 and its association with risk of coronary heart disease. **(A)** Top 30 metabolites selected by elastic net regression in SCCS. Metabolites were ranked by the absolute value of regression coefficients. **(B)** *Spearman* correlation between MetaSig and LE8 score in the SCCS. The dashed line denotes median LE8 score. **(C)** *Spearman* correlation between MetaSig and LE8 score in the SWMHS. **(D)** The mediation effect of MetaSig on the association between LE8 score and risk of CHD in the SCCS. **(E)** The mediation effect of MetaSig on the association between LE8 score and risk of CHD in the SWMHS. SCCS, Southern Community Cohort Study; SWMHS, Shanghai Women's

and Men's Health Studies; LE8, Life's Essential 8; MetaSig, metabolite signature; ACME, average causal mediation effects; ADE, average direct effects; CHD, coronary heart disease.

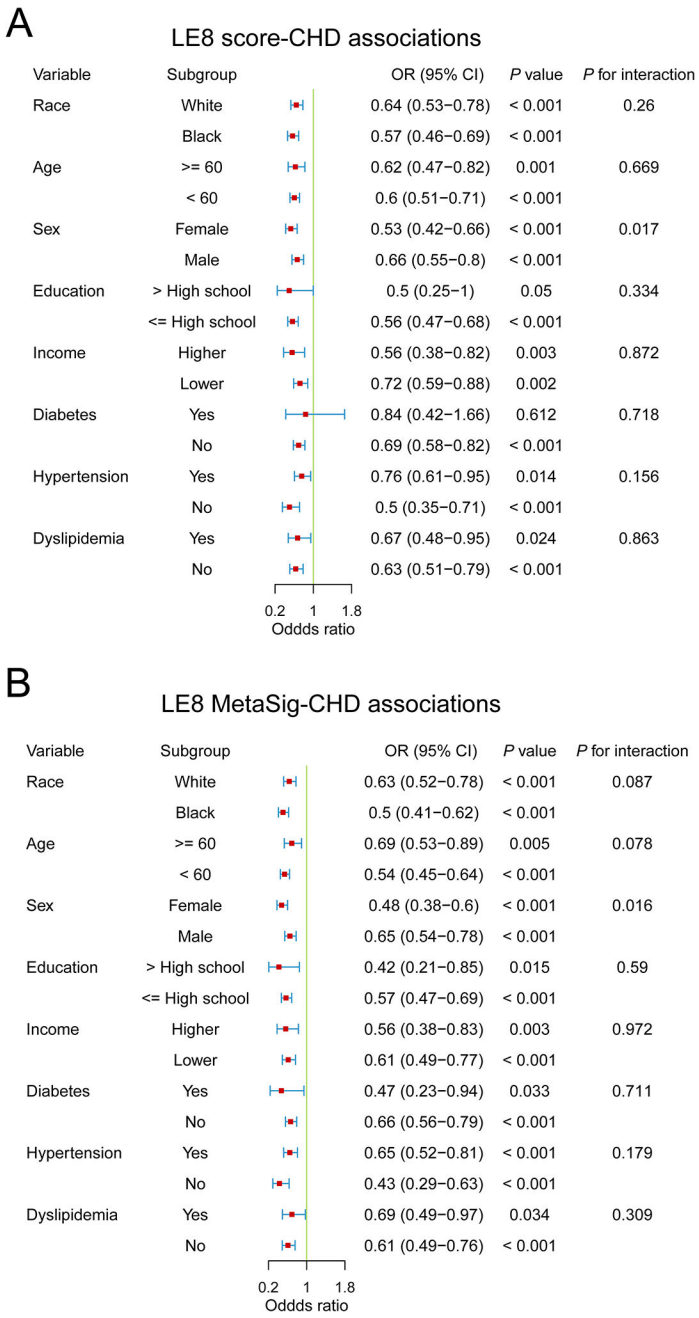

Figure 3.

Subgroup analyses for the associations of LE8 score and its metabolite signature with risk of coronary heart disease in the Southern Community Cohort Study. **(A)** Subgroup analysis for the association between LE8 score and risk of CHD. **(B)** Subgroup analysis for the association between MetaSig and risk of CHD. Conditional logistic regression models were used, adjusted for potential confounders. For income, lower income denotes low income, and higher income denotes middle and high income. MetaSig, metabolite signature; CHD, coronary heart disease; LE8, Life's Essential 8; OR, odds ratio; CI, confidence interval.

Table 1.

Characteristics of study participants in the Southern Community Cohort Study

	Black participants (*N*=598)		White participants (*N*=596)	
	CHD (*N*=299)	Control (*N*=299)	CHD (*N*=298)	Control (*N*=298)
Age, years	54.9 (8.8)	54.7 (8.7)	55.2 (8.7)	55.1 (8.6)
Male, *n* (%)	149 (49.8)	149 (49.8)	148 (49.7)	148 (49.7)
Education, *n* (%)				
Less than high school	120 (40.1)	109 (36.5)	108 (36.2)	84 (28.2)
Completed high school	107 (35.8)	108 (36.1)	118 (39.6)	118 (39.6)
Vocational school or some college	57 (19.1)	60 (20.1)	52 (17.4)	54 (18.1)
College or graduate school	15 (5.0)	22 (7.4)	20 (6.7)	42 (14.1)
Income, *n* (%)*				
Low	194 (64.9)	185 (61.9)	196 (65.8)	167 (56.0)
Middle	100 (33.4)	104 (34.8)	92 (30.9)	111 (37.2)
High	5 (1.7)	10 (3.3)	10 (3.4)	20 (6.7)
Alcohol intake, *n* (%)†				
None	154 (51.5)	140 (46.8)	175 (58.7)	140 (47.0)
Moderate	94 (31.4)	107 (35.8)	98 (32.9)	129 (43.3)
Heavy	51 (17.1)	52 (17.4)	25 (8.4)	29 (9.7)
Family history of CHD, *n* (%)	107 (35.8)	89 (29.8)	168 (56.4)	142 (47.7)
History of diabetes, *n* (%)	116 (38.8)	56 (18.7)	96 (32.2)	40 (13.4)
History of dyslipidemia, *n* (%)	102 (34.1)	91 (30.4)	155 (52.0)	108 (36.2)
History of hypertension, *n* (%)	210 (70.2)	179 (59.9)	177 (59.4)	133 (44.6)
Life's Essential 8 score	45.9 (11.9)	52.2 (13.2)	45.0 (13.5)	51.5 (13.5)
Life's Essential 8 score category, *n* (%)‡				
High (80–100)	0 (0)	7 (2.3)	3 (1.0)	10 (3.4)
Moderate (50–79)	114 (38.1)	174 (58.2)	100 (33.6)	148 (49.7)
Low (0–49)	185 (61.9)	118 (39.5)	195 (65.4)	140 (47.0)
Health behaviors score	43.8 (18.4)	47.4 (20.5)	42.0 (19.2)	46.3 (21.0)
Health factors score	47.2 (20.4)	56.7 (21.3)	48.0 (20.7)	56.2 (20.1)
Diet score	39.8 (32.2)	41.6 (30.6)	36.9 (30.3)	40.8 (32.3)
Physical activity score	22.8 (39.8)	24.2 (40.5)	19.9 (38.8)	21.3 (39.1)
Smoking score	43.0 (42.2)	47.8 (42.5)	40.0 (40.3)	46.5 (42.0)
Sleep score	72.3 (29.2)	77.1 (26.6)	71.2 (29.7)	78.1 (26.6)
Body mass index score	50.0 (34.5)	56.9 (35.3)	50.4 (34.1)	57.7 (34.2)
Blood lipids score	36.8 (32.8)	44.6 (31.8)	25.8 (28.7)	27.9 (27.6)
Blood glucose score	54.3 (34.3)	69.6 (30.0)	60.9 (34.0)	73.3 (26.7)
Blood pressure score	47.7 (35.1)	55.8 (37.3)	54.9 (38.3)	65.9 (38.9)

Data were mean (standard deviation) or *n* (%) as indicated.

*Annual household income <$15,000, $15,000 to <$25,000, and ≥$25,000 for low, middle, and high levels of income, respectively.

[†]Alcohol intake was grouped as none, moderate (>0 to ≤2 drinks per day in men or >0 to ≤1 drink per day in women; 1 drink = 14 g ethanol), and heavy drinking (>2 drinks per day in men or >1 drink per day in women).

[‡]The cutoffs were provided by the American Heart Association[3].

Table 2.

The associations of Life's Essential 8 score, health behaviors score, health factors score, and their related metabolite signatures with risk of CHD*

		OR (95% CI)	*P*
	SCCS		
Life's Essential 8	LE8 score	0.61 (0.53–0.69)	< 0.001
	LE8 MetaSig	0.57 (0.49–0.65)	< 0.001
	LE8 MetaSig (adjusting for LE8 score)	0.66 (0.55–0.78)	< 0.001
Health behaviors	Health behaviors score	0.77 (0.67–0.88)	< 0.001
	Health behaviors MetaSig	0.73 (0.63–0.85)	< 0.001
	Health behaviors MetaSig (adjusting for health behaviors score)	0.79 (0.67–0.94)	0.007
Health factors	Health factors score	0.61 (0.53–0.7)	< 0.001
	Health factors MetaSig	0.57 (0.49–0.66)	< 0.001
	Health factors MetaSig (adjusting for health factors score)	0.68 (0.55–0.84)	< 0.001
	SWMHS		
Life's Essential 8	LE8 score	0.52 (0.42–0.65)	< 0.001
	LE8 MetaSig	0.57 (0.46–0.69)	< 0.001
	LE8 MetaSig (adjusting for LE8 score)	0.69 (0.55–0.86)	< 0.001
Health behaviors	Health behaviors score	0.73 (0.59–0.9)	0.003
	Health behaviors MetaSig	0.69 (0.55–0.87)	0.001
	Health behaviors MetaSig (adjusting for health behaviors score)	0.77 (0.59–0.99)	0.043
Health factors	Health factors score	0.5 (0.4–0.62)	< 0.001
	Health factors MetaSig	0.57 (0.47–0.7)	< 0.001
	Health factors MetaSig (adjusting for health factors score)	0.80 (0.62–1.04)	0.093

* For associations of LE8 score and its related metabolite signature with risk of CHD, we used the conditional logistic regression, adjusted for age, education, income, alcohol intake, family history of CHD. For associations of health behaviors score and health factors score and their related metabolite signatures with risk of CHD, we used the conditional logistic regression, adjusted for age, education, income, alcohol intake, family history of CHD, and mutual adjustments of health factors score/health behaviors score. SCCS, Southern Community Cohort Study; SWMHS, Shanghai Women's and Men's Health Studies; CHD, coronary heart disease; LE8, Life's Essential 8; MetaSig, metabolite signature; OR, odds ratio; CI, confidence interval.