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Mediterranean diet and associated metabolite signatures in relation to MASLD progression: A prospective cohort study

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Abstract

Background:

Mediterranean diet (MED) is recommended for managing metabolic dysfunction–associated steatotic liver disease (MASLD). However, associations between MED adherence, related metabolite signatures, and risks of liver-related events (LRE) and mortality in MASLD patients remain unclear.

Methods:

We performed a prospective analysis using UK Biobank data, including 47,429 MASLD participants free of LRE at baseline. MED adherence was assessed as alternate Mediterranean Diet (aMED) score through a validated questionnaire. Metabolic biomarkers were measured using high-throughput nucleic magnetic resonance (NMR) spectroscopy. Cox regression and restricted cubic splines assessed the association of aMED, its components, with risk of LRE and mortality. Mediation analysis evaluated the role of metabolites in the relationship between aMED, its components, and MASLD progression.

Results:

Over a median follow-up of 13.3 years, 296 LRE cases and 3616 deaths occurred. Higher aMED scores (6–9) were associated with lower risks of LRE (HR: 0.553, 95% CI: 0.351–0.874) and mortality (HR: 0.854, 95% CI: 0.762–0.956) compared with the lowest scores (0–3), with linear dose–response relationships. Vegetables and legumes were associated with lower LRE risk, while vegetables, nuts, fish, MUFA:SFA ratio, and moderate alcohol intake were linked to reduced mortality. Of 143 metabolites, 46 were significantly associated with aMED. Omega-3 fatty acids, the omega-3 to total fatty acid ratio, and albumin accounted for 7.9%, 11.9%, and 2.6% of the reduction in LRE, and 19.4%, 23.1%, and 4.7% of the mitigation in mortality, respectively.

Conclusions:

Adherence to MED is linked to reduced LRE risk and mortality in MASLD patients. Metabolic biomarkers, particularly small HDL particles and omega-3 fatty acids, may mitigate MASLD progression.

Keywords: cohort study, mediation effect, Mediterranean diet, metabolic dysfunction–associated steatotic liver disease, metabolomics

INTRODUCTION

Metabolic dysfunction–associated steatotic liver disease (MASLD) has been proposed as an alternative term for nonalcoholic fatty liver disease (NAFLD) to better reflect its strong association with metabolic syndrome (MetS).¹ MASLD is one of the most prevalent chronic liver diseases globally, with the estimated prevalence growing appreciably from 25% in 2005 or earlier to 37% in 2016 and beyond.² MASLD has emerged as a dominant public health threat and contributes to a heavy disease burden. Early intervention is essential to prevent MASLD from progressing to severe outcomes such as liver fibrosis, cirrhosis, HCC, and ultimately death.³ Given the lack of effective pharmacological treatments for MASLD, adopting healthy lifestyle habits is regarded as the primary clinical recommendation for managing MASLD.⁴ Especially, diet plays a vital role in the reduction of hepatic steatosis in populations with MASLD.⁵

The Mediterranean diet (MED) is a healthy dietary pattern, emphasizing the intake of plant-based foods, healthy fats, and moderate alcohol consumption, which has been linked to various health benefits,⁶ including a reduced risk of cardiovascular disease, MetS, and lower mortality. The association between the MED pattern and a reduced risk of MASLD has been extensively studied. Existing epidemiological evidence has indicated that MED could mitigate MASLD risk,⁷ and a meta-analysis revealed potential protective effects of MED in reducing liver cancer, with a pooled relative risk (RR) of 0.58 (95% CI: 0.46, 0.73).⁸ Hereby, it has been recommended for the management of MASLD.⁹ Very recently, 2 cohort studies suggested that MED may alleviate the progression of MASLD.^{10,11} However, the underlying mechanisms and the role of metabolite signatures in this relationship remain to be fully clarified.

Metabolites detected in plasma provide significant potential for health assessment, diagnosis, and disease prediction.¹² Metabolomic signatures are increasingly recognized as critical players in the progression of MASLD.¹³ Prior research has shown that metabolic profile alterations detected are associated with MASLD, particularly extremely large VLDL triglycerides, which reflect both its presence and potential future risk.¹⁴ The

MED may lower LDL levels and increase HDL levels, contributing to the alleviation of hepatic steatosis.¹⁵ However, there is limited evidence linking MED-related metabolic biomarkers with the incidence of LRE and mortality in MASLD patients.¹² Identifying biomarkers associated with MED and LRE may offer valuable tools for elucidating the metabolic pathways affected by MED.¹⁶

In this study, we conducted a prospective cohort study using UK Biobank data. We aimed to (1) assess the association between adherence to MED and the risk of incident LRE and mortality in patients with MASLD; and (2) investigate the effect of metabolic biomarkers in the relationship between MED, LRE, and mortality.

METHODS

Study population

We derived data from the UK Biobank, an ongoing population-based prospective study, and details of the UK Biobank have been described elsewhere (<http://www.ukbiobank.ac.uk>). Briefly, the UK Biobank study recruited over 500,000 participants aged 37–73 from 22 assessment centers across England, Wales, and Scotland from March 2006 to December 2010. Information on sociodemographics, habitual diet, lifestyle factors, and medical history was gathered through touch-screen questionnaires, face-to-face interviews, and electronic records. Physical measurements and biological specimens were collected through standardized procedures.

We included patients with prevalent MASLD at recruitment, which was defined as the presence of fatty liver, accompanied by at least 1 of 5 cardiometabolic risk factors, according to the multi-society Delphi consensus statement.¹ Given the restricted sample size of participants undergoing MRI-based hepatic steatosis quantification ($n < 50,000$), fatty liver index (FLI) was employed as a validated surrogate marker in accordance with international expert consensus recommendations for large-scale epidemiological studies.¹⁷ FLI was estimated according to triglycerides, body mass index (BMI), abdominal circumference and GGT as prior investigation, and fatty liver was defined as $FLI \geq 60$.¹⁸ After the exclusion of individuals who were pregnant, had a history of cancer, non-steatotic liver disease, without alcohol information, or excessive drinking (female > 20 g/d, male > 30 g/d), a total of 126,217 eligible participants were recruited. We further excluded individuals who had a history of LREs before baseline, without valid baseline dietary data, with implausible total energy intake (< 500 kcal/d or > 5000 kcal/d), leaving 47,429 participants for analysis (Supplemental Figure S1, <http://links.lww.com/HC9/C105> ). The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland (Approval No.: 21/NW/0157). All participants signed written informed consent forms.

Assessment of the Mediterranean diet

Participants were invited to complete the Oxford WebQ questionnaire on 5 different occasions over 5 years, which has been validated in previous studies and extensively utilized in several epidemiological studies examining dietary patterns associated with chronic diseases.¹⁹ Between April 2009 and September 2010, a total of 70,000 participants completed Oxford WebQ in the clinic, and over 320,000 individuals finished an online 24-

hour recall dietary questionnaire in response to email invitations from February 2011 through June 2012. The average measures were calculated based on data from participants who had completed at least one of the questionnaires.²⁰ We adapted the alternate MED (aMED) score,²¹ which is a modified version of the traditional MED score, to estimate adherence to MED in the UK Biobank population.²² It is constructed based on the consumption of 9 food components [vegetables, legumes, fruits, nuts, whole grains, fish, the ratio of monounsaturated fatty acid (MUFA) to saturated fatty acid (SFA), red/processed meat, and alcohol], and each component was scored as either 0 or 1 point.²³ Participants who consumed above the median intake for each component were assigned 1 point; otherwise, they received 0 points, except for red/processed meat (where intakes below the median were assigned 1 point), and alcohol (where intakes of $5 \text{ g/d} \leq \text{alcohol} \leq 15 \text{ g/d}$ were assigned 1 point). Finally, the aMED score ranges from 0 to 9, and we further classified it into 3 categorical variables (0–3, 4–5, and 6–9 scores) in line with previous studies.²⁴ Details of the components and scoring criteria for the aMED score are described in Table S1 of the Supplemental Material, <http://links.lww.com/HC9/C105> .

Assessment of metabolites

A venous blood sample was obtained at baseline and stored in a freezer at -80°C . Before preparation, frozen samples were thawed gradually at $+4^{\circ}\text{C}$ overnight, followed by gentle mixing and centrifugation (3 min at $3400g$, $+4^{\circ}\text{C}$) to remove any potential precipitate. In all, 249 metabolic biomarkers (168 original measurements and 81 ratios), including lipids, fatty acids, amino acids, ketone bodies, and other low-molecular-weight metabolic biomarkers, were quantified using high-throughput nuclear magnetic resonance (NMR) spectroscopy between June 2019 and April 2020 in the Nightingale metabolic biomarker platform. Detailed information about the NMR platform and experimentation has been described elsewhere (https://biobank.ctsu.ox.ac.uk/ukb/ukb/docs/nmrn_companion_doc ) . In this study, we incorporated 143 metabolites that were directly derived from measures in absolute concentrations (except for fatty acids) and could not be inferred from other biomarkers.²⁵ The values of all metabolic biomarkers were first log-transformed and then Z-transformed. For biomarkers with values of zero, these were replaced with the smallest non-zero value within the group, divided by the square root of 2.²⁵

Assessment of outcome

Incident cases of LRE were identified through cancer and death registries, defined as a composite endpoint that includes complications of cirrhosis (K74.60) and/or HCC (C22.0) and other liver diseases and conditions (Supplemental Material Table S2, <http://links.lww.com/HC9/C105> ) , based on the International Classification of Diseases (ICD)-10 codes.²⁶ Person-years of follow-up were calculated as the interval from the dates of first dietary assessment until the occurrence of LRE, death, loss to follow-up, or the end of the study period, whichever came first. Dates of death were obtained from death certificates provided by the National Health Service Information Centre for participants in England and Wales, and from the National Health Service Central Register for participants in Scotland.²⁷

Assessment of variables

In accordance with previous studies, we collected a set of covariates including (1) demographic characteristics [age, sex, ethnicity, educational attainment, body mass index (BMI), index of multiple deprivation (IMD)]; (2) lifestyle factors (current smoking status, physical activity, sleep duration, total energy intake); (3) chronic comorbidities (hypertension, diabetes); (4) medication use (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blocker, beta blocker, statin, multivitamin, mineral supplements); (5) laboratory data (total cholesterol, LDL, HDL, triglycerides, fasting glucose, hsC-reactive protein). Physical activity levels were assessed using the metabolic equivalent (MET) derived from the International Physical Activity Questionnaire-Short Form (IPAQ-SF). The height and weight of participants were measured to calculate BMI, which was defined as weight in kilograms divided by the square of height in meters. Information on comorbidities was collected through the baseline questionnaire, verbal interviews, and electronic health records. Laboratory data were measured using fasting venous blood samples.

Statistical analysis

The baseline characteristics were described as means (SD) or medians (IQR) for continuous variables and as numbers (percentages) for categorical variables. Missing covariate data were imputed using the multiple imputation method. Cox proportional hazards regression models were employed to evaluate the linkage between aMED and incident LRE and all-cause mortality. We adopted a crude model stratified by sex and age at baseline and adjusted for intake of energy. In the multivariable-adjusted model, we additionally adjusted for demographic characteristics, lifestyle factors, chronic comorbidities, medication use, and laboratory data. Schoenfeld tests of proportional hazards assumptions presented no violations, with all p -values >0.05 . Restricted cubic spline (RCS) with 3 knots, placed at the 10th, 50th, and 90th percentiles [according to Akaike information criterion (AIC) and Bayesian information criterion (BIC); Supplementary Table S3, <http://links.lww.com/HC9/C105> , were used to assess the potential nonlinear associations between aMED and outcomes.²⁸

We performed a 2-stage analysis to investigate the effect of metabolic biomarkers on the association between aMED and LRE or mortality in the MASLD population. In the first stage, we fitted multivariable-adjusted linear regression models to estimate associations between aMED score and metabolic biomarkers, adjusting for the above-mentioned covariates. The Benjamini–Hochberg method was used, and the false discovery rate (FDR) adjusted p -value <0.05 was considered statistically significant.²⁹ In the second stage, Cox proportional hazards models were employed to assess the relationships between significant metabolites and LRE or all-cause mortality, with follow-up duration identical to that used in the primary analysis. Principal component analyses were conducted to capture the most important patterns from a large number of correlated biomarkers, and we found that 12 principal components of 143 metabolites potentially explained over 90% of the variance. If the associations were statistically significant in the 2-stage analysis, mediating analyses were performed to assess the mediating role of the metabolites in the associations between aMED and LRE or mortality.

We also conducted several sensitivity analyses to test the robustness of our results. To reduce the potential effect of reverse causation, participants who had died or been diagnosed with LRE within the first 2 years of follow-up were excluded. E -values were calculated to assess the robustness of the results to potential unmeasured confounding factors. Participants with at least 2 dietary assessments were included in sensitivity analyses to evaluate the robustness of the associations of aMED scores with liver-related events (LRE) and mortality risks. In

addition, we employed stratified analysis to estimate effect modifications by individual characteristics (eg, demographic factors, lifestyle factors, and chronic comorbidities). Statistical significance of interactions between subgroups was examined using the likelihood ratio test.

Data analyses were performed using the R version 4.1.3 (R Foundation for Statistical Computing), with the “survival” package for Cox regression models, “rms” package for smoothing nonlinear terms, “mice” package for multiple imputation, and “mediator” for mediation analysis. A 2-sided test $p < 0.05$ or an FDR-adjusted p -value < 0.05 was defined as statistically significant.

RESULTS

Table [1](#) describes the baseline characteristics of UK Biobank participants with MASLD across different aMED scores. The mean (SD) age of 47,429 patients included in this study was 57.3 (7.7) years, and 61.7% of participants were male. Individuals with higher aMED scores were generally more likely to be non-smokers, have attained a college or university degree, have a higher IMD, and engage in physical activities with higher MET. In addition, individuals with a higher score of aMED tended to have a larger energy intake, longer sleep duration, and greater use of multivitamin and mineral supplements. The correlations between the 9 component scores were generally weak ($r < 0.30$), except for the correlation between vegetables and fruit intake ($r = 0.48$; Supplemental Figure S2, <http://links.lww.com/HC9/C105> [↗](#)). Dietary scores also showed minimal variation across assessments (Supplemental Table S4, <http://links.lww.com/HC9/C105> [↗](#)).

TABLE 1.

Baseline characteristics across the aMED score among UK Biobank participants

Characteristics	aMED score			Overall (n=47,429)
	0–3 (n=23,616)	4–5 (n=18,389)	6–9 (n=5424)	
Age, mean (SD), year	57.01 (7.82)	57.55 (7.63)	57.92 (7.49)	57.32 (7.72)
Male, n (%)	14,734 (62.39)	11,263 (61.25)	3244 (59.81)	29,241 (61.65)
White, n (%)	22,408 (94.88)	17,375 (94.49)	5136 (94.69)	44,919 (94.71)
BMI, mean (SD), kg/m ²	31.60 (4.61)	31.45 (4.51)	31.31 (4.39)	31.51 (4.54)
Physical activity, median (IQR), MET hours/week	23.10 (38.35)	23.75 (36.75)	24.50 (37.80)	23.40 (37.70)
College or university degree, n (%)	7442 (31.51)	7172 (39.00)	2439 (44.97)	17,053 (35.95)
Index of multiple deprivation, mean (SD)	17.64 (13.93)	16.52 (13.15)	15.35 (12.16)	16.95 (13.46)
Energy intake, mean (SD), kJ	8531.36 (2651.33)	8868.84 (2453.61)	9045.19 (2272.51)	8720.96 (2542.25)
Current smokers, n (%)	2203 (9.33)	1178 (6.41)	276 (5.09)	3657 (7.71)
Sleep duration, mean (SD), hour	8.10 (1.12)	8.12 (1.07)	8.13 (1.08)	8.11 (1.09)
Hypertension, n (%)	8321 (35.23)	6682 (36.34)	1999 (36.85)	17,002 (35.85)
Diabetes, n (%)	326 (1.38)	217 (1.18)	69 (1.27)	612 (1.29)
Medications, n (%)				
ACEI	3433 (14.54)	2711 (14.74)	783 (14.44)	6927 (14.60)
ARBs	961 (4.07)	816 (4.44)	240 (4.42)	2017 (4.25)
Calcium channel blocker	984 (6.36)	931 (8.16)	328 (10.08)	2243 (7.44)
Beta blocker	2089 (8.85)	1565 (8.51)	469 (8.65)	4123 (8.69)
Statin	5468 (23.15)	4318 (23.48)	1254 (23.12)	11,040 (23.28)
Multivitamin	3001 (12.71)	2547 (13.85)	798 (14.71)	6346 (13.38)
Mineral supplements	4808 (20.36)	4184 (22.75)	1325 (24.43)	10,317 (21.75)
Laboratory data, mean (SD)				
Total cholesterol, mmol/L	5.69 (1.21)	5.69 (1.23)	5.71 (1.22)	5.69 (1.22)

Characteristics	aMED score			Overall (n=47,429)
	0–3 (n=23,616)	4–5 (n=18,389)	6–9 (n=5424)	
LDL, mmol/L	3.64 (0.91)	3.64 (0.92)	3.64 (0.91)	3.64 (0.92)
HDL, mmol/L	1.22 (0.28)	1.23 (0.28)	1.23 (0.28)	1.22 (0.28)
Triglycerides, mmol/L	2.38 (1.16)	2.38 (1.16)	2.40 (1.15)	2.38 (1.16)
Fasting glucose, mmol/L	5.34 (1.59)	5.32 (1.49)	5.28 (1.36)	5.32 (1.53)
hsC-reactive protein, mg/L	3.61 (4.80)	3.42 (4.60)	3.25 (4.50)	3.49 (4.69)

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Abbreviations: aMED, alternate Mediterranean diet; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; MET hours/week, metabolic equivalent, hours of physical activity per week.

Table 2 presents the association of aMED score with HR of LRE incidence and mortality. Over a median follow-up of 13.3 years (IQR: 12.7, 14.1 y), 296 cases of LRE and 3616 deaths were documented. There was sufficient evidence of inverse associations between the aMED score and reduced risks of LRE incidence and mortality in both crude and multivariable-adjusted models. In multivariable-adjusted model, the estimated HRs for LRE incidence and mortality were 0.796 (95% CI: 0.622, 1.019) and 0.953 (95% CI: 0.889, 1.023) for individuals with aMED scores of 4–5, and 0.553 (95% CI: 0.351, 0.874) and 0.854 (95% CI: 0.762, 0.956) for those with aMED scores of 6–9, respectively, compared with participants with the lowest category of aMED score (0–3). A one-unit increase in the aMED score was associated with an 11.9% decreased risk of LRE incidence (HR: 0.881, 95% CI: 0.814, 0.953) and a 3.0% reduced risk of mortality (HR: 0.970, 95% CI: 0.949, 0.992). Figure 1 demonstrates dose–response associations between aMED score and the risks of LRE incidence and mortality in MASLD patients. Approximately linear dose–response associations were observed for both LRE incidence ($P_{\text{nonlinear}}=0.91$) and mortality ($P_{\text{nonlinear}}=0.07$). The risk of LRE incidence and mortality progressively declined as the aMED score increased.

TABLE 2.

Association of aMED score and liver-related events and mortality in MASLD population

	Case/person-years	IR ^a	Model 1 HR (95% CI)	Model 2 HR (95% CI)
LRE				
aMED score				
0–3 (n=23,616)	168/309,975	54.20	1	1
4–5 (n=18,389)	107/242,714	44.08	0.79 (0.62, 1.01)	0.80 (0.62, 1.02)
6–9 (n=5424)	21/71,834	29.23	0.51 (0.33, 0.81) ^b	0.55 (0.35, 0.87) ^c
<i>P</i> trend			<0.01	<0.01
Per unit increase			0.87 (0.81, 0.94) ^d	0.88 (0.81, 0.95) ^b
Mortality				
aMED score				
0–3 (n=23,616)	1863/310,611	599.79	1	1
4–5 (n=18,389)	1390/243,075	571.84	0.92 (0.85, 0.98) ^c	0.95 (0.89, 1.02)
6–9 (n=5424)	363/71,940	504.59	0.78 (0.70, 0.88) ^d	0.85 (0.76, 0.96) ^b
<i>P</i> trend			<0.001	<0.01
Per unit increase			0.95 (0.93, 0.97) ^d	0.97 (0.95, 0.99) ^b

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Note: Model 1 is a crude Cox regression model adjusted for energy and stratified by sex and age. Model 2 is a multivariable-adjusted model additionally adjusted for sociodemographic characteristics (ethnicity, education attainment, index multiple deprivations, and BMI), lifestyle factor (smoking status, physical activity, and daily sleeping time), medications (ACEI, ARB, calcium channel blocker, beta blocker, statin, multivitamins, and mineral use), comorbidities (hypertension and diabetes) and blood-based measurements (total cholesterol, LDL, HDL, triglycerides, fasting glucose, and hsC-reactive protein).

^a Per 100,000.

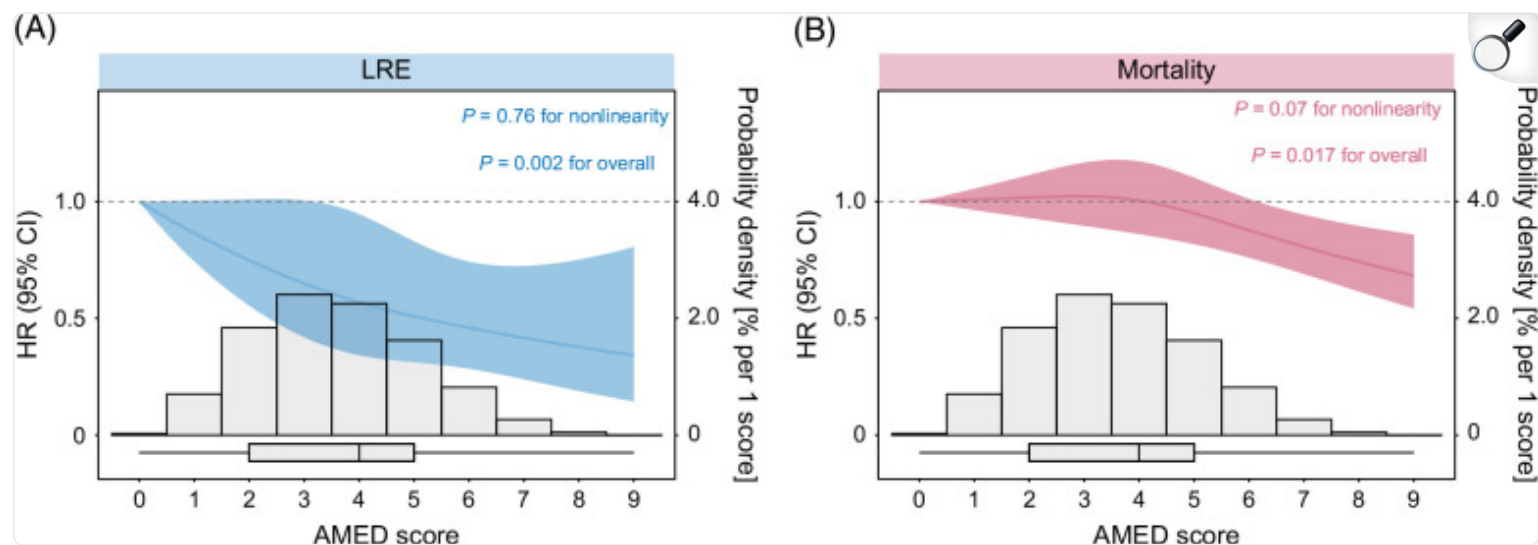
^b $p<0.01$.

^c $p<0.05$.

^d $p<0.001$.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; aMED, alternate Mediterranean diet; ARB, angiotensin II receptor blockers; IR, incidence rate; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease.

FIGURE 1.

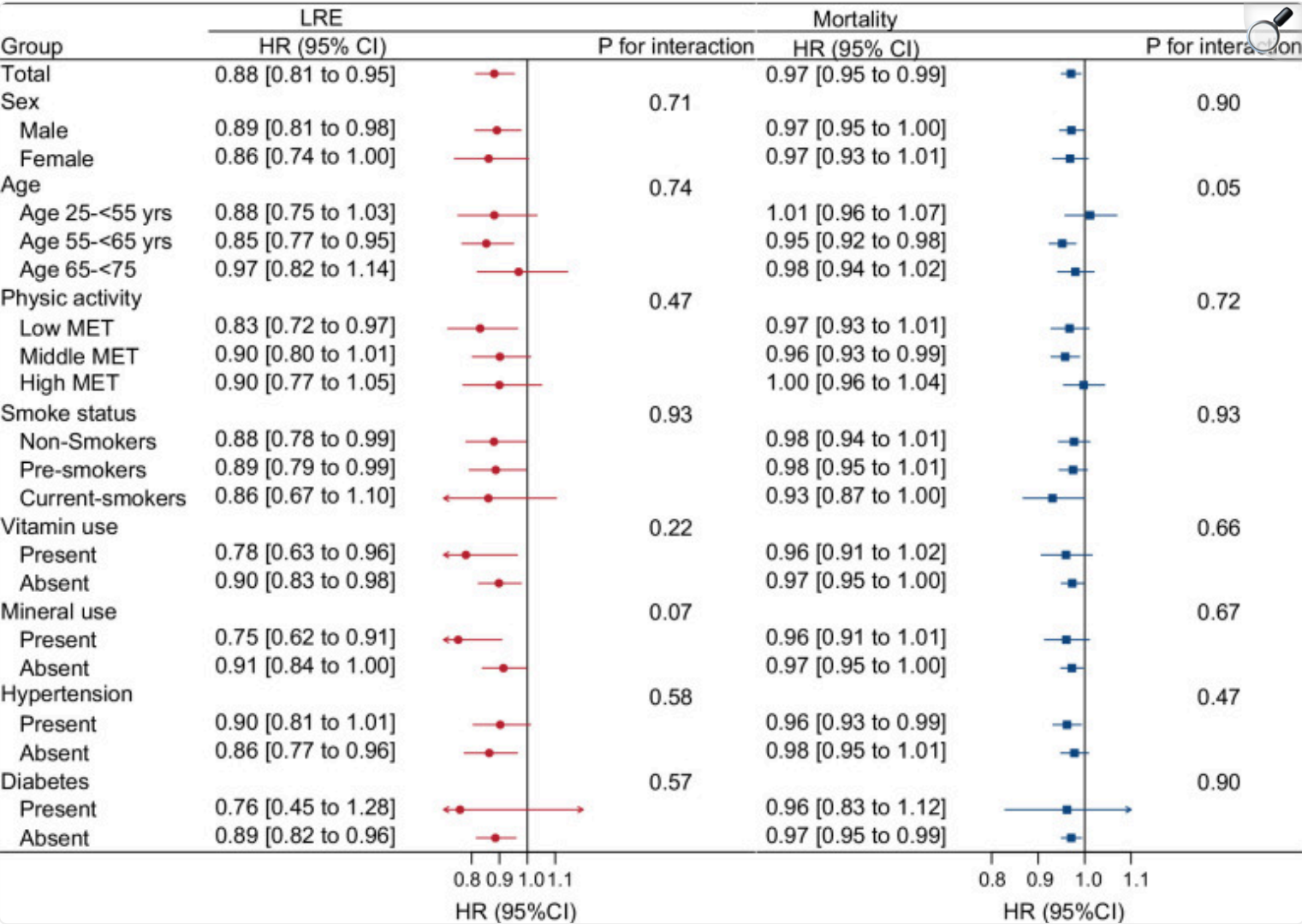


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Concentration–response curves between aMED score and liver-related events and mortality in the MASLD population. Abbreviations: aMED, alternate Mediterranean Diet; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease.

The main results were robust in sensitivity analyses (Supplemental Table S5, <http://links.lww.com/HC9/C105>). Compared with our primary findings, the estimated effects remained largely unchanged after excluding LRE incidence and death that occurred within the first 2 years of follow-up. The *E*-value ranged from 1.29 to 3.28 for LRE incidence and 1.19 to 2.94 for mortality (Supplemental Table S6, <http://links.lww.com/HC9/C105>). Subgroup analyses stratified by demographic and behavioral characteristics (Figure 2) showed consistent associations of aMED scores with the risks of LRE incidence and mortality, with no significant differences observed between subgroups. Protective and analogous associations were observed for 9 aMED constituents with risks of LRE incidence and mortality (Supplemental Tables S7, S8, <http://links.lww.com/HC9/C105>). Among these, only vegetables (HR: 0.938, 95% CI: 0.899, 0.978) and legumes (HR: 0.715, 95% CI: 0.529, 0.966) exhibited significant inverse associations with LRE risk. Several aMED components, including vegetables, nuts, fish, the MUFA:SFA ratio, and moderate alcohol consumption, were significantly and negatively associated with risk of mortality. The robustness of the primary findings was confirmed in sensitivity analyses restricted to participants with at least 2 dietary assessments (*n*=26,991). As shown in Supplemental Table S9, <http://links.lww.com/HC9/C105>, the results corroborated the main model, showing consistent associations between aMED scores, metabolomic markers, and outcomes of interest.

FIGURE 2.

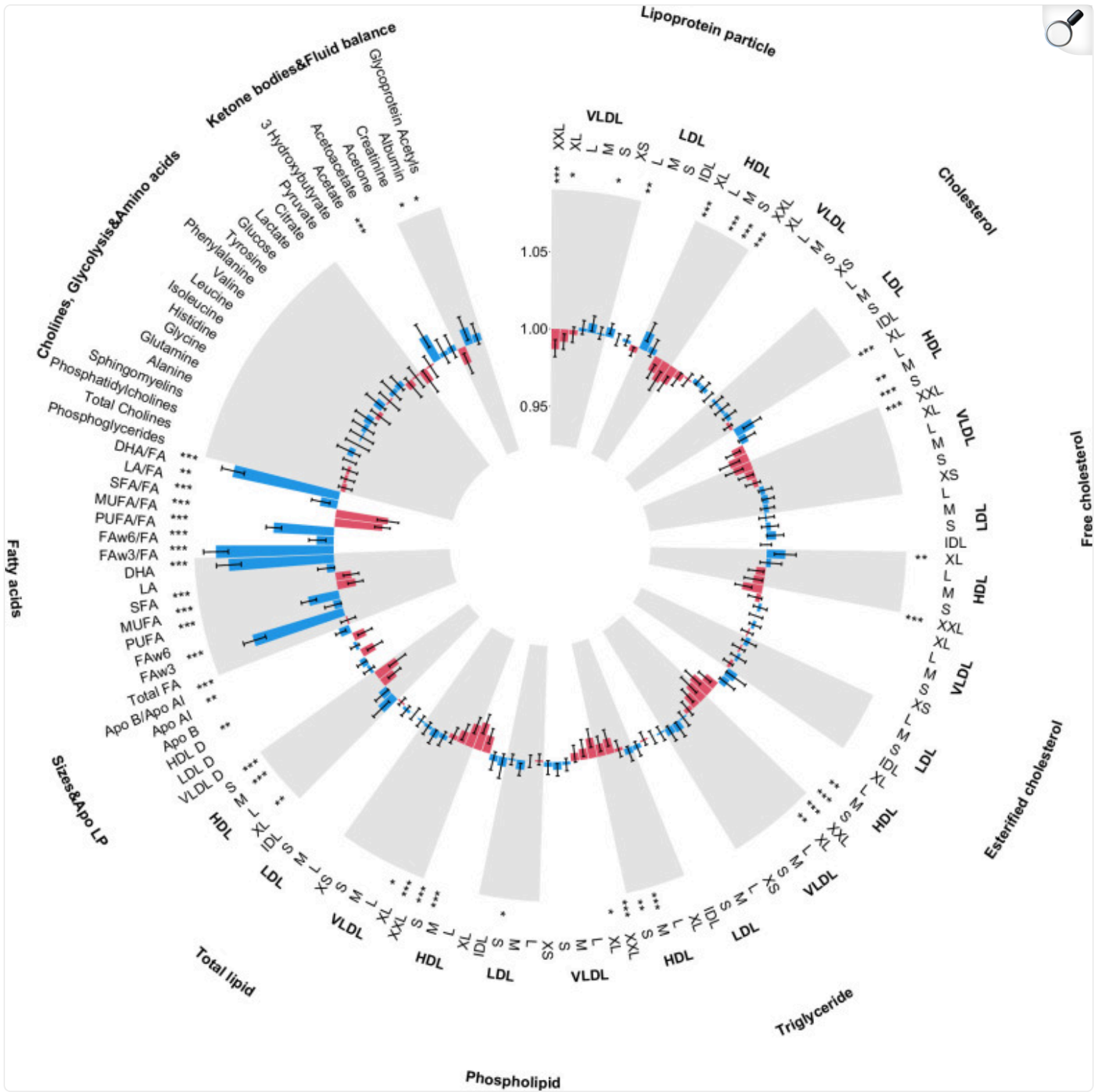


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Subgroup analyses of HR with 95% CI for LRE incidence and mortality associated with a unit rise in aMED score. Abbreviations: aMED, alternate Mediterranean diet; LRE, liver-related events; MET, metabolic equivalent.

Figure 3 illustrates the associations between aMED score and 143 metabolic biomarkers (per SD). After multivariable adjustment in multiple linear models, 46 of the 143 metabolites were significantly associated with aMED score, with FDR-adjusted p -values <0.05 . Among those metabolites, very large HDL particles ($n=3$), unsaturated fatty acids ($n=8$), albumin, and acetate were positively associated with aMED score, with ORs ranging from 1.006 to 1.075. In contrast, aMED scores were negatively associated with extremely and very large VLDL ($n=11$), small and middle HDL ($n=13$), saturated fatty acids ($n=2$), apolipoprotein A1, and creatinine. The association between the 9 aMED constituents and metabolites is shown in Figure 4. Of the 46 aMED-associated metabolites, 9 showed significant positive correlations with vegetables (eg, primarily consisting of large LDL, albumin, and unsaturated fatty acids), while 5 (eg, extremely large VLDL) demonstrated significant negative correlations with vegetables.

FIGURE 3.

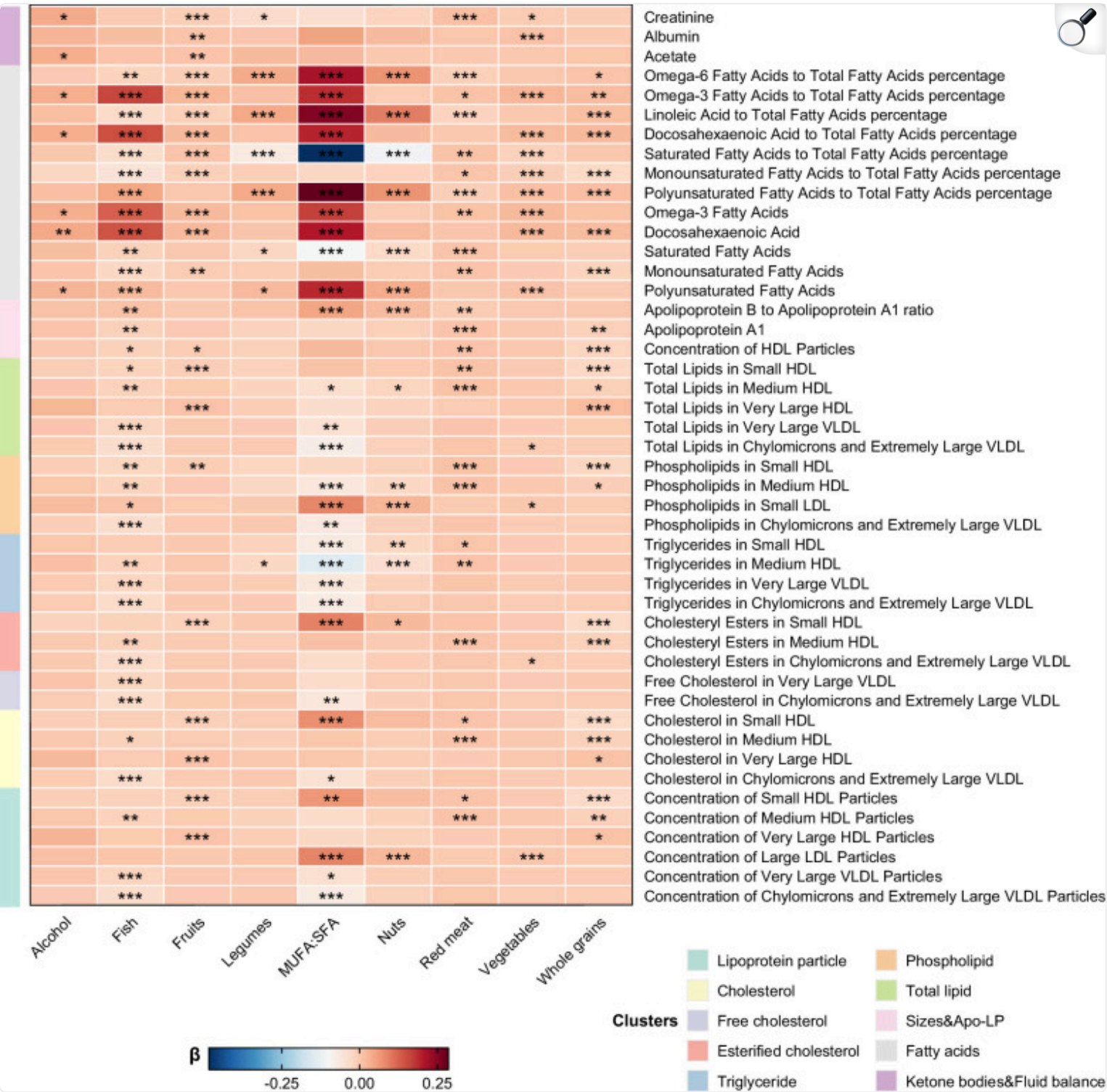


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Associations of aMED with 143 metabolites (per SD) in patients with MASLD. HRs (per unit) were stratified by sex and age and adjusted for sociodemographic characteristics (ethnicity, education attainment, index multiple deprivations, and BMI), lifestyle factor (smoking status, physical activity, and daily sleeping time), medications (ACEI, ARB, calcium channel blocker, beta blocker, statin multivitamins, and mineral use), comorbidities (hypertension and diabetes) and blood-based measurements (total cholesterol, LDL, HDL, triglycerides, fasting glucose, and hsC-reactive protein). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ (FDR-adjusted p -values). Abbreviations: ACEI, angiotensin-

converting enzyme inhibitors; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; Apo-LP, apolipoprotein; ARB, angiotensin II receptor blockers; BMI, body mass index; DHA, docosahexaenoic acid; FA, fatty acids; FDR, false discovery rate; HDL, high-density lipoproteins; HDL-D, high-density lipoprotein particle diameter; IDL, intermediate-density lipoproteins; L, large; LA, linoleic acid; LDL, low-density lipoproteins; LDL-D, low-density lipoprotein particle diameter; LP, lipoprotein; M, medium; MASLD, metabolic dysfunction–associated steatotic liver disease; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; S, small; SFA, saturated fatty acids; VLDL, very-low-density lipoproteins; VLDL-D, very-low-density lipoprotein particle diameter; XL, very large; XS, very small; XXL, extremely large.

FIGURE 4.



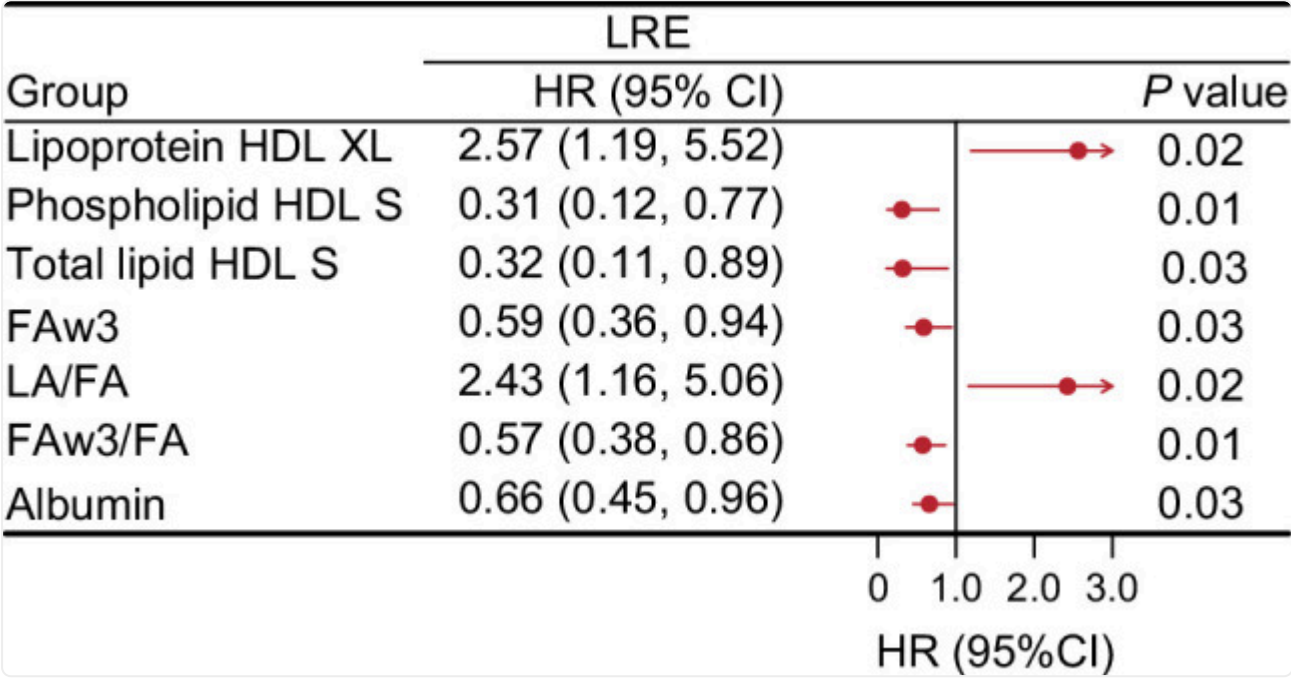
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Association between 9 components of aMED * and aMED-related metabolites*. * Continuous variables. Coefficients (β) of 9 components of aMED were stratified by sex and age and adjusted for sociodemographic characteristics (ethnicity, education attainment, index multiple deprivations, and BMI), lifestyle factor (smoking status, physical activity, and daily sleeping time), medications (ACEI, ARB, calcium channel blocker, beta blocker, statin multivitamins, and mineral use), and comorbidities (hypertension and diabetes). Abbreviations: aMED, alternate Mediterranean diet; ACEI, angiotensin-

converting enzyme inhibitors; ARB, angiotensin II receptor blockers; LP, lipoprotein; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

We further explored the associations between aMED-related metabolites and LRE incidence and mortality. Cox regression models revealed that 7 metabolite candidates were associated with LRE, and 21 metabolites were found to be associated with mortality (Figure 5 and Supplemental Figure S3, <http://links.lww.com/HC9/C105>). Specifically, higher levels of phospholipid in small HDL particles and the omega-3 fatty acids to total fatty acids percentage were associated with reduced risk of LRE. Conversely, significant positive correlations were observed between mortality and serum levels of very large HDL particles, cholesterol, free cholesterol, total lipids, and the ratio of saturated fatty acids to total fatty acids. Figure 6 summarizes the mediation analysis of metabolites in the associations of aMED score and the risks of LRE and mortality in MASLD patients. Omega-3 fatty acids, the ratio of omega-3 fatty acids to total fatty acids, and albumin significantly mediated the associations between aMED scores and both the risk of LRE and mortality, accounting for 2.6%–11.9% and 4.7%–23.1% of the total effect, respectively.

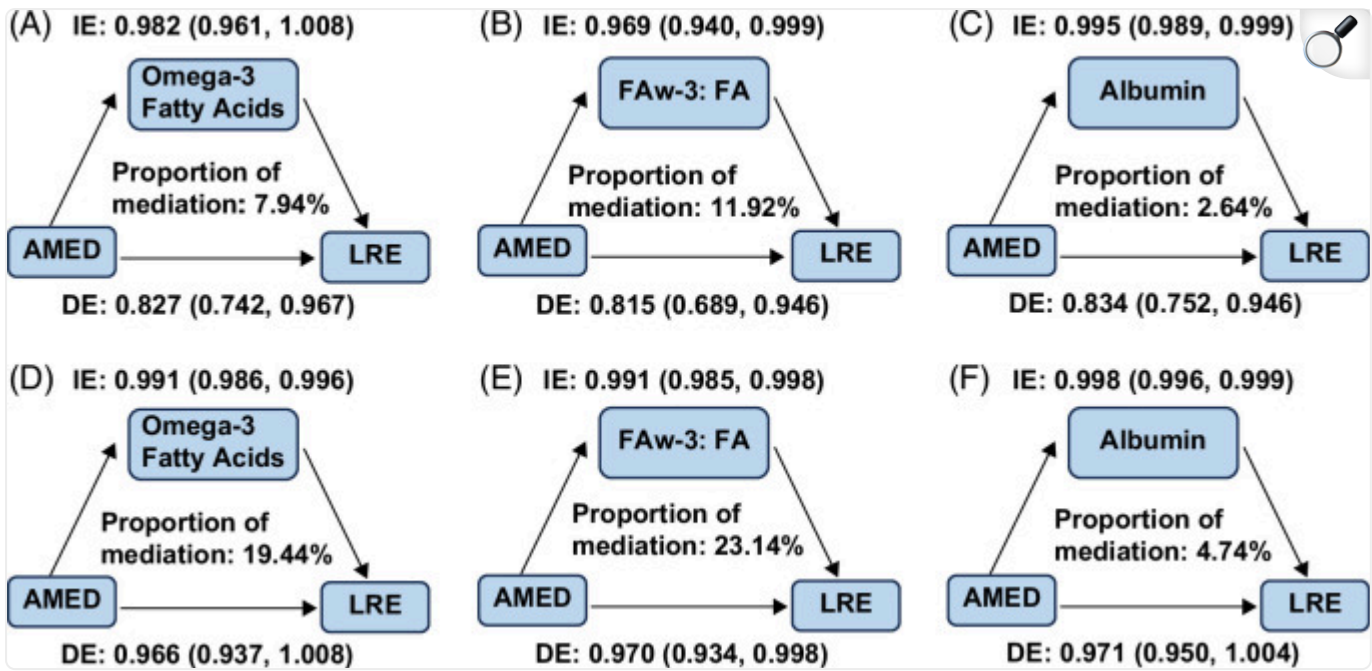
FIGURE 5.



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Associations of metabolites (per SD) with risk of LRE in patients with MASLD. Abbreviations: FA, fatty acids; FAw3, omega-3 fatty acids; LA, linoleic acid; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease; S, small; XL, very large.

FIGURE 6.



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Mediating effects of biomarkers on the association of aMED with risk of LRE (A–C) and mortality (D–F) among the MASLD population. Abbreviations: aMED, alternate Mediterranean diet; DE, direct effect; FA, fatty acids; FAw3, omega-3 fatty acids; IE, indirect effect; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease.

DISCUSSION

This prospective cohort study, using data from over 47,000 UK Biobank participants, investigated the relationship between MED adherence and the risk of LREs and mortality in MASLD patients, along with its effects on metabolites. We found that a higher aMED score was associated with lower risks of LRE and mortality in a linear dose–response manner. The vegetable and legume components were linked to reduced LRE incidence, while most aMED components were associated with lower mortality. Out of 143 metabolites, 46 were significantly associated with aMED, including very large HDL and linoleic acid: total fatty acids, which were linked to LRE incidence, and metabolites like very large HDL, cholesterol, and free cholesterol, which were associated with mortality. Omega-3 fatty acids, the omega-3 to total fatty acid ratio, and albumin partially mediated the associations between MED adherence and both LRE incidence and mortality, providing insights into the underlying mechanisms.

Existing evidence suggested that adherence to the MED may offer numerous health benefits for patients with MASLD, including a reduction in hepatic steatosis.^{10,30} For example, a randomized controlled trial involving 56 subjects with MASLD found a significant reduction in hepatic steatosis after 12 weeks of MED adherence ($p < 0.01$), with mean (SD) relative reductions of 32.4% ($\pm 25.5\%$).³¹ Another study reported that adherence to

MED significantly reduced body weight, proton density fat fraction of the liver, total cholesterol, GGT, and triglyceride concentrations in patients with MASLD.³² Besides, a prospective observational cohort study performed in 655 consecutive MASLD outpatients demonstrated that better adherence to the MED showed lower platelet activation and liver collagen deposition.³³ Consistent with prior studies, our results indicated the potential benefits of the MED in the progression of MASLD, specifically in ameliorating the risk of LRE and mortality. This finding is also supported by an analogous study, which reported a protective effect of MED on chronic liver disease and severe liver disease.¹¹

In the present study, several components of the aMED, particularly vegetables and legumes, were associated with a reduced risk of MASLD progression. Identical to our findings, previous studies have suggested that higher consumption of vegetables might lower liver fat content,³⁴ reduce the risk of developing MASLD, and decrease the risk of end-stage liver disease and all-cause mortality in patients with MASLD.¹⁰ These findings support the idea that a diet rich in whole vegetables and legumes may serve as both a preventive strategy and therapeutic approach for the management of MASLD.⁹ The benefits of vegetables and legumes may not only stem from their ability to reduce total caloric intake or from the wide range of micronutrients they provide,³⁵ but also through mechanisms involving the gut–brain–liver axis,³⁶ alleviating endoplasmic reticulum stress, inflammation, and lipid accumulation. Regarding other components of aMED, prior randomized controlled clinical trials have identified that increased consumption of nuts and reduced intake of red meat benefit patients with MASLD.³⁷ In our study, we also found that food groups (such as nuts, fish, and the MUFA:SFA ratio) were negatively associated with mortality in patients with MASLD, with HR ranging from 0.82 to 0.96. While potential protective effects of aMED components were observed, more sophisticated studies are still required for further validation.

Previous studies have indicated that adherence to MED was associated with specific metabolites, which can characterize both adherence to MED and metabolic responses to it.³⁸ Consistent with prior metabolomic study,¹⁶ our study found that adherence to the MED was positively correlated with unsaturated fatty acids and HDL, while being negatively associated with saturated fatty acids and VLDL. A quasi-experimental study from Sweden further found that a 6-day MED intervention notably enhanced other beneficial metabolites such as caffeine and beta-carotene.³⁹ Another randomized clinical trial from Spain found that acylcarnitines and steroids were significantly associated with the aMED.⁴⁰ As for components of aMED, positive associations were observed between fish/nuts and unsaturated fatty acids such as omega-3/omega-6 fatty acids, which were in line with findings from Spanish and American cohort studies.¹⁹ However, a cohort study from Finland observed that among the alternate Mediterranean diet score components, fish consumption mainly contributed to variations in phospholipids.⁴¹ These inconsistencies highlight the need to explore the relationship between food components and other sensitive or specific metabolites beyond lipids, to comprehensively characterize dietary biomarkers.⁴²

Metabolites, as intermediates or end products of metabolism, may play critical roles in liver cell physiology and may serve as key signals for the progression of MASLD.⁴³ In line with previous studies,⁴⁴ our analyses showed that 7 aMED-related lipid metabolites were significantly related to LRE, and 21 were associated with mortality. Of these metabolites, small HDL particles, omega-3 fatty acids, and albumin were inversely related to LRE, while the ratio of saturated fatty acids to total fatty acids showed positive correlation with mortality. These metabolic signatures not only hold promise as potential biomarkers for predicting the progression of MASLD but also suggest shared metabolic pathways.⁴⁵ We further found 3 serum aMED-related lipid metabolites or indices (ie, omega-3 fatty acids, the ratio of omega-3 fatty acids to total fatty acids, and albumin), partially mediated the

association between aMED and the incidence of LRE and mortality. A double-blinded, placebo-controlled, randomized controlled trial also demonstrated a reduction in liver fat following omega-3 fatty acid intervention over a 12-month period.⁴⁶ Previous studies also reported the protective effect of small-sized HDL particles.⁴⁷ Other metabolites, which might have a mediating role in the progression of MASLD, warrant further investigation. The potential mechanisms of omega-3 fatty acids in reducing the progression of MASLD are likely related to their anti-inflammatory and antifibrotic effects, as well as their ability to reduce liver injury by suppressing de novo lipogenesis and enhancing mitochondrial, peroxisomal, and microsomal fatty acid oxidation.⁴⁸ Further research focusing on metabolites is needed to elucidate their role as potential biomarkers for the early detection of MASLD progression.

A key strength of our study is the use of the UK Biobank, a nationwide, prospective cohort with a well-validated follow-up of 13.3 years. This allowed for detailed assessment of aMED-related metabolites and their mediating role in MASLD progression, offering mechanistic insights into aMED's potential preventive effects. The comprehensive data also enabled adjustment for multiple confounders, improving the reliability of our findings. In addition, our analysis of both linear and nonlinear associations between aMED and outcomes provides a unique contribution to this study. However, there are several limitations that should be acknowledged. Firstly, our observational design limits the ability to draw causal inferences between MED adherence, the risk of LRE or mortality, and the potential metabolites involved. Secondly, given that dietary assessment relied on self-reports, recall bias was unavoidably introduced to some extent. However, the Oxford WebQ Online 24-Hour Dietary Questionnaire employed in the study had undergone extensive validation against biomarkers.⁴⁹ Dietary scores also showed minimal variation across assessments, as detailed in Supplemental Table S4, S9, <http://links.lww.com/HC9/C105>.⁵⁰ Thirdly, the generalizability and reproducibility of our findings may be constrained by the fact that participants were predominantly middle-aged, white, European individuals. Further physiological studies conducted in diverse and independent populations are warranted to validate the findings of our study. Fourthly, although we accounted for a number of covariates, some unmeasured factors may still influence the association between aMED and the progression of MASLD. The estimated *E*-value indicated that unmeasured confounders were unlikely to significantly bias the observed associations (Supplemental Table S6, <http://links.lww.com/HC9/C105>). Fifthly, we did not fully assess the impact of dietary changes over time. However, dietary patterns tend to remain stable in individuals.⁵⁰ Sixthly, the timing of metabolite testing (2006–2010 and 2012–2013) and dietary evaluation (2009–2012) exhibited temporal misalignment, with the initial metabolite measurements preceding dietary assessments for most participants. However, our analysis benefits from validated metabolic reliability metrics between repeated measurements, suggesting moderate-to-high temporal stability for most metabolites. Furthermore, dietary patterns in our cohort demonstrated minimal variability across multiple assessments. Future studies incorporating contemporaneous metabolomic testing and dietary assessments are warranted to confirm the interplay between diet, metabolites, and health outcomes. Notably, the fatty liver index (FLI) was utilized as a validated surrogate measure to assess hepatic steatosis, rather than direct quantification via MRI-PDFF (magnetic resonance imaging–proton density fat fraction). This methodological approach may introduce measurement bias; thus, future studies employing MRI-PDFF-based assessments are warranted to validate our findings.

CONCLUSIONS

In conclusion, our study provides evidence that better adherence to the MED and its components was associated with a reduced risk of LRE and mortality in patients with MASLD. The observed reductions in risk may be partly explained by several aMED-related metabolic biomarkers, such as albumin and omega-3 fatty acids. However, the potential biological mechanisms underlying aMED-related metabolites remain unexplained. Future interventional and experimental studies are essential to further identify additional mediating biomarkers and to uncover the pathways and underlying mechanisms involved in these associations.

Supplementary Material

[hc9-9-e0791-s001.pdf](#) (754.2KB, pdf)

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DATA AVAILABILITY STATEMENT

All research data were obtained from the UK Biobank (<https://www.ukbiobank.ac.uk>) under application number 51671. Further information is available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

Kai Wang: writing—original draft, writing—review and editing, and formal analysis; Shijian Xiang: writing—review and editing, validation, and visualization; Qiangsheng He: data curation, writing—review and editing, and methodology; Anran Liu, Chumei Huang, Zhen Yang, Renjie Li, Jiaxin Hu, Ruisheng Cai, Ningning Mi, and Zixin Liang: writing—review and editing; Zuofeng Xu and Jinqiu Yuan: writing—review and editing, supervision, and funding acquisition; Bin Xia: data curation, writing—review and editing, supervision, and funding acquisition.

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CONFLICTS OF INTEREST

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.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The UK Biobank was approved by the National Research Ethics Committee (REC ID: 16/NW/0274). Electronic written informed consent was obtained from all participants.

Footnotes

Kai Wang, Shijian Xiang, and Qiangsheng He contributed equally to this work and shared the first authorship.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AIC, Akaike information criterion; aMED, alternate Mediterranean diet; ARB, angiotensin II receptor blockers; BIC, Bayesian information criterion; BMI, body mass index; FDR, false discovery rate; FLI, fatty liver index; ICD, International Classification of Diseases; IMD, index of multiple deprivation; IPAQ-SF, International Physical Activity Questionnaire-Short Form; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease; MET, metabolic equivalent; MetS, metabolic syndrome; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; MUFA, monounsaturated fatty acid; NMR, nucleic magnetic resonance; RCS, restricted cubic spline; SFA, saturated fatty acid.

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