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The metabolic vulnerability index as a novel tool for mortality risk stratification in a large-scale population-based cohort

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ABSTRACT

Metabolic malnutrition and inflammation—key mechanism links to redox imbalance—are fundamental pathologies that accelerate aging and disease progression, ultimately leading to death. The recently proposed metabolic vulnerability index (MVX) integrates multiple circulatory biomarkers closely linked to both metabolic and inflammatory factors. This study aims to assess MVX's potential to predict mortality in community-based population. In this large community-based prospective study, we included UK Biobank participants who underwent plasma metabolomics analysis. Gender-specific MVX scores were calculated based on six established biomarkers of mortality. Linear and non-linear associations between MVX and mortality were assessed using Cox proportional hazards models and restricted cubic spline models, respectively. Among the 274,092 UKB participants, 24,241 all-cause deaths occurred during a median follow-up period of 13.7 years. A significant, graded positive association was observed between MVX quartiles and all-cause mortality risk (P for trend <0.05), with the highest MVX quartile exhibiting the greatest risk (HR = 1.21 and 95 % CI = 1.16–1.25 after full adjustment). Females had higher MVX score than males ($P < 0.05$), but males with the same MVX score faced a greater mortality risk. Baseline age and comorbidities interacted (P for interaction <0.05 and synergy index >1) with MVX on mortality risk. Longitudinal analyses showed that females with persistently high MVX score had a significantly increased risk of mortality (HR = 1.39 in fully adjusted model). Collectively, these findings highlight MVX as a novel tool that captures metabolic and potential redox vulnerabilities in community residents, and serves as a valuable resource for identifying high-risk individuals of mortality. Further research is warranted to investigate the underlying mechanisms and establish causal relationships.

1. Introduction

As life expectancy increases and populations age rapidly worldwide, understanding the factors that influence longevity, and mortality is becoming increasingly crucial for public health. The biological mechanisms underlying mortality are intricate, involving both genetic factors and a wide range of exposures accumulated over the lifespan [1]. Moreover, the nonlinear and inverse associations of traditional risk

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factors, such as body mass index (BMI) [2] and blood pressure [3], with mortality in older adults complicate mortality prediction. Given the high prevalence of multimorbidity in older adults, an ideal tool for mortality risk prediction or stratification should capture overall health status rather than focus solely on specific pathological markers [4].

Circulating metabolites, which are shaped by both endogenous and exogenous factors [5,6], have emerged as promising biomarkers for extensive diseases and health conditions [7]. Several cohort studies have identified associations between circulating metabolites and an increased risk of all-cause mortality [8–11]. However, the single metabolite may not capture the broader metabolic context. The recently proposed metabolic vulnerability index (MVX) is a composite index that effectively reflects overall metabolic malnutrition and inflammation [12]. MVX comprises six nuclear magnetic resonance (NMR)-based plasma biomarkers: glycoprotein acetyls (GlycA), small high-density lipoprotein particles (sHDL), citrate, and the branched-chain amino acids (isoleucine, leucine, and valine). GlycA is a composite, stable biomarker of systemic inflammation, derived from glycan residues of several acute-phase reactant proteins [13]. In contrast, sHDL has anti-inflammatory properties, representing equal-weighted lipoprotein components and providing better mortality prediction than HDL cholesterol [14,15]. While GlycA and sHDL serve as indicators of inflammation, citrate, isoleucine, leucine, and valine are markers of metabolic malnutrition [12,16].

Previous hospital-based studies have shown that MVX significantly impacts patient survival [12,16]. Metabolic imbalance directly induces oxidative stress, endoplasmic reticulum stress and downstream reactive oxygen species (ROS) [17]. The physiological or pathological changes represented by MVX usually begin at the preclinical stage, suggesting its value in mortality prediction and risk stratification may extend beyond patient populations. Evaluating the effectiveness of MVX in community-based population can provide a comprehensive characterization of metabolic health status and identify early actionable targets for health management. Additionally, addressing the knowledge gap regarding the longitudinal association between MVX changes and mortality is critical for refining dynamic risk assessment.

Using long-term follow-up data from 274,092 middle-aged participants in the UK Biobank (UKB), this study aims to evaluate the potential of MVX in mortality risk prediction and stratification among community residents. In addition, conducted detailed stratification and interaction analyses to explore other contributing risk factors. Finally, the associations between changes in MVX over time and mortality risk were examined using repeated metabolite measurements. We aim to provide robust scientific evidence and practical guidance for applying MVX as a tool for mortality prediction and risk stratification in community-based population.

2. Materials and methods

2.1. Study design and participants

This study was based on the UKB [18], a population-based prospective cohort recruiting over half a million residents from England, Scotland and Wales. The baseline survey, conducted from 2006 to 2010, captured a wide range of health-related information for each participant, such as sociodemographic data, lifestyle factors, physical measurements, medical history, and clinical examinations. The first repeated assessment visit started from 2012 to 2013 to track health-related changes over time. Blood samples were collected under the protocol described elsewhere at each visit for further detection [19]. In this study, we excluded 33 individuals who withdrew informed consent before the commencement of our analysis (October 13, 2023) and those lacking baseline data for calculating the MVX (n = 228,264). For the longitudinal analysis of MVX variability, individuals without follow-up data for MVX calculation (n = 258,430) were also excluded. Finally, the analysis of baseline MVX included 274,092 participants, while the analysis of longitudinal MVX variability included 15,689 participants. A flowchart detailing participants inclusion is shown in eFig. 1. Ethical approval for the UKB was obtained from the North West Multi-centre Research Ethics Committee, and all participants provided electronically signed informed consent. This study was conducted using the UKB resource under the application number of 92718.

2.2. Ascertainment of outcomes

The primary outcome of this study was all-cause mortality, while the secondary outcomes included cause-specific mortality and the corresponding incidence of related diseases. The UKB study group has matched, validated, and cleaned individual-level health data from various external sources under strict criteria, which are available at http://www.ukbiobank.ac.uk/. We obtained the cause and date of death for each participant through linkage to national death registries. Disease records and corresponding dates were extracted from hospital inpatient data. Incident diseases were defined as those first diagnosed after the baseline survey. The end of follow-up in this study was determined by the earliest occurrence of death/incident disease (depending on the outcome analyzed), loss to follow-up, or the end of data collection in October 2022. Follow-up time was defined as the duration between the baseline assessment and the end date. Causes of death and disease diagnosis were coded according to the International Classification of Diseases, Tenth Revision (ICD-10). In addition to all-cause mortality, cause-specific mortality and incident disease were defined using ICD-10 codes: cancer (C00-97), circulatory disease (I00-99), respiratory disease (J00-99)), ischemic heart disease (IHD, I20-25), stroke (I60/I61/I63/I64), and chronic obstructive pulmonary disease (COPD, J43-44).

2.3. Metabolic biomarker profiling and MVX calculation

EDTA plasma samples from the UKB, collected at both baseline and the first follow-up visit, were randomly selected for metabolic biomarker profiling using high-throughput NMR spectroscopy at Nightingale Health. Detailed experimental procedures and quality controls have been published elsewhere [20]. The sex-specific MVX multi-marker score was calculated based on six metabolites as previously described [12], ranging from 1 to 100, with a higher score indicating greater metabolic vulnerability. The equation for MVX calculation is shown in the supplementary Methods. The annual rate of change in MVX was determined by subtracting the baseline MVX score from the score obtained at the first follow-up visit and then dividing the difference by the number of years between the two assessments. Detailed information on covariates was in the **Supplementary Methods**.

2.4. Statistical analysis

Characteristics of participants are presented as median (P_{25}, P_{75}) for continuous variables and frequency (%) for categorical variables. Differences across quartiles of the baseline MVX score were assessed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables, respectively.

Cox regression models with age as the timescale were used to assess associations between MVX scores and all-cause mortality. Deviance residual analysis revealed no influential observations. As the proportional hazard assumption, testing by Schoenfeld residuals, was violated, HRs should be interpreted as an average effect over the follow-up period [21,22]. The MVX score was analyzed both as a continuous variable (transformed to the estimate the per standard deviation [SD] increment) and as a categorical variable divided into quartiles, with the lowest quartile serving as the reference in the Cox models for a comprehensive assessment. Additionally, Martingale residuals of Cox regression models indicated nonlinearity, which was further analyzed by restricted cubic spline (RCS) models. Kaplan-Meier survival curves were plotted to compare survival rates between the low MVX (quartile 1–3) and high

MVX (quartile 4) groups. As MVX is a composite index, we also analyzed the individual associations between six biomarkers comprising the MVX score and mortality.

Given that the MVX score was initially developed and validated in cardiovascular patients, we also conducted a sensitivity analysis among subpopulation with cardiovascular diseases at baseline. Subgroup analyses based on demographic and health-related covariates were also performed, along with tests for interaction effects between MVX and the specific covariates. In addition to all-cause mortality as the primary outcome, we investigated the associations between baseline MVX and secondary outcomes, including 5-, 10-, and 15-year all-cause mortality, specific cause mortality, and the risk of incident disease. Specifically, 5-year, 10-year, and 15-year mortality were defined as deaths occurring within 5, 10, and 15 years after the baseline survey, respectively.

Regarding the change patterns of the MVX score during the median 4.4 years of follow-up, MVX score at baseline and follow-up visits were categorized as low or high according to the median and further grouped into four levels: low-low (as the reference), low-high, high-low, high-high. The impact of longitudinal changes in the MVX score on mortality risk was explored using RCS and Cox regression models with age as the timescale in total population and stratified by sex, respectively. Additionally, the relative contributions of MVX and each covariate to mortality prediction were quantified, as described in the **Supplementary Methods**.

Two models were developed for all multivariate Cox regressions with age as the timescale: Model 1 was adjusted for sex, ethnicity (White or others), Townsend deprivation index (TDI); Model 2 was further adjusted for BMI, estimated glomerular filtration rate (eGFR), current smoking status (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and baseline Charlson comorbidity index (CCI) = 0 (yes or no). The false discovery rate (FDR)-adjusted *P* value was calculated for multiple comparisons, with FDR-adjusted $P < 0.05$ considered statistically significant. All statistical tests were two-sided, and analyses and were performed using *R* (version 4.4.1).

3. Results

3.1. Participant characteristics

Among the 274,092 UKB participants, 24,241 (8.8 %) all-cause deaths were documented during a median follow-up period of 13.7 years. The baseline characteristics of the participants are summarized in Table 1. The median MVX score for the total study population was 44.0, with an interquartile range from 35.0 to 53.5. After grouped by quartiles, participants with higher MVX score were more likely to be female, older, and current smokers, and had higher TDI, higher BMI, and lower eGFR ($P < 0.05$). Participants with lower MVX scores had a reduced disease burden compared to those with higher metabolic vulnerability, as indicated by lower baseline prevalence of hypertension, diabetes, and dyslipidemia, and a lower proportion of individuals without baseline comorbidity (CCI = 0, $P < 0.05$). Participants with the highest MVX quartile had been recorded the most deaths (about 10 % of the total population, $P < 0.001$, eFig. 2). Cancer and circulatory diseases were the leading causes of both mortality (accounting for 47.5 % and 21.1 % of total deaths, respectively) and incident diseases (eTable 1).

3.2. Baseline MVX and all-cause mortality

In the fully adjusted model 2, each SD increment of MVX score was associated with a 1.12-fold (95 % confidence interval [CI]: 1.10–1.13) higher risk of all-cause mortality in the total population, and with 1.07-fold and 1.17-fold risks in the cardiovascular disease (CVD) and non-CVD subpopulations, respectively (Fig. 1A). Compared to the lowest quartile of MVX (Q1), participants in the highest quartile exhibited the greatest HRs for all-cause mortality (HR and 95 % CI: 1.41 [1.37, 1.47] and 1.21 [1.16, 1.25] in model 1 and 2, respectively, Fig. 1A), with *P* for trend <0.05 indicating an increase trend across MVX quartiles. The sensitivity analyses adjusted for NMR parameters were consistent with the main results (eTable 2).

The sex-stratified nonlinear associations (Fig. 1B) showed that the highest risk of mortality was observed in the top MVX quartile, regardless of sex. Notably, the risk of mortality associated with MVX score significantly increased when the MVX exceeded the median level. Furthermore, the histogram shows that females had significantly higher MVX scores than males, yet males with the same MVX score faced a greater all-cause mortality risk compared to females. The Kaplan-Meier

Table 1
Baseline characteristics across MVX quartiles (N = 274,092).

Characteristics	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Female	147948 (54.0)	22320 (32.6)	36707 (53.6)	43925 (64.1)	44996 (65.7)
Age, year	58.0 [50.0, 63.0]	57.0 [49.0, 63.0]	58.0 [50.0, 63.0]	58.0 [50.0, 63.0]	59.0 [51.0, 64.0]
White Ethnicity	246875 (90.1)	61133 (89.2)	61774 (90.2)	61862 (90.3)	62106 (90.6)
TDI	−2.2 [-3.7, 0.4]	−2.3 [-3.7, 0.2]	−2.3 [-3.7, 0.2]	−2.2 [-3.7, 0.4]	−2.0 [-3.5, 1.0]
Current smoking status	28859 (10.5)	6537 (9.5)	6367 (9.3)	7098 (10.4)	8857 (12.9)
BMI, kg/m^2	26.8 [24.2, 29.9]	25.7 [23.5, 28.3]	26.5 [24.0, 29.4]	27.0 [24.4, 30.3]	28.2 [25.3, 31.7]
Hypertension	81373 (29.7)	17513 (25.6)	18964 (27.7)	20539 (30.0)	24357 (35.5)
Diabetes	15018 (5.5)	2844 (4.2)	3293 (4.8)	3730 (5.4)	5151 (7.5)
Dyslipidemia	53720 (19.6)	12707 (18.5)	12708 (18.5)	13181 (19.2)	15124 (22.1)
eGFR, ml/min per 1.73 m^3	92.7 [82.7, 99.9]	93.1 [84.1, 100.4]	92.6 [82.8, 99.8]	92.5 [82.4, 99.7]	92.3 [81.4, 99.6]
Baseline CCI = 0	239038 (87.2)	60837 (88.8)	60638 (88.5)	60028 (87.6)	57535 (84.0)
GlycA, μmol/L	802.9 [728.2, 885.2]	710.4 [664.6, 752.7]	785.1 [737.1, 825.3]	839.7 [779.1, 884.8]	937.7 [867.4, 1000.1]
sHDL, μmol/L	9.7 [8.9, 10.6]	9.3 [8.5, 10.2]	9.7 [8.9, 10.5]	9.8 [9.0, 10.6]	10.1 [9.2, 11.1]
Citrate, μmol/L	64.4 [56.3, 73.3]	61.2 [53.4, 69.8]	64.3 [56.6, 72.9]	65.2 [57.3, 74.1]	66.8 [58.6, 75.9]
Isoleucine, μmol/L	48.0 [38.9, 59.8]	45.6 [38.4, 54.2]	49.0 [40.6, 59.0]	48.2 [38.5, 60.9]	50.3 [38.0, 68.3]
Leucine, μmol/L	100.1 [84.5, 118.9]	99.2 [87.4, 112.4]	101.7 [88.1, 117.8]	98.7 [81.9, 119.9]	101.0 [78.8, 131.3]
Valine, μmol/L	205.4 [180.1, 234.8]	197.3 [179.1, 216.4]	208.2 [186.5, 230.9]	207.1 [177.2, 239.6]	217.0 [175.7, 264.2]
MVX score	44.0 [35.0, 53.5]	29.2 [24.7, 32.4]	39.7 [37.4, 41.8]	48.3 [46.1, 50.7]	60.7 [56.6, 66.9]
Follow-up, year	13.7 [12.9, 14.4]	13.7 [12.9, 14.4]	13.7 [13.0, 14.4]	13.7 [13.0, 14.4]	13.7 [12.9, 14.4]

Characteristics of participants are presented as median (P_{25}, P_{75}) for continuous variables, and frequency (%) for categorical variables.
Differences of variables between baseline MVX quartiles were assessed using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables, with all $P < 0.05$.
Abbreviation: TDI Townsend Deprivation Index; BMI Body Mass Index; eGFR estimated Glomerular Filtration Rate; Charlson Comorbidity Index; GlycA Glycoprotein Acetyls; sHDL Particle Number of Small High-Density Lipoprotein; MVX metabolic vulnerability index.

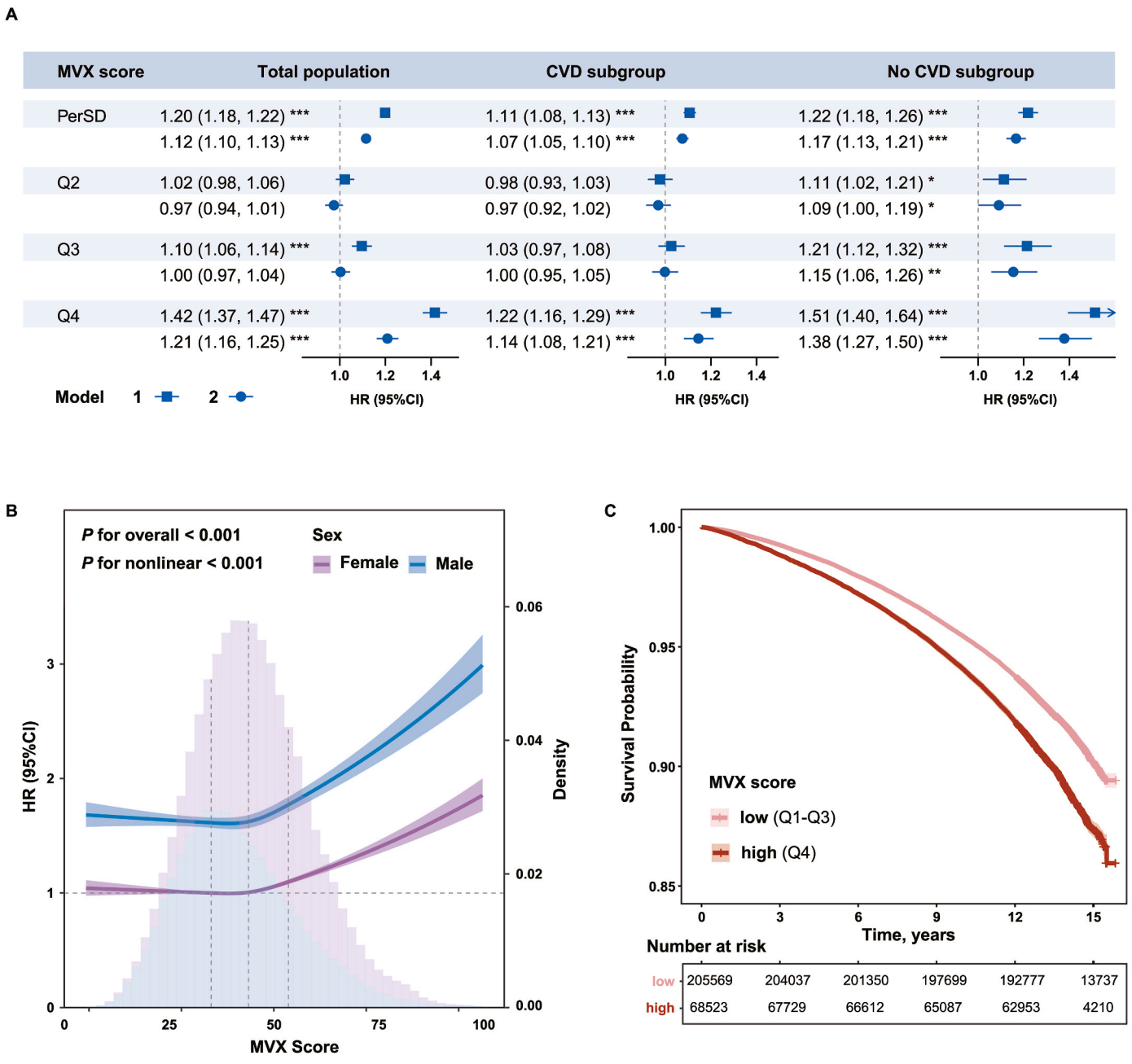

Fig. 1. Associations between baseline MVX and all-cause mortality. (A) Associations in the total population, CVD and non-CVD subpopulation. Hazard ratios for quartile 2 to 4 (Q2-Q4) of MVX were calculated using quartile 1 as the reference. Model 1 was adjusted for sex, ethnicity (White or others), and TDI; Model 2 was adjusted for Model 1 variables plus BMI, eGFR, current smoking status (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no) and baseline CCI = 0 (yes or no). *** FDR-$P < 0.001$; ** FDR-$P < 0.01$; * FDR-$P < 0.05$. All P for trend across MVX quartiles were <0.05. (B) Histogram of baseline MVX score and nonlinear associations stratified by sex (knots = P_{25}, P_{50}, and P_{75}). The grey dotted lines represent the P_{25}, P_{50}, P_{75} of baseline MVX score, respectively. (C) Kaplan-Meier survival curves stratified by baseline MVX groups. Abbreviation: CI confidence interval; CVD cardiovascular disease; HR Hazard ratio; MVX metabolic vulnerability index; Q1-4 1st-4th quartile; SD standard deviation.

curve (Fig. 1C) shows that individuals with an MVX score below the 75th percentile had a significantly higher overall survival probability than those in the highest quartile group ($P < 0.0001$).

Since the MVX score was calculated based on six metabolic markers, the associations of individual markers with all-cause mortality are presented in eTable 3. GlycA and Citrate levels were associated with a higher risk of all-cause mortality, whereas sHDL and branched-chain amino acid (BCAA, including isoleucine, leucine, and valine) levels were negatively associated with all-cause mortality. The relative importance of each variable in predicting all-cause mortality is visualized in eFig. 3. After matching age, sex, baseline CCI group, smoking status, and TDI, the MVX score emerged as one of the dominant predictors of mortality, with a relative contribution of 10.2 %. Notably, inflammation-related markers were the most significant contributors: GlycA accounted for 35.2 % and sHDL for 27.3 % of the predictive power. Notably, adding MVX to traditional model significantly improved mortality prediction (ΔC-statistic = 0.004, 95%CI = 0.002–0.006, $P < 0.001$; net reclassification improvement [NRI] = 0.052, 95%CI = 0.035–0.067, $P < 0.001$).

Subgroup analyses stratified by covariates such as age, sex, ethnicity, TDI, BMI, eGFR, current smoking status, hypertension, diabetes, dyslipidemia, and baseline CCI demonstrated that the association between

the MVX score and all-cause mortality remained statistically significant across all strata (Table 2). Additionally, we observed that baseline age and CCI exhibited multiplicative (*P* for interaction <0.05) and positive additive interactions (the lower 95 % confidence limit of synergy index >1) with the MVX score in relation to mortality risk. Specifically, the additive interaction effect between baseline age and the MVX score on mortality risk was 1.08 times (95 % CI: 1.07–1.09) greater than the sum of their individual effects. Similarly, the additive interaction between baseline CCI and the MVX score contributed to 9.38 % (95 % CI: 7.31%–11.45 %) of all deaths.

3.3. Baseline MVX, specific mortality, and incident disease

To comprehensively investigated the associations between the MVX score and mortality, we analyzed overall mortality at 5, 10, and 15 years, as well as cause-specific mortality and the risks of incident diseases corresponding to each cause of death, considered as secondary outcomes (Fig. 2). The baseline MVX score displayed a consistent association with mortality over the 15-year follow-up period, though this association weakened over time, with HRs of 1.20, 1.13, and 1.08 for 5-, 10-, and 15-year mortality, respectively. The MVX score was significantly associated with both the incidence and mortality of circulatory and respiratory diseases, but only with mortality in the case of cancer and stroke. Notably, across all specific causes, the HRs for mortality were greater than those for incident disease, the strongest association was observed in COPD-specific mortality (HR: 1.22, 95 % CI: 1.11–1.33, FDR-$P < 0.001$).

3.4. Longitudinal MVX score and all-cause mortality

In the longitudinal analysis, 15,689 participants experienced changes in their MVX score over a median follow-up of 9.7 years, among which 922 (5.9 %) deaths occurred. An increase in the MVX score during follow-up, indicating worsening metabolic vulnerability, was significant associated with mortality risk ($P = 0.041$, Fig. 3A). Compared to participants who constantly maintained low MVX levels, those with consistently high MVX levels had a 24 % higher risk of all-cause mortality (HR: 1.24, 95 % CI: 1.04–1.46) after adjusting for sex, ethnicity, and TDI (Fig. 3B). However, this association was modest when additional health-related covariates were included in model 2 (HR: 1.09, 95 % CI: 0.91–1.29). Stratified analyses by sex showed that females with high MVX score both at baseline and follow-up had a significantly increased risk of mortality (HR: 1.39, 95 % CI: 1.04–1.84 in model 2).

4. Discussion and conclusion

To our knowledge, the present study represents the largest population-based cohort study investigation of longitudinal MVX and mortality. We evaluated the NMR-based MVX score in relation to incident mortality over 13.7 years of follow-up in a cohort of 274,092 UKB participants. A significant, graded positive association was observed between MVX quartiles and mortality risk in both short and long-term. Females generally had higher MVX scores than males, yet males exhibited greater mortality risks at the same MVX level. Additionally, individuals with persistently high MVX scores at both baseline and follow-up had a higher mortality risk compared to those with consistently low MVX scores, especially among females. Our findings suggest that sex-stratified MVX is a promising indicator for stratifying mortality risk in population-level screening.

Predicting lifespan and mortality risk has long been a hot spot of medical research. Several studies have highlighted the influence of common risk factors like obesity, hypertension, and hyperlipemia on mortality risk [23,24]. However, these effects tend to diminish with age [25,26], and in some cases, may even reverse in older adults compared to middle-aged individuals [2,3]. This phenomenon, known as mortality crossover, poses a significant challenge to the effectiveness of traditional risk factors in mortality prediction. Moreover, a meta-analysis of intervention trials aimed at modifying these risk factors revealed that weight loss did not significantly reduce mortality risk, particularly in individuals over the age of 60 [27]. With populations living longer and the global shift towards deaths at older ages, there is an urgent need for a more reliable indicator to predict long-term mortality and guide risk stratification in community-based population.

Inflammation and metabolic disorders are closely interconnected, forming fundamental pathways that contribute to many diseases, often beginning even at subclinical stage of the disease continuum [28].

Table 2
Subgroup analyses on associations between baseline MVX and all-cause mortality.

Subgroup		HR (95 % CI)	Multiplicative effect *P*	RERI	AP, %	Synergy Index
Sex	Male	1.02 (1.00, 1.03)	**1.78e-48**	**−0.22 (-0.28, -0.15)**	**−6.48 (-8.14, -4.82)**	0.92 (0.90, 0.93)
	Female	1.34 (1.30, 1.38)				
Age, year	≤median	1.14 (1.11, 1.18)	**6.55e-04**	**0.04 (0.02, 0.06)**	**2.60 (1.64, 3.55)**	**1.08 (1.07, 1.09)**
	>median	1.11 (1.09, 1.13)				
Ethnicity	White	1.11 (1.09, 1.12)	**9.62e-03**	−0.04 (−0.08, 0.00)	**−2.50 (-4.95, -0.06)**	0.93 (0.88, 0.98)
	Others	1.21 (1.15, 1.28)				
TDI	≤median	1.12 (1.10, 1.15)	1.68e-01	0.00 (−0.00, 0.01)	0.27 (−0.06, 0.61)	1.02 (1.00, 1.04)
	>median	1.12 (1.09, 1.14)				
BMI	≤median	1.17 (1.15, 1.20)	4.46e-01	**0.00 (0.00, 0.00)**[a]	**0.10 (0.02, 0.17)**	1.01 (1.00, 1.02)
	>median	1.10 (1.08, 1.12)				
eGFR	≤median	1.12 (1.10, 1.15)	**1.98e-08**	**−0.00 (-0.00, -0.00)**[b]	**−0.12 (-0.16, -0.09)**	1.00 (0.99, 1.00)
	>median	1.11 (1.08, 1.14)				
Current smoker	no	1.12 (1.10, 1.14)	**1.20e-03**	0.03 (−0.04, 0.11)	1.20 (−1.63, 4.02)	1.02 (0.97, 1.07)
	yes	1.07 (1.04, 1.11)				
Hypertension	no	1.12 (1.10, 1.15)	4.16e-01	0.01 (−0.01, 0.04)	1.06 (−0.87, 2.98)	1.04 (0.96, 1.12)
	yes	1.10 (1.08, 1.13)				
Diabetes	no	1.12 (1.10, 1.14)	8.58e-01	0.04 (−0.00, 0.08)	2.69 (−0.31, 5.70)	1.09 (0.97, 1.24)
	yes	1.11 (1.06, 1.16)				
Dyslipidemia	no	1.11 (1.09, 1.13)	3.47e-01	0.01 (−0.01, 0.03)	0.97 (−1.21, 3.15)	1.17 (0.69, 1.99)
	yes	1.12 (1.09, 1.15)				
Baseline CCI	= 0	1.08 (1.06, 1.10)	**1.32e-04**	**0.20 (0.17, 0.24)**	**9.38 (7.31, 11.45)**	**1.21 (1.14, 1.29)**
	>0	1.16 (1.13, 1.19)				

a: 0.001 (0.000, 0.002); b: −0.002 (−0.002, −0.001).
All analyses were adjusted for sex, ethnicity (White or others), TDI, BMI, eGFR, current smoking status (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and baseline CCI = 0 (yes or no). Bold font represents statistical significantly interaction.
Abbreviation: AP attributable proportion due to interaction; BMI Body Mass Index; CCI Charlson Comorbidity Index; CI confidence interval; eGFR estimated Glomerular Filtration Rate; HR Hazard ratio; MVX metabolic vulnerability index; RERI relative excess risk due to interaction; TDI Townsend Deprivation Index.

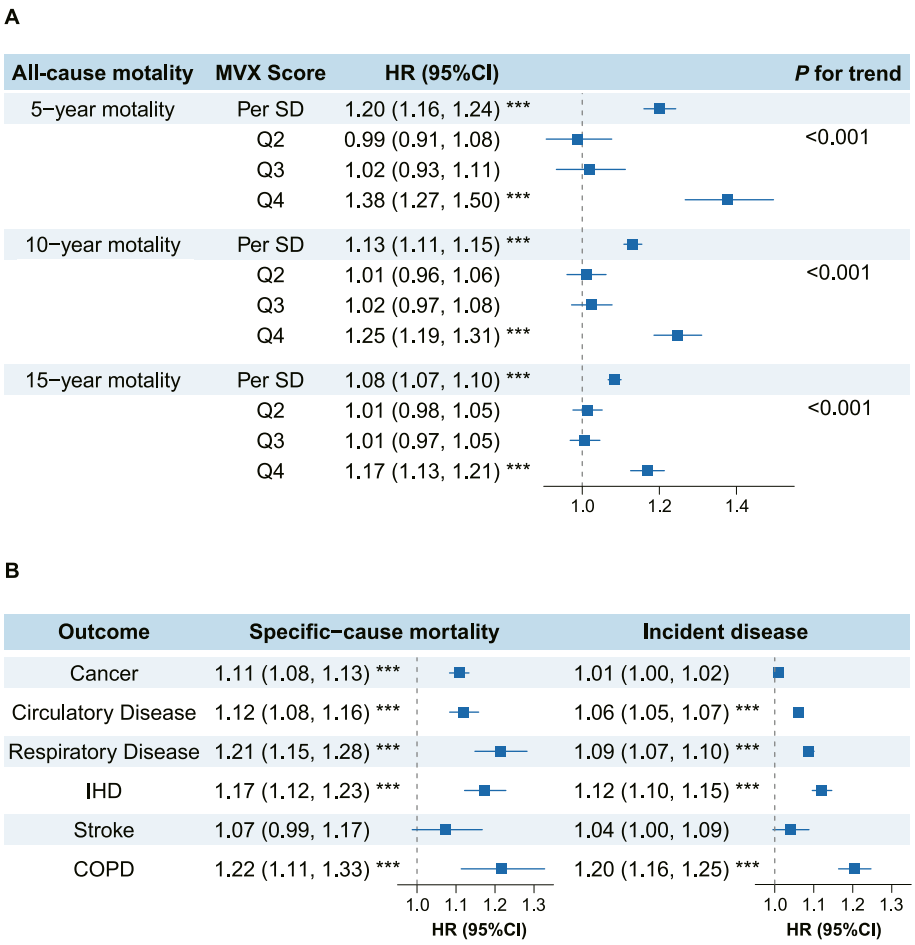

Fig. 2. Associations between baseline MVX score and long-term mortality, cause-specific mortality, and disease incidence (A) Associations between baseline MVX score and 5-, 10-, 15-year all-cause mortality. (B) Associations between baseline MVX score and specific cause mortality, and risk of incident disease. HRs for quartile 2 to 4 (Q2-Q4) of MVX were calculated using quartile 1 as the reference. Adjustments were made for sex, ethnicity (White or others), TDI, BMI, eGFR, current smoking status (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and baseline CCI = 0 (yes or no). *** FDR-$P < 0.001$. Abbreviation: CI confidence interval; COPD Chronic obstructive pulmonary disease; HR Hazard ratio; IHD Ischemic heart disease; MVX metabolic vulnerability index; Q2-4 2nd-4th quartile; SD standard deviation.

Although the determinants of circulating metabolites and derived MVX score are indeed complex and multifactorial [6], evidence supports the biochemical stability and long-term applicability of plasma metabolites. GlycA has a low intraindividual variability (4.3 % over 5 weeks) [29], and plasma branched-chain amino acids (isoleucine, leucine, valine) demonstrated the minimal fluctuations over decades [30]. Numerous studies have explored the possibility of circulating metabolites as predictors of long-term mortality. For instance, circulating GlycA has been identified as a novel pro-inflammatory marker associated with increased risk of all-cause mortality in a meta-analysis of seven population-based prospective cohort studies [31], which aligns with our findings. Pro-inflammatory mediators and redox imbalance are mechanistically linked in the initiation and progression of various chronic diseases, as ROS overproduction and accumulation are driven by the respiratory burst of inflammatory cells during inflammatory responses [32]. Citrate, a key component in energy metabolism through the Krebs cycle, was also observed to be positively associated with 5-year mortality in the Estonian Biobank cohort [8]. Additionally, we found negative associations between sHDL and BCAA with all-cause mortality, consistent with other studies [15,16]. Elevated metabolic vulnerability drives systemic metabolic dysregulation, directly disrupting redox homeostasis by triggering oxidative stress and endoplasmic reticulum stress [17].

The challenge with using individual metabolites for mortality prediction lies in their limited scope and the differing directions of association between metabolites and mortality. The development of MVX effectively addresses this issue by offering a more comprehensive view of an individual's overall metabolic and inflammatory status, though its full potential for mortality prediction has yet to be fully recognized. The association between MVX and mortality risk was initially identified and validated in cardiovascular patient cohorts [12,16]. Our study extends these findings to community-based population. In the hospital-based CATHGEN cohort [12], the median MVX score was 50, where its relative contribution to mortality prediction surpassing that of many established risk factors. In our study, the median MVX score was slightly lower at 44, reflecting a healthier metabolic-inflammatory profile in community residents. Even after adjusting for key confounders like age and sex, MVX had a significant relative contribution to mortality risk (10.2 %), comparable to BMI (12.8 %) and hypertension (12.6 %) in the current study. This suggests that greater metabolic vulnerability could explain some of the additional mortality risks in community-based population. The graded increase in mortality risk across MVX quartiles in this study mirrors findings from earlier studies [12,16], offering robust evidence for the utility of MVX in risk stratification.

Recent large-scale studies have demonstrated that plasma metabolites can predict disease and mortality up to 20 years [11,33], which is consistent with our finding that MVX is significantly associated with both 5-year and 15-year mortality. However, the observed attenuation of MVX's effect size over longer follow-up periods (higher hazard ratios for 5-year versus 15-year mortality) may reflect the growing influence of unmeasured aging-related processes over time, which could diminish

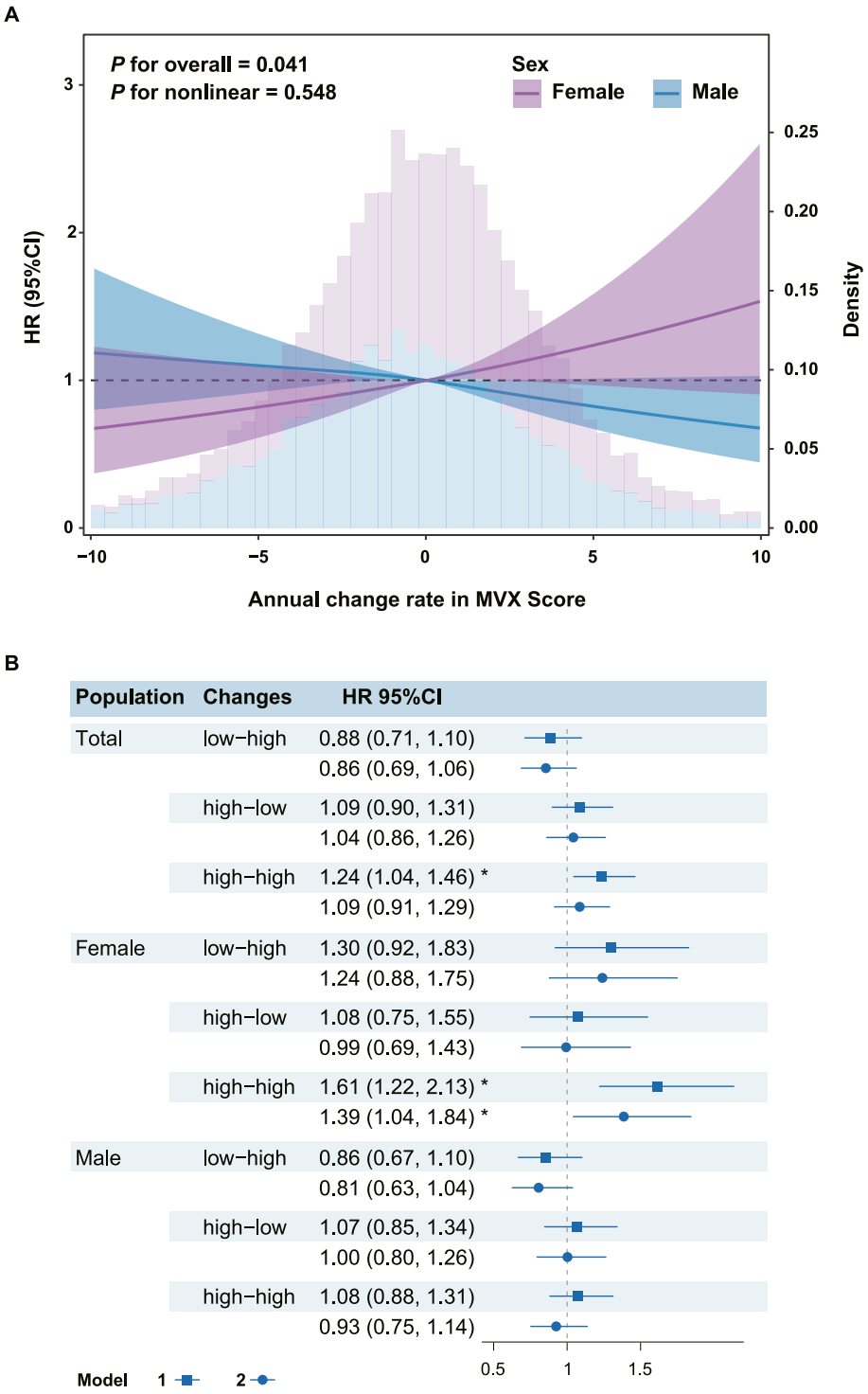

Fig. 3. Associations between longitudinal changes in MVX and all-cause mortality (A) Histogram of annual change rate in MVX score and nonlinear associations stratified by sex (knots = P_{25}, P_{50}, and P_{75}). (B) Associations of longitudinal MVX change patterns with all-cause mortality in the total population, and separately for female and male, using low-low as the reference. Model 1 was adjusted for sex, ethnicity (White or others), and TDI; Model 2 adjusted for Model 1 variables plus BMI, eGFR, current smoking status (yes or no), hypertension (yes or no), diabetes (yes or no), dyslipidemia (yes or no), and baseline CCI = 0 (yes or no). *$P < 0.05$. Abbreviation: CI confidence interval; HR Hazard ratio; MVX metabolic vulnerability index; SD standard deviation.

MVX's relative contribution to mortality risk. Notably, a recent study similarly reported declining predictive performance of aging biomarkers for mortality risk as follow-up extends from 1 to 15 years [34]. To further validate the hypothesis that metabolic vulnerability is a key driver of multimorbidity and mortality [35], we examined specific causes of death and found significant associations between MVX and several cause-specific mortalities, as well as related incident disease risks. Given the dynamic nature of circulating metabolites, major concerns arose regarding the relevance of single-point measurements for predicting long-term outcomes were addressed by analyzing the impact of longitudinal changes in MVX utilizing repeated NMR data. Our results indicated that females with consistently high metabolic vulnerability across two assessments had the highest mortality risk, providing preliminary evidence for further monitoring and intervention of high-risk

populations.

Sex differences in lifespan and mortality are largely driven by hormonal factors [36]. In this study, we found a significant interaction between sex and MVX in predicting mortality risk. Males exhibited higher mortality risk at equivalent MVX levels because of estrogen's protective metabolic effects on females [37]. However, the menopausal estrogen decline in middle-aged females may intensify metabolic burden [37,38], as evidenced by their higher baseline MVX scores compared to males. The longitudinal association between MVX changes and mortality was significant only in females, particularly those with persistently high MVX levels, which may be attributable to the cumulative effects of elevated baseline metabolic vulnerability. Our findings indicate that females maintaining persistently high MVX scores are the critical high-risk subgroup for clinical screening and intervention. Therefore, while MVX robustly predicts mortality in both sexes, its interpretation and clinical application must account for sex-specific biological contexts, particularly the interplay between hormonal status and metabolic vulnerability.

The evidence from this large-scale population cohort highlights MVX's significant potential in mortality risk stratification, extending its application beyond hospital patients to community-based population. Our study has several strengths. MVX captures systemic metabolic vulnerability and oxidant/antioxidant imbalance—pathophysiological processes that often precede overt overweight or hypertension—thereby identifying high-risk individuals earlier and enabling personalized interventions. Moreover, the longitudinal analysis underscores the importance of tracking changes in MVX over time. Individuals with consistently high MVX score were found to be at greater risk of death, emphasizing the need to classify them as a high-risk group for targeted intervention. However, potential limitations of this study deserve consideration and further investigation. First, the specific population structure of the UKB, such as predominantly White ethnicity (>90 % White), may limit external validity [39], necessitating replication in multi-ethnic cohorts with comparable NMR metabolomic data. Additionally, while we explored longitudinal changes in MVX, the classification of MVX changes remains preliminary. More detailed analysis of the trajectories of metabolic alterations and their association with mortality risk requires further follow-up data. Despite adjusting for key covariates (e.g., demographics, clinical measurements and comorbidities), residual confounding from unmeasured genetic and environmental factors might has potential influences. Further research on determinants of circulating metabolites could inform targeted interventions, while molecular experiments are also warranted to validate the causal association of MVX with mortality and its underlying mechanisms.

In summary, the MVX score, derived from six NMR metabolites, was strongly associated with mortality in this large population-based cohort, demonstrating its potential as a promising indicator for mortality risk stratification. Individuals in the top MVX quartile faced the highest mortality risk in both the short and long term. However, timely improvement in metabolic vulnerability could potentially reduce future risk. The findings of this study hold significant implications for early identification of high-risk individuals and could inform personalized prevention strategies aimed at improving long-term health outcomes. As metabolic vulnerability may represent a universal pathway to mortality, further research is warranted to investigate the underlying mechanisms and establish causal relationships.

CRediT authorship contribution statement

Jialin Li: Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Qiuhong Man:** Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. **Yingzhe Wang:** Writing – review & editing. **Mei Cui:** Writing – review & editing. **Jincheng Li:** Methodology. **Kelin Xu:** Data curation. **Zhenqiu Liu:** Data curation. **Li Jin:** Supervision. **Xingdong Chen:** Funding acquisition, Supervision. **Chen Suo:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Yanfeng Jiang:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2025.103585.

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