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Research paper

Plasma metabolites, metabolic risk score and the risk of depression and anxiety disorders: A prospective cohort study

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ABSTRACT

Background: The prospective associations between metabolites and depression and anxiety risk are limited. Therefore, we conducted this cohort study to estimate the associations of depression and anxiety risk with metabolites, metabolic risk score (MRS), and the combinations and interactions of MRS with lifestyles.

Methods: This study included 30,127 participants with plasma metabolites data and mental health assessments in the UK biobank. XG-Boost and LASSO-COX regression were used to select metabolites. Cox regression was used to construct MRS and estimate the associations between metabolites, MRS, the combinations and interactions of MRS with lifestyles and depression and anxiety risk. Restricted cubic splines were used to evaluate non-linear relationships.

Results: During a median follow-up of 94.03 months, 1581 depression and 1807 anxiety were identified. Totally 148 and 42 metabolites were significantly associated with depression and anxiety risk, respectively. Intermediate and high MRS were significantly associated with increased depression risk (HR = 1.88[1.43–2.46] and 3.18 [2.37–4.27], $P < 0.001$) and anxiety risk (HR = 1.34[1.03–1.73], $P = 0.027$ and 1.67[1.24–2.24], $P < 0.001$) with a non-linear pattern ($P_{nonlinear} < 0.001$). Intermediate and high MRS combined with lifestyle, BMI, sleep duration, physical activity, diet, and smoking were significantly associated with depression and anxiety risk. High MRS combined with favorable lifestyle was also significantly associated with depression and anxiety risk. Significant additive interaction was identified between MRS and lifestyles on depression risk.

Conclusions: Plasma metabolites and MRS were significantly associated with depression and anxiety risk. Maintaining normal metabolite levels is crucial for depression and anxiety prevention, even among individuals with healthy lifestyle.

1. Background

Depression and anxiety are significant contributors to the global burden of mental health-related illnesses (Malhi and Mann, 2018; Friedrich, 2017; Lancet Psychiatry, 2022), afflicting approximately 320 million and 260 million individuals worldwide, which represent 4.4 % and 3.6 % of the global population, respectively (Herrman et al., 2022; Herrman et al., 2019). Depression and anxiety not only affect the patients themselves but also their families, and even have profound deleterious effects on social integration and the economy (Ronaldson et al., 2021). Moreover, depression and anxiety frequently co-occur in patients, with 50–60 % of individuals with depression disorder having a history of anxiety disorder (Zhou et al., 2017; Moffitt et al., 2007). However, detection and diagnosis of depression and anxiety remain

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challenging, due to the heterogeneity of clinical symptoms, severity and longitudinal courses (Prigge et al., 2022). Thus far, the precise physiological mechanisms and reliable predictive biomarkers for depression and anxiety remain insufficiently defined (Okely et al., 2021; Harvey et al., 2018; Cheng et al., 2021; Masana et al., 2019).

Metabolites such as lipids (Ahmed et al., 2020; Parekh et al., 2017; MahmoudianDehkordi et al., 2021), amino acids (Mann et al., 2014), and biogenic amines (Grace, 2016) play important roles in the pathophysiology of depression and anxiety. A meta-analysis of 22 case-control studies demonstrated that levels of kynurenine and kynurenic acid were significantly lower in depression patients than in controls (Ogyu et al., 2018). A cross-sectional study in Singapore identified four amino acid metabolites (glutamic acid, aspartic acid, glycine, and 3-hydroxykynurenine) which could effectively distinguish major depression disorder patients from healthy controls (AUC = 0.68)(Ho et al., 2023). However, no prospective cohort study has estimated the associations between metabolites and the risk of depression and anxiety. In addition, the effect of single metabolite was small or moderate, a combination of metabolic biomarkers may have stronger effect on depression and anxiety due to its high heterogeneity (Julkunen et al., 2023). Although depression and anxiety often coexist, the metabolomic profiles associated with depression and anxiety are not always identical (Beuchel et al., 2019). Certain inflammation-related and atherosclerosis-associated lipoproteins associated with depression were not significantly associated with anxiety (de Kluiver et al., 2021). Therefore, further prospective cohort studies are warranted to comprehensively estimate the associations between metabolites and risk of depression and anxiety.

Lifestyle factors, such as poor dietary habits, intake of high-sugar high-fat and processed foods, insufficient sleep, lack of physical activity, smoking, and excessive alcohol consumption, could influence metabolites levels and components, and thereby increasing the risk of depression and anxiety (Fulton et al., 2022; Dutheil et al., 2016; Hahad et al., 2022; Castro et al., 2023; Fluharty et al., 2017; Paris et al., 2024). Whereas, regular physical activity (Laird et al., 2023; Kim et al., 2019; McDowell et al., 2019), consumption of fruits, vegetables, and whole grains (Dharmayani et al., 2022; Chen et al., 2023; De Szabo Edelenyi et al., 2021; Chi et al., 2016) could significantly reduce the risk of depression and anxiety. Combining metabolites with lifestyle factors may be beneficial for identifying individuals at high risk of depression and anxiety. However, current studies are limited to the associations between separate metabolites or lifestyle factors and risk of depression and anxiety. Further studies especially prospective cohort studies are warranted to estimate the combined effects of metabolites and lifestyle factors on the risk of depression and anxiety.

In this study, we conducted a prospective cohort study in the UK Biobank to estimate the associations between metabolites and the risk of depression and anxiety, to develop metabolic risk score (MRS) by incorporating multiple metabolites and estimate its associations with depression and anxiety risk. Additionally, we estimated the associations of depression and anxiety risk with the combinations of MRS with lifestyles and individual lifestyle factors.

2. Methods

2.1. Study population

The UK Biobank cohort recruited 502,411 individuals aged 40 to 69 years old between 2006 and 2010 (Fry et al., 2017). This study included 157,345 participants who completed the online mental health questionnaires during 2016–2017. We further excluded participants with depression, anxiety, and bipolar disorder at baseline based on self-report, psychiatric medication, and medical records (n = 19,761), cancer at baseline (n = 10,447), and those without plasma metabolites data (n = 97,010). Ultimately, 30,127 participants were included in this study (Additional file 1: Fig. S1). Approval for the UK Biobank study was granted by the North West Multicenter Research Ethics Committee (REC reference 21/NW/0157) (Sudlow et al., 2015).

2.2. Covariates assessment

The following information was collected from every participant: age, sex, ethnic background, education level, Townsend Deprivation Index (TDI), lifestyle factors (smoking, alcohol drinking, physical activity, diet and sleep duration etc.), and physical examinations (BMI), systolic blood pressure (SBP), and pulse rate. The TDI was derived based on residents' postal codes and census data on unemployment rates, non-car ownership, non-home ownership, and household overcrowding. We established a healthy lifestyle score based on the score of smoking, alcohol drinking, sleep duration, healthy diet, BMI, and physical activity. Score of 1 point was given to no current smoking, healthy diet, BMI >18.5 and < 25 kg/m^2, sleep duration ≥7 and ≤ 9 h, moderate alcohol drinking and physical activity; 0 point otherwise. Healthy diet was defined as decreased consumption of processed meats and red meats, but increased intake of fruits, vegetables and fish. Moderate alcohol drinking was defined as <14 g/day for women and <28 g/day for men. Moderate physical activity was defined as 150 or more minutes of moderate-intensity activity weekly or 75 or more minutes of vigorous activity weekly. The healthy lifestyle was defined as unfavorable (0–1 point), moderate (2 points), and favorable lifestyle (3–4 points) according to the healthy lifestyle score. Detailed definitions of lifestyle factors were described in Additional file 1: Table S1-S2.

2.3. Assessment of outcomes

Depression and anxiety disorders were determined by the 2016 mental health web-questionnaire (Davis et al., 2020), employing the Patient Health Questionnaire-9 (PHQ-9 ≥ 15) and the Generalized Anxiety Disorder-7 (GAD-7 ≥ 15) scales. The mental-health questionnaires of PHQ-9 and GAD-7 were shown in Additional file 1: Table S3-S4.

2.4. Metabolic biomarker profiling

This study utilized metabolic biomarker data from Nightingale Health Ltd.'s high-throughput H-NMR metabolomics platform, which quantified the plasma levels of 249 metabolites from 118,461 randomly selected EDTA plasma samples collected at recruitment. According to Julkunen H (Julkunen et al., 2023), the NMR metabolites data was processed by removing extreme values beyond four times the IQR (interquartile range), correcting metabolites concentrations through linear regression to model the effect of technical and spectrometer variables, and applying natural logarithmic transformation ($\log[x + 1]$) followed by standardization (Z-transformation).

In this study, the 249 metabolites were categorized into 18 subgroups: amino acids (10), apolipoproteins (2), cholesterol (7), cholesteryl esters (4), fatty acids (9), fluid balance (2), free cholesterol (4), glycolysis related metabolites (4), inflammation (1), ketone bodies (4), lipoprotein particle concentrations (4), lipoprotein particle sizes (3), lipoprotein subclasses (98), other lipids (4), phospholipids (4), ratios/percentages (81), total lipids (4), and triglycerides (4).

2.5. Metabolic risk score

Metabolites associated with depression and anxiety were identified by the LASSO regularized Cox regression model with 10-fold cross-validation and XG-Boost algorithm (using gain values as weights). In LASSO-Cox regression model, the penalty weight parameter of α was set to 1, the penalty complexity parameters of λ were 0.0003195 and 0.0005776 for depression and anxiety, respectively. In XG-Boost algorithm, the Gain value represents the average improvement in the model's performance achieved by selecting a particular feature for splitting at each tree node across all trees. A higher gain indicates a more effective feature for making splits and enhancing the model's predictive

power. The number of metabolites we preserved in the XG-boost model was the same as Lasso regression for every outcome (Additional file 1: Table S6).

The metabolites identified by both the LASSO-COX regression model and XG-Boost algorithm were imported in Cox regression model with forward and backward selection methods to establish an optimal Cox regression model. The remaining metabolites in the optimal Cox regression model were used to construct metabolic risk scores (MRS) for depression and anxiety respectively (Additional file 1: Table S7).

$$MRS^{*} = \ln h\,(t, x) = \ln h_0\,(t) + \beta_i \times x_i$$

*MRS - metabolites risk score

β represents the coefficient of metabolites within the MRS model, x denotes the natural log-transformed and standardized (*Z*-transformation) concentration of metabolites· Here, i represents the i-th metabolite.

Participants were categorized into three groups based on the cutoff value of 20 % and 80 % of MRS: low MRS (< −0.4102), medium MRS (−0.4102–0.4078), and high MRS (> 0.4078) for depression; low MRS (< −0.3161), medium MRS (−0.3161–0.3170), and high MRS (> 0.3170) for anxiety.

2.6. Statistical analysis

Continuous variables were described as mean (standard deviation, SD), categorical variables were described as frequency (percentage). Follow-up time was defined as the period from the date of baseline assessment to the diagnosis date of depression and anxiety by the mental health web-questionnaire.

The Cox regression model was applied to estimate the associations between 249 metabolites and risk of depression and anxiety, with corresponding Hazard Ratios (HR) and 95 % Confidence Intervals (CIs). The initial model 1 was minimally adjusted for sex and age. The extended multivariable adjustment model 2 was further adjusted for TDI, educational level (college or university degree or other professional qualifications, A/AS levels or equivalent or O levels/GCSEs or equivalent, none of the above), SBP, glucose, and pulse rate. The fully adjusted model 3 was additionally adjusted for healthy lifestyles (unfavorable, intermediate and favorable).

The Cox regression model was used to estimate the associations between MRS and the risk of depression and anxiety adjusting for age, sex, TDI, educational level, SBP, pulse rate, glucose and healthy lifestyles. The potential non-linear dose-response relationships between MRS and depression and anxiety risk were estimated by the restricted cubic splines, with 3 knots located at the 75th, 50th, and 25th percentiles of distribution. Subgroup analyses were conducted by stratifying for age, sex, BMI, individual lifestyle factors (sleep duration, physical activity, diet, smoking, and alcohol drinking) and healthy lifestyles. Sensitivity analyses were conducted by using interpolated dataset with missing values of covariates filled by chained equation imputation.

Crossover analyses were performed to estimate the combined effects of MRS with individual lifestyle factors and healthy lifestyles on the risk of depression and anxiety in the Cox regression models. Interaction analyses were conducted for depression and anxiety. For the multiplicative interaction, we added an interaction term ("MRS*lifestyles") in the multivariable cox regression model to estimate the significance and magnitude of multiplicative interaction. For the additive interaction, the biological interactions between MRS and lifestyles on depression and anxiety were evaluated with relative excess risk ratio (RERI), attribution percentage (AP), and synergy index (SI).

The statistical analyses were performed using R software version 4.3.2, with *p*-value <0.05 (two-sided) indicating statistical significance.

3. Results

3.1. Baseline characteristics of the study participants

We identified 1581 depression and 1807 anxiety during the median follow-up time of 94.03 months (interquartile range 85.30 to 101.73), respectively. The mean (SD) age of participants was 57 (7.79) years, with 16,199 males and 13,928 females. Detailed baseline characteristics were provided in Additional file 1: Table S5.

3.2. Associations between metabolites and the risk of depression and anxiety

A total of 148 and 42 metabolites were significantly associated with the risk of depression and anxiety, respectively (Additional file 1: Table S8-S9). Shared metabolic biomarkers of both depression and anxiety accounted for 18.92 % of depression-related metabolites and 66.67 % of anxiety-related metabolites. The metabolites were significantly associated with decreased risk of depression (68.92 %) and anxiety (45.24 %). Metabolites associated with depression risk predominantly included cholesterol, free cholesterol, glycolysis-related metabolites, lipoprotein subclasses, triglycerides, phospholipids, and their proportions in lipids of different particle sizes. Conversely, metabolites associated with anxiety risk were more concentrated in lipoprotein subclasses, triglycerides, and phospholipid proportions. Interestingly, in both depression and anxiety, all subclasses of fatty acids, concentrations of lipoprotein particles, and certain lipid subclasses (cholesterol, esterified cholesterol, free cholesterol, phospholipids) consistently exhibited protective effects, whereas triglycerides and phospholipids mostly exhibited risk effects (Additional file 1: Table S10).

3.3. Associations between MRS and the risk of depression and anxiety

In this study, MRSs for depression and anxiety were constructed using 21 and 16 metabolites (Additional file 1: Table S6), respectively. Detailed steps of metabolites selection and parameters of the MRS models are presented in Additional file 1:Tables S7. Compared with low MRS, the medium and high MRS significantly increased the risk of depression, with HRs and 95 % CIs of 1.88 (1.43–2.46) and 3.18 (2.37–4.27), respectively. As shown in Fig. 1, the medium and high MRS also significantly increase the risk of anxiety, with HRs and 95 % CIs of 1.34 (1.03–1.73) and 1.67 (1.24–2.24), respectively. We further observed non-linear relationships between MRS and the risk of depression and anxiety in the restricted cubic splines (Fig. 2). MRS was negatively associated with the risk of depression and anxiety when MRS <0, but positively associated with the risk of depression and anxiety when MRS >0.

In the subgroup analyses, high MRS was significantly associated with the risk of depression in all the subgroups, but high MRS was only significantly associated with the risk of anxiety in the favorable and unfavorable lifestyle subgroups. However, in the subgroup analyses stratified by individual lifestyle factors, the association between high MRS and anxiety risk became non-significant in the subgroups of 18.5 < BMI <25, inactivity, current smoking and heavy alcohol drinking (Table 1). To further assess the robustness of the results, we performed sensitivity analyses using interpolated dataset and identified consistently significant results in the total analyses and subgroup analyses (Additional file 1: Table S11).

3.4. Joint effect of MRS with healthy lifestyle and individual lifestyle factors on the risk of depression and anxiety

In this study, there was a joint effect of MRS and lifestyles on the risk of depression. Comparing with favorable lifestyle and low MRS, intermediate and high MRS combined with favorable, moderate and

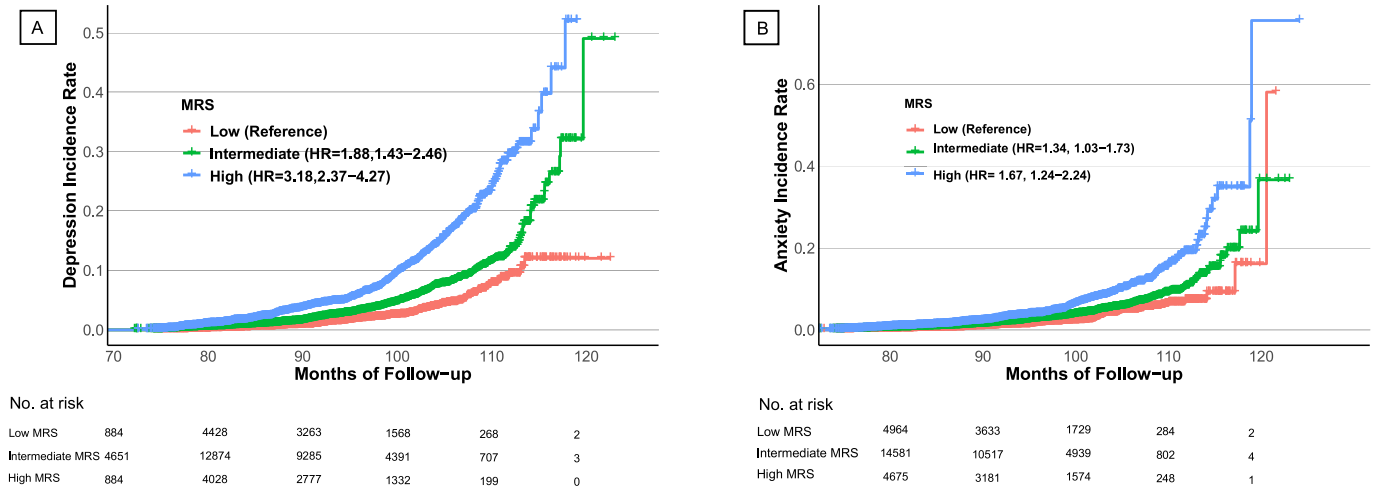

Fig. 1. Incidence rates of depression and anxiety across MRS during follow-up. Panel a and b represent the incidence rates of depression and anxiety. Participants were defined as high metabolic score risk (MRS), intermediate MRS and low MRS populations according to the top 20 %, 20 %–80 %, and the bottom 20 % of MRS, respectively. HRs and the 95 % CIs derived from Cox regression model adjusting for age, sex, TDI, education, SBP, pulse rate and glucose are provided in legend.

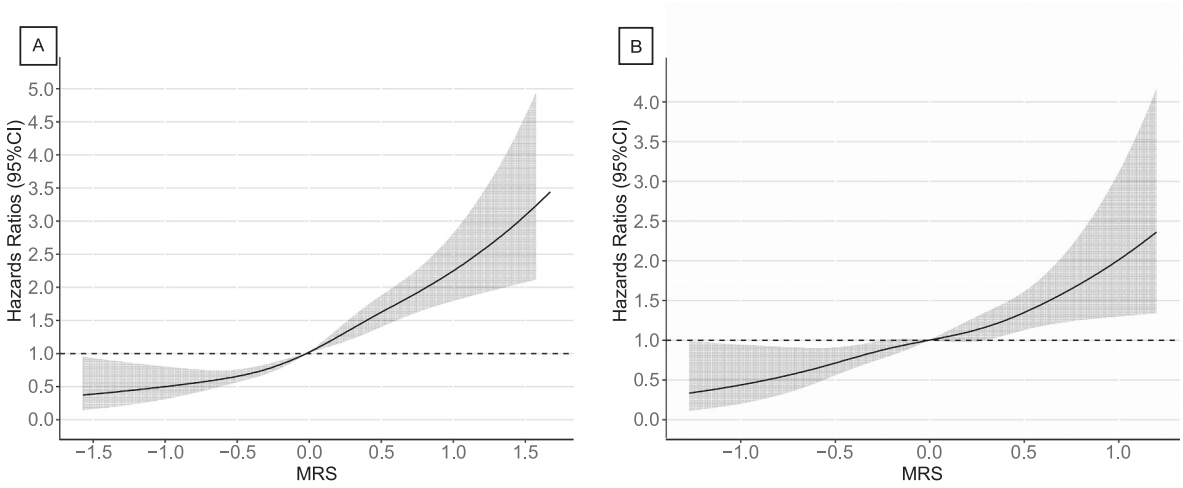

Fig. 2. Restricted cubic splines for the relationships of MRS and the risk of depression and anxiety. Panel a and b represent restricted cubic splines for the relationships of MRS and the risk of depression and anxiety in a Cox regression model adjusting for age, sex, TDI, education, pulse rate, SBP and glucose.

unfavorable lifestyles significantly increased depression risk, with HRs and 95 % CIs of 2.20 (1.42–3.40), 2.68 (1.73–4.15) and 4.38 (2.86–6.70) for intermediate MRS and 3.68 (2.24–6.03), 5.67 (3.58–8.98) and 6.46 (4.14–10.07) for high MRS, respectively. Low MRS combined with moderate and unfavorable lifestyles were also significantly associated with depression risk, with HRs and 95 % CIs of 1.90 (1.08–3.35) and 2.16 (1.14–4.11), respectively. Both Intermediate and high MRS combined with smoking, heavy drinking, diet score, sleep duration, and BMI significantly increased the risk of depression. Low MRS combined with individual lifestyle factors were not significantly associated with the risk of depression (Fig. 3a).

Comparing with favorable lifestyle and low MRS, high MRS combined with favorable, moderate and unfavorable lifestyles significantly increased anxiety risk, with HRs and 95 % CIs of 1.72 (1.10–2.69), 1.86 (1.18–2.93) and 2.33 (1.49–3.66), respectively. Intermediate MRS only significantly increased anxiety risk in individuals with moderate and unfavorable lifestyles, with HRs and 95 % CIs of 1.60 (1.07–2.39) and 1.99 (1.33–2.97), respectively. Low MRS combined with moderate and unfavorable lifestyles were not significantly associated with anxiety risk. High MRS combined with individual lifestyle factors significantly increased the risk of anxiety, except for sleep duration 7 ~ 9 h and inactivity. Intermediate MRS combined with sleep duration <7 and >9 h, inactivity, heavy drinking, diet score, smoking status and BMI significantly increased the risk of anxiety. Low MRS combined with sleep duration, diet score, physical activity and drinking were not significantly associated with the risk of anxiety (Fig. 3b).

3.5. *Interaction analyses of MRS and lifestyles on the risk of depression and anxiety*

To characterize the additive and multiplicative interaction, the median of lifestyle score and MRS were used as cutoff values. As show in Table 2, no significant multiplicative interaction was observed between MRS and lifestyles on the risk of depression. Significant additive interaction was identified between MRS and lifestyles on depression risk with AP of 0.16 (0.07–0.29) and SI of 1.30 (1.04–1.62), respectively, demonstrating a synergistic interaction between MRS and lifestyles on depression risk, with 16.4 % of depression risk attributed to the synergistic interaction between MRS and lifestyles. However, no additive and multiplicative interaction was observed for anxiety risk. Sensitivity analyses using interpolated dataset also identified consistent results in the combination analyses (Additional file 1: Table S12-S13).

Table 1
Stratification analyses of the associations between MRS and the risk of depression and anxiety.

Stratification		Depression				Anxiety			
	Low MRS [a]	Intermediate MRS [a]		High MRS [a]		Intermediate MRS[a]		High MRS [a]	
	Reference	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	*p value*	HR (95%CI)	P-value
Sex									
Female	1	1.68 (1.17–2.40)	0.005	3.25 (2.19–4.83)	<0·001	1.33 (0.95–1.86)	0.096	1.96 (1.21–3.17)	0.006
Male	1	2.10 (1.38–3.19)	<0·001	3.24 (2.08–5.04)	<0·001	1.30 (0.87–1.95)	0.198	1.58 (1.03–2.41)	0.035
Age (years)									
<60	1	1.92 (1.42–2.60)	<0·001	1.92 (1.42–2.60)	<0·001	1.46 (1.10–1.95)	0.009	1.93 (1.41–2.65)	<0·001
≥60	1	1.80 (0.98–3.30)	0.057	4.42 (2.30–8.50)	<0·001	1.78 (1.05–2.99)	0.031	3.38 (1.85–6.17)	<0·001
BMI (kg/m^2)									
>18.5& < 25	1	1.77 (1.16–2.69)	0.008	2.91 (1.76–4.81)	<0·001	1.12 (0.76–1.65)	0.566	1.24 (0.79–1.96)	0.350
Abnormal	1	1.79 (1.24–2.60)	0.002	2.90 (1.96–4.29)	<0·001	1.60 (1.10–2.33)	0.014	2.04 (1.33–3.12)	0.001
Sleep duration (hours/day)									
≥7 and ≤9	1	1.68 (1.22–2.32)	0.002	2.41 (1.67–3.46)	<0·001	1.33 (0.95–1.85)	0.095	1.55 (1.06–2.28)	0.025
<7 or > 9	1	2.19 (1.27–3.78)	0.005	4.52 (2.56–7.97)	<0·001	1.42 (0.89–2.25)	0.142	1.82 (1.08–3.09)	0.025
Physical activity status									
Regular	1	1.54 (1.08–2.22)	0.018	2.70 (1.80–4.03)	<0·001	1.27 (0.95–1.71)	0.104	1.75 (1.25–2.44)	0.001
Inactivity	1	2.21 (1.10–4.44)	0.026	3.02 (1.45–6.28)	0.003	1.81 (0.88–3.71)	0.107	1.40 (0.62–3.15)	0.417
Smoking status									
No current	1	1.54 (1.08–2.22)	0.018	2.70 (1.80–4.03)	<0·001	1.30 (0.90–1.89)	0.163	1.70 (1.11–2.59)	0.014
Current	1	2.14 (1.39–3.30)	0.001	3.32 (2.10–5.27)	<0·001	1.43 (0.97–2.12)	0.074	1.56 (0.99–2.46)	0.056
Alcohol consumption status									
Moderate alcohol	1	1.66 (1.20–2.28)	0.002	2.45 (1.72–3.49)	<0·001	1.53 (1.10–2.14)	0.012	1.80 (1.23–2.64)	0.003
Heavy alcohol	1	2.09 (1.21–3.62)	0.008	4.54 (2.54–8.09)	<0·001	1.04 (0.66–1.64)	0.870	1.38 (0.82–2.32)	0.232
Diet status									
Healthy	1	1.86 (1.31–2.65)	<0·001	3.02 (2.04–4.47)	<0·001	1.28 (0.91–1.79)	0.159	1.55 (1.06–2.29)	0.026
Unhealthy	1	1.66 (1.07–2.59)	0.024	2.88 (1.80–4.62)	<0·001	1.51 (0.96–2.37)	0.076	1.81 (1.08–3.04)	0.025
Life scores									
Favorable	1	2.05 (1.20–3.49)	0.009	3.04 (1.74–5.31)	<0·001	1.23 (0.86–1.75)	0.253	1.61 (1.06–2.44)	0.024
Moderate	1	1.42 (0.90–2.23)	0.132	3.07 (1.88–5.01)	<0·001	1.09 (0.73–1.61)	0.678	1.36 (0.87–2.14)	0.181
Unfavorable	1	2.18 (1.41–3.38)	<0·001	3.53 (2.13–5.85)	<0·001	1.37 (0.91–2.05)	0.129	1.68 (1.07–2.66)	0.026

[a] Low, intermediate and high MRS were defined as participants falling with the bottom 20 %, 20 %–80 %, and the top 20 % of the metabolic risk score.

4. Discussion

This study identified 148 and 42 metabolites significantly associated with the risk of depression and anxiety, respectively. MRS was significantly associated with the risk of depression independent of age, sex, BMI, sleep duration, physical activity, smoking, drinking and diet. The associations between high MRS and anxiety risk were only significant in the subgroups of sex, age, abnormal BMI, sleep duration, physical regular, moderate alcohol drinking, no current smoking, diet, and favorable and unfavorable lifestyles. Significant combined effects of high MRS with healthy lifestyle, smoking, drinking, physical activity, BMI, diet and sleep duration were identified on the risk of depression and anxiety. Sensitivity analyses and subgroup analyses further confirmed the significant results. Additive interaction was identified between MRS and healthy lifestyle on depression risk. However, there is no interaction of MRS and lifestyle on anxiety risk.

This study identified 28 shared metabolites for depression and anxiety, accounting for 18.9 % and 66.7 % of the metabolites for depression and anxiety, respectively. These shared metabolites consistently showed either risk or protective effect for depression and anxiety, suggesting a potential common pathogenesis of the two psychological disorders (Zhou et al., 2017; Moffitt et al., 2007). Pyruvate, a glycolysis metabolite, was identified to be significantly associated with both depression and anxiety risk, increased level of pyruvate could decrease mitochondrial function and reduce cellular energy supply, thereby increasing the risk of depression and anxiety (Gu et al., 2021; Jiang et al., 2024; Filiou and Sandi, 2019). The increased levels of monounsaturated fatty acids involved in fatty acid β-oxidation and changes in fatty acid composition such as unsaturation, also occur within mitochondrial metabolic dysregulation and demonstrated protective effects against depression and anxiety (Scola et al., 2018; Kelaiditis et al., 2023; Shimada et al., 2022). However, citrate and linoleic acid were identified as risk factors for depression but not for anxiety. We firstly identified a significant association between 3-hydroxybutyric acid (a fatty acid metabolite) and the risk of depression.

In depression, reduced levels of cholesteryl esters and free cholesterol showed protective effects, but increased concentrations and proportions of triglycerides and phospholipids in various VLDL, IDL, HDL, and LDL particles, as well as elevated MUFA levels showed risk effect, which were consistent with findings from European, American, and Japanese cohort studies (Chourpiliadis et al., 2024; Huang et al., 2021; Howard et al., 2019; Hidese et al., 2018), but contradicted findings from WHI cohort study (Persons et al., 2016). This discrepancy may be due to the postmenopausal women in WHI population, whose lipid metabolism is influenced by hormonal changes. Additionally, linoleic acid, DHA, sphingomyelin, and apolipoprotein B, affecting cell membrane fluidity and function (Rydin et al., 2023; Zubenko et al., 1987) and lipid metabolic dysregulation (Zhang et al., 2023b; Yan et al., 2023; Mohammadi et al., 2022; Wang et al., 2020), were negatively associated with the risk of depression and anxiety. This study identified negative associations between cholesteryl esters and free cholesterol levels and anxiety risk. However, one Swedish cohort study identified significant associations between lipid metabolism and the risk of anxiety (Chourpiliadis et al., 2024). The concentrations and proportions of triglycerides and phospholipids in different lipoprotein particles may explain the discrepancy.

The MRS, comprehensively considered multiple metabolites, was significantly associated with the risk of depression and anxiety, with greater HR for depression than for anxiety. In the subgroup analyses, high MRS was more significantly associated with depression risk in the subgroups of unfavorable lifestyle, females, ≥60 years, sleep <7 or >9 h, physical inactivity, smoking, heavy drinking, and healthy diet. The previous study reported that women are more prone to depression and anxiety (Salk et al., 2017), different hormone level may explain the minor discrepancy between females and males (Slavich and Sacher, 2019; Kundakovic and Rocks, 2022). Additionally, individuals under 60 years with high MRS are more susceptible to depression and anxiety, as metabolic disorders in older age are more likely to trigger depression and anxiety (Zhang et al., 2023a).

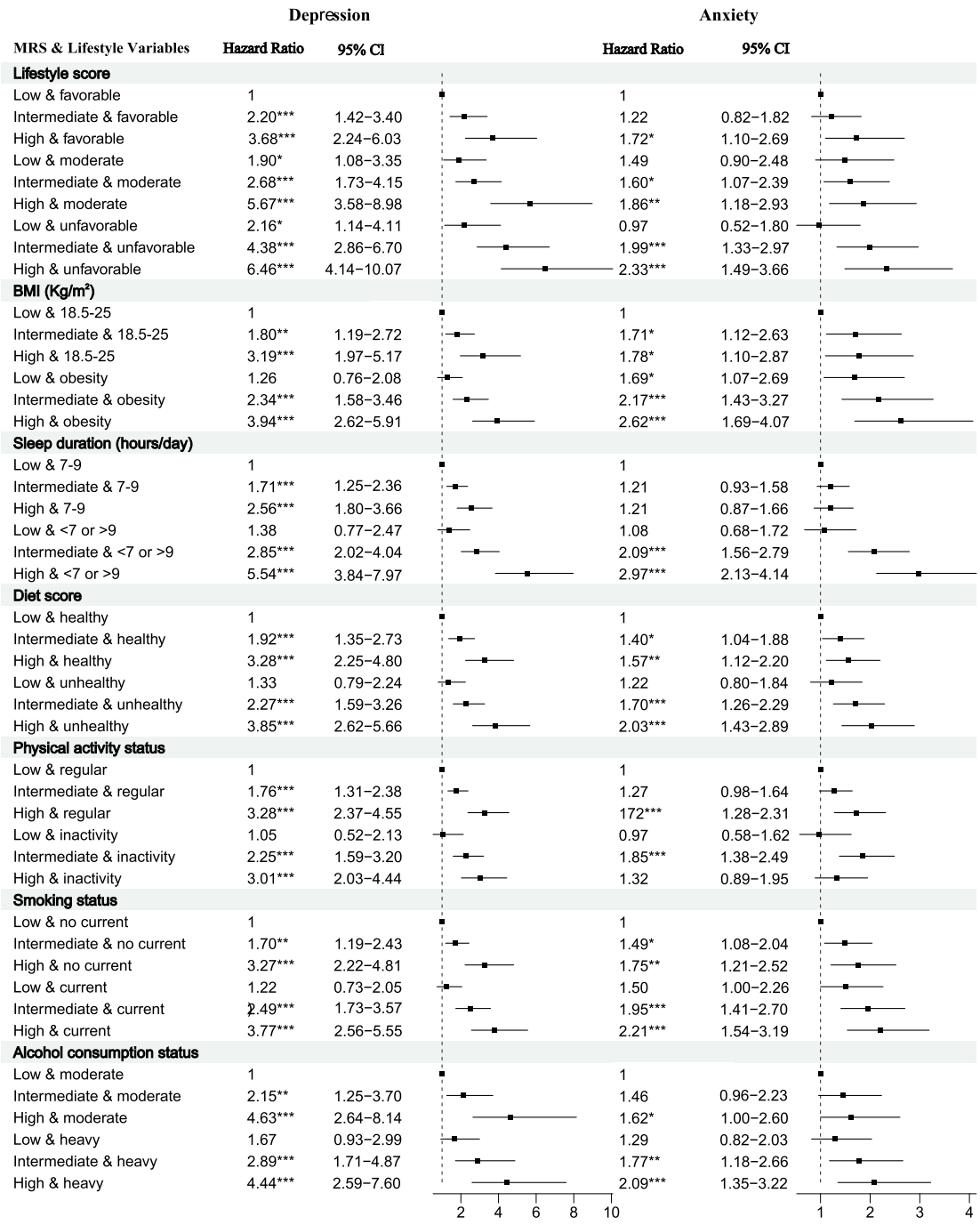

Fig. 3. Combined effects of MRS and lifestyle factors on the risk of depression and anxiety. Participants were defined as high metabolic score risk (MRS), intermediate MRS and low MRS populations according to the top 20 %, 20 %–80 %, and the bottom 20 % of MRS, respectively. HRs and the 95 % CIs were derived from Cox regression model adjusting for age, sex, TDI, education, pulse rate, SBP and glucose. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Lifestyle has long been considered as a risk factor for depression and anxiety (Xu et al., 2023; Johnson et al., 2022). The NHANES cohort study indicated that short sleep duration (<7 h) increases the risk of depression and anxiety (Chunnan et al., 2022). Additionally, European and American cohort studies showed that high-quality diets, moderate exercise, and excessive alcohol consumption increase the risk of depression and anxiety (Pearce et al., 2022; Varaee et al., 2023; Aledavood et al., 2019). However, few studies had integrated lifestyle factors and MRS to estimate their combined effects on depression and anxiety risk. Significant combination effects of MRS with healthy lifestyle and individual lifestyle factors on the risk of depression and anxiety were identified in this study. Sleep duration, smoking and alcohol were reported to have influence on neurotransmitter systems (such as GABA and glutamate)(Al-Kuraishy et al., 2024; Meyer-Bockenkamp et al., 2023), glucose (Yazici et al., 2022; Chen et al., 2022) and lipid metabolism (van Reedt Dortland et al., 2013), leading to structural and functional changes in the brain, and thereby inducing depression and anxiety. Not surprisingly, we identified significant combination effects of high MRS with healthy lifestyles and individual healthy lifestyle factors on depression risk. Even individuals with favorable lifestyle but high MRS also faced an increased risk of depression and anxiety, implying that MRS should be combined with lifestyle in depression and anxiety prevention.

As far as we know, this is the first study focusing on the associations

Table 2
Interaction effects between MRS and lifestyle on the risk of depression and anxiety.

	Depression		Anxiety	
	HR (95%CI)	*P value*	HR (95%CI)	*P value*
Multiplicative scale				
MRS[a] lifestyle	0·923 (0·678–1·255)	0·609	1·019 (0·755–1·375)	0·905
Additive scale				
Favorable lifestyle and Low MRS	1 (Reference)		1 (Reference)	
Unfavorable lifestyle and low MRS	1·72 (1·35–2·19)	<0·001	1·30 (1·03–1·65)	0·025
Favorable lifestyle and high MRS	2·20 (1·28–3·78)	0·004	1·21 (0·72–2·01)	0·469
Unfavorable lifestyle and high MRS	3·49 (2·23–5·47)	<0·001	1·61 (1·05–2·44)	0·027
RERI	0·57 (−0·20–1·39)		0·09 (−0·46–0·30)	
AP	0·16 (0·07–0·29)		0·06 (−0·08–0·29)	
SI	1·30 (1·04–1·61)		1·18 (0·63–2·23)	

[a] Low and high MRS were defined as participants falling with the bottom 50 %, and the top 20 % of the metabolic risk score, low HLS were defined as unfavorable and moderate lifestyle, high HLS were defined as favorable lifestyle. HRs and the 95 % CIs derived from Cox regression model adjusting for age, sex, TDI, education, SBP, pulse_rate and glucose are provided in legend.

between metabolites, MRS and risk of depression and anxiety in a large cohort of UK Biobank. We also estimated joint associations and interactions of MRS with healthy lifestyle and individual lifestyle factors on the risk of depression and anxiety, because of the important impact of lifestyle on metabolites. However, limitations should also be noted. First, we only estimated baseline metabolites, but not changes of metabolites during follow-up, which may not comprehensively estimate associations between metabolites changes and depression and anxiety risk. Second, depression and anxiety outcomes are derived from the UK Biobank questionnaire. Although PHQ-9 and GAD-7 are effective screening tools, clinical evaluation remains necessary for accurate diagnosis, reporting bias may also exist due to underreporting or avoidance of medical care. Third, although we adjusted for various confounders, reverse causality and unmeasured confounders could not be fully excluded. Forth, this cohort was mainly recruited from predominantly white and middle-aged population, socioeconomically less deprived areas, which limited the generalizability of the findings. Therefore, additional longitudinal studies and diverse methodological approaches are warranted to further explore the relationships between metabolic biomarkers and the risk of depression and anxiety.

5. Conclusions

148 and 42 metabolites were significantly associated with the risk of depression and anxiety, respectively, Intermediate and high MRS significantly increase the risk of depression and anxiety. Individuals with favorable lifestyle but high MRS still face an increased risk of depression and anxiety. Therefore, maintaining normal metabolite levels is crucial for preventing depression, even among individuals with healthy lifestyles.

CRediT authorship contribution statement

Xi Chen: Writing – original draft, Methodology, Conceptualization. **Canjia Zhang:** Writing – review & editing, Methodology, Formal analysis. **Ying Lin:** Writing – review & editing. **Yuanhai Yang:** Writing – review & editing. **Yang Zhao:** Writing – review & editing, Validation. **Yuying Wu:** Writing – review & editing, Validation. **Xueru Fu:** Writing – review & editing, Validation. **Xi Li:** Writing – review & editing, Validation. **Botang Guo:** Writing – review & editing, Validation. **Miaomiao Yang:** Writing – review & editing. **Jiaqi Lin:** Writing – review & editing, Software, Data curation. **Zibo Ni:** Writing – review & editing, Software, Data curation. **Xingxing Hu:** Writing – review & editing. **Jien Pan:** Writing – review & editing, Software, Data curation. **Kejia Wu:** Writing – review & editing, Software, Data curation. **Ming Zhang:** Writing – review & editing, Supervision. **Thongmuang Pimporn:** Supervision, Writing – review & editing. **Fulan Hu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Soontornchai Sarisak:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Dongsheng Hu:** Writing – review & editing, Supervision, Conceptualization, Funding acquisition.

Ethics approval and consent to participate

All human research procedures were approved by the Institutional Ethics Committee and conducted in accordance with the Helsinki Declaration (as revised). Written informed consent was obtained from all participants. This research has been conducted using the UK Biobank Resource under the project number of 81,680.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.119673.

Data availability

The UK Biobank dataset is publicly accessible to qualified researchers through a formal application process via the institutional portal (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access), with supplementary implementation details obtainable by contacting the corresponding author (hufu1525@163.com).

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