

Metabolic Syndrome and the Risk of Depression and Anxiety: A Prospective Cohort Study

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Abstract

Background: The relationship between metabolic syndrome (MetS) and incident depression and anxiety remains unclear. This study prospectively examined whether MetS increases the risk of new-onset depressive and anxiety disorders.

Methods: This prospective cohort study included 316,263 participants from a large population-based cohort, with MetS defined according to NCEP ATP III guidelines. Multivariable Cox regression models estimated the association of MetS and its five components with outcomes. Restricted cubic splines were applied to explore dose-response relationships, and mediation analyses assessed the potential role of nine inflammatory markers.

Results: Over a median follow-up of 14.07 years, 13,714 depression and 13,903 anxiety incident cases were identified. MetS was associated with increased risks of depression (HR 1.27, 95% CI 1.22–1.32) and anxiety (HR 1.17, 95% CI 1.12–1.21), with clear dose-response relationships (all $P_{\text{trend}} < 0.001$). Further RCS analysis revealed a J-shaped association between SBP and depression. Among individual components, reduced HDL-C showed the strongest positive association with depression (HR 1.31, 95% CI 1.26–1.36) and anxiety (HR 1.20, 95% CI 1.15–1.24). The combination of elevated WC and reduced HDL-C demonstrated the highest risk for depression (HR 1.30, 95% CI 1.24–1.36) and anxiety (HR 1.20, 95% CI 1.14–1.26). Mediation analyses indicated that leukocyte and neutrophil counts explained 7.0% of the MetS-depression association and 12.0–14.0% of the MetS-anxiety association. Subgroup analyses revealed stronger associations in participants aged under 58 years and those with higher education.

Conclusions: Our findings suggest that MetS, particularly the phenotype characterized by central obesity and dyslipidemia, may serve as a modifiable risk marker for depression and anxiety. The partial mediation by inflammatory markers supports the role of systemic low-grade inflammation in linking metabolic dysfunction to mental disorders, highlighting the potential value of integrating metabolic and inflammatory screening into mental health risk assessment.

Introduction

- Depression and anxiety disorders are leading contributors to the global burden of mental disorders, marked by high prevalence and recurrence, substantial disability, and impaired quality of life, accounting for approximately two-thirds of all mental disorder cases globally^{[1][2]}. According to the Global Burden of Disease Study 2023, anxiety disorders and major depressive disorder are the 11th and 15th leading causes of years lived with disability, respectively, among 304 diseases^[3]. Despite advances in treatment, a substantial proportion of affected individuals remain undiagnosed or inadequately treated^[4]. Therefore, identifying modifiable, particularly early-warning, risk factors is critical for primary prevention.
- Metabolic syndrome (MetS) is a cluster of metabolic abnormalities including central obesity, dyslipidemia, elevated blood pressure, and hyperglycemia; diagnosed when three or more are

present according to NCEP ATP III^{[5][6]}. This condition not only increases the risk of type 2 diabetes, cardiovascular diseases, and all-cause mortality, but its association with common mental disorders such as depression and anxiety has also been increasingly recognized^{[7][8]}. Previous research has predominantly focused on the impact of mental disorders on subsequent metabolic dysfunction, whereas the reverse direction whether metabolic syndrome precedes and increases the risk of incident depression and anxiety remains comparatively understudied^{[9][10][11]}. Although several cross-sectional and retrospective studies have suggested associations between metabolic abnormalities and elevated risk of these mental disorders^{[9][12]}, they are limited by small sample sizes, short follow-up periods, potential reverse causality, and inadequate discussion on the effect of each individual component. High-quality evidence from large-scale prospective cohorts remains scarce, and the dose-response relationship, component-specific risks, and underlying mechanisms between MetS and these mental disorders are not fully understood.

- Chronic low-grade inflammation has been proposed as a key pathway linking MetS to mental disorders. Multiple systemic inflammatory markers are often elevated in individuals with MetS^[13]. Metabolic dysregulation can induce adipose tissue inflammation, oxidative stress, and immune activation, which may affect neurotransmitter metabolism, hypothalamic-pituitary-adrenal (HPA) axis function, and neuroplasticity, thereby contributing to depression and anxiety^{[14][15][16]}. However, prospective evidence rigorously evaluating the mediating effect of these inflammatory markers is still limited.
- Based on the UK Biobank (UKB) cohort, this study comprehensively investigated the association between MetS and the risk of incident depression and anxiety using multivariable-adjusted Cox proportional hazards models with sequential adjustments for sociodemographic factors, lifestyle behaviors, and dietary habits. We examined the dose-response relationship of MetS as a whole and its five individual components with the risk of these outcomes. We further explored the associations of all possible combinations of two, three, and four MetS components to identify the component combination conferring the strongest risk. We also assessed the potential mediating and interactive effects of systemic inflammatory markers. Additionally, we conducted subgroup analyses across eight factors, with interaction *P*-values estimated by including product terms in the models. This study seeks to provide high-quality epidemiological evidence to elucidate the mechanisms linking metabolic disorders and mental disorders and to inform targeted prevention strategies.

Materials and Methods

1.1 Study design and participants

- This prospective cohort study used data from the UKB, a large-scale population-based resource comprising over 500,000 individuals aged 37–73 years recruited across the UK between 2006 and 2010. Participants underwent comprehensive baseline assessments, including touchscreen questionnaires, physical measurements, and biological samples. Publicly available data can be

accessed via the UKB website (<https://www.ukbiobank.ac.uk/>). Of the 502,355 participants assessed at baseline, we excluded study withdrawals ($n = 428$), those with prevalent depression or anxiety ($n = 54,019$), and those with missing data on any MetS components ($n = 106,171$), covariates ($n = 15,831$), or inflammatory markers ($n = 9,643$). A total of 316,263 subjects were ultimately enrolled, as detailed in **Supplementary Fig. 1**.

1.2 Assessment of exposures

- MetS was defined primarily based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines^[17] NCEP ATP III requires the presence of ≥ 3 of the following 5 aspects: (1) increased waist circumference (WC, ≥ 102 cm for men, ≥ 88 cm for women); (2) elevated triglycerides (TG, ≥ 1.7 mmol/L, or taking cholesterol-lowering medications); (3) decreased high-density lipoprotein cholesterol (HDL-C, < 1.0 mmol/L for men, < 1.3 mmol/L for women, or taking cholesterol-lowering medications); (4) elevated blood pressure (BP, systolic BP [SBP] ≥ 130 mmHg or diastolic BP [DBP] ≥ 85 mmHg, or taking antihypertensive medications); and (5) hyperglycemia (plasma glucose ≥ 5.6 mmol/L or taking glucose-lowering medications). Due to the limited sample size of subjects with available fasting blood glucose levels in the UKB, glycated hemoglobin (HbA1c) was adopted as an alternative biomarker. Hyperglycemia was therefore defined as HbA1c ≥ 42.0 mmol/mol, aligning with International Diabetes Federation (IDF) guidelines^[18].

1.3 Assessment of outcomes

- The primary outcomes were incident depression and anxiety. These conditions were identified through the “First Occurrences” records in the UKB, which integrates diagnostic information from primary care records, hospital inpatient records, death registries and self-reported health conditions. Specifically, depression cases were defined according to ICD-10 codes F32 and F33, while anxiety cases were defined according to ICD-10 codes F40 and F41. The follow-up period was calculated from the baseline interview date until the first diagnosis of anxiety or depression, death, or the end of follow-up (May 1st, 2023), whichever occurred first.

1.4 Assessment of covariates

- To mitigate potential confounding, we adjusted for a comprehensive set of covariates categorized into sociodemographic characteristics, lifestyle behaviors, and dietary habits. The sociodemographic characteristics included age, sex, ethnicity, education level, and the Townsend Deprivation Index (TDI). Lifestyle factors accounted for body mass index (BMI), smoking status, alcohol consumption, and levels of physical activity. Dietary habits were assessed based on the intake of both processed and unprocessed meats, fish, vegetables, and fruits. In this study, age and TDI were treated as continuous variables, while the remaining variables were categorized. Detailed classification criteria are provided in the **Supplementary Table 1**.

1.5 Statistical analysis

- Baseline characteristics are summarized as medians (interquartile ranges, IQRs) for non-normally distributed continuous variables and number (%) for categorical variables.
- The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of MetS and its components with incident depression and anxiety. MetS was examined as a binary variable (yes vs. no) and as a cumulative score ranging from 0 to 5. We treated the score as a categorical variable and as a continuous variable to test for linear trends (P_{trend}). Furthermore, to determine whether specific MetS components or combinations were more strongly associated with the risk of incident depression or anxiety, we evaluated each component individually and in all possible combinations. We conducted three models in the primary analysis: Model A adjusted for sex, age, education level, ethnicity, and TDI; Model B further adjusted for BMI, smoking, alcohol consumption, and physical activity; and Model C further included dietary factors (intake of meat, vegetables, fruits, and fish). In analyses of individual MetS components, a fourth model (Model D) mutually adjusted for the other components. Additionally, we used restricted cubic splines (RCS) with three knots at the 10th, 50th, and 90th percentiles to explore dose-response relationships between each MetS component and depression or anxiety.
- To explore the potential inflammatory mechanism, we conducted mediation analysis using each of the nine inflammatory markers from baseline blood samples as a mediator. The total effect of MetS on depression and anxiety was decomposed into direct and indirect effects (quantified by the mediation proportion). These markers included C-reactive protein (CRP), leukocyte count, platelet count, neutrophil count, lymphocyte count, monocyte count, as well as the percentages of neutrophils, lymphocytes, and monocytes in leukocytes. As all markers exhibited skewed distributions, log-transformation and z-score standardization were applied prior to analysis. We also assessed the interaction between MetS and each of the nine inflammatory markers on both multiplicative and additive scales, calculating the relative excess risk due to interaction (RERI) and the attributable proportion (AP).
- Subgroup analyses were performed stratified by age (< 58 vs. ≥ 58 year), sex (Male vs. Female), ethnicity (White vs. Non-white), education level (Higher, Middle, Other), BMI (< 25 vs. ≥ 25 kg/m²), smoking status (Current, Never, Previous), alcohol consumption (Current, Never, Previous), and physical activity (yes vs. no), with interaction *P*-values estimated by including product terms in the models.
- Several sensitivity analyses were conducted to verify the robustness of the primary findings. First, to reduce potential reverse causality, we excluded incident cases that occurred within the first two years of follow-up. Second, we re-evaluated the associations using the IDF definition of MetS. Third, we re-modeled the component of MetS by dividing them into tertiles, quartiles, and quintiles. Fourth, to minimize bias from ethnic differences in metabolic thresholds, we repeated the analyses by excluding non-white participants. Fifth, we used the Fine-Gray model to account for death as a competing risk.

- All statistical analyses were performed using R version 4.5.1, with a two-sided P -value < 0.05 considered statistically significant.

Results

2.1 Baseline characteristics

- During a median follow-up of 14.07 years involving 316,263 participants, 13,714 incident cases of depression and 13,903 cases of anxiety were identified. Compared to controls, participants in both case groups were more likely to be female, had lower educational attainment, and lower TDI scores (all $P < 0.001$). Unfavorable lifestyle profiles were more common among cases, including higher proportions of current or former smoking, underweight or obesity, insufficient physical activity and meat consumption (all $P < 0.001$). Notably, the baseline prevalence of MetS was significantly higher in the depression (41.71%) and anxiety (37.63%) groups compared to controls ($P < 0.001$). Elevated TG (depression: 53.32%; anxiety: 49.81%) and BP (depression: 69.78%; anxiety: 71.13%) were the most frequent components. In addition, both the depression and anxiety groups had significantly higher levels of CRP, leukocyte, platelet, neutrophil count, neutrophil percentage, and lymphocyte count compared to their respective controls (all $P < 0.001$). Detailed baseline characteristics are presented in Table 1.

Table 1
The baseline characteristics of participants stratified by depression and anxiety status.

n	Overall	Non-Depression	Depression	P	Non-Anxiety	Anxiety	P
	316,263	302,549	13,714		302,360	13,903	
Age, yrs, median(IQR)	58.00 [50.00, 63.00]	58.00 [50.00, 63.00]	57.00 [49.00, 63.00]	< 0.001	58.00 [50.00, 63.00]	59.00 [50.00, 64.00]	< 0.001
Sex				< 0.001			< 0.001
Female	165,982 (52.48)	157,666 (52.11)	8316 (60.64)		156,863 (51.88)	9119 (65.59)	
Male	150,281 (47.52)	144,883 (47.89)	5398 (39.36)		145,497 (48.12)	4784 (34.41)	
Ethnicity				< 0.001			< 0.001
White	301,308 (95.27)	288,163 (95.25)	13,145 (95.85)		287,984 (95.25)	13,324 (95.83)	
Asian	6466 (2.04)	6273 (2.07)	193 (1.41)		6247 (2.07)	219 (1.58)	
Black	4135 (1.31)	3979 (1.32)	156 (1.14)		3974 (1.31)	161 (1.16)	
Other	4354 (1.38)	4134 (1.36)	220 (1.60)		4155 (1.37)	199 (1.43)	
TDI,median(IQR)	-2.26 [-3.70, 0.25]	-2.29 [-3.71, 0.19]	-1.67 [-3.37, 1.35]	< 0.001	-2.28 [-3.70, 0.21]	-1.90 [-3.53, 0.98]	< 0.001
Education				< 0.001			< 0.001
Higher	122,185 (38.64)	117,925 (38.98)	4260 (31.06)		117,772 (38.95)	4413 (31.74)	
Middle	143,718 (45.44)	137,228 (45.36)	6490 (47.32)		137,213 (45.38)	6505 (46.79)	
Other	50,360 (15.92)	47,396 (15.66)	2964 (21.62)		47,375 (15.67)	2985 (21.47)	
BMI,kg/m²				< 0.001			< 0.001
< 18.5	1580 (0.50)	1481 (0.49)	99 (0.72)		1476 (0.49)	104 (0.75)	

n	Overall	Non-Depression	Depression	<i>P</i>	Non-Anxiety	Anxiety	<i>P</i>
	316,263	302,549	13,714		302,360	13,903	
18.5–25	105,247 (33.27)	101,445 (33.53)	3802 (27.72)		100,778 (33.33)	4469 (32.14)	
25–30	135,856 (42.96)	130,373 (43.09)	5483 (39.98)		130,221 (43.07)	5635 (40.53)	
≥ 30	73,580 (23.27)	69,250 (22.89)	4330 (31.58)		69,885 (23.11)	3695 (26.58)	
Smoking				< 0.001			< 0.001
Current	30,783 (9.73)	28,538 (9.43)	2245 (16.37)		28,964 (9.58)	1819 (13.08)	
Never	174,896 (55.30)	168,511 (55.70)	6385 (46.56)		167,827 (55.51)	7069 (50.85)	
Previous	110,584 (34.97)	105,500 (34.87)	5084 (37.07)		105,569 (34.91)	5015 (36.07)	
Alcohol				< 0.001			< 0.001
Current	294,106 (92.99)	281,835 (93.15)	12,271 (89.48)		281,524 (93.11)	12,582 (90.50)	
Never	12,428 (3.93)	11,794 (3.90)	634 (4.62)		11,762 (3.89)	666 (4.79)	
Previous	9729 (3.08)	8920 (2.95)	809 (5.90)		9074 (3.00)	655 (4.71)	
Physical activity				< 0.001			< 0.001
No	65,089 (20.58)	61,554 (20.35)	3535 (25.78)		61,769 (20.43)	3320 (23.88)	
Yes	251,174 (79.42)	240,995 (79.65)	10,179 (74.22)		240,591 (79.57)	10,583 (76.12)	
Unprocessed meat intake				< 0.001			< 0.001
No	261,986 (82.84)	250,883 (82.92)	11,103 (80.96)		250,816 (82.95)	11,170 (80.34)	
Yes	54,277 (17.16)	51,666 (17.08)	2611 (19.04)		51,544 (17.05)	2733 (19.66)	

n	Overall	Non-Depression	Depression	P	Non-Anxiety	Anxiety	P
	316,263	302,549	13,714		302,360	13,903	
Processed meat intake				0.008			< 0.001
No	99,547 (31.48)	95,088 (31.43)	4459 (32.51)		95,358 (31.54)	4189 (30.13)	
Yes	216,716 (68.52)	207,461 (68.57)	9255 (67.49)		207,002 (68.46)	9714 (69.87)	
Fish intake				< 0.001			0.591
No	150,328 (47.53)	143,604 (47.46)	6724 (49.03)		143,751 (47.54)	6577 (47.31)	
Yes	165,935 (52.47)	158,945 (52.54)	6990 (50.97)		158,609 (52.46)	7326 (52.69)	
Vegetable intake				0.008			0.062
No	288,784 (91.31)	276,348 (91.34)	12,436 (90.68)		276,150 (91.33)	12,634 (90.87)	
Yes	27,479 (8.69)	26,201 (8.66)	1278 (9.32)		26,210 (8.67)	1269 (9.13)	
Fruit intake				0.273			0.636
No	199,063 (62.94)	190,370 (62.92)	8693 (63.39)		190,339 (62.95)	8724 (62.75)	
Yes	117,200 (37.06)	112,179 (37.08)	5021 (36.61)		112,021 (37.05)	5179 (37.25)	
Elevated WC				< 0.001			< 0.001
No	214,113 (67.70)	206,218 (68.16)	7895 (57.57)		205,447 (67.95)	8666 (62.33)	
Yes	102,150 (32.30)	96,331 (31.84)	5819 (42.43)		96,913 (32.05)	5237 (37.67)	
Elevated TG				< 0.001			< 0.001
No	163,831 (51.80)	157,429 (52.03)	6402 (46.68)		156,853 (51.88)	6978 (50.19)	
Yes	152,432 (48.20)	145,120 (47.97)	7312 (53.32)		145,507 (48.12)	6925 (49.81)	

n	Overall	Non-Depression	Depression	<i>P</i>	Non-Anxiety	Anxiety	<i>P</i>
	316,263	302,549	13,714		302,360	13,903	
Reduced HDL-C				< 0.001			< 0.001
No	213,352 (67.46)	205,314 (67.86)	8038 (58.61)		204,663 (67.69)	8689 (62.50)	
Yes	102,911 (32.54)	97,235 (32.14)	5676 (41.39)		97,697 (32.31)	5214 (37.50)	
Elevated BP				0.031			0.171
No	92,956 (29.39)	88,812 (29.35)	4144 (30.22)		88,942 (29.42)	4014 (28.87)	
Yes	223,307 (70.61)	213,737 (70.65)	9570 (69.78)		213,418 (70.58)	9889 (71.13)	
Hyperglycemia				< 0.001			< 0.001
No	291,373 (92.13)	279,116 (92.25)	12,257 (89.38)		278,702 (92.18)	12,671 (91.14)	
Yes	24,890 (7.87)	23,433 (7.75)	1457 (10.62)		23,658 (7.82)	1232 (8.86)	
The number of MetS components				< 0.001			< 0.001
0	48,895 (15.46)	47,062 (15.56)	1833 (13.37)		46,960 (15.53)	1935 (13.92)	
1	90,617 (28.66)	87,447 (28.90)	3170 (23.11)		86,937 (28.76)	3680 (26.47)	
2	70,882 (22.41)	67,891 (22.44)	2991 (21.81)		67,826 (22.43)	3056 (21.98)	
3	60,600 (19.16)	57,668 (19.06)	2932 (21.38)		57,793 (19.11)	2807 (20.19)	
4	34,836 (11.01)	32,782 (10.84)	2054 (14.98)		32,995 (10.91)	1841 (13.24)	
5	10,433 (3.30)	9699 (3.20)	734 (5.35)		9849 (3.26)	584 (4.20)	
MetS				< 0.001			< 0.001

n	Overall	Non-Depression	Depression	<i>P</i>	Non-Anxiety	Anxiety	<i>P</i>
	316,263	302,549	13,714		302,360	13,903	
No	210,394 (66.53)	202,400 (66.90)	7994 (58.29)		201,723 (66.72)	8671 (62.37)	
Yes	105,869 (33.47)	100,149 (33.10)	5720 (41.71)		100,637 (33.28)	5232 (37.63)	
CRP, mg/L, median(IQR)	1.29 [0.64, 2.67]	1.28 [0.64, 2.64]	1.61 [0.77, 3.42]	< 0.001	1.29 [0.64, 2.65]	1.48 [0.70, 3.14]	< 0.001
Leukocyte, ×10⁹/L, median (IQR)	6.62 [5.62, 7.80]	6.60 [5.61, 7.80]	6.94 [5.86, 8.20]	< 0.001	6.61 [5.61, 7.80]	6.85 [5.79, 8.07]	< 0.001
Platelet, ×10⁹/L, median (IQR)	247.00 [212.60, 285.60]	246.70 [212.40, 285.10]	253.10 [217.20, 293.00]	< 0.001	246.70 [212.30, 285.10]	252.80 [217.00, 293.00]	< 0.001
Neutrophil, ×10⁹/L, median (IQR)	4.00 [3.26, 4.93]	4.00 [3.25, 4.91]	4.23 [3.42, 5.21]	< 0.001	4.00 [3.26, 4.92]	4.14 [3.37, 5.12]	< 0.001
Neutrophil, %, median (IQR)	61.10 [55.60, 66.40]	61.10 [55.60, 66.40]	61.60 [56.10, 67.00]	< 0.001	61.10 [55.60, 66.40]	61.50 [55.90, 66.90]	< 0.001
Monocyte, ×10⁹/L, median (IQR)	0.45 [0.36, 0.57]	0.45 [0.36, 0.57]	0.46 [0.37, 0.59]	< 0.001	0.45 [0.36, 0.57]	0.45 [0.36, 0.57]	0.760
Monocyte, %, median	6.88 [5.60, 8.28]	6.89 [5.60, 8.30]	6.70 [5.40, 8.10]	< 0.001	6.89 [5.60, 8.30]	6.70 [5.44, 8.06]	< 0.001
Lymphocyte, ×10⁹/L, median (IQR)	1.87 [1.50, 2.29]	1.87 [1.50, 2.28]	1.91 [1.57, 2.35]	< 0.001	1.87 [1.50, 2.28]	1.90 [1.55, 2.35]	< 0.001
Lymphocyte, %, median	28.59 [23.90, 33.50]	28.60 [23.92, 33.50]	28.26 [23.56, 33.34]	< 0.001	28.60 [23.90, 33.50]	28.44 [23.80, 33.42]	0.069

2.2 Associations of MetS with Risks of Depression and Anxiety

- In the fully adjusted model, MetS was significantly associated with an increased risk of both depression (HR 1.27, 95%CI 1.22–1.32, $P < 0.001$) and anxiety (HR 1.17, 95%CI 1.12–1.21, $P < 0.001$). A dose-response relationship was observed between the number of MetS components and

the risk of both outcomes (all $P_{\text{trend}} < 0.001$). Specifically, the risk of depression increased from HR 1.13 to 1.62 (2–5 components), and the risk of anxiety rose from HR 1.09 to 1.44 (1–5 components), as detailed in Fig. 1.

- Regarding individual MetS components (**Supplementary Table 2**), elevated WC, elevated TG, reduced HDL-C and hyperglycemia were independently associated with an increased risk of both depression (WC: HR 1.23, 95% CI: 1.17–1.29; TG: HR 1.18, 95% CI: 1.13–1.22; HDL-C: HR 1.31, 95% CI: 1.26–1.36; hyperglycemia: HR 1.23, 95% CI: 1.16–1.30, all $P < 0.001$) and anxiety (WC: HR 1.11, 95% CI: 1.06–1.17; TG: HR 1.11, 95% CI: 1.07–1.15; HDL-C: HR 1.20, 95% CI: 1.15–1.24; hyperglycemia: HR 1.09, 95% CI: 1.03–1.16; all $P < 0.05$) in Model C, while elevated BP was associated with a lower risk of depression (HR 0.95, 95% CI 0.91–0.99; $P = 0.014$). Notably, after mutual adjustment for other MetS components (Model D), these associations remained robust, except for the associations of elevated TG and hyperglycemia with anxiety risk. RCS analyses further demonstrated dose-response relationships between MetS components and the risks of depression and anxiety (**Supplementary Fig. 2**). WC, TG, and HbA1c were positively associated with both outcomes, whereas HDL-C showed a nonlinear inverse association, with risk increasing at lower levels and plateauing at higher (HDL-C: P for nonlinearity < 0.001). For depression, SBP was nonlinearly inversely associated, with risk declining as SBP increased, while DBP exhibited a U-shaped relationship with the lowest risk at approximately 85 mmHg (all P for nonlinearity < 0.001). No significant associations were observed between SBP or DBP and anxiety risk.
- Additional results on associations between specific combinations of MetS components and the risks of depression and anxiety are presented in **Supplementary Table 3 and Supplementary Table 4**. Among the two-component combinations, the combination of increased WC and reduced HDL-C exhibited the highest risk for depression (HR 1.30, 95% CI: 1.24–1.36, $P < 0.001$) and anxiety (HR 1.20, 95% CI: 1.14–1.26, $P < 0.001$). The combination of elevated TG and reduced HDL-C also showed significantly increased risks for depression (HR 1.30, 95% CI: 1.25–1.35, $P < 0.001$) and anxiety (HR 1.21, 95% CI: 1.16–1.25, $P < 0.001$). For three- and four- component clusters, combinations including increased WC, reduced HDL-C, and hyperglycemia showed the strongest association with depression, whereas clusters involving increased WC, elevated TG, and reduced HDL-C were most strongly linked to anxiety. Overall, combinations involving increased WC and reduced HDL-C consistently demonstrated the most robust associations with both outcomes.

2.3 Mediation analysis of inflammatory markers

- Mediation effects of inflammatory markers on the associations between MetS and mental health outcomes are shown in Fig. 2. Regarding the MetS-depression association, both leukocyte and neutrophil counts mediated 7.0% of the total effect (95% CI: 4%–11% and 4%–10%, respectively), while CRP accounted for 4.0% (95% CI: 2%–6%) of the total effect. For the MetS-anxiety association, leukocyte and neutrophil counts exhibited larger mediation proportions, accounting for 14.0% (95% CI: 8%–21%) and 12.0% (95% CI: 6%–17%) of the total effect, respectively. Monocyte count

significantly mediated the MetS-anxiety association (mediation proportion = 5.0%, 95% CI: 1%-8%, $P = 0.01$). The remaining inflammatory markers had negligible ($< 1\%$) or non-significant mediation effects ($P > 0.05$). No significant multiplicative or additive interactions between MetS and inflammatory markers were observed for either outcome (all P for interaction > 0.05) (Supplementary Table 5).

2.4 Subgroup and sensitivity analysis

- Subgroup analyses stratified by age, sex, ethnicity, education, BMI, smoking, alcohol consumption, and physical activity are presented in Fig. 3. In the analyses stratified by the median age of 58 years, the risks of depression and anxiety associated with MetS were significantly higher in the younger subgroup (depression: HR 1.26, 95% CI: 1.19–1.33; anxiety: HR 1.18, 95% CI: 1.11–1.25; all P for interaction < 0.05). Education level also significantly modified the associations, with the strongest HRs observed in the higher education group (depression: HR 1.37, 95% CI: 1.27–1.47; anxiety: HR 1.28, 95% CI: 1.19–1.38; P for interaction < 0.01). No significant modifications were observed for the other stratification factors (all P for interaction > 0.05). The results remained consistent across all sensitivity analyses, confirming the robustness of our primary findings.

Discussion

In this large-scale prospective cohort study, we discovered that MetS and its individual components were significantly associated with increased risks of either depression or anxiety. Among the five MetS components, reduced HDL-C exhibited the strongest effect, and combinations involving elevated WC and reduced HDL-C showed the most robust associations with both outcomes; RCS analysis further revealed a nonlinear pattern for SBP in relation to depression and anxiety. Mediation analyses showed that systemic inflammatory markers partially mediated the MetS-depression and MetS-anxiety associations. For depression, leukocyte and neutrophil counts each mediated 7.0% (95% CI: 4%-11% and 4%-10%, respectively), and CRP mediated 4.0% (95% CI: 2%-6%). For anxiety, larger proportions were observed in leukocyte count 14.0% (95% CI: 8%-21%), neutrophil count 12.0% (95% CI: 6%-17%), and monocyte count 5.0% (95% CI: 1%-8%). Among the examined subgroup factors, only age and educational attainment significantly modified the associations between MetS and the risk of depression and anxiety (both P interaction < 0.01). The associations were more pronounced in middle-aged individuals than in older adults, possibly due to the higher prevalence of age-related comorbidities and polypharmacy in the elderly, which may attenuate the net effect of MetS^[19] Similarly, stronger associations were also observed in the higher education subgroup, which may be explained by sedentary occupations and work-related stress that exacerbate metabolic disturbances, as well as greater health awareness that may lead to more frequent symptom reporting^{[20][21]}.

The positive associations of MetS with depression and anxiety observed in this study are largely consistent with previous research. A meta-analysis of 11 cohort studies reported that MetS was associated with a 29% increased risk of depression (RR 1.29, 95% CI 1.12–1.48)^[22], while Cen *et al.*

found a 13.6% increased risk of anxiety (HR 1.14, 95% CI 1.09–1.19)^[23]. Moreover, Chen *et al.* demonstrated that a metabolite-based metabolic risk score was positively associated with both depression and anxiety in a non-linear, J-shaped dose-response manner^[24]. Compared with the low-score group, the intermediate and high score groups showed significantly increased risks (depression: HR 1.88, 95% CI 1.43–2.46 and HR 3.18, 95% CI 2.37–4.27; anxiety: HR 1.34, 95% CI 1.03–1.73 and HR 1.67, 95% CI 1.24–2.24), highlighting cumulative metabolic burden as a key driver of mental disorder risk. In contrast, a 1-year prospective cohort study by Takeuchi *et al.* reported a significant positive association between the number of MetS components and incident depression ($P_{\text{trend}} < 0.01$) but no significant association with anxiety^[25]. This null finding may be partly due to the relatively small sample size ($n = 956$)^[25], and also suggesting that the underlying mechanisms linking metabolism to depression and anxiety may differ^[26].

In single-component analysis, elevated WC, reduced HDL-C and elevated TG were independently associated with the risks of depression and anxiety, which is consistent with previous studies. A landmark meta-analysis by Pan *et al.* demonstrated that central obesity, hypertriglyceridemia, and low HDL-C were the MetS components most strongly associated with depression risk^[27]. Similarly, Chourpiliadis *et al.* reported that elevated TG (HR 1.15, 95% CI: 1.10–1.20) and reduced HDL-C (HR 0.88, 95% CI: 0.80–0.97) were associated with increased risk of depression, anxiety, and stress-related disorders in a large Swedish cohort with up to 30 years of follow-up^[28]. Collectively, these converging findings underscore the predominant role of dyslipidemia and central obesity as key metabolic drivers of common mental disorders.

An increase in WC reflects the accumulation of visceral fat, which can affect the function of brain regions related to emotion regulation, such as the hippocampus and prefrontal lobe, by inducing HPA axis dysfunction and insulin resistance^{[29][30]}. Meanwhile, insulin resistance associated with central obesity can impair insulin signaling in the brain, disrupting hypothalamic regulation of energy balance and emotional responses^{[23][30]}. A decrease in HDL-C may affect the synthesis of neurosteroids that regulate mood and interfere with the function of GABA_A receptors, thereby increasing the risk of anxiety and depression^{[31][32]}. Elevated TG is often accompanied by an increase in free fatty acids, which can induce oxidative stress and mitochondrial dysfunction in the brain, and damage the energy metabolism and synaptic plasticity of hippocampal neurons^[30]. The above-mentioned mechanisms collectively suggest that these metabolic abnormalities may independently affect the occurrence of depression and anxiety through neuroendocrine, metabolic and neurotoxic pathways.

Unlike the other metabolic components, RCS analysis revealed a distinct pattern for SBP on depression. Specifically, a J-shaped relationship was observed for depression, with the risk increasing as SBP decreased. Although this inverse association appears counterintuitive, accumulating evidence has reported similar observations, with higher blood pressure being associated with lower depressive symptoms and reduced psychological distress. The inverse association for depression aligns with the baroreceptor feedback framework proposed by Schaare *et al.*, in which elevated blood pressure may

attenuate affective processing through central nervous system inhibition, thereby reducing responsiveness to negative stimuli and potentially explaining the plateauing protective effect at higher SBP levels^[33]. This finding is also consistent with other studies reporting that higher blood pressure is associated with better mood and lower distress^{[34][35]}. The elevated depression risk observed at low SBP levels in our data may be partially explained by physiological studies demonstrating non-monotonic baroreceptor responses. Bolter et al. reported that approximately 30% of aortic baroreceptor fibres in rabbits exhibited a J-shaped response curve, with a nadir in the region of 40–55 mmHg, below which firing frequency paradoxically increased as pressure decreased^[36]. This suggests that at very low blood pressures, afferent baroreceptor signals to the brainstem may paradoxically increase, potentially affecting autonomic and emotional regulation. Collectively, the observed nonlinear relationship highlights that depressive risk may be particularly increased among individuals with relatively low SBP, and underscores the importance of considering mental health when managing individuals with low blood pressure.

To investigate the biological mechanisms underlying the association between MetS and depression and anxiety, this study examined the mediating role of multiple inflammatory markers, covering multiple dimensions such as blood cell count and acute-phase proteins^[37]. The results showed that both white blood cell and neutrophil counts significantly mediated the association between MetS and both outcomes (mediating ratio 7%-14%), and CRP also mediated 4.0% of MetS-depression. Although previous studies reported differences in specific inflammatory markers and effect sizes, these markers collectively reflect a systemic low-grade inflammatory state, providing prospective evidence for the hypothesis that “the inflammatory pathway is a central mechanism of metabolism-mental comorbidity”^{[23][37][38][39]}. This study also found that the mediating effects of different inflammatory markers varied between depression and anxiety. Milaneschi et al^[40] demonstrated that CRP was significantly but weakly associated with anxiety symptoms such as irritability and worry control, while it was more strongly and widely associated with energy-related symptoms of depression such as appetite changes, fatigue, and sleep disturbances. Meng et al.^[38] and Li et al.^[39] further observed the cumulative mediating effects of inflammation and inflammation-oxidative stress in depression. The above differences suggest that anxiety and depression may have different neuroimmune bases, among which depression is more closely related to broader energy metabolism and chronic, cumulative physiological load. The effect of white blood cell and neutrophil counts is stronger than that of CRP, which may reflect differences in their functional roles within the immune response. Specifically, white blood cells can influence neurotransmitter metabolism through the blood-brain barrier, whereas CRP is more commonly a downstream marker, highlighting an area worthy of further investigation^[41].

This study has the following limitations. Firstly, MetS and its components were assessed only at a single baseline measurement, which may not capture changes in metabolic status over time and may underestimate the association between cumulative exposure and long-term risk. Secondly, although multiple confounding factors have been adjusted, the possibility of residual confounding still cannot be completely ruled out. Finally, participants in the UKB were predominantly of European descent and had

relatively high socioeconomic status, limiting the generalizability of the findings to other ethnic groups or clinical populations.

In conclusion, MetS was associated with a higher risk of incident depression and anxiety, with elevated WC and reduced HDL-C conferring the greatest risk. Inflammation partially mediated these associations. These findings support integrating metabolic and inflammatory risk assessment into strategies for the early prevention of common mental disorders. Further intervention studies are warranted to determine whether targeting metabolic dysfunction and inflammation can reduce the risk of depression and anxiety.

Declarations

Ethics approval and consent to participate

Ethical approval for the UK Biobank study was obtained from the North West Multi-Centre Research Ethics Committee (21/NW/0157), and this study was conducted under Application ID 113769. Written informed consent was obtained from all participants prior to enrollment.

Consent to participate

All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contribution

XZ and YM conceived the study. SS wrote the first and successive drafts of the manuscript. SS, XY, and ZH analyzed the data. JL, FP and QZ contributed to study design. All authors revised the manuscript for

important intellectual content. XZ, YM and SS had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data Availability

The data used in this study are available from the UK Biobank (<https://www.ukbiobank.ac.uk/>) subject to approval by UK Biobank. The data were accessed under Application ID 113769.

Data are available in a public, open access repository. Data were accessed from <https://www.ukbiobank.ac.uk>.

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Figures

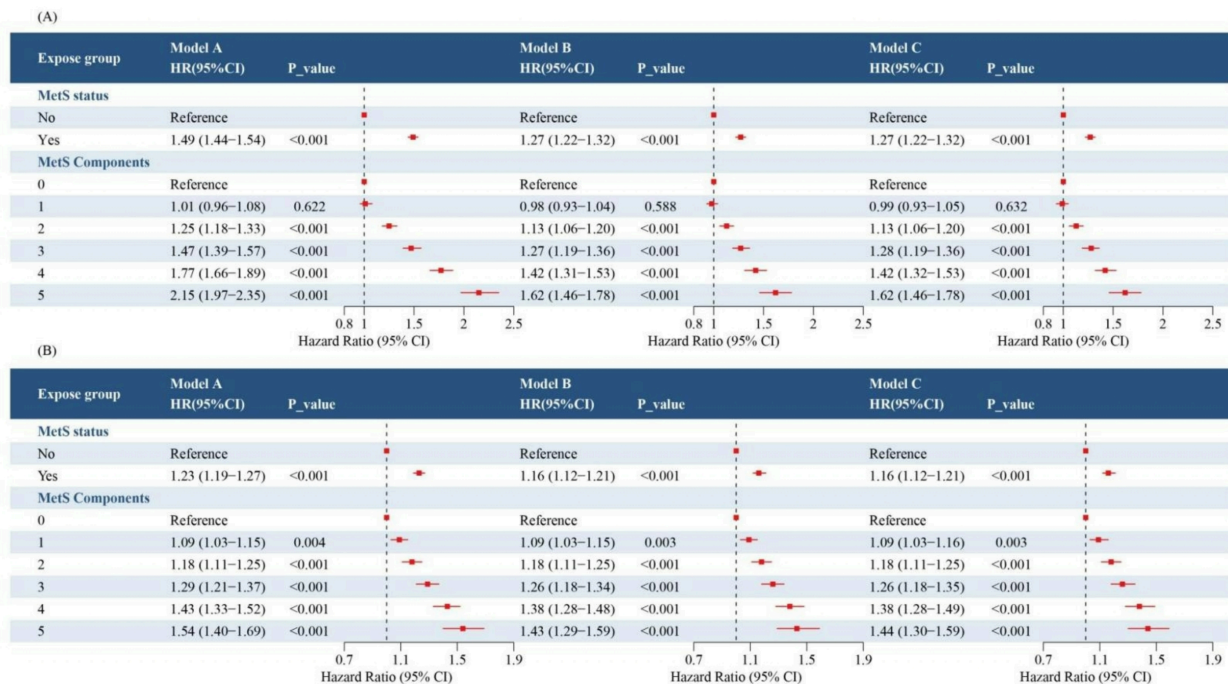


Figure 1

Association between MetS and risk of incident depression (A) and anxiety (B) in the UK Biobank.

Notes: HRs and 95% CIs were derived from Cox proportional hazards models with four adjustment models: Model A included sex, age, education, ethnicity, and TDI; Model B further adjusted for BMI, smoking, alcohol consumption, and physical activity; Model C further included dietary factors (intake of fish, vegetables, fruits, unprocessed meat, and processed meat).

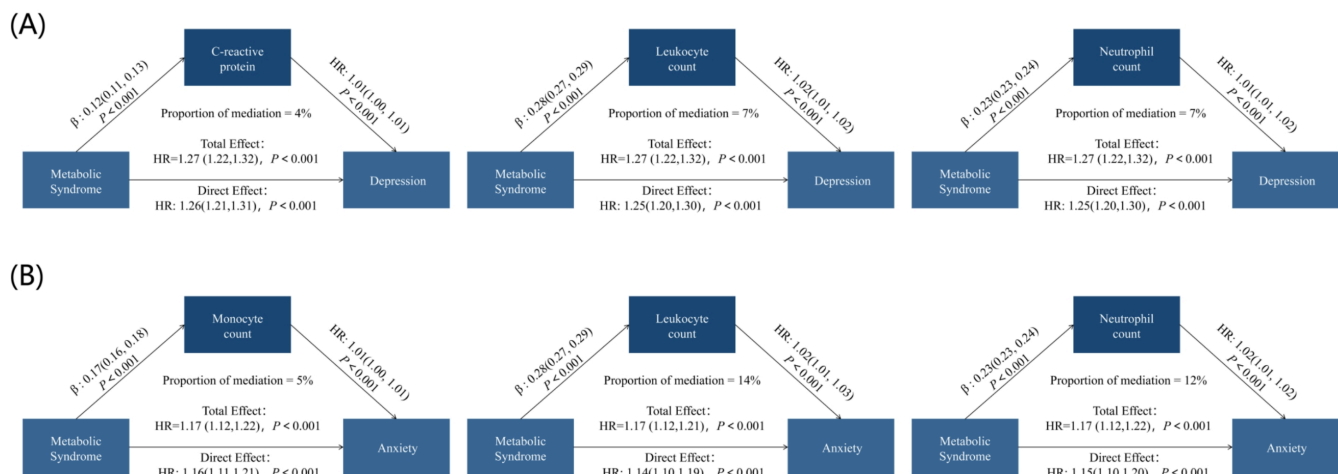


Figure 2

Mediation analyses of the association between MetS and incident depression (A) and anxiety (B) by inflammatory markers in the UK Biobank.

Note: Mediation analyses included nine inflammatory markers: C-reactive protein (CRP), leukocyte count, platelet count, neutrophil count, lymphocyte count, monocyte count, as well as the percentages of neutrophils, lymphocytes, and monocytes in leukocytes. Only markers with significant mediation effects are shown in the figure ($P < 0.05$) .

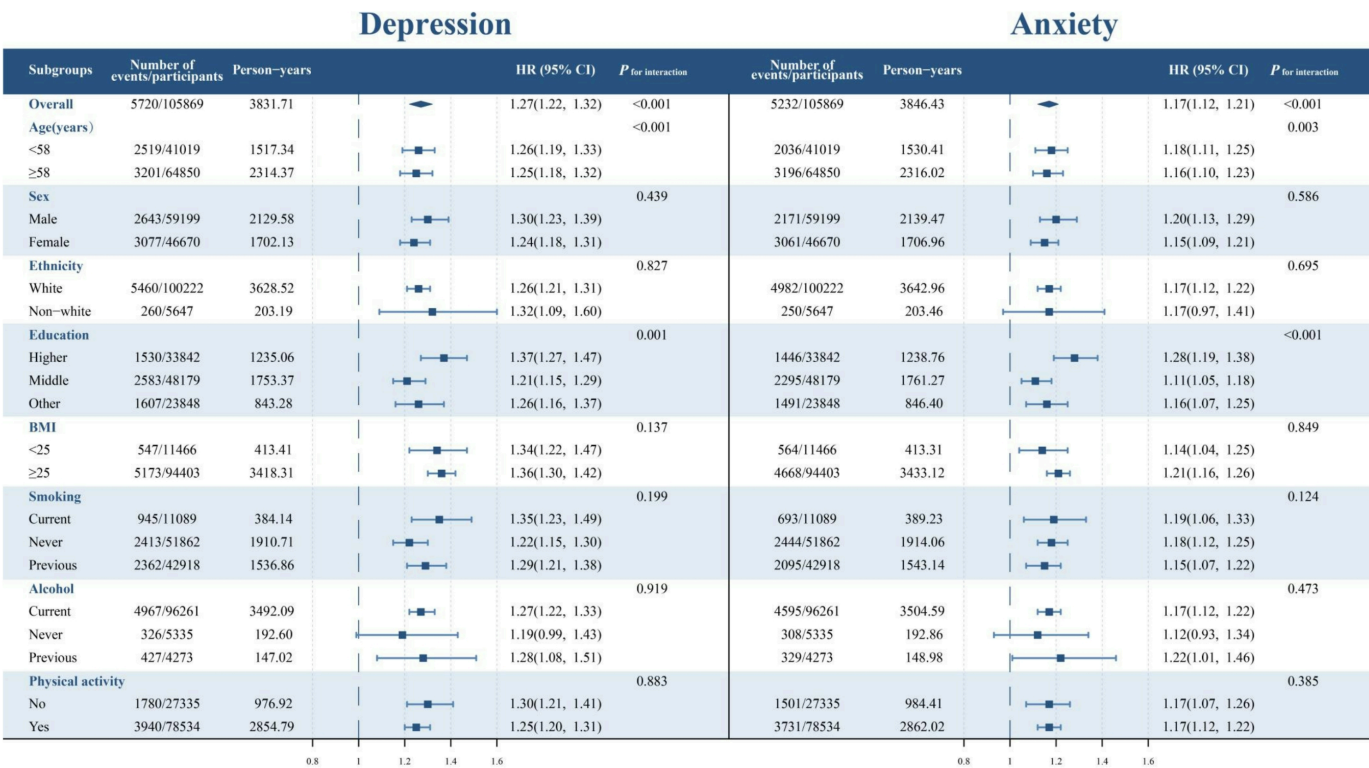


Figure 3

Stratified analyses for the association between MetS and risk of incident depression and anxiety in the UK Biobank

Notes: HR, hazard ratio; CI, confidence interval; BMI, body mass index. All subgroup analyses were adjusted for all covariates in Model C: sex, age, education, ethnicity, TDI, BMI, smoking, alcohol consumption, physical activity, fish intake, vegetable intake, fruit intake, unprocessed meat intake, and processed meat intake. When a variable served as the stratifying variable, that covariate was excluded from the adjustment model to avoid overadjustment. Interaction P -values were estimated by including product terms between MetS and each stratifying variable in the models.

Supplementary Files

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