

Association between Cardiometabolic Multimorbidity and Depression Risk in Middle-aged and Older Chinese Adults: An Analysis Based on the China Health and Retirement Longitudinal Study (CHARLS) Database: A Prospective Cohort Study

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Abstract

Background

Cardiometabolic multimorbidity (CMM) and depression are increasingly prevalent among middle-aged and older adults. However, prospective evidence regarding the association between CMM and subsequent depressive symptoms remains limited. This study aimed to examine this association among middle-aged and older Chinese adults.

Methods

This prospective cohort study included 10,726 participants aged ≥ 45 years from the China Health and Retirement Longitudinal Study, with baseline assessment in 2011 and follow-up through 2020. CMM was defined as the coexistence of at least two cardiometabolic diseases, including diabetes, heart disease, and stroke. Depressive symptoms were assessed using the 10-item Center for Epidemiologic Studies Depression Scale, with a score ≥ 12 indicating depressive symptoms. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Interaction, propensity score, E-value, subgroup, machine learning, and sensitivity analyses were conducted to assess the robustness of the findings.

Results

Among the participants, 386 had CMM. The prevalence of depressive symptoms was higher in the CMM-positive group than in the CMM-negative group (38.6% vs. 33.0%, $P = 0.022$). After adjustment for demographic characteristics, lifestyle factors, clinical variables, and laboratory biomarkers, CMM was independently associated with an increased risk of depressive symptoms (HR 1.25, 95% CI 1.05–1.49, $P = 0.011$). Multiple propensity score analyses produced generally consistent positive associations, with the strongest estimate observed using inverse probability of treatment weighting (HR 1.52, 95% CI 1.29–1.79, $P = 0.001$). The E-value was 1.81 for the point estimate and 1.28 for the lower confidence limit. Evidence of additive interaction between CMM and cognitive dysfunction was observed. Boruta and SHAP analyses also identified CMM as an important predictor of depressive symptoms. The association remained significant after excluding participants with baseline depressive symptoms (HR 1.32, 95% CI 1.02–1.72, $P = 0.037$).

Conclusions

CMM was independently associated with an increased risk of depressive symptoms among middle-aged and older Chinese adults. These findings highlight the importance of incorporating routine depression screening and integrated mental health management into the care of individuals with CMM.

Introduction

Depression is one of the most prevalent mental health conditions globally, representing a substantial public health burden among older populations. Epidemiological studies estimate that the prevalence of depressive symptoms among older adults in China ranges from 23.6% to 44.5%, which is considerably higher than the global average[1–3]. Depression not only severely impairs patients' quality of life and social functioning but is also closely associated with cognitive decline, increased suicide risk, elevated cardiovascular events, and all-cause mortality [4–6]. Against the backdrop of rapid population ageing in China, the identification of modifiable risk factors for depression has become an urgent public health priority.

Cardiometabolic multimorbidity (CMM), defined as the co-occurrence of two or more cardiometabolic diseases (including diabetes, heart disease, and stroke), has emerged as a major health challenge in ageing societies. The prevalence of CMM among middle-aged and older adults in China ranges from 5.94% to 16.9%, and this disease burden is projected to increase further under the dual pressures of population ageing and rising obesity rates[7–9]. Compared with individuals who have a single cardiometabolic disease, those with CMM face greater cumulative health risks, including increased all-cause mortality, accelerated cognitive decline, and significantly reduced quality of life[10–12].

The potential association between CMM and depression is biologically plausible. These two conditions share multiple pathophysiological mechanisms, including chronic low-grade systemic inflammation, insulin resistance, endothelial dysfunction, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, all of which may concurrently promote the development and progression of both disorders[13, 14]. Furthermore, the cumulative burden of managing multiple chronic conditions—including polypharmacy, lifestyle restrictions, persistent concerns about disease progression, and declining self-management capacity—may also contribute to the onset of depressive symptoms through psychosocial pathways[15, 16]. Previous studies have demonstrated that individual cardiometabolic diseases (such as diabetes and hypertension) are significantly associated with increased depression risk[2]. However, whether the co-occurrence of multiple cardiometabolic diseases exerts a synergistic effect on depression risk beyond the simple addition of individual disease effects remains unclear.

Previous research on CMM has predominantly focused on its associations with mortality and physical health outcomes, whereas the relationship between CMM and mental health outcomes—particularly depression—has not been adequately investigated. Several studies using CHARLS data have examined the longitudinal trajectories of frailty, cognitive impairment, and depressive symptoms, confirming the close interrelationships among these conditions in older Chinese adults[17–19]. Another study analysed the detection rate and influencing factors of depression among Chinese patients with diabetes, reporting a detection rate as high as 67.5% [2]. Additionally, research on the triglyceride-glucose-waist-to-height ratio (TyG-WHtR) and CMM has further highlighted the importance of comprehensive metabolic risk assessment in multimorbidity prevention and control[20]. However, to our knowledge, no study to date has specifically adopted a multidimensional analytical approach incorporating machine learning

algorithms to systematically examine the association between CMM and depression risk among middle-aged and older adults in China.

Therefore, this study aims to investigate the independent association between CMM and the risk of incident depression among middle-aged and older adults in China using CHARLS data from the 2011 baseline survey with follow-up through 2020 (Wave 5). We employed a strategy combining traditional epidemiological methods with advanced machine learning techniques, including multivariable Cox proportional hazards regression, interaction analysis, multiple propensity score methods, E-value sensitivity analysis, subgroup analysis, and random forest-based feature selection algorithms, to provide robust, multidimensional evidence for the association between CMM and depression.

Methods

Study Design and Data Source

This prospective cohort analysis used data from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS is a nationally representative prospective cohort study that completed baseline data collection (Wave 1) between June 2011 and March 2012, enrolling 17,708 participants aged ≥ 45 years from 28 provinces, 150 counties or districts, and 450 villages or communities across China[21]. The survey employed a multi-stage probability proportional to size sampling strategy. Comprehensive data were collected through face-to-face interviews, covering demographic characteristics, health status, lifestyle behaviours, physical examinations, and blood biochemical measurements. Participants were subsequently followed up in 2013 (Wave 2), 2015 (Wave 3), 2018 (Wave 4), and 2020 (Wave 5). CHARLS was approved by the Institutional Review Board of Peking University (IRB00001052-11015), and all participants provided written informed consent.

Study Participants

This analysis was restricted to participants from the 2011 CHARLS baseline survey who were followed up through 2020 (Wave 5). The inclusion and exclusion process was as follows: (1) an initial sample of 17,708 participants was identified; (2) 96 participants with missing CMM status were excluded ($n = 17,612$); (3) 4,568 participants with missing depression data at the 2020 Wave 5 follow-up were excluded ($n = 13,044$); (4) 2,318 participants with missing key covariates were excluded ($n = 10,726$). Ultimately, 10,726 participants were included in the analysis, comprising 10,340 CMM-negative and 386 CMM-positive individuals. A detailed flowchart is provided in Fig. 1.

Assessment of CMM

CMM was defined as the co-occurrence of two or more cardiometabolic diseases (CMDs), which included diabetes, heart disease, and stroke[12].

Diabetes was diagnosed based on any of the following criteria: fasting plasma glucose (FPG) ≥ 7.0 mmol/L, glycated haemoglobin (HbA1c) $\geq 6.5\%$, current use of glucose-lowering medications, or self-reported physician diagnosis of diabetes.

Heart disease and stroke were identified based on self-reported data or cardiovascular medication use collected during the baseline survey. Participants were asked standardised questionnaire items: "Have you ever been diagnosed with coronary heart disease, angina, congestive heart failure, or other heart diseases by a doctor?" and "Have you ever been diagnosed with stroke by a doctor?" Participants who met the diagnostic criteria for two or three CMDs were classified as CMM-positive (CMM+); those with no CMD or only one CMD were classified as CMM-negative (CMM-).

Assessment of Depression

Depressive symptoms were evaluated using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D has been validated in Chinese populations and demonstrates satisfactory reliability and validity[22]. The scale comprises four dimensions: depressed mood, positive mood, somatic symptoms, and interpersonal problems. Each item is scored on a 4-point Likert scale (0 = rarely or none of the time, 1 = some of the time, 2 = often, 3 = most of the time), with two positively worded items reverse-scored. Total scores range from 0 to 30, with higher scores indicating more severe depressive symptoms. Following the criteria used in previous studies of middle-aged and older adults in China, a CES-D score ≥ 12 was used as the cut-off point for depressive symptoms. In this study, the outcome of interest was depressive symptoms (CES-D score ≥ 12) ascertained at the 2020 Wave 5 follow-up survey[23].

Covariates

Based on previous literature and clinical relevance[2], the following covariates were included: (1) demographic characteristics: age (continuous variable, years), sex (male/female), marital status (married/other), educational level (illiterate/primary school or lower/junior high school/high school or higher), and place of residence (urban/rural); (2) lifestyle factors: smoking status (yes/no) and alcohol consumption (yes/no); (3) clinical characteristics: body mass index (BMI, kg/m²), hypertension (yes/no), and dyslipidaemia (yes/no); (4) laboratory biomarkers: white blood cell count (WBC, $\times 10^9$ /L), platelet count ($\times 10^9$ /L), blood urea nitrogen (BUN, mmol/L), fasting glucose (GLU, mmol/L), creatinine (Crea, μ mol/L), total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), C-reactive protein (CRP, mg/L), glycated haemoglobin (HbA1c, %), uric acid (UA, μ mol/L), and cognitive dysfunction (CDs).

Statistical Analysis

Descriptive Analysis

Continuous variables were presented as mean $\pm$ standard deviation (for normally distributed data) or median (interquartile range) [M (IQR)] (for non-normally distributed data). Categorical variables were expressed as frequencies (percentages). Baseline characteristics between the CMM + and CMM- groups were compared using independent samples t-test or Mann-Whitney U test (continuous variables) and chi-square test (categorical variables).

Cox Proportional Hazards Regression Analysis

Three multivariable Cox proportional hazards regression models were constructed to examine the association between baseline CMM and the risk of depression at the 2020 Wave 5 follow-up. Follow-up time was calculated from the date of the 2011 baseline survey to the date of the 2020 Wave 5 survey or the last available follow-up visit. The proportional hazards assumption was tested using Schoenfeld residuals and was not violated. Model 1 was unadjusted. Model 2 was adjusted for demographic characteristics (age, sex, marital status, educational level, place of residence), lifestyle factors (smoking, alcohol consumption), BMI, hypertension, and dyslipidaemia. Model 3 further adjusted for laboratory biomarkers (WBC, platelet count, BUN, GLU, Crea, TC, TG, CRP, HbA1c, UA, CDs) in addition to the covariates in Model 2. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI) and P values.

Interaction Analysis

Interaction analysis was performed to evaluate whether the association between CMM and depression was modified by cognitive dysfunction. Additive interaction measures included relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI), calculated using regression coefficients and their covariance matrices from Cox proportional hazards regression models[22]. Multiplicative interaction was assessed by including the product term of CMM and cognitive dysfunction in the Cox proportional hazards regression model.

Propensity Score Analysis

To control for potential selection bias and confounding, multiple propensity score methods were employed as sensitivity analyses: (1) propensity score adjustment; (2) 1:1 propensity score matching (caliper value = 0.05); (3) inverse probability of treatment weighting (IPTW); (4) stabilised marginal mean weighting (SMRW); (5) average treatment effect in the treated weighting (PA); (6) overlap weighting (OW). Propensity scores were estimated using a logistic regression model with all covariates as predictors.

E-value Analysis

E-values were calculated to assess the potential impact of unmeasured confounding on the observed CMM-depression association. The E-value represents the minimum strength of association (on the risk ratio scale) that an unmeasured confounder would need to have with both the exposure and the

outcome to fully explain away the observed association[24]. E-values were calculated for both the point estimate and the lower bound of the 95% confidence interval.

Subgroup Analysis

Subgroup analyses were conducted by age (< 60 years vs. ≥60 years), sex (male vs. female), smoking status (yes vs. no), and alcohol consumption (yes vs. no) to evaluate the consistency of the CMM-depression association across different population strata. Interaction terms between CMM and subgroup variables were tested in the fully adjusted model (Model 3).

Machine Learning Analysis

Machine learning algorithms were applied to identify important predictors of depression and to validate the independent predictive value of CMM. The Boruta algorithm, a random forest-based wrapper feature selection method, was used to determine confirmed, tentative, and rejected feature categories from candidate predictors [25]. Additionally, SHAP (SHapley Additive exPlanations) values were computed to quantify the contribution of each feature to the depression prediction model output [26]. Features with mean |SHAP value| > 0 were considered to be important predictors making a substantive contribution to depression prediction.

Sensitivity Analysis

Three sensitivity analyses were conducted to evaluate the robustness of the main findings: (1) analysis of the full population with depression data (n = 17,612) without applying the covariate missingness exclusion criteria; (2) multivariable Cox proportional hazards regression analysis of the above full population; (3) exclusion of participants with pre-existing depressive symptoms at baseline to assess whether the association between CMM and incident depression risk was driven by prevalent cases.

Statistical Software

All data were analyzed using R (version 4.2.2, <http://www.R-project.org>, The R Foundation) and the Free Statistics analysis platform (version 2.4.0, Beijing, China). A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of the study participants stratified by CMM status. Among the 10,726 participants, 3,562 (33.2%) had depressive symptoms. Compared with the CMM- group, participants in the CMM+ group were older (60.3 ± 8.6 years vs. 57.4 ± 8.8 years, $P < 0.001$), had higher BMI [25.1 ($22.3 - 27.7$) kg/m^2 vs. 23.2 ($21.0 - 25.9$) kg/m^2 , $P < 0.001$], and were more likely to reside in urban areas (49.0% vs. 35.2%, $P < 0.001$). The prevalence of hypertension (70.7% vs. 41.4%, $P < 0.001$) and dyslipidaemia (43.0% vs. 10.4%, $P < 0.001$) was significantly higher in the CMM+ group. Regarding

laboratory parameters, the CMM+ group exhibited higher levels of glucose (145.5 ± 56.1 vs. 108.3 ± 30.0 mg/dL), triglycerides [137.6 ($98.2 - 222.8$) vs. 108.0 ($76.1 - 159.3$) mg/dL], CRP [1.4 ($0.7 - 2.8$) vs. 1.0 ($0.5 - 2.1$) mg/L], and HbA1c (6.0% vs. 5.2%) (all $P < 0.001$). Notably, the prevalence of depression was significantly higher in the CMM+ group than in the CMM- group (38.6% vs. 33.0% , $P = 0.022$).

Table 1

Baseline characteristics of study participants by cardiometabolic multimorbidity (CMM) status

Variables	Total (n = 10726)	CMM- (n = 10340)	CMM+ (n = 386)	p
age, Mean $\pm$ SD	57.5 $\pm$ 8.8	57.4 $\pm$ 8.8	60.3 $\pm$ 8.6	< 0.001
Gender, n (%)				0.093
Male	4895 (45.6)	4735 (45.8)	160 (41.5)	
Female	5831 (54.4)	5605 (54.2)	226 (58.5)	
Marital status, n (%)				0.279
Married	9598 (89.5)	9259 (89.5)	339 (87.8)	
other	1128 (10.5)	1081 (10.5)	47 (12.2)	
Education, n (%)				0.121
Illiterate	2895 (27.0)	2800 (27.1)	95 (24.6)	
Junior high school and lower	6582 (61.4)	6348 (61.4)	234 (60.6)	
High school and higher	1249 (11.6)	1192 (11.5)	57 (14.8)	
Place of residence, n (%)				< 0.001
City	3832 (35.7)	3643 (35.2)	189 (49)	
Rural	6894 (64.3)	6697 (64.8)	197 (51)	
Smoking, n (%)				0.996
no	6698 (62.4)	6457 (62.4)	241 (62.4)	
yes	4028 (37.6)	3883 (37.6)	145 (37.6)	
Drinking, n (%)				0.104
no	6635 (61.9)	6381 (61.7)	254 (65.8)	
yes	4091 (38.1)	3959 (38.3)	132 (34.2)	
BMI, Median (IQR)	23.3 (21.0, 26.0)	23.2 (21.0, 25.9)	25.1 (22.3, 27.7)	< 0.001
hypertention, n (%)				< 0.001
no	6168 (57.5)	6055 (58.6)	113 (29.3)	
yes	4558 (42.5)	4285 (41.4)	273 (70.7)	

Variables	Total (n = 10726)	CMM- (n = 10340)	CMM+ (n = 386)	p
dyslipidemia, n (%)				< 0.001
no	9484 (88.4)	9264 (89.6)	220 (57)	
yes	1242 (11.6)	1076 (10.4)	166 (43)	
WBC, Mean $\pm$ SD	6.2 $\pm$ 1.8	6.2 $\pm$ 1.8	6.6 $\pm$ 1.9	< 0.001
Platelet, Mean $\pm$ SD	214.1 $\pm$ 73.7	214.4 $\pm$ 74.0	206.0 $\pm$ 66.6	0.028
BUN, Mean $\pm$ SD	15.6 $\pm$ 4.4	15.6 $\pm$ 4.4	15.5 $\pm$ 4.3	0.637
GLU, Mean $\pm$ SD	109.6 $\pm$ 32.0	108.3 $\pm$ 30.0	145.5 $\pm$ 56.1	< 0.001
Crea, Mean $\pm$ SD	0.8 $\pm$ 0.2	0.8 $\pm$ 0.2	0.8 $\pm$ 0.3	< 0.001
TC, Mean $\pm$ SD	194.5 $\pm$ 39.7	194.3 $\pm$ 39.5	197.9 $\pm$ 43.6	0.082
TG, Median (IQR)	109.7 (77.0, 161.1)	108.0 (76.1, 159.3)	137.6 (98.2, 222.8)	< 0.001
CRP, Median (IQR)	1.0 (0.5, 2.1)	1.0 (0.5, 2.1)	1.4 (0.7, 2.8)	< 0.001
Hba1c, Mean $\pm$ SD	5.3 $\pm$ 0.8	5.2 $\pm$ 0.7	6.0 $\pm$ 1.4	< 0.001
UA, Mean $\pm$ SD	4.4 $\pm$ 1.2	4.4 $\pm$ 1.2	4.6 $\pm$ 1.3	< 0.001
CDs, n (%)	3335 (31.1)	3229 (31.2)	106 (27.5)	0.116
depression, n (%)	3562 (33.2)	3413 (33)	149 (38.6)	0.022

Association between CMM and Depression

Table 2 presents the results of the Cox proportional hazards regression analyses. In the unadjusted model (Model 1), the association between CMM and depression risk was positive but did not reach statistical significance (HR 1.13, 95% CI 0.96 – 1.33, P = 0.145). After adjustment for demographic characteristics and lifestyle factors (Model 2), the association was strengthened and approached significance (HR 1.18, 95% CI 0.99 – 1.39, P = 0.061). In the fully adjusted model (Model 3), CMM was significantly and independently associated with depression risk after further controlling for laboratory biomarkers (HR 1.25, 95% CI 1.05 – 1.49, P = 0.011), indicating that CMM patients had a 25% higher risk of depression compared with non-CMM participants. The HR values showed an increasing trend with progressive levels of covariate adjustment, suggesting that the association between CMM and depression could not be explained by measured confounders.

Table 2

Association between cardiometabolic multimorbidity (CMM) and depression risk: Cox proportional hazards regression and interaction analyses

Variable	Model1		Model2		Model3	
	HR(95%CI)	P_value	HR(95%CI)	P_value	HR(95%CI)	P_value
CMM-	1(Ref)		1(Ref)		1(Ref)	
CMM+	1.13 (0.96 ~ 1.33)	0.145	1.18 (0.99 ~ 1.39)	0.061	1.25 (1.05 ~ 1.49)	0.011
Multiplicative scale	1.24(0.88–1.74)					0.22
RERI	0.47(-0.13-1.07)					0.06
AP	0.23(-0.01-0.46)					0.03
SI	1.78(0.92–3.47)					<0.001
Model 1: unadjusted.						
Model 2: Adjustment Age, Gender, Marital status, Education, Place of residence, Smoking, Drinking, BMI, hypertension, dyslipidemia. Model 3: Adjustment Age, Gender, Marital status, Education, Place of residence, Smoking, Drinking, BMI, hypertension, dyslipidemia, WBC, Platelet, BUN, GLU, Crea, TC, TG, CRP, Hba1c, UA, CDs.						

Interaction Analysis

We further assessed the interaction between CMM and cognitive dysfunction (CDs) on depression risk. No significant multiplicative interaction was observed (HR = 1.24, 95% CI: 0.88–1.74, $P = 0.22$). However, significant additive interactions were detected between CMM and CDs. The relative excess risk due to interaction (RERI) was 0.47 (95% CI: – 0.13 to 1.07, $P = 0.06$, marginally significant), the attributable proportion (AP) was 0.23 (95% CI: – 0.01 to 0.46, $P = 0.03$), and the synergy index (SI) was 1.78 (95% CI: 0.92–3.47, $P < 0.001$). These findings indicate that CMM and CDs may act synergistically to increase the risk of depression on the additive scale, with approximately 23% of the depression risk among individuals with both conditions attributable to their interaction per se. Table 2.

Propensity Score Analysis

Table 3 presents the results of the sensitivity analyses using multiple propensity score methods. CMM remained positively associated with depression risk across all methods. The propensity score-adjusted HR was 1.21 (95% CI 1.02 – 1.44, $P = 0.032$). Among the weighting methods, IPTW showed the strongest association (HR 1.52, 95% CI 1.29 – 1.79, $P = 0.001$), followed by OW (HR 1.22, 95% CI 0.94 – 1.57, $P = 0.029$) and PA (HR 1.21, 95% CI 0.95 – 1.54, $P = 0.042$). The estimates from propensity score matching (HR 1.21, 95% CI 0.95 – 1.55, $P = 0.117$) and SMRW (HR 1.17, 95% CI 0.99 – 1.37, $P = 0.169$) were

attenuated and did not reach statistical significance, although the direction of the association remained consistent. The overall consistency in the direction and magnitude of the estimates across multiple propensity score methods provides corroborating evidence for the independent association between CMM and depression.

Table 3

Propensity score-based sensitivity analyses of the association between cardiometabolic multimorbidity (CMM) and depression

Models	CMM: 1 vs 0	HR (95%CI)	P value
Unmatched.crude	1.0(Ref)	1.13 (0.96 ~ 1.33)	0.145
Multivariable.adjusted	-	1.25 (1.05 ~ 1.49)	0.011
PropensityScore.adjusted	-	1.21 (1.02 ~ 1.44)	0.032
PropensityScore.Matched	-	1.21 (0.95 ~ 1.55)	0.117
Weighted.IPTW	-	1.52 (1.29 ~ 1.79)	0.001
Weighted.SMRW	-	1.17 (0.99 ~ 1.37)	0.169
Weighted.PA	-	1.21 (0.95 ~ 1.54)	0.042
Weighted.Ow	-	1.22 (0.94 ~ 1.57)	0.029
Adjustment Age, Gender, Marital status, Education, Place of residence, Smoking, Drinking, BMI, hypertension, dyslipidemia, WBC, Platelet, BUN, GLU, Crea, TC, TG, CRP, Hba1c, UA, CDs.			

E-value Analysis

The E-value analysis results are presented in Table 4. For the fully adjusted model HR of 1.25, the corresponding E-value was 1.81, indicating that an unmeasured confounder would need to have a risk ratio association of at least 1.81 with both CMM and depression to fully explain away the observed association. For the lower bound of the 95% confidence interval (HR 1.05), the E-value was 1.28. These results suggest that the observed association between CMM and depression demonstrates reasonable robustness against moderate unmeasured confounding.

Table 4

E-values for the association between cardiometabolic multimorbidity (CMM) and depression

Parameter	Point Estimate	Lower Bound	Upper Bound
RR	1.25	1.05	1.49
E-values	1.81	1.28	-
Note: The E-value represents the minimum strength of association (on the risk ratio scale) that an unmeasured confounder would need to have with both exposure and outcome to fully explain away the observed association. The E-value for the lower bound of the confidence interval indicates the minimum confounding strength needed to shift the estimate to the null.			

Subgroup Analysis

Figure 2 presents the results of the subgroup analyses. The positive association between CMM and depression remained consistent across all subgroups. No significant multiplicative interactions were found between CMM and age, sex, smoking, or alcohol consumption (all interaction P values > 0.05), indicating that this association was consistent across populations with different demographic and lifestyle characteristics.

Machine Learning Analysis

Figure 3 presents the results of the Boruta feature selection algorithm. Among 18 candidate features, 11 were confirmed as important predictors of depression, including sex, educational level, cognitive dysfunction, rural residence, smoking, age, uric acid, marital status, alcohol consumption, CMM, and creatinine. The remaining 7 features (glucose, CRP, platelet count, BMI, HbA1c, WBC, dyslipidaemia, BUN, total cholesterol, triglycerides, and hypertension) were classified as non-significant predictors.

Figures 4 and 5 present SHAP summary plots that quantify the contribution of each feature to depression prediction. Ranked by mean |SHAP value|, the most important predictors were sex (0.0431), rural residence (0.0245), educational level (0.0245), cognitive dysfunction (0.0241), creatinine (0.0190), age (0.0181), uric acid (0.0181), smoking (0.0163), alcohol consumption (0.0079), CMM (0.0049), and marital status (0.0035). CMM was identified by the machine learning algorithm as one of the important predictors of depression, with a predictive contribution independent of traditional risk factors, further supporting the main findings from the epidemiological regression analyses.

Sensitivity Analysis

Supplementary Table 1 presents the baseline characteristics of the full population (n = 17,612) without applying the covariate missingness exclusion criteria; the distribution characteristics were generally consistent with those of the main analysis population. Supplementary Table 2 presents the multivariable Cox proportional hazards regression results for this full population, showing that CMM remained significantly associated with depression in the fully adjusted model (HR 2.02, 95% CI 1.39 – 2.94, P < 0.001). Supplementary Table 3 presents the analysis after excluding participants with baseline depression (n = 7,696); in this subset, CMM remained significantly associated with incident depression in the fully adjusted model (HR 1.32, 95% CI 1.02 – 1.72, P = 0.037), further supporting the robustness of the main findings.

Discussion

In this nationally representative prospective cohort study of 10,726 middle-aged and older Chinese adults followed from 2011 to 2020, we found a significant independent association between cardiometabolic multimorbidity (CMM) and increased depression risk. After comprehensive adjustment

for demographic characteristics, lifestyle factors, and extensive laboratory biomarkers, CMM patients had a 25% higher risk of depression compared with non-CMM participants (HR 1.25, 95% CI 1.05 – 1.49). This core finding was consistently validated through multiple advanced statistical approaches: multiple propensity score methods consistently showed positive associations, most of which remained statistically significant; E-value analysis indicated robustness against unmeasured confounding, subgroup analyses demonstrated consistency across different populations, and machine learning algorithms identified CMM as one of the important predictors of depression. The convergence of evidence from these multiple dimensions substantially strengthens the reliability and internal validity of our findings.

The positive association between CMM and depression risk identified in this study is generally consistent with previous literature reports, while extending beyond them in study design and analytical depth. Bai et al. [2] used CHARLS 2018 data to analyse the detection rate and influencing factors of depressive symptoms among middle-aged and older adults with diabetes in China, reporting that 68.2% of diabetic patients had depressive symptoms, and finding that age, educational level, self-rated health status, physical pain, and number of comorbid chronic conditions were significantly associated with depression. Yuan et al. [1] identified four co-occurrence trajectories of frailty, cognitive impairment, and depressive symptoms through eight-year longitudinal follow-up of older adults in China, revealing the heterogeneous association patterns and bidirectional interactions among these conditions. Our study makes several important contributions to the existing literature: first, whereas previous studies have generally treated CMM as a covariate or examined depression as one of several outcomes of CMM, our study specifically focuses on the direct association between CMM and depression and quantifies the independent effect size of this association; second, our study employs a multidimensional analytical strategy ranging from traditional regression to machine learning algorithms, achieving "triangulation" of the CMM-depression association, which has not been addressed in previous research.

It is noteworthy that in this study, the HR values for the association between CMM and depression showed a gradual increasing trend as the level of covariate adjustment deepened (from unadjusted to fully adjusted: 1.13→1.18→1.25). This phenomenon suggests that the association between CMM and depression may be partially mediated by certain intermediate factors (such as inflammatory markers) and may also be related to the more complex clinical phenotype of CMM patients [13]. Furthermore, the interaction analysis did not show significant synergistic effects among the CMM components, suggesting that the effect of CMM on depression risk may primarily reflect the cumulative burden of multiple cardiometabolic diseases rather than amplified biological interactions between diseases[27, 28]. This finding is consistent with the observation reported by Tang et al.[29] that multimorbidity increases mortality risk in a linear or sublinear manner.

The underlying mechanisms linking CMM and depression are multifactorial and multilevel, involving interactions among inflammatory, metabolic, and neuroendocrine pathways[30]. The inflammatory hypothesis represents the central framework for explaining this association. Chronic low-grade systemic inflammation is a well-established key pathophysiological link between cardiometabolic diseases and

depression. Pro-inflammatory cytokines—including interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), and C-reactive protein (CRP)—are chronically elevated in patients with CMM and may promote depression through the following pathways [31]: (1) activation of peripheral immune cells, with pro-inflammatory signals transmitted to the central nervous system via vagal afferent nerves [32]; (2) circulating inflammatory mediators directly compromising blood-brain barrier integrity, entering brain parenchyma to activate microglia and astrocytes, thereby triggering neuroinflammatory responses[32]; (3) inflammatory signalling pathways (such as NF- κ B and JAK-STAT pathways) interfering with neurotransmitter metabolism, reducing serotonin and dopamine bioavailability while promoting glutamate excitotoxicity[33]. In this study, CRP levels were significantly higher in the CMM+ group than in the CMM- group, and although adjustment for CRP in the multivariable model did not completely eliminate the effect of CMM, the indirect role of inflammatory pathways remains significant.

Insulin resistance and brain energy metabolism dysfunction constitute a second key pathway. As a core pathophysiological feature of type 2 diabetes and obesity, insulin resistance not only impairs peripheral glucose homeostasis but also directly affects insulin signalling in the brain. The hippocampus and prefrontal cortex—key brain regions for emotional regulation—are insulin-sensitive and have high densities of insulin receptors. Insulin resistance can lead to glucose utilisation disorders, mitochondrial dysfunction, and downregulated expression of neurotrophic factors (such as brain-derived neurotrophic factor, BDNF) in these regions, thereby impairing neuroplasticity and synaptic function [34] and increasing vulnerability to depression.

Cerebrovascular endothelial dysfunction and microvascular injury represent a third linking pathway. Hypertension and dyslipidaemia are common components of CMM, both of which can cause vascular endothelial damage, cerebral small vessel disease, and impaired cerebral blood flow autoregulation. Imaging studies have shown that patients with cardiometabolic diseases commonly exhibit cerebrovascular lesions such as white matter hyperintensities, lacunar infarcts, and cerebral microbleeds, which may directly or indirectly affect functional connectivity of emotion regulation networks (such as the limbic system-prefrontal cortex circuit), thereby increasing depression risk [35]. Furthermore, endothelial dysfunction may exacerbate neurodegeneration and mood dysregulation by reducing the bioavailability of brain-derived neurotrophic factor and nitric oxide[36].

Psychosocial mechanisms are also important. Patients with CMM face the burden of polypharmacy (taking multiple medications daily on average), frequent healthcare visits, strict dietary and exercise restrictions, persistent concerns about disease progression and complications, and reduced social participation due to declining physical function. These cumulative psychosocial stressors can activate the HPA axis through chronic stress responses, leading to sustained elevation of cortisol levels, which in turn impairs hippocampal neurogenesis, promotes inflammatory responses, and exacerbates depressive symptoms [37]. Concurrently, reduced quality of life and decreased self-efficacy associated with CMM may also indirectly contribute to the development and progression of depression through behavioural pathways (such as reduced physical activity and social isolation) [38].

The findings of this study have important implications for clinical practice and public health policy. First, CMM should be regarded as an important indication for depression risk screening. The results of this study suggest that systematic depression symptom screening (using tools such as PHQ-9 or the abbreviated CES-D) should be incorporated into routine follow-up of CMM patients to enable early identification and timely intervention of mood disorders. Second, comprehensive management strategies for CMM should integrate mental health as an essential component. For CMM patients with diagnosed depression, psychological interventions (such as cognitive behavioural therapy) and necessary antidepressant medication should be combined with standard glucose-lowering, blood pressure-lowering, and lipid-lowering treatments, with attention to interactions between multiple medications. Third, at the public health policy level, this study supports the integration of cardiometabolic disease and mental health prevention and control into the overall framework of chronic disease management, breaking down the "mind-body separation" management barriers through integrated healthcare delivery models.

This study has several strengths. First, it is based on the nationally representative CHARLS database with a large sample size and broad coverage, allowing the findings to be generalisable to a wider population of middle-aged and older adults in China. Second, covariate assessment is comprehensive, covering multiple dimensions including demographics, lifestyle, clinical characteristics, and laboratory biomarkers, enabling thorough control of potential confounders. Third, the study employed a diverse analytical strategy combining traditional epidemiological methods with advanced machine learning techniques, including six propensity score methods, E-value sensitivity analysis, and Boruta-SHAP-based feature selection, providing multidimensional, multi-method triangulation evidence for the CMM-depression association and substantially strengthening the reliability of the study conclusions.

This study also has several limitations. The diagnosis of CMM components partially relied on self-reported data, which may be subject to recall bias and reporting bias. Although we combined laboratory test results and medication use information for comprehensive determination, information bias cannot be completely excluded. Depressive symptoms were assessed using the CES-D scale rather than structured clinical diagnosis; while the CES-D has good psychometric properties in Chinese populations, some degree of misclassification may still occur, and the scale cannot distinguish between different severity levels of depressive symptoms. In addition, loss to follow-up between the 2011 baseline and the 2020 Wave 5 survey may have introduced attrition bias, although the sensitivity analysis in the full population yielded consistent results. Despite comprehensive covariate adjustment and the use of E-values to assess the impact of unmeasured confounding, the possibility of residual confounding in observational studies always exists.

Based on the findings and limitations of this study, future research could be pursued in the following directions: first, prospective studies with longer follow-up and repeated assessments should be conducted to further clarify the temporal causal sequence between CMM and depression and to identify the dynamic trajectories of their association; second, in-depth exploration of the molecular mechanisms underlying the CMM-depression association is warranted, particularly omics studies (such as

proteomics and metabolomics) targeting inflammatory-metabolic-neurotransmitter interaction pathways; third, randomised controlled trials should be conducted to evaluate the effectiveness of integrated intervention models based on comprehensive CMM management (addressing both physical disease control and mental health promotion) in improving depression outcomes; fourth, real-world healthcare big data should be utilised to construct clinical decision support tools for depression risk prediction in CMM patients, facilitating precision prevention and individualised intervention.

In summary, this study provides robust evidence validated through multiple dimensions and methods based on a nationally representative sample, demonstrating that cardiometabolic multimorbidity is independently associated with increased depression risk among middle-aged and older adults in China. The high consistency of results from traditional regression analysis, multiple propensity score methods, E-value sensitivity analysis, and machine learning feature selection highlights the authenticity and clinical importance of this association. These findings emphasise that in the context of population ageing, systematic depression screening for CMM patients and integrated multidisciplinary intervention based on the principle of "simultaneous treatment of mind and body" are of significant public health importance for the prevention and control of depression. Future longitudinal and interventional studies are needed to further clarify the causal relationship between the two conditions and to explore effective integrated prevention and control strategies.

Abbreviations

AP Attributable Proportion

BDNF Brain-Derived Neurotrophic Factor

BMI Body Mass Index

BUN Blood Urea Nitrogen

CD/CDs Cognitive Dysfunction

CES-D Center for Epidemiologic Studies Depression Scale

CHARLS China Health and Retirement Longitudinal Study

CI Confidence Interval

CMM Cardiometabolic Multimorbidity

CMD(s) Cardiometabolic Disease(s)

CRP C-reactive Protein

Crea Creatinine

FPG Fasting Plasma Glucose

GLU Fasting Glucose

HPA Hypothalamic-Pituitary-Adrenal

HbA1c Glycated Haemoglobin

IL-6 Interleukin-6

IPTW Inverse Probability of Treatment Weighting

IQR Interquartile Range

JAK-STAT Janus Kinase-Signal Transducer and Activator of Transcription

NF- κ B Nuclear Factor-kappa B

OR Odds Ratio

OW Overlap Weighting

PA Average Treatment Effect in the Treated Weighting

PHQ-9 Patient Health Questionnaire-9

RERI Relative Excess Risk due to Interaction

SD Standard Deviation

SHAP SHapley Additive exPlanations

SI Synergy Index

SMRW Stabilised Marginal Mean Weighting

TC Total Cholesterol

TG Triglycerides

TNF- α Tumour Necrosis Factor-alpha

UA Uric Acid

WBC White Blood Cell

Declarations

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.

Ethics approval and consent to participate

The China Health and Retirement Longitudinal Study (CHARLS) was conducted in accordance with the Declaration of Helsinki. The CHARLS study protocol was approved by the Institutional Review Board of Peking University (IRB00001052-11015). All CHARLS participants provided written informed consent before enrollment. The present study is a secondary analysis of publicly available, de-identified CHARLS data; no direct contact with participants was required.

Human Ethics and Consent to Participate declarations

The CHARLS protocol was approved by the Institutional Review Board of Peking University (IRB00001052-11015) and was carried out in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from all CHARLS participants. The present secondary analysis used only de-identified, publicly available data and did not involve direct interaction with human participants.

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Author Contribution

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Xiaoqin Qu: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft.
Xiaoping Xu: Conceptualization, Methodology, Writing – review & editing, Supervision.
Yihe Wang: Data curation, Formal analysis, Validation.
Junyao Fu: Data curation, Investigation, Resources.
Quan Liu: Formal analysis, Visualization, Validation.
Qingshan Deng: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.
Jingcheng Jiang: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Data Availability

The datasets used in this investigation are publicly available online. Detailed descriptions of the survey and corresponding data can be accessed at the China Health and Retirement Longitudinal Study (CHARLS) official website: <http://charls.pku.edu.cn/>. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

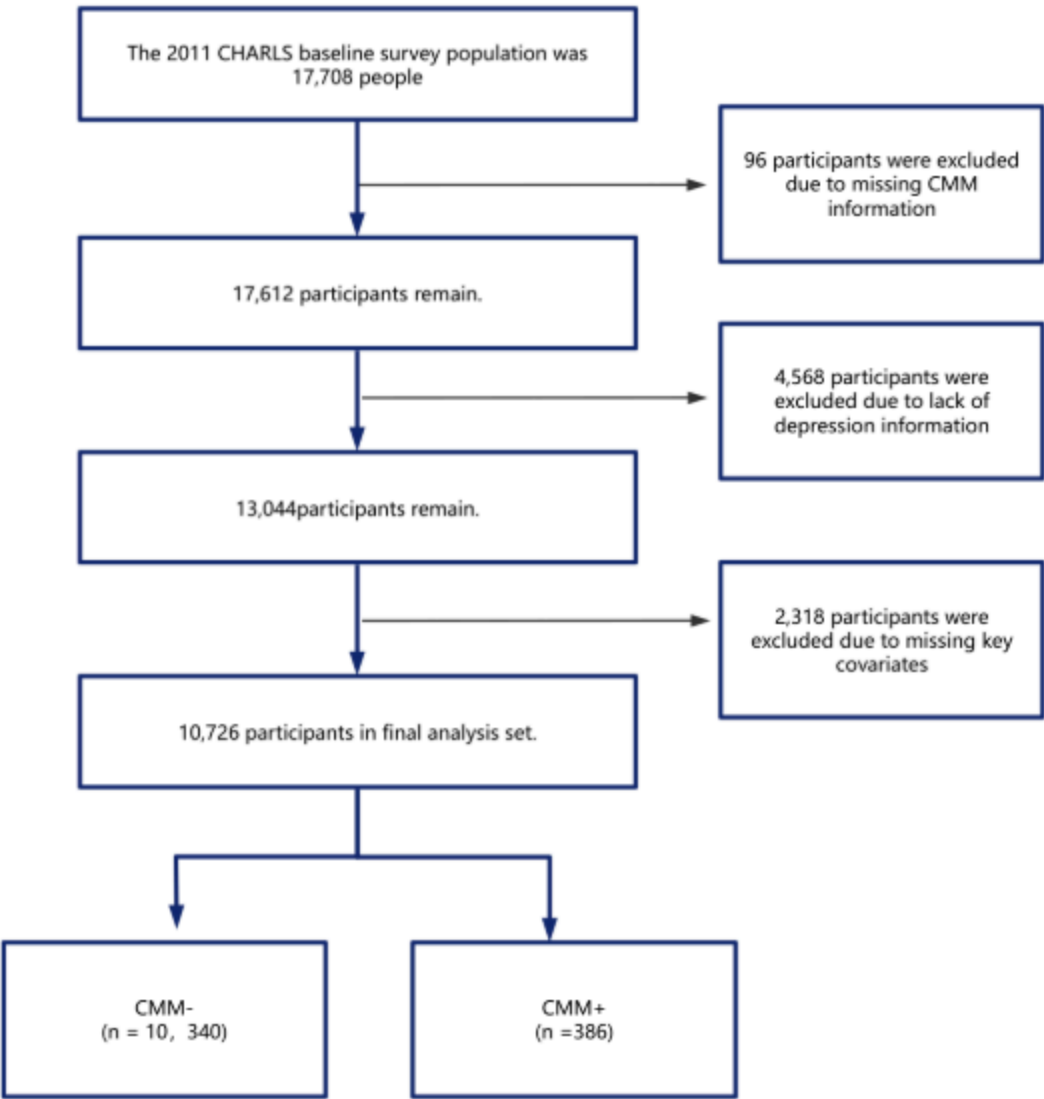


Figure 1

Flowchart of participant selection and exclusion criteria.

From the 2011 CHARLS baseline survey population of 17,708 individuals, 96 were excluded due to missing CMM information, 4,568 due to missing depression data at the 2020 Wave 5 follow-up, and 2,318 due to missing key covariates, resulting in a final analytical sample of 10,726 participants (10,340 CMM-negative and 386 CMM-positive).

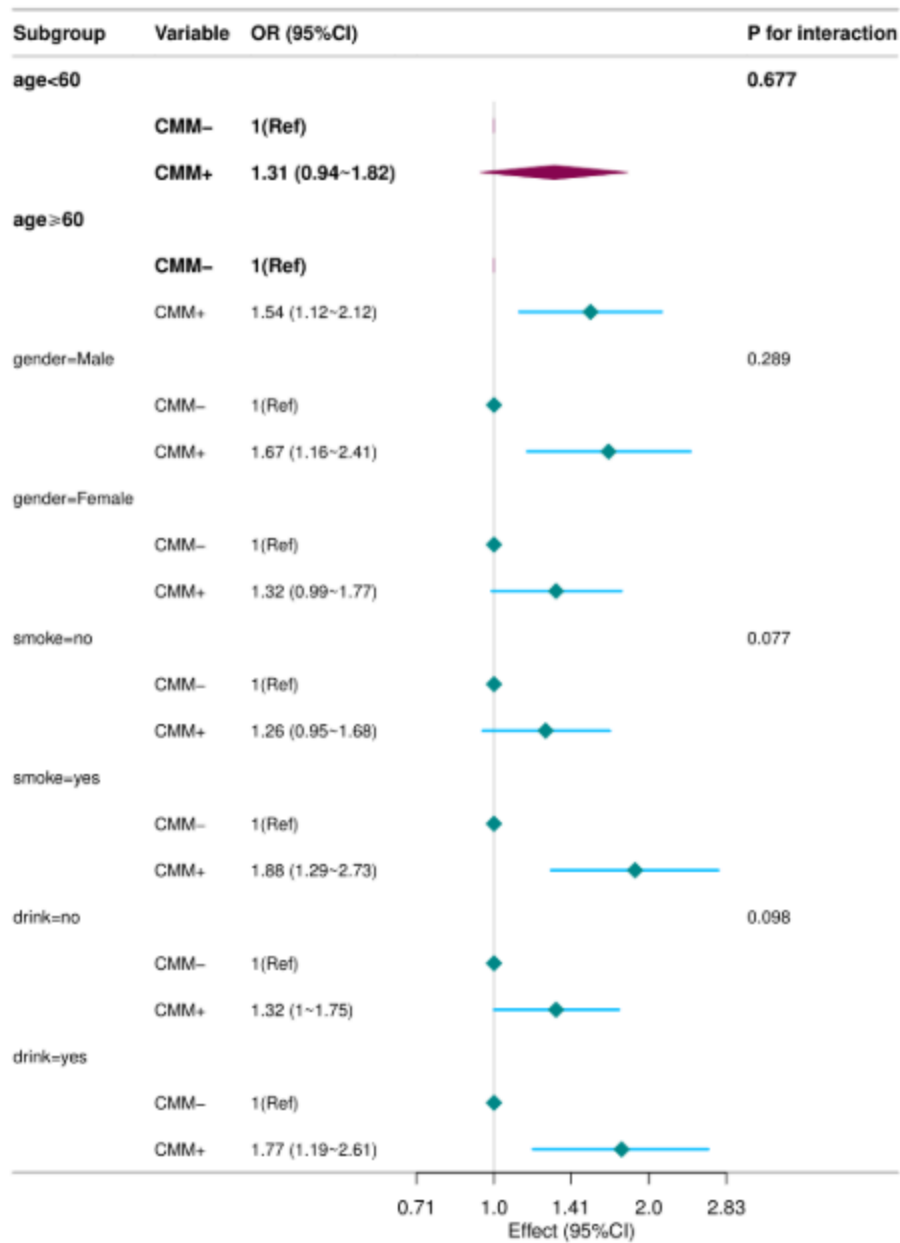


Figure 2

Subgroup analyses of the association between cardiometabolic multimorbidity (CMM) and depression risk.

Forest plot showing hazard ratios and 95% confidence intervals for the CMM-depression association stratified by age, sex, smoking status, and alcohol consumption. All interaction P values >0.05.

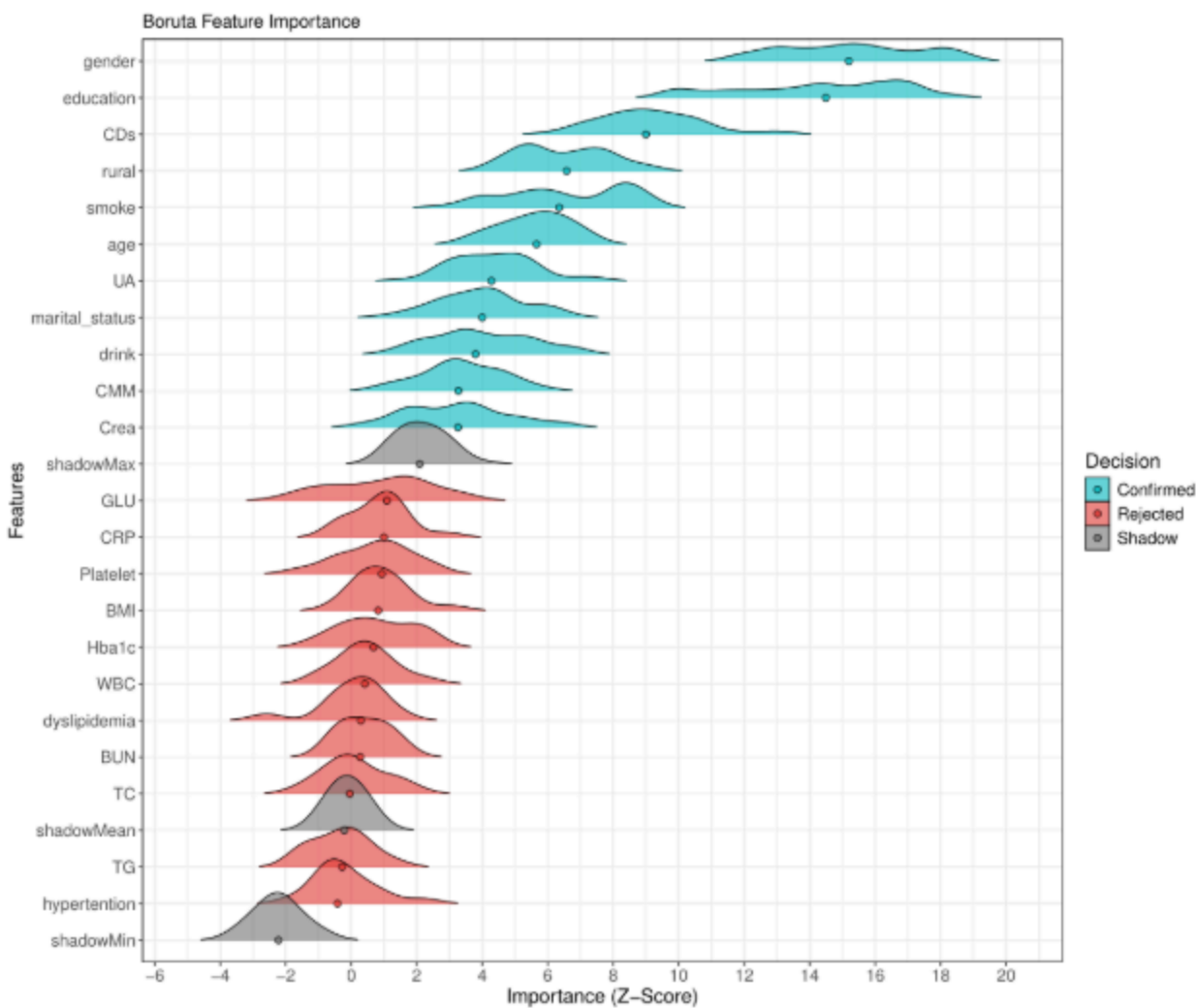


Figure 3

Boruta feature selection algorithm results.

Feature importance (Z-score) plot showing confirmed, rejected, and shadow features for depression prediction. Among 18 candidate features, 11 were confirmed as important predictors, including CMM.

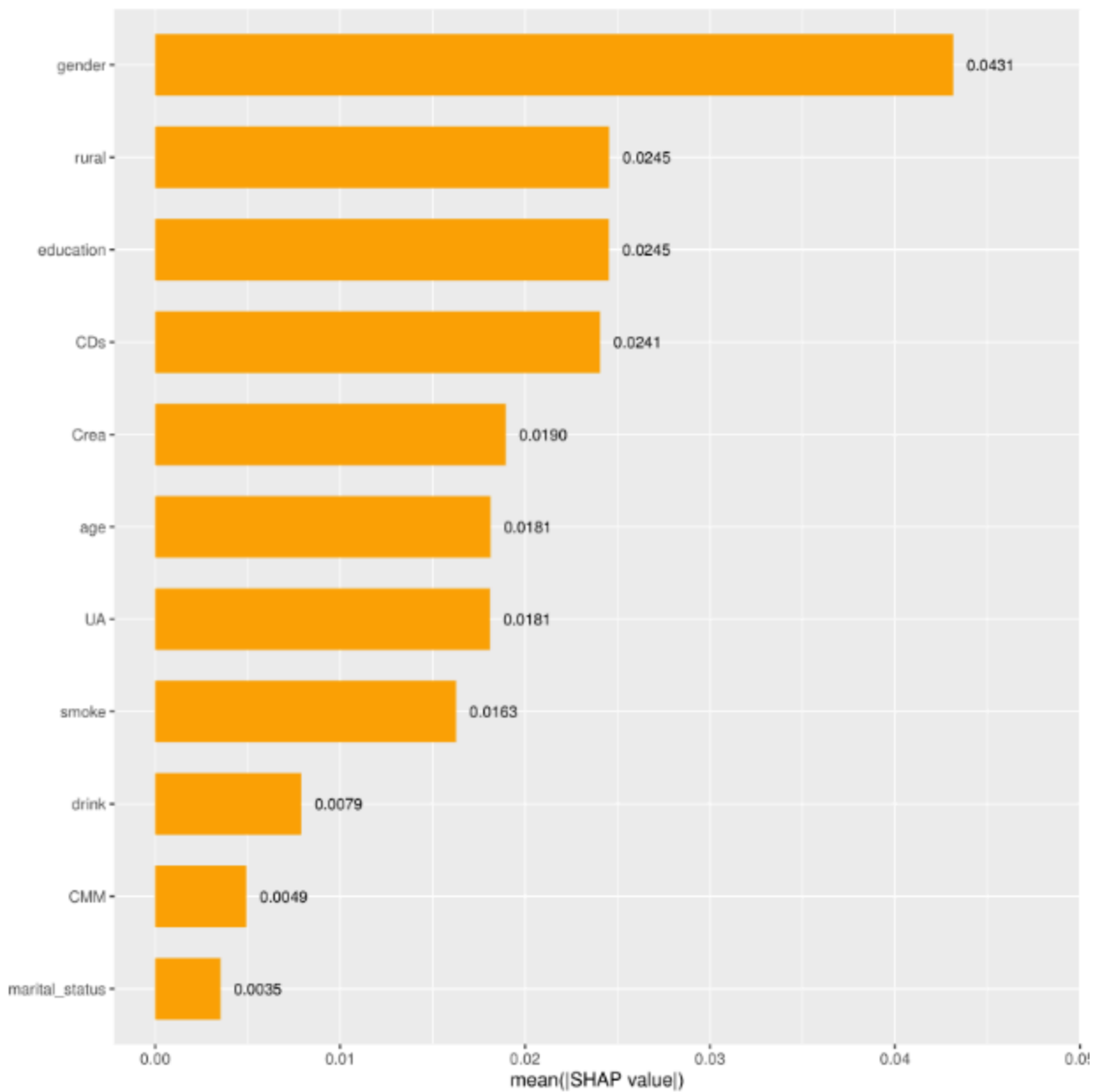


Figure 4

SHAP feature importance bar plot.

Features ranked by mean |SHAP value|, showing the relative contribution of each predictor to the depression prediction model. CMM was identified as an important predictor with a mean |SHAP value| of 0.0049.

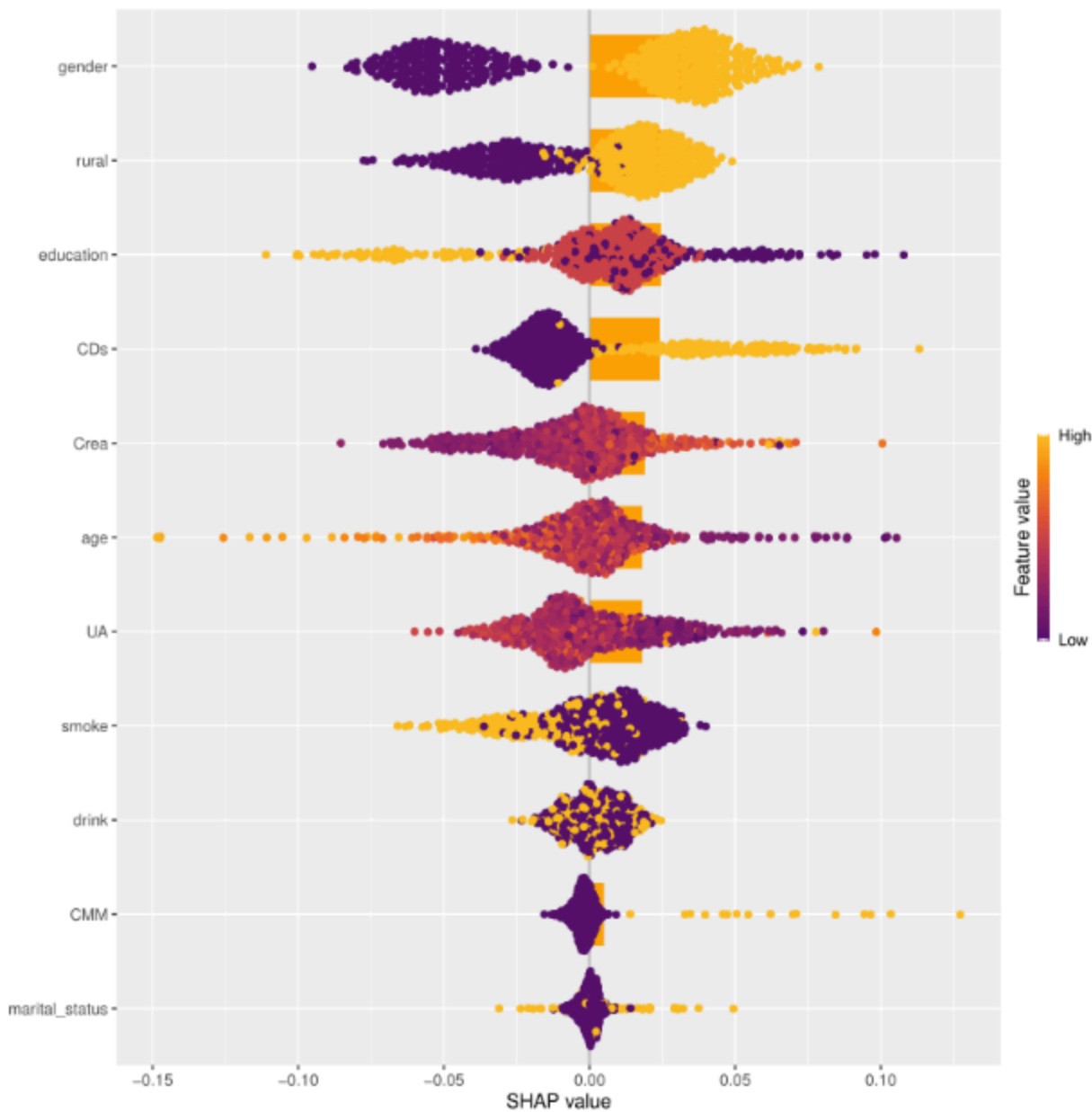


Figure 5

SHAP summary dot plot.

Distribution of SHAP values for each feature, showing the direction and magnitude of each feature's contribution to depression prediction. Red indicates higher feature values; blue indicates lower feature values.

Supplementary Files

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