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Associations Between Metabolic Syndrome, Depression, Plasma proteomics, and Neuroimaging Among Adults in the UK Biobank

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Abstract

Background Metabolic syndrome (MetS) is reported to be associated with increased incident depression. And previous research have linked depression development and plasma proteomic alterations. However, the association between MetS and depression, as well as the proteomic alterations or joint effects of depression related-proteins on brain macrostructure remain unclear.

Methods This population-based retrospective cohort study leveraged data from 368,223 UK Biobank participants and 2911 plasma proteins profiled at baseline. MetS was defined as the presence of ≥3 of the following:elevated waist circumference; elevated levels of triglycerides, blood pressure, HbA1c; and reduced high-density lipoprotein cholesterol. Cox proportional hazard models were used to assess associations of MetS with depression. The least absolute shrinkage and selection operator(LASSO) regression was used to identify depression related proteins. The pearson correlation analysis was used to assess the relationship of identified proteins and brain structure. Then, mediation analysis was performed to uncover the potential mechanisms involving identified proteins and imaging-derived phenotypes.

Results During a follow-up of 16.3 years, 13238 incident cases of depression were identified. MetS was associated with a increased risk of depression. We identified 93 proteins with significant associations with depression using LASSO regression, including proteins such as LDLR, FABP4, SMOC1, LPL, IGFBP1, and CA14. Additionally, dysregulation of the 93 proteins is correlated with brain regions implicated in depression, including the hippocampus and middle temporal. Further biological pathway enrichment analysis showed that most identified proteins were involved in cell adhesion, signaling receptor binding, and cholesterol metabolism, highlighted the pivotal roles of the immune response. Finally, mediation analysis revealed proteomic scores -neuroimaging have a strong mediating effect.

Conclusions MetS was associated with a increased risk of depression, and we identified the proteomic signatures associated with MetS related- depression. These findings have crucial implications for understanding the intricate connections between MetS, depression, protein and brain health.

Introduction

With an increasingly ageing population, metabolic syndrome (MetS) has become a growing public health issue[1, 2]. MetS is a condition characterized by the cluster of cardiometabolic and vascular risk factors, including larger waist circumference, hypertriglyceridemia, reduced HDL cholesterol, hypertension, and hyperglycemia[1]. Often considered a “pre-disease” state, MetS is strongly associated with an increased risk of developing cardiovascular and cerebrovascular diseases. Accordingly, it is important to understand the relationships between MetS and MetS-related diseases.

Cerebral small vessel disease (SVD), which is commonly observed on neuroimaging among elderly individuals, including white matter hyperintensities (WMHs), lacunes, cerebral microbleeds (CMBs), recent small subcortical infarcts, brain atrophy, and enlarged perivascular spaces (EPVS). Increasing

studies indicated that SVD is a major vascular contributor to cognitive impairment, gait impairment, mood disturbance and stroke[3]. Depression is a growing global health concern with a prevalence exceeding 5%[4]. Although growing evidence has found an association of depression with SVD[5, 6], the specific mechanisms by which these determinants remain to be fully elucidated. MetS is a key mediator of SVD, and SVD could lead to depression. Up to now, fewer studies had systematically studied the effect of MetS on mood disturbance, especially depression, compared to cerebrovascular diseases. Although past study showed that MetS increased the risk of depression[7], the complex mechanisms underlying are far less known. So, a essential unanswered question for public health is the extent to understand underlying pathogenesis between MetS, SVD ,and depression. As is well known, proteins are important for cellular functions and provide direct insights into disease pathophysiology[8, 9]. Moreover, high-throughput proteomics profiling can not only deepen molecular under standing, but also help to reveal potential therapeutic targets[10]. Although several studies have investigated the relationship between plasma proteins and depression[11–15], these results are often constrained by small sample sizes or limited proteomic coverage. So, we need to conduct a large-scale proteomic sample profiling. On the other hand, the mechanisms of depression pathophysiology are closely related to neural circuits and networks[16]. A recent study has shown that depression-risk proteins were significantly associated with white matter macrostructure and microstructure[17]. However, none of the studies, to date, has examined proteomics profiling and brain structure together among MetS-related depression.

To address this concern, we aimed to investigate the association of MetS with plasma proteomics, several structural neuroimaging outcomes and depression from the UK Biobank, which represents one of the largest general population cohorts to have collected large-scale brain imaging data and plasma proteomics. To our knowledge, this is the largest and most comprehensive study to evaluate the association between MetS, depression linked proteins, brain structure, and incident depression, enabling a robust assessment of these associations.

Methods

Data sources

This study utilized data from UK Biobank, a population-based prospective cohort of approximately 500,000 participants aged 40–69 years recruited between 2006 and 2010 in England, Scotland, and Wales.We evaluated the associations between plasma proteomics and brain structure and depression among participants with MetS.

Study population

Depression was identified using the International Classification of Disease, Tenth Revision(ICD)-10 codes. MetS was defined as the presence of three or more of the following components[1, 18]:1) abdominal obesity (larger waist circumference:≥102 cm in men; ≥88 cm in women); 2) elevated

triglyceride levels [TG, (≥ 150 mg/dL)] or lipid-modifying medications; 3) elevated blood pressure (systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg or antihypertensive medication use; 4) elevated fasting blood glucose level (≥ 100 mg/dL or ≥ 5.6mmol/L) or Hemoglobin A1c (HbA1c) ≥ 5.7%(39 mmol/mol), or glucose-lowering therapy; 5) reduced HDL cholesterol level (< 40 mg/dL in men; < 50 mg/dL in women). Participants were categorized into two groups: no MetS (reference) and MetS.

Blood proteomics

Briefly, the UK Biobank collected baseline plasma samples from participants in a standardized manner, which included stringent quality control[19, 20]. And used the Olink Explore 3072 Proteomics platform to measure the concentrations of 2923 unique proteins. A total of 2911 proteins were included in this study after removing proteins with a missing rate of 20% or higher (AMY1A_AMY1B_AMY1C, BPIFA2, CFH, CST1, CTSS, ENDOU, GLIPR1, LEG1, NPM1, OLFM4, PCOLCE, and PSTPIP2). Then, the missing values of the remaining proteins were interpolated based on the k-nearest neighbors algorithm(KNN). Finally, protein levels were reported as Normalized Protein Expression (NPX) values. To explore the functional enrichment of the significant proteins identified, the enrichment analysis was performed according to Gene Ontology(GO) terms and Kyoto Encyclopedia of Genes and Genomes(KEGG) pathways.

Neuroimaging Measures

Brain MRI data were acquired on a standard Siemens Skyra 3T scanner equipped with a 32-channel head coil, according to the UKB official website (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf). Imaging derived phenotypes (IDPs) were derived from T1- and T2-weighted brain MRI scans made available by the UKB neuroimaging group[21]. Based on previous study[22], the total brain, total white matter (WM), total hippocampus, total grey matter (GM), total GM in hippocampus, GM in the superior frontal gyrus, GM in the middle frontal gyrus, GM in the inferior

frontal gyrus, GM in the frontal pole, GM in the precentral gyrus, GM in the precuneus, GM in the postcentral gyrus, GM in the inferior temporal gyrus, GM in the parahippocampal gyrus, GM in the middle temporal gyrus, caudate, thalamus, putamen and amygdala volumes were chosen to be used in the present study.

Covariates

Sociodemographic factors and baseline medical history were assessed through self- administered touchscreen questionnaire. Factors known to be associated with depression and MetS were included in the analyses as confounders, including age, sex, ethnicity, education, smoking status, alcohol status, and prevalent status of hypertension, diabetes, hyperlipidemia, and heart disease. An “unknown/missing”

response category was generated for covariates which respondents select “prefer not to response” or “do not know,” or in cases of missing data.

Statistical Analysis

Descriptive statistics were used to compare baseline demographic and clinical features between study participants with and without MetS; mean and standard deviation(SD) value were calculated for normally distributed variables, and median and interquartile range were calculated for skewed variables. Cumulative incidence curves for depression were plotted by the Kaplan–Meier (K–M) curve, with statistical differences evaluated by the log-rank test. Furthermore, cumulative incidence function(CIF) was used to account for competing risks from other potential confounders. The multiple Cox proportional hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of MetS and target events.

Additionally, we conducted subgroup analyses by age(< 60 years, ≥ 60 years), gender(male, female), education (college/university degree or lower), drinking status, smoking status, diabetes, and hypertension, respectively. And, robustness of these findings were assessed through several sensitivity analyses. First, we excluded participants who diagnosed within one year after baseline. Second, we added adjustment for physical activity, use of aspirin, and Townsend deprivation index.

In addition, we further performed mediation analysis to boost explaining the association between proteins, brain structural, and target events. Temporally, MetS diagnosed and proteomic alterations precede change in brain structural, which subsequently lead to target events incidence. First, we conducted the least absolute shrinkage and selection operator(LASSO) regression analyses to filter out plasma proteins included in the final analysis. Second, The associations of selected proteins with brain structure were examined using pearson correlation analysis. Finally, the mediation analysis was conducted for a subset of UKB participants for whom proteomic, neuroimaging, and also MetS’s data were available, by using the ‘CMAverse’ R package.

All statistical analyses were conducted via R software (version 4.5.2), with a two-sided *P* value < 0.05 considered statistically significant.

Results

Participants’ characteristics

A total of 368,223 participants were included, of whom 46.2% were men and 53.8% were women, with a mean age of 58.0 years, and among whom 131,818(35.8%) had MetS. Table 1 shows the characteristics of study participants at baseline. Baseline characteristics showed that, compared to participants without MetS, those with MetS were more likely to be older, male, and have lower educational qualifications. However, participants without MetS were more likely to be current/previous drinking.

Table 1
Characteristics of study participants at baseline

Number of participants		**No MetS**	**MetS**	**Overall**	**P-value**
		236405	**131818**	**368223**	
Age.median.IQR		56.00 [48.00, 62.00]	60.00 [54.00, 65.00]	58.00 [50.00, 63.00]	< 0.001
Sex					
	Female	134867 (57.0)	63103 (47.9)	197970 (53.8)	< 0.001
	Male	101538 (43.0)	68715 (52.1)	170253 (46.2)	
Ethnicity, White, n (%)		226168 (95.7)	123984 (94.1)	350152 (95.1)	
Education level					
	College or University degree	86607 (36.6)	33716 (25.6)	120323 (32.7)	< 0.001
	Other professional qualifications	42928 (18.2)	38557 (29.3)	81485 (22.1)	
	Secondary Education	106870 (45.2)	59545 (45.2)	166415 (45.2)	
Smoking status					
	Current	23112 (9.8)	15177 (11.5)	38289 (10.4)	< 0.001
	Previous	76621 (32.4)	51942 (39.4)	128563 (34.9)	
	Never	136672 (57.8)	64699 (49.1)	201371 (54.7)	
Alcohol intake					
	Current	221418 (93.7)	118461 (89.9)	339879 (92.3)	

Data are reported as n (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; FBG, fasting blood glucose; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c. *P*-values were calculated by $\chi 2$ test or t-test, as appropriate.

Number of participants		No MetS	MetS	Overall	P-value
		236405	**131818**	**368223**	
	Previous	6866 (2.9)	6002 (4.6)	12868 (3.5)	
	Never	8121 (3.4)	7355 (5.6)	15476 (4.2)	< 0.001
DBP.median.IQR		80.00 [73.50, 87.00]	85.00 [78.50, 91.50]	82.00 [75.00, 89.00]	< 0.001
SBP.median.IQR		132.00 [121.00, 145.50]	142.50 [132.50, 154.00]	136.50 [124.50, 149.50]	< 0.001
Diabetes, n (%)		1322 (0.6)	17565 (13.3)	18887 (5.1)	
Hypertension, n (%)		100327 (42.4)	102651 (77.9)	202978 (55.1)	
Hypertriglyceridemia, n (%)		51164 (21.6)	96988 (73.6)	148152 (40.2)	
Coronary atherosclerotic disease,n(%)		3955 (1.7)	10525 (8.0)	14480 (3.9)	
anti-hypertension, n(%)		24670 (10.4)	51129 (38.8)	75799 (20.6)	
anti-diabetes, n (%)		154 (0.1)	3823 (2.9)	3977 (1.1)	
anti-hypertriglyceridemia, n (%)		14218 (6.0)	49446 (37.5)	63664 (17.3)	
Waist circumference.median.IQR		85.00 [77.00, 93.00]	99.00 [91.00, 107.00]	90.00 [80.30, 99.00]	< 0.001
TG.median.IQR		1.23 [0.93, 1.63]	2.12 [1.65, 2.83]	1.48 [1.04, 2.14]	< 0.001
FBG.median.IQR		4.85 [4.55, 5.15]	5.16 [4.74, 5.79]	4.93 [4.60, 5.31]	< 0.001
HDL.median.IQR		1.51 [1.30, 1.78]	1.21 [1.03, 1.42]	1.40 [1.17, 1.68]	< 0.001

Data are reported as n (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; FBG, fasting blood glucose; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c. *P*-values were calculated by $\chi 2$ test or t-test, as appropriate.

Number of participants		No MetS	MetS	Overall	P-value
		236405	**131818**	**368223**	
HbA1c.median.IQR		34.30 [32.10, 36.40]	37.70 [34.60, 41.10]	35.20 [32.70, 37.90]	< 0.001
Data are reported as n (%) unless otherwise indicated.					
Abbreviation: IQR, interquartile range; DBP, diastolic blood pressure; SBP, systolic blood pressure; TG, triglycerides; FBG, fasting blood glucose; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c. *P*-values were calculated by χ2 test or t-test, as appropriate.					

Table 2
Associations between MetS and incident depression

Models		HR(95%CI)	P value	P format
Model 1	No-adjusted model	1.389 (1.342–1.437)	$2.66235106307414*10^{-78}$	< 0.001
Model 2	Age-, race-, and sex-adjusted model	1.527 (1.473–1.582)	$3.98184107672435*10^{-121}$	< 0.001
Model 3	Multivariable-adjusted model	1.264 (1.209–1.323)	$1.85812305617309*10^{-24}$	< 0.001

Table 3
Sensitivity analysis of the association between MetS and depression.

model		HR(95%)CI	P value	P format
Excluding the participants who diagnosed as depression within 1 years of follow-up				
Model 1	No-adjusted model	1.387 (1.339–1.437)	$2.25876423826974*10^{-74}$	< 0.001
Model 2	Age-, race-, and sex-adjusted model	1.525 (1.471–1.581)	$3.21337070256489*10^{-115}$	< 0.001
Model 3	Multivariable-adjusted model	1.271 (1.214–1.331)	$2.29777210715492*10^{-24}$	< 0.001
Physical activity-, use of aspirin-, and Townsend deprivation index-adjusted				
Model 1	No-adjusted model	1.389 (1.342–1.437)	$2.66235106307414*10^{-78}$	< 0.001
Model 2	Age-, race-, and sex-adjusted model	1.527 (1.473–1.582)	$3.98184107672435*10^{-121}$	< 0.001
Model 3	Multivariable-adjusted model	1.231 (1.176–1.288)	$2.59734538535169*10^{-19}$	< 0.001

MetS and depression outcome

Firstly, we investigated the association between MetS and the risk of depression. The Kaplan-Meier curves revealed that the participants with MetS had a higher cumulative risk than those without MetS, indicating a close association between MetS and increased depression risk, with a statistically significant difference (Fig. 1 log-rank $P < 0.001$). Then, we explored the associations between MetS and incident depression in participants without a diagnosis of depression at baseline by the Cox models adjusted for age, sex ,race, smoking status, alcohol status, qualification, history of stroke and coronary atherosclerotic heart disease, and found that MetS was associated with the risk of depression in all models(Table.2P < 0.001). The model 1 was not adjusted, the model 2 was adjusted for age, sex, and race, and the model 3 was adjusted for all covariates.

Subgroup analyses and sensitivity analyses

To further investigated the associations between MetS and the risk of depression, we conducted a series of subgroup and sensitivity analyses. Figure 2 shows the associations between MetS and risk of incident depression outcome across subgroups. The results consistently indicate that MetS is associated with a increased risk of depression in subgroup analyses stratified by age, sex, race, smoking status, alcohol status, qualifications, and medication history. In the sensitivity analyses, the findings remained robust

after excluding the participants who diagnosed as depression within 1 years of follow-up, further adjustment for physical activity, use of aspirin, and Townsend deprivation index(Table.3).

Associations between depression and proteomic scores and neuroimaging

We observed that MetS increased the risk of incident depression, to explore the potential mechanism, we further conducted a large-scale analysis to assess the association between baseline plasma protein and neuroimaging among included participants. Firstly, we filtered out 660 proteins from 2911 proteins by Bonferroni correction(supplementary Table S1.). 152 proteins were down-regulated and 508 proteins were up-regulated among the screened proteins. Then, 93 proteins related to depression were identified using the LASSO regression analysis(Fig. 3 and supplementary Table S2.). Among the screened proteins, low-density lipoprotein receptor(LDLR, hazard ratio [95% confidence interval (CI)] = 1.51 [1.39–1.65], $p = 2.51 \times 10^{-17}$), fatty acid-binding protein(FABP4, 2.67 [2.42–2.94], $p = 4.22 \times 10^{-84}$), SPARC-related modular calcium-binding protein 1(SMOC1, 1.29 [1.18–1.40], $p = 1.67 \times 10^{-5}$), lipoprotein lipase(LPL, 0.62 [0.57–0.68], $p = 1.70 \times 10^{-22}$), insulin-like growth factor-binding protein 1(IGFBP1, 0.54 [0.50–0.58], $p = 2.17 \times 10^{-48}$), and carbonic anhydrase 14(CA14, 0.52 [0.48–0.57], $p = 1.77 \times 10^{-48}$) showed the strongest association with depression(Table S1). It is well known that depression is closely linked to neural circuits and networks, so we examined the correlation between depression-related proteins and brain structures by using pearson correlation analysis. We observed extensive associations of the selected proteins with the brain macrostructure(Fig. 4). The result implied the potentially complex relationship between depression-related plasma proteins and brain regions involved in the pathogenesis of depression.

Biological function of depression-related proteins

To further explored the biological function of the screened depression-related proteins, we used the GO and KEGG pathway enrichment analysis to gain insights into their potential biological features and regulatory mechanisms. The results showed that most proteins were mainly enriched in extracellular space, and cell surface, involving cell adhesion, signaling receptor binding, and cholesterol metabolism(Fig. 5).

Mediation effects of proteomic scores and neuroimaging

Neural networks have been long recognised as the most important factors for incident depression. In the study, we found that the depression-associated protein scores were higher in the MetS groups(supplementary Fig.S1). Additionally, the depression-associated proteins were significantly associated with the brain structure.The further mediation analyses showed that proteomic scores - neuroimaging have a strong mediating effect, explaining 64.97%(95% CI: 0.95%, 329.56%. Table S3.). Also, mediation analysis by protein levels showed 9 plasma proteins(LEP, TNFRSF10A, CD4,PRAP1, SPON2, THBS4, CRELD1, KIT, and SCARA5) and total GM volume were nominally significantly associated

with incident depression($p \leq 0.05$, Table S4). Although the mediation effects were significant, relatively small mediation proportions were observed for neuroimaging(Table S5).

Additional analyses

MetS is associated with cerebral small vessel diseases, stroke and cerebral hemorrhage are more common type of cerebral small vessel diseases. So, we further investigated the mediation effects of proteomic scores and neuroimaging in stroke and cerebral hemorrhage. Analyses presented in the Supplement Table S6 showed that the mediating effect of proteomic scores and neuroimaging in stroke and cerebral hemorrhage didn't achieve statistical significance. This may be due to fewer ending events and the different causal associations between protein levels and neuroimaging.

Discussion

This study using data from UK Biobank database has provided comprehensive insights regarding the association between MetS and incident depression. Previous studies, including meta-analysis, cross-sectional and prospective cohort studies have reported that MetS and its components significantly increase the risk of depression[7, 23–26]. Consistent with previous studies, our study indicated MetS are at higher risk of developing depression. Given MetS increase the risk of depression, the underlying mechanisms between MetS and depression need to be further explored.

Although the mechanisms of depression, often known as disruption of neural circuits, and components of MetS(such as blood glucose, hypertension, diabetes, and hypercholesterolaemia) are considered to be related to changes in brain structure and plasma proteomics[27–29], the underlying mechanisms and mediating roles of plasma proteins and brain structures remain to be fully elucidated among individuals with MetS. To understand the intricate nature of depression pathophysiology, Yu et al directly investigated connections between proteomics and pathways among participants with or without depression, shedding light on the intricate relationship between depression-related plasma proteins and various factors such as brain structure, genetic risks, and environmental factors[17]. However, no prior study has endeavoured to probe the relationship of depression-associated plasma proteins and neuroimaging among individuals with MetS. In this study, by leveraging Olink data from the UK Biobank database, we uncovered a series of plasma proteins that were related to incident depression, of which LDLR, FABP4, SMOC1, LPL, IGFBP1, and CA14 have the strongest correlations. Notably, LDLR, a membrane protein, is closely related to low density lipoprotein(LDL) metabolism and microbial infection[30–36]. Xu et al demonstrated that Apolipoprotein E(ApoE) played a pivotal role in the pathophysiology of depression, and LDLR participated in the process[37]. And our study found that LDLR associated with the volume of the total brain, total white matter (WM), total GM, thalamus, temporal, amygdala, and so on, suggesting that LDLR may take part in the process of MetS-related depression. FABP4, a member of the intracellular lipid-binding protein family. Maekawa et al found that the Fabp4 knockout mice had autism spectrum disorder-like behavioural phenotypes and increased spine density on apical dendrites of pyramidal neurons, which indicated an 'adipo-brain axis' may take part in the pathophysiology of autism spectrum disorder[38]. Moreover, Sun et al indicated that FABP4 may

influence neurodevelopment through systemic metabolic changes[39]. Our study showed that FABP4 was related to the volumes of WM, GM, hippocampus, frontal lobe, temporal lobe, and so on by protein-brain structure association analysis. These brain structural alterations are strongly correlated with depression. Apart from LDLR and FABP4, the other proteins are also relevant to the neurological disorders and mental disorders. For example, SOMC1, a glucose-responsive hepatokine and regulator of glucose homeostasis, was strongly interacted with amyloid beta (Aβ)in human mild cognitive impairment and Alzheimer's disease brain tissue and with phosphorylated tau in human Alzheimer's disease brain tissue, indicated that SMOC1 may participate in pathology process in Alzheimer's disease by Balcomb et al[40]. LPL, a triglyceride-hydrolyzing enzyme, is also present in the brain and known for it's role in the regulation of energy balance and body weight and cognition, impacts central nervous system processes and systems biology[41, 42]. Other protein of interest, IGFBP1, a binding protein that is produced primarily by the liver outside of pregnancy and is highly expressed by the placenta[43]. Prior studies have demonstrated that IGFBP1 may participate in the pathophysiology of depression and possibly influence the effect of antidepressant treatment[44, 45]. Given the association between depression and brain structure, we further performed analysis of the correlation between proteins and neuroimaging. The results showed that identified proteins were strongly associated with brain macrostructure alterations. In consideration of no study investigated large-scale proteomic profiles in brain regions of individuals with MetS, evidence from our exploratory analyses have potentially shed light on the underlying mechanisms between proteomic changes and depressive pathology in individuals with MetS.

To further elucidate the potential biological mechanisms of identified proteins, we performed functional enrichment analysis to investigate biological function of depression-associated proteins. The results indicated that identified proteins associated with depression were primarily enriched in metabolism- and inflammation-related pathways. Our result is consistent with the prior studies, which suggested that neuroinflammation[46, 47], PPAR signaling pathway[48, 49], cholesterol metabolism[50], PI3K-Akt signaling pathway[51, 52], and MAPK signaling pathway[53–55] are involved in depression development. So, it hints that future therapeutic interventions for depression might benefit from anti-inflammatory therapy based on our results and prior studies.

The key strengths of this study include a comprehensive evaluation of the relationship of depression-related proteins with several neuroimaging measures among participant with MetS. To the best of our knowledge, this is the largest and most comprehensive study which evaluate the association between MetS, proteomics, multi-modal structural brain imaging, and depression to-date. Additionally, we performed several sensitivity analyses to examine the robustness of these findings, including excluding depression diagnoses within 1 year of follow-up duration; additional adjustment for physical activity, use of aspirin, and Townsend deprivation index. Moreover, benefit from the large population and the rich phenotypic data available within the UK Biobank, the robustness of our findings was further enhanced.

Nevertheless, several limitations needed to be consideration. First, MetS was defined by baseline measurements, but brain imaging was assessed several years later, so we could not account for lifelong

trends in MetS status over time. Second, we did not investigate the association between depression and the severity and duration of MetS and its individual components since lack of related information. Third, our study was limited by lack of the relationship of MetS components and identified proteins. Fourth, although we have identified a set of proteins associated with depression and brain structural alterations, the specific pathological mechanisms underlying these associations require further investigation and validation. Fifth, although some plasma proteins were associated with depression in our study, the direct relationship between protein alteration and depression development are uncertain since the lack of a large-scale prospective cohort assessed cerebrospinal fluid (CSF) protein data and depression development. However, due to plasma proteomics' accessible nature, future studies should further investigate the asscociation of plasma proteins alteration and CSF proteins. Finally, it is important to acknowledge that this was an observational cohort study in a UK population, and the population is predominantly composed of individuals of White European descent. Therefore, we could not extend our findings to other racial and ethnic groups, and is a priority for future study.

Conclusion

In conclusion, this large plasma proteomic study found that MetS, a cluster of vascular risk factors associated with cardiovascular disease and SVD, was linked to significantly increase incident depression, and identified 93 protein signatures associated with depression among participant with MetS, including key proteins like LDLR, FABP4, SMOC1, LPL, IGFBP1, and CA142. These findings shed light on the pathophysiological of depression among individuals with MetS, and have the potential to inform targeted preventive strategies.

Declarations

Data availability

The data that support the findings of this study are available from the UK Biobank team.

Ethics statement

The UKB cohort was approved by the NHS National Research Ethics Service North West (reference number: 16/NW/0274).

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Supplementary material

Supplementary material is available at online

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Author Contribution

YG had full access to the data in this study and takes responsibility for the data and the accuracy of the data analysis. Study concept and design: YG, LL. Acquisition of data: YL, HX. Analysis and interpretation of data: LL, HX. Drafting of the manuscript: LL, YL. Statistical analysis: TM, GM. All authors read and approved the final manuscript.

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Figures

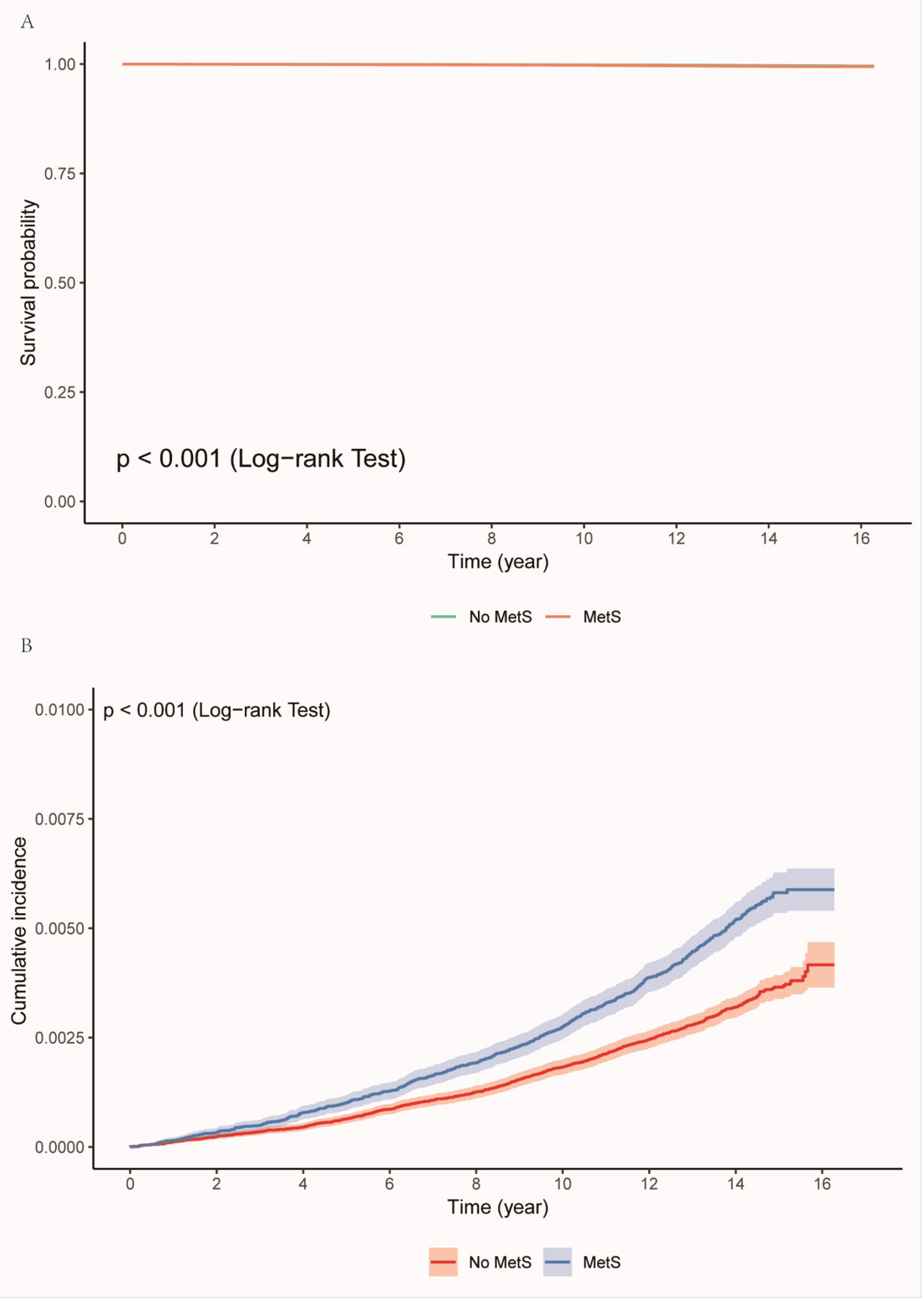


Figure 1

MetS association with incident depression. A, Kaplan-Meier survival curves showing survival probability without depression stratified by groups. B, cumulative incidence function curves(CIF) showing cumulative incidence of depression stratified by groups. P values are calculated using the log-rank test.

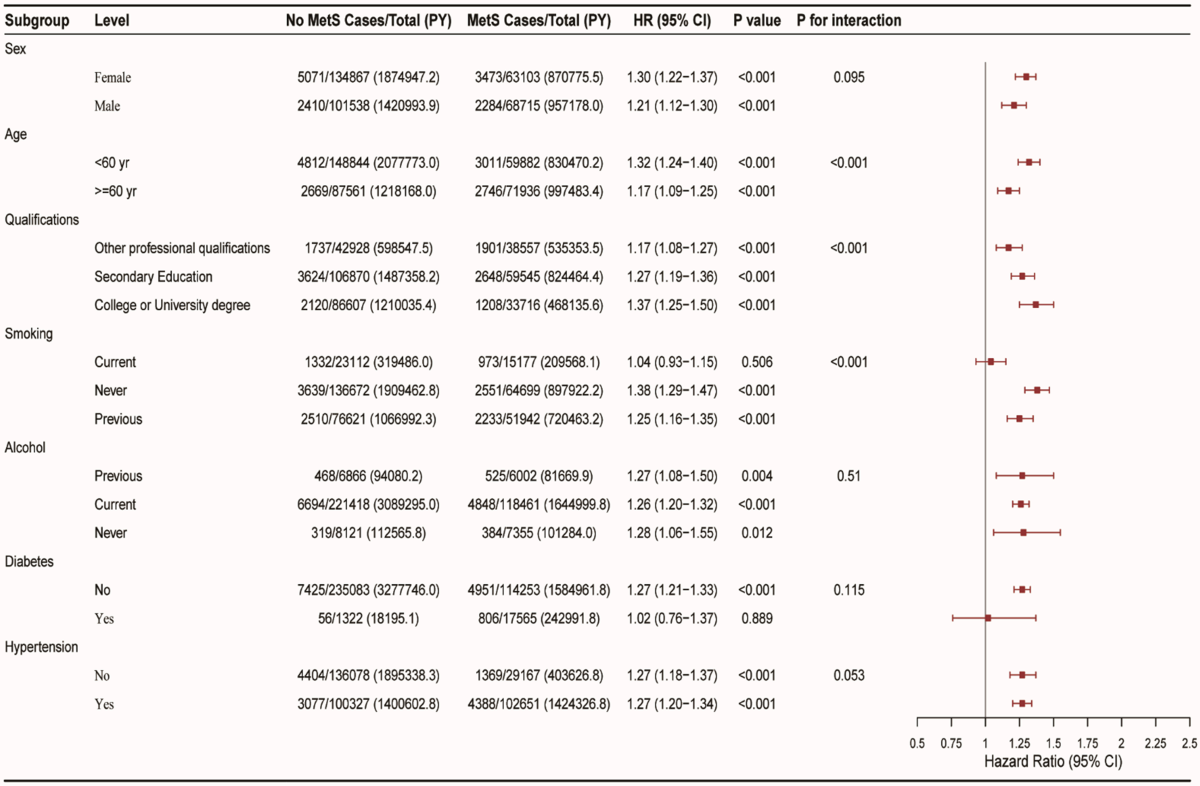


Figure 2

Hazard Ratio for the incident depression in subgroups.

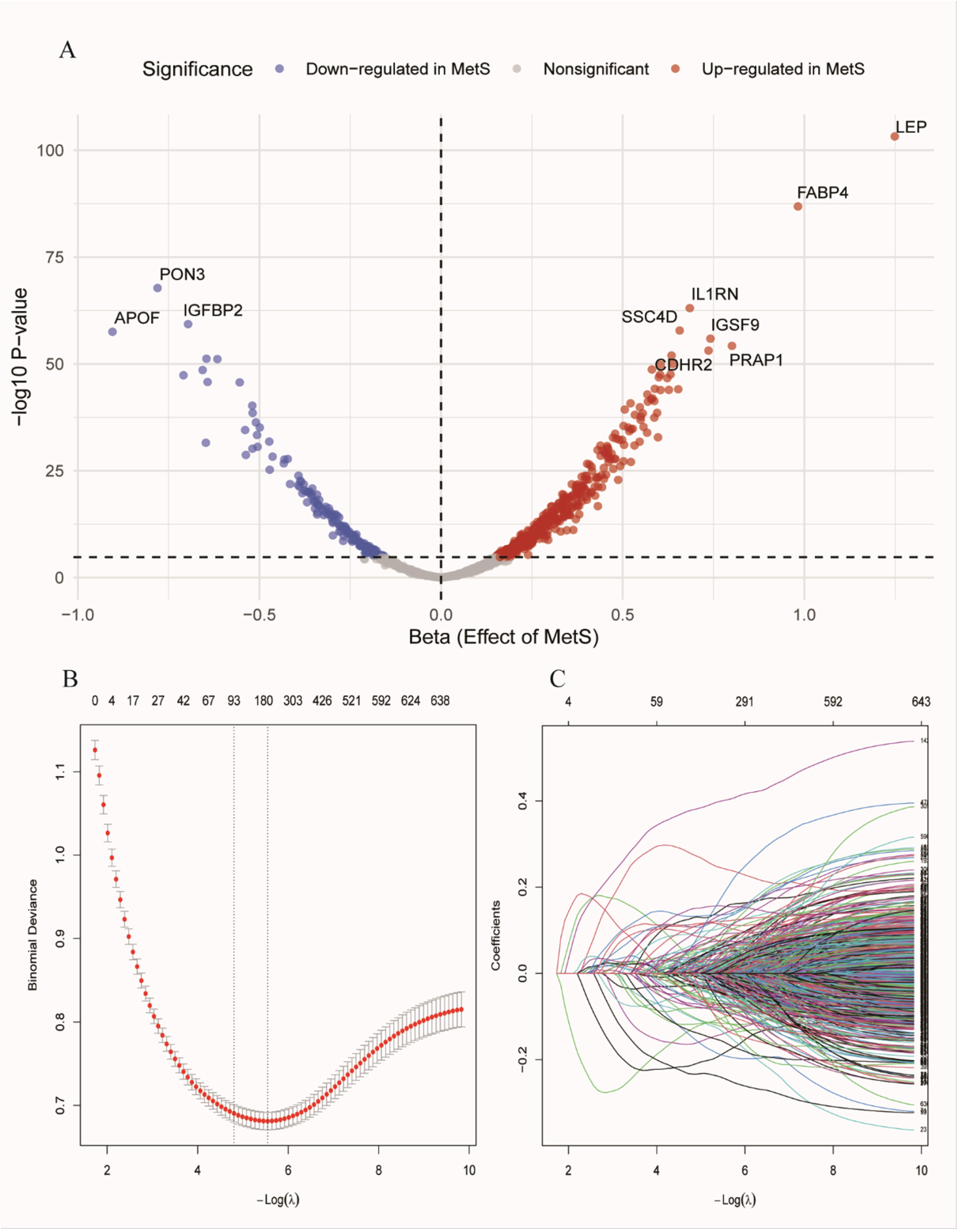


Figure 3

Identified depression-related proteins by Bonferroni correction and LASSO regression analysis. A, volcano plot showing the characteristics of identified proteins.

B, The cross-validation curve of LASSO regression. C, LASSO coefficient profiles of the identified proteins.

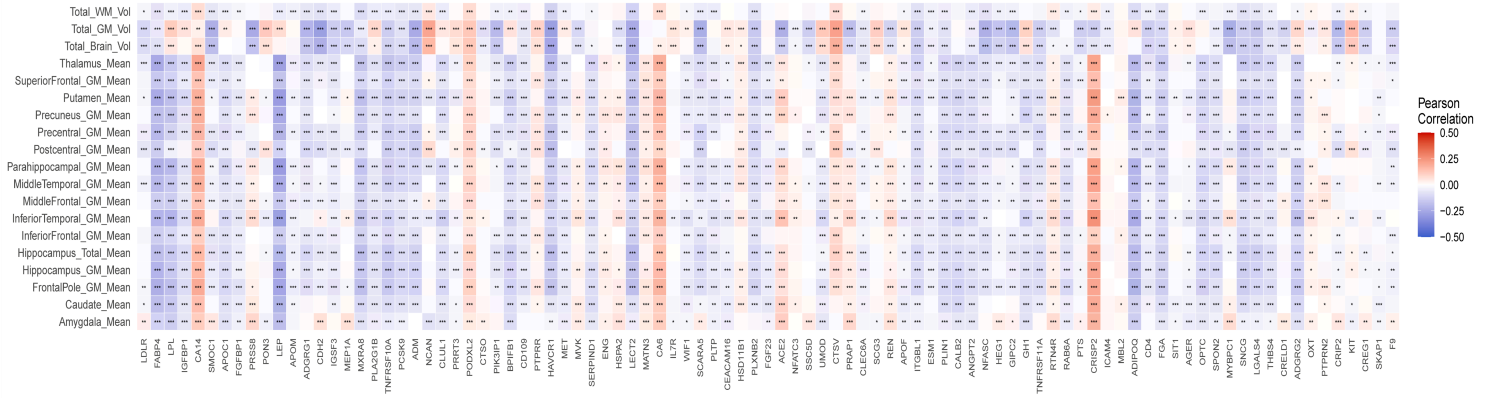


Figure 4

Association between depression-related proteins and brain structure. Theheatmap showed the extensive a ssociations of the identified proteins with the brain macrostructure by pearson correlation analysis.

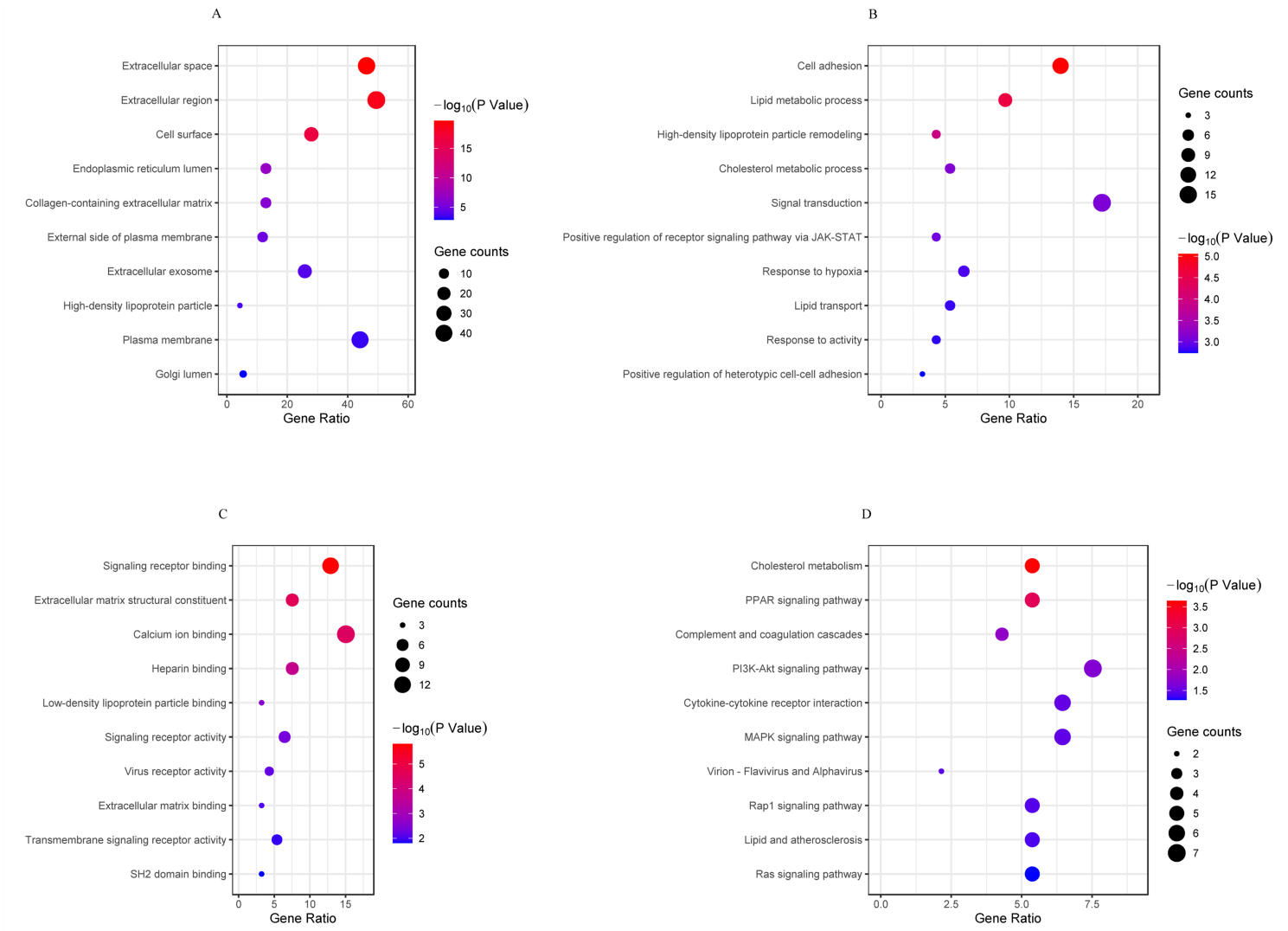


Figure 5

Biological function analysis of depression-related proteins. A, cellular components of identified proteins. B, biological process of identified proteins. C, molecular function of identified proteins. D, biological pathway enrichment analysis.

Supplementary Files

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