Association between TG/HDL-C and depression in US adults
A nationally representative cross-sectional study

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Abstract

Lipid profile disturbances are frequently observed in depressive patients. Triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) can be reflective of the level of blood lipids. However, it remains unclear whether higher TG/HDL-C increases the risk of depression. This study aimed to investigate the association between TG/HDL-C and depression. In this cross-sectional study, 20,406 participants were analyzed from the National Health and Nutrition Examination Survey between 2005 and 2020. A weighted multivariable logistic regression model, restricted cubic spline regression model and threshold effect analysis were used to explore the association of TG/HDL-C with depression risk. A total of 20,406 participants who had complete data on TG/HDL-C and depression measurement were included in this study (median age 47 years, 50.51% female). Participants with depression had higher TG/HDL-C than those without depression (0.97 [0.54–1.64] vs 0.82 [0.50–1.38], $P < .001$). TG/HDL-C was associated with an increased risk of depression after adjusting for all covariates (in model 3: odds ratio (OR) = 1.31, 95% confidence interval (CI): 1.04–1.64, $P = .02$). Moreover, a nonlinear J-shaped relationship was observed between TG/HDL-C ratio and the risk of depression, with an inflection point of 0.402 by threshold effect analysis. These findings indicate that TG/HDL-C has a J-shaped association with the risk of depression (P for non-linearity = .008).

Abbreviations: AA = associate of arts, BMI = body mass index, CI = confidence interval, DSM-IV = diagnostic and statistical manual of mental disorders-IV, GED = general educational development, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein cholesterol, HPA = hypothalamic-pituitary-adrenal, IPR = income-to-poverty ratio, LDL = low-density lipoprotein, MEC = mobile exam center, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, PHQ-9 = patient health questionnaire 9, RCS = restricted cubic spline, SSRIs = selective serotonin reuptake inhibitors, TC = total cholesterol, TG = triglyceride, TG/HDL-C = triglyceride-to-high-density lipoprotein cholesterol, VIF = variance inflation factor.

Keywords: cholesterol levels, depression, NHANES, triglyceride level

1. Introduction

Depression, a complex neuropsychiatric condition, is characterized by persistent dysthymia and anhedonia, manifesting as a marked diminution in pleasure or interest in activities of daily living. The estimated prevalence rate of depression is approximately 4.7%, including 5% of adults.[1,2] Depression can lead to psychosocial dysfunction, worsen the affected person's life situation, and increase suicides and mortality.[3] According to the Global Burden of Disease Study, depression represents the predominant contributor to disability-adjusted life years among all psychiatric disorders, resulting in a significant economic burden of the healthcare systems.[4] The etiology of depression is multifaceted, including social, biological and psychological factors. Despite advancements in understanding its causes and pathophysiology, the specific risk factors and underlying mechanisms of depression remain incompletely understood. Given the increasing prevalence of depression and its profound impact on both individuals and society, elucidating multifactorial etiopathogenesis and identifying modifiable risk factors associated with depression remain paramount for developing targeted preventive and therapeutic interventions. By early identifying high-risk individuals and implementing preventive strategies, the heavy burdens experienced by families and communities caused by depression might potentially be alleviated.

Accumulating evidence indicated a close relationship between depression and levels of lipids.[5,6] Commonly, the principal components of the lipid profile comprise low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

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(HDL-C), triglycerides (TG), and total cholesterol (TC).[7,8] Specifically, previous investigations have demonstrated that individuals with depression presented special patterns of lipids profiles. However, these associations were demonstrated to be inconsistent and even contradictory. For instance, some studies reported decreased TC in depressive individuals,[9] while other studies found elevated TC[10] or revealed no specific association.[11] This inconsistency was also shown in HDL-C, LDL-C and TG.[5] Moreover, a cross-sectional study from Korea found that lipid ratios, including TC/HDL-C, LDL-C/HDL-C and TG/HDL-C, were not associated with depression.[12] Despite heterogeneous findings have been reported in the literatures, abnormal lipids profiles are frequently observed in depressive individuals.[13] In tryptophan hydroxylase-2 knockout mice, the elevated oxidative stress caused alteration of plasma lipid metabolism and thus resulted in 5-hydroxytryptamine deficiency.[14] These findings suggested a biologically plausible link between lipid metabolism and the pathogenesis of depression.

Recent epidemiological evidence has established the triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-C) as an emerging clinically relevant biomarker for metabolic syndrome and cardiovascular disorders.[15] Based on the revealed association between cardiovascular events and the development of depression,[16,17] combined with the biologically plausible link of lipids metabolism to depression, here we hypothesized that an alteration of TG/HDL-C may be independently associated with the incidence of depression. The association between blood TG/HDL-C and the depression risk among US adults was investigated using cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) collected from 2005 to 2020.

2. Material and methods

2.1. Study design and subjects

Comprehensive analyses of data extracted from NHANES 2005 to 2006, 2007 to 2008, 2009 to 2010, 2011 to 2012, 2013 to 2014, 2015 to 2016, 2017 to 2018 and 2019 to 2020 were conducted, as the participants in these cycles received the depression questionnaire, namely the patient health questionnaire (PHQ-9). The NHANES employs a complex, multistage, probability-sampled, cross-sectional design conducted biennially to assess the health and nutritional status of the noninstitutionalized US civilian population through standardized interviewer-administered questionnaires, comprehensive physical examinations, and systematic collection of biological specimens. The complex sampling methodology, standardized research protocols, data collection procedures, and statistical analytical approaches have been extensively documented in peer-reviewed publications and are available online. The study protocol was approved by the National Center for Health Statistics Research Ethics Review Board, and all eligible study participants signed written informed consents before enrollment. Detailed methodological documentation and comprehensive program information for the NHANES are publicly accessible through the NHANES website.

The present investigation included adult participants (age ≥ 18 years). Participants without blood TG or HDL-C data, or who did not finish the PHQ-9 were excluded. This study was conducted and reported in alignment with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

2.2. Depression symptoms assessment (outcome)

Depression was assessed using the PHQ-9, a validated 9-item screening instrument that evaluates both the presence and severity of depression. The PHQ-9 is a self-administered diagnostic instrument that consists of 9 signs corresponding to the diagnostic criteria for depression as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[19] PHQ-9 evaluates the frequency and severity of depression experienced by individuals during the preceding 2-week period. Each item is scored on a 4-point ordinal scale (range, 0–3), with the aggregate severity score ranging from 0 to 27 points. In general, a total PHQ-9 score of 10 or higher was considered diagnostic of depression, as previous studies demonstrated that a PHQ-9 score of 10 or higher yielded a sensitivity of 85% and a specificity of 89% for the diagnosis of depression.[19,20] Therefore, all participants were categorized into 2 groups based on their PHQ-9 scores: those scoring <10 points (classified as non-depression) and those scoring 10 points or greater (classified as having depression).

2.3. Laboratory measurements (exposure)

Blood specimens were collected from participants at a mobile examination center (MEC) by NHANES personnel after a minimum 8-hour fasting period. Blood TC, TG and HDL-C concentrations were quantified using direct enzymatic methods. Based on measured values of TG, TC and HDL-C, LDL-C concentrations were calculated by means of the Friedewald formula (LDL-C = TC – HDL-C – [TG/5]) for participants with TG levels below 400 mg per deciliter; for those with higher TG levels, direct LDL-C measurements were performed.[21] The TG/HDL-C (continuous) was calculated as the quotient of serum TG concentration to HDL-C concentration (measured in mg/dL). Detailed information regarding laboratory techniques and quality assurance procedures is available in the Laboratory Procedures Manual of NHANES.

2.4. Covariates assessment

Sociodemographic characteristics were assessed through standardized self-administered questionnaires, including age (continuous), gender, race, education level and income-to-poverty ratio (IPR) (continuous). The IPR was calculated as the annual total annual household income divided by the federal poverty threshold, which was based on corresponding state and survey year. Participants were stratified into 3 income categories according to their IPR: high income (IPR of 4 or greater), middle income (IPR of 1 to <4), and low income (IPR < 1).[22] Education level was categorized as low (less than a high school diploma), middle (high school graduate or General Educational Development), and high (some college education or higher). Height and weight measurements were obtained by certified health professionals using calibrated equipment and standardized protocols at the MEC. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Evaluated comorbidities included diabetes mellitus and hypertension. The diagnosis of diabetes mellitus or hypertension was established based on either physician documentation of the condition or current use of antihypertensive or antihyperglycemic medications. The following variables were also included as covariates: smoking status (never, former, now), alcohol intake (never, former, mild, moderate, heavy), LDL-C (continuous) and TC (continuous). Detailed definitions of all covariates were available at NHANES website. For missing covariates, we generated multiple imputations of the dataset by chained equation with predictive matching algorithms. Five imputed datasets were generated to address potential bias from incomplete observations in the analysis cohort ("mice" R package, version 4.1.3). Multicollinearity among independent variables was assessed using variance inflation factors (VIF).[23] VIF analysis demonstrated no evidence of significant collinearity among the predictor variables (Table S1, Supplemental Digital Content, https://links.lww.com/MD/O806).
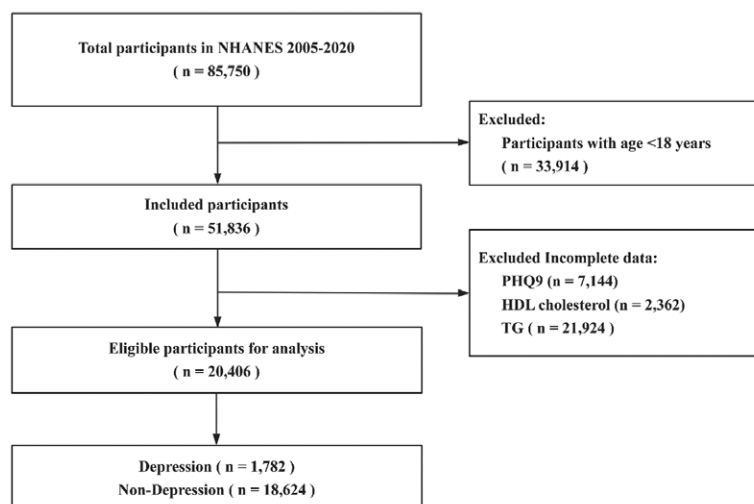
Figure 1. Flowchart of participants' enrollment process. HDL-= high density lipoprotein cholesterol, NHANES = National Health, and Nutrition Examination Survey, PHQ9 = patient health questionnaire 9, TG = triglyceride.

2.5. Statistical analysis

All statistical analyses incorporated the complex multistage probability sampling design of NHANES. According to NHANES weighting specifications, the sample weights were recalculated as follows: weight = 1/8 * WTS2YR, where WTS2YR represents the 2-year sample weight for each survey period, and Weight is the sample weight calculated after combining 8 survey periods. Descriptive statistics were presented as follows: continuous variables with normal distribution are presented as means (± standard deviations), non-normally distributed continuous variables as medians (interquartile range [IQR]), and categorical variables as frequencies (percentages). Between-group comparisons were performed using the weighted Student t tests, Mann–Whitney U tests, and χ^2 tests, respectively.

The association between TG/HDL-C and depression prevalence was assessed using multivariable logistic regression models. The odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated in the "survey" R package. Three logistic regression models were established: Model 1, no potential confounding factors were adjusted; Model 2, adjusted for sociodemographic characteristics including age, gender, and race; Model 3 was the fully adjusted model, which further adjusted for BMI, education level, PIR, hypertension, diabetes mellitus, smoking status, alcohol intake. We incorporated both continuous and categorical models into the multivariable logistic regression analysis. In the continuous model, TG/HDL-C was log-transformed due to the skewness of its distribution to mitigate the influence of extreme values (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/O807). In the categorical model, TG/HDL-C was stratified into quartiles, and a linear trend was assessed by treating the median value of each quartile as a continuous variable. Besides, the potential nonlinear association between the TG/HDL-C and depression risk was evaluated using weighted restricted cubic spline (RCS) analyses, with knots placed at the 25th, 50th, and 75th percentiles. These analyses were conducted within the framework of Model 3. Moreover, to identify potential threshold effects, a 2-piecewise linear regression model was fitted after adjustment for all confounding factors. The optimal threshold point was determined by maximizing the log-likelihood function. The presence of a threshold effect was assessed through comparison of a 2-piecewise linear model with the single-linear model using likelihood ratio testing.

Subgroup analyses were performed to examine the modification effect of age (age was categorized into 3 levels, <40, 40–60, and >60 year), gender, race, BMI (BMI was divided into 2 levels, <24 and ≥24 kg/m²), education level, PIR, hypertension, diabetes mellitus, smoking status, and alcohol intake on the association between TG/HDL-C and depression. To evaluate potential interaction effects, multiplicative interaction terms were constructed between the TG/HDL-C and prespecified subgroup variables in the multivariable models.[24] Sensitivity analyses were conducted to evaluate the robustness of our findings. To mitigate the potential influence of extreme values, we reconstructed our models after excluding participants with extreme BMI levels (<15 or ≥40 kg/m²).

All analyses accounted for complex sampling design of NHANES, including stratification, clustering, and sampling weights. The statistical analyses were executed with R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). The threshold for determining statistical significance employed 2-tailed probability assessments with an alpha level set at 0.05.

3. Results

3.1. Baseline characteristics of the study population

Of 85,750 participants enrolled in the NHANES from 2005 to 2020, we identified 51,836 adults (≥18 years) who were eligible for this study. We excluded 31,430 participants who had missing data on TG or HDL-C measurement, or who responded "refused" or "don't know" to items on the PHQ-9. The final analytical cohort comprised 20,406 participants from the NHANES (2005–2020) with complete data on TG/HDL-C and depression assessments. The participants had an average age of 47 years, and 50.51% were women. The process of participant selection is shown in Figure 1. Of the 20,406 participants in the analytical cohort, 1782 (8.73%) met the diagnostic criteria for depression. The percentage of depression in female is 11.15% (1152 of 10,331 participants), while in male, it is 6.25% (630 of 10,075 participants). Non-Hispanic White participants constituted the largest racial and ethnic group in both the depression (63.04%) and non-depression cohorts (68%). Participants living below the federal poverty threshold (PIR < 1) were more prevalent in the depression group (659 [28.24%] of 1782 participants) than in the non-depression group (3707 [13.33%] of 18,624 participants). The proportion of participants who were current smokers was higher in depressive participants (38.66%) compared to non-depressive participants (18.19%). The proportion of

people who had hypertension was higher in depressive participants (48.35%) than in non-depressive participants (36.66%). Similarly, the proportion of people who had diabetes mellitus was higher in depressive participants (23.03%) compared to non-depressive participants (15.45%). Depressive participants had a higher BMI than non-depressive participants. The mean BMI was higher among participants with depression than among those without depression (29.44 [24.60–35.30] vs 27.71 [24.10–32.35] kg/m², P < .0001). Besides, in comparison to the non-depression group, participants in depression group had lower HDL-C (1.32 [1.06–1.58] vs 1.34 [1.11–1.63] mg/dL, P < .0001) and higher TG (1.26 [0.82–1.89] vs 1.12 [0.77–1.66] mg/dL, P = .001). Baseline sociodemographic and clinical characteristics of the study cohort are presented in Table 1.

3.2. Association between TG/HDL-C and depression: logistic regression analysis

Patients with depression demonstrated significantly higher median TG/HDL-C than those without depression (0.97 [0.54–1.64] vs 0.82 [0.50–1.38]; P < .001) (presented in Fig. 2).

In the continuous model, multivariable logistic regression analysis revealed that TG/HDL-C was independently associated with depression (presented in Table 2). This association remained significant after adjustment for multiple potential confounders: Model 1 (OR, 1.89; 95% CI, 1.65–2.61; P < .0001), Model 2 (2.25; 1.81–2.80; P < .0001), and Model 3 (1.31; 1.04–1.64; P = .02).

In the categorical model, the TG/HDL-C were converted into quartiles: Q1 group (TG/HDL-C ≤ 0.499, n = 5111), Q2 group (0.499 < TG/HDL-C ≤ 0.828, n = 5084), Q3 group (0.828 < TG/HDL-C ≤ 1.394, n = 5108), Q4 group (TG/HDL-C > 1.394, n = 5103). The risk of depression was significantly higher among participants in the Q4 group than among those in the Q1 group in Model 1 and Model 2 (Model 1: 1.54; 1.28–1.86; P < .0001; P for trend = .32; Model 2: 1.97; 1.61–2.41; P < .0001; P for trend = 0.15), but not in Model 3 (1.20; 0.97–1.49; P = .09; P for trend = .54). Participants in the Q3 group exhibited a higher incidence of depression compared with those in the Q1 group in Model 2 (Model 2: 1.39; 1.12–1.72; P = .003; P for trend = .15), but not in Model 1 and Model 3 (Model 1: 1.22; 0.99–1.49; P = .06; P for trend = .32; Model 3: 0.99; 0.80–1.23; P = .92; P for trend = .54). There was no significant difference in


Table 1

Characteristics of the study population, NHANES 2005 to 2020.

Characteristics	Total (N = 20,406)	Non-depression, (N = 18,624)	Depression, (N = 1782)	P-value
Age, yr	47.00 (32.00, 60.00)	47.00 (32.00, 60.00)	47.00 (35.00, 59.00)	.614
Gender				
Female	10,331 (50.51)	9179 (49.44)	1152 (63.72)	<.0001
Male	10,075 (49.49)	9445 (50.56)	630 (36.28)	
Race				
Mexican American	3217 (8.73)	2951 (8.81)	266 (7.81)	<.0001
Non-Hispanic Black	4383 (10.45)	3963 (10.18)	420 (13.80)	
Non-Hispanic White	8432 (67.62)	7718 (68.00)	714 (63.04)	
Other Hispanic	2007 (5.73)	1768 (5.53)	239 (8.15)	
Other race – including multi-racial	2367 (7.46)	2224 (7.48)	143 (7.19)	
PIR				
Low	4366 (14.45)	3707 (13.33)	659 (28.24)	<.0001
Middle	10,889 (50.00)	10,011 (49.89)	878 (51.26)	
High	5151 (35.56)	4906 (36.78)	245 (20.51)	
Education level				
Low	1885 (4.93)	1625 (4.61)	260 (8.89)	<.0001
Middle	8134 (35.93)	7313 (35.25)	821 (44.30)	
High	10,387 (59.14)	9686 (60.14)	701 (46.81)	
Smoking status				
Never	11,362 (54.79)	10,604 (56.14)	758 (38.12)	<.0001
Former	4917 (25.48)	4513 (25.66)	404 (23.22)	
Now	4127 (19.73)	3507 (18.19)	620 (38.66)	
Diabetes mellitus				
No	16,170(83.98)	14,904(84.55)	1266 (76.97)	<.0001
Yes	4236 (16.02)	3720 (15.45)	516 (23.03)	
Hypertension				
No	11,961(62.46)	11,104(63.34)	857 (51.65)	<.0001
Yes	8445 (37.54)	7520 (36.66)	925 (48.35)	
Drinking status				
Never	2978 (11.01)	2716 (11.04)	262 (10.59)	<.0001
Former	2624 (11.30)	2357 (11.01)	267 (14.83)	
Mild	7264 (38.30)	6783 (39.09)	481 (28.53)	
Moderate	3251 (17.81)	2969 (17.83)	282 (17.54)	
Heavy	4289 (21.59)	3799 (21.03)	490 (28.52)	
BMI, kg/m²	27.80 (24.10, 32.60)	27.71 (24.10, 32.35)	29.44 (24.60, 35.30)	<.0001
TG, mg/dL	1.13 (0.77, 1.67)	1.12 (0.77, 1.66)	1.26 (0.82, 1.89)	<.0001
HDL-C, mg/dL	1.34 (1.09, 1.63)	1.34 (1.11, 1.63)	1.32 (1.06, 1.58)	.001
TC, mg/dL	4.86 (4.19, 5.59)	4.86 (4.19, 5.56)	4.89 (4.16, 5.66)	.345
LDL-C, mg/dL	2.85 (2.28, 3.47)	2.85 (2.28, 3.47)	2.87 (2.22, 3.54)	.497
TG/HDL-C	0.83 (0.50, 1.40)	0.82 (0.50, 1.38)	0.97 (0.54, 1.64)	<.001

Continuous variables were presented as mean (SD) or median (IQR), according to their distribution; categorical variables were presented as n (%).

BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NHANES = National Health and Nutrition Examination Survey, PIR = income-to-poverty ratio, TC = total cholesterol, TG = triglyceride, TG/HDL-C = triglyceride-to high-density lipoprotein cholesterol, WC = waist circumference.
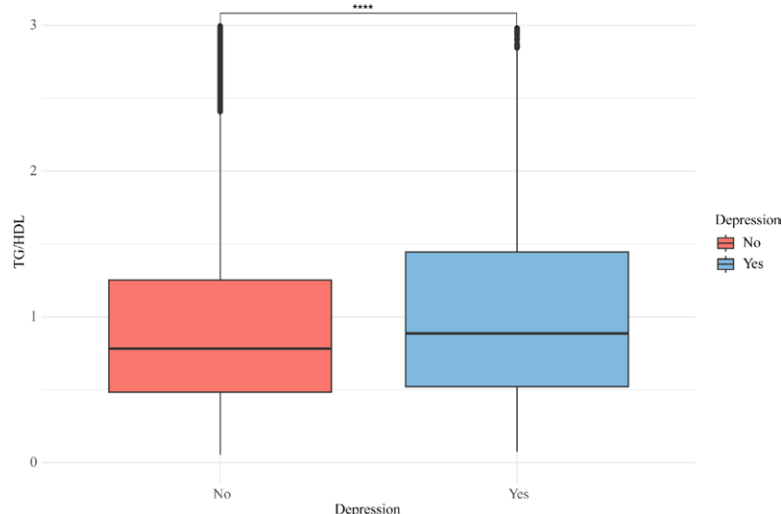
Figure 2. Log10-transformed TG/HDL-C in non-depression group and depression group. "****" indicates $P < .0001$, as compared with non-depression group. PHQ-9 = patient health questionnaire 9, TG/HDL-C = triglyceride-to-high-density lipoprotein cholesterol.

Table 2

Weighted logistic regression analysis of TG/HDL-C with depression, NHANES 2005 to 2020.

	Model 1		Model 2		Model 3	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Log10 TG/HDL-C	1.89 (1.65, 2.61)	<.0001	2.25 (1.81, 2.80)	<.0001	1.31 (1.04, 1.64)	.02
Q1	Reference		Reference		Reference	
Q2	0.99 (0.81, 1.20)	.89	1.06 (0.87, 1.30)	.56	0.87 (0.71, 1.08)	.20
Q3	1.22 (0.99, 1.49)	.06	1.39 (1.12, 1.72)	.003	0.99 (0.80, 1.23)	.92
Q4	1.54 (1.28, 1.86)	<.0001	1.97 (1.61, 2.41)	<.0001	1.20 (0.97, 1.49)	.09
P for trend	.32		.15		.54	

Model 1 was not adjusted for covariates.
Model 2 was adjusted for age, gender, race, or ethnicity.
Model 3 was adjusted for all covariates including age, gender, race or ethnicity, PIR, education level, alcohol intake, diabetes mellitus, hypertension, smoking status, BMI.
BMI = body mass index, CI = confidence interval, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, PIR = income-to-poverty ratio, TG/HDL-C = triglyceride-to high-density lipoprotein cholesterol.

depression incidence between participants in the Q2 group and those in the Q1 group ($P > .05$).

3.3. Nonlinear association: restricted cubic spline analysis

RCS analysis revealed a nonlinear, J-shaped association between the TG/HDL-C and depression after full adjustment for potential confounders (P for non-linearity = .008) (Fig. 3), with an inflection point at a log10-transformed TG/HDL-C of –0.395 by threshold effect analysis (TG/HDL-C equal to 0.402) (as presented in Table 3). Therefore, below the threshold ratio of 0.402, there was no significant association between the TG/HDL-C and the risk of depression (OR, 1.13; 95% CI, 0.35–3.67; $P = .84$). However, above the threshold ratio of 0.402, higher TG/HDL-C was significantly linked to a higher risk of depression (OR, 1.65; 95% CI, 1.29–2.10; $P < .001$) (Table 3).

3.4. Subgroup analyses and sensitivity analyses

We performed prespecified subgroup analyses to assess whether the association between TG/HDL-C and the depression risk was consistent across the different subgroups. As presented in Figure 4, statistically significant interactions were demonstrated between TG/HDL-C and gender, hypertension in relation to depressive symptoms (P for interaction = .004, .014, respectively). The interaction was not significant after

stratification by age, race, PIR, education level, BMI, smoking status, alcohol intake and diabetes mellitus. The association between TG/HDL-C and depression remained consistent across different subgroups (except for gender and hypertension subgroups), with no significant interactions observed (P for interaction > 0.05). Sensitivity analyses were conducted to assess the robustness of the observed associations (Table S2, Supplemental Digital Content, https://links.lww.com/MD/O808). The direction and magnitude of the effect of TG/HDL-C in these associations remained consistent across sensitivity analyses.

4. Discussion

Using data from NHANES (2005 to 2020), we examined the association between TG/HDL-C and depression in a cross-sectional cohort of 20,406 participants. TG/HDL-C was significantly higher among subjects with depression than among those without depression. Moreover, we observed a nonlinear, J-shaped association between TG/HDL-C and depression. According to subgroup analysis, significant interaction effects were found between TG/HDL-C and subgroup variables of gender and hypertension. Participants with depression had a higher level of TG/HDL-C, this finding was consistent across different gender, with the association being greater in female participants. It was notable that the association between TG/HDL-C and the
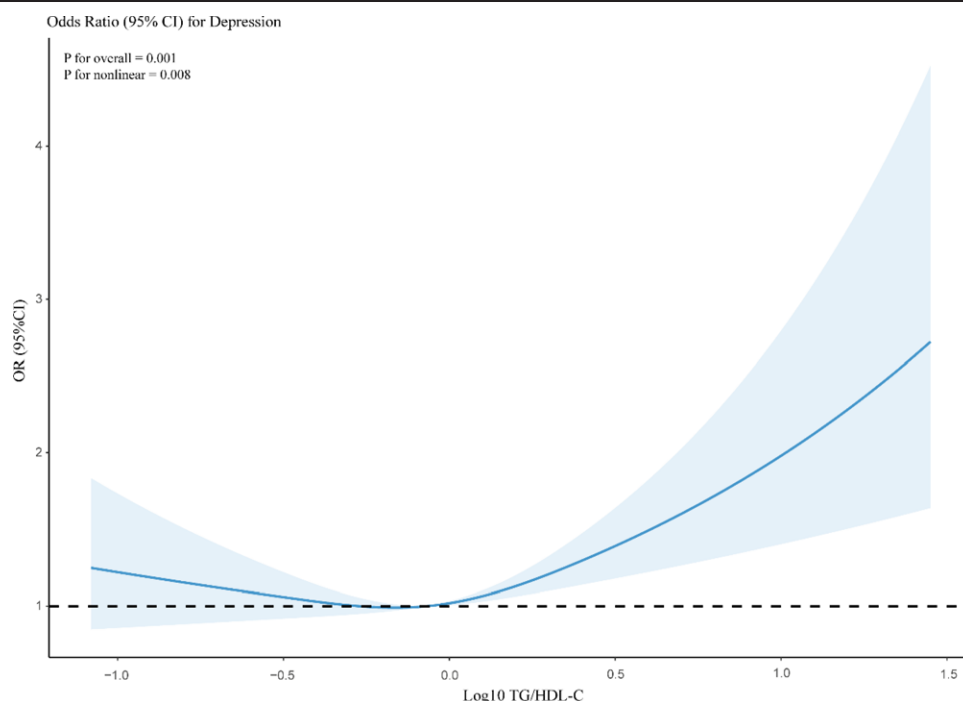
Figure 3. Odds ratio of depression according to log10-transformed TG/HDL-C in overall population. A nonlinear association was found (*P* for non-linearity = .018) between log10-transformed TG/HDL-C and risk of depression in a restricted cubic spline regression model. The solid line and shadow represented the odds ratio of depression and 95% confidence interval, respectively. All covariates were adjusted in this model. TG/HDL-C = triglyceride-to-high-density lipoprotein cholesterol.

Table 3

Threshold effect analysis of TG/HDL-C on the risk of depression.

Outcome	OR (95% CI)	*P*-value
One-line logistic regression model	1.31 (1.04, 1.64)	.020
Two-piecewise logistic regression model		
TG/HDL-C < −0.395	1.13 (0.35, 3.67)	.835
TG/HDL-C ≥ −0.395	1.65 (1.29, 2.10)	<.001
Log-likelihood ratio test		.141

Notes, adjusted for all covariates including age, gender, race or ethnicity, PIR, education level, alcohol intake, diabetes mellitus, hypertension, smoking status, BMI.
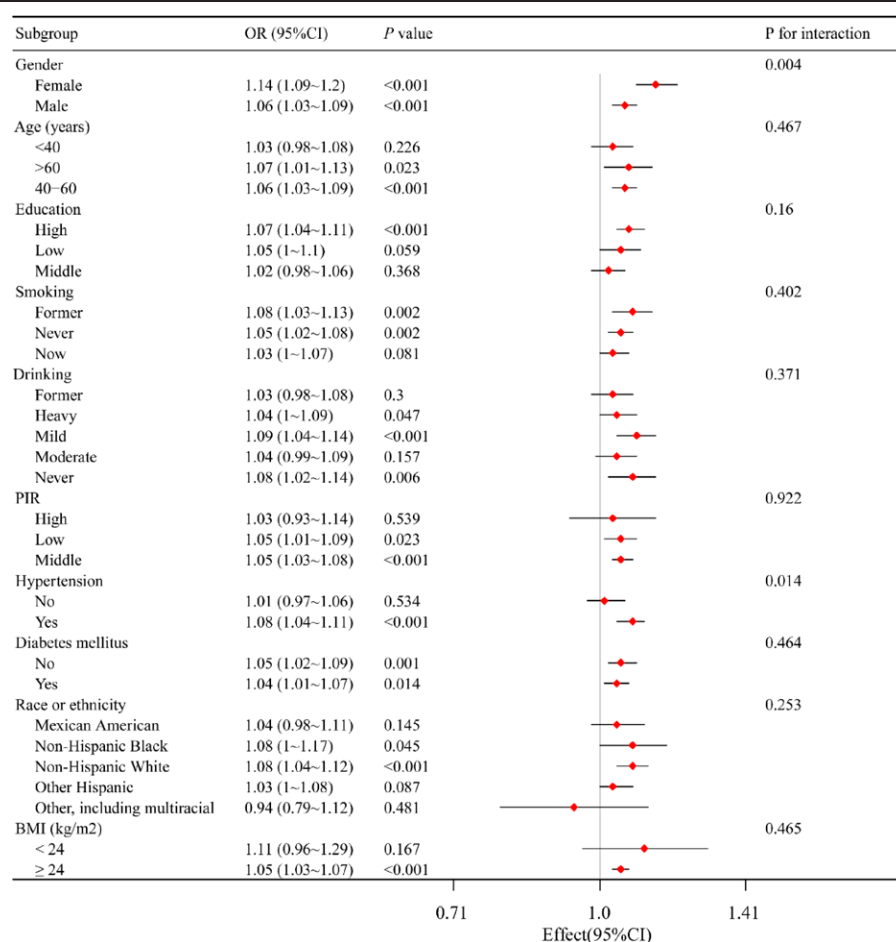
BMI = body mass index, CI = confidence interval, TG/HDL-C = triglyceride-to high-density lipoprotein cholesterol, OR = odds ratio, PIR = income-to-poverty ratio.

depression risk was statistically significant only in participants with hypertension, which was not reported in participants without hypertension.

Depression is a prevalent psychiatric condition worldwide and represents a significant global public health burden, characterized by substantial morbidity and increased risk of suicide-related mortality.[25–27] The clinical manifestations of depression are diverse, and the specific pathogenesis of depression is unclear. Emerging evidence suggests that altered lipid metabolism may contribute to the pathophysiology of mental disorders, including depression, and has been associated with suicidal behavior.[28–30] Alteration in serum lipid profile is associated with the development of depression.[5,31] It was demonstrated that low serum cholesterol levels can affect neuronal membrane fluidity and lipid-mediated adhesion properties, potentially resulting in diminished serotonergic receptor density and functionality in cerebral tissues.[32] Moreover, low serum cholesterol levels can affect synaptic plasticity, which can further lead to the development of depression. Notably, it appears that there are shared biological pathways and genetic factors that underlie both depressive symptoms and abnormal lipid metabolism.[33–35] Furthermore, it has been demonstrated that this genetic effect

is especially pronounced for TG and HDL-C.[36] In our study, serum lipid profiles were compared between participants with depressive disorder and without depressive disorder. The findings demonstrated significantly higher TG concentrations and lower HDL-C levels among patients meeting diagnostic criteria for depression. Neither TC nor LDL-C concentrations demonstrated significant between-group differences. These findings were aligned with the findings of a recent meta-analysis, which demonstrated that higher TG concentrations and lower HDL-C levels were significantly associated with depression.[5] These findings suggest that disturbance in serum lipid homeostasis may contribute significantly to the pathogenesis of depressive disorder.

In recent years, the TG/HDL-C has emerged as a marker of considerable clinical interest. Accumulating evidence from clinical investigations suggested that elevated TG/HDL-C may independently predict the risk of several cardiometabolic disorders, including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, hyperuricemia, and chronic kidney disease.[15,37] To our knowledge, this investigation represents the first systematic examination of the association between TG/HDL-C and depression. The results demonstrated a significant association between an elevated TG/HDL-C and depression risk. After accounting for potential confounding variables, the TG/HDL-C remained significantly elevated in patients with depression compared to those without depression. Moreover, in multivariate analyses, after adjustment for potential confounding variables, we identified a significant nonlinear dose-response association between TG/HDL-C and the risk of depression. When the log10-transformed TG/HDL-C was higher than −0.395 (TG/HDL-C = 0.402), the risk of developing depression increased significantly. These findings suggest that an elevated TG/HDL-C may represent a potential biomarker for early detection of depressive disorders. Therapeutic interventions targeting the normalization of serum TG/HDL-C warrant investigation as a possible strategy for both prevention and amelioration of depressive symptoms. Prospective randomized controlled trials

Subgroup	OR (95%CI)	P value		P for interaction
Gender				0.004
Female	1.14 (1.09~1.2)	<0.001		
Male	1.06 (1.03~1.09)	<0.001		
Age (years)				0.467
<40	1.03 (0.98~1.08)	0.226		
>60	1.07 (1.01~1.13)	0.023		
40–60	1.06 (1.03~1.09)	<0.001		
Education				0.16
High	1.07 (1.04~1.11)	<0.001		
Low	1.05 (1~1.1)	0.059		
Middle	1.02 (0.98~1.06)	0.368		
Smoking				0.402
Former	1.08 (1.03~1.13)	0.002		
Never	1.05 (1.02~1.08)	0.002		
Now	1.03 (1~1.07)	0.081		
Drinking				0.371
Former	1.03 (0.98~1.08)	0.3		
Heavy	1.04 (1~1.09)	0.047		
Mild	1.09 (1.04~1.14)	<0.001		
Moderate	1.04 (0.99~1.09)	0.157		
Never	1.08 (1.02~1.14)	0.006		
PIR				0.922
High	1.03 (0.93~1.14)	0.539		
Low	1.05 (1.01~1.09)	0.023		
Middle	1.05 (1.03~1.08)	<0.001		
Hypertension				0.014
No	1.01 (0.97~1.06)	0.534		
Yes	1.08 (1.04~1.11)	<0.001		
Diabetes mellitus				0.464
No	1.05 (1.02~1.09)	0.001		
Yes	1.04 (1.01~1.07)	0.014		
Race or ethnicity				0.253
Mexican American	1.04 (0.98~1.11)	0.145		
Non-Hispanic Black	1.08 (1~1.17)	0.045		
Non-Hispanic White	1.08 (1.04~1.12)	<0.001		
Other Hispanic	1.03 (1~1.08)	0.087		
Other, including multiracial	0.94 (0.79~1.12)	0.481		
BMI (kg/m2)				0.465
< 24	1.11 (0.96~1.29)	0.167		
≥ 24	1.05 (1.03~1.07)	<0.001		

0.71　　1.0　　1.41
Effect(95%CI)

Figure 4. The association between TG/HDL-C and the risk of depression according to different subgroups. BMI = body mass index, CI = confidence interval, OR = odds ratio, PIR = income-to-poverty ratio, TG/HDL-C = triglyceride-to high-density lipoprotein cholesterol.

are required to establish causal relationships and assess the clinical relevance of modifying the TG/HDL-C in the management of depression. Statins are one of the most prescribed medications worldwide, which is used for regulating serum lipid levels.[38] It has been reported that stains alone might have a beneficial effect on depression and suicidal behavior.[39–42] Furthermore, recent studies demonstrated that statins had a protective effect against depression when used as an add-on therapy with antidepressant medications such as selective serotonin reuptake inhibitors.[43,44] Emerging evidence, including our findings, suggested that the serum TG/HDL-C may serve as an objective diagnostic biomarker for depression. Furthermore, therapeutic modulation of this ratio could represent a novel preventive strategy to reduce the incidence of depression in clinical practice.

Serum cholesterol such as HDL-C has been implicated in the pathophysiological mechanisms underlying depression.[29,45] HDL-C is carried by a lipoprotein, HDL.[46] HDL possess antioxidative properties and can inhibit intracellular reactive oxygen species generation.[46] Thus, levels of HDL-C may be expressive of HDL antioxidative activities.[47] A substantial body of evidences have showed elevated oxidative stress in patients with depression, oxidative stress has been established as a pivotal mechanism in the pathophysiology of depression.[47,48] Hence, downregulation of antioxidative activities due to decreased HDL-C levels may result in the development of depression, HDL-C may work as an antidepressant through antioxidative activities. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been consistently demonstrated in patients with depressive disorder.[49] Blood cholesterol and TG increase due to the hyperactivity of HPA axis. Therefore, elevated TG and

cholesterol may be found in depressed patients, which is consistent with our results.

Depression is independently associated with increased cardiovascular morbidity and mortality, as demonstrated by longitudinal epidemiological studies.[17,50] Similarly, perturbations in serum lipid profiles have been well-documented as independent cardiovascular risk factors.[51] Patients exhibiting dyslipidemia demonstrated not only an elevated risk for depression, but also a significantly increased incidence of adverse cardiovascular outcomes. Patients with concurrent depression and dyslipidemia exhibit a significantly higher risk of adverse cardiovascular outcomes, including acute coronary syndrome and congestive heart failure. Dyslipidemia independently increased the risk of adverse cardiovascular events among patients with depression, suggesting a potential synergistic interaction between these comorbid conditions.[6] Therefore, routine lipids monitoring and lipids level regulating have a protective effect both on depression and cardiovascular events. This large-scale cross-sectional study indicates a clear distinctive TG/HDL ratio between depression group and non-depression group, potentially opening new prevention or treatment methods for depression and its associated cardiovascular comorbidity.

The present investigation has several notable strengths. First, this study represents the first population-based investigation to examine the association between TG/HDL-C and incident depression in a nationally representative sample of US adults. The current investigation included a substantially larger sample size than prior studies examining the relationship between serum lipid parameters and depression.[31] Second, standardized measurement protocols and validated analytical methods were

rigorously implemented in accordance with NHANES quality control procedures, which makes our results more credible. Third, multivariate analyses were used to adjust for potential confounding variables, and sensitivity analyses demonstrated consistent findings across predefined subgroups. Finally, the current study sheds new light on the pathogenic mechanism of depression and early intervention for depression in clinical practice. Our findings demonstrated that the serum TG/HDL-C may serve as a clinically relevant biomarker for the diagnosis of depression. Present depression diagnosis mainly relies on patients' subjective descriptions and spoken information.[8] Thus, misdiagnoses for depressed patients based on such subjective interviews are inevitable,[52] which can result in confusion in clinical practice. To address the limitations of depression diagnosis, the development of objective methods to identify depressed patients has been justified. In current study, TG/HDL-C may be a blood biomarker for depression in clinical use.

Several limitations warrant consideration when interpreting these findings. Firstly, the diagnosis of depression is based on self-reported questionnaires (PHQ-9), a validated screening instrument, rather than structured clinical interviews or diagnostic criteria, which may lead to inaccurate results due to reporting or recall bias. Secondly, there are many unknown and unmeasured confounding factors which we did not take into account. In the present study, we did not consider factors such as marital status, prior medication use and nutritional data, which may have potential effects on depression and lipid parameters and may have partially diluted the effect estimates. Thirdly, the study sample consisted of participants older than 18 years of age. In fact, depression is common in adolescents in recent years, 1 in 7 10 to 19-year-olds experiences a depression globally.[53] Consequently, we may miss some important information as we did not include the participants younger than 18 years old, which may bias current results. Finally, the main limitation of this investigation is its cross-sectional design, which inherently precluded the establishment of temporal relationships or causal inference between serum TG/HDL-C and incident depression. Further investigation of the relationship between TG/HDL-C and the development of depression through longitudinal cohort studies would provide more definitive evidence of causality.

5. Conclusion

In conclusion, these findings demonstrated a significant association between elevated TG/HDL-C and depression. We observed a J-shaped association between TG/HDL-C and incident depression. When TG/HDL-C is higher than 0.402, the risk of depression increases significantly, indicating that TG/HDL-C may serve as a biomarker for early identification for depression. These findings suggest that routine TG/HDL-C monitoring and interventions should be conducted in the early-stage of depression to decrease the risk of cardiovascular morbidity. Further prospective longitudinal investigations and randomized controlled trials are warranted to elucidate the potential causal relationship between TG/HDL-C and depression.

Acknowledgments

Author contributions

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References

[1] Kessler RC, Sampson NA, Berglund P, et al. Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. Epidemiol Psychiatr Sci. 2015;24:210–26.

[2] Ferrari AJ, Somerville AJ, Baxter AJ, et al. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. Psychol Med. 2013;43:471–81.

[3] Gonda X, Petschner P, Eszlari N, et al. Genetic variants in major depressive disorder: from pathophysiology to therapy. Pharmacol Ther. 2019;194:22–43.

[4] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9:137–50.

[5] Wei Y, Cai D-B, Liu J, et al. Cholesterol and triglyceride levels in first-episode patients with major depressive disorder: a meta-analysis of case-control studies. J Affect Disord. 2020;266:465–72.

[6] Hu J, Ji Y, Lang XE, Zhang X-Y. Prevalence and clinical correlates of abnormal lipid metabolism in first-episode and drug-naïve patients with major depressive disorder: a large-scale cross-sectional study. J Psychiatr Res. 2023;163:55–62.

[7] Gowey MA, Khodneva Y, Tison SE, et al. Depressive symptoms, perceived stress, and metabolic health: The REGARDS study. Int J Obes (Lond). 2019;43:615–32.

[8] Kuwano N, Kato TA, Setoyama D, et al. Tryptophan-kynurenine and lipid related metabolites as blood biomarkers for first-episode drug-naive patients with major depressive disorder: an exploratory pilot case-control study. J Affect Disord. 2018;231:74–82.

[9] Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. Lancet. 1993;341:75–9.

[10] Nakao M, Yano E. Relationship between major depression and high serum cholesterol in Japanese men. Tohoku J Exp Med. 2004;204:273–87.

[11] Brown SL, Salive ME, Harris TB, Simonsick EM, Guralnik JM, Kohout FJ. Low cholesterol concentrations and severe depressive symptoms in elderly people. BMJ. 1994;308:1328–32.

[12] Han AL. Association between lipid ratio and depression: a cross-sectional study. Sci Rep. 2022;12:6190.

[13] Bot M, Milaneschi Y, Al-Shehri T, et al; BBMRI-NL Metabolomics Consortium. Metabolomics profile in depression: a pooled analysis of 230 metabolic markers in 5283 cases with depression and 10,145 controls. Biol Psychiatry. 2020;87:409–18.

[14] Weng R, Shen S, Burton C, et al. Lipidomic profiling of tryptophan hydroxylase 2 knockout mice reveals novel lipid biomarkers associated with serotonin deficiency. Anal Bioanal Chem. 2016;408:2963–73.

[15] Kosmas CE, Rodriguez Polanco S, Bousvarou MD, et al. The triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio as a risk marker for metabolic syndrome and cardiovascular disease. Diagnostics (Basel, Switzerland). 2023;13:929.

[16] Melo APS, Dippenaar IN, Johnson SC, et al. All-cause and cause-specific mortality among people with severe mental illness in Brazil's public health system, 2000–15: a retrospective study. Lancet Psychiatry. 2022;9:771–81.

[17] Geraets AFJ, Schram MT, Jansen JFA, et al. The cardiometabolic depression subtype and its association with clinical characteristics: the Maastricht Study. J Affect Disord. 2022;313:110–7.

[18] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.

[19] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.

[20] Mitchell AJ, Yadegarfar M, Gill J, Stubbs B. Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: a diagnostic meta-analysis of 40 studies. BJPsych Open. 2016;2:127–38.

[21] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.

[22] Zhang Y, Mustieles V, Wang Y-X, et al. Folate concentrations and serum perfluoroalkyl and polyfluoroalkyl substance concentrations in adolescents and adults in the USA (National Health and Nutrition Examination Study 2003–16): an observational study. Lancet Planet Health. 2023;7:e449–58.

[23] Charidimou A, Martinez-Ramirez S, Reijmer YD, et al. Total magnetic resonance imaging burden of small vessel disease in cerebral amyloid angiopathy. JAMA Neurol. 2016;73:994–1001.

[24] van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw. 2011;45:1–67.

[25] Dong M, Wang S-B, Li Y, et al. Prevalence of suicidal behaviors in patients with major depressive disorder in China: a comprehensive meta-analysis. J Affect Disord. 2018;225:32–9.

[26] Kupferberg A, Bicks L, Hasler G. Social functioning in major depressive disorder. Neurosci Biobehav Rev. 2016;69:313–32.

[27] Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol. 2015;19:pyv082.

[28] Liu X, Li J, Zheng P, et al. Plasma lipidomics reveals potential lipid markers of major depressive disorder. Anal Bioanal Chem. 2016;408:6497–507.

[29] Parekh A, Smeeth D, Milner Y, Thure S. The role of lipid biomarkers in major depression. Healthcare (Basel). 2017;5:5.

[30] Peng YF, Xiang Y, Wei YS. The significance of routine biochemical markers in patients with major depressive disorder. Sci Rep. 2016;6:34402.

[31] van Reedt Dortland AKB, Giltay EJ, van Veen T, van Pelt J, Zitman FG, Penninx BWJH. Associations between serum lipids and major depressive disorder. J Clin Psychiatry. 2010;71:729–36.

[32] Engelberg H. Low serum cholesterol and suicide. Lancet. 1992;339:727–9.

[33] Lopez-Leon S, Janssens ACJW, González-Zuloeta Ladd AM, et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry. 2008;13:772–85.

[34] López-León S, Aulchenko YS, Tiemeier H, Oostra BA, van Duijn CM, Janssens ACJW. Shared genetic factors in the co-occurrence of symptoms of depression and cardiovascular risk factors. J Affect Disord. 2010;122:247–52.

[35] Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. Transl Psychiatry. 2017;7:e1007–e1007.

[36] Knoblauch H, Busjahn A, Münter S, et al. Heritability analysis of lipids and three gene loci in twins link the macrophage scavenger receptor to HDL cholesterol concentrations. Arterioscler Thromb Vasc Biol. 1997;17:2054–60.

[37] Wu Z, Zhou D, Liu Y, et al. Association of TyG index and TG/HDL-C ratio with arterial stiffness progression in a non-normotensive population. Cardiovasc Diabetol. 2021;20:134.

[38] Urquhart L. Top drugs and companies by sales in 2018. Nat Rev Drug Discov. 2019;18:816.

[39] Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. Arch Intern Med. 2003;163:1926–32.

[40] Kim SW, Kang H-J, Jhon M, et al. Statins and inflammation: new therapeutic opportunities in psychiatry. Front Psychiatry. 2019;10:103.

[41] Yatham MS, Yatham KS, Ravindran AV, Sullivan F. Do statins have an effect on depressive symptoms? A systematic review and meta-analysis. J Affect Disord. 2019;257:55–63.

[42] Parsaik AK, Singh B, Murad MH, et al. Statins use and risk of depression: a systematic review and meta-analysis. J Affect Disord. 2014;160:62–7.

[43] Köhler Forsberg O, N Lydholm C, Hjorthøj C, et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. Acta Psychiatr Scand. 2019;139:404–19.

[44] Köhler O, Gasse C, Petersen L, et al. The effect of concomitant treatment with ssris and statins: a population-based study. Am J Psychiatry. 2016;173:807–15.

[45] Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Prog Neurobiol. 2010;91:275–99.

[46] Camont L, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. Trends Mol Med. 2011;17:594–603.

[47] Liu T, Zhong S, Liao X, et al. A meta-analysis of oxidative stress markers in depression. PLoS One. 2015;10:e0138904.

[48] Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. J Affect Disord. 2010;125:287–94.

[49] Mello AF, Mello MF de, Carpenter LL, Price LH. Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. Braz J Psychiatry. 2003;25:231–8.

[50] Meng R, Yu C, Liu N, et al; China Kadoorie Biobank Collaborative Group. Association of depression with all-cause and cardiovascular disease mortality among adults in China. JAMA Netw Open. 2020;3:e1921043.

[51] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1046–81.

[52] Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet. 2009;374:609–19.

[53] Shorey S, Ng ED, Wong CHJ. Global prevalence of depression and elevated depressive symptoms among adolescents: a systematic review and meta-analysis. Br J Clin Psychol. 2022;61:287–305.