Journal of Clinical Lipidology (2020) 14, 515–521

Journal of Clinical Lipidology

Low levels of cholesterol and the cholesterol type are not associated with depression: Results of a cross-sectional NHANES study

M. Soledad Cepeda, MD, PhD*, David M. Kern, PhD, Clair Blacketer, MPH, Wayne C. Drevets, MD

Department of Epidemiology, Janssen Research & Development, Titusville, NJ, USA (Drs Cepeda, Kern, and Blacketer); and Central Nervous System, Janssen Research & Development, San Diego, CA, USA (Dr Drevets)

KEYWORDS:
Depression;
Cholesterol;
Triglycerides;
Population study;
NHANES;
Decision tree model

BACKGROUND: Reports suggest low levels of cholesterol are associated with depression. However, results have not been replicated, the direction of the associations among types of cholesterol levels is not consistent, there is large study heterogeneity, and many studies have small samples.

OBJECTIVE: The objective of the study was to assess the association of cholesterol with depression.

METHODS: This is a cross-sectional study using the National Health and Nutrition Examination Survey (NHANES). The NHANES is a research program that collects health information from a representative U.S. sample. We included subjects aged ≥18 years who responded to NHANES surveys from 2009 to 2015. Subjects were classified as having major depression if the Patient Health Questionnaire scores were ≥10. Exposures were total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels. We considered the age, body mass index, gender, smoking, alcohol use, health status, and exposure to statins and antipsychotics as potential confounders. To assess the association of the exposures with depression, we used decision tree and logistic regression models.

RESULTS: A total of 19,527 subjects were analyzed, and 8% had depression. Subjects with depression were more likely to be women and smokers, and to have higher body mass index, poor health, higher levels of total cholesterol and triglycerides and lower levels of high-density lipoprotein cholesterol than subjects with no depression. After adjustment, low levels of total cholesterol (<129 mg/dL) were associated with decreased risk of depression compared with higher levels, OR = 0.64 and 95% CI (0.42–0.98).

CONCLUSION: This large population-based study found no association of low cholesterol or any other lower type of cholesterol levels with increased risk of depression. These findings are generalizable to the U.S. population.

Ethics approval and consent to participate: The NHANES Institutional Review Board (IRB), which changed its name in 2003 to the NCHS Research Ethics Review Board (ERB), reviewed and approved all the survey cycles used in this study.

Availability of data and materials: The NHANES data are publicly available.

Conflict of interests: All authors are Janssen Research and Development employees. No drugs are mentioned in this article. Janssen Research and Development is developing products for treatment of major depression.

Authors' contributions: MSC: study design, analysis, interpretation of results, drafting manuscript. DK: study design, interpretation of results, reviewing manuscript. CB: study design, accessing and creating analytic dataset, interpretation of results, reviewing manuscript. WD: study design, interpretation of results, reviewing manuscript.

* Corresponding author. Janssen Research & Development, 1125 Trenton Harbourton Road, Titusville, NJ 08560, USA.

E-mail address: scepeda@its.jnj.com

Submitted March 3, 2020. Accepted for publication June 1, 2020.

https://doi.org/10.1016/j.jacl.2020.06.001

Background

There is some evidence suggesting that low levels of cholesterol are associated with depression and suicidality. Systematic reviews of the literature and meta-analyses of the observational studies that have examined the association of cholesterol levels with depression and suicidality[1,2] have found that study results are not consistently replicated. A closer look at the findings also shows that the direction of the associations between cholesterol levels and types of cholesterol levels are not consistent, or the associations only apply to a specific subgroup.

For example, high levels of high-density lipoprotein cholesterol (HDL-C) levels have been found to be associated with an increased risk of depression and suicidality, but only in men.[3] High levels of triglycerides were found to be associated with depression,[4,5] while there has been no association between low-density lipoprotein cholesterol (LDL-C) levels[1,5] and total cholesterol with depression.[4,5]

Some studies that have reported the association of low levels of cholesterol with depression have limited controls for confounding.[1,2,4] The crucial role of controlling for confounding factors for the validity of observational study findings is well established. For example, in a study that assessed the effect of lipids on depressive symptoms after menopause, the authors analyzed the data using the linear trend across quintiles of lipid levels, and after adjustment for potential confounders, all the results became nonsignificant.[6]

In addition to the high degree of heterogeneity, the meta-analyses of the observational studies that have examined the association of cholesterol levels with depression revealed the small sample sizes of the included studies.[1,2]

Therefore, we sought to conduct a study whose findings can be generalizable to the U.S. population, with a large sample size, with controls for confounding factors, have high-quality laboratory results, and include a reliable measure of depression. The National Health and Nutrition Examination Survey (NHANES) was the source that met all of these criteria.

Objective

The objective of the study was to assess the association of cholesterol with depression.

Methods

We designed and conducted a cross-sectional analysis using data from the NHANES.

The NHANES is a major program of the National Center for Health Statistics. The National Center for Health Statistics is part of the Centers for Disease Control and Prevention and has the responsibility for producing vital and health statistics for the United States. The NHANES is a national research program designed to assess the health and nutritional status of adults and children in the United States. It collects health information from a representative sample of the U.S. population through interviews, medical examinations, and laboratory tests. The survey examines a nationally representative sample of about 5000 persons each year. Findings from the surveys are used to determine the prevalence of major diseases and risk factors for diseases and help develop public health policy, design health programs and services, and expand the health knowledge for the nation.[7,8]

We included subjects aged 18 years and older who responded to the NHANES from 2009 to 2015 who had data available for total cholesterol or HDL-C and completed the Patient Health Questionnaire (PHQ-9). We selected these years of surveys because of the consistency of the use of PHQ-9 to assess depression and consistency of the laboratory equipment, laboratory site, and laboratory method to access lipid levels.

Outcome

Depression was assessed with the PHQ-9. The PHQ-9 is a 9-item depression screening instrument that asks participants to choose 1 of 4 responses about the frequency of depressive symptoms during the previous 2 weeks.[9] Subjects were classified as having depressive symptoms if the PHQ-9 scores were $\geq$10. Scores $\geq$10 represent moderate or more severe depressive symptoms.[10] This score has shown to have a sensitivity of 0.88 and a specificity of 0.80 when compared with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depressive disorders.[11]

Exposure

The primary exposures of interest were total cholesterol levels and HDL-C levels.

LDL-C and triglyceride levels were considered secondary exposures as these variables were present for only a subset of participants, consisting of subjects who fasted at least 8.5 hours or more, but less than 24 hours and provided samples in the morning.

There were no changes to the biosample collection and assay methods, laboratory equipment, or laboratory sites during the survey cycles included in the study. The NHANES quality assurance and quality control protocols meet the 1988 Clinical Laboratory Improvement Act mandates. In addition, the NHANES uses several methods to monitor the quality of the analyses performed by the contract laboratories, including performing blind split samples collected on "dry run" sessions and repeat testing at random on 2% of specimens.

The following total cholesterol categories were created: $\leq$80, >80 to 129, >129 to 200, >200 to 239, and >239 mg/dL. The following HDL-C categories were created: $\leq$40, >40 to <60, and $\geq$60 mg/dL. The following LDL-C categories were created: <80, 80 to <100,100 to

<130, 130 to <160, 160 to <190, and ≥190 mg/dL, and the following triglycerides categories were created: <150 and ≥ 150 mg/dL. Because only 5 subjects had total cholesterol levels ≤80, for the analysis, we grouped this category with the one ">80 to 129 mg/dL." These categories are similar to the ones used in previous studies.[4,6]

Potential confounder variables

We considered the age, body mass index (BMI), gender, smoking status, alcohol use, current health status, and current exposure to statins and antipsychotics as potential confounding variables. Statins were considered potential confounders because of their role in decreasing lipid levels, and antipsychotic drugs were considered potential confounders because their use has been associated with hyperlipidemia.[12]

Participants were classified as never, former, and current smokers. Current smokers were those subjects reporting at least 100 cigarettes in their lifetime and currently smoking every day or some days. Former smokers were those subjects reporting smoking at least 100 cigarettes in their lifetime but who do not currently smoke. For alcohol use, participants were classified as never, former, and current drinkers. Current drinkers were those subjects reporting at least 12 drinks in their lifetime and who report at least 1 drink in the past 12 months. Former drinkers were those subjects who reported drinking at least 12 drinks in their lifetime and no drinks in the past 12 months. These categorizations have been used previously when studying depression in the NHANES.[13]

Health status was reported as excellent, very good, good, fair, or poor after the question "Would you say your health in general is…" Subjects were considered exposed to statins or antipsychotics if they reported taking any drug that belongs to the statin class or the antipsychotics class in the past 30 days of taking the survey.

Analysis

Exposures were analyzed as s categorical and continuous variables. The primary analysis was the categorical approach because the results are less susceptible to the effect of outliers.

We used decision tree models to assess whether a data-driven approach could identify categories for total cholesterol and HDL-C according to their association with depression. A decision tree is a nonparametric method that creates simple decision rules inferred from the data that can be used to optimally select cutoffs for continuous variables. The outcome was depression (PHQ-9 scores ≥ 10), and total cholesterol and HDL-C were the exposures. We used area under the curve (AUC) as a measure of performance. An AUC of 1 indicates perfect discrimination and 0.5 a model that is no better than a flip of a coin.

In addition, we built logistic regression models to assess the association between depression (PHQ-9 score ≥ 10) and total cholesterol levels, HDL-C levels, triglyceride levels, and LDL-C levels. To control for potential confounding, we added the age as a continuous variable, the BMI as a continuous variable, the gender, smoking status, alcohol use, current health status, and exposure to statins or antipsychotics (yes vs no) to the regression model. We also included in the model the interaction term between total cholesterol and statin use. This interaction allowed us to assess whether the effect of cholesterol levels on depression changed depending on the therapeutic effect of statins. In this model, total cholesterol levels were categorized as <200 mg/dL and ≥200 mg/dL to facilitate interpretation of the interactions and to decrease the number of variables in the model.

We required at least 8 subjects with depression per variable included in the logistic regression model to provide valid and reliable estimates.[14] In the logistic regression models, the exposures were modeled as continuous or categorical variables. Odds ratios >1 would indicate an increased risk of depression.

Incorporating complex survey design in the analysis

To correctly account for the complex survey design, in the analyses, we included the primary sampling unit variable (sdmvpsu) for variance estimation, the pseudo-stratum variable (sdmvstra) as the stratification variable, and the Mobile Examination Center examination (wtmec) as the weight variable. The NHANES provides sample weights to be used in conjunction with the data to allow analysts to produce estimates that are representative of the U.S. population. When combining multiple cycles of data as in this study, the 2-year weights must be adjusted. Using the estimation procedure guidelines provided by the NHANES, we multiplied the weight variable by 1/4 because we included 4 survey periods. STATA version 14.2 was used to conduct the analyses.[15]

Results

A total of 23,879 subjects were aged 18 years and older and participated in the surveys. Of these subjects, 20,527 responded to the PHQ-9 questionnaire, of whom 19,527 had total cholesterol data and thus were included in the analysis.

Eight percent of the subjects had the PHQ-9 scores suggestive of depression. Subjects with depression were more likely to be women, be former or current smokers, to have a higher BMI, and to report having poor health than subjects with no depression, (Table 1).

Subjects with depression had slightly higher levels of total cholesterol, higher levels of triglycerides, and lower

levels of HDL-C than subjects with no depression, (Table 1).

Association of depression with the cholesterol type

The decision tree models could not discriminate between subjects with and without depression based on total cholesterol (AUC of 0.54) or HDL-C (AUC of 0.52).

The logistic regression models that had depression as an outcome and the cholesterol type as the only variable found an association between HDL-C and triglycerides with depression, Table 2. Compared with low levels of HDL-C, higher levels (>40 mg/dL) were associated with lower risk of depression. For triglycerides, high levels of triglycerides were associated with an increased risk of depression (Table 2).

After adjustment for the age, gender, BMI, smoking, drinking habits, health status, statin and antipsychotics use, having <129 mg/dL of total cholesterol is associated with a decreased risk of depression compared with higher levels (Table 2).

The results remained similar when total cholesterol, HDL-C, LDL-C, or triglycerides were considered as continuous variables (Table 3). The interaction term between cholesterol levels and statin use was not significant ($P = .24$) and did not change the estimates.

Discussion

We designed and conducted a large population-based study to assess the association of cholesterol with depression, whose findings can be generalizable to the U.S. population. We found no association between low levels of cholesterol and an increased risk of depression. Instead, after performing statistical adjustment for the age, gender, BMI, smoking, drinking habits, health status, and statin or antipsychotics use, having <129 mg/dL of total cholesterol was associated with a decreased risk of depression compared with higher levels (OR = 0.64; 95% confidence interval [CI] [0.42–0.98]). In this study, we assessed not only total cholesterol but also HDL-C, LDL-C, and triglycerides. The study covered several years of survey respondents, and during this time, the same laboratory and assay were used, providing assurance to the quality of the data and validity of the study results.

In the present study, the 8% prevalence of depression was similar to the prevalence reported in other studies that also were conducted in the NHANES[13,16] as well as to the

Table 1 Characteristics of subjects with and without depression based on the PHQ-9 score

Subjects characteristics	No depression	Depression	*P* value
The number of subjects (%)	17,737 (92)	1790 (8)	
Age (mean ± SE)	46.32 ± 0.33	45.86 ± 0.54	0.49
Women (%)	50	65	<0.0001
Men (%)	50	35	
BMI (mean ± SE)	28.89 ± 0.10	30.8 ± 0.25	<0.001
Smoking status			
Current (%)	18	39	<0.0001
Former (%)	25	22	
Never (%)	57	38	
Drinking status			
Current (%)	74	67	<0.0001
Former (%)	14	22	
Never (%)	11	10	
Health status			
Excellent (%)	11	2	<0.0001
Very good (%)	34	12	
Good (%)	40	34	
Fair (%)	13	36	
Poor (%)	1	14	
Statins use(%)	13	14	0.10
Antipsychotic use (%)	0.6	4	<0.0001
Cholesterol			
Cholesterol (mean ± SE)	192.85 ± 0.60	195.83 ± 1.36	0.025
HDL-C (mean ± SE)	53.8 ± 0.28	51.6 2 ± 0.49	<0.001
LDL-C (mean ± SE)	114.19 ± 0.66	115.78 ± 0.66	0.48
Triglycerides (mean ± SE)	125.85 ± 2.16	145.58 ± 2.24	0.006

BMI, body mass index; PHQ-9, Patient Health Questionnaire; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 2 Association of total cholesterol, HDL-C, LDL-C, and triglycerides levels with depression before and after adjustment

Type	No depression	Depression	Unadjusted overall *P* value	Unadjusted odds ratio (95% CI)	Adjusted Odds ratio* (95% CI)
Total cholesterol (mg/dL)	N (%)	N (%)			
≤80	5 (0.019)	0	.16	0.76 (0.52 to 1.12)	0.64 (0.42 to 0.98)
>80 to 129	834 (4)	68 (4)			
>129 to 200	10,118 (56)	986 (54)		0.80 (0.68 to 0.96)	0.84 (0.68 to 1.05)
>200 to 239	4669 (27)	493 (28)		0.87 (0.71 to 1.06)	0.93 (0.74 to 1.18)
>239	2111 (12)	243 (14)		Reference	Reference
HDL-C (mg/dL)					
≤40	3891 (21)	488 (26)	.0001	Reference	Reference
>40 to <60	8633 (48)	860 (48)		0.84 (0.72 to 0.98)	0.98 (0.83 to 1.17)
≥60	5213 (31)	442 (26)		0.68 (0.58 to 0.81)	0.94 (0.79 to 1.12)
LDL-C (mg/dL)					
<80	1071 (15)	91 (16)	.74	1.05 (0.50 to 2.21)	1.02 (0.43 to 2.48)
80 to < 100	1332 (21)	127 (18)		0.88 (0.41 to 1.91)	1.01 (0.41 to 2.47)
100 to <130	2080 (33)	204 (33)		1.03 (0.51 to 2.10)	1.08 (0.45 to 2.56)
130 to <160	1295 (21)	134 (22)		1.09 (0.55 to 2.18)	1.25 (0.55 to 2.81)
160 to < 190	474 (7)	49 (9)		1.25 (0.58 to 2.72)	1.38 (0.58 to 3.27)
≥190	152 (3)	16 (3)		Reference	Reference
Triglycerides (mg/dL)					
<150	4938 (75)	411 (65)	.0003	0.60 (0.46 to 0.78)	0.78 (0.58 to 1.06)
≥150	1579 (24)	223 (35)		Reference	Reference

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CI, confidence interval.
*Adjusted by the age, BMI, gender, smoking status, alcohol use, current health status, and current exposure to statins and antipsychotics.

10% prevalence reported in a national survey that used Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria to define the presence of major depressive disorder within the previous year.[17]

The findings of this study contrast with other research findings, suggesting that low levels of cholesterol were associated with an increased risk of depression.[1,3] Although the evidence includes a meta-analysis of 30 observational studies, a high degree of heterogeneity among the studies was reported,[1] and a large majority of the included studies had a small sample size, with only 7 of the 30 studies including more than 500 subjects. The authors of the meta-analysis found that the magnitude of the association of total cholesterol levels with depression decreased as the sample size increased and became nonsignificant when the analysis was restricted to studies with more than 500 subjects. In addition, the meta-analysis did not find any association of depression with HDL-C or LDL-C levels, and triglyceride levels were not assessed.

A more recent study, not included in the meta-analysis described previously, based on the Women's Health initiative, characterized the relation between the cholesterol type and depression. It included women aged 50 years and older, and the data were analyzed with a cross-sectional and follow-up perspective.[6] The prospective analysis (with a follow-up of 7 and 11 years) found that low levels of LDL-C were associated with a higher risk for depression with a hazard ratio of 1.26 (95% CI: 1.05–1.50) and that

Table 3 Association of cholesterol, HDL-C, LDL-C, and triglycerides levels as continuous variables with depression before and after adjustment

Type of cholesterol	Unadjusted odds ratio* (95% CI)	Adjusted odds ratio*,† (95% CI)
Total cholesterol (mg/dL)	1.02 (1.002–1.03)	1.02 (1.003–1.03)
HDL-C (mg/dL)	0.92 (0.88–0.96)	0.98 (0.84–1.02)
LDL-C (mg/dL)	1.01 (0.98–1.05)	1.02 (0.98–1.06)
Triglycerides (mg/dL)	1.01 (1.00–1.02)	1.00 (0.98–1.01)

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CI, confidence interval.
*Odds ratio per 10-unit change in the lipid of interest.
†Adjusted by the age, BMI, gender, smoking status, alcohol use, current health status, and current exposure to statins and antipsychotics.

low levels of HDL-C (<43 mg/dL) were associated with lower risk of depression, with a hazard ratio of 0.81 (95% CI: 0.67–0.98). In contrast, the cross-sectional analysis, similar to our study, found no associations of low cholesterol levels with an increased risk of depression. A possible explanation for the discrepancy between the cross-sectional and prospective analyses is that subjects who were present in the prospective analysis were different from the ones who were not followed up, a selection bias that is common when there is loss to follow-up, especially when only 53% of the subjects were observed prospectively over the entire follow-up period. Nonetheless, prospective studies are better suited to understand causality than cross-sectional studies.

We assessed the association of the cholesterol type levels with depression using a variety of approaches, including machine learning (decision tree), a data-driven approach, and more traditional analytic methods such as logistic regression. We also assessed cholesterol as continuous and categorical variables and adjusted for important confounders, in analyses enabled by the richness of the NHANES data, and the results remained similar.

The findings of our study even suggest the opposite of that previously reported, by indicating that lower total cholesterol levels are associated with decreased risk for depression. Depression has been associated with higher cardiovascular risk, and we observed that subjects with depression have a higher burden of disease, are current or former smokers, and have a higher BMI than subjects with no depression factors that contribute to cardiovascular diseases. Furthermore, our study findings have internal validity that is not present in many of the studies that have observed an association between low levels of cholesterol and depression[1,4,18] because the direction of our estimates is consistent across the cholesterol types. Another population-based study that included participants of the Netherlands Study of Depression and Anxiety[19] found that the association of lipid patterns and depression was secondary to life style–related factors. In the present study, we controlled for life style variables and the BMI among others, strengthening the validity of our findings.

The results of this study are also consistent with epidemiological evidence showing that obesity and depression are positively associated, and that total cholesterol levels are also positively associated with obesity.[20] A recent study that analyzed 9 Dutch clinical and population-based studies assessed the association of 230 metabolite measurements with depression found that high levels of triglycerides and total cholesterol were associated with increased risk of depression. These authors also found that controlling for factors such as the BMI decreased the strength of associations and that remaining confounding due to related health factors could not be ruled out. However, these authors highlighted that depression and lipid dysregulation could emerge from a shared etiology because genome-wide association studies have reported a significant association between triglycerides and depression, and the BMI and depression.[21] Potentially consistent with this hypothesis and with the findings of the present study, in studies of patients receiving statins to prevent heart disease, the use of any statin reduced the odds of developing depression in comparison to individuals not using statin medications.[22] Moreover, a recent meta-analysis concluded that statins significantly reduced depression severity relative to placebo administration in patients with major depressive disorder.[23]

Contrary to the studies that previously have assessed the association of cholesterol and risk of depression, our study was based on a sample that is representative of the U.S. population and not based on selective samples whose findings cannot be generalized, as those results may represent idiosyncrasies of the selected participants.

A limitation of the design of this study is that to assess depression, we used the PHQ-9. Although the PHQ-9 scores ≥10 are shown to have 88% sensitivity and 80% specificity[11] for major depressive disorders, depression in this study was not formally diagnosed by a mental health professional. Errors in depression classification could lead to underestimation of the association between depression and cholesterol levels. In addition, this is a cross-sectional study where it is difficult to establish causality. However, we did not find an association of low levels of cholesterol and an increased risk of depression.

This is a cross-sectional study, so the relation between high levels of cholesterol and depression does not imply or establish causality. We did not control for familial or social determinants of depression. If these factors are also associated with high lipid levels, they could explain the positive association of high cholesterol levels with depression.

Conclusion

In summary, this population-based study found no association of low cholesterol levels or any other lower type of cholesterol levels and an increased risk of depression. In contrast, we found that after adjustment for the age, gender, BMI, smoking, drinking habits, health status, and statin or antipsychotics use, low levels of total cholesterol (<129 mg/dL) were associated with a decreased risk of depression compared with higher levels (OR = 0.64; 95% CI [0.42–0.98]). These findings are generalizable to the U.S. population.

Acknowledgments

The authors acknowledge Gayle Murray for editorial assistance.

References

1. Shin JY, Suls J, Martin R. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. *Ann Behav Med*. 2008;36:33–43.

2. Wu S, Ding Y, Wu F, Xie G, Hou J, Mao P. Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies. *J Psychiatry Neurosci*. 2016;41:56–69.
3. Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. *Lancet*. 1993; 341:75–79.
4. Oh J, Kim TS. Serum lipid levels in depression and suicidality: the Korea National Health and Nutrition Examination Survey (KNHANES) 2014. *J Affect Disord*. 2017;213:51–58.
5. Huang TL. Serum lipid profiles in major depression with clinical subtypes, suicide attempts and episodes. *J Affect Disord*. 2005;86:75–79.
6. Persons JE, Robinson JG, Coryell WH, Payne ME, Fiedorowicz JG. Longitudinal study of low serum LDL cholesterol and depressive symptom onset in postmenopause. *J Clin Psychiatry*. 2016;77:212–220.
7. CDC, National Center for Health Statistics. National Health and Nutrition Examination Survey. Vol. 2015. Atlanta, GA: Centers for Disease Control and Prevention; 2015.
8. CDC, National Center for Health Statistics. National Health and Nutrition Examination Survey, 2013-2014. Atlanta, GA: Centers for Disease Control and Prevention; 2015.
9. Shim RS, Baltrus P, Ye J, Rust G. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005-2008. *J Am Board Fam Med*. 2011;24:33–38.
10. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
11. Munoz-Navarro R, Cano-Vindel A, Medrano LA, et al. Utility of the PHQ-9 to identify major depressive disorder in adult patients in Spanish primary care centres. *BMC Psychiatry*. 2017;17:291.
12. Saari K, Koponen H, Laitinen J, et al. Hyperlipidemia in persons using antipsychotic medication: a general population-based birth cohort study. *J Clin Psychiatry*. 2004;65:547–550.
13. Cepeda MS, Katz EG, Blacketer C. Microbiome-gut-brain axis: probiotics and their association with depression. *J Neuropsychiatry Clin Neurosci*. 2017;29:39–44.
14. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003;158: 280–287.
15. Mirel LM, Mohadjer LK, Dohrmann SM, et al. National Health and Nutrition Examination Survey: Estimation procedures, 2007–2010. National Center for Health Statistics. *Vital Health Stat 2*. 2013;(159):1–17.
16. Cepeda MS, Stang P, Makadia R. Depression is associated with high levels of C-reactive protein and low levels of fractional exhaled nitric oxide: results from the 2007-2012 National Health and Nutrition Examination Surveys. *J Clin Psychiatry*. 2016;77:1666–1671.
17. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75:336–346.
18. Messaoud A, Mensi R, Mrad A, et al. Is low total cholesterol levels associated with suicide attempt in depressive patients? *Ann Gen Psychiatry*. 2017;16:20.
19. van Reedt Dortland AK, Giltay EJ, van Veen T, van Pelt J, Zitman FG, Penninx BW. Associations between serum lipids and major depressive disorder: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry*. 2010;71:729–736.
20. Garrison RJ, Wilson PW, Castelli WP, Feinleib M, Kannel WB, McNamara PM. Obesity and lipoprotein cholesterol in the Framingham offspring study. *Metabolism*. 1980;29:1053–1060.
21. Bot M, Milaneschi Y, Al-Shehri T, et al. Metabolomics profile in depression: a pooled analysis of 230 metabolic markers in 5283 cases with depression and 10,145 controls. *Biol Psychiatry*. 2019;87: 409–418.
22. Redlich C, Berk M, Williams LJ, Sundquist J, Sundquist K, Li X. Statin use and risk of depression: a Swedish national cohort study. *BMC Psychiatry*. 2014;14:348.
23. 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.