Longitudinal Study of Low Serum LDL Cholesterol and Depressive Symptom Onset in Postmenopause

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ABSTRACT

Objective: The aim of this study was to characterize the relationship between serum low-density lipoprotein cholesterol (LDL-c) and subsequent depressive symptoms onset in postmenopausal women. We secondarily assessed serum high-density lipoprotein (HDL-c), total cholesterol, and triglycerides.

Method: This population-based prospective cohort study utilizes data from 24,216 women between 50 and 79 years of age who were participants of the Women's Health Initiative, which originally ran from 1993 to 2005 and has since incorporated 2 extension studies, with the most recent culminating in 2015. Fasting lipids were measured for all participants at baseline and for a subset through 6 years of follow-up. Depressive symptoms were characterized using the Burnam 8-item scale for depressive disorders (Center for Epidemiologic Studies-Depression/Diagnostic Interview Schedule short form) at baseline and during follow-up, using a cut point of 0.06 to indicate presence of depressive symptoms.

Results: The lowest quintile of LDL-c was associated with an increased risk of subsequent depressive symptoms (hazard ratio [HR] = 1.25, 95% CI = 1.05–1.49, $P = .01$), and follow-up analyses demonstrated that the elevated risk appeared to be confined to the lowest decile (LDL-c < 100 mg/dL). Further, this elevated risk was moderated by lipid-lowering drug treatment. Elevated risk was demonstrated among those who reported no lipid-lowering medication use (HR = 1.23, 95% CI = 1.03–1.47, $P = .02$), but not among those reporting use (HR = 0.65, 95% CI = 0.18–2.29, $P = .50$).

Conclusions: Among postmenopausal women, untreated serum LDL-c below 100 mg/dL was associated with an increased risk of developing depressive symptoms. No excess risk was observed in those attaining LDL-c < 100 mg/dL with lipid-lowering therapy. These findings have important implications for risk assessment, treatment considerations, and mechanistic insight.

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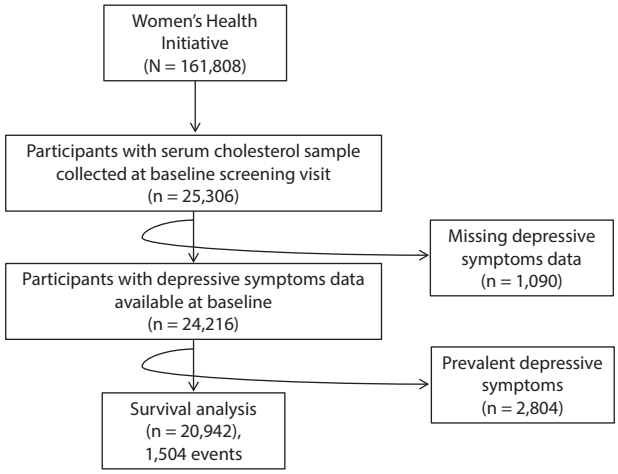
Observation of a relationship between low cholesterol level and suicide has led to the exploration of low serum cholesterol as a clinically relevant biomarker for suicide risk,[1] which is relevant to the assessment of depression risk among older individuals due to the close link between suicide and depression among this population subset.[2] Cholesterol is thought to play a role in depression pathophysiology via serotonergic function: serotonin transporter activity is modulated by cell membrane cholesterol, depletion of which results in diminished serotonin transporter function.[3] Although studies have largely demonstrated an inverse association between serum total cholesterol and depression,[4] these findings have not been consistently replicated.[5,6]

Inconsistencies in the association between depression and cholesterol have raised interest in the roles of individual lipid fractions, particularly serum low-density lipoprotein cholesterol (LDL-c). LDL-c is the main component of the total cholesterol measurement, demonstrating a strong correlation with total cholesterol ($r = 0.91$).[7] In this sense, total cholesterol serves as an imperfect surrogate and, as such, would be expected to demonstrate greater inconsistency than would occur when using LDL-c itself. Several studies[8,9] demonstrate a cross-sectional relationship between low LDL-c and depressive symptoms; although these findings suggest utility of serum LDL-c as a clinical marker, the temporal relationship between serum LDL-c and depressive symptoms is not well understood, leaving it challenging to determine whether low serum LDL-c precedes the development of depression or whether depression leads to decreases in cholesterol via nutritional or metabolic changes.[10]

As serum cholesterol levels vary with age and gender, it is important to study the relationship between cholesterol and depression in various subgroups. Although several studies[11–13] have been conducted among all-female cohorts, to date this association has not been adequately assessed among women who have completed the menopausal transition, such as the members of the Women's Health Initiative (WHI) cohort. The WHI provides an opportunity to evaluate the temporal relationship between serum lipid fractions and depressive symptoms among a large cohort of postmenopausal women and provides evidence toward the distinction between cholesterol as a predictor of depression rather than a consequence or epiphenomenon.[10] In our primary analysis, we will assess the associations between LDL-c and subsequent depressive symptoms, and secondarily assess other lipid measures (total cholesterol, high-density lipoprotein cholesterol [HDL-c], and triglycerides). We will also evaluate the potential for effect modification by lipid-lowering medication use in the relationship between LDL-c and subsequent development of depressive symptoms.

Figure 1. Cohort Selection[a]



[a]Our sample of 24,216 participants was selected from the broader Women's Health Initiative cohort, with serum cholesterol and depressive symptoms assessed at baseline. The 20,942 participants who were not depressed at baseline were utilized for survival analysis.

METHOD

Study Sample

The WHI originally ran from 1993 to 2005 and has since incorporated 2 extension studies, with the most recent culminating in 2015. The study consisted of 3 concurrent clinical trials and an observational study,[14] including a total of 161,808 postmenopausal women between the ages of 50 and 79 years at baseline. Participants were enrolled into the WHI between 1993 and 1998 over the course of 3 screening visits.[14] A number of WHI ancillary studies included biomarkers; of these, serum lipid data were collected as a component of both the SNP Health Association Resource (SHARe) cardiovascular disease biomarkers study[15,16] and the European American Hormone Trial (EA HT) biomarkers study (accession number: phs00675.v2.p3; available at: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000675.v2.p3). The SHARe study included 12,007 African American and Latina members of the WHI study cohort. The EA HT biomarkers study consisted of 5,060 participants from the Genome-wide Association Studies of Treatment in Randomized Clinical Trials (GARNET) study (accession number: phs00315.v6.p3; available at: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000315.v6.p3) and 7,479 members of the WHI Memory Study.[17] In addition, serum lipids were collected for a randomly selected subset of 8.6% of hormone trial participants and 4.3% of dietary modification participants, oversampled for racial and ethnic minorities.[17] Our study was conducted using a 24,216-participant subset of the WHI for whom both depressive symptom and serum lipid data were available; participant selection is described in greater detail in Figure 1. To account for sampling differences between studies, all multivariable analyses were adjusted for race/ethnicity, age, region, and WHI treatment assignment.

Clinical Points

- Cross-sectional studies suggest that low-density lipoprotein cholesterol (LDL-c) may play a role in depression pathophysiology; however, the directionality of this relationship is unclear.
- An LDL-c level < 100 mg/dL is associated with incident depressive symptoms in postmenopausal women and may represent a biomarker warranting further investigation.
- No association among users of lipid-lowering medication suggests clinicians should not underutilize lipid-lowering agents in those with or at risk of depression.

Cholesterol Fractions

Fasting blood samples were originally collected as a part of WHI screening and enrollment and centrifuged, then serum and plasma were frozen at −70°C; serum total cholesterol, HDL-c, and triglyceride values were subsequently obtained via direct assay, and LDL-c values were derived using the Friedewald formula (total cholesterol-HDL cholesterol-triglyceride/5).[18,19] Low-density lipoprotein cholesterol values could not be calculated for 470 participants (1.9%) and were omitted from analysis. Cholesterol fractions were measured for all included participants at baseline and among a 10%–15% subsample at years 1, 3, and 6.

Depressive Symptoms

All participants included in this study had baseline depressive symptom data available. One-year follow-up data were collected for 16,636 participants, and for some follow-up data extended to the 19th study year. Baseline depressive symptoms were assessed at the second screening visit, a mean of 21 days after baseline lipid assessment. Depressive symptoms were assessed via the 8-item shortened, combined Center for Epidemiologic Studies-Depression/Diagnostic Interview Schedule, developed by Burnam et al[20] in 1988 using participants from the Los Angeles Epidemiologic Catchment Area Study and the Psychiatric Screening Questionnaires for Primary Care Patients study for use in the National Study of Medical Care Outcomes. The algorithm used by Burnam et al[20] multiplies each of the 8 items by a coefficient based on predictive ability and then rescales the point scores to a score between 0 and 1, with higher scores representing greater symptom severity. This study uses a score of 0.06 as the cut point for presence of depressive symptoms, as established by Burnam et al[20] and used in previous WHI analyses.[21–24] This scale has been used in a variety of studies, sometimes under other names, including the Brief Screening Instrument, the Medical Outcomes Study Depression Screen, the 8-item Rand Screening Instrument, and the Rand Short Depression Screener.[25–33] In published studies of the WHI cohort, it has been referenced as the Burnam 8-item scale for depressive disorders[21,22,24] or, more simply, the Burnam score.

As a sensitivity analysis, we subsequently expanded our event definition to include antidepressant use (defined as use

of tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, benzodiazepines, or other antidepressants), suicide, or Burnam score greater than 0.06 as an event. Antidepressant use was not considered in our primary definition because of the potential for antidepressant medications to be prescribed off-label for the treatment of vasomotor symptoms following menopause[34–36] and because antidepressant use may modulate lipid fractions.[37,38]

Selected Covariates

To account for the effects of confounding, the covariates selected for inclusion are those that have been previously determined or are otherwise likely to be associated with depressive symptomatology or serum cholesterol levels: WHI treatment assignment, age, education, race/ethnicity, marital status, family income, health insurance, body mass index (BMI), blood pressure, heart disease, stroke, peripheral artery disease, smoking status, alcohol intake, leisure-time physical activity, diabetes, cancer, colitis, thyroid disease, and cholesterol-lowering medications. Covariates were assessed via questionnaire response or clinical measurement.[14] Diabetes was identified via self-report of diabetes diagnosis or treatment.[39] Coronary heart disease includes the adjudicated report of myocardial infarction, coronary artery disease, bypass or angioplasty, or angina. Body mass index was categorized based on the World Health Organization (WHO) clinical cut points of underweight (BMI < 18.5), normal (BMI, 18.5–24.9), overweight (BMI, 25.0–29.9), obesity I (BMI, 30.0–34.9), obesity II (BMI, 35.0–39.9), and obesity III (BMI ≥ 40.0),[40] and systolic and diastolic blood pressure were categorized based on clinical hypertension guidelines.[41] Leisure-time physical activity was derived via questionnaire response and converted into metabolic equivalent hours per week (MET-h/wk) based on established criteria.[42] Alcohol consumption was categorized based on national guidelines for women (none, 0 servings per week; moderate, 1–7 servings per week; heavy, > 7 servings per week).[43] Lipid-lowering medication use was defined as reported use of at least 1 of the following medications during the study period: antihyperlipidemics, 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors (statins), nicotinic acid derivatives, intestinal cholesterol absorption inhibitors, fibric acid derivatives, or bile sequestrants.

Statistical Analysis

All analyses were conducted using SAS 9.3 (SAS Inc). Scatterplots and regression diagnostics were used to assess distribution of the data. Study participants were contrasted across selected covariates by presence or absence of depressive symptoms using χ^2 analysis (Table 1). To most accurately characterize the nature of the relationship between serum cholesterol and depressive symptoms, several models were examined. In primary analysis, each cholesterol measure was evaluated using cholesterol quintiles derived based on study data, with the highest quintile designated as the reference category. We primarily assessed the associations between depressive symptoms and LDL-c, and secondarily assessed HDL-c, total cholesterol, and triglycerides.

Cross-sectional analysis. We used logistic regression to evaluate the cross-sectional relationships between baseline serum cholesterol quintiles and prevalent depressive symptoms, using the highest quintile as the reference value. To explore the potential for dose-response, models were reevaluated modeling serum lipids as continuous variables. For each serum lipid measure, a preliminary bivariate analysis was conducted, followed by more extensive covariate adjustment to allow for assessment of the impact of additional covariates on the relationship between depressive symptoms and cholesterol. Models were adjusted for age, WHI trial arm, ethnicity, US region, marital status, income, education, insurance coverage, heart disease, stroke, peripheral artery disease, diabetes, cancer, thyroid disease, colitis, cholesterol-lowering medications, systolic blood pressure, diastolic blood pressure, BMI, smoking status, alcohol consumption, and physical activity level.

Survival analysis. Time to onset of depressive symptoms was assessed using semiparametric survival models. Extended Cox regression analyses were modeled using the SAS PROC PHREG function. These models assumed proportional hazards, and this assumption was tested by statistical evaluation of time dependence and by graphical analysis. Including only participants for whom depressive symptoms were not present at baseline (n = 20,942), we evaluated the potential for differences in event timing due to the effects of serum lipid fractions. For the purpose of this analysis, onset of depressive symptoms was considered to be a nonrepeatable event, and participants who did not have an event were censored 5 years after the last lipid assessment, up to year 11 of follow-up.

Serum lipid fractions were modeled as time-varying effects, for which missing values were assumed to be unchanged from the most recent previous measurement. In primary analysis, the final serum lipid measurement was carried forward as a fixed effect for an additional 5 years, creating a total follow-up time of up to 11 years (mean ± SD = 4.87 ± 3.07). A sensitivity analysis was next conducted to challenge the assumption that the final serum lipid measurement may be relevant for as long as 5 years; the exposure window was shortened to only 1 additional year of follow-up after the final lipid measurement, creating a total follow-up period of up to 7 years (mean ± SD = 3.89 ± 2.34).

Because of their potential to fluctuate over time, BMI, blood pressure, and cholesterol-lowering medication use were modeled as time-varying effects. Baseline values for the remaining covariates—WHI treatment assignment, age, education, ethnicity, marital status, family income, health insurance, heart disease, stroke, peripheral artery disease, thyroid disease, colitis, smoking status, alcohol intake, physical activity, diabetes, and cancer—were also included in the adjusted model.

Use of a lipid-lowering medication was selected as the sole a priori effect moderator and was assessed through

Table 1. Baseline Participant Characteristics by Depressive Symptoms

Variable	No. Missing	Depressive Symptoms: Yes (n = 2,804) %	Depressive Symptoms: No (n = 20,942) %	*P* Value[a]
Age, y	0			**<.001**
50–59		42.4	29.8	
60–69		40.6	45.2	
70–79		17.0	24.9	
Region	0			**<.001**
Northeast		21.3	20.7	
South		36.7	32.3	
Midwest		18.1	22.4	
West		23.9	24.6	
Race/ethnicity	0			**<.001**
American Indian		0.7	0.4	
Asian		1.0	1.7	
African American		38.8	34.3	
Latina		22.5	13.4	
White		36.6	49.7	
Other		0.4	0.4	
HRT participant	0			**<.001**
Yes		49.2	55.7	
No		50.8	44.3	
Dietary modification participant	0			.33
Yes		34.6	35.5	
No		65.4	64.5	
Calcium/vitamin D participant	0			**<.001**
Yes		36.9	42.2	
No		63.1	57.8	
Observational study participant	0			**<.001**
Yes		31.1	24.6	
No		68.9	75.4	
Diastolic blood pressure, mm Hg	6			.31
< 90		90.8	91.3	
≥ 90		9.2	8.7	
Systolic blood pressure, mm Hg	0			**.0006**
≤ 120		35.6	32.2	
120–140		41.8	42.8	
> 140		22.6	25.0	
Lipid-lowering medication	94			**.027**
Yes		2.5	3.3	
No		97.5	96.7	
Antidepressant medication	94			**<.001**
Yes		4.9	1.4	
No		95.1	98.6	
Coronary heart disease	0			.60
Yes		7.3	7.0	
No		92.7	93.0	
Stroke	0			.61
Yes		5.3	5.5	
No		94.7	94.5	
Peripheral artery disease	0			**.0055**
Yes		1.8	1.2	
No		98.2	98.8	
Diabetes ever	19			**<.001**
Yes		12.4	8.9	
No		87.6	91.1	
Cancer ever	203			**<.001**
Yes		8.3	5.2	
No		91.7	94.8	
Thyroid disease ever	0			.15
Yes		21.0	19.8	
No		79.0	80.2	
Colitis ever	0			**.032**
Yes		1.4	1.0	
No		98.6	99.0	
Body mass index	178			**<.001**
< 18.5 (underweight)		0.6	0.5	
18.5–24.9 (normal)		19.6	24.5	
25.0–29.9 (overweight)		31.6	35.3	
30.0–34.9 (obesity I)		26.5	23.4	
35.0–39.9 (obesity II)		13.2	10.6	
≥ 40.0 (obesity III)		8.5	5.7	
Alcohol servings per week	76			**<.001**
None		56.8	51.2	
≤ 7		36.9	39.9	
> 7		6.3	8.9	
Leisure-time physical activity, MET h/wk	1,048			**<.001**
< 7.5		19.2	26.8	
7.5–15		18.7	20.7	
≥ 15		62.1	52.5	
Smoking	315			**<.001**
Never smoked		45.6	52.9	
Past smoker		38.8	38.8	
Current smoker		15.6	8.3	
Any health insurance	352			**<.001**
Yes		85.0	93.8	
No		15.0	6.2	
Income	795			**<.001**
< $20,000		38.0	22.4	
$20,000–$49,999		39.0	46.2	
≥ $50,000		18.3	28.8	
Don't know		4.7	2.6	
Education	184			**<.001**
No high school diploma		16.9	8.1	
High school diploma or some college		60.0	57.2	
Bachelor's degree or higher		23.1	34.7	
Marital status	145			**<.001**
Never married		4.5	4.4	
Divorced		26.6	19.4	
Widowed		23.4	21.1	
Married		44.0	53.6	
Marriage-like		1.5	1.5	

(continued)

[a]*P* values in bold are statistically significant at the .05 level.
Abbreviations: HRT = hormone replacement therapy, MET = metabolic equivalent.

inclusion of an interaction term. Significant findings were pursued with survival analysis stratified by lipid-lowering medication use. To account for potential differences between lipid-lowering medication types and given the current relevance of statins as a first-line treatment,[44] a sensitivity analysis was next conducted in which the definition of lipid-lowering medication use was restricted to include statin users only.

RESULTS

Cross-Sectional Analyses

Participants with depressive symptoms at baseline (2,804 [11.8%]) were more likely to be younger than 60 years, be African American or Latina, reside in the southern United States, earn less than $20,000 per year, report more leisure-time physical activity, or have peripheral artery disease, a

Table 2. Cross-Sectional Analysis of Depressive Symptoms by Cholesterol Quintiles

	Unadjusted			Multivariable-Adjusted[a]		
Variable	Odds Ratio	95% CI	*P* Value[b]	Odds Ratio	95% CI	*P* Value
LDL cholesterol, mg/dL			.23[c]			.39[c]
≥175	Reference			Reference		
153–174	0.92	0.82–1.05	.21	0.97	0.85–1.12	.70
134–152	0.90	0.79–1.01	.083	0.90	0.79–1.04	.14
114–133	0.89	0.79–1.01	.064	0.89	0.78–1.03	.11
<114	0.98	0.87–1.11	.78	0.97	0.85–1.12	.69
HDL cholesterol, mg/dL			**<.0001**[c]			.95[c]
≥66	Reference			Reference		
56–65	1.13	1.00–1.28	.05	1.05	0.91–1.20	.52
50–55	1.18	1.04–1.35	**.012**	1.01	0.88–1.18	.85
43–49	1.21	1.07–1.38	**.0026**	1.01	0.87–1.16	.94
<43	1.43	1.26–1.62	**<.0001**	1.04	0.90–1.21	.60
Total cholesterol, mg/dL			.063[c]			.38[c]
≥260	Reference			Reference		
236–259	0.95	0.84–1.08	.46	0.98	0.85–1.12	.73
216–235	0.88	0.77–0.99	**.04**	0.89	0.77–1.02	.09
195–215	0.95	0.84–1.08	.42	0.92	0.80–1.06	.24
<195	1.05	0.93–1.19	.43	0.99	0.86–1.13	.83
Triglycerides, mg/dL			**.0022**[c]			.08[c]
≥185	Reference			Reference		
136–184	1.00	0.89–1.13	.96	1.07	0.93–1.22	.35
106–135	0.95	0.84–1.07	.38	1.04	0.91–1.20	.56
80–105	0.81	0.72–0.92	**.0014**	0.88	0.76–1.02	.09
<80	0.86	0.76–0.98	**.022**	0.98	0.84–1.14	.78

[a]Adjusted for age, trial arm of Women's Health Initiative, ethnicity, US region, marital status, income, education, insurance coverage, heart disease, stroke, peripheral artery disease, diabetes, cancer, thyroid disease, colitis, cholesterol-lowering medications, systolic blood pressure, diastolic blood pressure, body mass index, smoking status, alcohol consumption, and leisure-time physical activity.
[b]*P* values in bold are statistically significant at the .05 level.
[c]Linear trend across quintiles.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

history of cancer, BMI greater than 30, a history of colitis, or systolic blood pressure below 120 mm Hg. They were also less likely to be married, use lipid-lowering medications, drink alcohol, or have health insurance or a college degree (Table 1). In cross-sectional analysis, there was no association between baseline LDL-c quintiles and depressive symptoms in unadjusted or multivariable-adjusted analyses. Other lipid fractions demonstrated significant differences across quintiles in unadjusted analyses, but this appears to be largely accounted for by confounding, as no such association remained following multivariable adjustment (Table 2). In analysis of serum lipids modeled as continuous variables, LDL-c, HDL-c, total cholesterol, and triglycerides demonstrated no linear, quadratic, or cubic relationship to depressive symptoms.

Survival Analyses

A total of 1,504 depressive events were observed during follow-up in those who were free of depression at baseline. In an unadjusted analysis, participants in the lowest quintile of LDL-c at baseline, corresponding to serum LDL-c levels below 114 mg/dL, had a higher risk of subsequent development of depressive symptoms relative to those in the highest quintile (LDL-c ≥ 175 mg/dL) (hazard ratio [HR] = 1.25, 95% CI = 1.07–1.47, *P* = .006) (Table 3); these findings persisted after covariate adjustment (HR = 1.25, 95% CI = 1.05–1.49, *P* = .01). Similar multivariable findings were observed after expanding the event definition to include onset of at least 1 of the following: Burnam score greater than 0.06, antidepressant use, or suicide (2,054 events) (HR = 1.40, 95% CI = 1.21–1.63, *P* < .0001), as well as when analyses were conducted using the shortened follow-up period of 7 years (1,463 events) (HR = 1.26, 95% CI = 1.05–1.50, *P* = .01) (Table 4). To examine for a potential threshold effect, the lowest LDL-c quintile was recategorized into 2 deciles (< 100 mg/dL and 100–114 mg/dL, respectively) and, for comparison, evaluated using the highest quintile (≥ 175 mg/dL) again as the reference category. In multivariable-adjusted analysis, the effect of LDL-c persisted in the lowest decile (HR = 1.33, 95% CI = 1.09–1.63, *P* = .006) but was not significant in the next lowest decile (HR = 1.16, 95% CI = 0.94–1.44, *P* = .18).

There was suggestion of a significant interaction between the lowest quintile of serum LDL-c (< 114 mg/dL) and use of lipid-lowering medication on outcome ($\chi^2 = 4.32$, *P* = .04). In subsequent stratified analysis, the association between low LDL-c and development of depressive symptoms in the lowest LDL-c quintile relative to the highest quintile was confined solely to the nonmedicated group (HR = 1.23, 95% CI = 1.03–1.47, *P* = .02), with no such association observed among those who reported lipid-lowering medication use (HR = 0.65, 95% CI = 0.18–2.29, *P* = .50). Further, this association was found to be restricted to the lowest decile of LDL-c (< 100 mg/dL) in those reporting no lipid-lowering medication use (HR = 1.32, 95% CI = 1.07–1.62, *P* = .009), with no association seen among those reporting lipid-lowering medication use (HR = 0.28, 95% CI = 0.25–3.86, *P* = .27). These effects persisted after narrowing the definition of lipid-lowering medication use to include only statin users.

In analysis of HDL-c using 11 years of follow-up data, low HDL-c was associated with a lower risk of developing depressive symptoms during the follow-up period for the 2 lowest quintiles relative to the highest quintile (≥ 66 mg/dL) (HDL-c < 43 mg/dL: HR = 0.81, 95% CI = 0.67–0.98, *P* = .03; HDL-c, 43–50 mg/dL: HR = 0.82, 95% CI = 0.69–0.98, *P* = .02) only after multivariate adjustment. Findings remained significant after secondarily expanding the event definition to include depressive symptoms, antidepressant use, or suicide (HDL-c < 43 mg/dL: HR = 0.73, 95% CI = 0.62–0.86, *P* = .0002; HDL-c, 43–50 mg/dL: HR = 0.76, 95% CI = 0.65–0.88, *P* = .0004). Similar relationships were also observed in the sensitivity analysis (7-year follow-up) with significant findings in the lowest HDL-c quintile (< 43 mg/dL) (HR = 0.81, 95% CI = 0.67–0.98, *P* = .03) and marginally significant findings in the next lowest quintile

Table 3. Hazard Analysis for 11-Year Follow-Up

	Unadjusted			Multivariable-Adjusted[a]		
Variable	Hazard Ratio	95% CI	*P* Value[b]	Hazard Ratio	95% CI	*P* Value[b]
LDL cholesterol, mg/dL						
≥175	Reference			Reference		
153–174	1.10	0.93–1.30	.27	1.20	1.00–1.43	.055
134–152	1.06	0.90–1.25	.50	1.16	0.97–1.39	.11
114–133	1.06	0.90–1.25	.49	1.09	0.90–1.30	.40
<114	1.25	1.07–1.47	**.0055**	1.25	1.05–1.49	**.014**
HDL cholesterol, mg/dL						
≥66	Reference			Reference		
56–66	1.04	0.89–1.21	.63	1.00	0.85–1.18	.99
50–56	1.04	0.89–1.22	.61	0.92	0.78–1.10	.38
43–50	1.00	0.85–1.16	.95	0.82	0.69–0.98	**.03**
<43	1.09	0.92–1.28	.31	0.81	0.67–0.98	**.029**
Total cholesterol, mg/dL						
≥260	Reference			Reference		
236–259	0.99	0.84–1.18	.94	1.09	0.91–1.31	.33
216–235	1.10	0.94–1.30	.23	1.17	0.98–1.40	.08
195–215	1.05	0.89–1.24	.58	1.07	0.89–1.28	.48
<195	1.15	0.98–1.36	.08	1.11	0.93–1.33	.23
Triglycerides, mg/dL						
≥185	Reference			Reference		
136–184	0.93	0.80–1.09	.39	0.957	0.81–1.13	.61
106–135	0.91	0.78–1.07	.25	1.004	0.85–1.19	.97
80–105	0.92	0.78–1.07	.28	1.041	0.87–1.24	.65
<80	0.80	0.68–0.95	**.0089**	0.962	0.79–1.17	.69

[a]Adjusted for trial arm of Women's Health Initiative, body mass index, lipid-lowering medication, blood pressure, smoking status, coronary heart disease, stroke, peripheral artery disease, age, US region, ethnicity, marital status, health insurance, alcohol consumption, leisure-time physical activity, cancer, income, education, diabetes, thyroid disease, and colitis.
[b]*P* values in bold are statistically significant at the .05 level.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 4. Hazard Analysis for 7-Year Follow-Up

	Unadjusted			Multivariable-Adjusted[a]		
Variable	Hazard Ratio	95% CI	*P* Value[b]	Hazard Ratio	95% CI	*P* Value[b]
LDL cholesterol, mg/dL						
≥175	Reference			Reference		
153–174	1.11	0.91–1.31	.25	1.19	0.99–1.43	.06
134–152	1.08	0.91–1.27	.43	1.17	0.97–1.40	.09
114–133	1.07	0.91–1.27	.42	1.10	0.91–1.32	.32
<114	1.27	1.08–1.49	**.0039**	1.26	1.05–1.50	**.012**
HDL cholesterol, mg/dL						
≥66	Reference			Reference		
56–66	1.04	0.90–1.21	.60	1.02	0.86–1.20	.86
50–56	1.04	0.88–1.22	.64	0.93	0.78–1.11	.44
43–50	1.00	0.85–1.17	.98	0.83	0.70–1.00	.05
<43	1.09	0.93–1.29	.30	0.81	0.67–0.98	**.034**
Total cholesterol, mg/dL						
≥260	Reference			Reference		
236–259	1.03	0.87–1.22	.74	1.13	0.94–1.35	.21
216–235	1.12	0.95–1.32	.17	1.20	1.00–1.44	.05
195–215	1.06	0.89–1.25	.52	1.09	0.91–1.31	.37
<195	1.18	1.00–1.39	.05	1.14	0.95–1.36	.17
Triglycerides, mg/dL						
≥185	Reference			Reference		
136–184	0.94	0.80–1.10	.44	0.97	0.81–1.15	.70
106–135	0.91	0.78–1.07	.27	1.01	0.85–1.20	.95
80–105	0.93	0.79–1.09	.37	1.05	0.88–1.26	.56
<80	0.81	0.69–0.96	**.014**	0.97	0.80–1.17	.74

[a]Adjusted for trial arm of Women's Health Initiative, body mass index, lipid-lowering medication, blood pressure, smoking status, coronary heart disease, stroke, peripheral artery disease, age, US region, ethnicity, marital status, health insurance, alcohol consumption, leisure-time physical activity, cancer, income, education, diabetes, thyroid disease, and colitis.
[b]*P* values in bold are statistically significant at the .05 level.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

(HDL-c, 43–50 mg/dL), relative to the highest (HR = 0.83, 95% CI = 0.70–1.00, *P* = .05). No significant associations were demonstrated between total cholesterol or triglycerides and the onset of depressive symptoms.

DISCUSSION

We found evidence for an association between low serum LDL-c and subsequent depressive symptoms. Follow-up analyses suggest that this increased risk appears to be restricted to individuals when serum LDL-c is below 100 mg/dL. The association between low serum LDL-c and subsequent depressive symptoms appears to be moderated by lipid-lowering treatment, such that risk was not associated with treatment of dyslipidemia. There was some suggestion of a small, however nonsignificant, protective effect of lipid-lowering medication; while this effect may be due in part to healthy user bias,[45] the magnitude of the difference makes this an unlikely sole explanation for the demonstrated interaction, which is corroborated by several studies[46–50] failing to show any significant association between medically lowered serum lipids and depression.

The association between low LDL-c and subsequent depressive symptoms in the absence of lipid-lowering therapy suggests that low LDL-c, while predictive of depression risk, is not necessarily causative, and may be supportive of the presence of an unknown third factor that both causes low serum LDL-c and increases the risk of developing depression. To this end, the role of circadian dysregulation may warrant further investigation. The suprachiasmatic nuclei, located within the hypothalamus and responsible for coordinating the sleep-wake cycle to various physiological processes,[51,52] have been separately linked to both lipid metabolism[53,54] and depression[55–57]; however, the precise nature of this relationship is unclear. Additionally, animal studies suggest a link between cholesterol depletion and altered serotonin-1A receptor function, which underscores the importance of LDL due to its function in delivery of cholesterol to the cell membrane.[58,59]

Overall, these findings are consistent with those of multiple other studies that included men[8,9] and younger women,[13] suggesting that the findings from this cohort of postmenopausal women may be largely generalizable. Altogether, individuals who

have low levels of LDL-c without the use of lipid-lowering treatments may represent a subgroup at risk for depression. Given the presumed heterogeneity of major depression, this at-risk group may represent a more homogeneous risk, thus potentially proving useful for mechanistic study.

Additionally, lower levels of HDL-c were generally found to be associated with a reduced risk of developing depressive symptoms, relative to higher levels. These findings contradict those of studies demonstrating an association between low HDL-c and depression,[6,60–62] although they are consistent with those of several smaller cross-sectional studies[9,63] and a meta-analysis.[4] Because this study's findings regarding HDL-c run in contrast to the greater body of existing literature and the majority of existing studies on the association between HDL-c and depression are cross-sectional, the findings of this study underscore the need for cholesterol fractions to be addressed separately and for additional research to be conducted to further clarify the relationship between HDL-c and depression before mechanistic insight can be drawn.

Notable strengths of this study include the sample size and duration of follow-up, as well as the utilization of biomarkers to assess cholesterol levels. The study also assesses the new onset of depressive symptoms prospectively, mitigating the potential for reverse-causality—namely, the potential for depression subsequently lowering cholesterol levels. Depressive symptoms were assessed systematically but not at a high intensity during follow-up. Our time-to-event analyses are thus limited in that they can only approximate the onset of depressive symptoms, and it is possible that clinically significant depressive symptoms between assessments could have been missed. Presumably, any such incomplete ascertainment of exposure would not bias results away from the null hypothesis. Further, data on clinician diagnosis of major depressive disorder were not available as a component of WHI data collection, and the Burnam scale is not sufficient for the diagnosis of major depressive disorder, which is ideally made by a structured clinical interview. For this reason, we have referred to our outcome as depressive symptoms throughout. Baseline prevalence of depressive symptoms in this study sample was 11.8%, which is within the range of that which would be expected based on the general population prevalence of major depression.[64]

A few findings in cross-sectional analyses differ from what would be anticipated. Subjects with depression at baseline reported greater participation in leisure-time physical activity. Self-reported physical activity is commonly overreported[65] and differential overreporting is possible. Because the WHI calculation of MET-hours captures the perceived difficulty of activities, it is possible that those with depressive symptoms, who are more likely to perceive activities as strenuous, were more likely to overreport their activity. Future study with directly measured physical activity would be useful to determine if depressed participants differentially overreport when using self-reported activity measures that focus on difficulty. Participants with depressive symptoms were also less likely to use alcohol. Several recent studies have similarly failed to show a positive association between alcohol use and depression in women.[66–68]

Depression is independently associated with vascular disease[69] and vascular mortality[70,71] and may convey risk of a magnitude similar to conventional risk factors.[72] Those with depression may thus reflect a neglected at-risk group. Yet, those with psychiatric disorders such as recurrent major depression are underscreened and undertreated for dyslipidemia,[73,74] only further contributing to health disparity. Our findings suggest that there is no reason for concern that treatment of lipids may worsen depression, perhaps alleviating one factor contributing to the underscreening and undertreatment of dyslipidemia in those with depression. Similarly, our data do not support the concern that treatment-induced low LDL-c worsens the risk of depressive symptoms.

Low serum LDL-c (< 100 mg/dL) is associated with the subsequent onset of depressive symptoms in postmenopausal women. There does not appear to be any such association for low LDL-c levels in the setting of lipid-lowering medications; to this end, clinicians should not underutilize lipid-lowering agents in those with or at-risk of depression. The presence of very low LDL-c without treatment may represent a biomarker associated with depression risk and warrants further study.

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