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Serum lipid changes following the onset of depressive symptoms in postmenopausal women

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Abstract

A cross-sectional association between depression and serum low-density lipoprotein cholesterol (LDL-c) has been noted in psychiatric literature, raising the question of temporality: does low LDL-c predict depression, does depression lead to changes in LDL-c levels, or is this relationship bidirectional? In a previous longitudinal analysis of postmenopausal women ages 50–79 who participated in the Women's Health Initiative (WHI), we detected an association between low LDL-c and the subsequent onset of depressive symptoms (HR=1.25, 95% CI 1.05–1.49, $p=0.01$). This current study uses the WHI cohort to explore the question of temporality in the opposite direction, examining the influence of depressive symptoms on subsequent changes in LDL-c levels. This study provides no evidence to suggest an association between depression and subsequent changes in LDL-c level (-2.78 mg/dL, 95% CI -7.49 to 1.92 , $p=0.25$), nor was any association detected for total cholesterol, HDL, or triglyceride changes over time. Further, this study demonstrates that the relationship between depression and serum LDL changes is not mediated by changes in weight, exercise, or energy intake.

1 Introduction

A cross-sectional association between low serum low density lipoprotein cholesterol (LDL-c) and depression has been noted across psychiatric literature (Khalid et al., 1998; Aijanseppa et al., 2002; Igna et al., 2008; Ancelin et al., 2010; Bove et al., 2010; Lehto et al., 2010; Fang et al., 2013; Kale et al., 2014; Patra et al., 2014); however, cross-sectional studies are limited in that they are unable to demonstrate temporality, a critical step in determining if a causal relationship exists. To this end, the directionality of the relationship between LDL-c and depression has been underexplored and remains as of yet unclear. In a

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previous publication, we conducted a longitudinal analysis of this association in one direction – prior LDL-c and its influence on depressive symptoms subsequently – using data from the Women’s Health Initiative (WHI) and detected an association between low LDL-c and the subsequent onset of depressive symptoms (Cox Proportional Hazards Regression, HR=1.25, 95% CI 1.05–1.49, $p=0.01$) (Persons et al., 2016). This finding suggests that low LDL-c is predictive of depression, which has been supported mechanistically in recent studies. A study conducted by Freemantle et al. detected evidence of elevated cholesterol turnover and synaptic cholesterol depletion in the prefrontal cortex tissue of suicide cases (Freemantle et al., 2013). Similarly, Beasley et al. found evidence of cholesterol depletion and diminished neurotransmitter release function in postmortem visual association cortex samples of individuals with depression (Beasley et al., 2005). Together, these studies provide evidence suggesting that the mechanism guiding the relationship between low cholesterol and depression pathogenesis may involve cholesterol depletion-mediated alterations in central nerve terminal structure and function in turn altering neurotransmitter uptake and release, including serotonin, ultimately leading to depression. This evidence in support of LDL-c changes preceding the onset of depression, however, does not negate the possibility that the relationship between LDL-c and depression may be bidirectional – in other words, it may be simultaneously true that low LDL-c precedes the onset of depression and that depression leads to subsequent changes in LDL-c levels. Despite this possibility, no prospective analyses have been conducted to investigate the longitudinal association between LDL-c and depression in this opposing direction – that is, whether LDL-c levels change following the onset of depression. From cross-sectional analyses, there is reason to believe that depression may lead to subsequent changes in LDL-c. Knox et al., using 15 years of follow-up data from the CARDIA study, observed an association between depression and LDL-c, with both current depression and history of depression demonstrating an association with low LDL-c (Knox et al., 2006). The suggestion that low serum cholesterol can occur, at least in part, as a consequence of depression is further supported by the observation that weight loss is a common feature of depression, and that serum cholesterol levels tend to rise following depression treatment (Law et al., 1994).

To address this gap in the literature, the aim of this study was to determine the magnitude and direction of change in LDL-c, and secondarily in HDL-c, total cholesterol, and triglycerides, following the onset of depressive symptoms. The hypothesis is that individuals with new-onset depressive symptoms are more likely to experience subsequent decreases in LDL-c relative to individuals without depressive symptoms.

2 Methods

2.1 Study sample

This study was conducted using secondary data from the Women’s Health Initiative (WHI) clinical trials. The WHI was sponsored in 1991 by the National Heart, Lung, and Blood Institute of the NIH in conjunction with the National Cancer Institute, The National Institute of Aging, the National Institute of Arthritis and Musculoskeletal and Skin Disease, and the Office of Research on Women’s Health (Anderson et al., 2003; Karydas et al., 2006). The WHI consisted of three concurrent clinical trials and an observational study and included a

total of 161,808 postmenopausal women between the ages of 50–79 at study enrollment, which occurred between 1993 and 1998 (The Women’s Health Initiative Study Group, 1998). The WHI originally ran for 15 years, from 1993 to 2005, and has since incorporated two extension studies, with the most recent having culminated in 2015. A number of WHI ancillary studies included biomarkers; of these, serum lipid data was collected as a component of both the SNP Health Association Resource (SHARe) CVD Biomarkers study, which included 12,007 African American and Latina members of the WHI cohort (Carty et al., 2012), and the European American Hormone Trial (EA HT) Biomarkers study, which included 5060 participants from the Genome-wide Association Studies of Treatment in Randomized Clinical Trials (GARNET) study and 7479 members of the Women’s Health Initiative Memory Study (WHIMS). 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/ethnic minorities (Shumaker et al., 2004).

The participant selection process for this current study can be seen in greater detail in Fig. 1. This study was conducted using a 2538-participant subset of the Women’s Health Initiative clinical trials. In identifying the participant subset for these analyses, first the 25,306 participants for whom baseline serum lipid data were available were identified and selected from the full Women’s Health Initiative cohort (n=161,808). Participants were next excluded if they had no depressive symptom data available or if LDL-c could not be calculated via the Friedewald formula. Of the remaining 23,746-participant sample, 2804 participants with depressive symptoms present at the baseline assessment were excluded, due to the inability to distinguish between new-onset and prevalent cases. Participants reporting use of antidepressant (n=67) or lipid-lowering medications (n=965) were also excluded from analysis because both classes of medication are known for eliciting lipid changes, albeit in opposite directions. From this sample, 14,130 participants had year one depressive symptom data and of those, 2538 participants also had year three serum lipid data, creating the final cohort.

2.2 Depressive symptoms

The presence or absence of depressive symptoms was the dependent (predictor) variable of interest for these analyses. Depressive symptoms were assessed via the 8-item shortened combined Center for Epidemiologic Studies-Depression (CES-D)/Diagnostic Interview Schedule (DIS), which was developed by Burnam et al. in 1988 for use in the National Study of Medical Care Outcomes (MOS) (Burnam et al., 1988). This scale has been used across numerous studies in a wide variety of contexts and under an almost equally wide variety of names, including the Brief Screening Instrument (BSI), the Medical Outcomes Study Depression Screen (MOS-D), the 8-item Rand Screening Instrument, and the Rand Short Depression Screener (Johnson et al., 1994; Kemper et al., 1994; Mulrow et al., 1995; Watson and Kemper, 1995; Houghton et al., 1996; Duncan et al., 1997; Lynch et al., 1997; Samsa et al., 1997; Imayama et al., 2011). For the sake of clarity, this measurement tool will hereafter be referred to as the Burnam scale and the score derived thereof as the Burnam score, as has been done across other published studies of the WHI cohort (Bertone-Johnson et al., 2011; Goveas et al., 2011; Lakey et al., 2012).

The algorithm used by Burnam et al. multiplies each of the eight 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 cut-point of 0.06 as the cut-point, as initially established by Burnam et al. and utilized in several other studies of the WHI cohort (Burnam et al., 1988; Bertone-Johnson et al., 2011; Goveas et al., 2011; Lakey et al., 2012; Persons et al., 2014, 2016). A limitation of the Burnam scale is the relatively low ability to distinguish between major depressive disorder and other psychiatric disorders with depressed mood as a component, and as such refers to Burnam scores lying above the 0.06 cut-off as ‘presence of depressive symptoms’.

All included participants scored below the Burnam scale cut-off for the presence of depressive symptoms at the baseline assessment. Participants with a first report of presence of depressive symptoms at the one-year follow-up assessment were considered to be ‘depressed’, with those reporting no depressive symptoms from baseline through the end of year three were considered to be ‘non-depressed’.

2.3 Serum lipids

Change in serum LDL-c levels from baseline to year three served as the dependent (response) variable for these analyses. Fasting blood samples were originally collected during WHI screening and enrollment, centrifuged, and 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 from the Friedewald formula (total cholesterol-HDL cholesterol-triglyceride/5) (Bray et al., 2008; Rossouw et al., 2008). Serum LDL-c changes from baseline to year three were compared for ‘depressed’ relative to ‘non-depressed’ participants. Secondly, changes in total cholesterol, HDL-c, and triglycerides were also assessed.

2.4 Statistical analysis

All analyses were conducted using SAS 9.3. Descriptive analyses were conducted using Wilcoxon Rank-Sum analyses. In primary analysis, linear regression models were used to assess the association between the new onset of depressive symptoms and changes in LDL-c levels; secondarily, changes in HDL-c, total cholesterol, and triglycerides were also assessed. The criterion for statistical significance was predefined at the $\alpha=0.05$ level.

2.4.1 Power—Power analysis was conducted under the assumptions of an independent t -test and using $\alpha=0.05$ as the criterion for statistical significance. Under these assumptions, univariate analysis was at 80% power to detect an effect size of 0.25 SD.

2.4.2 Covariates—To account for sampling differences between studies, all multivariable analyses were adjusted for race, age, and WHI treatment assignment in accordance with WHI procedures.

2.5 Mediation

The relationship between depression and subsequent serum lipid changes is further complicated by the relationships between each and diet, weight, and physical activity, in

addition to those between depression and lipid levels; to this end, Igna et al. propose that depression acts on LDL-c through a direct pathway, but also exerts influence through an indirect pathway, via weight, eating habits, and other health-related behaviors such as physical activity (Igna et al., 2008).

The Baron and Kenny approach was used to test for mediation (Baron and Kenny, 1986). The Baron and Kenny approach was selected because it is a well-established approach to mediation analysis and has been used across a number of recent studies within the psychiatric literature (du Prel et al., 2014; Montemagni et al., 2014; Pagani et al., 2014; Parveen et al., 2014; Wicke et al., 2014; Yiaslas et al., 2014; du Prel and Peter, 2015; Park et al., 2015; Soltero et al., 2015; Yoshikawa et al., 2015; Barbui et al., 2016; Barth et al., 2016; Lepnurm et al., 2016; Oh and Kim, 2016). This approach tests the zero-order relationships between the independent variable (IV), depression, the dependent variable (DV), serum LDL changes, and the potential mediators (M). This approach employs the following steps:

1. Regress DV on IV
2. Regress M on IV
3. Regress DV on M
4. Regress DV and M on IV

In keeping with this approach, progression on to step 4 is contingent upon the detection of statistically significant relationships in steps 1–3; failing this, it can be reasonably concluded that mediation is not in effect, barring the presence of suppression. To test the significance of the mediation effect and to ensure that mediation was not missed due to suppression, a Sobel-Goodman test was also conducted.

2.5.1 Physical activity—As part of the WHI study protocol, physical activity was measured via self-reported questionnaire (Anderson et al., 2003). Responses were converted into a Metabolic Equivalent (MET) score and reported as a continuous measure of MET-hours per week (Ainsworth et al., 1993). The MET is a practical and well-accepted unit of measurement used to quantify energy expenditure, with one MET equivalent to an individual's resting metabolic rate: approximately 3.5 mL of oxygen per kilogram per minute (Jette et al., 1990). Physical activity data for both baseline and year three was available for 2328 participants.

2.5.2 Diet—Diet was measured as energy intake (EI) in kilocalories per day and was captured as a component of the WHI via self-administered food frequency questionnaire (Anderson et al., 2003). The food frequency questionnaire was administered to all WHI participants at the baseline enrollment visit, and to a randomly-selected 33% subset at the three-year follow-up assessment. EI data for both baseline and year three was available for 699 participants.

2.5.3 Body weight—While it has been suggested that changes in weight, eating habits, and physical activity each independently influence serum lipid changes following the onset of depression (Igna et al., 2008), there is strong evidence to suggest that weight loss itself is

the primary mediator of this relationship. A meta-analysis of 32 randomized controlled trials examining the effect of diet on serum lipid levels found calorie restriction and the resulting weight loss, independent of dietary fat intake, to be largely responsible for serum LDL decreases (Schwingshackl and Hoffmann, 2013) – an earlier meta-analysis by Dattilo and Kris-Etherton estimates this decrease in serum LDL to be approximately 0.77 mg/dL per kilogram of weight loss (Dattilo and Kris-Etherton, 1992).

Body weight was captured using total body weight (TBW) in kilograms. Anthropometric data was collected as a component of WHI by certified clinical staff – weight was measured with light clothing and no shoes, using a balance beam scale (Anderson et al., 2003). TBW data for both baseline and year three was available for 2511 participants.

3 Results

3.1 Descriptive analysis

146 participants had depressive symptoms at year one. At baseline, mean (SD) serum LDL was 133.87 mg/dL (34.83), and did not differ significantly by later depressed status at year one ($p=0.54$). Baseline mean (SD) serum total cholesterol, HDL, and triglycerides were 220.94 mg/dL (37.14), 58.9 mg/dL (15.06), and 140.78 mg/dL (64.35), respectively, and did not differ significantly by subsequent depressed status at year one. Baseline univariate analyses for all serum lipids and potential mediating variables can be seen in Table 1.

Univariate analyses of the change from baseline to year three for all serum lipids and potential mediating variables can be seen in Table 2. The overall mean (SD) change from baseline to year three for serum LDL-c was -7.92 mg/dL (28.41). The mean (SD) change was -9.31 mg/dL (29.92) among participants reporting depressive symptoms at year one and -7.84 mg/dL (28.31) among participants who reported no depressive symptoms, which did not differ significantly. The overall mean (SD) change from baseline to year three for total cholesterol, HDL-c, and triglycerides were -6.51 mg/dL (29.34), 0.43 mg/dL (9.48), and 4.95 mg/dL (51.10), respectively, and did not differ significantly by depressed status at year one.

3.2 Linear regression analysis

Linear regression analysis provides no evidence to suggest a difference in serum LDL-c changes from baseline to year three for individuals who developed depressive symptoms at year one relative to those who did not (-2.78 mg/dL, 95% CI = -7.49 to 1.92 , $p=0.25$), nor was any association detected for total cholesterol (-3.61 mg/dL, 95% CI = -8.52 to 1.29 , $p=0.15$), HDL-c (0.047 mg/dL, 95% CI = -1.51 to 1.61 , $p=0.95$), or triglyceride (-4.03 mg/dL, 95% CI = -12.60 - 4.53 , $p=0.36$) changes (Table 3).

3.3 Mediation

Although no evidence of a direct effect of depression and subsequent changes in serum LDL was detected, for completeness a Sobel test was conducted to account for the potential influence of a suppression effect between depression and serum LDL changes; the results of

this test indicate that the relationship between depression and serum LDL changes is not mediated by weight ($p=0.73$), exercise ($p=0.80$), or energy intake ($p=0.93$).

4 Discussion

This study fails to provide evidence of an association between depression and subsequent serum LDL-c changes. In secondary analysis, no association was found between depression and subsequent changes to total cholesterol, HDL-c, or triglycerides. These findings have important implications for the field of depression research in that they suggest that the association between depression and low LDL-c evidenced across numerous cross-sectional studies is not easily dismissed as merely the consequence of physiological or behavioral changes following the onset of depression. This is reinforced by previous detection of significant findings in the opposite direction in this same cohort – Persons et al., using a 24,216-participant subset of the Women's Health Initiative, determined low LDL-c to be associated with an increased risk of subsequent development of depressive symptoms (Persons et al., 2016).

Strengths of this study include the large sample size and the utilization of biomarkers to assess cholesterol levels. Participants reporting depressive symptoms at baseline were excluded from analyses and the new onset of depressive symptoms was identified prospectively, reducing the potential for reverse-causality.

4.1 Limitations

Despite notable strengths, this study is limited in its ability to measure depression. Depressive symptoms were assessed systematically but not at a high frequency over follow-up. Further, the Burnam scale is not sufficient for the diagnosis of major depressive disorder, which is ideally made by a structured clinical interview. Given the timing of assessments, there is a possibility that serum lipid values changed between baseline and the time of onset of depression symptoms, such that examination of baseline-to-year-three changes may not precisely reflect post-depression changes. This study was conducted using only postmenopausal women and as such the findings may not necessarily apply to men or younger individuals, although the WHI's oversampling for racial minorities does increase its generalizability to postmenopausal women of all races.

4.2 Conclusions

Overall, this study suggests that low serum LDL-c occurring subsequent to the onset of depression due to behavioral or physiological changes does not explain the cross-sectional association between depression and low serum LDL-c noted in previous studies.

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Highlights

- Cross-sectional studies show that low LDL-c is associated with depression, but cannot address temporality.
- This study shows no association between depression and subsequent LDL-c changes.
- Low LDL-c in depression does not appear to be a consequence of changes following the onset of depression.

Fig. 1.
Cohort selection.

Table 1

Baseline participant characteristics by new-onset depression status.

	Total	Depressed at year 1		Non-depressed		p-Value
		Mean (SD)				
Serum Lipids (mg/dL)	<i>n</i> =	2538	146	2392		
LDL		133.87 (34.83)	132.23 (35.65)	133.97 (34.79)		0.54
HDL		58.90 (15.06)	60.01 (16.88)	58.84 (14.94)		0.49
Total cholesterol		220.94 (37.14)	220.39 (37.54)	220.98 (37.12)		0.88
Triglycerides		140.78 (64.35)	140.58 (68.23)	140.80 (64.12)		0.65
Physical Activity (MET-hr/wk)	<i>n</i> =	2328	138	2190		
Leisure-time physical activity		10.39 (12.84)	7.73 (11.87)	10.56 (12.88)		0.001
Weight (kg)	<i>n</i> =	2536	146	2390		
Total body weight		76.17 (17.14)	75.51 (18.69)	76.21 (17.05)		0.27
Energy Intake	<i>n</i> =	2532	146	2386		
Kilocalories/day		1693.67 (749.23)	1747.57 (746.03)	1690.38 (749.45)		0.30

Table 2

Magnitude and direction of change from baseline to year three by new-onset depression status.

	Total	Depressed at year 1	Non-depressed	p-Value
	mean (SD)			
	2538	146	2392	
Serum Lipids (mg/dL)	n=			
LDL	7.92 (28.41)	9.31 (29.92)	7.84 (28.31)	0.692
HDL	0.43 (9.48)	0.12 (10.27)	0.45 (9.43)	0.774
Total cholesterol	6.51 (29.34)	9.07 (30.39)	6.36 (29.28)	0.538
Triglycerides	4.95 (51.10)	0.96 (54.34)	5.19 (50.90)	0.567
Physical Activity (MET-hr/wk)	2289	135	2157	
Leisure-time physical activity	1.03 (11.88)	1.30 (11.74)	1.01 (11.89)	0.960
Weight (kg)	2511	144	2367	
Total body weight	0.04 (9.47)	0.23 (16.77)	0.06 (8.84)	0.132
Energy Intake	700	39	661	
Kilocalories/day	225.12 (617.07)	235.29 (509.99)	224.52 (623.14)	0.950

Table 3

Linear Regression of Serum Lipid Changes from Baseline to Year Three by New-onset Depression Status at Year One (depressed/not depressed
n=146/2392).

	β	95% Lower CI	95% Upper CI	SE	p-Value
LDL-c (mg/dL) ^a	2.78	7.49	1.92	2.40	0.25
HDL-c (mg/dL) ^a	0.047	1.51	1.61	0.80	0.95
Total cholesterol (mg/dL) ^a	3.61	8.52	1.29	2.50	0.15
Triglycerides (mg/dL) ^a	4.03	12.60	4.53	4.37	0.36

^a Adjusted for age, race, and WHI clinical trial.