Cholesterol and depressive symptoms in older men across time

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Abstract
This study aimed to examine reciprocal relations between cholesterol and depression. We assessed cholesterol and depressive symptoms twice over a 3-year interval, using 842 men from the Veterans Affairs Normative Aging Study (M = 64, standard deviation = 8). Because depressive symptoms were skewed, we used zero-inflated Poisson analyses. Cross-lagged models showed that cholesterol levels at T1 predicted the existence of depressive symptoms at T2, covarying T1 depressive symptoms, age, smoking status, body mass index, and medications. Depressive symptoms at T1 did not predict cholesterol at T2. Low cholesterol levels may be risk factors for development of depressive symptoms in late life.

Keywords
aging, cholesterol, cross-lagged models, depressive symptoms, older men

Introduction
Cholesterol levels continue to be a major public health problem in the United States (National Cholesterol Education Program (NCEP), 2002). Stress and psychological symptoms are thought to increase cholesterol levels, although there are conflicting findings (Giltay et al., 2009; Nakao and Yano, 2004; Shin et al., 2008). There are also concerns about the effect of lowering cholesterol on depressive symptoms (NCEP, 2002). Most studies that have examined the relationship between cholesterol and depressive symptoms were cross-sectional and could not examine reciprocal relationships. Our goal is to examine this possible cross-lagged effect, or reciprocal relationship, between cholesterol and depressive symptoms using longitudinal data.

Research about the relationship between cholesterol and depressive symptoms have had varied results. Some studies found that total cholesterol (TC) was inversely related to depressive symptoms (Giltay et al., 2009; Shin et al., 2008) while others have found a positive association between depressive symptoms and cholesterol (Nakao and Yano, 2004). Furthermore, some studies have indicated no significant relationship between TC and depressive symptoms (Van Reedt Dortland et al., 2013).

These contradictory findings may be the result of differences in study designs, such as who was sampled and when measurements were taken. Most studies were cross-sectional, with notable exceptions (e.g. Van Reedt Dortland et al., 2013) and involved populations with high levels of depressive symptoms. To the best of our knowledge, no study has used longitudinal data to examine the reciprocal relationship between depressive symptoms and cholesterol levels among the general population. It is possible that there is a bidirectional relationship between cholesterol and depressive symptoms.

Present study
This longitudinal study examined the bidirectional relationship between TC and depressive symptoms over two
occasions. Using longitudinal data collected over a 3-year interval, we examined whether TC level predicted depressive symptoms, or if depressive symptoms predicted cholesterol levels. We also examined whether the cross-lagged relationships were positive or negative (inverse) when controlling for demographic characteristics, health behaviors, and medication use, which have been strongly related to both depressive symptoms (Risch et al., 2009) and cholesterol (Niaura et al., 1992). Given the relationships among stress, cholesterol, and depressive symptoms (Shin et al., 2008), we ran two models, with and without stressful life events (SLE), to explore whether stress might alter the relationships found in the model.

**Method**

**Sample**

The Veterans Affairs (VA) Normative Aging Study (NAS) is a longitudinal study of normal aging that originally enrolled 2280 men in the 1960s. NAS participants were screened for good health and social ties to the Boston area. The sample consists primarily of non-Hispanic White men who were roughly split across blue- and white-collar occupations, and it reflects the demographic composition of Boston at that time (Spiro III and Bossé, 2001). We selected 1029 men who had their cholesterol measured between 1989 and 1991 (Time 1). Of these, 824 (80%) had a repeated cholesterol measurement approximately 3 years later (1992–1994, Time 2); these comprise the final sample. The mean age of the sample at Time 1 was 63.89 (standard deviation (SD) = 7.52, range = 43–90). Compared to the 202 men who had their cholesterol measured between 1989 and 1991 (Time 1), t(1027) = 5.65, p < .001, but were not different in TC, t(1027) = 0.36, p = .72, or the number of depressive symptoms at Time 1, t(624) = 1.04, p = .30.

**Procedure**

Since 1984, men reported every 3 years for a biomedlical examination; psychosocial variables, including depressive symptoms, were collected around the time of the examination beginning in 1987. The triennial medical exams included a fasting blood draw. Beginning in 1987, participants received the Health and Social Behavior (HSB) survey (Aldwin et al., 2011) by mail a month prior to their medical exam, and were asked to return it on the day of the exam. The HSB included measures of depressive symptoms and SLE. The response rates for the HSB were typically over 95 percent (Aldwin et al., 2011).

**Measures**

**Total cholesterol.** TC was obtained from a morning fasting blood sample. The means were 224.05 (SD = 36.28) and 227.42 (SD = 36.87) at T1 and T2, respectively. TC was used rather than lipid fractions because TC provides the best opportunity to assess the relationship between serum lipids and depression (Shin et al., 2008).

**Depressive symptoms.** The HSB included the Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983), which includes a six-item depression subscale. Each item is rated on a 5-point scale, indicating how often they felt that way in the past month, ranging from 0 (“not at all”) to 4 (“extremely”). The six items included “Thoughts of ending your life,” “Feeling blue,” and “Feelings of worthlessness.” Cronbach’s alpha for the sample was 0.85. The BSI depression subscale was highly correlated with the CES-D (Center for Epidemiologic Studies Depression Scale), r = .78, p < .001, in a community sample of 316 men and women, 50 years and older (Levinsohn et al., 1991). On both occasions, all six items were highly skewed (range = 2.19–6.73). Consequently, we used a simple count of depressive symptoms (range = 0–6), which yielded a zero-inflated Poisson (ZIP) distribution, particularly because 67 percent of the men reported no depressive symptoms at T1.

**Covariates.** Controlling for variables possibly related to TC and depressive symptoms, we initially added age, education, body mass index (BMI), smoking status, use of medication for treating cholesterol, and number of SLE at both T1 and T2. Education was assessed at baseline (0 = high school or less; 1 = college or beyond). A total of 66 percent of the sample had at least college education level. BMIs at T1 (M = 27.14, SD = 3.61) and T2 (M = 27.49, SD = 3.77) were measured at each medical examination. Self-reported smoking status (0 = no; 1 = yes) and medication use were also measured at the medical examinations. Only 9 and 8 percent of the sample were smokers at T1 and T2, respectively. Medication use was treated as a dummy with 1 for those who took at least one of the three medications, that is, beta-blocker, steroids, and statin. In both T1 and T2, approximately 20 percent of the sample used any of the medications. In addition, number of SLE was added to the model because meta-analyses have found a moderate to strong association between the total number of negative life events and greater risk of depression (Risch et al., 2009). To measure SLE, we used the Elders Life Stress Inventory (ELSI; Aldwin, 1990). The ELSI is a 30-item measure that assesses the occurrence of life events that more typically happen with middle-aged and older adults, such as institutionalization of a parent or spouse, or retirement, which occurred within the last 12 months. For this study, the ELSI was scored omitting two items related to worsening health because the analyses concerned health outcomes. Scores reflect a total sum of 28 items. On average, the study sample reported 1.55 and 0.88 SLE at T1 and T2, respectively. Among these variables, in the final model, we only included variables that were significant (see Figure 1).
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Because depressive symptoms had ZIP distributions, two coefficients were generated. The first coefficient is based on a logistic model to predict a dichotomous outcome (i.e., the presence or absence of any depressive symptom). The second coefficient is from a Poisson regression predicting the number of depressive symptoms among those who have at least one symptom (Long and Freese, 2006). Mplus predicts the absence rather than the presence of depressive symptoms; consequently, for ease of interpretation we reversed the sign of the coefficient for the dichotomous outcome so that it indicates the presence of depressive symptoms at T2. It should be noted that with the ZIP models, unstandardized regression coefficients are most interpretable and therefore are most commonly used (Muthén, 2009).

We then computed another model, examining the effects of SLE, to explore whether stress affected the relationships among the variables. Because of the nonnormal relationships among the variables, we computed simple Z scores to examine the significance of the difference between the coefficients across the models.

**Results**

Cholesterol at T1 was positively correlated with cholesterol at T2, \( r = .66, p < .001 \). The number of depressive symptoms at T1 was positively correlated with the number of depressive symptoms at Time 2, \( r = .67, p < .001 \). In general, the covariates were only weakly associated with cholesterol or depressive symptoms.

The results of the trimmed cross-lagged model described the relationships among cholesterol and depressive symptoms over time, controlling for age and smoking status, at T1, and medication use and BMI, at T2 (see Figure 1).

Mplus generates two coefficients for ZIP variables (i.e., depressive symptoms). The first predicts the possibility of the absence of symptoms (which we reversed to indicate the presence of depressive symptoms), and the second predicts the number of symptoms for those who have any symptoms. Individuals who reported any depressive symptoms at T1 were also likely to report depressive symptoms at T2, \( b = 1.25, p < .01 \), and the numbers of the symptoms were also positively related, \( b = 0.19, p < .001 \). As noted earlier, in the ZIP regression models, unstandardized regression coefficients are most interpretable (Muthén, 2009) and therefore the ones we presented.

The cross-lagged analysis showed that depressive symptoms at T1 were unrelated to cholesterol at T2. Higher cholesterol at T1 was associated with a decreased likelihood of having any depressive symptoms at T2, \( b = -0.01, p < .05 \), but was not related to the number of symptoms, \( b = 0.00 \), n.s. In other words, an individual having one SD (36.30 mg/dL) above the mean (224.06 mg/dL) in TC at T1 was 30 percent less likely to have any depressive symptoms at T2.

In the trimmed model, age and smoking were controlled at T1, and BMI and medication use were controlled at T2. At T1, age was negatively associated with cholesterol, \( b = -0.44, p < .01 \). Smoking was positively associated with depressive symptoms.

At T2, BMI was significantly associated with an increase in both the number of depressive symptoms among those with any symptoms, \( b = 0.03, p < .05 \), and cholesterol level, \( b = 0.58, p < .05 \). Medication use was associated with a decrease in cholesterol at T2, \( b = -6.00, p < .05 \).
We estimated a model including the measure of SLE, which was significantly associated with the number of depressive symptoms at both T1 and T2, $bs = 0.08$ and 0.33, $ps < .01$, respectively. However, the inclusion of SLE did not significantly alter the relationships among the variables in the model. The coefficients for cholesterol at T1 predicting the presence of depressive symptoms at T2 were identical across models. While the autocorrelations between cholesterol and depressive symptoms were slightly altered slightly, the change was not significant, $Z_1 = .074$ and .015, respectively. Because SLE did not affect the relationship between cholesterol and depressive symptoms, we presented only the more parsimonious model omitting SLE (see Figure 1).

Discussion

We examined the bidirectional relationship between cholesterol levels and depressive symptoms over a 3-year interval, using a cross-lagged panel model. We found that those whose cholesterol was one $SD$ higher than the mean at T1 were 30 percent less likely to have any depressive symptoms at T2. In other words, those higher in cholesterol were less likely to report any depressive symptom at T2. However, there was no relationship between cholesterol at Time 1 and the number of depressive symptoms at T2. The relationship between cholesterol and depression was fairly weak, in part because of the low number of depressive symptoms reported by this relatively healthy sample of older men. Furthermore, it was interesting that this relationship was independent of the number of SLE experienced.

The findings of this study partly support the literature suggesting that those with lower cholesterol were more likely to report symptoms of depression (Gilley et al., 2009; Shin et al., 2008). We found that lower TC at T1 was associated with the presence of depressive symptoms at T2, but was not related to the number of depressive symptoms at T2 among those who reported having any symptoms. This is contrary to earlier findings of a positive association between depression severity and TC (Van Reedt Dortland et al., 2013). It should be noted that prior study samples included or oversampled persons with a depression or anxiety diagnosis, whereas the men in this study were from a nonclinical population. Because of the very low rates of depressive symptoms reported by our sample, we may have underestimated the relationship between depressive symptoms and increased cholesterol. Replication of our study on more diverse and vulnerable populations that include women, minorities, or those undergoing treatment for mental health issues may yield different results.

Despite the limitations, the findings of this study are important because we found a modest negative relationship between cholesterol and depressive symptoms in a relatively healthy, nonclinical sample. These longitudinal results support the recent meta-analysis by Shin et al. (2008) that TC and depressive symptoms are inversely related in cross-sectional studies. This suggests that physicians and their patients need to be cognizant of a potential risk of depression as they seek to lower cholesterol in individuals who have no history of depression.

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Declaration of conflicting interests

The views expressed in this article are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs.

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