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Depressive Symptoms Are Associated with Reduced Cardiac Function Among Hispanics: Results from the PREVENCIÓN Study

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Abstract

Background—Depressive symptoms are common among patients with heart failure and are often associated with adverse outcomes, including re-hospitalization and mortality. However, little is known about the association between depressive symptoms and *subclinical* markers of heart failure and cardiac function in community-based samples and little research has focused on South American Hispanics. The current study examined the cross-sectional association between depressive symptoms and cardiac function in South American Hispanic community-based adults.

Methods—Participants included 527 adults enrolled in the Peruvian Study of Cardiovascular Disease (PREVENCIÓN). Depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). Markers of cardiac function were assessed by impedance cardiography and included cardiac output, cardiac index, stroke volume, and stroke volume index. Several multiple regression analyses were used to examine the association between depressive symptoms and markers of cardiac function.

Results—In adjusted analyses, depressive symptoms were associated with reduced cardiac output, cardiac index, stroke volume, and stroke volume index. These associations remained significant between depressive symptoms and cardiac output ($\beta = -0.106$, $p = 0.014$), cardiac index ($\beta = -0.099$, $p = 0.029$), and stroke volume ($\beta = -0.095$, $p = 0.022$), and a trend was still observed between depressive symptoms and stroke index ($\beta = -0.083$, $p = 0.061$), even after having controlled for demographic factors (age, gender, education), cardiovascular risk factors (smoking status, body mass index, low- and high-density lipoprotein cholesterol, triglycerides, fasting glucose, serum creatinine), and comorbidities (diabetes mellitus, hypertension, hypercholesterolemia).

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Conflict of Interest

The authors declare they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Santa Maria Catholic University Human Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conclusions—In the PREVENCIÓN sample tested, depressive symptoms were independently associated with cardiac function among Hispanic adults, even above and beyond pertinent factors such as demographic factors, cardiovascular risk factors, and comorbidities. Future studies should determine whether depressive symptoms are prospectively associated with systolic dysfunction, and examine the bio-behavioral pathways of this association.

Keywords

Depressive symptoms; Cardiac function; Impedance cardiography; Heart failure; South American Hispanics

Introduction

Depressive symptoms are common among those with heart failure [1–3], a condition defined as a heterogeneous syndrome which leads to an inability of the heart to adequately perfuse and oxygenate systemic tissue beds while maintaining normal cardiac filling pressures. Myocardial systolic and diastolic functions are potential mechanisms which lead to heart failure [4–6]. Estimates of clinical depression in this population show the prevalence of clinically significant depression to be at 21.5%, approximately 2 to 3 times greater than the general population [7]. Depressive symptoms in this population lead to adverse health outcomes. Among patients with heart failure, depressive symptoms are a significant predictor of all-cause mortality [8] cardiovascular mortality, [9] short-term health declines in heart failure specific health status [10], and hospitalization/re-hospitalization [11–13] and are associated with lower heart rate variability independent of physical fitness [14].

Despite the well-documented association between depressive symptoms and heart failure, it is unclear whether depressive symptoms precede the onset of the disease or develop as a consequence. Some research suggests that depressive symptoms may emerge as a result of prevalent heart failure, due to the debilitating symptoms associated with the condition [15, 16], or as a psychological consequence of being diagnosed with the condition [17]. In contrast, some studies suggest that depressive symptoms may influence the onset of heart failure [18, 19]. Williams and colleagues found that depression was an independent risk factor for incident heart failure among elderly women [20]. Another study found that among individuals with isolated systolic hypertension, depression was an independent predictor of incident heart failure [21]. However, it is still unclear whether depressive symptoms contribute to the development of heart failure. In the current study, we address this gap by examining the cross-sectional association between depressive symptoms and *subclinical* markers of heart failure.

Indeed, subclinical cardiac dysfunction, which precedes overt clinical heart failure, can be evidenced by cardiac output and stroke volume markers. These two comprehensive indices (cardiac output and stroke volume) are observed to decline prior to the development of clinically manifest heart failure [22]. Currently, little (if any) research is available on the association between depressive symptoms and subclinical markers of heart failure, a literature gap that will also be addressed by the current study. As such, the current study examines whether depressive symptoms are associated with several markers of cardiac

function, including cardiac output and stroke volume in addition to cardiac index and stroke index.

Furthermore, the extant research examining depression and heart failure focuses on samples of non-Hispanic white populations almost exclusively. The generalizability of this critical association is thus limited. The importance of heart failure research and its association with depression in the South American Hispanic population is evidenced by epidemiological data [23]. These data show recent changes in Latin American countries' healthcare, such as healthcare advances [24], along with an associated increase in non-communicable diseases such as heart failure [25, 26]. Indeed, heart failure and other cardiovascular diseases are expected to emerge as the leading cause of morbidity and mortality in the South American Hispanic population [27]. Such epidemiological changes highlight the need to empirically identify such preceding heart failure factors within the broader Hispanic population, particularly in community-based studies [28].

Therefore, the aim of the current study is to examine the cross-sectional association between depressive symptoms and cardiac function, including cardiac output, cardiac index, stroke volume, and stroke index, in a sample of South American Hispanic community-based adults. The data are from the Peruvian Study of Cardiovascular Disease (PREVENCION) Study. It is anticipated that there will be a significant association between elevated depressive symptoms and cardiac function, after adjusting for demographic factors, cardiovascular risk factors, and comorbidities. Specifically, elevated depressive symptoms are hypothesized to be associated with reduced cardiac function after full covariate adjustment.

Methods

Study Participants

The data from the current study are from the Peruvian Study of Cardiovascular Disease Prevalence (PREVENCION). PREVENCION is a population-based study based in Arequipa, the second largest city in Peru. Its population is comparable with the Peruvian urban population, and it is also largely representative of other South American countries, such as Bolivia and Ecuador. A total of 2517 adults between 20 and 87 years old were enrolled in PREVENCION. For recruitment, a probabilistic, multistage sampling process was implemented to ensure participant representation from various geographic locations and socioeconomic statuses [29]. Exclusion criteria of enrollment included individuals living in Arequipa for less than 5 years, pregnant women, and individuals with a diagnosis of any malignant neoplasm. See Medina-Lezama, Chirinos and colleagues for a full description of the study objectives, study design, and sampling methods [29, 30]. The study aimed to examine the prevalence of cardiovascular disease and risk factors in the adult population.

Participants for the current study included 527 adults who participated in a psychosocial ancillary investigation of PREVENCION. This subsample of participants completed baseline assessments of psychosocial measures between the months of January through December 2005. All study procedures/materials were approved by the Santa Maria Catholic University Human Research Committee. Informed consent was obtained from all individual participants included in the study. The analytic sample from the current study and the full

study sample were comparable in regards to age ($p = 0.22$) and gender representation ($p = 0.19$). The analytic sample was more likely to have a higher education status ($p < 0.001$), than the full study sample.

Measures

Depressive Symptoms

Depressive symptoms were assessed with the Hospital Anxiety and Depression (HADS) [31]. This scale was translated and administered in Spanish and has been previously validated in samples of Latin American participants [32]. Participants responded to a 7-item depression subscale, and a 7-item anxiety subscale on a 4-point Likert scale. The current study focuses on the depressive symptom subscale. The items for this scale were found to be highly reliable ($\alpha = 0.74$). Higher scores indicate higher levels of depressive symptoms.

Measures of Cardiac Function

Impedance cardiography was used to assess several indices of cardiac function. Impedance cardiography measures changes in impedance during the cardiac cycle to calculate various indices of cardiac function and is a validated tool for cardiac output and stroke volume measurement [33]. Protocol for impedance cardiography has been previously described [34]. The BioZ device (CardioDynamics, San Diego, CA), which has been validated in measurement of stroke volume and cardiac output [33], was used in the PREVENCIÓN cohort. Four dual sensors were placed on each participant (2 above the base of the neck and one on either side of the thorax at the mid-axillary line). The indices of cardiac function obtained from impedance cardiography were cardiac output and stroke volume. Both parameters were additionally indexed to body surface area (cardiac index and stroke index).

Demographic and Cardiovascular Risk Factors

Participant age was measured in years. Participants indicated their gender as either female or male. Education status was measured on a continuous four-point scale (1 = less than elementary school; 2 = elementary school; 3 = high school; 4 = college educated). See Table 1 for additional demographic factors.

Current smokers were defined as those reporting having smoked ≥ 100 cigarettes during their lifetime and smoking at the time of the survey [35]. Height was measured with a stadiometer and weight with a calibrated scale. Participants were barefoot and wearing light clothing. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Samples of venous blood were obtained after at least 8 h of fast and serum was used for biochemical measurements. Low-density lipoprotein cholesterol (LDL), triglycerides, fasting glucose, and serum creatinine were measured enzymatically by automated methods (Cobas Mira Assay, Roche, Basel, Switzerland). High-density lipoprotein cholesterol (HDL) was measured after precipitation of apo-B-containing lipoproteins [36]. All coefficients of variations for these measurements were $< 10\%$. Serum creatinine was measured by a kinetic compensated Jaffe assay in a Roche Cobas Mira analyzer (Roche, Basel, Switzerland). Blood pressure was measured between 7:00 and 10:00 am using a mercury

sphygmomanometer after a resting period of at least 5 min, with the auscultatory method, according to recommendations from the seventh report of the Joint National Committee for the diagnosis, evaluation, and treatment of high blood pressure [37]. At least two measurements were performed in each of two separate days, and all measurements were used to calculate a final mean value for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Diabetes mellitus status was defined as fasting glucose ≥ 126 mg/dl or undergoing pharmacological treatment with glucose-lowering medication. Hypertension status was defined as having been previously diagnosed with hypertension or undergoing anti-hypertensive treatment (pharmacologic/non-pharmacologic). Hypercholesterolemia status was defined as having been previously diagnosed with hypercholesterolemia or undergoing cholesterol-lowering medications.

Statistical Plan

Preliminary statistical analyses included an assessment of multicollinearity, linearity, normality, homoscedasticity, outliers, and independence. Both triglycerides and fasting glucose were slightly skewed and were log-transformed to restore normality. The log-transformed variables were included in the models for the primary analyses. An analysis of descriptive statistics was first conducted for all primary study variables. Data for continuous variables are presented as means and standard deviations. Between-group comparisons were made with the independent t test. Proportions were compared with the χ^2 test (see Table 1). Four multiple regression analyses were conducted to test for a significant association between depressive symptoms and indices of cardiac function. For each analysis, model 1 was unadjusted. Model 2 was adjusted for demographic characteristics including, age, gender, and education. In addition to demographic factors, model 3 was also adjusted for known cardiovascular risk factors, including smoking status, BMI, LDL, HDL, triglycerides, fasting glucose, and serum creatinine. Model 4 was adjusted for demographic factors and cardiovascular risk factors and adjusted for common comorbidities of heart failure, including diabetes mellitus, hypertension, and hypercholesterolemia [38]. In a sensitivity analysis, we also adjusted for systolic blood pressure (SBP). All descriptive statistics and primary study analyses were conducted in SPSS (V.26).

Results

Sample Characteristics

The study sample comprised of 527 adults (57.10% female). Mean age was 50.95 ($SD = 16.72$), and the age range of the analytic sample was 20–87 years old. The mean depression score on the HADS was 5.69 (3.51). Mean values for cardiac function markers include the following: cardiac output ($M = 5.18$; $SD = 1.15$), cardiac index ($M = 2.92$; $SD = 0.54$), stroke volume ($M = 81.23$; $SD = 18.74$), and stroke volume index ($M = 45.69$; $SD = 8.75$).

Bivariate Correlations Among Relevant Clinical Variables

In this sample, depressive symptoms were negatively correlated (all values $p < 0.05$) with cardiac output ($r = -0.204$), cardiac index ($r = -0.166$), stroke volume ($r = -0.196$), and stroke index ($r = -0.160$). In addition, there was a positive correlation between depressive symptoms and SBP ($r = 0.120$). All cardiac function markers were significantly correlated with each other (all values $p < 0.001$). The bivariate correlations among all relevant clinical variables are presented in Table 2.

Depressive Symptoms and Cardiac Function Markers

In order to examine associations between depressive symptoms and cardiac function, separate multiple regression models were run for each cardiac marker independently. Depressive symptoms were associated with reduced cardiac output ($\beta = -0.201$, $p < 0.001$), cardiac index ($\beta = -0.164$, $p < 0.001$), stroke volume ($\beta = -0.198$, $p < 0.001$), and stroke volume index ($\beta = -0.160$, $p < 0.001$) in unadjusted analyses. After controlling for demographic factors, cardiovascular risk factors, and comorbidities, depressive symptoms remained independently associated with cardiac output (adj $R^2 = 0.192$) $F(14, 487) = 9.48$, $p < 0.001$ ($\beta = -0.106$, $p = 0.014$), cardiac index (adj $R^2 = 0.096$) $F(14, 487) = 4.80$, $p < 0.001$ ($\beta = -0.099$, $p = 0.029$), and stroke volume (adj $R^2 = 0.235$) $F(14, 488) = 12.03$, $p < 0.001$ ($\beta = -0.095$, $p = 0.022$). A trend was observed in the association between depressive symptoms and stroke index (adj $R^2 = 0.138$) $F(14, 488) = 6.76$, $p < 0.001$ ($\beta = -0.083$, $p = 0.061$). All models are presented in Table 3. In a sensitivity analysis, systolic blood pressure (SBP) was controlled for. Associations remained unchanged (results not shown).

Discussion

This is the first study to examine the association between depressive symptomatology and cardiac function (i.e., cardiac output, cardiac index, stroke volume, stroke volume index). In support of our hypothesis, a significant association between elevated depressive symptoms and these markers of cardiac function was present, after adjusting for several demographic, cardiovascular risk factors, and comorbidities. The findings uniquely show increased depressive symptoms are associated with reduced cardiac function.

While no studies have examined depressive symptoms and predictors of subclinical heart failure previously, the findings build upon the limited extant research showing depressive symptoms are associated with the onset of heart failure [39]. Indeed, this study supports the previous findings of comorbidity between depression and heart failure [40] and adds to the current literature the finding that depressive symptoms are a significant predictor of cardiac function and, therefore, a potential risk factor for heart failure. This addition is needed; indeed, Frasure-Smith and colleagues, in their literature review, found that many cardiology organizations do not currently include depression as a possible cardiac risk factor [41].

There are several pathways potentially linking depression to the onset of heart failure: behavioral and inflammatory. One is behavioral, in which individuals with elevated depressive symptoms may be less likely to adhere to medication, less likely to be physically active, more likely to use tobacco and alcohol, and more likely to consume a high-fat diet

[42]. Researchers found these behaviors may contribute to the development of heart failure [40]. In addition to the behavioral pathway, depression may ignite an inflammatory cascade, resulting in the development of heart failure. Although examining the potential pathways were beyond the scope of the current study, future research should examine the behavioral and biological pathways involved with the association between depressive symptoms and cardiac function.

The current study is also among the first to examine the association between depressive symptoms and cardiac function in a community sample of South American Hispanics. By doing so, we provide evidence suggesting that the critical association between depressive symptoms and heart failure is present and relevant in communities outside the non-Hispanic white population. Further, the current study adds to the literature and offers important implications for the epidemiological transition in Latin America. Researchers have examined the effectiveness in treating depression in patients with prevalent heart failure [7, 13], in part because the costs for care of patients hospitalized with heart failure are generally higher among those with comorbid depression [43]. Based on the extant literature, treating elevated depressive symptoms among Hispanics with prevalent heart failure may help improve quality of life and reduce costs.

Importantly, our findings highlight that it may also be necessary to address these depressive symptoms at an earlier time point within the broader Hispanic community. Specifically, elevated depressive symptoms could be evaluated and possibly treated before clinically manifest heart failure is present. In doing so, this *may* help thwart the development of heart failure, which may in turn reduce the emerging burden of heart failure and other cardiovascular diseases in Latin America. Therefore, the overall results of the current study and the existing literature highlight a clear need for healthcare professionals to address elevated depressive symptoms. Researchers should develop and test interventions aimed at identifying and treating depressive symptoms in culturally competent and relevant ways, particularly among individuals with a cardiovascular risk factor (e.g., hypertension) who may be at an increased risk for heart failure.

Important strengths of the study include the sample size and the ability to detect associations after adjusting for demographic, cardiovascular risk factors, and common comorbidities. The current study also uniquely focused on a community-based sample of South American Hispanics in Peru, which addressed several gaps in the literature. In addition, the current study provided evidence of a novel association with cross-sectional data. Despite these strengths, several limitations exist.

While our population-based sample was representative of individuals in Peru and other South American countries, the results are still limited in their ability to be generalized to a global population. Although we did not test these associations outside of samples in Latin America, we anticipate that these findings will replicate. Further, these results may offer important implications for countries that currently face a relatively high burden of heart failure. For instance, in the USA, heart failure represents the leading cause of hospitalization for older adults, and the prevalence of heart failure is expected to increase within the upcoming years as the population continues to age [44, 45]. Empirically

examining predictors of subclinical heart failure may help reduce the impact of an existing burden. Further, the cross-sectional nature of the data limits causal inferences about the identified association. Future research should expand on the work of the current study by investigating this association in populations over time. In addition, while the HADS is a reliable and validated scale of depressive symptoms, we did not have all the necessary information to identify clinically significant depression. To accurately assess this, the American Psychiatric Association specifies that the Structured Clinical Interview (SCID-5) for DSM-5, a semi-structured interview, must be used. It may be informative for researchers to consider measuring depressive symptoms *and* clinically significant depression in future studies.

It is also necessary for researchers to build upon the current study to gain a more comprehensive understanding of this association by taking into consideration cultural constructions of depressive symptoms. Within the Hispanic population, there are unique cultural-specific factors associated with depressive symptoms [46] and some unique manifestations of symptoms [47]. For instance, descriptions of “nervios” (meaning “nerves” in English) have been described as a culturally relevant somatic expression of depression [48]. While the HADS has been validated in samples of Latin American participants, these cultural-specific items of depression are not included in the general scale. We encourage researchers to incorporate a culturally inclusive measure of depressive symptoms to capture these important aspects of depression.

Conclusion

In summary, the findings demonstrate that there is a significant independent association between depressive symptoms and cardiac function among South American Hispanics. Specifically, increased depressive symptoms are associated with decreased cardiac function.

Depressive symptoms may be a risk factor for heart failure, and identifying/treating these symptoms may be beneficial in preventing heart failure. Future studies should examine this association using longitudinal designs, explore the bio-behavioral pathways involved in this association, and test interventions aimed at reducing depressive symptoms.

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Table 1

Descriptive characteristics of the study sample

	Overall M (SD)	Female (n = 301) M (SD)	Male (n = 226) M (SD)	p value
Demographics				
Age, years	50.95 (16.72)	51.48 (16.48)	50.24 (17.04)	.40
Education, highest level	3.47 (0.68)	3.39 (0.71)	3.57 (0.62)	.002
Marital status				
Single (%)	135 (25.90%)	85 (16.28%)	50 (9.58%)	.04
Married (%)	328 (62.80%)	175 (33.52%)	153 (29.31%)	
Other (%)	59 (11.30%)	40 (7.66%)	19 (3.64%)	
Race				
Mixed (%)	467 (88.60%)	272 (51.61%)	195 (37.00%)	.31
White (%)	58 (11.00%)	28 (5.31%)	30 (5.69%)	
Black (%)	2 (0.40%)	1 (0.19%)	1 (0.19%)	
Employment status				
Unemployed (%)	14 (2.80%)	3 (0.60%)	11 (2.19%)	.01
Employed (%)	489 (97.20%)	285 (56.66%)	204 (40.56%)	
Access to social security				
Yes (%)	160 (53.20%)	90 (29.90%)	70 (23.26%)	.68
No (%)	141 (46.80%)	76 (25.25%)	65 (21.59%)	
Cardiovascular disease^a				
Yes (%)	32 (6.07%)	16 (3.04%)	16 (3.04%)	.40
No (%)	495 (93.93%)	285 (54.08%)	210 (39.85%)	
Cardiovascular risk factors				
Smoking status (%)				
Yes (%)	95 (18.00%)	41 (7.78%)	54 (10.25%)	.002
No (%)	432 (82.00%)	260 (49.34%)	172 (32.64%)	
BMI (kg/m ²)	26.60 (4.65)	26.51 (5.15)	26.72 (3.89)	.59
LDL (mg/dL)	124.25 (31.13)	126.93 (32.27)	120.72 (29.24)	.02
HDL (mg/dL)	46.45 (10.41)	47.91 (9.36)	44.53 (11.40)	<.001

	Overall M (SD)	Female (n = 301) M (SD)	Male (n = 226) M (SD)	p value
Log-transformed triglycerides (mg/dL)	2.20 (0.21)	2.16 (0.20)	2.25 (0.20)	< .001
Log-transformed fasting glucose (g/dL)	1.91 (0.07)	1.91 (0.07)	1.90 (0.08)	.90
Serum creatinine (mg/dL)	0.80 (0.19)	0.72 (0.13)	0.91 (.20)	< .001
Systolic blood pressure (mmHg)	121.74 (19.95)	120.66 (20.35)	123.15 (19.36)	.16
Diastolic blood pressure (mmHg)	77.64 (9.46)	76.51 (9.40)	79.13 (9.37)	.002
Comorbidities				
Diabetes mellitus (DM) (%)				.24
Yes (%)	47 (8.90%)	23 (4.36%)	24 (4.55%)	
No (%)	480 (91.10%)	278 (52.75%)	202 (38.33%)	
Hypertension (%)				.27
Yes (%)	117 (22.20%)	72 (13.66%)	45 (8.54%)	
No (%)	410 (77.80%)	229 (43.45%)	181 (34.35%)	
Hypercholesterolemia (%)				.70
Yes (%)	37 (7.00%)	20 (3.80%)	17 (3.23%)	
No (%)	490 (93.00%)	281 (53.32%)	209 (39.66%)	
Primary variables				
Depressive symptoms	5.69 (3.51)	6.06 (3.60)	5.19 (3.33)	.005
Stroke volume	81.23 (18.74)	75.77 (16.25)	88.50 (19.39)	< .001
Stroke index	45.69 (8.75)	44.82 (8.65)	46.86 (8.77)	.008
Cardiac output	5.18 (1.15)	4.89 (0.97)	5.55 (1.26)	< .001
Cardiac index	2.92 (0.54)	2.90 (.53)	2.93 (.55)	.55

^a Any cardiovascular disease including cerebrovascular accident, transient ischemic attack, valvular heart disease, or pathological q-waves on an electrocardiogram

Table 2

Correlations among relevant clinical variables

	1	2	3	4	5	6	7
1. Depressive symptoms	--						
2. Stroke volume	- 0.196***	--					
3. Stroke index	- 0.160***	0.873***	--				
4. Cardiac output	- 0.204***	0.719***	0.541***	--			
5. Cardiac index	- 0.166***	0.520***	0.604***	0.855***	--		
6. Systolic blood pressure	0.120**	- 0.090*	- 0.194***	- 0.067	- 0.171***	--	
7. Diastolic blood pressure	0.030	- 0.008	- 0.149***	0.080	- 0.053	0.682***	--

* $p < .05$;** $p < .01$;*** $p < .001$

Table 3

Associations between depressive symptoms and cardiac function markers

Model	Cardiac output			Cardiac index			Stroke volume			Stroke index		
	<i>B</i>	95% CI ^a	β^b	<i>B</i>	95% CI	β	<i>B</i>	95% CI	β	<i>B</i>	95% CI	β
Model 1												
Depressive symptoms	-0.066	[-.094, -.038]	-0.201	-0.025	[-.038, -.012]	-0.164	-1.05	[-1.51, -.594]	-0.198	-0.401	[-.617, -.184]	-0.16
Model 2 ^c												
Depressive symptoms	-0.035	[-.063, -.007]	-0.108	-0.014	[-.028, -.001]	-0.094	-0.480	[-.924, -.036]	-0.09	-0.173	[-.394, .048]	-0.069
Model 3 ^d												
Depressive symptoms	-0.035	[-.062, -.007]	-0.106	-0.015	[-.029, -.002]	-0.100	-0.514	[-.946, -.081]	-0.097	-0.210	[-.426, .006]	-0.084
Model 4 ^e												
Depressive symptoms	-0.035	[-.062, -.007]	-0.106	-0.015	[-.029, -.002]	-.099	-.505	[-.938, -.073]	-0.095	-.207	[-.423, .010]	-0.083

^aThe 95% confidence interval^bStandardized coefficient^cModel 2 was adjusted for demographic factors, including age, gender, and education^dModel 3 was adjusted for demographic factors, and cardiovascular risk factors, including smoking status, BMI, LDL, HDL, triglycerides, glucose, and creatinine^eModel 4 was adjusted for demographic factors, cardiovascular risk factors, and comorbidities, including diabetes mellitus, hypertension, and hypercholesterolemia