Association of Depressive Symptoms and Heart Rate Variability in Vietnam War-Era Twins A Longitudinal Twin Difference Study

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Association of Depressive Symptoms and Heart Rate Variability in Vietnam War–Era Twins
A Longitudinal Twin Difference Study

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IMPORTANCE Depressive symptoms are associated with lower heart rate variability (HRV), an index of autonomic dysregulation, but the direction of the association remains unclear.

OBJECTIVE To investigate the temporal association between depression and HRV.

DESIGN, SETTINGS, AND PARTICIPANTS A longitudinal, cross-lagged twin difference study, with baseline assessments from March 2002 to March 2006 (visit 1) and a 7-year follow-up (visit 2) at an academic research center with participants recruited from a national twin registry. Twins (n = 166) from the Vietnam Era Twin Registry, who served in the US military during the Vietnam War, and were discordant for depression at baseline were recruited.

MAIN OUTCOMES AND MEASURES At both visits, depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II), and HRV was measured through 24-hour electrocardiogram monitoring. To assess the direction of the association, within-pair differences in multivariable mixed-effects regression models were examined, and standardized β coefficients for both pathways were calculated. The associations were evaluated separately in monozygotic and dizygotic twins.

RESULTS In the final analytic sample (N = 146), all participants were men, 138 (95%) were white, and the mean (SD) age was 54 (3) years at baseline. Results showed consistent associations between visit 1 HRV and visit 2 BDI score across all HRV domains and models (β coefficients ranging from −0.14 to −0.29), which were not explained by antidepressants or other participant characteristics. The magnitude of the association was similar in the opposite pathway linking visit 1 BDI score to visit 2 HRV, with β coefficients ranging from 0.05 to −0.30, but it was largely explained by antidepressant use. In stratified analysis by zygosity, significant associations were observed in monozygotic and dizygotic twins for the path linking visit 1 HRV to visit 2 BDI score, although the associations were slightly stronger in dizygotic twins.

CONCLUSIONS AND RELEVANCE The association between depression and autonomic dysregulation, indexed by HRV, is bidirectional, with stronger evidence suggesting that autonomic function affects depression risk rather than vice versa. The opposite causal pathway from depression to lower HRV is mostly driven by antidepressant use. These findings highlight an important role of autonomic nervous system in the risk of depression and contribute new understanding of the mechanisms underlying the comorbidity of depression and cardiovascular disease.

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Depression is common with a lifetime prevalence of 16% in the United States, translating into 33 to 35 million adults with depression some time in their lives. Prior studies have provided strong evidence for an association between depression and cardiovascular disease (CVD) morbidity and mortality among individuals with and without cardiac disease. The underlying mechanisms and the pathophysiological pathways through which depression increases the risk of CVD incidence and mortality are multifactorial. Among these, autonomic nervous system (ANS) dysfunction has received prominent attention as a potentially modifiable mechanism for the association between depression and CVD.

Heart rate variability (HRV) is a measure of beat-to-beat heart rate fluctuations over time and represents a noninvasive index of cardiac ANS regulation. Reduced HRV is a marker of decreased ANS flexibility and may reflect an increase in the sympathetic nervous system and/or a decrease in the parasympathetic nervous system modulation. Reduced HRV predicts CVD morbidity and all-cause mortality, and vagal function indexed by HRV may provide a structural link connecting psychological moments to morbidity and mortality.

An association between depression and ANS dysfunction as evidenced by reduced HRV has been demonstrated among individuals with coronary artery disease (CAD), but the association is less clear in individuals without CAD. The temporal association also remains unclear. A number of studies reported different directions for the association between depression and unfavorable HRV indices and notably reduced cardiac vagal modulation. It has been reported that a lower HRV may be a predictor of depression. Furthermore, there has been a debate over whether a lower HRV in depression is driven by antidepressant use rather than depression per se.

Most studies are limited in their ability to assess the temporal association between depression and ANS dysregulation because of cross-sectional study designs with 1 exception, to our knowledge. Since depression and HRV are influenced by genetic factors, another limitation is the lack of attention to familial and genetic confounding factors, given that depression and ANS dysregulation could share common pathophysiology and genetic vulnerability.

The objective of this study was to investigate the direction of association between depression and HRV using a cross-lagged longitudinal twin difference design. The study of twin pairs discordant on exposure can be considered a natural “counterfactual” design because twins are matched for genes and early familial factors. Thus, when examining phenotypic differences between twins, confounding by these factors is minimized. To address the temporal association between depressive symptoms and HRV, we used a discordant twin pair approach that allowed us to examine the association of sibling differences in depressive symptoms and HRV across 2 times. The inclusion of both monozygotic (MZ) and dizygotic (DZ) twin pairs enabled us to evaluate the role of genetic predisposition in this association.

**Key Points**

**Question** What is the direction of the association between heart rate variability, an index of autonomic regulation, and depressive symptoms?

**Findings** In this longitudinal twin difference study that included 146 veteran twins (73 pairs), lower heart rate variability at baseline was independently associated with increasing depressive symptoms at follow-up. The opposite longitudinal association between depressive symptoms at baseline and lower heart rate variability at follow-up was less robust and mostly explained by antidepressant medication use.

**Meaning** Autonomic dysregulation is likely to be a risk factor for depression, rather than a consequence.

### Methods

#### Study Cohort

The Vietnam Era Twin Registry is a national sample of male twins who served on active duty during the Vietnam War (1964-1975). The present study is based on a follow-up of a subgroup of Vietnam Era Twin Registry twin pairs who participated in the Emory Twin Studies. The latter included twin pairs discordant for depression or posttraumatic stress disorder (PTSD), as well as control pairs without depression and PTSD. All the twins were born between 1946 and 1956 with no history of CVD based on previous survey. Twin pairs selected for the present follow-up study included those who were examined between March 2002 and March 2006 (visit 1), were discordant for major depressive disorder at any point before, and whose members were still alive, not institutionalized, and still part of the registry (121 pairs). Of these, 106 pairs (87.6%) were successfully contacted and 83 pairs (68.6%) completed visit 2, on average 6.6 years later. Figure 1 shows the construction of the analytical sample.
At both times, twin pairs were examined together at Emory University. Zygosity was verified by DNA typing.³⁷ We obtained twins’ medical history, anthropometric measurements, and behavioral and psychosocial assessments and used identical protocols and similar schedule at both visits. We obtained written informed consent from all participants, and the Emory University institutional review board approved this research.

Measurement of Depressive Symptoms
We used the Beck Depression Inventory-II (BDI-II), a validated scale providing a continuous measure of depressive symptoms. The BDI scale includes 21 items each scored from 0 to 3, with a total score ranging from 0 to 63 and a higher score indicating more depressive symptoms.³⁸-⁴⁰ The BDI was administered at both visits. We also administered the Structured Clinical Interview for DSM-IV to obtain a clinical diagnosis of major depressive disorder (lifetime and current) and PTSD.

Measurement of Heart Rate Variability
Twin twins wore an ambulatory electrocardiogram monitor for 24 hours. We followed previously published procedures to maximize accuracy of recordings and minimize confounding.⁴¹ We used frequency-domain methods to analyze the HRV data, using customized software as previously described.⁴² The HRV spectrum was computed using a fast Fourier transform with a Parzen window on the 24-hour R-R interval file. The file was edited to remove ectopics and noise as well as gaps filled in by interpolated linear splines. The power spectrum was integrated throughout 4 discrete frequency bands: ultra-low frequency (<0.0033 Hz), very low frequency (0.0033-0.04 Hz), low frequency (0.04-0.15 Hz), and high frequency (0.15-0.40 Hz).¹¹,⁴³ Heart rate variability data were collected at both visits using identical methodology, and data processing was performed blindly to twins’ depression status or other characteristics. More details on HRV data collection are described in the eMethods in the Supplement.

Other Measurements
Medical history and physical examination were obtained at both visits after identical protocols. Anthropometric data, blood pressure, fasting blood glucose, lipid profile, and health behaviors were measured as previously described.³⁰ Physical activity was measured using the Baecke habitual physical activity questionnaire.⁴⁴,⁴⁵ Prevalent CAD that might have occurred from the time of the initial screen was also assessed. Diabetes mellitus was defined as having a measured fasting glucose level more than 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or any treatment with antidiabetic medications.

Statistical Analysis
We compared each twin’s characteristics using paired t tests and McNemar statistics and assessed cross-sectional association between HRV and BDI score at each visit using Spearman correlation coefficients. To elucidate the pathways between BDI score and HRV, we used a cross-lagged analysis to compare the within-pair difference in BDI score at visit 1 with the within-pair difference in HRV at visit 2 and the converse (HRV at visit 1 and BDI score at visit 2).³²,⁴⁶ This allowed examination of the longitudinal course of within-pair differences in both variables. In a study of twins, within-pair differences intrinsically control for potential confounding by shared genes and familial influences and also environmental factors during ambulatory monitoring because twins were examined together.

Our primary analysis focused on the associations between the within-pair difference in visit 1 BDI score and that in visit 2 HRV and the converse. We used multivariable mixed-effects regression models and accounted for twin pair as random effect. The HRV data were log-transformed owing to nonnormality. To allow comparisons across directional paths, the β coefficients were standardized and can be interpreted as the number of SDs the dependent variable will change, per SD difference in the predictor variable. For our longitudinal associations, for example, the β coefficients describe the number of SDs the 2 twins will differ in BDI score (or HRV) at visit 2, for a 1-SD difference, within pairs, in HRV (or BDI score) at visit 1.

To avoid model overfitting, for each pathway we constructed a series of models. The base model included visit 1 within-pair difference of the independent variable, and between-pair effects of both independent and dependent variables. We then progressively adjusted for baseline covariates, including potential confounding factors (smoking, β-blocker use, education, alcohol use, physical activity, and history of CAD); cardiovascular risk factors, which could be in the pathway between depression and reduced HRV (body mass index [calculated as weight in kilograms divided by height in meters squared], hypertension, and diabetes); and, last, antidepressant use.

To test whether there was a genetic influence underlying the association, we evaluated effect modification due to zygosity by adding appropriate interaction terms. Because MZ twins share 100% of genes, while DZ twins on average only share 50%, if a larger difference in HRV (or BDI score) at visit 2 is found in association with BDI score (or HRV) at visit 1 within DZ pairs than MZ pairs, this suggests that genetic factors play a role in this association.

Because somatic and cognitive dimensions of depressive symptoms have shown differential associations with cardiovascular risk factors and outcomes⁴⁷,⁴⁸ as well as with HRV,⁴⁹ in secondary analyses we examined somatic and cognitive subscales of the BDI score separately. Finally, we substituted the BDI scale with current episode of major depression evaluated by DSM-IV to examine if the results remained robust. Given the known comorbidity between depression and PTSD, we also examined whether the results were robust to adjustment for PTSD.

Missing data were rare (<3%) for all variables in the analytical sample with usable ambulatory electrocardiogram data. A 2-sided P value of less than .05 denoted statistical significance. All statistical analyses were performed using SAS, version 9.4 (SAS Institute) and Stata, version 14.0 (StataCorp).
Table 1. Characteristics of 146 Participants at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Participants Characteristics</th>
<th>Mean (SD)</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>54 (3)</td>
<td>61 (3)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td></td>
<td>138 (95)</td>
<td>NA</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td>14 (2)</td>
<td>14 (2)</td>
</tr>
<tr>
<td><strong>Health factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>30 (5)</td>
<td>32 (17)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td></td>
<td>30 (21)</td>
<td>28 (26)</td>
</tr>
<tr>
<td>Alcohol use, drinks/wk</td>
<td></td>
<td>4.7 (10.2)</td>
<td>4.2 (8.5)</td>
</tr>
<tr>
<td>Baecke score for physical activitya,b</td>
<td></td>
<td>7.2 (2.0)</td>
<td>6.8 (1.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td>129 (17)</td>
<td>133 (17)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td>81 (11)</td>
<td>78 (11)</td>
</tr>
<tr>
<td><strong>History of hypertension, No. (%)</strong></td>
<td></td>
<td>50 (34)</td>
<td>50 (33)</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dLa</td>
<td></td>
<td>124 (35)</td>
<td>105 (30)</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td></td>
<td>39 (10)</td>
<td>39 (8)</td>
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<tr>
<td>Prevalent CAD, No. (%)</td>
<td></td>
<td>11 (8)</td>
<td>18 (26)</td>
</tr>
<tr>
<td>Fasting glucose level, mg/dLa</td>
<td></td>
<td>101 (18)</td>
<td>108 (28)</td>
</tr>
<tr>
<td>Diabetes, No. (%)a</td>
<td></td>
<td>20 (14)</td>
<td>28 (19)</td>
</tr>
<tr>
<td>BDI score</td>
<td></td>
<td>6.7 (8.4)</td>
<td>7.0 (7.5)</td>
</tr>
<tr>
<td>Lifetime history of major depression, No. (%)</td>
<td></td>
<td>57 (39)</td>
<td>66 (46)</td>
</tr>
<tr>
<td>Current major depressive episode, No. (%)</td>
<td></td>
<td>5 (3)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Lifetime history of PTSD, No. (%)a</td>
<td></td>
<td>20 (14)</td>
<td>37 (25)</td>
</tr>
<tr>
<td>Current PTSD, No. (%)</td>
<td></td>
<td>7 (5)</td>
<td>13 (9)</td>
</tr>
<tr>
<td><strong>Medication use, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockersa</td>
<td></td>
<td>11 (8)</td>
<td>31 (21)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
<td>33 (23)</td>
<td>42 (29)</td>
</tr>
<tr>
<td>Statina</td>
<td></td>
<td>41 (28)</td>
<td>66 (46)</td>
</tr>
<tr>
<td>ACE inhibitor*</td>
<td></td>
<td>24 (16)</td>
<td>38 (26)</td>
</tr>
<tr>
<td><strong>Heart rate variability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultra-low frequencya</td>
<td></td>
<td>9.0 (0.6)</td>
<td>9.1 (0.6)</td>
</tr>
<tr>
<td>Very low frequencya</td>
<td></td>
<td>7.5 (0.7)</td>
<td>7.3 (0.7)</td>
</tr>
<tr>
<td>Low frequencya</td>
<td></td>
<td>6.5 (0.8)</td>
<td>6.3 (0.9)</td>
</tr>
<tr>
<td>High frequencya</td>
<td></td>
<td>5.2 (1.0)</td>
<td>5.0 (1.0)</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>9.3 (0.6)</td>
<td>9.1 (0.6)</td>
</tr>
<tr>
<td>Low frequency/high frequency ratio</td>
<td></td>
<td>4.2 (2.9)</td>
<td>4.3 (3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BDI, Beck Depression Inventory; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; NA, not available; PTSD, posttraumatic stress disorder.

SI conversion factor: To convert low-density and high-density lipoprotein to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

a Indicates significant difference between 2 visits at P < .05. P values were calculated using paired t test (continuous variables) and McNemar statistics (categorical variables).

b Physical activity level was assessed by scoring of the Baecke questionnaire.

Heart rate variability was log-transformed, except for low frequency/high frequency ratio.

Results

Participant Characteristics

Of the 166 male twins (mean [SD] age, 54 [3] years at baseline) recruited (Table 1), 128 (77.1%) at visit 1 and 140 (84.3%) at visit 2 had usable ambulatory electrocardiogram data, defined as at least 18 hours of recording with at least 80% non-interpolated intervals. To calculate within-pair differences in HRV, 146 twins (73 pairs) who had usable electrocardiogram data for both twins at either visit were included in the final analysis. The twins excluded (n = 20) owing to missing HRV data were similar to those included with respect to demographics and health-related factors. The mean (SD) follow-up time was 7 (2) years, and 40 twin pairs (55%) were MZ.

Compared with the twins at visit 1, the same twins at visit 2, on average, smoked more, were more physically inactive, and were more likely to have a history of CAD and diabetes. The prevalence of both major depressive disorder and PTSD were also higher at visit 2. Twins at visit 2 also reported more medication use, including antidepressants. All domains of HRV were reduced at visit 2, but the mean BDI score remained similar.

Association Between HRV and BDI Score

Heart rate variability and BDI score showed mild to moderate Spearman correlations at both visits (Table 2). A detailed analysis of the cross-sectional association between these 2 variables is presented in eTable 1 and eTable 2 in the Supplement.

Cross-lagged longitudinal analyses showed consistent inverse associations between visit 1 HRV and visit 2 BDI score across all domains and models (Table 3). After adjusting for potential confounding factors and CVD risk factors, the associations persisted with β coefficients ranging from −0.15 to −0.23 (model 3). Adding antidepressants did not substantially impact these associations. The results indicated that for each 1-SD lower HRV in a twin compared with his cotwin at visit 1, he was expected to have, on average, 0.14 to 0.22 SD (between 13%–20%) higher BDI score than his cotwin at visit 2.

In contrast, the longitudinal associations of visit 1 BDI score with visit 2 HRV was less consistent (Table 3). The strongest associations were seen for high frequency (β coefficients: −0.22 to −0.30) and weakest for low frequency (0.05 to −0.13). Furthermore, these associations were largely explained by antidepressant use, which, when added to the model, weakened the associations. Except for high frequency, which showed comparably significant associations in both pathways, other HRV bands only showed significant associations from visit 1 HRV to visit 2 BDI score (Figure 2).

In stratified analysis by zygosity, significant associations between visit 1 HRV and visit 2 BDI score were observed in both MZ and DZ twins, although they were more robust in DZ twins (eFigure in the Supplement). In the opposite direction, MZ and DZ twin pairs showed inconsistent and mostly non-significant associations. Interaction terms with zygosity were not significant.

In secondary analyses, visit 1 HRV was more strongly associated with visit 2 BDI somatic subscale, and the association was less robust with the cognitive subscale (eTable 3 and eTable 4 in the Supplement). When we replaced the BDI score with current episode of major depression, the interpretation of results remained similar (eTable 5 in the Supplement), although the analysis was limited by the small number of twins with current depression (5 [3%] at baseline and 10 [7%] at
follow-up). Adding PTSD in any of the models did not materially change the results.

Discussion

In this longitudinal cross-lagged study of Vietnam War-era veteran twins, reduced HRV at baseline was associated with increased depressive symptoms at follow-up in all HRV domains, independent of other health-associated factors and medications. This was true in both MZ and DZ twins, with DZ twins showing a slightly stronger association, although the interaction with zygosity was not significant. A similar association was noted in the opposite temporal pathway, between BDI score at visit 1 and change in HRV at visit 2, but it was less consistent and could largely be explained by antidepressant use at visit 1. These findings are generally consistent with a bidirectional inverse association between depression and HRV. However, they also suggest that the pathway linking a lower HRV to future depression or worsening of depressive symptoms is stronger than the opposite pathway. Thus, autonomic nervous dysfunction indexed a reduced HRV is more likely to be a risk factor for depression, rather than a consequence.
Our results expand previous predominantly cross-sectional studies of an inverse association between reduced HRV and depression. Notably, our findings agree with a prior longitudinal study that used a design similar to ours and also suggested a causal direction from decreased HRV to depression rather than vice versa. This evidence supports the hypothesis that ANS disturbances, as reflected by reduced HRV, precede depressive symptoms and may be involved in the etiology of depression.

The exact mechanisms through which ANS dysfunction may affect depression susceptibility are unknown. Emotional regulation and social behavior, which are involved in the risk of depression, have been associated with brain areas, including the prefrontal cortex and the amygdala, that regulate vagal modulation and cardiac ANS control. Therefore, there could be shared pathophysiology involving disturbed ANS function that links both depression vulnerability and cardiac ANS regulation. According to a theory proposed in 2017, psychological moments both affect and are affected by vagal function, indexed through HRV, in ways that can influence long-term risks of morbidity and mortality. In addition, inflammation can be influenced by autonomic changes and has been implicated in the development of depression.

Other evidence supports the possibility that disturbed ANS function may be implicated in the etiology of depression. Reduced modulation of vagal activity has been associated with poor health conditions and physiological systems. Vagal stimulation improves mood and reduces depressive symptoms both in human and animal studies. The strongest association with depressive symptoms in our analysis was for the high frequency domain; this is almost exclusively influenced by the parasympathetic nervous system, suggesting that disordered parasympathetic regulation (eg, a higher vagal withdrawal or a lower capacity for parasympathetic inhibition of ANS arousal) is important in the pathophysiology of depression.

Chronic stress and prolonged negative emotions can lead to increased sympathetic and reduced parasympathetic modulation, suggesting that depression may precede reduced HRV. However, based on our findings, this association is likely driven by antidepressant use. In this respect, our data agree with prior evidence that the longitudinal association between depression and reduced HRV is largely explained by antidepressant use. For example, in a longitudinal study, individuals with depression who started using various classes of antidepressants exhibited a decrease in cardiac vagal control, indexed by respiratory sinus arrhythmia, compared with antidepressant-naïve individuals with depression or individuals who stopped using antidepressants. Our results support these previous findings of a potential inhibitory effect of antidepressants on cardiac vagal modulation.

In stratified analysis by zygosity, the association between visit 1 HRV and visit 2 depressive symptoms was more robust in DZ than in MZ pairs. This suggests that genetic predisposition may play a role in the link between disordered ANS function and depression and is consistent with a prior hypothesis of a shared genetic control between depression and HRV. However, our relatively small sample size of precluded drawing conclusions on this aspect, as the interaction with zygosity was not significant.

Limitations
Our study has a number of limitations. First, our sample included mostly white, middle-aged men, limiting generalizability. Second, respiration, which may affect high frequency and low frequency, was not taken into account in our assessment; thus, our findings for these frequency bands may be confounded by respiration. This may explain why high frequency showed robust associations in both pathways. However, for the pathway linking baseline HRV to follow-up BDI score, the results for ultra-low frequency and very low frequency were consistent with those for high frequency and low frequency; thus, respiration may not be a major factor explaining our results. Third, the relatively small sample size may have increased the type II error in some analyses, for example for testing interactions with zygosity, and limited our ability to examine clinical depression in detail. However, our matched twin study design should have improved the internal validity and precision of our analysis, and results for current depressive episode showed a similar pattern with those for the BDI score. The twin study design enabled us to control for potential genetic and familial confounding, and confounding from other factors was also minimized because the twins were assessed together to match environmental influences on HRV. The longitudinal assessments of both depression and HRV was an additional strength of this study that added validity to our results.

Conclusions
We found that lower HRV is associated with worsening depressive symptoms longitudinally. Although a bidirectional pathway was observed, use of antidepressants explained most of the association between baseline depressive symptoms and reduced HRV at follow-up. Thus, ANS dysregulation is more likely to be a risk factor for depression, rather than a sequela. These findings point to a central role of the ANS in the regulation of mood and depression vulnerability and may help guide future research toward the identification of individuals at higher risk for depression. Our results also suggest that future interventions modulating ANS regulation may be useful for the prevention and treatment of depression. Finally, these data may inform future research centered on clarifying the mechanisms underlying the association between depression and cardiovascular morbidity and mortality.
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Original Investigation Research

Drafting of the manuscript: Huang, Shah, Su, Lampert, Levantsevych, Bremner, Vaccarino.

Author Contributions: Drs Huang and Vaccarino had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Goldberg, Lampert, Bremner, Vaccarino.

Acquisition, analysis, or interpretation of data: Huang, Shah, Su, Lampert, Levantsevych, Shallenberger, Pimple, Bremner, Vaccarino.

Drafting of the manuscript: Huang, Vaccarino.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Huang, Goldberg.

Obtained funding: Bremner, Vaccarino.

Administrative, technical, or material support: Shah, Goldberg, Lampert, Levantsevych, Shallenberger, Pimple, Bremner, Vaccarino.

Study supervision: Shah, Bremner, Vaccarino.

Conflict of Interest Disclosures: None reported.

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