ORIGINAL ARTICLE

Association Between Major Depressive Disorder and Heart Rate Variability in the Netherlands Study of Depression and Anxiety (NESDA)

Carmilla M. M. Licht, MSc; Eco J. C. de Geus, PhD; Frans G. Zitman, MD, PhD; Witte J. G. Hoogendijk, MD, PhD; Richard van Dyck, MD, PhD; Brenda W. J. H. Penninx, PhD

Context: It has been hypothesized that depression is associated with lower heart rate variability and decreased cardiac vagal control. This may play an important role in the risk of cardiovascular disease among depressed individuals.

Objective: To determine whether heart rate variability was lower in depressed individuals than in healthy controls in a large adult sample.

Design: Cross-sectional analyses from a large depression cohort study.

Setting: The Netherlands Study of Depression and Anxiety.

Participants: Two thousand three hundred seventy-three individuals (mean age, 41.8 years; 66.8% female) who participated in the Netherlands Study of Depression and Anxiety. Included were 524 controls, 774 individuals with a diagnosis of major depressive disorder (MDD) earlier in life (remitted MDD), and 1075 individuals with current MDD based on the Composite International Diagnostic Interview. This sample was sufficiently powered to examine the confounding effects of lifestyle, comorbid anxiety, and antidepressants.

Main Outcome Measures: The standard deviation of normal-to-normal beats (SDNN) and cardiac vagal control, as indexed by respiratory sinus arrhythmia (RSA), were measured during 1½ hours of ambulatory recording of electrocardiograms and thorax impedance. Multivariate analyses were conducted to compare SDNN and RSA across depression groups after adjustment for demographics, health, lifestyle, comorbid anxiety, and psychoactive medication.

Results: Individuals with remitted and current MDD had a lower mean SDNN and RSA compared with controls (SDNN, 3.1-5.7 milliseconds shorter, $P \leq .02$; RSA, 5.1-7.1 milliseconds shorter, $P < .001$; effect size, 0.125-0.269). Comorbid anxiety and lifestyle did not reduce these associations. However, accounting for psychoactive medication removed the association with SDNN and strongly attenuated the association with RSA. Depressed individuals who were using selective serotonin reuptake inhibitors, tricyclic antidepressants, or other antidepressants had significantly shorter SDNNs and RSAs (effect size, 0.207-0.862) compared with controls and depressed individuals not taking medication.

Conclusions: This study shows that depression is associated with significantly lowered heart rate variability. However, this association appears to be mainly driven by the effect of antidepressants.

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DEPRESSION RESULTS IN UNfavorable health outcomes, such as cardiovascular morbidity and mortality.[1-6] Alterations in the autonomic nervous system have been hypothesized to be an underlying physiological mechanism that may partly explain these unfavorable health outcomes among depressed persons.[7-11] Such alterations are believed to reduce heart rate variability, a well-known prognostic risk factor for cardiovascular disease (eg, myocardial infarct and arrhythmias), and mortality.[12-18] In research on autonomic nervous system correlates of depression, most attention has been focused on low cardiac vagal control, which may impair social engagement and flexible adjustment to environmental demands[19-22] and may be a major determinant of a reduction in heart rate variability.

Cardiac vagal control can be assessed by examining heart rate variability, particularly that in the respiratory frequency range. This part of heart rate variability is also known as respiratory sinus arrhythmia (RSA).[23] In a recent meta-analysis, Rottenberg[22] examined the association between depression and RSA. The meta-analysis summarized 13 studies that reported on RSA measures, with a total of 312 depressed sub-

Author Affiliations are listed at the end of this article.

jects and 374 controls. Depressed persons were found to have a significantly shorter RSA, though the summarized effect size was small to medium according to Cohen conventions (d=0.332). As pointed out by Rottenberg, data collection and analysis differed considerably among the studies and only a few of them had the required sample size to address confounding by lifestyle (smoking, use of alcohol, high body mass index, and low physical activity) and comorbid anxiety. However, many of these factors—substance use, low physical activity, and comorbid anxiety—occur frequently in depression and have been associated with decreased cardiac vagal control.[24,25] Finally, antidepressants are a particularly relevant source of potential confounding when examining the association between depression and cardiac vagal control. The suppressive effects of tricyclic antidepressants (TCAs) on autonomic function are already well established.[26-31] The effect of other antidepressants on autonomic function, however, are not as well studied and inconsistent results have been reported.[29,32-34] The present study reports cross-sectional analyses from a large depression cohort study (Netherlands Study of Depression and Anxiety [NESDA], N=2981). We examined whether heart rate variability, as indexed by the standard deviation of normal-to-normal beats (SDNN), and cardiac vagal control, as indexed by RSA derived from peak-valley estimation,[35,36] differed between depressed individuals and healthy controls. The study was sufficiently powered to examine the extent to which these associations are confounded by lifestyle, comorbid anxiety, and effect of antidepressants.

METHODS

PARTICIPANTS

Study participants came from NESDA, an ongoing 8-year longitudinal cohort study conducted among 2981 adults (age, 18-65 years). The study examines the etiology and predictors of a long-term course of depression and anxiety disorders. Its rationales, methods, and recruitment strategy have been described elsewhere.[37] The NESDA sample consists of 652 persons without depression or an anxiety disorder and 2329 with a remitted or current diagnosis of depression or an anxiety disorder. To represent various settings and stages of psychopathology, individuals with depression or anxiety disorders were recruited from 3 different areas in the Netherlands: the general population, primary care, and mental health care organizations. Community-based participants were previously identified in 2 population-based studies (the NEMESIS and Ariadne studies[37]); primary care participants were identified through a 3-stage screening procedure (involving the Kessler Psychological Distress Scale [K10][38,39] and the short form of the Composite International Diagnostic Interview [CIDI], telephone interview) conducted among patients of 65 general practitioners; and mental health care patients were recruited when they were newly enrolled at 1 of 17 participating mental health organization locations.

Participants in NESDA were assessed during a 4-hour clinic visit to 1 of 7 field center locations (September 2004-February 2007). During this visit, depressive disorders were ascertained using the lifetime version of the CIDI. The CIDI establishes diagnoses according to *DSM-IV* criteria[40] and has shown high interrater and test-retest reliability and validity for depressive disorders.[41] The severity of depression was measured in all participants using the 30-item Inventory of Depressive Symptomatology, Self-Report (IDS-SR).[42]

To test whether SDNN and RSA differed across persons with and without a depressive disorder, 3 distinct depression groups were created for the present study: 524 controls with no history of depression or anxiety disorders and low scores on a depressive symptom questionnaire (IDS-SR score ≤14); 774 persons with a major depressive disorder (MDD) diagnosis (according to CIDI) earlier in life but not within the past 6 months (remitted MDD group); and 1075 persons with a CIDI-confirmed MDD diagnosis within the past 6 months (72% had experienced a depressive episode in the past month) (current MDD group). The remaining 608 individuals were excluded from the analyses: 128 controls had an IDS-SR score greater than 14; 404 patients had an anxiety disorder, minor depression, or dysthymia in absence of an MDD diagnosis; and 76 had missing physiological data owing to equipment failure during assessment or poor electrocardiogram quality.

MEASUREMENTS

The baseline assessment consisted of a blood sample, cognitive computer task, medical examination, psychiatric interview, saliva collection, and administration of several written questionnaires concerning, eg, mood, lifestyle, medical history, and medication use. In this way, extensive information about psychological, biological, physical, and demographic determinants were collected. The study protocol was approved by the ethics review board of the VU University Medical Center and subsequently by local review boards of each participating center. All participants signed an informed consent at baseline.

PHYSIOLOGICAL MEASUREMENTS

Physiological recording was performed using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS; Vrije Universiteit, Amsterdam, the Netherlands). The VU-AMS is a lightweight portable device that records electrocardiograms and changes in thorax impedance from 6 electrodes placed on the chests and backs of participants.[43,44] Recording is unobtrusive, and participants, who maintain full freedom of movement, tend to adjust very rapidly to this type of recording. The NESDA participants wore the VU-AMS device during a large part of the baseline assessments while participating in other assessments (medical examination, interviewing, and computer task). The start of the various assessments was indicated by an event marker to divide the total recording into fixed periods (resting baseline, breaks, interview 1, computer task, and interview 2). Movement registration by a vertical accelerometer was used to excise periods in which participants were not stationary. Removal of breaks and nonstationary moments (about 15 minutes) left an average registration of 99.9 minutes (standard deviation [SD], 23.0 minutes). This registration consisted of a supine resting condition (with 3 blood pressure measurements; mean time, 9.7 minutes [SD, 3.0 minutes]) and 3 test conditions in which the participants were sitting upright: interview session 1 (investigating somatic health, functioning, and health care use; mean, 38.2 minutes [SD, 12.7 minutes]), interview session 2 (investigating family and personal history and life events; mean, 35.6 minutes [SD, 12.7 minutes]), and a computer task (Implicit Association Task; mean, 16.2 minutes [SD, 4.0 minutes]). The Implicit Association Task is a computerized reaction time task designed to measure implicit associations between self-describing items and anxiety- and depression-related items.[45]

From the electrocardiogram and the thorax impedance data, interbeat interval time series and respiration signal were extracted as described elsewhere.[43,46,47] From these signals, the mean

Table 1. Sample Characteristics by MDD Diagnosis

Characteristic	Participants, %			*P* Value[a]
	Control (n=524)	With Remitted MDD (n=774)	With Current MDD (n=1075)	
Age, mean (SD), y	40.7 (14.8)	43.5 (12.6)	40.8 (12.1)	<.001
Female sex	59.7	70.5	67.4	<.001
Education, mean (SD), y	13.0 (3.1)	12.4 (3.2)	11.6 (3.2)	<.001
Body mass index[b]				
Mean (SD)	25.1 (4.6)	25.6 (4.7)	25.9 (5.5)	.01
Underweight	3.2	2.3	4.1	.004
Normal weight	53.1	49.1	47.5	
Overweight	29.6	32.8	28.1	
Obese	14.1	15.8	20.3	
Physical activity, resting metabolic rate × min of physical activity per week				
Mean (SD)	3.9 (3.0)	3.9 (3.1)	3.6 (3.3)	.14
Low	12.8	15.2	21.1	<.001
Moderate	37.2	37.3	36.3	
High	50.0	47.5	42.6	
Smoking status				
Nonsmoker	37.4	23.5	26.4	<.001
Former smoker	36.1	37.0	28.4	
Moderate smoker	21.9	29.3	27.8	
Heavy smoker	4.6	10.2	17.4	
Alcohol use				
Nondrinker	10.5	15.2	21.7	<.001
Mild drinker	48.5	44.2	45.6	
Moderate drinker	23.9	24.7	17.6	
Heavy drinker	17.2	15.9	15.2	
Heart or blood pressure medication	13.9	15.5	13.0	.32
Heart or coronary disease	4.0	7.1	5.4	.05
Chronic diseases, mean (SD), No.	0.95 (1.0)	1.28 (1.3)	1.46 (1.3)	<.001
Medication use				
Tricyclic antidepressant	0.2	2.8	4.2	<.001
Selective serotonin reuptake inhibitor	0.6	16.3	29.2	<.001
Other antidepressant	0.0	3.9	11.2	<.001
Benzodiazepine	1.0	4.7	15.0	<.001
Other psychotropic medication	5.5	6.3	5.1	.53
Comorbid anxiety				
Panic disorder	0	41.3	52.0	<.001
Social phobia	0	32.3	41.7	<.001
Generalized anxiety disorder	0	28.8	39.0	<.001
Respiration rate, mean (SD), breaths/min	17.2 (1.2)	17.0 (1.2)	17.1 (1.2)	.07
IDS-SR score, mean (SD)	5.6 (3.9)	17.6 (10.3)	31.9 (13.0)	<.001

Abbreviations: IDS-SR, Inventory of Depressive Symptomatology, Self-Report; MDD, major depressive disorder.
[a] Comparison using analyses of variance (continuous variables) and χ^2 statistics (categorical variable).
[b] Calculated as weight in kilograms divided by height in meters squared.

heart rate, SDNN, and RSA were computed for each of the 4 conditions (rest, interview 1, computer task, and interview 2). Heart rate and SDNN were directly derived from the interbeat interval time series as was a first RSA measure, the root mean square of successive differences (RMSSD). A second RSA measure was obtained by directly combining the electrocardiogram data with the respiration signal to obtain the variation in the interbeat intervals restricted to the typical respiratory frequency range (0.15-0.40 Hz). Extraction of RSA by this peak-valley estimation (pvRSA) has been detailed elsewhere.[36,48] A third, more labor-intensive measure of RSA could have been obtained in the frequency domain, like the high-frequency power of the interbeat interval time series by Fourier or Wavelet analysis.[49] It has been shown, however, that high-frequency power essentially identifies the same between-subject variation as RMSSD and pvRSA and that all 3 measures can be used interchangeably.[36,46] Because results from RMSSD and pvRSA strongly converged in the current data, we have focused on pvRSA. This measure has the added advantage over the frequency domain method of yielding information on the respiratory frequency of participants. This is important because the widespread use of RSA as a proxy for individual differences in cardiac vagal control[23,50] suffers from potential confounding by individual differences in respiratory behavior.[51,52]

COVARIATES

Respiration rate has often been associated with RSA and several studies have asserted that research investigating RSA should take respiration rate into account.[43,53] Therefore, we adjusted analyses for respiration rate. Sociodemographic characteristics included age, sex, and education in years. In addition, various health indicators were considered covariates, as these have been linked with both depression status and cardiac vagal control. Body mass index was calculated as weight in kilograms divided by height in meters squared and categorized following World Health Orga-

nization international standards[54]: underweight (<18.5), normal weight (≥18.5 and <25), overweight (≥25 and <30), and obese (≥30). Physical activity was measured using the International Physical Activity Questionnaire[55] and expressed as one's resting metabolic rate multiplied by minutes of physical activity per week. Individuals were divided into the following smoking categories: nonsmoker, former smoker, smoker (<20 tobacco consumptions a day), and heavy smoker (≥20 tobacco consumptions a day). Similar categories were made for alcohol use: nondrinker, mild drinker (<7 glasses a week), moderate drinker (7-14 glasses a week), and heavy drinker (≥15 glasses a week). Self-reports were used to ascertain the presence of heart disease (including coronary disease, cardiac arrhythmia, angina pectoris, heart failure, and myocardial infarction) and the number of other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcers [stomach or intestinal]). It was determined whether or not participants were using heart medication by recording medication names from the medicine bottles they brought in. We classified medications by using the World Health Organization Anatomical Therapeutic Chemical (ATC) system.[56] A dichotomous variable for heart medication was computed, giving participants a *yes* if they frequently (daily or >50% of the time) used a medication, with the following ATC codes: cardiac therapy, C01; antihypertensive drugs, C02; diuretic drugs, C03; peripheral vasodilator drugs, C04; vasoprotective drugs, C05; β-blocking agents, C07; and calcium-channel blockers, C08.

Subsequently, potentially explanatory variables were determined. The presence or absence of a comorbid lifetime panic disorder (with or without agoraphobia), comorbid lifetime social phobia, or comorbid lifetime generalized anxiety disorder was assessed using CIDI. In addition, frequent use (daily or >50% of the time) of psychoactive medication was determined. We distinguished benzodiazepine drugs (ATC codes N03AE, N05BA, N05CD, and N05CF), selective serotonin reuptake inhibitors (SSRIs) (ATC code N06AB), TCAs (ATC code N06AA), and other antidepressants (including monoamine oxidase inhibitors, nonselective N06AF, and antidepressants classified as N06AX) from nondepression-related psychoactive medication (anesthetic drugs, ATC code N01; analgesic drugs, ATC code N02; antiepileptic drugs, ATC code N03; anti-Parkinson disease drugs, ATC code N04; psycholeptic drugs, ATC code N05; psychostimulants, ATC code N06B; antidementia drugs, ATC code N06D; and other nervous system drugs, ATC code N07). For all psychoactive medication, a derived daily dose was calculated by dividing the participant's mean daily dose by the daily dose recommended by the World Health Organization.[56]

STATISTICAL ANALYSIS

Data were analyzed using SPSS, version 15.0 (SPSS Inc, Chicago, Illinois). Characteristics across the 3 depression groups were compared using analysis of variance and χ^2 statistics. Mixed model analysis was used to compare heart rate, SDNN, and RSA between the control, remitted MDD, and current MDD groups across the 4 different interview conditions to establish whether the association between MDD group and cardiac measure was constant across assessment conditions. Analyses of covariance were used to compare heart rate, SDNN, and RSA between MDD groups. These analyses were repeated with consideration of covariates (respiration rate, age, sex, education, body mass index, smoking, alcohol use, physical activity, heart disease, heart medication, and number of comorbid diseases). Effect sizes were calculated with Cohen *d*, defined as the difference in the means of 2 groups, divided by the pooled standard deviation of these groups. Subsequently, the role of 2 main explanatory variables (comorbid anxiety and psychoactive medication) was examined by entering information on these variables in the analyses of covariance. We distinguished between MDD participants taking and not taking various types of psychoactive medication and compared their cardiac measures with those of controls in fully corrected analyses of covariance. Finally, to explore a potential dose-response association, a sex- and age-adjusted partial correlation between the derived daily dose and cardiac measures was computed for each antidepressant group.

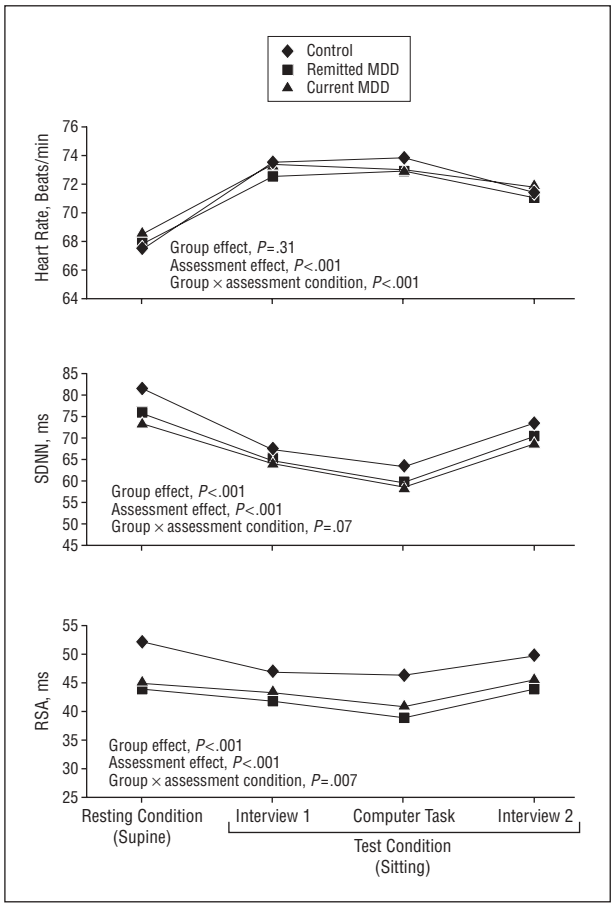

Figure 1. Autonomic nervous system activity during assessment conditions across depression groups. MDD indicates major depressive disorder; RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal beats.

RESULTS

The mean age of the study sample (N=2373) was 41.6 years (SD, 13.0 years); 66.8% of participants were female; and 50.2% had less than 12 years of education. **Table 1** presents demographic characteristics, disease status, lifestyle habits, and medication use according to MDD status. Compared with the nondepressed participants, depressed individuals were more likely to be female, had less education, had higher body mass indexes, performed less physical activity, were more likely to smoke but less likely to drink, had more heart disease and other chronic diseases, were more likely to use antidepressants, and had higher IDS-SR scores.

Figure 1 shows heart rate, SDNN, and RSA results per assessment condition for the 3 depression groups. It illustrates that heart rate is approximately the same in

Table 2. Heart Rate, SDNN, and RSA by MDD Diagnosis in Resting and Test Conditions

Characteristic	Mean (SE)			Controls vs Remitted MDD		Controls vs Current MDD	
	Controls (n=524)	Participants With Remitted MDD (n=774)	Participants With Current MDD (n=1075)	*t* Score[a]	*P* Value	*t* Score[a]	*P* Value
Heart Rate, Beats/min							
Resting condition							
Unadjusted	67.5 (0.4)	67.7 (0.4)	68.5 (0.3)	0.5	.63	2.0	.04
Adjusted[b]	67.7 (0.4)	67.8 (0.4)	68.4 (0.3)	0.3	.89	1.4	.17
Adjusted[c]	68.1 (0.4)	67.9 (0.3)	68.2 (0.3)	−0.2	.73	0.2	.87
Test condition							
Unadjusted	73.6 (0.4)	72.1 (0.4)	72.7 (0.3)	−1.6	.12	−0.6	.57
Adjusted[b]	73.1 (0.4)	72.3 (0.4)	72.6 (0.3)	−1.4	.16	−0.9	.38
Adjusted[c]	73.2 (0.4)	72.4 (0.4)	72.4 (0.3)	−1.5	.14	−1.6	.13
SDNN, ms							
Resting condition							
Unadjusted	81.4 (1.5)	75.9 (1.2)	73.5 (1.1)	−2.8	.005	−4.2	<.001
Adjusted[b]	79.9 (1.4)	77.9 (1.2)	72.8 (1.0)	−1.1	.26	−4.1	<.001
Adjusted[c]	79.1 (1.4)	77.7 (1.2)	73.4 (1.0)	−0.8	.43	−3.2	.001
Test condition							
Unadjusted	68.4 (1.1)	64.8 (0.9)	64.1 (0.8)	−2.5	.01	−3.1	.002
Adjusted[b]	67.5 (1.1)	65.9 (0.9)	63.7 (0.7)	−1.2	.25	−2.9	.003
Adjusted[c]	67.1 (1.1)	65.7 (0.9)	64.0 (0.8)	−1.0	.31	−2.3	.02
RSA, ms							
Resting condition							
Unadjusted	52.1 (1.4)	43.9 (1.1)	45.1 (0.9)	−4.7	<.001	−4.2	<.001
Adjusted[b]	51.6 (1.1)	45.6 (0.9)	44.2 (0.8)	−4.1	<.001	−5.3	<.001
Adjusted[c]	51.4 (1.2)	45.5 (0.9)	44.3 (0.8)	−4.0	<.001	−5.0	<.001
Test condition							
Unadjusted	47.7 (1.1)	41.6 (0.9)	43.4 (0.8)	−4.2	<.001	−3.2	.002
Adjusted[b]	47.5 (0.9)	43.1 (0.8)	42.4 (0.7)	−3.6	<.001	−4.4	<.001
Adjusted[c]	47.6 (1.0)	42.9 (0.8)	42.5 (0.7)	−3.8	<.001	−4.3	<.001

Abbreviations: MDD, major depressive disorder; RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal beats.
[a] Based on *t* statistics for contrast comparison with 1 *df*.
[b] Adjusted for respiration rate, age, sex, and education.
[c] Adjusted for respiration rate, age, sex, education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic diseases, and heart medication.

each group ($P=.31$) but that depressed individuals have significantly lower SDNNs and RSAs than controls ($P<.001$). Heart rate was significantly lower and SDNN and RSA were significantly higher in the supine resting condition compared with the sitting and more active test conditions ($P<.001$). Mixed model analysis reported an interaction effect for MDD status and assessment condition in heart rate ($P<.001$), SDNN ($P=.07$), and RSA ($P=.007$). This was due to a slightly larger group difference during supine resting than during interview 1, the cognitive computer task, or interview 2. Because the differences in heart rate, SDNN, and RSA between MDD groups in the latter 3 test conditions were very similar, they were collapsed into a single test condition.

Table 2 presents unadjusted and adjusted results of the mean heart rate, SDNN, and RSA for the control, remitted MDD, and current MDD groups for the resting and test conditions. In neither condition did the remitted MDD group ($P=.73$, fully adjusted for resting condition; $P=.14$, for test condition) or current MDD group ($P=.87$, fully adjusted for resting condition; $P=.13$, for test condition) differ significantly from the controls for heart rate. However, the current MDD and remitted MDD groups differed significantly from the control group in mean SDNN and RSA in both conditions ($P<.01$, unadjusted). In adjusted analyses, the current MDD but not the remitted MDD group continued to have significantly lower SDNNs compared with controls. Effect sizes for lower SDNNs among the current MDD group were small to modest (in resting condition, $d=0.176$; in the test condition, $d=0.125$). Depressed participants also showed significantly lower RSAs than controls; for this parameter, lower values were found in the remitted as well as the current MDD groups. The effect sizes were 0.215 and 0.232 for current MDD and remitted MDD, respectively, vs controls at resting and 0.226 and 0.269 during the test condition. There were no significant differences in RSA between the remitted and current MDD groups themselves ($P=.39$, for resting conditions; $P=.70$, for test conditions).

To examine whether comorbid anxiety disorders and psychoactive medication contributed to the lower SDNN and RSA found in participants with MDD, these variables were examined in subsequent adjusted analyses of covariance. Inclusion of indicators for comorbid panic disorder, social phobia, and generalized anxiety disorder did not change the differences in SDNN or RSA between MDD groups. After correction for psychoactive

Table 3. SDNN and RSA by Medication Group[a]

Study Group	No. of Participants	IDS-SR Score, Mean	Resting Condition: Measure, Mean (SE), ms	Resting Condition: *t* Score[b]	Resting Condition: *P* Value	Resting Condition: Cohen *d*	Test Condition: Measure, Mean (SE), ms	Test Condition: *t* Score[b]	Test Condition: *P* Value	Test Condition: Cohen *d*
SDNN										
Controls[c]	515	5.6	79.5 (1.4)				67.4 (1.1)			
Participants with MDD not taking medication										
With mild symptoms[d]	585	15.9	79.8 (1.3)	0.2	.86	0.011	67.4 (1.0)	–0.03	.97	0.002
With severe symptoms[e]	433	35.9	77.8 (1.5)	–0.8	.44	0.051	67.9 (1.2)	0.3	.79	0.018
Participants with MDD taking medication										
TCA	67	34.3	56.1 (3.9)	–5.6	<.001	0.727	46.6 (3.0)	–6.5	<.001	0.849
SSRI	435	34.4	71.7 (1.5)	–3.7	<.001	0.243	62.3 (1.2)	–3.1	.002	0.207
Other AD	134	34.8	62.1 (2.7)	–5.6	<.001	0.542	57.8 (2.1)	–4.1	<.001	0.395
Benzodiazepine	63	37.0	72.2 (4.1)	–1.7	.10	0.227	64.0 (3.1)	–1.0	.30	0.139
Other psychoactive medication	104	31.3	81.1 (3.2)	0.5	.64	0.051	65.9 (2.4)	–0.6	.57	0.062
RSA										
Controls[c]	515	5.6	51.8 (1.2)				48.0 (1.0)			
Participants with MDD not taking medication										
With mild symptoms[d]	585	15.9	48.8 (1.1)	–1.9	.05	0.116	45.7 (0.9)	–1.7	.08	0.107
With severe symptoms[e]	433	35.9	48.5 (1.2)	–1.9	.05	0.127	45.4 (1.0)	–1.3	.07	0.120
Participants with MDD taking medication										
TCA	67	34.3	31.5 (3.1)	–6.0	<.001	0.787	29.4 (2.6)	–6.0	<.001	0.862
SSRI	435	34.4	39.0 (1.2)	–7.5	<.001	0.493	39.1 (1.0)	–6.2	<.001	0.413
Other AD	134	34.8	34.3 (2.2)	–7.0	<.001	0.680	35.6 (1.8)	–6.6	<.001	0.575
Benzodiazepine	63	37.0	46.5 (3.2)	–1.5	.12	0.207	44.2 (2.7)	–1.8	.19	0.175
Other psychoactive medication	104	31.3	49.4 (2.6)	–0.9	.39	0.094	44.0 (2.1)	–1.8	.09	0.183

Abbreviations: AD, antidepressant; IDS-SR, Inventory of Depressive Symptoms Symptomatology, Self-Report; MDD, major depressive disorder; RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal beats; SE, standard error; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Adjusted for respiration rate, age, sex, education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic diseases, and heart medication.

[b] Based on *t* statistics for contrast comparison with 1 *df*.

[c] Controls are the reference group. All *t* scores, *P* values, and effect sizes are for comparison of the group with controls.

[d] Based on an IDS-SR score of less than 25.

[e] Based on an IDS-SR score of 25 or higher.

medication, however, the differences between MDD groups and controls were strongly attenuated; differences in SDNN between the current MDD group and the controls lost significance ($P=.37$, resting condition; $P=.72$, test condition), though they remained significant for RSA in the resting condition ($P=.05$) and borderline significant in the test condition ($P=.10$).

Because the differences between MDD groups disappeared for SDNN and were strongly attenuated for RSA after considering psychoactive medication, the individuals with MDD (either current or remitted) were further divided on the basis of medication use: those taking and not taking certain medications. Since individuals with MDD not using psychoactive medications had a lower mean severity IDS-SR score than those taking medication, nonmedicated MDD participants were divided into a mildly to moderately depressed group (IDS-SR score <25) and a severely depressed group (IDS-SR score ≥25). The latter nonmedicated group had a similar mean IDS-SR score as the depressed individuals using medication (**Table 3**). Eventually 6 groups of individuals with MDD were distinguished: 585 mildly to moderately depressed individuals not taking medication (IDS-SR score <25), 436 severely depressed individuals not taking medication (IDS-SR score ≥25), 67 depressed individuals taking TCAs, 435 depressed individuals taking SSRIs (no TCA users), 137 depressed individuals taking other antidepressants (no TCA or SSRI users), 63 depressed individuals taking benzodiazepines (no antidepressants), and 104 depressed individuals taking other psychoactive medications (no antidepressants or benzodiazepines). Analyses of covariance were performed to compare these groups for the resting and test conditions.

Table 3 and **Figure 2** present the fully adjusted analyses of covariance results for SDNN and RSA across the different groups. For SDNN, the difference across MDD groups appears to be entirely due to psychoactive medication use, as depressed participants not taking medication, with either mild to moderate or severe symptoms, did not have significantly lower SDNNs than controls. For RSA, the depressed groups not using psychoactive medications still had significantly lower resting RSAs compared with the control group; this was independent of severity of symptoms (controls vs MDD participants with IDS-SR scores <25, $P=.05$; controls vs MDD participants with IDS-SR scores ≥25, $P=.05$). The effect sizes, however, were reduced by half. In the test condition, significance decreased to borderline levels only (controls

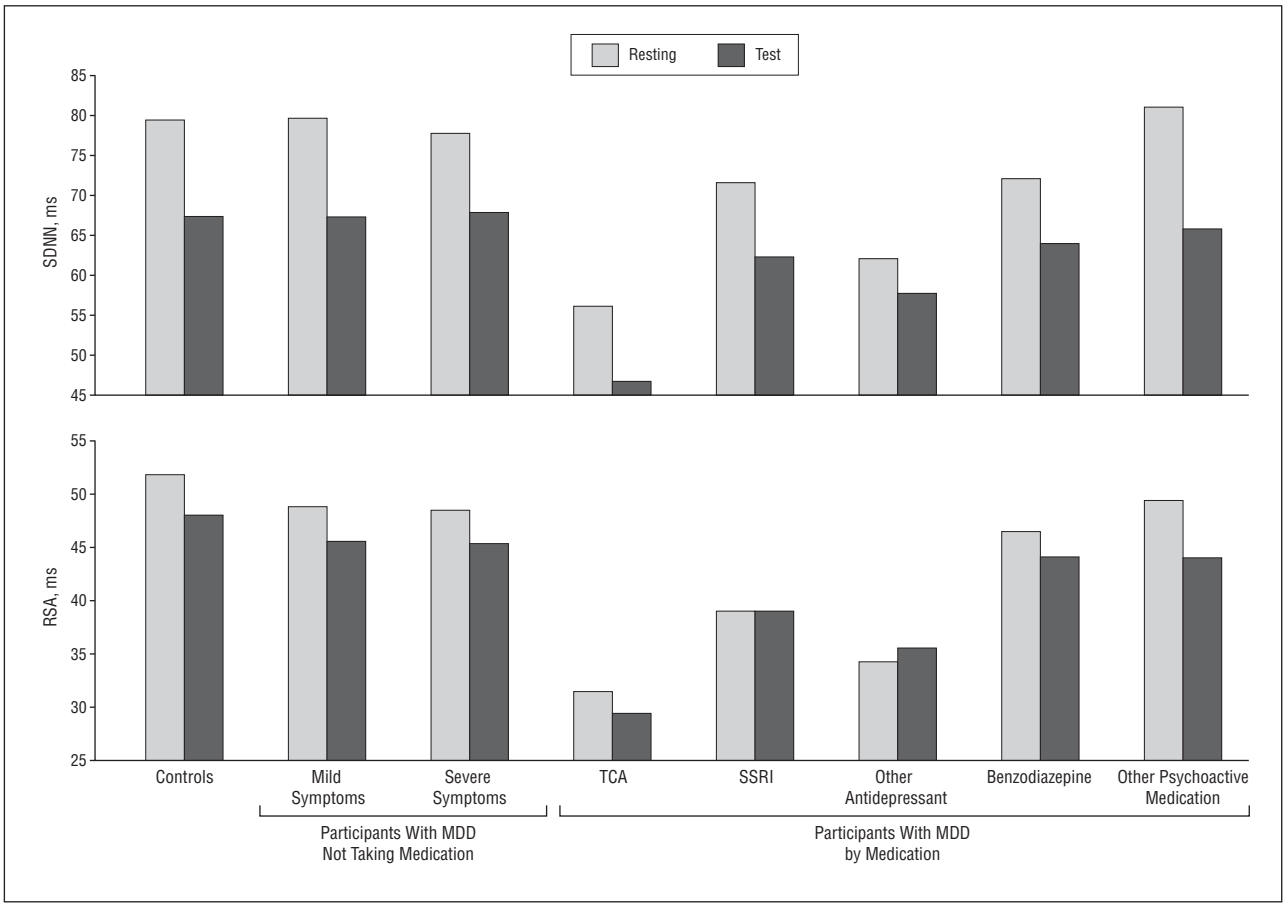

Figure 2. Mean adjusted standard deviation of normal-to-normal beats (SDNN) and respiratory sinus arrhythmia (RSA) in major depressive disorder (MDD) medication group for resting and test conditions. Values were adjusted for respiration rate, age, sex, education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic diseases, and heart medication. Mild MDD was defined as a score of less than 25 on the 30-item Inventory of Depressive Symptomatology, Self-Report; severe MDD was defined as a score of 25 or greater. SSRI indicates selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

vs MDD participants with IDS-SR scores <25, $P=.08$; controls vs MDD participants with IDS-SR scores ≥ 25, $P=.07$).

Depressed participants taking benzodiazepines did not differ from controls by SDNN or RSA (Figure 2 and Table 3). In contrast, SDNN and RSA differed significantly between controls and depressed individuals taking TCAs, SSRIs, or other antidepressants in both conditions ($P \leq .002$, all). Depressed participants using one of these medications had significantly lower SDNNs and RSAs than controls, with effect sizes ranging from 0.207 to 0.862.

Table 4 presents the results of partial correlations between the derived daily dose of each antidepressant group and their correlations with SDNN and RSA. Correlations were only calculated for medication types that were used by at least 20 participants. All antidepressants had a negative correlation with the heart rate variability measures, indicating that SDNN and RSA were lower when dosage was higher. Within medication classes (TCAs, SSRIs, and other antidepressants), correlations were similar and consistent across medication types. Differences between significant and nonsignificant correlations are therefore mainly due to differences in sample size and very likely not due to differential effects for specific medications within medication type. Repeating all of these analyses using RMSSD yielded a very similar pattern of results (data not shown).

COMMENT

This large-scale cohort study showed rather clearly that, when compared with healthy controls, depressed individuals have significantly lower total heart rate variability and significantly lower heart rate variability in the respiratory frequency range, which is considered to reflect lower cardiac vagal control.[23,50] This is in keeping with a previous meta-analysis of much smaller studies.[22] Comorbid anxiety or lifestyle factors, including physical activity, did not explain the lower SDNNs or RSAs in depressed individuals. Instead, the association appeared to be driven mainly by the effects of antidepressants. Depressed participants taking antidepressants showed significantly lower SDNNs ($d=0.207$ to $d=0.849$) and lower RSAs ($d=0.413$ to $d=0.862$), whereas differences between controls and depressed individuals not taking antidepressants were much smaller for RSA (approximately, $d=0.118$) and even nonsignificant for SDNN.

We found not only consistently lower SDNNs and RSAs in depressed patients using TCAs, SSRIs, and other antide-

Table 4. Correlation Between Derived Daily Dose (DDD) and SDNN or RSA Among Depressed Individuals Using Psychoactive Medication

Psychoactive Medication	No. of Participants	DDD,[a] Mean (SD)	Resting Condition				Test Condition			
			DDD and SDNN[b]		DDD and RSA[b]		DDD and SDNN[b]		DDD and RSA[b]	
			r	*P* Value	*r*	*P* Value	*r*	*P* Value	*r*	*P* Value
Tricyclic antidepressants										
All combined	67	0.85 (0.59)	−0.295	.02	−.281	.03	−0.394	.002	−0.335	.008
Clomipramine	28	0.93 (0.52)	−0.316	.12	−.304	.14	−0.504	.01	−0.290	.16
Amitriptyline	30	0.67 (0.56)	−0.276	.16	−.271	.17	−0.317	.11	−0.252	.22
SSRIs										
All combined	435	1.36 (0.65)	−0.205	<.001	−0.161	<.001	−0.204	<.001	−0.168	<.001
Fluoxetine	59	1.31 (0.52)	−0.219	.12	−0.080	.57	−0.148	.29	−0.121	.39
Citalopram	97	1.43 (0.65)	−0.189	.07	−0.186	.08	−0.167	.11	−0.148	.16
Paroxetine	197	1.27 (0.56)	−0.235	.001	−0.169	.02	−0.224	.002	−0.166	.02
Sertraline	43	1.72 (0.93)	−0.142	.38	−0.112	.49	−0.342	.03	−0.266	.10
Fluvoxamine	46	1.29 (0.61)	−0.159	.33	−0.274	.09	−0.114	.49	−0.215	.18
Other antidepressants										
All combined	137	1.26 (0.60)	−0.151	.09	−0.278	.001	−0.201	.02	−0.295	.001
Mirtazapine	36	1.03 (0.44)	−0.147	.42	−0.204	.26	−0.348	.05	−0.248	.17
Venlafaxine	100	1.31 (0.60)	−0.168	.10	−0.069	.51	−0.188	.06	−0.110	.28

Abbreviations: RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal beats; SSRI, selective serotonin reuptake inhibitor.
[a] Derived daily dose is expressed as the daily dose used by participants divided by the defined daily dose assigned by the World Health Organization. The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. Analyses for specific psychoactive medications were performed when at least 20 participants were using that particular medication.
[b] Adjusted for sex and age.

pressants, but also an indication for a dose-response effect for all 3 medication classes, as a higher derived daily dose was significantly associated with lower heart rate variability. The lower SDNNs and RSAs in TCA and other antidepressant users compared with controls were consistent with results from other studies.[27-33] Rechlin[29] found a decrease in heart rate variability in amitriptyline users (n=8) compared with nonmedicated depressed patients (n=32). Tulen et al[30] also reported such an effect for imipramine (n=10) and mirtazapine (n=10). In addition, Volkers et al[33] found a reduction in parasympathetic activity after use of imipramine (n=17) and fluvoxamine (n=24). Roose et al[32] also found a reduction in heart rate variability ($P<.01$) and an 11% increase in heart rate ($P<.001$) after nortriptyline treatment (n=40). Our results also agree with those obtained by Glassman et al[31] in the Sertraline Antidepressant Heart Attack Randomized Trial. In 258 patients with acute coronary syndrome who were randomized to either placebo or sertraline after a coronary event, power in the low-frequency range significantly decreased in the sertraline group and high-frequency power decreased by 9.2% during treatment, though this difference failed to be significant.

Although antidepressant medication explained a large part of the observed differences in RSA between the depressed and nondepressed groups, we also found somewhat lower RSAs in nonmedicated depressed individuals than in controls. These effects of depression, which were not significantly present for SDNN, do not seem to be caused by depressed mood at the time of baseline assessment, independent of a history of depression. Respiratory sinus arrhythmia was not lower in the current MDD group than in the remitted MDD group. Instead, both groups had significantly lower cardiac vagal control compared with controls. Hence, our results are compatible with theoretical models, like the polyvagal theory, that have explicitly linked the parasympathetic nervous system to the etiology of depression, in part because impairments of low vagal tone are associated with reduced social engagement and a less flexible behavioral response to environmental changes.[19-22] In the context of this theory, it has been suggested that depressed individuals may show less context-appropriate vagal withdrawal.[22,57] A limitation of our study is that it cannot directly test this theory, as this requires task manipulations that induce a substantial amount of stress, which were not included in NESDA. Our contrast between resting and test conditions does not qualify as stress manipulation and was also confounded with a postural change (supine vs sitting). Consequently, we could not assess the effect of depression on stress-induced vagal reactivity.

The association between antidepressant use and low heart rate variability was robust in our study, but we acknowledge that the cross-sectional setup is a further limitation of our study. Without experimental longitudinal data, we do not know whether antidepressants caused the low SDNNs and RSAs or whether such effects would be reversed when individuals stop taking their medications. We also cannot completely exclude the possibility that depressed individuals taking antidepressants differed from the depressed individuals not taking medication by 1 or more clinical aspects. However, the most likely aspect, difference in depression symptom severity, did not seem to explain the findings. These study limitations are balanced by strong points. We used a large sample of patients, both medicated and nonmedicated, who were ascertained in multiple ways to obtain a representative population sample of patients. In addition, the availability of prolonged ambulatory recordings in the nearly complete sample provided us with stable and reliable indicators of heart rate variability.

Our findings demonstrate that depressed persons have lower total heart rate variability with lower cardiac vagal control, but these effects are mostly derived from depressed persons using antidepressants. Because it has been widely established that lowered heart rate variability is a risk factor for cardiovascular morbidity and mortality,[12-18] our findings could be of importance to clinical practice. It is an open question whether the lower SDNNs and RSAs outweigh the beneficial effects of antidepressant medication on future heart disease. In view of the large number of patients comorbid for depression and heart disease, we argue that this question needs to be addressed.

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Author Affiliations: Department of Psychiatry, Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, the Netherlands (Ms Licht and Drs Hoogendijk, van Dyck, and Penninx); Department of Biological Psychology (Dr de Geus), and Center for Neurogenomics and Cognitive Research (Drs de Geus and Hoogendijk), Vrije Universiteit, Amsterdam; Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands (Drs Zitman and Penninx); and Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands (Dr Penninx).
Correspondence: Brenda W. J. H. Penninx, PhD, Department of Psychiatry, VU University Medical Center, AJ Ernststraat 887, 1081 HL, Amsterdam, the Netherlands (b.penninx@vumc.nl).
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