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ORIGINAL ARTICLE

Association Between Smoking and Heart Rate Variability Among Individuals with Depression

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Abstract
Background Both depression and smoking have been independently associated with lower heart rate variability (HRV), suggesting dysregulation of cardiac autonomic function. However, no studies have systematically explored the effects of smoking on HRV among depressed patients.
Purpose This study examined differences in HRV based on smoking status among depressed individuals.
Methods Electrophysiological data were examined among 77 adult outpatients without a history of myocardial infarction, who met criteria for major depressive disorder or dysthymia. Frequency domain [low frequency (LF), high frequency (HF), LF/HF ratio, respiratory sinus arrhythmia (RSA)] parameters of HRV, and heart rate and inter-beat interval (IBI) data were compared between depressed smokers (n=34) and depressed nonsmokers (n=44).
Results After controlling for covariates, depressed smokers, compared to depressed nonsmokers, displayed significantly lower LF, HF, and RSA.
Conclusions Among depressed patients, smoking is associated with significantly lower HRV, indicating dysregulated autonomic modulation of the heart.

Keywords Smoking · Depression · Heart rate variability · Cardiac autonomic regulation · Autonomic nervous system

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Major depressive disorder (MDD) and dysthymia are among the most common psychiatric disorders in the United States, with lifetime prevalence rates estimated at 16 and 3 %, respectively [1]. Depression is a significant public health problem that is associated with functional impairment and increased healthcare expenditures [2]. In fact, it is projected that depression will be the second largest global disease burden by the year 2020, second only to cardiovascular disease (CVD) [3]. Accumulating evidence suggests that these two conditions may be interrelated. Specifically, 20–40 % of patients with CVD have comorbid depression [4, 5], and those with MDD are at significant risk for the progression of CVD [6] and cardiac mortality [7–9].

This covariation between depression and heightened risk of cardiac events has led to the hypothesis that alterations in cardiac autonomic balance may serve as a physiological mechanism underlying this relationship. These alterations in the autonomic nervous system, typically evidenced by decreased parasympathetic and increased sympathetic modulations [10], have been associated with reduced heart rate variability (HRV). HRV is a measure of vagal tone, and reflects the degree of variability from mean heart rate across time. While at rest, heart rate occurs naturally in irregular intervals, due to parasympathetic dominance, which slows heart rate. Conversely, sympathetic nervous system activation accelerates heart rate thereby decreasing HRV. High

variability in beat-to-beat intervals is a sign of healthy cardiac function, which helps to buffer against possible adverse cardiac events [11]. High sympathetic tone, reflected as reductions in HRV, makes the heart vulnerable to arrhythmia and sudden death [12]. A growing body of literature has demonstrated that depressed patients exhibit dysfunctional HRV, as evidenced by lower levels of time-domain measures (i.e., standard deviation of the normal inter-beat intervals) and lower levels of frequency-domain indices (power spectrum data capturing high-frequency and low-frequency ranges) [13]. These results underscore the possibility that patients with clinical depression experience considerable autonomic dysregulation [14], which in turn, may explain their unfavorable health outcomes.

In concert with the deleterious effects of clinical depression on vagal tone, cigarette smoking has also been shown to negatively affect cardiac autonomic function. Specifically, chronic smokers free from cardiac and cardiovascular disease, compared to non-smokers, display reduced indices of HRV [15]. In addition, duration of smoking has been found to be inversely associated with measures of HRV [15]. Studies examining the temporal effects of cigarette smoking on cardiac modulation have provided additional evidence supporting the impact of tobacco on HRV. Specifically, among long-term smokers, cigarette smoking appears to acutely instigate cardiac dysregulation [16, 17], whereas smoking cessation acutely enhances autonomic cardiac tone [18, 19].

Individuals with depression are significantly more likely than the general population to be smokers [20] and have greater difficulties quitting smoking [21]. Given that both depression and cigarette smoking adversely affect autonomic cardiac function, it is reasonable to believe that both of these conditions may simultaneously affect HRV. Although several studies have acknowledged the influence of tobacco use on cardiovascular activity among depressed individuals by including smoking status as a covariate in multivariate analysis [22, 23], no studies have *systematically* explored the negative effects of smoking on HRV among depressed patients. Given the public health consequences associated with both smoking and depression, it is important to examine the potential harmful effects of smoking on cardiac autonomic functioning among individuals diagnosed with depression; a group that is already at elevated risk for cardiac events.

The primary aim of the present study was to examine differences in frequency-domain measures of HRV as a function of smoking status among clinically depressed patients, all of whom had no history of myocardial infarction. A secondary aim was to examine associations between depression severity and HRV, smoking characteristics (frequency, duration, and expired-air carbon monoxide (CO) levels at time of testing) and HRV, as well as examine whether depression severity moderated associations between smoking status and HRV.

Method

Participants

Participants were 77 veterans (67 males, ten females) referred by VA Boston Healthcare System mental health providers and via flyers posted within the medical center. Inclusionary criteria for the current report were comprised of: (a) being an adult between the ages of 18 and 70; (b) a DSM-IV [24] diagnosis of MDD and/or dysthymia; and (c) ability to read and write English. Exclusionary criteria included: (a) a bipolar spectrum disorder (i.e., bipolar I/II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified); (b) presence of a psychotic-spectrum diagnosis; (c) current suicidal or homicidal intent and/or plan; (d) unstable and severe psychiatric symptoms (e.g., psychiatric hospitalization within the last 2 months verified by medical chart review, and/or symptoms that interfered with a participant's ability to engage in study screening procedures); (e) lifetime history of myocardial infarction; and (f) limited mental competency and/or inability to provide informed, written consent.

During an initial telephone interview, potential participants were given a detailed description of the study and engaged in a preliminary screen to determine primary inclusion/exclusion criteria, socio-demographic information, and medical conditions. Screenings were conducted by a trained research assistant, and reviewed by the second author. Individuals who met eligibility criteria for the study were scheduled to present to the laboratory on average within 19 days of the initial telephone interview. All participants were asked to refrain from using any illicit substances and/or alcohol before entering the laboratory. Participants who smoked were asked to bring their preferred cigarettes to the laboratory and permitted to smoke ad lib during circumscribed periods throughout the study visit. Therefore, they entered the laboratory at their preferred nicotine levels.

Measures

Diagnostic Interview and Self-Report Outcome Measures

Participants were assessed for all current (past month) DSM-IV axis I disorders (including MDD and dysthymia) with the Structured Clinical Interview for the DSM-IV Axis I Disorders, Patient Edition, with psychotic screen (SCID-I/P (w/Psychotic Screen) [25]). Severity of depressive symptoms was assessed using the Beck Depression Inventory-II (BDI-II; 26), which is a 21-item self-report instrument that has demonstrated excellent test–retest reliability and good validity [26]. Participants also completed a survey assessing socio-demographic characteristics (age, education level, gender, ethnicity, and marital status) and medical history (e.g., medical condition(s) and current medications). Medical history

was collected during an initial phone screening interview, and self-reported medication use was verified with participant's medical records using the VA centralized patient record system. Smoking characteristics included current smoking frequency (number of cigarettes/day during past 7 days) and smoking duration. Nicotine dependence was assessed via the six-item Fagerstrom Test for Nicotine Dependence [27].

Heart Rate Variability Measures

HRV measures were derived according to the recommendations of the Society for Psychophysiological Research Committee on Impedance Cardiography [28]. All cardiac data was measured using a three-channel electrocardiograph. These signals were collected in real-time using a MindWare BioLab 2.4 acquisition system (MindWare Technologies, Gahanna, OH, USA), which was then digitized (1,000 Hz) using an analog-to-digital conversion board. A series of inter-beat intervals (IBI, based on detection of QRS complexes, part of the electrocardiographic wave representing ventricular depolarization) were automatically derived by the BioLab software, and mean IBI and mean heart rate (HR) were calculated. Artifacts were identified automatically by the algorithm developed by Berntson and colleagues [29], and edited accordingly. Frequency-domain parameters of HRV were calculated using Fast Fourier Transform to derive the spectral distribution. Indices included (in milliseconds squared) low-frequency (LF) power (.04–.15 Hz), high-frequency (HF) power (.15–.40 Hz), and the ratio of these two indices (LF/HF), which reflected sympathovagal balance [30]. Finally, respiratory sinus arrhythmia (RSA; cardiac vagal control assessed within the respiratory frequency range [31]) was quantified as the integral power within the respiratory frequency band (0.12 to 0.40 Hz).

Procedures

Upon arrival to the laboratory, all study procedures were reviewed and participants provided written, informed consent. Expired-air blood alcohol levels were then assessed via a portable breathalyzer (Prestige AL6000; AK Solutions, Palisades Park, NJ, USA) to confirm sobriety. Smoking status was objectively confirmed via expired-air carbon monoxide levels using a hand-held breathalyzer (EC50 Micro 4; Bedfont Scientific Ltd, Harrietsham, Kent, England). Participants then completed a diagnostic clinical interview (i.e., SCID-I/P) to determine final eligibility. Immediately afterward, all participants completed psychiatric and smoking-related self-report questionnaires as described above. Physiological data was collected during spontaneous breathing for all participants individually while sitting upright in a comfortable chair in a quiet room in the laboratory. During data collection, participants were asked to stare at a blank screen approximately 6 ft in front of them. Electrocardiographic recordings were assessed between 12 pm and 3 pm in an attempt to reduce circadian variation of HRV parameters. Electrocardiographic data were measured using 8-mm disposable electrodes filled with electrolyte paste and placed on the left and right forearms. Respiration rate was measured using a respiration monitor belt (MindWare Technologies, Gahanna, OH, USA) fitted around the chest of the participant. Electrocardiographic and respiration parameters were collected for 18 consecutive minutes and consisted of: (a) an initial 5-min resting period; (b) an 8-min experimental period, during which participants engaged in mood-induction tasks; and (c) a 5-min recovery period. For the purposes of the current study, only electrocardiographic and respiration data from the initial 5-min resting period were examined. All study procedures were approved by the local Institutional Review Board.

Statistical Analysis

Participants reporting zero cigarettes/day were classified as nonsmokers, whereas those reporting one or more cigarettes/day were classified as smokers. Pack years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years smoked. Outcome data that were more than ±3 standard deviations from the mean were identified as statistical outliers and removed from all analyses. Comparisons of demographic, psychiatric, and medical characteristics between depressed smokers and depressed nonsmokers were compared with *t* tests or Pearson chi-squared tests, as appropriate. Fisher's exact tests were used in cases with low cell counts. Characteristics shown to differ significantly ($p<.05$) between smokers and nonsmokers (gender, marital status, chronic disease status [not including CVD or hypercholesterolemia], anti-depressant medication use, and use of angiotensin-converting enzyme (ACE) inhibitor antihypertensive medications) were entered as covariates in all multivariate analyses. Age and current use of beta-blocker medications were also included as theoretically driven covariates, given that both variables previously have been associated with HRV parameters [32–34]. Finally, respiration rate was included as a covariate, given that this measure covaries with RSA [35]. Main effects of smoking status were examined for all electrophysiological outcome measures (IBI, HR, RSA, LF, HF, and LF/HF) using general linear modeling, using one-way analysis of covariance models.

To examine the secondary aims, covariation between depression severity and all HRV parameters was examined via a series of hierarchical linear regression models with the above covariates entered in step 1 of the model, and BDI-II score entered in step 2 of the models. To explore whether depression severity moderated associations between smoking status and HRV, hierarchical linear regression analyses were performed with covariates entered in step 1, smoking status and BDI-II score entered in step 2, and the interaction term for smoking

and BDI-II score entered in step 3. These models were run separately for all HRV parameters. A final set of hierarchical linear regression analyses was utilized among the subsample of depressed smokers to examine the unique associations between smoking frequency (cigarettes/day), smoking duration (years), pack years, and expired-air CO levels, and each HRV outcome variable. In these analyses, the above covariates, with the addition of BDI-II score, were entered in step 1 of the model, and smoking characteristics were entered in step 2 of the models. All analyses were performed using SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Participant Characteristics

The total sample (n=77) ranged in age from 25 to 70 years with a mean age of 50.57 years (SD=10.69). The majority of the sample was White (79.2 %); breakdowns of other races/ethnicities were as follows: 11.7 % Black/African-American; 3.9 % Latina/o; 2.6 % Asian; and 2.6 % "other." With respect to psychiatric diagnosis, 69 participants were diagnosed with MDD only, four with dysthymia only, and four with both MDD and dysthymia. Overall, depression symptomatology as assessed by the BDI-II was in the severe range (M=31.06; SD=9.82), and participants reported a mean symptom duration of 24.82 years (SD=16.62). The majority of the sample (67.5 %) reported taking an anti-depressant medication at the time of enrollment (SSRI: n=30, SNRI: n=8, SARI: n=7, NDRI: n=15, tricyclics: n=3, and tetracyclics: n=5). Twenty-three participants reported hypertension; no participants reported any other form of CVD (e.g., coronary artery disease, cardiac dysrhythmia, and history of myocardial infarction). All participants who reported hypertension were taking blood pressure-lowering medications (ACE inhibitors: n=10, calcium channel blockers: n=3, *beta blockers:* n=7, diuretics: n=8, and angiotensin II receptor antagonists: n=2). Fifteen participants reported hypercholesterolemia and all were taking cholesterol-lowering medications (i.e., HMG-CoA reductase inhibitors [statins]). Rates of hypertension, χ^2 (1)=3.36, p=.07, φ=.24, and hypercholesterolemia, χ^2 (1)=.42, p=.52, φ=.11, did not differ between smokers and nonsmokers. The subsample of depressed smoking participants (n=34), reported smoking an average of 14.91 (SD=7.33) cigarettes per day, for a mean duration of 27.91 years (SD=13.59), resulting in an average of 22.38 pack years (SD=16.50). Smoking participants reported a moderate level of nicotine addiction per the Fagerstrom Test for Nicotine Dependence (M=4.97; SD=2.47).

Comparisons between depressed smokers (n=34) and depressed nonsmokers (n=43) indicated that these groups differed with respect to gender, marital status, chronic disease status, and expired-air CO levels (see Table 1). Specifically, depressed smokers were less likely to be married, χ^2 (1)=9.53, p=.002, φ=.35; less likely to have a chronic medical condition, χ^2 (1)=6.05, p=.01, φ=.28; more likely to be male, χ^2 (1)=5.44, p=.02, φ=.27; and had higher expired-air CO levels, t(74)=8.10, p<.001, d=2.14. With respect to medication use, depressed smokers reported lower rates of anti-depressant medication, χ^2 (1)=8.54, p=.003, φ=.33, as well as lower rates of ACE inhibitors, χ^2 (1)=5.44, p=.02, φ=.27. The groups did not differ in their use of any other class of antihypertensive medication, nor did they differ in rates of statin use.

Analyses of Heart Rate Variability

There were significant between-group differences in HRV parameters as a function of smoking status for measures of RSA, LF, and HF (see Table 2). After controlling for covariates, depressed smokers, compared to depressed nonsmokers, demonstrated significantly lower RSA, F(1, 68)=9.60, p=.003, η^2=.13, power=.86; LF, F(1, 66)=12.74, p=.001, η^2=.17, power=.94; and HF, F(1, 63)=7.38, p=.009, η^2=.11, power=.76. Depressed smokers and depressed nonsmokers did not differ with respect to IBI, F(1, 68)=.19, p=.67, η^2=.003; HR, F(1, 68)=.20, p=.66, η^2=.003; and LF/HF ratio, F(1, 66)=.39, p=.53, η^2=.01. However, post hoc power analyses based upon observed effect sizes [36] revealed that these latter analyses were underpowered (IBI: power=.07; HR: power=.07; LF/HF: power=.10).

After controlling for covariates, depression severity as measured by the BDI-II was not associated with any of the HRV parameters (βs, .08–.17; ts, .56–1.34; ps, .19–.58; sr^2, .01–.02), nor were there any significant smoking status by depression level interaction effects (βs, .31–.75; ts, .79–1.75; ps, .08–.43; sr^2, .01–.04). Post hoc power analyses revealed that analyses of the interaction effects for HF (power, .80) and LF (power, .86) were adequately powered. However, analyses exploring associations between depression severity and all HRV indices (Power, .05–.60), as well as the majority of analyses exploring the interaction between smoking status and depression severity on HRV parameters (IBI, HR, RSA, LF/HF, power, .09–.67) were underpowered.

Among the subset of depressed smokers (n=34), hierarchical linear regression analyses revealed that, after controlling for covariates, there were no unique associations between either current smoking rate (βs, .06–.27; ts, .42–2.05; ps, .09–.68; sr^2, .003–.05), smoking duration (βs, .002–.27; ts, .01–1.37; ps, .19–.99; sr^2, <.001–.05), pack years (βs, <.001–.24; ts, <.001–1.61; ps, .12–.99; sr^2, <.001–.04), or expired-air CO levels (βs, .04–.26; ts, .28–1.43; ps, .17–.81; sr^2, <.001–.05) and any index of HRV. Post hoc power analyses

Table 1 Demographic, psychiatric, and medical characteristics of the depressed participant sample as a function of smoking status

Characteristic	Smokers (n=34)		Nonsmokers (n=43)		
	Mean (SD)	n (%)	Mean (SD)	n (%)	ES[a]
Age (years)	49.85 (10.14)		51.14 (11.19)		0.11
Education (years)	13.09 (1.51)		14.14 (2.02)		0.56
Gender					
Male		33 (97.1)		34 (79.1)	
Female		1 (2.9)		9 (20.9)	0.27*
Ethnicity					
White/Caucasian		26 (76.5)		35 (81.4)	
Black/African-American		6 (17.6)		3 (7.0)	
Latina/o		1 (2.9)		2 (4.7)	
Asian/Asian-American		1 (2.9)		1 (2.3)	
Other		0 (0.0)		2 (4.7)	0.22
Marital status					
Married		4 (11.8)		19 (44.2)	
Unmarried		30 (88.2)		24 (55.8)	0.35***
Number of axis I diagnoses[b]	3.15 (1.76)		2.86 (1.49)		0.18
Comorbid anxiety disorder		24 (70.6)		32 (74.4)	0.04
BDI-II score	32.18 (8.26)		30.19 (10.92)		0.21
Alcohol dependence, current[b]		5 (14.7)		5 (11.6)	0.05
CO level (ppm)[c]	10.00 (5.67)		1.36 (.53)		2.14***
Chronic medical condition[d]		16 (47.1)		32 (74.4)	0.28**
Cardiovascular disease		6 (17.6)		17 (39.5)	0.24
Hypercholesterolemia		5 (14.7)		10 (23.3)	0.11
Anti-depressant medication use		17 (50.0)		35 (81.4)	0.33***
Antihypertensive medication use		6 (17.6)		14 (32.6)	0.17
ACE inhibitor		1 (2.9)		9 (20.9)	0.27*
Calcium channel blocker		1 (2.9)		2 (4.7)	0.04
Beta blocker		1 (2.9)		6 (14.0)	0.19
Diuretic		4 (11.8)		4 (9.3)	0.04
Angiotensin II receptor antagonist		1 (2.9)		1 (2.3)	0.02
Anti-hypercholesterolemia medication use		5 (14.7)		9 (20.9)	0.08

N=77

CO carbon monoxide, *ES* effect size, *BDI-II* Beck Depression Inventory—II (BDI-II; 26), *ppm* parts per million

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

[a] Effect sizes reported as Cohen's d and Cramer's φ for continuous and categorical variables, respectively

[b] Assessed with the SCID-I for the DSM-IV [25]

[c] Statistical outlying data was removed for one participant

[d] Not including cardiovascular diseases and hypercholesterolemia. Chronic medical conditions were evaluated by self-report and included diseases of the nervous system (epilepsy, migraines, neuropathy, fibromyalgia, and multiple sclerosis), respiratory system (chronic obstructive pulmonary disease, asthma, and sleep apnea), endocrine system (diabetes), genitourinary system (endometriosis), digestive system (hepatitis and esophageal reflux), musculoskeletal system (arthritis, osteoarthritis, disk disorder, and carpel tunnel), as well as cancer

demonstrated that associations between smoking frequency, smoking duration, pack years, and expired-air CO levels and HF (power, .97–.98) and RSA (power, .92–.98) were adequately powered. However, analyses were inadequately powered with respect to IBI (power, .09–.15), HR (power, .07–.11), LF (power, .30–.38), and LF/HF ratio (power, .48–.51).

Discussion

The current study examined differences in cardiac autonomic function (assessed via HRV) as a function of smoking status among clinically depressed participants with no history of myocardial infarction. Results indicated that, among

Table 2 Electrophysiological measures of heart rate variability among depressed participants as a function of smoking status

Characteristic	Smokers (n=34)		Nonsmokers (n=43)				
	Mean	SD	Mean	SD	$(F)^a$	p value	η^2
Interbeat interval (ms)[b]	823.05	136.79	852.34	125.13	.19	.67	.003
Heart rate (bpm)[b]	74.03	10.80	71.95	10.37	.20	.66	.003
Respiratory sinus arrhythmia (ms^2)[b]	4.30	1.44	4.98	1.69	9.60	.003	.13
Low-frequency power (ms^2)[c]	105.16	87.22	215.33	201.41	12.74	.001	.17
High-frequency power (ms^2)[d]	180.90	289.71	324.40	409.78	7.38	.009	.11
LF/HF (ms^2)[c]	1.16	.88	1.01	1.11	.39	.53	.01

N=77. Means represent estimated marginal means

LF/HF low-frequency to high-frequency ratio

[a] Model adjusted for gender, marital status, comorbid non-cardiovascular chronic disease status, anti-depressant medication use, use of cardiovascular/heart medication, and respiration rate

[b] Statistical outlying data was removed for one participant

[c] Statistical outlying data was removed for three participants

[d] Statistical outlying data was removed for six participants

the subset of HRV parameters examined, depressed smokers (compared to depressed nonsmokers), displayed significantly lower LF, HF, and RSA. Taken together, these results indicated that depressed smokers displayed increased sympathetic tone and worse autonomic cardiac function compared to depressed nonsmokers, even after controlling for demographic and medical characteristics, as well as medication use. These findings are in line with other studies demonstrating that both time- and frequency-domain indices of HRV are lower among smokers compared to nonsmokers [15, 16, 37, 38].

Regarding secondary aims, depression level—irrespective of smoking status—was not associated with HRV, nor was there a significant smoking status by depression severity interaction. Given that the sample was comprised entirely of individuals meeting diagnostic criteria for MDD and/or dysthmia, this may suggest that *severity* of depression symptoms does not contribute to cardiac dysregulation above and beyond the *breadth* of symptoms necessary for a clinical diagnosis. Alternatively, restricted range in depression scores in the study's clinical sample may have contributed to lack of significant associations between depression and HRV outcomes. Furthermore, it is possible that, had this study also recruited non-depressed participants, we would have observed differences in HRV parameters as a function of depression diagnosis, and perhaps a depression diagnosis by smoking status interaction effect.

Secondary aims of the present study also included examining associations between smoking characteristics and HRV parameters. Interestingly, there were no associations between smoking characteristics (frequency, duration, pack years, and expired-air CO levels) and any electrophysiological measure, among the subsample of smokers. This may be attributable to the fact that any level of smoking may have deleterious effects on cardiac autonomic function, thereby making lighter smokers indistinguishable from heavy smokers with respect to HRV parameters. In fact, it has been shown that inhalation of even a single cigarette acutely instigates cardiac dysregulation [39]. Similar findings have been observed for a single dose of nicotine gum (approximately equivalent to one cigarette) [40]. Alternatively, the sample size for the within smoking group analyses was relatively small (n=34), which resulted in insufficient power to detect statistically significant relations between smoking measures and a number of indices of HRV. Thus, larger studies are needed to better characterize the relationships between measures of smoking intensity and HRV among individuals with depression, dimensional effects of depression severity on HRV, and the interaction between smoking and depression on HRV.

Although several studies examining the effects of tobacco use on cardiovascular activity among depressed individuals have included smoking status as a covariate in multivariate analysis [22, 23], to our knowledge, the present study was the first to systematically explore the negative effects of smoking on HRV among depressed patients. Despite this investigation's novel findings, several study limitations should be noted. First, the data were cross-sectional in nature and, therefore, direct casual inferences cannot be made. The association between smoking, depression, and cardiac function warrants further investigation, using longitudinal designs in various populations, in order to establish direct causal influences of depression and smoking on autonomic function. Second, time-domain HRV parameters were not assessed in the present study, given that the initial version of the software program used did

not support the processing of these parameters. However, frequency domain analyses enjoy widespread use and have a number of advantages over time-domain measures [41]. Lastly, similar to other studies involving veteran participants, there was a preponderance of men (87 %), especially among the smoking subgroup (97 %) in the study sample. Thus, results should be interpreted cautiously, particularly when translating study findings to women.

In conclusion, results of the present study indicated that cigarette smoking was associated with increased autonomic dysregulation among individuals diagnosed with clinical depression. These results are noteworthy given the frequent co-occurrence of depression and smoking and the fact that depressed patients are already at elevated risk for cardiac events. Although in need of replication and further study, findings from the current investigation suggest that smoking increases these risks further among depressed groups, potentially by promoting additional disruptions in healthy cardiac function.

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Equity Holdings: Compellis

Royalty/Patent, *Other Income*: Patent for Sequential Parallel Comparison Design (SPCD) and patent application for a combination of azapirones and bupropion in Major Depressive Disorder (MDD), copyright royalties for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER. Patent for research and licensing of SPCD with RCT Logic; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd.

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References

1. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatr*. 2005;62:617-627.
2. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder. *J Am Med Assoc*. 2003;289:3095-3105.

3. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet*. 1997;349:1498-1504.
4. Carney RM, Rich MW, Tevelde A, et al. Major depressive disorder in coronary artery disease. *Am J Cardiol*. 1987;60:1273-1275.
5. Gonzalez MB, Snyderman TB, Colket JT, et al. Depression in patients with coronary artery disease. *Depression*. 1996;4:57-62.
6. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*. 1996;93:1976-1980.
7. Baune BT, Adrian I, Jacobi F. Medical disorders affect health outcome and general functioning depending on comorbid major depression in the general population. *J Psychosom Res*. 2007; 62:109-118.
8. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: Epidemiology, biology, and treatment. *Arch Gen Psychiatr*. 1998;55:580-592.
9. Penninx BWJH, Beekman ATF, Honig A, et al. Depression and cardiac mortality: Results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58:221-227.
10. Miyawaki E, Salzman C. Implications and potential uses of heart rate variability. *Integr Psychiatr*. 1991;7:21-28.
11. Bigger JT, Kleiger RE, Fleiss JL, et al. Components of heart rate variability measured during healing of acute myocardial infarction. *Am J Cardiol*. 1988;61:208-215.
12. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*. 2003;107:565-570.
13. Kemp AH, Quintana DS, Gray MA, et al. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biol Psychiatry*. 2010;67:1067-1074.
14. Nahshoni E, Aravot D, Aizenberg D, et al. Heart rate variability in patients with major depression. *Psychosomatics*. 2004;45:129-134.
15. Barutcu I, Esen AM, Kaya D, et al. Cigarette smoking and heart rate variability: Dynamic influence of parasympathetic and sympathetic maneuvers. *Ann Noninvasive Electrocardiol*. 2005; 10:324-329.
16. Hayano J, Yamada M, Sakakibara Y, et al. Short-and long-term effects of cigarette smoking on heart rate variability. *Am J Cardiol*. 1990;65:84-88.
17. Kobayashi F, Watanabe T, Akamatsu Y, et al. Acute effects of cigarette smoking on the heart rate variability of taxi drivers during work. *Scand J Work Environ Health*. 2005;31:360-366.
18. Stein PK, Rottman JN, Kleiger RE. Effect of 21 mg transdermal nicotine patches and smoking cessation on heart rate variability. *Am J Cardiol*. 1996;77:701-705.
19. Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. *Hypertension*. 1999;33:586-590.
20. Lasser K, Boyd J, Woolhandler S, et al. Smoking and mental illness: A population-based prevalence study. *J Am Med Assoc*. 2000;284:2606-2610.
21. Niaura R, Britt DM, Shadel WG, et al. Symptoms of depression and survival experience among three samples of smokers trying to quit. *Psychol Addict Behav*. 2001;15:13-17.
22. Kamphuis MH, Geerlings MI, Dekker JM, et al. Autonomic dysfunction: A link between depression and cardiovascular mortality? The FINE Study. *Eur J Cardiovasc Prev Rehabil*. 2007;14:796-802.
23. Licht CM, de Geus EJ, Zitman FG, et al. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry*. 2008;65:1358-1367.
24. American Psychiatric Association: Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author, 1994.
25. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/PSY SCREEN)*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
26. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory manual*. 2nd ed. San Antonio: The Psychological Corporation; 1996.
27. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. *Br J Addict*. 1991;86:1119-1127.
28. Berntson GG, Bigger JT, Eckberg DL, et al. Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology*. 1997;34:623-648.
29. Berntson GG, Quigley KS, Jang JF, Boysen ST. An approach to artifact identification: Application to heart period data. *Psychophysiology*. 1990;27:586-598.
30. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res*. 1986;59:178-193.
31. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation. 1996, 93:1043–1065.
32. Antelmi I, De Paula RS, Shinzato AR, et al. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am J Cardiol*. 2004;93:381-385.
33. Liao D, Barnes RW, Chambless LE, et al. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability—The ARIC study. Atherosclerosis Risk in Communities. *Am J Cardiol*. 1995;76:906.
34. Lampert R, Ickovics JR, Viscoli CJ, Horwitz RI, Lee FA. Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. *Am J Cardiol*. 2003;91:137.
35. de Geus EJC, Willemsen GHM, Klaver CHAM, van Doornen LJP. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. *Biol Psychol*. 1995;41:205-227.
36. Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale: Erlbaum; 1988.
37. Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. *Am J Cardiol*. 1993;72:897-903.
38. Levin FR, Levin HR, Nagoshi C. Autonomic functioning and cigarette smoking: Heart rate spectral analysis. *Biol Psychiatry*. 1992;31:639-643.
39. Karakaya O, Barutcu I, Kaya D, et al. Acute effect of cigarette smoking on heart rate variability. *Angiology*. 2007;58:620-624.
40. Sjoberg N, Saint DA. A single 4 mg dose of nicotine decreases heart rate variability in healthy nonsmokers: Implications for smoking cessation programs. *Nicotine Tob Res*. 2011;13:369-372.
41. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: A review. *Med Biol Eng Comput*. 2006;44:1031-1051.