THE ROLE OF HEART RATE VARIABILITY AND INFLAMMATION IN DEPRESSION DEVELOPMENT AND SEVERITY A DECADE LATER

by

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ABSTRACT

MARIA GRACE ALESSI. The Role of Heart Rate Variability and Inflammation In Depression Development and Severity A Decade Later.
(Under the direction of DR. JEANETTE M. BENNETT)

Lower heart rate variability (HRV) and higher inflammation are indices of dysregulated stress physiology associated with current depression (e.g., diagnosis, depressive symptoms) and potentially related to depression development. Given the increasing biological vulnerabilities associated with age, physiological stress sensitivity may be particularly relevant in the development of depression among older adults. While existing meta-analyses report a small-to-medium effect size between HRV and depression severity in unmedicated depressed adults, conflicting findings contest that this association is driven by the cardiovascular effects of antidepressant use. Additionally, findings from at least one longitudinal study suggest that lower HRV may be more strongly linked to depression in males compared to females. Few studies have explored sex differences in HRV and depression, and no longitudinal studies exist examining the relationships among inflammation, HRV, and depression. In a national sample of middle-aged and older adults (MIDUS), this study examined the extent to which sex as well as inflammation moderated the relationship between HRV and concurrent depression (n = 158) as well as future depression development in a larger longitudinal sample (n = 591). Controlling for inflammation, higher high frequency (HF)-HRV significantly predicted less severe depressive symptoms in both medicated (β = -.222, p = .036) and unmedicated cross-sectional samples (β = -.259, p = .044). There was no significant moderation by sex though *post-hoc* analyses revealed this relationship was driven by females (β = -.329, p =

.029). There was no evidence of significant moderation by inflammation. While higher HF-HRV did not significantly predict new incidence of depression in the longitudinal analyses, *post-hoc* analyses suggest that higher HF-HRV may distinguish between subclinical and clinical major depression among those endorsing past-year depression (*OR* = .567, *p* = .010). These findings suggest that dysregulated stress physiology is associated with greater depression severity independent of antidepressant use, particularly among females. Autonomic dysregulation may further predict risk of developing a major depressive episode among middle-aged and older adults endorsing depression.

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LIST OF ABBREVIATIONS

BMI	body mass index
CAD	coronary artery disease
CAN	central autonomic network
CES-D	Center for Epidemiological Studies Depression scale
CIDI-SF	Composite International Diagnostic Interview - Short Form
CRP	C-reactive protein
CVD	cardiovascular disease
DSM-5	Diagnostic Statistical Manual
ECG	electrocardiography
ELISA	enzyme-linked immunosorbent assay
HF-HRV	high-frequency heart rate variability
HPA	hypothalamic-pituitary-adrenal
HRV	heart rate variability
IL-6	interleukin-6
LF-HRV	low-frequency heart rate variability
MDD	major depressive disorder
MIDUS	Midlife in the United States
M2	MIDUS II
M2P4	MIDUS II Project 4
M3	MIDUS III
SDNN	standard deviations of NN intervals
sE-selectin	soluble E-selectin

sICAM-1	soluble intercellular adhesion molecule-1

CHAPTER 1: INTRODUCTION

Depression is one of the most common mental illnesses, with lifetime rates of up to 15-20% estimated in community samples (Kessler et al., 1994, 2003). Psychological stress predicts depression risk with an estimated 80% of first-onset major depressive episodes preceded by a major life stressor (Kendler et al., 2000; Mazure, 1998; Monroe & Reid, 2009). While many people experience stressful life events, most do not develop clinical depression, suggesting that stress sensitivity likely plays a role in predisposing some people to depression but not others (Hammen, 2015).

Though less prevalent compared to in younger adults, depression in mid- and late-life is associated with higher rates of morbidity as well as suicide risk and is an increasingly serious public health concern as the global population rapidly ages (Blazer, 2003; Covinsky et al., 2010; Hasin et al., 2005). The etiology of depression development later in life is complex and highly heterogeneous, but the increasing prevalence of biological vulnerabilities (e.g., cardiovascular, inflammatory) as well as unique stressors associated with older age (e.g., caregiving, physical illness, job loss) implicate a potential primary role of physiological stress sensitivity in the development of depression among older adults (Fiske et al., 2009).

Depression and depressive symptoms are associated with dysregulated physiology of the neuroendocrine and autonomic nervous systems, which play a critical role in arousal and the stress response (Kemp et al., 2010; Pariante & Lightman, 2008). However, the relationship between autonomic dysregulation, indexed by heart rate variability (HRV), and depression remains contested and many studies have reported

mixed findings. Moreover, elevated inflammation, a universal response mechanism to chronic stress (Bennett et al., 2018), is associated with both lower HRV and depression. No longitudinal studies exist investigating the role of both HRV and inflammation, as indices of dysregulated stress physiology, in depression development. Using secondary data analysis from a large nationally representative longitudinal study (Midlife in the United States; MIDUS), this study examined the extent to which dysregulated stress systems predict the development and severity of mid- and late-life depression.

1.1 HRV as an index of emotional regulation

Heart rate variability, or variation in the time interval between heart beats, is a measure of cardiac vagal control and reflects the capacity of the parasympathetic nervous system to inhibit autonomic arousal (Thayer & Lane, 2000). The sinoatrial node, or 'pacemaker' of the heart, is innervated by both the sympathetic and parasympathetic branches of the autonomic nervous system. At rest, parasympathetic control of the heart via the vagus nerve acts as a 'brake' to decrease heart rate below the intrinsic firing rate of the sinoatrial node (Berntson et al., 1997). Sympathetic control over heart rate occurs comparatively slowly, over the span of seconds, while parasympathetic control occurs more quickly, within milliseconds. Thus, rapid changes (i.e., greater variability) in heart rate are thought to be primarily due to parasympathetic inhibition of autonomic arousal (Berntson et al., 1997). Lower HRV is a well-established risk factor for increased cardiac morbidity and mortality (Thayer et al., 2010), and the majority of studies to date have focused on HRV in the context of cardiovascular disease (CVD; Carney & Freedland, 2009).

HRV is also associated with emotional regulation (Beauchaine & Thayer, 2015). The ability to effectively regulate emotions depends on rapid coordination of physiological arousal systems to adaptively respond to dynamic changes in the environment, making autonomic flexibility integral for emotional regulation (Appelhans & Lueken, 2006). People with higher resting HRV exhibit lower levels of anxiety as well as rumination and are more likely to utilize adaptive coping strategies compared to those with lower HRV (Chalmers et al., 2014; O'Connor et al., 2002; Ottaviani et al., 2016). In contrast, lower HRV is associated with poorer attentional regulation and affective information processing (Thayer & Lane, 2000).

According to the neurovisceral integration model (Thayer & Lane, 2000), cardiac vagal control is regulated by a central autonomic network (CAN), a functionally integrated regulation system in the brain that governs cognitive, behavioral, and physiological responses to environmental challenges through inhibitory control. Vagal tone is thought to be a direct reflection of CAN output and as such, can be considered a physiological proxy for emotion regulation. Moreover, accumulating neuroimaging data suggest that heart rate oscillations in turn modulate neural connectivity, particularly in brain regions implicated in emotion regulation such as the ventromedial prefrontal cortex and the amygdala (Mather & Thayer, 2018). Biofeedback studies conducted in healthy athletes (Paul & Garg, 2012), coronary artery disease (CAD) and stroke patients (Lin et al., 2015), as well as veterans with posttraumatic stress disorder (Tan et al., 2011), demonstrate that training to increase heart rate oscillations significantly reduces symptoms of stress and anxiety (Hedges' g = .81; Goessl, Curtiss, & Hofmann, 2017).

HRV may therefore directly affect emotion regulation as part of a bidirectional feedback loop with regulatory brain networks.

1.2 HRV and depression: mixed findings and medication confounds

As affective disorders are characterized by emotion dysregulation and impaired ability to flexibly adapt to environmental demands (Beauchaine & Thayer, 2015), elevated sympathetic and reduced parasympathetic control would be expected in depression, contributing to lower HRV (Thayer & Lane, 2000). Lower resting HRV is implicated in clinical depression; however, findings are mixed with several studies reporting no significant differences in HRV between depressed patients and non-depressed controls without CVD (Dawood et al., 2007; Sayar et al., 2002; Udupa et al., 2007). Two meta-analyses report small-to-moderate effect sizes of lower resting HRV in depression. Rottenberg and colleagues (2007) found comparable HRV reductions in both physiologically healthy depressed patients (d = .33) and cardiovascularly compromised (e.g., hypertensive) depressed patients (d = .28) compared to non-depressed controls. In another meta-analysis, Kemp and colleagues (2010) evaluated resting HRV in unmedicated clinically depressed adults and found evidence of dysregulation across various measures of HRV (d = -.30 – .66). Moreover, depression severity was negatively associated with HRV (r = -.36). Reasons for the relatively small effect sizes observed remain inconclusive and only cross-sectional studies were reviewed, precluding investigation into a possible etiological role of lower HRV in depression.

These mixed findings may be accounted for by potential confound of medication use. Evidence from some studies suggest that reduced HRV is driven primarily by the effects of antidepressants rather than depression *per se*. Tricyclic

antidepressants (TCAs) are well-known to exhibit strong effects on cardiac output and can increase resting heart rate, thereby reducing HRV (van Zyl et al., 2008). In a large cross-sectional Netherlands cohort study of mid-life depression, lower HRV in participants with both remitted and current major depressive disorder (MDD) compared to controls was no longer significant after accounting for antidepressant use (Licht et al., 2008). Additionally, participants with higher daily antidepressant dosages exhibited lower HRV, indicating a dose-response effect. Subsequent longitudinal analysis of this same sample demonstrated that antidepressant use at baseline predicted reduced HRV while unmedicated participants showed no change in HRV two years later (Licht et al., 2010). A second longitudinal study conducted in an Irish national cohort of older adults with depression observed lower HRV in participants taking antidepressants but found no differences in HRV between unmedicated depressed participants and healthy controls (O'Regan et al., 2015). This evidence provides further support that antidepressants, rather than depression, significantly reduce HRV.

Despite these findings, evidence also exists for reduced HRV in depression in the absence of antidepressant use. In a large United Kingdom cohort study of unmedicated middle-aged civil service employees, lower HRV was significantly associated with higher concurrent depressive symptoms and predicted an increased likelihood of developing depression 10 years later (Jandackova et al., 2016). In contrast, depressive symptoms at baseline did not predict lower HRV a decade later, suggesting that autonomic dysfunction may play a causal role in depression development. Notably, these cross-sectional and longitudinal associations were significant in males only, though these relationships were in the expected direction among females. Another longitudinal

study conducted in a mid-life sample of male Vietnam veterans may support these findings; controlling for antidepressant use, reduced HRV at baseline predicted elevated depressive symptoms 7 years later but not vice versa (Huang et al., 2018). Together, these results implicate autonomic dysfunction as a risk factor for depression rather than a consequence, and further pose the intriguing possibility that this relationship may be sex-dependent.

1.3 Sex differences in HRV & depression

While very few studies investigating HRV and depression have explored sex differences, these results converge with findings from a small college-aged sample in which lower HRV was associated with greater depressive symptoms in males but fewer depressive symptoms in females (Thayer et al., 1998). Given the paucity of studies investigating either longitudinal associations or potential sex differences in the relationship between HRV and depression, the findings from Jandackova et al. (2016) need to be replicated. It remains unclear why the relationship between HRV and depression may be stronger in males. Evidence exists, however, for sex differences in cardiac functioning, stress responsivity, and chronic disease prevalence.

For example, females tend to exhibit greater parasympathetic inhibition of cardiac autonomic activity, while males exhibit greater sympathetic activation (Dart et al., 2002; Liao et al., 1995; Moodithaya & Avadhany, 2012). Females display reduced baroreflex sensitivity and are less responsive to changes in blood pressure compared to males (Convertino, 1998; Dart et al., 2002), while males are more likely to develop cardiac diseases (Baena Díez et al., 2005).

Sex differences in both autonomic and endocrine stress reactivity are also observed. Males diagnosed with coronary artery disease (CAD) show stronger peripheral vasoconstrictive responses to psychological stress compared to females with CAD, suggesting greater physiological stress reactivity (Hassan et al., 2008). Males also display greater cortisol increases to psychological stress compared to females (Kudielka & Kirschbaum, 2004).

Additionally, females are more likely to develop depression and display different clinical characteristics compared to males, such as more frequent depressive episodes and differences in symptom profiles (Silverstein et al., 2013; Smith et al., 2008). More specifically, some studies report greater frequency of physical and somatoform symptoms of depression in females compared to males (Kudielka & Kirschbaum, 2004).

1.4 HRV, inflammation, & depression

In addition to HRV, another proxy of dysregulated stress physiology associated with depression is systemic inflammation. Under conditions of acute stress, inflammation is normally suppressed by cortisol, the hormone product of the hypothalamic-pituitary-adrenal (HPA) axis, following resolution of a transient stressor (Cline & Melmon, 1966). When repeatedly activated by chronic stress, however, the body's stress response systems are thought to become dysregulated and desensitized to their own feedback mechanisms, contributing to a low-grade inflammatory response (Bennett et al., 2018).

Cytokines, the chemical messengers of the immune system, are thought to contribute to the neurovegetative symptoms such as fatigue and appetite loss that overlap with both sickness behavior in acute illness adaptation and depressive symptoms, a theory known as the 'cytokine hypothesis' (Dantzer & Kelley, 2007). Multiple clinical

studies report elevated proinflammatory cytokines and other markers of inflammation, most commonly interleukin-6 (IL-6) and C-reactive protein (CRP), in medically healthy depressed patients (Miller & Raison, 2016). Elevated inflammatory markers also predict onset of depressive symptoms in longitudinal studies (Gimeno et al., 2009; Kiecolt-Glaser et al., 2015; Liu et al., 2017), mirroring the directionality of the longitudinal relationship between HRV and depression (Huang et al., 2018; Jandackova et al., 2016).

HRV is inversely associated with inflammation (Haarala et al., 2011; Singh et al., 2009) and higher CRP levels are a well-established clinical marker of cardiac disease risk (Willerson & Ridker, 2004). Within the MIDUS II biomarker sample (N = 1,255), significant inverse relationships between indices of HRV and fibrinogen, CRP, and IL-6 have been reported (Cooper et al., 2015). At least one longitudinal study, conducted in a sample of 106 medically healthy German industrial employees, found that lower HF-HRV at baseline predicted higher CRP levels 4 years later (Jarczok et al., 2014). These findings suggest that lower HRV, as possibly the more acute indicator of physiological stress dysregulation, may precede the more chronic indicators of stress dysregulation (i.e., systemic inflammation) which in turn predict depression development.

Notably, only 9% of the sample recruited by Jarczok and colleagues (2014) was female, precluding exploration of possible sex differences. Epidemiological studies report higher CRP levels in females compared to males (Khera et al., 2005; Lakoski et al., 2006; Nazmi et al., 2008) while findings on sex differences with other inflammatory markers (i.e., IL-6, TNFα) have been inconsistent (Kiecolt-Glaser et al., 2005; López-Bermejo et al., 2007; Sadeghi et al., 2005). Additionally, females are more likely to be diagnosed with inflammatory-related diseases (Jacobson et al., 1997). Given these sex

differences, the potential moderating impact of sex is an important component to examine in the relationship between HRV and inflammation.

Relatively few studies have investigated the role of both HRV and inflammation in depression. The majority of existing studies to date have been conducted almost exclusively in cross-sectional samples of cardiac patients or participants with elevated risk factors for cardiac disease (Carney et al., 2007; Pizzi et al., 2008). In a large sample of patients with heart disease, the inverse relationship between HRV and inflammatory markers was stronger in patients with elevated depressive symptoms compared to those without (Frasure-Smith et al., 2009). A single cross-sectional study in a large community sample found associations between depressive symptoms and elevated immunometabolic risk factors (i.e., CRP, IL-6, body mass index, blood pressure) as well as lower HRV (Hu et al., 2018). None of these studies examined the potential influence of sex on these relationships.

1.5 Study Aims

To date, no longitudinal studies exist examining the relationships among inflammation, HRV, and depression. Thus, this study aimed to investigate the role of dysregulated stress physiology in the severity and development of mid- and late-life depression. The questions examined include:

a) Does autonomic dysregulation (e.g., reduced HRV) predict the severity of current depressive symptoms and likelihood of future depression development in both medicated and unmedicated middle-aged and older adults?
b) Does the relationship between HRV and depression differ between males and females?

c) Does systemic inflammation differentially moderate the relationship between HRV and depression by sex?

1.6 Hypotheses

Hypothesis 1: Lower HRV will be associated with higher concurrent depressive symptoms in the overall sample, with the relationship stronger among men than women (see Figure 1).

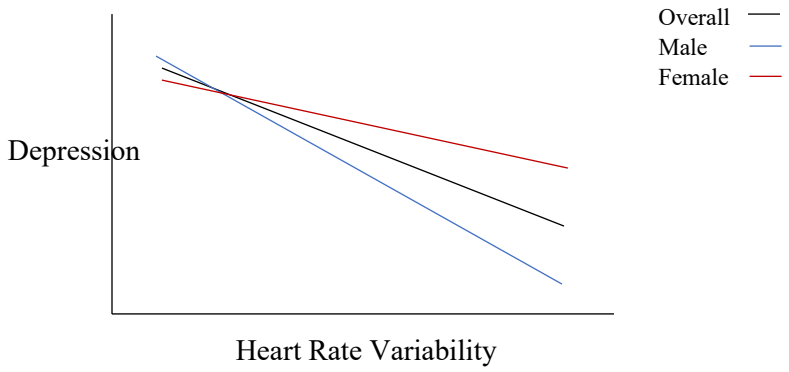

Figure 1. Proposed results for Hypothesis 1 showing the relationship between heart rate variability and concurrent depressive symptoms for the overall sample as well as by sex.

Rationale: Lower HRV is associated with greater depressive symptoms in meta-analyses (Kemp et al., 2010; Rottenberg, 2007), and at least one large population-based study observed this significant association in males but not females (Jandackova et al., 2016).

Hypothesis 2: Lower HRV will predict a greater likelihood of developing future depression in the overall sample, with the relationship stronger among men than women (see Figure 2).

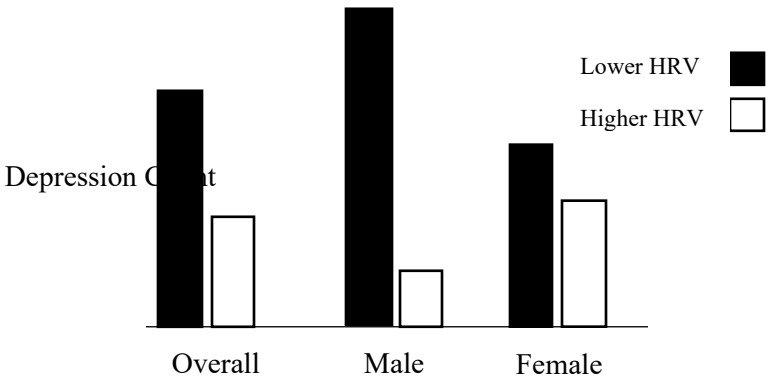

Figure 2. Proposed results for Hypothesis 2 showing the greater likelihood of developing depression in individuals with lower heart rate variability (HRV) at time point 1 compared to those with higher HRV at time point 1 for the overall sample as well as by sex.

Rationale: At least two longitudinal studies report lower HRV predicts elevated future depressive symptoms in males (Huang et al., 2018; Jandackova et al., 2016).

Hypothesis 3: Inflammation will significantly affect the relationship between HRV and depression.

Hypothesis 3a: For those with higher inflammation, lower HRV will be related to more severe concurrent depressive symptoms and a greater likelihood of developing future depression, while HRV and depression (concurrent symptoms and future development) will not be related among those with lower inflammation (see Figures 3 and 4).

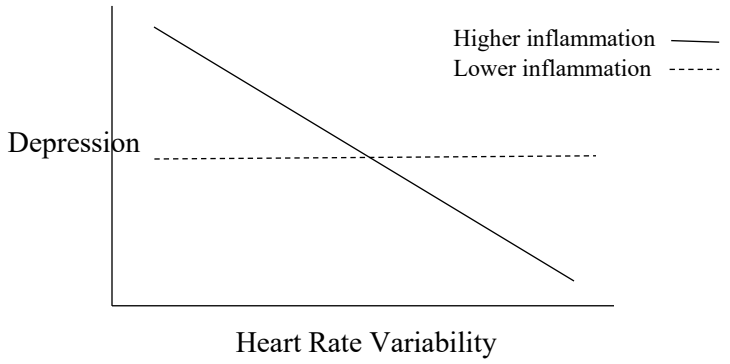

Figure 3. Proposed results for Hypothesis 3a showing a two-way interaction between heart rate variability and inflammation on concurrent depressive symptoms.

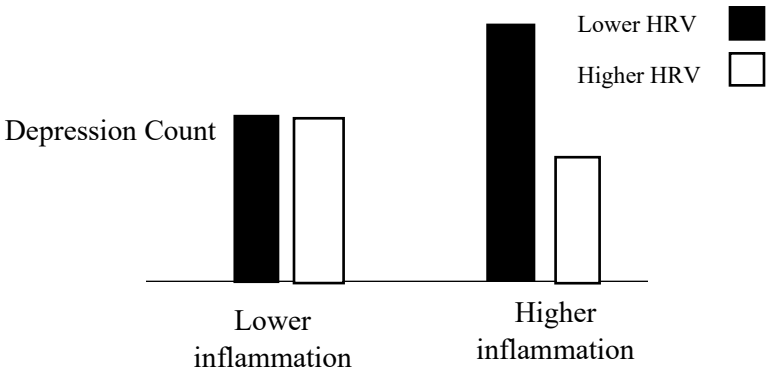

Figure 4. Proposed results for Hypothesis 3a showing the greater likelihood of developing depression in individuals with lower heart rate variability (HRV) and higher inflammation at time point 1 compared to those with higher HRV irrespective of inflammatory burden at time point 1.

Rationale: Higher inflammation is independently associated with both depression and lower HRV, and one prior study suggests that the inverse relationship between inflammation and HRV may be stronger in depressed individuals compared to non-depressed individuals (Frasure-Smith et al., 2009).

Hypothesis 3b: This relationship will be further moderated by sex (i.e., 3-way interaction). For males, lower HRV will be associated with greater depression (concurrent symptoms or future development), regardless of inflammation level.

For females with higher inflammation, lower HRV will be associated with greater levels of depression (concurrent symptoms and future development), while HRV will not predict depression in females with lower inflammation (see Figures 5 and 6).

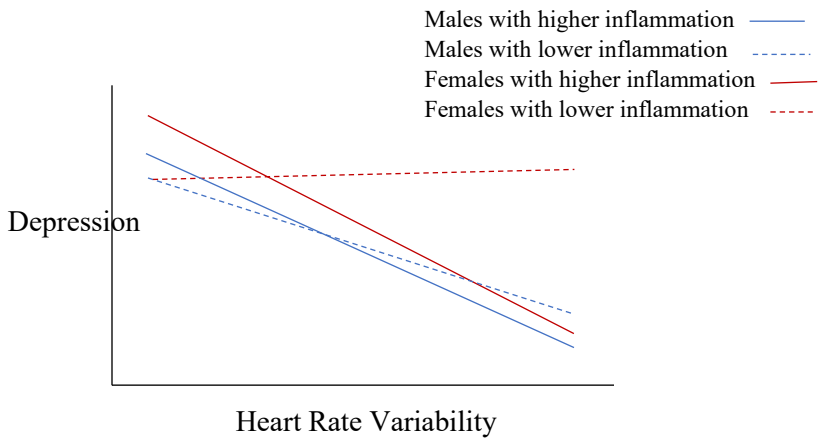

Figure 5. Proposed results for Hypothesis 3b showing a three-way interaction among heart rate variability, inflammation, and sex on concurrent depressive symptoms.

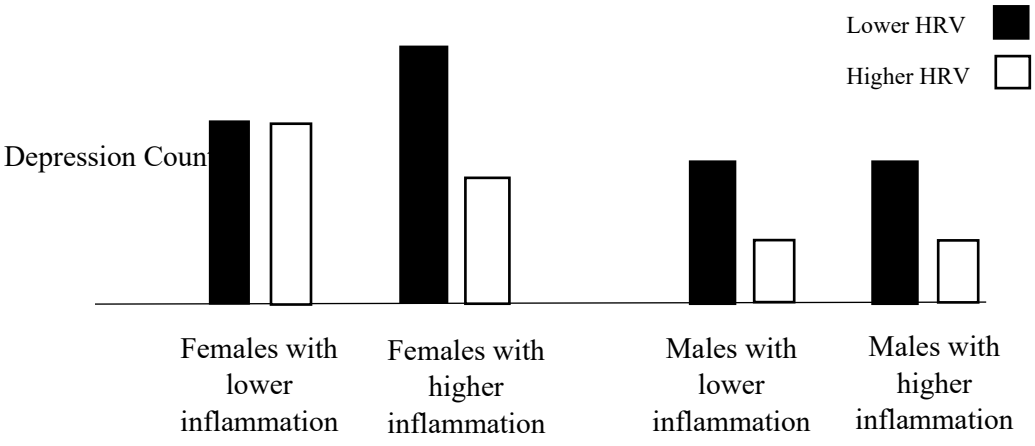

Figure 6. Proposed results for Hypothesis 3b showing a three-way interaction among heart rate variability, inflammation, and sex on likelihood of developing depression.

Rationale: Females exhibit greater parasympathetic inhibition of cardiac control yet are more prone to depression as well as higher inflammatory levels, while

males exhibit greater sympathetic activation of cardiac control (Kudielka & Kirschbaum, 2004; Moodithaya & Avadhany, 2012).

CHAPTER 2: MATERIALS AND METHODS

2.1 Participants

This study utilized secondary data analysis in a sample of middle-aged and older adults enrolled in Midlife Development in the U.S. (MIDUS), a series of longitudinal studies investigating the biopsychosocial predictors of health and well-being. Participants were initially recruited in 1995-96 using a nationally representative sample, obtained through random-digit dialing procedures, and included siblings of respondents as well as a national sample of twins. The current study uses data from the MIDUS II's Project 4 (M2P4) biomarker project conducted 2004-09, as well as longitudinal data from the second follow-up (MIDUS III; M3) collected in 2013-14. All living participants who completed the phone interview for MIDUS II (M2; n = 3,191) were eligible to participate in the biomarker project, a comprehensive laboratory-based biological assessment. Participants were excluded if their baseline blood pressure was 180/100 mmHg or higher, as determined by three manual blood pressure readings taken five minutes apart. The biomarker sample has previously been reported as not significantly different from the nationally representative sample on age, sex, race, marital status, or income, though respondents in the biological protocol were significantly more likely to have a college degree (Dienberg Love et al., 2010).

The biomarker project collected data from a total of 1,255 M2 participants ages 35 – 86 years and included a physical exam with assessment of clinically relevant biological indicators of health during an overnight stay at University of California Los Angeles, University of Wisconsin, or Georgetown University. Institutional Review Board approval was obtained for each site and informed written consent was provided by all

participants. Clean resting HRV data was successfully obtained from 967 participants. As the relationship between resting HRV and concurrent depressive symptoms in this larger (and mostly non-depressed) sample has been previously reported as non-significant (Sloan et al., 2017), M2P4 cross-sectional analyses included a subsample (n = 158) of participants with clean resting HRV data and clinically significant depressive symptoms (CES-D ≥ 16; Radloff, 1977) in order to examine the association between HRV and depression severity. To investigate whether resting HRV predicts future depression development, those who endorsed a history of physician-diagnosed depression at the time of biomarker data collection were excluded, leaving 591 M3 participants for longitudinal analyses.

2.2 Measures

*Heart Rate Variability***.** On the morning following the overnight stay, participants completed a psychophysiological protocol. All procedures were standardized, including meals where caffeine consumption was not permitted. Electrocardiography (ECG) electrodes were placed on both shoulders and left lower abdominal quadrant. Respiration volume was calibrated prior to resting baseline and respiration rate monitored continuously during the protocol by inductive plethysmography using stretch bands around the chest and abdomen. Analog signals from the stretch bands were sampled at 20 Hz, digitized, and summed into a single waveform for analysis. Respiration rate was calculated breath-by-breath using proprietary analysis software and the mean resting respiratory rate was computed.

While participants were seated for an 11-minute resting baseline, beat-to-beat analog ECG signals were collected and digitized at a sampling rate of 500 Hz by a 16-bit

analog-to-digital board. Research staff visually reviewed all ECG waveforms to correct software errors in identifying normal R waves, in accordance with established procedures (Berntson et al., 1990; Dykes et al., 1986). RR interval series spectra were calculated using an interval method for computing Fourier transforms (DeBoer et al., 1984). Consecutive RR wave intervals were used to calculate HRV. High frequency (HF; 0.15 – 0.50 Hz) HRV was computed as the mean value from two baseline 300-second epochs and log-transformed. Due to the differential effects of the ANS on the timing of heart beats, HF-HRV reflects primarily PNS influence. To avoid multiple comparisons and as previous reports indicate larger effect sizes for HF-HRV on depression than lower frequency (Jandackova et al., 2016; Kemp et al., 2010), HF-HRV was the predictor variable of interest in analyses.

Inflammation. Before breakfast after the overnight stay, all participants provided a blood sample following a 12-hour fast. Five inflammatory markers were collected: interleukin-6 (IL-6), C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1), soluble E-selectin (sE-selectin), and fibrinogen. IL-6, sCAM-1, and sE-selectin levels were measured using high-sensitivity enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, US) at the University of Wisconsin–Madison. CRP and fibrinogen were measured using a particle enhanced immunonepholometric assay (BNII nephelometer, Dade Behring Inc., Deerfield, IL) at the University of Vermont. All intra- and inter-assay coefficients of variance were within an acceptable range (<10%) and inflammatory markers were log-transformed to correct for skewed distributions.

To best capture systemic inflammation, a composite inflammatory variable was created**.** Each biomarker was divided into quartiles, with individuals at the highest quartile coded 1 for greatest inflammatory burden. All others were coded as 0 and scores across all biomarkers summed, creating a composite ranging from 0 – 5. This approach has been utilized by several prior studies using the M2P4 dataset (Ong & Williams, 2019; Piazza et al., 2018; Ransome et al., 2018).

Depressive symptomology and incident development. Depressive symptoms were measured at the psychophysiological visit (M2P4) by self-report using the Center for Epidemiologic Studies Depression Scale (CES-D), a popular self-report measure for assessing symptoms associated with depression in the general population (Radloff, 1977). The CES-D assesses the frequency of 20 depressive symptoms using a 4-point Likert scale to yield a total score of 0 to 60, corresponding with greater depression severity. A cutoff score ≥16 on the CES-D is considered indicative of clinical depression (Radloff, 1977). The reliability of this measure within the MIDUS biomarker project sample has been previously reported (Cronbach's alpha = .90; Cosco, Prina, Stubbs, & Wu, 2017).

Longitudinal self-reported past-year depression was assessed approximately 10 years later (M3) with the Composite International Diagnostic Interview - Short Form (CIDI-SF), designed to estimate the prevalence of major depression (Kessler et al., 1998). Respondents were classified as having had a major depressive episode based on clinical criteria in the Diagnostic Statistical Manual (DSM-5; i.e., depressed mood for most of the day, nearly every day for at least two weeks, etc.). For major depressive episodes, the CIDI-SF has a total classification accuracy of 93% (Kessler et al., 1998) and is a reliable measure (Cronbach's alpha = 0.89; Gigantesco & Morosini, 2008). While the CES-D is a

dimensional scale of depressive symptoms and the CIDI-SF a categorical classification of major depression, these measures yield comparable rates of clinical depression in community samples (Suthers et al., 2004)

In order to broadly capture new depression incidence, the screener questions from the CIDI-SF assessing the core symptoms of depression (depressed mood and anhedonia) were combined. At M3, participants were asked whether they experienced sad or depressed mood for 2+ consecutive weeks within the past year OR a loss of interest in most pleasurable activities for 2+ consecutive weeks within the past year. Future incident depression in the current study was thus defined as a response of 'yes' to either depressed mood or anhedonia within the past year at M3. Participants who responded no to either question but also report new antidepressant medication use since M2P4 were also included in the M3 depressed group as evidence of depression development (Jandackova et al., 2016).

Covariates. Confounds known to be associated with HRV and/or depression were included as covariates in analyses, in addition to controlling for respiration rate. Sociodemographic covariates included age at biomarker collection, race, and highest level of education completed. Due to low number of other identified races (n = 2), all non-white participants were collapsed into one category and are predominately African-American.

Lifestyle factors, assessed by self-reported questionnaires at the time of psychophysiological data collection, included current exercise, current alcohol consumption, and current tobacco use. Participants were asked whether they currently engage in regular exercise or light – vigorous physical activity of any type for 20+

minutes at least 3 times/week. Current alcohol consumption was assessed as average number of alcoholic beverages in the past month and current tobacco use included endorsement of either current regular cigarette smoking or current regular use of cigars, snuff, or chewing tobacco.

Cardiometabolic-related conditions were operationalized as the total number of conditions endorsed: physician-diagnosed heart disease, hypertension, TIA/stroke, diabetes, or obesity. Obesity was defined as a hip-to-waist ratio greater than 0.9 in males and 0.85 in females, in accordance with WHO guidelines (Nishida et al., 2010). Medication use included current use of any blood pressure medication as well as any anti-depressants.

2.3 Data analysis

All analyses were conducted using SPSS Version 26. Sample characteristics are summarized using mean and standard error of the mean for continuous variables as well as count and percentage for categorical variables. Independent sample *t*-tests for continuous variables and χ^2 analyses for categorical variables were conducted to assess for significant differences in characteristics between groups of interest. To examine Hypothesis 1, a hierarchical linear regression (Step 1 covariates, Step 2 sex and HRV, Step 3 Sex x HRV interaction) was used to investigate the cross-sectional relationship between HRV and depression severity as well as examine sex differences. The Hypothesis 1 analyses were repeated after removing participants who reported current use of antidepressants ($n = 40$) to investigate the impact of medication use on the relationship between HRV and depression severity. To test Hypothesis 2, a series of logistic regressions was used to examine the role of HRV, sex, and their interaction in the

development of depression. To examine Hypothesis 3, 2-way interactions between inflammation and HRV as well as inflammation and sex were included in linear hierarchical and logistic regressions to predict concurrent depressive symptoms and likelihood of developing future depression, respectively. To investigate Hypothesis 3b, a 3-way interactive term (sex x HRV x inflammatory composite) was added to the regression models.

All analyses controlled for sociodemographic factors (age, maximum years of education), lifestyle factors (current smoking status, current alcohol consumption, and exercise), cardiometabolic comorbidities, current medication use (antidepressants, blood pressure medications), and respiration rate. Additionally, depressive symptoms at M2P4 were included as a covariate in all longitudinal analyses. Exploratory analyses further examined associations of interest to clarify the impact of sex, inflammation, and depression severity on significant findings.

CHAPTER 3: RESULTS

3.1 Cross-sectional biomarker samples: characteristics and descriptive statistics

Cross-sectional analyses (M2P4) were conducted in two overlapping samples, the first of which included all depressed adults regardless of antidepressant medication use (n = 158) and the second comprising of unmedicated depressed adults only (n = 118). Demographic characteristics of the biomarker sample can be found in Table 1 in the appendix and are presented by antidepressant use (medicated or unmedicated). Given this study's primary aim to investigate sex differences in depression severity, demographic and clinical characteristics of variables of interest are further displayed by sex in Table 1 in the appendix. Among the overall sample, more females (30.2%) than males (17.7%) were on an antidepressant; however, this difference did not reach statistical significance, $\chi^2(1, N = 158) = 3.36$, $p = .067$. Males and females did not significantly differ in age, race, depression severity, HF-HRV, or inflammation in the overall sample. In the unmedicated subsample, females were more likely to be non-white than males, $\chi^2(1, N = 118) = 7.1$, $p = .008$; males and females did not significantly differ in age, depression severity, HF-HRV, or inflammation.

Descriptive statistics and zero-order correlations of study variables in the overall M2P4 depressed sample are reported in Table 2. Greater depression severity was significantly associated with lower HF-HRV (r = -.187, p = .019) and use of antidepressant medication (r = .203, p = .010). HF-HRV was significantly positively associated with race, such that non-white participants exhibited higher HF-HRV (r = .253, p = .000). As non-white participants were predominately African-American in this sample, this finding is consistent with literature documenting higher resting HRV among

individuals of African ancestry compared to those of European ancestry (Hedges' g = 0.93; Hill et al., 2015). HF-HRV was also significantly negatively associated with age (r = -.230, p = .004).

3.2 Higher HF-HRV predicts lower concurrent depression severity

Controlling for respiration rate, demographics, lifestyle factors, and co-morbidities, higher HF-HRV significantly predicted fewer depressive symptoms (β = -.217, p = .039; see Figure 7 in appendix). As neither sex nor the interaction between HF-HRV and sex significantly predicted depressive symptoms (see Table 3), hypothesis 1 was partially supported. In the unmedicated subsample, HF-HRV no longer significantly predicted depressive symptoms though remained trending in the expected direction (β = -.243, p = .057). Neither sex nor the interaction between HF-HRV and sex significantly predicted depressive symptoms in the unmedicated sample (see Table 4).

3.3 Inflammation does not interact with sex and HF-HRV

To investigate the interaction between inflammation, sex, and HF-HRV on concurrent depression severity, inflammation along with 2-way and 3-way interactive terms were added to the linear hierarchical regression model. In the overall sample (n = 158), there was a significant main effect of HF-HRV (β = -.222, p = .036) but not sex or inflammation (p's > .05). No interactions were significant (see Table 5). In the unmedicated subsample (n = 118), HF-HRV significantly predicted fewer depressive symptoms (β = -.259, p = .044) after additionally controlling for inflammation. As there were no significant main or interactive effects of sex with HF-HRV and inflammation (p's > .05, see Table 6), hypothesis 3 was not supported.

3.4 Longitudinal sample: characteristics and descriptive statistics

Longitudinal analyses were conducted in the total sample of non-depressed participants with useable biomarker data at M2P4 and follow-up data at M3 (n = 591). Demographic and biomarker clinical characteristics of variables of interest between those who did (n = 107) and did not (n = 484) endorse past-year depression at follow-up are presented in Table 7 and displayed by sex. Those who did not develop depression were significantly older, t (589) = 3.69, p = .000 and had significantly fewer depressive symptoms at biomarker collection, t (589) = 28.8, p = .000, than those who developed depression. There were no significant differences between groups in sex, race, HF-HRV, or inflammation. Notably, the majority of the African-American participants included at biomarker collection were missing longitudinal follow-up data at M3, resulting in the longitudinal sample being predominantly white.

Descriptive statistics and zero-order correlations of study variables in the longitudinal sample are reported in Table 8. While depressive symptoms and HF-HRV were no longer significantly correlated in the larger and primarily non-depressed sample, higher HF-HRV was weakly positively associated with female sex (r = .081, p = .049) and negatively associated with age (r = -.297, p = .000). Higher inflammation was also weakly correlated with female sex (r = .087, p = .035) and positively correlated with greater depressive symptoms at biomarker collection (r = .112, p = .006).

3.5 HF-HRV does not predict future depression development

A logistic regression model was run to investigate the main and interactive effects of sex and HF-HRV on future depression development. Controlling for respiration rate, demographics, lifestyle factors, co-morbidities, and baseline depressive symptoms, sex was notably trending in predicting future depression (OR = 1.64, p = .051; see Table 9)

such that females were over 60% more likely to develop depression than males. There were no significant main or interactive effects of HF-HRV on future depression development; hypothesis 2 was therefore not supported.

3.6 Inflammation does not significantly interact with sex and HF-HRV

To investigate the interaction between inflammation, sex, and HF-HRV on future depression development, inflammation along with 2-way and 3-way interactive terms were added to the logistic regression model. Sex was a significant predictor of depression development (OR = 1.66, p = .048); however, as there were no significant 2-way or 3-way interactions (see Table 10), hypothesis 3 was not supported.

3.7 Exploratory analyses

Given the emergence of a significant relationship between HRV and concurrent depressive symptoms in the unmedicated sample after controlling for inflammation, *post hoc* analyses were conducted to further explore the relationship between inflammation and depression. Inflammation did not significantly predict concurrent depressive symptoms in either the overall or unmedicated cross-sectional biomarker samples, nor likelihood of developing depression in the longitudinal sample (p's > .05).

Regression models were re-run separately for males and females in order to explore the extent to which the variance in the relationship between HRV and depressive symptoms may be differentially driven within each sex. Significant findings are reported. In the overall cross-sectional biomarker sample, higher HF-HRV remained a significant predictor of concurrent depressive symptoms (β = -.329, p = .029) in depressed females but not males (see Table 11). The relationship between HRV and depressive symptoms in females and males is displayed in Figure 8. The covariates included in model 1 explained

37.3% of the variance in depressive symptoms among males (R^2 = .373), but just 8.9% of the variance among females (R^2 = .089); including HF-HRV in the model explained 9% additional variance among females (ΔR^2 = .090). Notably, use of antidepressants was a trending predictor in males (β = .329, p = .054) but not females.

In the unmedicated sample, the relationship between HF-HRV and depressive symptoms was not significant in either sex (see Table 12), though remained trending in the expected direction among females (β = -.349, p = .096). Again, covariates explained considerably more variance in depressive symptoms among depressed males (R^2 = .242) than females (R^2 = .144), and including HF-HRV in the model further explained an additional 9.5% of variance among depressed females (ΔR^2 = .095) but none among males (ΔR^2 = 0).

Further, *post hoc* analyses examined whether HF-HRV may differentially predict subclinical from clinical depression. As depression at M3 was assessed in a step-wise fashion, in which only participants who endorsed clinically significant levels of past-year depression (i.e., greater than 50% of the time for at least 2+ weeks) completed the remainder of the depression measure, presence of a major depressive episode was distinguishable from subthreshold depression within the dataset. Of the 107 eligible participants endorsing any past-year depression, 38 met full diagnostic criteria for a major depressive episode. Demographic and clinical characteristics between these subclinical and clinical subgroups are described in Table 13 and displayed by sex. Participants who developed subclinical depression at M3 were significantly older than those who met criteria for a major depressive episode, $t(105) = 3.30$, p = .001. Subclinical

and clinical subsamples did not significantly differ in race, baseline depressive symptoms, HF-HRV, or inflammation (*p*'s > .05).

A logistic regression was run to explore whether baseline HF-HRV could distinguish subthreshold depression from a major depressive episode. Significant findings are reported in Table 14. Controlling for respiration rate, demographics, lifestyle factors, co-morbidities, and baseline depressive symptoms, HF-HRV significantly predicted the development of a major depressive episode, such that higher HF-HRV predicted a nearly 45% reduced likelihood of developing major depression (*OR* = .567, *p* = .010). Neither sex nor its interaction with HRV were significant.

CHAPTER 4: DISCUSSION

This study explored the role of dysregulated stress physiology on the development and severity of mid- and late-life depression. The relationship between HRV and current depressive symptoms as well as future depression development and the potential moderating effects of sex and inflammation were examined. Higher HF-HRV significantly predicted less severe concurrent depression, particularly among females, but did not predict incidence of new depression development in the larger longitudinal sample at follow-up.

This study failed to replicate the results of the 2016 Jandackova Whitehall study, in which HRV significantly predicted both current and future depressive symptoms in males but not females. The discrepant findings may be due to differences in samples; the Whitehall sample was predominately white (>85-90%) and middle-aged (ages 35-55) while the MIDUS biomarker sample was more diverse with respect to both race and age. Furthermore, the Whitehall sample exclusively consisted of participants employed by the British civil service as part of an ongoing cohort study of health effects related to the social hierarchy gradient within the service. Prior evidence suggests that the effects of social status stress in this cohort may be particularly pronounced in males. Within the Whitehall sample, higher occupational status predicts greater blood pressure changes among males (Carroll et al., 1997), and work stress increases likelihood of weight gain in obese males but not females (Kivimäki et al., 2006). In contrast, the MIDUS biomarker (M2P4) sample was recruited from a nationally representative US sample and includes more diverse exposure to various socioeconomic stressors as well as employment.

While there was no evidence of an interactive effect between HRV and sex on depressive symptoms, *post-hoc* analyses revealed that the relationship between HRV and concurrent depression severity was primarily driven by females. Reasons for this stronger relationship in females but not males remain unclear; females were not significantly more depressed than males though in this sample females were more likely to be non-white. Further, the sociodemographic, lifestyle, and health covariates included in regression models accounted for nearly 30% less variance in the relationship between HRV and concurrent depression in females compared to males, suggesting that the physiological effects of these covariates differed between depressed males and females in this sample. This finding may reflect the differential impact of other sociocultural and economic stressors, as well as biological factors that modulate cardiac output. In this study's larger longitudinal sample, females also displayed significantly higher HF-HRV than males, a finding that has been replicated in several large studies (Antelmi et al., 2004; Moodithaya & Avadhany, 2012). As this sex difference diminishes with age, dropping off around menopause (Kuo et al., 1999), the female sex hormone estrogen is hypothesized to be a protective factor contributing to lower sympathetic activity and reduced risk of cardiovascular disease in females (Yang et al., 2013).

Relatedly, the relationship between HRV and depression is likely further moderated by aging. It is well-established that HRV decreases with increasing age as sympathetic modulation of cardiac output predominates in later life. While relatively few studies have examined HRV in depressed older adults, a recent meta-analysis found small but significant reductions in LF-HRV but not HF-HRV in both clinical and community-based depressed older adult samples (g = .109; Brown et al., 2018). LF-HRV

incorporates both sympathetic and parasympathetic inputs and is strongly affected by age-related declines in heart functioning (Brown et al., 2012). Mixed indices of HRV may therefore better reflect the accelerated cardiovascular aging observed in older compared to younger depressed adults.

When additionally controlling for inflammation, HF-HRV significantly predicted depression severity in both the overall and unmedicated cross-sectional samples, though there was no evidence of an interactive effect between HRV and inflammation on depression severity or development. This finding suggests that HRV and inflammation may have independent effects on depression. Although systemic inflammation increases and HRV decreases with aging, these two markers are proxies for immunological and autonomic nervous system functioning, respectively, which are unique bodily systems responsible for different aspects of health. However, these systems are both related to autonomic function in complex ways, as inflammation can be affected at different stages by the initial fast PNS withdrawal and prolonged SNS hyperactivity, which are captured to different extents by different measures of HRV. Meta-analytic findings of the relationship between HRV and inflammation document a small negative association between higher inflammation and lower HRV (Williams et al., 2019); this is most robustly associated with CRP and white blood cell counts as well as mixed HRV indices that capture both parasympathetic and sympathetic functioning such as standard deviations of NN intervals on the ECG waveform (SDNN). Further, the negative relationship between CRP and HRV appears to weaken with increasing age and among females, suggesting both age and sex are critical moderators to investigate, particularly among older adult samples.

While the causal role of antidepressant use in the relationship between HRV and depression severity remains contested, these results further suggest that inflammation may be a crucial confound to control for. One mechanism by which antidepressants may improve mood is by reducing inflammation via effects on the HPA axis. Evidence from both *in vitro* and *in vivo* studies demonstrate that antidepressants can reverse glucocorticoid resistance, thereby increasing the anti-inflammatory effects of cortisol (Pariante, 2017), while levels of proinflammatory cytokines may predict treatment response to antidepressants (Cattaneo et al., 2013). The relatively weaker relationship typically observed between HRV and depression severity in unmedicated samples without accounting for inflammation may reflect greater variance in depressive symptoms due to the independent pathways that systemic inflammation and HRV approximate.

There was no evidence that inflammation directly predicted depression in this study, though the inflammatory composite was significantly correlated with higher depressive symptoms at M2P4 (r = .112). IL-6 and CRP in this study's inflammatory composite are more robustly associated with depression in the literature (Dowlati et al., 2010), while inflammatory markers like E-selectin are less commonly studied in relation to depression. Inclusion of inflammatory markers that are more strongly associated with depression, such as TNF-α and IL-1β, may therefore have better captured inflammatory-related depression.

Significant heterogeneity exists in studies investigating inflammation and depression, as not all depressed patients display evidence of elevated inflammatory markers (Pariante, 2017). Inflammatory-related depression may be more strongly related

to certain subtypes or symptoms of depression. For example, evidence from TNFα treatment trials for Hepatitis C demonstrates that cytokine administration induces neurovegetative symptoms (i.e., fatigue, psychomotor retardation, etc.) of depression in nearly all patients while more cognitive and affective symptoms of depression occur in 30-50% of patients, suggesting that inflammation may be more directly related to somatic and vegetative symptoms (Berk et al., 2013). Studies investigating inflammation across different subtypes of depression reveal that higher inflammation is associated with atypical depression (characterized by increased weight gain, hypersomnia, and mood reactivity) but not melancholic depression (Lamers et al., 2013). Further, inflammatory-related depression among older adults is related to higher BMI, greater co-morbidity burden, and poorer prognosis (Gallagher et al., 2017). As relatively few studies investigating HRV or inflammation have examined subtypes or symptom profiles of depression, future research is needed to elucidate potential differential relationships. Additionally, systemic inflammation is strongly linked to early childhood adversity and trauma (Pariante, 2017), suggesting that elevated inflammation and dysregulated stress systems later in life may be a "biological scar" due to early stress exposure. Thus, inflammatory-related depression may further be characterized by childhood trauma history.

There was no evidence that HRV predicted likelihood of developing depression up to 10 years later in this sample; however, *post-hoc* analyses revealed that lower HF-HRV at baseline significantly distinguished between subclinical and clinical levels of depression. This finding was observed in depressed adults without a prior depression diagnosis or past use of antidepressants, suggesting that HRV may be a relevant

biomarker in early detection of major depression. While the utility of HRV as a diagnostic tool in medical settings is not established, this longitudinal relationship highlights the importance of autonomic dysregulation for depression risk. Interventions aimed to improve autonomic regulation such as HRV biofeedback or psychological approaches (e.g., mindfulness) that improve physiological and psychological flexibility may therefore reduce the risk of developing depression in the general population.

The findings and conclusions from this study are limited by several notable factors. The sample sizes of depressed adults in both the cross-sectional and longitudinal analyses were relatively small as the MIDUS study did not specifically recruit for presence of mood disorders. A *post-hoc* G*power analysis of an alpha of .05 and a small effect size of 0.03 for the 3-way interaction indicates that the analyses were significantly under-powered at 0.19 with the cross-sectional depressed subsample (n = 158). However, the longitudinal sample (n = 591) at an alpha of .05 and observed *OR* of .151 was sufficiently powered to detect the three-way interaction (> .99). Nonetheless, the unequal distribution of sex among the depressed samples/groups may have contributed to skewed findings in which significant relationships were primarily driven by females than males.

Longitudinal relationships between HRV and depression were further limited by the significant number of missing non-white participants who were recruited for the biomarker sample but whose follow-up data was not included in the M3 dataset. As these participants' follow-up data can be accessed in additional datasets through a special permission request, future analyses may benefit from including these data in longitudinal analyses and potentially increasing the depressed sample size.

Additionally, methods used in these analyses to identify new incidences of depression development may either over- or under-report the true longitudinal depressed sample size. As the MIDUS data set was not originally intended to measure new depression development, this study restricted the longitudinal data set to participants without a history of physician-diagnosed depression or on an anti-depressant at biomarker (M2P4) collection. However, participants may have experienced past episodes of major depression that were never diagnosed or treated. Alternatively, participants without a history of depression may have developed clinically significant depression in the approximate decade following biomarker collection but did not endorse depression within the past year at M3 data collection. These participants would have then been included in the 'not depressed' group at follow-up. The lack of a significant relationship between baseline HRV and new depression development in the larger longitudinal sample may thus reflect potential categorical overlap between groups (i.e., participants with recent depression history labeled as non-depressed). Further, given prior evidence that mixed indices of HRV may be more strongly associated with depression later in life (Brown et al., 2018) in addition to the lack of observed sex differences in HRV after menopause (Yang et al., 2013), the inclusion of additional measures of HRV as well as age interactions with sex may have better captured the effect of HRV on depression development earlier vs. later in life in males and females.

Considering these limitations and the utilization of secondary data analysis in this investigation, a more appropriate examination of this study's hypotheses would incorporate a thorough assessment of depression as well as other measures of HRV and inflammation. To definitively exclude those with any prior history of major depression, a

psychiatric evaluation of past and current depressive symptoms using a semi-structured interview (e.g., Structured Clinical Interview for DSM Disorders; SCID) would screen out both treated and untreated depression. Follow-up assessment of depression development occurring any time after baseline by similar methods would also allow new incidents of depression to be classified more accurately and comprehensively than was feasible using the MIDUS dataset. As mixed indices of parasympathetic and sympathetic influences on cardiac function may be related more strongly to both inflammatory and age-related effects, use of additional HRV indices such as SDNN may better capture this study's relationships of interest. Lastly, inclusion of inflammatory markers that are more reliably associated with depression such as TNF-α and IL-1β may better predict new depression development rather than markers that are less commonly examined in depression (e.g., ICAM-1, E-selectin).

This study is the first to examine relationships between HRV and inflammation in predicting both depression severity and development. Greater autonomic dysregulation predicted higher concurrent depression severity in both unmedicated and medicated depressed middle-aged and older adults after controlling for inflammation. Against predictions, this relationship was stronger in females rather than males in this community-based sample. Autonomic dysregulation may distinguish between subclinical and clinical levels of future depression development, though more research is needed to replicate and elucidate this preliminary finding.

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APPENDIX

Table 1: Demographic and clinical characteristics of adults at M2P4 shown by sex and anti-depressant use

	Overall (n =158)		Medicated (n = 40)		Unmedicated (n = 118)	
Variable	Males n = 62	Females n = 96	Males n = 11	Females n = 29	Males n = 51	Females n = 67
Age (years)	52.7 (9.6)	52.3 (10.1)	51.1 (7.1)	56.3 (10.6)	53.1 (10.1)	50.5 (9.3)
Race (% White)	69.4%	54.2%	72.7%	79.3%	68.6%	43.3%
CES-D	23.6 (7.1)	23.7 (7.2)	30.4 (10.0)	24.5 (7.8)	22.1 (5.4)	23.4 (6.9)
HF-HRV (ms^2)	563.1 (2043.3)	453.6 (854.2)	205.8 (185.3)	250.5 (451.6)	640.2 (2247.8)	541.6 (968.4)
Inflammatory Composite	1.3 (1.4)	1.4 (1.3)	1.5 (1.3)	1.2 (1.3)	1.2 (1.4)	1.5 (1.3)

Note. *p<.05, **p<.01. Means and standard deviation or percentage reported. CES-D = Center for Epidemiological Studies Depression Scale; HF-HRV = High-Frequency Heart Rate Variability; Inflammatory Composite range 0-5.

Table 2: Descriptive statistics and zero-order correlations in overall M2P4 sample

Variable	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11	12	13
1. CES-D	23.7	7.12	--												
2. HF-HRV	5.12	1.41	-.187*	--											
3. Sex	.610	.490	.009	.010	--										
4. Inflammatory Composite	1.37	1.33	.027	-.042	.066	--									
5. Respiration Rate	17.1	1.97	.072	-.115	.082	.040	--								
6. Race	.390	.490	-.044	.283**	.146	.259**	-.218**	--							
7. Education	.895	.664	.002	-.047	-.053	-.170	-.191	-.157	--						
8. Age	52.5	9.87	-.140	-.230**	-.023	-.038	.043	-.193*	.014	--					
9. Exercise	.709	.456	-.069	-.152	-.059	-.211**	-.034	-.339**	.202*	.048	--				
10. Tobacco Use	.298	.459	.107	.133	.098	.133	-.146	.240**	-.202*	-.217**	.132	--			
11. Alcohol Use	2.42	2.11	.040	.095	.098	.015	-.049	.069	-.015	-.176*	-.114	.134	--		
12. Blood Pressure Med	.340	.474	.126	-.044	.077	.137	.140	-.026	-.037	.308**	.105	-.052	-.141	--	
13. Depression Med	.250	.436	.203*	-.140	.140	-.040	.024	-.203*	.103	.145	.075	-.060	-.213**	.172*	--
14. Cardiometabolic conditions	1.22	1.02	.149	-.109	-.135	.226**	.168*	.089	-.163	.341**	.179*	.080	-.101	.612**	.134

Note. $N = 158$. * $p < .05$, ** $p < .01$. *M* = mean, *SD* = standard deviation; CES-D = Center for Epidemiological Studies Depression Scale; HF-HRV = High-frequency Heart Rate Variability; Sex coded 0 = male, 1 = female; Inflammatory composite range 0 – 5; Race coded 0 = White, 1 = non-White; Education coded 0 = HS degree or fewer, 1 = BA degree or fewer, 2 = MA degree or greater; Exercise coded 0 = no, 1 = yes; Tobacco use coded 0 = no, 1 = yes; Alcohol use range coded 1 = everyday – 6 = never; Blood pressure medication coded 0 = no, 1 = yes; Depression medication coded 0 = no, 1 = yes; Cardiometabolic conditions range 0-5.

Table 3. Interactive effects of HF-HRV & sex on concurrent depressive symptoms in overall M2P4 sample

Variable	Model 1			Model 2			Model 3		
	b	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.156	.382	.043	.135	.385	.037	.132	.384	.036
Race	-1.20	1.65	-.083	-.461	1.71	-.032	-.461	1.71	-.032
Education	.352	1.13	.033	.324	1.11	.030	.379	1.11	.035
Age	-.167	.080	-.231*	-.187	.080	-.259*	-.192	.080	-.266*
Exercise	.599	1.69	-.038	-.925	1.67	-.059	-1.03	1.67	-.066
Tobacco Use	1.22	1.65	.078	1.40	1.64	.091	1.39	1.64	.090
Alcohol Use	.236	.344	.070	.282	.344	.083	.234	.346	.069
Blood Pressure Med	1.04	1.89	.069	1.52	1.92	.101	1.37	1.92	.091
Depression Med	3.25	1.70	.199	3.11	1.72	.190	2.91	1.73	.178
Cardiometabolic conditions	1.10	.920	.158	.795	.965	.114	.981	.979	.141
Sex				-.446	1.54	-.031	5.37	5.52	.369
HF-HRV				-1.09	.521	-.217*	-.413	.808	-.082
Sex x HF-HRV							-1.12	1.02	-.431
R^2		.126			.166			.177	
ΔR^2		.126			.041			.011	

Note. $N = 158$. * $p < .05$. HF-HRV = High-Frequency Heart Rate Variability.

Table 4: Interactive effects of HF-HRV & sex on concurrent depressive symptoms in unmedicated M2P4 subsample

Variable	Model 1			Model 2			Model 3		
	b	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.490	.420	.155	.440	.425	.139	.425	.425	.134
Race	-.443	1.72	-.035	.075	1.82	.006	.138	1.82	.011
Education	.893	1.23	.093	.940	1.22	.098	.972	1.22	.101
Age	-.148	.090	-.229	-.160	.089	-.248	-.163	.089	-.224
Exercise	.434	1.85	.031	.135	1.83	.010	-.027	1.84	-.002
Tobacco Use	-.502	1.75	-.037	-.346	1.74	-.026	-.274	1.75	-.020
Alcohol Use	.537	.390	.171	.502	.388	.162	.423	.397	.136
Blood Pressure Med	-.124	2.07	-.010	.105	2.09	.008	-.116	2.10	-.008
Cardiometabolic conditions	1.11	1.02	.170	.884	1.05	.136	1.06	1.07	.164
Sex				.733	1.64	.058	6.25	5.87	.476
HF-HRV				-1.04	.539	-.243	-.482	.806	-.112
Sex x HF-HRV							-1.00	1.07	-.455
R^2		.116			.172			.184	
ΔR^2		.116			.056			.012	

Note. $N = 118$. HF-HRV = High-Frequency Heart Rate Variability.

Table 5. Interactive effects of HF-HR, sex, & inflammation on concurrent depressive symptoms in overall M2P4 sample

Variable	Model 1			Model 2			Model 3			Model 4		
	b	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.156	.383	.043	.139	.387	.038	.091	.395	.025	.092	.398	.025
Race	-1.20	1.65	-.083	-.340	1.74	-.023	-.557	1.79	-.038	-.570	1.84	-.039
Education	.352	1.13	.033	.290	1.12	.027	.308	1.13	.029	.317	1.17	.030
Age	-.167	.080	-.231*	-.189	.080	-.262*	-.199	.082	-.276*	-.198	.083	-.275*
Exercise	-.599	1.68	-.038	-.944	1.69	-.064	-.199	1.71	-.064	-1.01	1.73	-.064
Tobacco Use	1.22	1.65	.078	1.43	1.65	.092	1.26	1.67	.081	1.26	1.69	.081
Alcohol Use	.236	.344	.069	.285	.345	.084	.265	.353	.078	.264	.356	.078
Blood Pressure Med	1.03	1.89	.068	1.55	1.93	.103	1.22	1.96	.081	1.21	1.97	.081
Depression Med	3.25	1.70	.199	3.08	1.73	.189	3.00	1.76	.184	2.98	1.82	.183
Cardiometabolic conditions	1.10	.920	.158	.843	.977	.121	1.12	1.00	.161	1.12	1.01	.161
Sex				-.420	1.55	-.029	3.29	6.05	.226	3.09	8.34	.212
HF-HRV				-1.12	.527	-.222*	-.783	1.01	-.156	-.801	1.17	-.160
Inflammation				-.223	.558	-.042	-1.33	2.02	-.249	-1.41	2.95	-.263
Sex x HF-HRV							-.956	1.05	-.368	-.915	1.57	-.350
Sex x Inflammation							.930	1.12	.163	1.07	3.99	.187
HF-HRV x Inflammation							.130	.388	.129	.147	.609	.146
Sex x HF-HRV x Inflammation										-.029	.799	-.028
R^2		.126			.168			.186			.186	
ΔR^2		.126			.042			.018			.000	

Note. $N = 158$. * $p < .05$ HF-HRV = High-Frequency Heart Rate Variability

Table 6. Interactive effects of HF-HR, sex, & inflammation on concurrent depressive symptoms in unmedicated M2P4 subsample

Variable	Model 1			Model 2			Model 3			Model 4		
	b	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.490	.420	.155	.454	.424	.143	.405	.442	.128	.398	.445	.126
Race	-.443	1.72	-.035	.408	1.84	.032	.227	1.94	.018	.520	2.00	.041
Education	.893	1.23	.093	.815	1.22	.085	.897	1.26	.093	.616	1.33	.064
Age	-.148	.090	-.229	-.161	.088	-.249	-.170	.092	-.262	-.175	.093	-.271
Exercise	.434	1.85	.031	-.027	1.83	-.002	-.171	1.88	-.012	.094	1.93	.007
Tobacco Use	-.502	1.75	-.037	-.224	1.74	-.017	-.183	1.78	-.014	-.232	1.79	-.017
Alcohol Use	.537	.390	.171	.521	.388	.166	.449	.408	.144	.469	.411	.150
Blood Pressure Med	-.124	2.07	-.009	.038	2.09	.003	-.092	2.16	-.007	-.116	2.17	-.008
Cardiometabolic conditions	1.11	1.02	.170	1.12	1.07	.171	1.26	1.10	.193	1.27	1.11	.195
Sex				.864	1.64	.068	4.87	6.53	.385	8.79	8.94	.694
HF-HRV				-1.11	.541	-.259*	-.871	1.02	-.203	-.466	1.20	-.109
Inflammation				-.653	.593	-.141	-1.29	2.03	-.279	.120	2.99	.026
Sex x HF-HRV							-.801	1.12	-.363	-1.59	1.66	-.719
Sex x Inflammation							.065	1.19	.013	-2.49	4.12	-.499
HF-HRV x Inflammation							.143	.397	.165	-.172	.631	-.198
Sex x HF-HRV x Inflammation										.534	.825	.608
R^2		.116			.189			.198			.204	
ΔR^2		.116			.072			.009			.006	

Note. $N = 118$. * $p < .05$ HF-HRV = High-Frequency Heart Rate Variability.

Table 7: Demographic and clinical characteristics of longitudinal M3 sample separated by sex and depression status

	Not depressed (n = 484)		Depressed (n = 107)	
Variable	Males n = 246	Females n = 238	Males n = 48	Females n = 59
Age (years)	57.5 (11.1)	57.2 (10.8)	53.5 (10.1)	52.9 (9.1)
Race (% White)	93.5%	93.7%	95.8%	88.1%
BL CES-D	5.6 (5.5)	5.4 (4.7)	10.8 (7.7)	10.7 (8.5)
HF-HRV (ms^2)	269.6 (1043.5)	277.4 (449.8)	332.0 (530.3)	265.4 (371.7)
Inflammatory Composite	.69 (.95)	.86 (1.1)	.73 (1.0)	.98 (1.2)

Note. * p<.05, **p<.01. Means and standard deviation or percentage reported. BL CES-D = Center for Epidemiological Studies Depression Scale collected at biomarker lab visit; HF-HRV = High Frequency Heart Rate Variability; Inflammatory Composite range 0-5.

Table 8: Descriptive statistics and zero-order correlations in overall M3 sample

	Variable	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11	12
1.	CES-D	6.42	6.09	--											
2.	HF-HRV	4.86	1.21	.074	--										
3.	Sex	.500	.500	-.001	.081*	--									
4.	Inflammatory Composite			.112*	-.074	.087*	--								
5.	Respiration Rate	17.0	1.72	.066	-.024	-.019	.062	--							
6.	Race	.066	.249	.062	.034	.020	.072	.067	--						
7.	Education	1.00	.685	-.066	.000	-.064	-.077	-.029	-.030	--					
8.	Age	56.6	10.8	-.188**	-.297**	-.025	.029	.093*	-.072	-.043	--				
9.	Exercise	.805	.396	-.033	.039	-.019	-.149**	-.013	-.041	.056	-.061	--			
10.	Tobacco Use	.102	.302	.170**	.118**	-.058	.140**	.002	-.026	-.107**	-.090*	-.090*	--		
11.	Alcohol Use	2.66	2.08	.074	.062	.042	.051	-.013	-.067	-.026	-.055	-.060	-.010	--	
12.	Blood Pressure Med	.290	.452	-.008	-.108**	-.029	.118**	.102*	.016	-.011	.335**	-.134**	-.039	-.015	--
13.	Cardiometabolic conditions	1.02	.943	.024	-.146**	-.300**	.172**	.085*	.001	.000	.344**	-.078	.006	-.065	.633**

Note. $N = 591$. * $p < .05$, ** $p < .01$. *M* = mean, *SD* = standard deviation; CES-D = Center for Epidemiological Studies Depression Scale; HF-HRV = High-Frequency Heart Rate Variability; Sex coded 0 = male, 1 = female; Inflammatory composite range 0 – 5; Race coded 0 = White, 1 = non-White; Education coded 0 = HS degree or fewer, 1 = BA degree or fewer, 2 = MA degree or greater; Exercise coded 0 = no, 1 = yes; Tobacco use coded 0 = no, 1 = yes; Alcohol use range coded 1 = everyday – 6 = never; Blood pressure medication coded 0 = no, 1 = yes; Cardiometabolic conditions range 0-5.

Table 9: Interactive effects of HF-HRV & sex predicting future depression onset in M3 sample

Variable	Block 1			Block 2			Block 3		
	b	SE *b*	*OR*	*b*	SE *b*	*OR*	*b*	SE *b*	*OR*
Respiration Rate	-.013	.068	.987	-.011	.069	.989	-.011	.069	.989
Race	-.001	.444	.999	-.026	.446	.975	-.013	.447	.987
Education	.229	.174	1.26	.254	.175	1.29	.239	.175	1.27
Age	-.034	.013	.966**	-.036	.013	.965**	-.037	.013	.964**
Exercise	-.145	.288	.865	-.119	.291	.888	-.104	.292	.901
Tobacco Use	.042	.368	1.04	.067	.374	1.07	.086	.375	1.09
Alcohol Use	-.025	.057	.975	-.025	.057	.976	-.028	.057	.973
Blood Pressure Med	-.071	.345	.932	-.214	.354	.807	-.200	.355	.819
Cardiometabolic conditions	.246	.163	1.28	.369	.174	1.45*	.375	.174	1.46*
CES-D	.124	.019	1.13**	.126	.019	1.13**	.125	.019	1.13**
Sex				.495	.253	1.64	1.78	.944	5.93
HF-HRV				-.019	.101	.981	.100	.131	1.11
Sex x HF-HRV							-.259	.183	.772
Nagelkerke R^2		.116			.122			.125	
Cox & Snell R^2		.189			.199			.204	

Note. $N = 591$. * $p < .05$, ** $p < .01$.

Table 10: Interactive effects of HF-HRV, sex, & inflammation predicting future depression onset in M3 sample

	Block 1			Block 2			Block 3			Block 4		
Variable	*b*	SE *b*	*OR*	*b*	SE *b*	*OR*	*b*	SE *b*	*OR*	*b*	SE *b*	*OR*
Respiration Rate	-.013	.068	.987	-.010	.069	.990	-.011	.069	.989	-.012	.069	.988
Race	-.001	.444	.999	-.014	.448	.986	-.005	.456	.995	.034	.456	1.04
Education	.229	.174	1.26	.252	.175	1.29	.238	.176	1.27	.256	.177	1.29
Age	-.034	.013	.966**	-.036	.013	.965**	-.037	.013	.963**	-.039	.013	.962**
Exercise	-.145	.288	.865	-.127	.292	.881	-.111	.294	.895	-.107	.295	.898
Tobacco Use	.042	.368	1.04	.083	.378	1.09	.099	.380	1.10	.088	.382	1.10
Alcohol Use	-.025	.057	.975	-.024	.057	.976	-.027	.057	.974	-.017	.058	.983
Blood Pressure Med	-.071	.345	.932	-.215	.355	.807	-.201	.355	.818	-.191	.358	.826
Cardiometabolic conditions	.246	.163	1.28	.378	.176	1.46*	.384	.176	1.47*	.395	.177	1.48*
CES-D	.124	.019	1.13**	.126	.019	1.13**	.126	.019	1.13	.122	.019	1.13**
Sex				.510	.257	1.67*	1.80	.983	6.06	3.01	1.25	20.3*
HF-HRV				-.024	.102	976	.092	.151	1.10	.216	.171	1.24
Inflammation				-.036	.109	.965	-.048	.428	.954	.632	.610	1.88
Sex x HF-HRV							-.259	.185	.772	-.508	.244	4.34
Sex x Inflammation							-.007	.218	.993	-1.31	.874	.271
HF-HRV x Inflammation							.004	.086	1.00	-.145	.129	.865
Sex x HF-HRV x Inflammation										-1.89	1.71	.151
Nagelkerke		.116			.122			.125			.129	
Cox & Snell		.189			.199			.204			.210	

Note. $N = 591$. * $p < .05$, ** $p < .01$. HF-HRV = High-Frequency Heart Rate Variability.

Table 11: HRV predicting concurrent depressive symptoms in overall M2P4 sample, split by sex

	Males						Females					
	Model 1			Model 2			Model 1			Model 2		
Variable	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.734	.558	.221	.746	.572	.224	-.232	.627	-.060	-.295	.602	-.076
Race	.143	2.56	.009	.108	2.61	.007	-2.03	2.48	-.141	-.898	2.43	-.062
Education	-.036	1.86	-.003	.000	1.90	.000	-.053	1.56	-.010	.035	1.50	.003
Age	-.131	.115	-.178	-.129	.117	-.176	-.167	.119	-.237	-.212	.116	-.297
Exercise	2.28	2.51	.142	2.32	2.56	.144	-1.83	2.44	-.118	-2.39	2.35	-.155
Tobacco Use	4.00	2.48	.244	3.98	2.51	.243	-.911	2.46	-.060	-.786	2.36	-.050
Alcohol Use	-.297	.525	-.084	-.316	.546	-.089	.441	.498	.133	.388	.478	.117
Blood Pressure Med	.746	2.70	.048	.692	2.76	.045	2.14	2.94	.144	2.69	2.83	.181
Depression Med	6.05	3.03	.329	6.01	3.09	.327	1.44	2.46	.092	1.08	2.36	.069
Cardio-metabolic conditions	1.68	1.47	.225	1.76	1.57	.235	.481	1.40	.071	.413	1.35	.061
HF-HRV				.121	.788	.024				-.167	.741	-.329*
R^2		.373			.373			.089			.179	
ΔR^2		.373			.000			.089			.090	

Note. N = 62 males and 96 females. * $p < .05$. HF-HRV = High-Frequency Heart Rate Variability.

Table 12: HRV predicting concurrent depressive symptoms in unmedicated M2P4 sample, split by sex

	Males						Females					
	Model 1			Model 2			Model 1			Model 2		
Variable	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*	*b*	SE *b*	*β*
Respiration Rate	.938	.530	.363	.935	.541	.362	.384	.851	.106	.367	.819	.102
Race	-.153	2.33	-.013	-.137	2.39	-.012	-.755	3.12	-.055	.781	3.13	.056
Education	.070	1.69	.008	.062	1.72	.007	1.37	2.01	.146	1.72	1.95	.183
Age	-.112	.107	-.211	-.112	.109	-.212	-.191	.159	-.258	-.220	.154	-.298
Exercise	2.74	2.36	.212	2.73	2.41	.212	-1.03	3.13	-.109	-1.69	3.05	-.114
Tobacco Use	.680	2.30	.054	.685	2.35	.055	-1.55	3.13	-.109	-.873	3.04	-.061
Alcohol Use	-.198	.486	-.072	-.187	.512	-.068	.947	.688	.279	.730	.674	.215
Blood Pressure Med	-.658	2.57	-.053	-.614	2.67	-.049	.470	3.72	.032	.761	3.60	.052
Cardio-metabolic conditions	1.58	1.28	.267	1.54	1.40	.260	.879	1.84	.129	.690	1.77	.101
HF-HRV				-.058	.707	-.016				-1.65	.950	-.349
R^2		.242			.242			.144			.239	
ΔR^2		.242			.000			.144			.095	

Note. $N = 51$ males and 67 females. * $p < .05$. HF-HRV = High-Frequency Heart Rate Variability.

Table 13: Demographic and clinical characteristics of *post-hoc* depressed sample shown by sex and depression status at M3

	Subclinical *n* = 69		Clinical *n* = 38	
Variable	Males *n* = 31	Females *n* = 38	Males *n* = 17	Females *n* = 21
Age (years)	56.2 (10.1)	54.6 (8.8)	48.6 (8.5)	49.8 (9.0)
Race (% White)	96.8%	92.1%	94.1%	81.0%
BL CES-D	9.6 (7.7)	10.6 (8.8)	12.9 (7.6)	10.8 (8.2)
HF-HRV (ms^2)	358.3 (589.8)	278.8 (374.3)	284.2 (412.2)	241.1 (374.7)
Inflammatory Composite	.71 (1.1)	.89 (1.1)	.76 (.97)	1.1 (1.3)

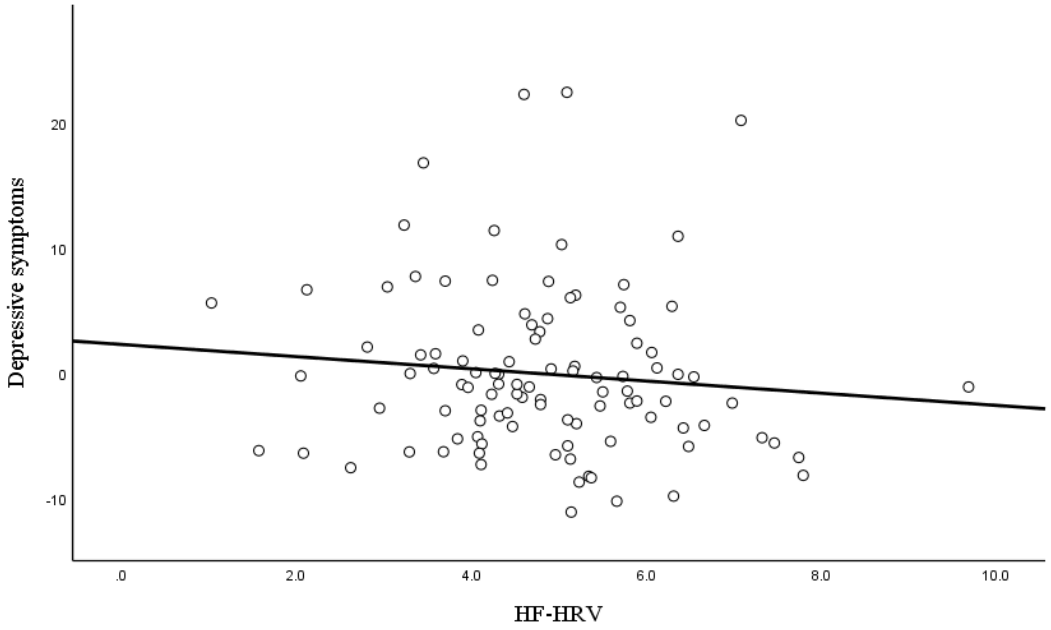
Note. * p<.05, **p<.01. Means and standard deviation or percentage reported. BL CES-D = Center for Epidemiological Studies Depression Scale at M2P4; HF-HRV = High Frequency Heart Rate Variability; Inflammatory Composite range 0-5.

Table 14: HRV predicting future Major Depressive Episode in *post-hoc* depressed M3 sample

Variable	Block 1			Block 2			Block 3		
	b	SE *b*	*OR*	*b*	SE *b*	*OR*	*b*	SE *b*	*OR*
Respiration Rate	-.146	.157	.864	-.192	.170	.826	-.194	.172	.824
Race	.769	.799	2.16	1.02	.874	2.76	.870	.893	2.39
Education	-.319	.354	.727	-.469	.374	.626	-.444	.375	.641
Age	-.071	.029	.931*	-.100	.033	.904**	-.104	.034	.901**
Exercise	.629	.612	1.88	.622	.637	1.86	.617	.639	1.85
Tobacco Use	-.368	.672	.692	-.079	.696	.924	-.144	.706	.866
Alcohol Use	-.146	.112	.864	-.139	.117	.870	-.145	.117	.865
Blood Pressure Med	-.941	.816	.390	-.377	.942	.686	-.522	.968	.594
Cardiometabolic conditions	.407	.344	1.50	.257	.400	1.29	.301	.407	1.35
BL CES-D	.006	.029	1.01	.004	.031	.945	.004	.031	1.01
Sex				-.057	.514	.945	-1.36	2.03	.257
HF-HRV				-.568	.221	.567*	-.394	.295	.500*
Sex x HF-HRV							.273	.411	1.31
Nagelkerke R^2		.157			.213			.217	
Cox & Snell R^2		.216			.293			.297	

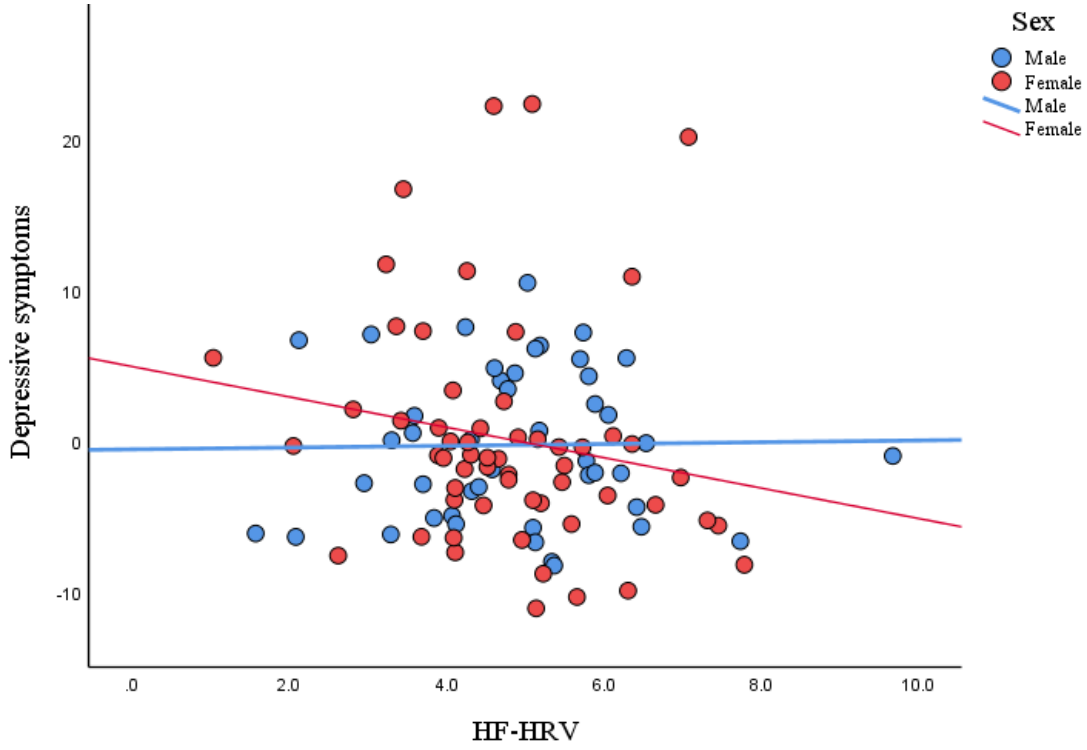
Note. $N = 107$. * $p < .05$, ** $p < .01$. HF-HRV = High-Frequency Heart Rate Variability; BL CES-D = Center for Epidemiological Studies Depression Scale at M2P4.

Figure 7. Higher HRV predicts less severe depression in overall M2P4 sample



Note. N = 158. Y-axis displays unstandardized regression residuals controlling for covariates and sex. HF-HRV = High-Frequency Heart Rate Variability and is natural-log transformed.

Figure 8. Higher HRV predicts less severe depression among females in overall M2P4 sample



Note. $N = 158$. Y-axis displays unstandardized regression residuals controlling for covariates and sex. HF-HRV = High-Frequency Heart Rate Variability and is natural-log transformed.