Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Ashley Rizzieri Date

The association of inflammatory response to a mental stress task and major depressive disorder amongst patients who experienced a myocardial infarction.

By
Ashley Rizzieri

Degree to be awarded: MPH
Global Health

_____

Viola Vaccarino, MD
Committee Chair

_____

Shivani A. Patel, MPH, PhD
Committee Member

The association of inflammatory response to a mental stress task and major depressive disorder amongst patients who experienced a myocardial infarction.

By
Ashley Rizzieri
Bachelors of Science

University of Rochester
2016

Thesis Committee Chair: Viola Vaccarino, MD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Health
2018

Abstract

The association of inflammatory response to a mental stress task and major depressive disorder amongst patients who experienced a myocardial infarction

By Ashley Rizzieri

Background: Major Depressive Disorder (MDD) is prevalent amongst MI patients and is associated with approximately a twofold increase in adverse events. Different inflammatory responses to stress in MI patients with MDD may contribute to worse adverse outcomes. The purpose of this study was to examine inflammatory responses to a mental stress test according to MDD status. Additionally, we explored this association stratified by sex.

Methods A secondary analysis of the Myocardial Infarction and Mental Stress 2 (MIMS2) study was performed, using data from 271 patients < 61 years of age hospitalized for MI in the previous 8 months. Participants were categorized into three groups: no history of MDD (n=175), previous MDD (n=52) and current (past month) MDD (n=44). Participants underwent a mental stress task within the parent study and inflammatory responses for Interleukin-6 (IL-6), C-Reactive Protein (CRP), Monocyte Chemoattractant Protein-1 (MCP1), Matrix Metalloproteinase- 9 (MMP9), and Vascular Endothelial Growth Factors (VEGF) were measured. We used mixed models to assess difference in inflammatory biomarker concentrations in response to mental stress (defined as the change in levels comparing post-stress values to pre-stress values) amongst the varying levels of MDD. Differences between women and men were assessed by estimating sex-stratified models and testing the interaction by sex in a model of all participants.

Results: IL-6 significantly increased from pre- to post- mental stress task ($p<.0001$) for all categories of MDD, but IL-6 responses to the mental stress task did not significantly differ across the categories of MDD. Furthermore, responses of CRP, MCP1, MMP9 and VEGF did not significantly differ across all three categories of MDD. Although women had higher levels of IL-6 than men throughout the mental stress task, the change in IL-6 means for all MDD categories did not significantly differ between men and women.

Conclusions: We found no significant association between MDD status and inflammatory changes in response to acute stress amongst MI patients. Further studies should explore other potential biological mechanisms that may explain the adverse prognosis associated with depression post-MI.

Acknowledgements

The final outcome of this project required a lot of guidance and assistance from many people and I am extremely privileged to have received this along the completion of my thesis. All that I have done is only due to such supervision and assistance and I would not forget to thank them.

I have the up most respect for and thank Dr. Viola Vaccarino for allowing me to work with her over the summer after my first year at Rollins School of Public Health and continuing to mentor me throughout my second year. It has been an honor to work with her.

I would also not forget to acknowledge Dr. Shivani Patel for her guidance as a committee member. She not only assisted with this thesis but helped shape my future career path.

Table of Contents

Chapter 1 Introduction

Cardiovascular Disease is the number one cause of death in the Unites States claiming more lives than cancer each year. Approximately half of these cases are attributed to myocardial infarctions (MI). Among patients who survive their first acute MI, the risk for another MI, stroke, and heart failure is substantial. About 17% men and 21% of women will have a recurrent MI within the next five years [1]. There are escalating health care costs following re-hospitalizations and treatment. The estimated total costs for heart disease in 2012 were approximately $207.3 billion, with MI accounting for $11.5 billion, one of the most expensive hospital discharges in the year 2011 [1]. Furthermore, the incidence of coronary heart disease (CHD) and MI for women lags behind men approximately by ten years. However, the one year mortality risk following an MI is 18% in men and 23% in women within the first year, and 36% of men and 45% of women will die within the following five years [1].

Major Depressive Disorder (MDD) is known to be more prevalent in people who have just suffered a major cardiac event. For those who have suffered an MI and have MDD, the risk of cardiac mortality is two times higher compared to those without MDD within the following 6 months [2]. Conventional lifestyle factors have been researched to partially describe the relationship between MDD and MI. These include an unhealthy diet, tobacco use, alcohol consumption, and limited physical exercise. Compared to people who are not depressed, those who are depressed tend to smoke more, engage in excessive alcohol consumption, have an unhealthy diet, and are less physically active, thus pathways linking depression to somatic comorbidities have used these behavioral factors to explain a causal relationship for cardiovascular disease [2,3].

Biological pathways have also been hypothesized to help explain the link between MDD and CVD, such as immune-inflammatory dysregulations [3]. Chronic low-grade elevations of pro inflammatory markers, especially Interleukin-6 (IL-6) and C-reaction Protein (CRP), have shown to increase cardiovascular morbidity and mortality and tend to be elevated in persons with MDD [3].

Identifying immune-inflammatory dysregulations may provide insight as to why depressed patients have a harder time during recovery post MI. Irregularities in inflammatory markers during an immune response to stress, may explain why persons who are both depressed and have CHD are less adherent and motivated to complete cardiac rehabilitation programs and less likely to make modifications to current lifestyle behaviors. Looking at inflammation markers in those with MDD by sex may also explain why the adverse events following an MI are worse in women than in men. Women are more likely to suffer from MDD and studies have suggested that being a woman enhances the risk of developing CVD in the future as well [4-8].

Research Objectives

The primary objective of the current study is to explore the association between the change in inflammatory markers post mental stress testing among MI patients who either never had MDD, previously had MDD, or currently have MDD. A secondary aim is to explore potential sex differences within this association.

Chapter 2 Literature Review

Global Burden of Cardiovascular Disease

As of 2013, all 194 countries of the World Health Organization (WHO) created a global action plan to reduce the preventable deaths caused by non-communicable diseases (NCDs) by 25% in the year 2025. This makes the focus on preventing Cardiovascular Diseases (CVD) and other related heart events a global priority because approximately 17 million premature deaths were due to NCDs and 37% were CVD related in 2015 [9]. Highlighting this importance, WHO designated two goals within this aim specifically reducing CVD by lowering the incidence of hypertension and increasing drug therapy and counseling for vulnerable populations [9]. In order to inform effective intervention, WHO Identified key risk factors for future CVD. These included tobacco use, alcohol consumption, unhealthy diet, physical inactivity, having, or being diabetic. Furthermore, tobacco cessation programs, taxing high fat foods, building sidewalk and biking lanes, introduction of medicine to control diabetes and hypertension have been implemented as prevention initiatives to address these risk factors. Although current trends suggest that the incidence of CHD and MI have decreased over time in developed countries, it still causes approximately a third of deaths for persons over 35 years of age [10].

National Burden of Coronary Heart Disease (CHD) / Myocardial Infarction (MI)

In 2017, 16.5 million adults in the US had CHD, with about 7.9 million cases attributed to MI [1]. Furthermore, it remains the leading cause of death in the United States, claiming more lives than cancer each year (Figure 1). CVD mortality has declined in the US since the 1980s, however it is unclear as whether the incidence of MI has declined as well. For instance, observational studies have suggested the incidence of MI to be constant throughout 1971 to 2006

[10, 11]. In contrast, a study conducted with about 5,258 MIs from Olmsted County showed that the overall rate of MI from 1995 to 2012 declined over time [12]. Changing definitions for an MI could have masked a decrease over time; a more sensitive troponin assay was administered in the year 2000 that included patients expressing a lower area of myocardium infarction than with the CK-MB marker alone [13]. Despite this contrast in previous literature, the majority of the literature points to an overall decline in incident MI, hospitalizations for MI, and mortality caused by MI [14-16].

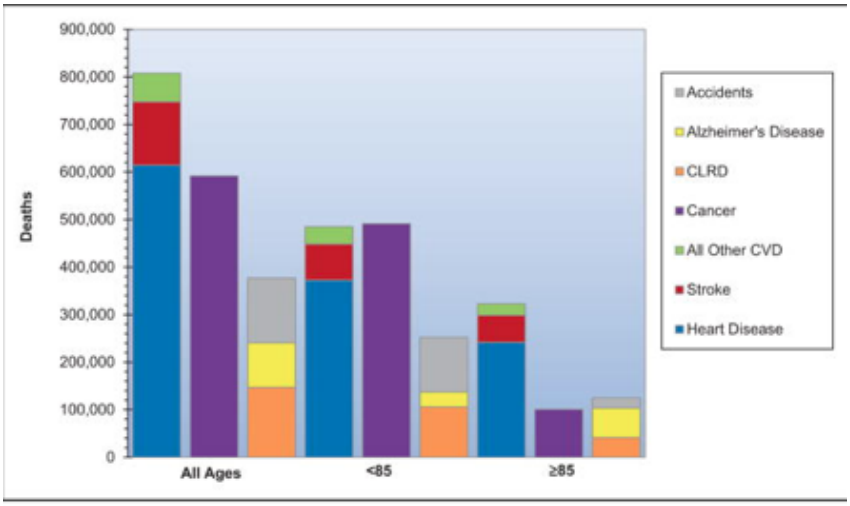


Figure 1. CVD surpasses cancer related deaths in the United States during 2014 based on report conducted by the American Heart Association [1].

Furthermore, MI affects different populations. The incidence of MI occurs earlier for men than women on average with the average age of the first MI at 65 years and 71 years respectively [1]. In the ARIC Surveillance study conducted from 2005 to 2013 the incidence of MI was higher for black males, white males, black females, and white females in that order [1]. Lastly, the risk of MI is positively correlated with age with more cases represented in the older population.

National Burden of MDD

Depression is projected to contribute to the greatest years lost to disability in the year 2030 [4]. According to the National Survey on Drug Use and Health in 2016, approximately 16 million adults in the U.S had at least one MDD episode, defined by the DSM-IV codes [17]. The prevalence of depression is greater for some populations. The prevalence amongst adults is almost double in women than in men, highest at younger age (below 26 years), and higher for adults reporting two or more races (Figure 2) [18]. MDD is associated with lower quality of life, functional impairments, and premature mortality. Depression can worsen one's health when coexisting with a physical illness. The World Health Organization conducted a world health survey of the prevalence of depression and chronic physical diseases based on ICD-10 criteria. They concluded the overall burden of disease is higher for those who have both depression and a chronic condition, compared to individuals who either have depression or a chronic illness alone [4]. Specifically, within the United States, studies have demonstrated an increase in medical symptoms for coronary artery disease, congestive heart failure, asthma, and osteoarthritis among participants with depression [14-16]. MDD in patients who have suffered cardiovascular related events can lead to an earlier time of death. Carney et al. (2008) concluded that major and minor depression were both risk factors of early death in a five-year survival analysis of patients who just experienced an MI [19].

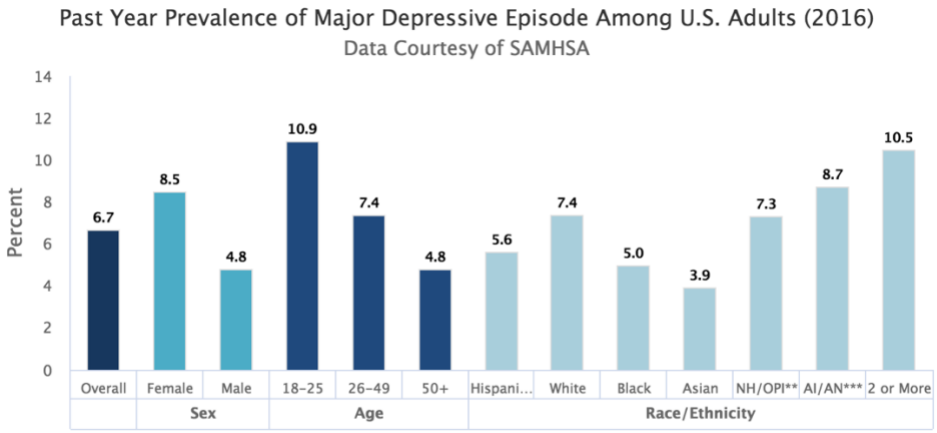


Figure 2. The prevalence of MDD was higher for females compared to males, for multi-racial adults, and for individuals between 18-25 years old [19].

The Link Between MDD and MI

There is a large body of literature that has evaluated the association between depression and CHD and/or MI. Depression has been identified as a risk factor for incident CHD [20]. A 2014 meta-analysis of thirty prospective cohort studies reported that persons diagnosed with depression were 1.3 times (95% confidence interval [CI]: 1.2-1.4) more likely to develop CHD than those were not depressed [21]. An earlier meta-analysis of 54 observational studies found the odds of CHD for those with depression were 1.6 (95% CI:1.4-1.8) times higher compared to those without depression [22].

Not only is depression a risk factor for incident CHD, but it also has been identified as a risk factor for cardiovascular morbidity and mortality in patients with established CHD. In 2014, Lichtman et al. conduced a review summarizing studies of depression as a risk factor of for cardiovascular morbidity and mortality in patients with established CHD [2]. The largest meta-analysis to date compared patients with and without depression after an MI. They concluded that depression was associated with a 2.7-fold increase in cardiac related death and 1.6-fold increase

in cardiovascular related events up to 2 years post MI [23]. Pooled data from the 'Emotions and Prognosis Post Infarct (EPPI) cohort' found that MI patients with depression were five times more likely to have a cardiac death compared no non-depressed patients over 6 months following the MI [2, 24]. However, there has been variability of these findings across different studies.

Lichtman et al. also highlighted an association between depression and non-fatal events in patients with CHD. Studies reporting on the Epidemiological Study of Acute Coronary Syndromes and Pathophysiology of Emotions (ESCAPE) found an association between MDD and major cardiac events in patients with acute coronary syndromes [2]. A study conducted in the Netherlands reported depression as a significant risk factor for poor outcomes in MI patients, such as recurrent MI [2]. One of the most recent meta-analyses reported effects of depression in MI patients to be 2.3 for all-cause mortality and 2.7 for cardiac mortality [23]. Given this body of information, a few clinical trials have explored administering depression treatment after MI, but none have found a significant difference between the groups receiving the intervention verse regular treatment. This highlights the importance of finding the biological mechanisms behind the association of MDD and MI. Analyzing inflammatory markers in response to mental stress may partially explain some of these mechanisms.

Why Study Sex Differences Within the Link Between MDD and MI?

Women are more susceptible to depression after cardiac related events. Prospective Registry Evaluating Outcomes After Myocardial Infarction (PREMIER) found that women under the age of 60 were three times more likely to develop depression post MI than men [25]. Although depression is more common amongst women, another study using the PREMIER registry concluded that the prevalence only modestly contributed to higher rates of re-

hospitalization and angina in women compared to men [26]. In 2016, a study of a prospective cohort found that women who were hospitalized after a myocardial infarction experienced significantly more anxiety and depression when compared to men [27]. In 2018, a study conducted amongst MI patients discovered that women have a 2-fold chance of developing mental stress induced myocardial ischemia (MSIMI) and also conventional stress ischemia compared to men [28]. Analyzing the potential sex differences in inflammation marker concentration during mental stress testing based on depression status could provide an explanation for the disparity described in the literature, given that women have a higher rate of depression than men after an MI.

Inflammatory Markers May Partially Explain the Link Between Depression and MI

Inflammation and CHD

Inflammation is known to play a role in atherosclerosis, coronary artery disease progression, and pathological processes involved in acute coronary syndromes including a myocardial infarction [29]. There is extensive research on the role of inflammation on risk of CVD. C-reactive protein (CRP) is commonly secreted by hepatocytes during an inflammatory stimulus, promotes expression of adhesion and inflammatory cells, and has been shown to increase in patients with unstable angina [30]. In 2008, a study found that compared to healthy controls who were subjected to an acute mental stress test and exercise, those who had coronary heart disease experienced higher levels of inflammation markers, including C reactive protein, soluble intercellular adhesion molecule-1 and Interleukin 6 [31].

Interleukin-6 (IL-6) is a common marker used for early detection of atherosclerosis which is involved in the recruiting and activating inflammatory cells in response to myocardial

ischemia. This marker stimulates the production of CRP in the liver so there is often a positive correlation of these two markers with the development of atherosclerosis [30]. This marker has shown the most robust changes in psychological stress [32].

Monocyte Chemoattractant Protein-1 (MCP-1) is a type of chemokine that aids in homing circulating leukocytes to the area of inflammation [33], and has been implicated in a few studies to play a role in remodeling of tissue after a myocardial infarction [34]. MCP-1 has been studied as a potential target for therapeutic intervention and positively associated with increased risk of cardiovascular events, including but not limited to myocardial infarctions [33, 35, 36].

Matrix metalloproteinase- 9 (MMP-9) is part of a group of proteolytic enzymes that contribute to the changes in extracellular matrix of cardiomyocytes and endothelial cells during cardiac remodeling [37, 38]. MMP-9 has been shown to play a role in the prognosis of cardiovascular disease and to be a predictor to cardiovascular disease [39], recurrent MI among patients who have a history of acute myocardial infarction [40], and late heart failure with adverse left ventricular remodeling in patients with ST-elevation myocardial infarction [41].

Vascular endothelial growth factors (VEGF) are important signaling proteins involved in angiogenesis, the formation of new capillary blood vessels during wound healing, embryological development, menstrual cycle, and inflammation, and play a role in various diseases and chronic conditions such as MI [42]. An increase in VEGF mRNA in infarcted heart compared to normal heart has been reported in rat studies [43, 44].On the other hand, expression of VEGF was found to play a triggering role in angiogenesis following an acute MI, but was not crucial in the later stages of angiogenesis in the infarcted myocardium [[42].

Depression and Inflammation

Many studies have suggested that certain inflammatory biomarkers are elevated for patients who are depressed. For example, Danner et al. 2003 saw 2.8 times higher levels of CRP in depressed men compared to healthy controls between the ages 17-39. No such trend was found in women [45]. In 2004, Ford DE et al. confirmed similar findings but acknowledged that a parallel trend in women could be masked by menstrual fluctuations [46]. Pace et al. in 2006 concluded that men with MDD exhibit enhanced inflammatory responsiveness when subjected to a psychological stress test, suggesting a link between MDD and inflammation, but women were not included in this study [47]. Despite a relative lack of data among women, a recent review concluded that women may be more vulnerable to inflammation-induced mood and behavior changes compared with men, and potentially more susceptible to CVD as a consequence of depression [48]. Analyzing the changes in inflammation markers for patients with and without depression could help explain why the prevalence of depression is higher in women than in men.

Depression, Inflammation, and CHD

Many studies have investigated the role inflammation plays within the association of Depression and risk of CHD. Recently, Carney et al. conducted a comprehensive review of mechanisms behind depression and coronary heart disease [20]. The majority of research has found that patients with depression have higher levels of IL-6, CRP and soluble intercellular adhesion molecule-1, but these inflammatory markers only partially explained the estimated risk of CHD. Miller et al. in 2002 found that when looking at markers in the pathogenesis of CHD, depression was associated with elevated levels of CRP and IL-6 [49]. A nested case control study using data generated from the Prospective Epidemiological study of myocardial infarctions

(PRIME), showed that European men with depression had a 46%, and 16% higher levels of CRP and IL-6 compared to healthy controls at baseline. After adjustment for these inflammatory markers, however, the association between depression and CHD was attenuated, but still significant [50]. Women were not included in this study. A study of only U.S. women provided similar results [51]. To contrast to the above studies, some researchers have suggested a null association between inflammation and depression [52, 53]. The Heart and Soul Study conducted in 2007 looked at depression and inflammatory biomarkers including white blood cell counts, CD40 ligand, CRP, fibrinogen, and IL-6 within patients who have CHD. No association was found between current depression and inflammation in outpatients with CHD and thus inflammatory markers were unlikely to explain adverse outcomes in relation to depression [54].

Few studies that have explored sex differences in inflammatory responses associated with depression and CHD. Lu et al. 2017 explored sex differences in inflammation at rest among young adults with acute myocardial infarction [55], but did not explore associations with MDD. This study concluded that after AMI, women experienced higher levels of inflammatory markers, CRP and lipoprotein-associated phospholipase A2, compared to men. A prospective study of only women with well-established CVD risk, found that depression and inflammation were independently associated with CVD risk [46]. Inflammation was measured at rest and women with MDD had 70% higher levels of CRP, and 25% higher levels of IL-6. This association did not substantially change between the unadjusted and adjusted models. Additionally, women with MDD had 2.6 higher odds of developing CVD than women without MDD [46]. Further research has explored sex differences in mental stress induced myocardial ischemia in survivors of CAD and acute MI [56, 57].The most recent study in 2018 confirmed that women who survive an MI, have a two-fold chance of developing mental stress induced ischemia, compared to men [53].

They found that psychosocial and clinical factors did not explain sex differences in inducible ischemia.

Aims of the Current Project

Aim 1. To compare the inflammatory response to acute mental stress in MI patients with and without depression. We hypothesize that current or previous depression leads to an increase in mental stress-related inflammatory markers including IL-6, CRP, MCP1, MMP9, and VEGF compared to those who have never been depressed.

Rationale and Innovation: This is one of the first studies to explore the differences in mental stress induced inflammation amongst MI patients by MDD status. Prior research has shown that depression is associated with higher levels of inflammation in the resting state, but little is known on whether differences occur during acute stress. This study can provide evidence for how depression specifically enhances, inhibits, or has no effect on inflammatory response to acute stress in post-MI patients. While many studies have examined inflammation at rest, and some studies have looked at differences in inflammatory responses to stress in MDD patients compared to non-MDD controls, few to none have investigated inflammatory responses by MDD status among post MI patients. This study will be one of the first to examine inflammatory responses to a mental stress task amongst MI patients with and without MDD.

Aim 2. To compare sex differences in inflammatory response to acute mental stress in MI patients with and without depression. Among patients with MI, we hypothesize that the inflammatory response to mental stress associated with depression is stronger for women. We expect that women who are currently or previously depressed, will have a higher positive change

in inflammatory biomarker concentrations with mental stress than men who are currently or previously depressed.

Rationale and Innovation: Women are known to have the highest rates of depression post MI compared to men post MI [25]. However, whether inflammation mediates the sex differences in MDD post MI remains unclear. Very few to no studies have explored sex differences in inflammatory responses to a mental stress task according to MDD status. Given that MDD is more prevalent amongst women, this is an association worth exploring. This study will be one the first to explore sex differences in mental stress induced inflammation in MI patients with varying levels of MDD.

Global Health Implications of the Results from Current Study

Depression is associated with MI, but currently there are no guidelines for assessing and treating depression as a risk factor for MI. This is concerning when we think that 322 million people currently have depression, which is about 4.4% of the global population [59]. In 2010, the Global Burden of Disease study (GBD) conducted a robust systematic review of MDD as an independent risk factor for ischemic heart disease (IHD) and the results were astounding. The relative risk of persons with MDD developing IHD was 1.56 [60]. The GBD study highlighted the need to assess depression in those at risk for IHD on an international level. Previous studies have looked at biological mechanisms to explain the prognosis for MI patients. By looking at inflammatory response to stress, we may be able to illuminate some of the mechanistic links between MDD and MI prognosis. In the future, physicians may be able to use this information to be better understand the mediating mechanisms between MDD and CVD. Furthermore, researchers may look at how these markers change in response to treatment of depression, such

as antidepressant use, and their contribution to potential adverse effects such as MI. The current study may contribute to clarifying the vast but conflicting literature exploring potential causal pathways of MDD and MI. This information may aid public health prevention and treatment efforts for MI, allowing the World Health Organization to be one step closer to their goal of reducing the amount of preventable non-communicable diseases by 25% in the year 2025.

Chapter 3 Methods

Parent Study Design

This is a secondary analysis of the Myocardial Infarction and Mental Stress 2 (MIMS2) study, which sought to examine sex differences in mental stress induced myocardial ischemia in young post-MI patients, and empirically assess the underlying vascular determinants for any differences found. The sample included 313 patients less than 61 years old, who were hospitalized for MI in the previous 8 months in the Emory hospital system [28].

Study Design and Participants

The analytic sample for this study included the MI patients from the MIMS2 study, including 313 men and women who were recruited from a pool of patients admitted to Emory-affiliated hospitals between August to March of 2012 (Emory University Hospital, Emory Hospital Midtown, Saint Joseph's Hospital, and Grady Memorial Hospital). MI patients between the ages of 18-60 were selected from an electronic dataset of patients who had a documented history of MI in the previous 8 months at the Emory affiliated hospitals in Atlanta, Georgia. MI patients were verified by medical records and defined by the standard criteria of [61].

Amongst the MI patients who completed the mental health testing, the participants were further divided into one of three categories, those with no history of major depression (n=175), with previous history of major depression (n=52), and currently depressed defined within the past month (n=44). MDD diagnosis was obtained through the Structured Clinical Interview for DSM IV (SCID) [17], and depressive symptoms were assessed through the Beck Depression Inventory II (BDI-II) [62]. Participants were excluded from the analysis if they were missing data for inflammatory markers at rest and post mental stress testing, but still included if they had

one or the other (Figure 3). A total of 32 participants were excluded due to missing data on inflammatory markers during the mental stress testing. In addition, ten participants were excluded based off missing data for MDD status, resulting in a total of 271 participants (Figure 3).

Procedures/Experiments

All study participants underwent a standardized mental stress test. After an initial resting phase, mental stress was induced through a standardized public speaking task, where participants were given a brief set of time to prepare and present a statement to a video camera and an audience wearing white coats. Participants were told their performance would be evaluated for content, quality and duration. Investigators collected blood pressure and heart rate at five minute intervals during a resting phase and then at one minute intervals during the task. Inflammatory responses for IL-6, CRP, MCP1, MMP9, and VEGF were measured by enzyme-linked immunosorbent assay at time 0 and 90 min after mental stress [28].

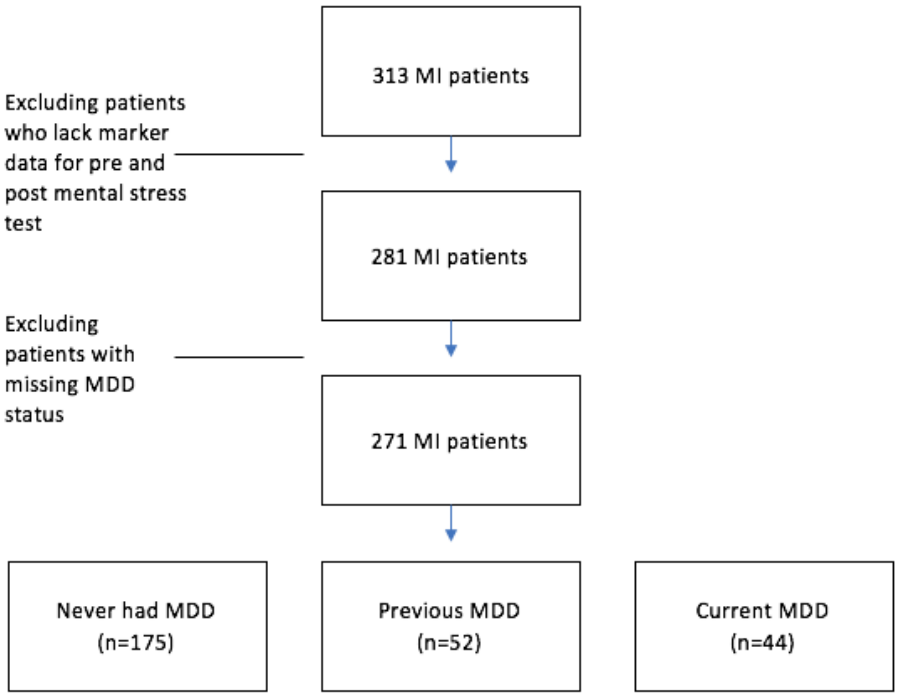


Figure 3. Schematic for choosing the study sample. The total sample size included 271 patients after exclusion criteria were applied.

Variables for this Study

The outcome of interest was inflammatory biomarker concentration for markers IL6, CRP, VEGF, MMP-9, and MCP1. The main exposure of interest is the mental stress task. A dichotomous variable indicating the time during the mental stress testing (0 = Pre-test and 1=Post -test) was used to measure the impact of the stress task on outcomes. MDD was used a modifier for the effect of stress and inflammation. A three-level categorical variable of MDD was constructed to identify history of depression amongst the MI patients (0= no MDD, 1=Previous MDD, and 2=Current MDD). Current MDD was defined as meeting the criteria for major depressive episode within the last month. Previous MDD was defined as meeting MDD criteria at any point during the lifetime but not having had a major depressive episode in the past

month. Behavioral, sociodemographic, and medical variables were measured by interview or review of medical records.

Statistical Analysis

The primary analysis was conducted using SAS 9.4. A descriptive data analysis was conducted using PROC UNIVARIATE to assess the distribution of desired variables within the dataset. Additionally, correlation analysis among the variables of interest was performed using the PROC CORR procedure. Participants with no previous history of MDD, previous history of MDD and current history of MDD were compared for demographic, behavioral, clinical, hemodynamic and changes of inflammatory biomarker concentration during mental stress testing. T-tests were used to test the significance amongst continuous variables and chi-squared tests measured significance amongst categorical variables. We analyzed log-transformed biomarker levels because the initial distributions of inflammatory markers were skewed [28]. For this reason, the results in the current analysis were presented as geometric means.

To explore potential differences in hemodynamic responses to the mental stress by depression status we used ANOVA models with systolic blood pressure, diastolic pressure, heart rate, and rate pressure product as the dependent variable and MDD category as the independent variable.

Mixed models for repeated measures were used to assess the difference in inflammatory biomarker concentration in response to induced mental stress amongst varying levels of major depressive disorder. This procedure was chosen in order to account for repeated observations from each participant. Models adjusted for demographic (age, sex), behavioral and medical history variables (current smoking, history of hypertension, history of diabetes) and medication

use (e.g., antidepressants, aspirin, statins, and beta blockers). . Differences amongst women in men were assessed by conducting sex-stratified analysis and then estimating an overall model to test the interaction between sex and depression status.

Chapter 4 Results

Study Sample and Baseline Characteristics

The mean age for MI patients was 50.6 (sd, 6.7) years and 49.5 (sd, 9.1) years for men and women respectively. Men accounted for 51% and women accounted for 49% of the population. Approximately 63% of the sample was African American, 41% were married, and 48% were currently employed. MI patients had an adverse medical profile including an average BMI of 31.6, about 82% had history of hypertension, 32% a history of diabetes mellitus, and 23% were current smokers. MI patients also exhibited unfavorable psychosocial profiles. Approximately 35% of MI patients had a lifetime history of MDD, and many experienced high levels of early life abuse (Table 1). As expected, many of the participants, but not all, were currently taking secondary prevention cardiovascular medications including statins, beta blockers, and aspirin (Table 1).

Hemodynamic Responses to Stress

Overall, the hemodynamic responses to the mental stress task were similar for MI patients across all three categories of MDD. Mean values at rest, during the stress task, and changes after stress task of systolic blood pressure, diastolic blood pressure, heart rate, and rate pressure product were not statistically significantly different by depression status(Table 2).

Inflammation Marker Distribution During Mental Stress Testing

The geometric means of CRP, MCP1, MMP9, and VEGF measured during the pre and post mental stress test within any of MDD groups in the unadjusted model were not significant. The interaction term of depression status and time (pre- or post- mental stress) was analyzed for

all markers and no statistically significant interaction was found. When adjusted for psychological, social, and medical conditions, the results did not change substantially (Table 3). However, for all participants, irrespective of whether they never had MDD, previously had MDD, and currently had MDD, there was a significant increase in geometric means for IL-6 by 0.47 ($p<.0001$), 0.59 ($p<.0001$), and 0.60 ($p<.0001$) respectively, from pre to post stress testing. Furthermore, those patients who were currently depressed started out with higher levels of IL-6 at pre-test compared to those who previously had MDD and those who never had MDD. The results remained almost identical in adjusted models. Concentrations of MCP-1 within the unadjusted model increased modestly from pre to post-test across all levels of MDD, but this increase was only significant for the total sample and approaching significance for those who never had MDD. In adjusted models, the increase in MCP-1 became significant for those who never had MDD. The interaction remained unchanged. Concentrations of VEGF showed a modest increase from pre to post-test across all levels of MDD status, but were only significant when all patients were taken together within the unadjusted model. Once adjusted, the change for the total became even more significant and the change for those who were currently depressed further approached significance ($p=0.05$). The interaction term, however, was not significant.

Sex Differences in Inflammatory Response

The pre and post test responses of the inflammatory markers to stress by depression status did not significantly differ between women and men. Analysis did reveal, however, that women had higher means of marker IL-6 than men during the pre and post mental stress testing ($p<.0001$) (Figure 4).

Furthermore, the data suggest the IL-6 means for women who were previously depressed (mean=0.70) looked more similar to women who were currently depressed (mean=0.70) at rest. However, post stress test, IL-6 means for women who were previously depressed (mean=1.25) looked more similar to those who never had depression (mean=1.19) (Table 4). The opposite pattern was observed in men. Men who were previously depressed had IL6 marker concentrations (mean=0.40) more similar to other men who had no history of MDD (mean=0.40) at rest. After the post stress test, men who were previously depressed (mean=1.04) looked more similar to other men who currently had MDD (mean=1.07) post stress testing (Table 4). None of these differences were statistically significant.

Chapter 5 Discussion

We found no significant association between inflammatory response to acute stress and depression amongst patients with MI in both the unadjusted and adjusted models. However, we found that resting values were elevated in depressed participants for IL-6.

Our results are consistent with previous studies reporting that inflammatory markers are unlikely to explain an association between MDD and MI [52-54]. Jansky et al. in 2005 found that amongst women who just experienced an acute MI, IL-6 and CRP were associated with vital exhaustion and self-rated health, but not depression [47]. Schins et al. also found no indication of increased inflammation, including IL-6 and CRP, in depressed patients post MI compared to non-depressed patients [48]. The Heart and Soul Study conducted in 2007 found that amongst 984 participants, depression was not associated with increased levels of inflammation among outpatients with CHD, but rather associated with lower levels of CRP and IL-6 instead [49]. Investigators from this study suggested that the results may be partially explained through a ceiling effect, where patients with CHD already experience increased levels of inflammation and depression can not further increase this [49]. Within the current study, it is unlikely that an enhanced inflammatory response to stress explains the well-established association between depression and adverse prognosis post-MI.

Our finding of a robust increase in IL-6 concentration amongst all MI patients from pre to post mental stress test is consistent with the literature [49, 50]. This marker is mostly pro inflammatory in cardiovascular disease and in other chronic conditions as well. Within the pro inflammatory response, IL-6 is able to increase signaling and recruitment of other markers by first binding to its receptor, SIL-6R, on any cells expressing the transducer gp130 [63]. In our

study, the MI patients with current MDD tended to have higher levels of IL-6 throughout the mental stress test, although the difference was not significant. It may be that depression leads to a chronic inflammatory state through independent pathways rather than influencing acute responses to stress. Future studies examining depression and inflammation are needed to explore this possibility.

It was expected that CRP levels would be higher for patients with MDD compared to those without. However, this was not the case. Those who previously had MDD showed a modest increase in CRP during mental stress testing, those who were currently had MDD showed a modest decrease, and those without history of MDD showed a larger decrease in CRP. With an increase in molecular IL-6 concentration, an increase in CRP production would be expected as well, but the opposite was true. This could be explained through the shorter time interval for collecting post mental stress data. Results may have differed if the analysis of inflammation markers post mental stress task occurred a few hours later. For example, CRP levels have been shown to spike after the onset of disease and within 4-6 hours post-acute tissue injury [64]. This could explain why CRP levels did not go up after stress.

Biomarkers MCP1 and VEGF significantly increased during the mental stress testing but there was no significant association with MDD. A rise in MCP1 has been proven to be associated with an increase in a variety of cardiovascular events, so this result may have clinical implications. It was reported that MCP1 plays a role in myocardial remodeling after an MI, by releasing white blood cells to the area of inflammation [28]. A rise in VEGF during mental stress in post MI patients aligns with the recent work of Zhao et al. 2010, who concluded that VEGF

played a triggering role in angiogenesis following a cardiac response to an MI [42]. The results suggest that in response to the stress task, VEGF played a role in the inflammatory response.

Women had higher levels of IL-6 marker concentration during both time points of the mental stress testing compared to men. Previous studies have found similar findings in post MI patients before and after mental stress testing. In 2016, Rooks et al. found that IL-6 concentrations at baseline and after mental stress testing were twice as high for women under the age of 50 compared to age-matched men [65]. The current study confirms that women have higher levels of IL-6 than men in general and irrespective of depression status, even for those who already suffered a cardiovascular related incident. Consistently higher levels of IL-6 over time may contribute why women experience adverse outcomes post MI. Although not significant, an interesting and unique trend was observed amongst MDD status and change of IL-6 for each sex (Figure 4). Women who were previously depressed had the most similar IL-6 concentration at baseline to those who currently had depression. During the post mental stress test, this subset of women expressed similar levels of IL-6 closer to those who never had depression. As indicated by the shallower slope in women who had previous but not current MDD (Figure 4), the signaling of IL-6 might not be playing as big of a role in recruiting and activating inflammatory cells as it might be playing in the other MDD groups. The opposite was true for men who were previously depressed. The IL-6 concentration for men who were previously depressed looked more similar to those who never had depression at baseline, but was almost identical to those who currently had depression post mental stress testing. The steeper slope represented in men who were previously depressed (Figure4), implies that IL-6 played a larger role in recruitment of cells to target inflammation for this group more so than the other MDD categories.

Identifying sex differences in CHD risk have been increasingly explored in order to enhance preventative initiatives. Reasons for these differences have been explained by a myriad of factors ranging from protective effects of female sex hormones, men being more physically active on average, women having healthier eating behaviors, higher risk for diabetes among women, and higher prevalence of hypertension among men [66-68]. Vaccarino et al. in 2018 concluded that different hemodynamic and vascular responses to mental stress induced myocardial ischemia may explain why young women with previous MI are more likely to develop adverse outcomes compared to men [28]. Different vascular responses to mental stress in patients with a history of CAD may correlate with inflammatory response patterns, although the differences we found between women and men were not statistically significant.

Limitations of the Current Study

The limitations of the current study may explain the non-significant result for the association between changes in molecular markers and depression. The sample size for some of the categories of MDD was small. The sample of MI patients without history of MDD was about three times larger than the sample for previously depressed and about four times larger than the sample for currently depressed. The smaller samples for the previously and currently depressed groups may limit the power of the current study. Furthermore, the sample included participants only from Emory affiliated institutions and the results cannot be generalized for the general population of post-MI patients. To increase generalizability of the results from the current study, future research should incorporate different populations and geographic areas. Lastly, the mental stress task performed in the parent study may have limited sensitivity and specificity for assessing inflammation responses to stress within this population of MI patients (53). This may have partially biased the results towards the null hypothesis.

Chapter 6 Conclusion

Behavioral and biological mechanisms for cardiovascular risk in those with depression have been postulated but there is no single study suggesting that inflammation plays more than a fractional role. This study suggests that inflammatory markers and categories of depression were not associated together within patients who experienced a myocardial infarction. Instead, the results suggest they may work independently from one another. For example, the means for IL-6 increased for men and women pre and post mental stress testing, despite MDD status, in the MI patients.

Future research may want to explore other possible biological factors that could explain the link between MDD and adverse prognosis post MI. A suggestive unique pattern of IL-6 amongst men and women with varying levels of MDD was identified through this study. Investigators looking at potential biological mechanisms explaining sex differences in adverse outcomes, may want to consider looking at this marker within participant populations who are depressed or have experienced other mental illnesses such as PTSD, anxiety, and dysthymic disorders as well.

Despite an overwhelming body of evidence supporting the association of depression and cardiovascular diseases, current national and international guidelines do not support depression as an official risk factor for CVD. More studies highlighting the biological role of mental illness in the onset of cardiovascular related diseases, especially amongst women, may promote a change in primary and secondary prevention practices by recognizing those with depression as a vulnerable. Updating the risk profile in this way for CVD will ultimately help the World Health Organization achieve their goal of a 25% reduction in preventable deaths by NCDs in the year 2025.

Table 1. Characteristics of the study population

	MI patients (n=313)
Demographic Factors	
Age, years, mean(SD)	50.64(6.74)
Men, %	50.89
Women, %	49.11
African American, %	63.70
Married, %	41.22
Employed, %	48.35
Education, years, mean(SD)	13.67(2.84)
Cardiovascular Risk Factors	
BMI, kg/m^2, mean (SD)	31.57(7.60)
History of Hypertension, %	81.49
Current Smoker, %	23.40
Previous Coronary angioplasty, %	69.93
Previous Coronary Bypass surgery, %	80.43
Previous MI %	20.00
History of Diabetes Mellitus, %	32.38
Medications,(%)	
Statins	84.59
Beta Blockers	84.23
ACE inhibitors	45.52
Aspirin	81.72
Antidepressants	12.19
Psychosocial Risk Factors	
Lifetime history of MDD, %	35.42
BDI total score, Mean (SD)	12.38(10.72)
Early Trauma Inventory Total Score, mean (SD)	7.98(5.88)
Physical Abuse, %	69.14
Emotional Abuse, %	48.31
Sexual Abuse, %	33.71
General Trauma, %	88.10
Lifetime Trauma Inventory Total Score, mean (SD)	19.29(12.03)
Cook-Medley Hostility Inventory Score, mean (SD)	18.50(9.25)
Spielberger's Anger Expression Scale Score, mean(SD)	30.01(13.25)

BDI: Beck Depression Inventory; BMI: Body mass index; MI: myocardial infarction

Table 2. Hemodynamic Responses to Mental Stress Test by MDD status

		MI patients		
	NON MDD (n=172)	**Previous MDD** (n=52)	**Current MDD** (n=44)	**P**
Systolic Blood Pressure (mmHg)				
Rest, min	123.20 (20.33)	122.21 (20.31)	127.39 (19.13)	0.39
Stress, max	163.50 (26.86)	159.49 (25.20)	166.82 (30.08)	0.42
Change *	40.23 (16.23)	38.43 (15.14)	39.43 (18.91)	0.78
Diastolic Blood Pressure(mmHg)				
Rest, min	75.85 (12.58)	75.17 (12.61)	79.09 (11.86)	0.24
Stress, max	104.40 (15.38)	100.82 (15.30)	105.59 (17.28)	0.11
Change *	28.69 (11.16)	26.51 (8.77)	28.50 (12.27)	0.45
Heart Rate(beats/min)				
Rest, min	58.89 (10.58)	62.56 (10.24)	61.27 (9.26)	0.05
Stress, max	83.07 (16.92)	81.92 (12.28)	83.75 (18.65)	0.86
Change *	24.16 (13.92)	19.96 (11.14)	22.48 (18.42)	0.18
RPP (during stress)	13677.63 (3973.26)	13131.92 (3135.13)	14006 (3995.77)	0.52

Values are all means (standard deviation), unless indicated otherwise.

MDD: Major Depressive Disorder; SD: standard deviation; RPP: Rate Pressure Product

* Difference between maximum value during stress and minimum value during rest.

Table 3. Inflammatory Marker Concentration for MI patients during Mental Stress Test by MDD status

	Unadjusted				Adjusted			
	Pre stress	Post stress	P		Pre stress	Post stress	P	
CRP								
Previous MDD	14.73	14.79	0.85		14.73	14.79	0.83	
Current MDD	15.26	15.22	0.90		15.28	15.22	0.96	
No MDD	14.67	14.47	0.19		14.67	14.47	0.52	
Total	14.78	14.66	0.30		14.78	14.65	0.25	
				0.50‡				0.66‡
Interleukin- 6								
Previous MDD	0.57	1.16	<.0001		0.58	1.16	<.0001	
Current MDD	0.63	1.23	<.0001		0.65	1.23	<.0001	
No MDD	0.47	0.94	<.0001		0.46	0.94	<.0001	
Total	0.51	1.02	<.0001		0.52	1.03	<.0001	
				0.32‡				0.70‡
MCP1								
Previous MDD	4.84	4.93	0.13		4.84	4.93	0.12	
Current MDD	4.89	4.92	0.72		4.89	4.92	0.54	
No MDD	4.79	4.85	0.08		4.80	4.85	0.02	
Total	4.82	4.87	0.03		4.82	4.86	0.03	
				0.80‡				0.80‡
MMP9								
Previous MDD	10.99	11.04	0.66		10.99	11.04	0.80	
Current MDD	10.91	10.96	0.71		10.90	10.96	0.64	
No MDD	11.01	11.10	0.20		11.00	11.09	0.18	
Total	10.99	11.07	0.14		10.98	11.06	0.35	
				0.75‡				0.93‡
VEGF								
Previous MDD	4.17	4.34	0.21		4.17	4.34	0.16	
Current MDD	4.16	4.34	0.15		4.15	4.34	0.05	
No MDD	4.18	4.27	0.16		4.17	4.26	0.70	
Total	4.18	4.30	0.02		4.17	4.28	<.01	
				0.49‡				0.74‡

Adjusted analysis for sociodemographic, medical, and psychological factors
*42 participants were excluded from analysis (n=271)
CRP: C-Reactive Protein; MCP1: monocyte chemotactic protein-1; MMP9: Matrix metallopeptidase 9;
VEGF: Vascular endothelial growth factor
¶ Data present as geometric means
‡ P value assessing significance for interaction between MDD status and change in inflammatory marker concentration pre and post mental stress testing

Table 4a. Interleukin-6 concentration during mental stress test for MI patients by MDD status and stratifi by sex (Unadjusted)

	Women(n=135)				**Men**(n=136)			
	Pre Stress	**Post Stress**	**P**		**Pre Stress**	**Post Stress**	**P**	
Interleukin-6								
Previous MDD	0.70	1.25	0.0039		0.40	1.04	0.0011	
Current MDD	0.70	1.34	0.0006		0.53	1.07	0.0101	
No MDD	0.60	1.19	<.0001		0.37	0.76	<.0001	
Total	0.64	1.23	<.0001		0.39	0.83	<.0001	
				0.9296‡				0.430

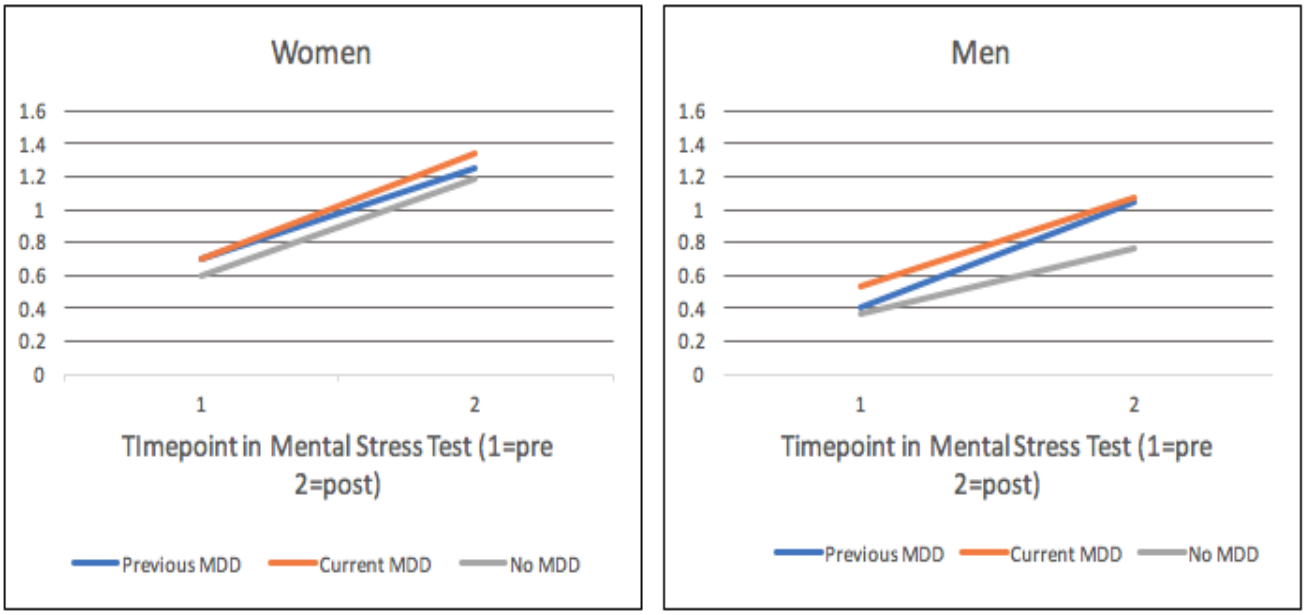
Unadjusted analysis, unadjusted for sociodemographic, medical, and psychological factors
*42 participants were excluded from analysis (n=271)
¶ Data present as geometric means
‡ P value assessing significance for interaction between MDD status and change in inflammatory marker concentration pre and post mental stress testing

Table 4b. Interleukin-6 concentration during mental stress test for MI patients by MDD status and stratifi by sex (Adjusted)

	Women(n=135)				**Men(**n=136)			
	Pre Stress	**Post Stress**	**P**		**Pre Stress**	**Post Stress**	**P**	
Interleukin-6								
Previous MDD	0.69	1.25	0.0012		0.40	1.04	0.0011	
Current MDD	0.72	1.34	0.0001		0.53	1.07	0.0016	
No MDD	0.59	1.17	<.0001		0.38	0.75	<.0001	
Total	0.64	1.23	<.0001		0.39	0.84	<.0001	
				0.9082‡				0.469

Adjusted analysis for sociodemographic, medical, and psychological factors. The results did not differ substantially from the unadjusted model.
*42 participants were excluded from analysis (n=271)
¶ Data present as geometric means
‡ P value assessing significance for interaction between MDD status and change in inflammatory marker concentration pre and post mental stress testing

Figure 4. Interleukin-6 concentration change during mental stress test for women (left) and men (right) MI patients respectively.



* Women had a higher initial molecular concentration of Interleukin-6 from pre to post-test than men. Although the interaction between MDD status and molecular change from pre to post stress was not significant, the data suggests a pattern that is different amongst each sex. (Left) Women who previously had MDD had a similar concentration of Interleukin-6 to women who currently had MDD, but looked similar to those who never had MDD by the post test. (Right) Men who previously had MDD had a similar concentration of Interleukin-6 to men who never had MDD at pre-test, but their marker concentration looked similar to those who previously had MDD by the post-test.

References

1. Benjamin, E.J., et al., *Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association.* Circulation, 2017.
2. Lichtman, J.H., et al., *Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association.* Circulation, 2014. **129**(12): p. 1350-69.
3. Baune, B.T. and P.J. Tully, *Cardiovascular Diseases and Depression: Treatment and Prevention in Psychocardiology*. 2016: Springer International Publishing.
4. Moussavi, S., et al., *Depression, chronic diseases, and decrements in health: results from the World Health Surveys.* Lancet, 2007. **370**(9590): p. 851-8.
5. Katon, W., E.H. Lin, and K. Kroenke, *The association of depression and anxiety with medical symptom burden in patients with chronic medical illness.* Gen Hosp Psychiatry, 2007. **29**(2): p. 147-55.
6. Egede, L.E., *Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability.* Gen Hosp Psychiatry, 2007. **29**(5): p. 409-16.
7. Kessler, R.C., et al., *Prevalence, Severity, and Comorbidity of Twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCS-R).* Archives of general psychiatry, 2005. **62**(6): p. 617-627.
8. Kang, H.-J., et al., *Comorbidity of Depression with Physical Disorders: Research and Clinical Implications.* Chonnam Medical Journal, 2015. **51**(1): p. 8-18.
9. Organization, W.H. *Cardiovascular Diseases (CVDs)*. 2017 [cited 2018 March 29].
10. Sanchis-Gomar, F., et al., *Epidemiology of coronary heart disease and acute coronary syndrome.* Annals of Translational Medicine, 2016. **4**(13): p. 256.
11. Roth, G.A., et al., *Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015.* J Am Coll Cardiol, 2017. **70**(1): p. 1-25.
12. Gerber, Y., et al., *The Changing Epidemiology of Myocardial Infarction in Olmsted County, Minnesota, 1995–2012: Trends in Myocardial Infarction Incidence and Recurrence.* The American journal of medicine, 2015. **128**(2): p. 144-151.
13. Parikh, N.I., et al., *Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study.* Circulation, 2009. **119**(9): p. 1203-10.
14. Yeh , R.W., et al., *Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction.* New England Journal of Medicine, 2010. **362**(23): p. 2155-2165.
15. Sacks, N.C., et al., *Trends in Acute Myocardial Infarction Hospitalizations: Are We Seeing the Whole Picture?* American heart journal, 2015. **170**(6): p. 1211-1219.
16. Carson, A.P., et al., *Declines in coronary heart disease incidence and mortality among middle-aged adults with and without diabetes.* Ann Epidemiol, 2014. **24**(8): p. 581-7.
17. First, M.B., et al., *The Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II). Part I: Description.* Journal of Personality Disorders, 1995. **9**(2): p. 83-91.
18. Health, N.I.o.M. *Major Depression* 2017 [cited 2018 May 29th].
19. Carney, R.M., et al., *Depression and five year survival following acute myocardial infarction: a prospective study.* J Affect Disord, 2008. **109**(1-2): p. 133-8.

20. Carney, R.M. and K.E. Freedland, *Depression and coronary heart disease.* Nat Rev Cardiol, 2017. **14**(3): p. 145-155.
21. Gan, Y., et al., *Depression and the risk of coronary heart disease: a meta-analysis of prospective cohort studies.* BMC Psychiatry, 2014. **14**: p. 371.
22. Nicholson, A., H. Kuper, and H. Hemingway, *Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies.* Eur Heart J, 2006. **27**(23): p. 2763-74.
23. Meijer, A., et al., *Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research.* Gen Hosp Psychiatry, 2011. **33**(3): p. 203-16.
24. Frasure-Smith, N., F. Lesperance, and M. Talajic, *Depression and 18-month prognosis after myocardial infarction.* Circulation, 1995. **91**(4): p. 999-1005.
25. Mallik, S., et al., *Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women.* Arch Intern Med, 2006. **166**(8): p. 876-83.
26. Parashar, S., et al., *Impact of Depression on Sex Differences in Outcome After Myocardial Infarction.* Circulation. Cardiovascular quality and outcomes, 2009. **2**(1): p. 33-40.
27. Kala, P., et al., *Depression and Anxiety after Acute Myocardial Infarction Treated by Primary PCI.* PLOS ONE, 2016. **11**(4): p. e0152367.
28. Vaccarino, V., et al., *Mental Stress–Induced-Myocardial Ischemia in Young Patients With Recent Myocardial Infarction.* Sex Differences and Mechanisms, 2018. **137**(8): p. 794-805.
29. Morimoto, H., et al., *Cardiac overexpression of monocyte chemoattractant protein-1 in transgenic mice prevents cardiac dysfunction and remodeling after myocardial infarction.* Circ Res, 2006. **99**(8): p. 891-9.
30. Mythili, S. and N. Malathi, *Diagnostic markers of acute myocardial infarction.* Biomedical Reports, 2015. **3**(6): p. 743-748.
31. Kop, W.J., et al., *Effects of acute mental stress and exercise on inflammatory markers in patients with coronary artery disease and healthy controls.* Am J Cardiol, 2008. **101**(6): p. 767-73.
32. Marsland, A.L., et al., *The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis.* Brain Behav Immun, 2017. **64**: p. 208-219.
33. Morimoto, H. and M. Takahashi, *Role of Monocyte Chemoattractant Protein-1 in Myocardial Infarction.* International Journal of Biomedical Science : IJBS, 2007. **3**(3): p. 159-167.
34. McDermott, D.H., et al., *CCL2 polymorphisms are associated with serum monocyte chemoattractant protein-1 levels and myocardial infarction in the Framingham Heart Study.* Circulation, 2005. **112**(8): p. 1113-20.
35. Hayashidani, S., et al., *Anti-monocyte chemoattractant protein-1 gene therapy attenuates left ventricular remodeling and failure after experimental myocardial infarction.* Circulation, 2003. **108**(17): p. 2134-40.
36. Dewald, O., et al., *CCL2/Monocyte Chemoattractant Protein-1 Regulates Inflammatory Responses Critical to Healing Myocardial Infarcts.* Circulation Research, 2005. **96**(8): p. 881-889.

37. Yabluchanskiy, A., et al., *Matrix metalloproteinase-9: Many shades of function in cardiovascular disease.* Physiology (Bethesda), 2013. **28**(6): p. 391-403.
38. Phatharajaree, W., A. Phrommintikul, and N. Chattipakorn, *Matrix metalloproteinases and myocardial infarction.* The Canadian Journal of Cardiology, 2007. **23**(9): p. 727-733.
39. Blankenberg, S., et al., *Plasma concentrations and genetic variation of matrix metalloproteinase 9 and prognosis of patients with cardiovascular disease.* Circulation, 2003. **107**(12): p. 1579-85.
40. Wilson, E.M., et al., *Region- and type-specific induction of matrix metalloproteinases in post-myocardial infarction remodeling.* Circulation, 2003. **107**(22): p. 2857-63.
41. Wagner, D.R., et al., *Matrix metalloproteinase-9 is a marker of heart failure after acute myocardial infarction.* J Card Fail, 2006. **12**(1): p. 66-72.
42. Zhao, T., et al., *Vascular endothelial growth factor (VEGF)-A: role on cardiac angiogenesis following myocardial infarction.* Microvasc Res, 2010. **80**(2): p. 188-94.
43. Li, J., et al., *VEGF, flk-1, and flt-1 expression in a rat myocardial infarction model of angiogenesis.* Am J Physiol, 1996. **270**(5 Pt 2): p. H1803-11.
44. Heba, G., et al., *Relation between expression of TNF alpha, iNOS, VEGF mRNA and development of heart failure after experimental myocardial infarction in rats.* J Physiol Pharmacol, 2001. **52**(1): p. 39-52.
45. Danner, M., et al., *Association between depression and elevated C-reactive protein.* Psychosom Med, 2003. **65**(3): p. 347-56.
46. Ford, D.E. and T.P. Erlinger, *Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey.* Arch Intern Med, 2004. **164**(9): p. 1010-4.
47. Pace, T.W., et al., *Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress.* Am J Psychiatry, 2006. **163**(9): p. 1630-3.
48. Derry, H.M., et al., *Sex Differences in Depression: Does Inflammation Play a Role?* Curr Psychiatry Rep, 2015. **17**(10): p. 78.
49. Miller, G.E., et al., *Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes.* Am J Cardiol, 2005. **95**(3): p. 317-21.
50. Empana, J.P., et al., *Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME).* Circulation, 2005. **111**(18): p. 2299-305.
51. Vaccarino, V., et al., *Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study.* J Am Coll Cardiol, 2007. **50**(21): p. 2044-50.
52. Janszky, I., et al., *Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease.* Brain Behav Immun, 2005. **19**(6): p. 555-63.
53. Schins, A., et al., *Inflammatory markers in depressed post-myocardial infarction patients.* J Psychiatr Res, 2005. **39**(2): p. 137-44.
54. Whooley, M.A., et al., *Depression and Inflammation in Patients With Coronary Heart Disease: Findings from the Heart and Soul Study.* Biological psychiatry, 2007. **62**(4): p. 314-320.

55. Lu, Y., et al., *Sex Differences in Inflammatory Markers and Health Status Among Young Adults With Acute Myocardial Infarction: Results From the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) Study.* Circ Cardiovasc Qual Outcomes, 2017. **10**(2): p. e003470.
56. Vaccarino, V., et al., *Sex differences in mental stress-induced myocardial ischemia in young survivors of an acute myocardial infarction.* Psychosom Med, 2014. **76**(3): p. 171-80.
57. Vaccarino, V., et al., *Sex Differences in Mental Stress-Induced Myocardial Ischemia in Patients With Coronary Heart Disease.* Journal of the American Heart Association, 2016. **5**(9).
58. Shaw, L.J., R. Bugiardini, and C.N.B. Merz, *Women and Ischemic Heart Disease: Evolving Knowledge.* Journal of the American College of Cardiology, 2009. **54**(17): p. 1561-1575.
59. Organization, W.H. *Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization*. 2017.
60. Charlson, F.J., et al., *The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment.* BMC Med, 2013. **11**: p. 250.
61. Thygesen, K., et al., *Third Universal Definition of Myocardial Infarction.* Circulation, 2012. **126**(16): p. 2020-2035.
62. Cohen, S., T. Kamarck, and R. Mermelstein, *A Global Measure of Perceived Stress.* Journal of Health and Social Behavior, 1983. **24**(4): p. 385-396.
63. Wolf, J., et al., *Different Soluble Forms of the Interleukin-6 Family Signal Transducer gp130 Fine-tune the Blockade of Interleukin-6 Trans-signaling.* Journal of Biological Chemistry, 2016. **291**(31): p. 16186-16196.
64. Slade, G.D., et al., *Acute-phase inflammatory response to periodontal disease in the US population.* J Dent Res, 2000. **79**(1): p. 49-57.
65. Rooks, C. R., et al., *Young Women Post-MI Have Higher Plasma Concentrations of Interleukin-6 Before and After Stress Testing*. Brain, Behavior, and Immunity, 2016. **51(1)**: p. 92–98.
66. Rosengren, A., et al., *Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study.* Lancet, 2004. **364**(9438): p. 953-62.
67. Anand, S.S., et al., *Risk factors for myocardial infarction in women and men: insights from the INTERHEART study.* European Heart Journal, 2008. **29**(7): p. 932-940.
68. Pedersen, L.R., et al., *Risk Factors for Myocardial Infarction in Women and Men: A Review of the Current Literature.* Curr Pharm Des, 2016. **22**(25): p. 3835-52.