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Associations of Overall Sleep Quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and Cardiovascular Inflammatory Biomarkers; a cross-sectional study

By

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Degree to be Awarded: MPH

Epidemiology

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By

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Bachelor of Arts
Boston University, College of Arts and Sciences
2013

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Associations of Overall Sleep Quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and Cardiovascular Inflammatory Biomarkers; a cross-sectional study
By Akshaya Krishnaswamy

Background: Previous research has demonstrated a link between sleep duration and cardiovascular disease (CVD) risk, potentially through systemic inflammation. However, most of this evidence has emerged from experimental sleep deprivation studies in healthy populations. The goal of this investigation was to examine the relationship between chronic sleep quality and circulating levels of inflammatory biomarkers among healthy patients and patients with a history of myocardial infarction (MI), as well as by race within these subgroups.
Methods: Individuals with a verified history of MI and matched community controls completed the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality and sleep-related symptoms in the previous month. Inflammatory biomarkers including interleukin-6 (IL-6), C-reactive protein (CRP), monocyte chemoattractant protein (MCP-1), and matrix metallopeptidase 9 (MMP-9) were measured from venous blood samples. We conducted unadjusted and adjusted linear regression analyses to assess the percent difference in each of these biomarkers for each 5-point increase in PSQI score within study groups.
Results: Mean overall PSQI score among MI cases and healthy controls was 8.08 and 5.90, respectively. The overall PSQI score was positively weakly correlated with IL-6 ($r=0.14$, $p=0.03$), CRP ($r=0.21$, $p=0.0007$), and MCP-1 ($r=0.24$, $p<.0001$) among MI cases, with slightly weaker but overall similar correlations among controls. There were similar correlations across races within each study group. While we did not detect significant interactions between PSQI score and study group, PSQI score and race, and PSQI score, study group, and race, associations between PSQI score and inflammatory biomarkers appeared stronger among MI cases. Linear regression analyses revealed that each 5-point increase in overall PSQI score was associated with a 7.1% difference in MCP-1 among MI cases ($p=0.003$), and a 6.0% ($p=0.2$) difference among controls after adjustment for demographic and clinical risk factors. The percent difference in other inflammatory biomarkers and PSQI score were weaker and tended to attenuate after adjustment.
Conclusion: Our data show poor sleep quality is significantly associated with elevated levels of inflammatory biomarker MCP-1, among MI cases and controls. These findings suggest that poor sleep quality is related to increased systemic inflammation in both healthy individuals and those with a prior MI.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality among both men and women in the United States. CVD includes coronary heart disease (CHD), the most common condition, followed by stroke, heart failure, hypertension, arterial diseases, and other cardiovascular diseases[1]. Sleep duration has demonstrated a U-shaped association[2–6] with CVD, wherein individuals with deficient or excessive sleep durations have a greater risk of experiencing CVD events, including myocardial infarction (MI), stroke[5,7–12], and dying from CVD[2–5,11–13] compared to individuals who sleep 7-8 hours per night as recommended by the National Institutes of Health (NIH)[14]. In most studies, these adverse associations between poor sleep quality and CVD risk were independent of age, sex, race-ethnicity, body mass index (BMI), diabetes, hypertension, depression, and other cardiovascular risk factors[6,15].

Proposed mechanisms underlying the association between sleep duration and CVD include dysregulation of the hypothalamic-pituitary axis (HPA), autonomic activity disturbances, increased sympathetic nervous system activity, and systemic inflammation[4,8,10,16,17]. Systemic inflammation is a well-established mechanism in the progression of CVD, as elevation of inflammatory biomarkers, including pro-inflammatory cytokines such as interleukin 6 (IL-6), and acute phase reactants such as C-reactive protein (CRP), has been show to predict cardiovascular events[3,4,13]. Several studies examining associations between sleep and circulating inflammatory biomarkers have demonstrated increases in CRP, IL-6, and tumor necrosis factor-alpha (TNF-α) with acute sleep deprivation[3,10,13,16,18,19], suggesting that sleep loss is associated with a

pro-inflammatory state. However, these studies have mainly focused on experimental sleep deprivation, rather than chronic sleep disturbance as it may occur in everyday life[11,20]. Additionally, existing evidence on associations between sleep, inflammatory biomarkers, and CVD have primarily been from studies conducted in healthy populations[2,6,9,10,15,18]. While an association between sleep duration and mortality has also been reported in individuals with CHD[2], whether inflammation plays a role is unknown. Examining the relationship between sleep disturbance and inflammatory biomarkers in persons with and without a history of MI might suggest that dysregulated immune function from poor sleep plays a role in the etiology of MI, or that experiencing an MI substantially worsens immune responses to poor sleep.

There are substantial racial disparities with regards to CVD, with African-Americans comprising the racial group at the highest risk of CVD mortality in the United States.[17] Evidence thus far has suggested that African-Americans are more likely to have worse self-reported sleep quality, more adverse sleep symptoms, and higher prevalence of both short and long sleep duration in comparison to other racial groups.[2,6,12,17,21,22] Given these health disparities, examining whether an association between poor sleep and inflammation is seen in African Americans in addition to other groups, and whether race modifies the association between sleep quality and inflammatory response could provide evidence that sleep duration may be partially implicated in the increased CVD burden observed in African-Americans. Currently, no previous study has examined these questions.

Based on current evidence suggesting a link between sleep duration and CVD, it is important to evaluate the role of elevated inflammatory markers as a potential mechanism linking sleep disturbance to CVD risk, and whether this mechanism is true in both African Americans and Whites. The objective of this project is to investigate the association between sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), and levels of inflammatory biomarkers involved in CVD, focusing on IL-6, CRP, matrix metallopeptidase 9 (MMP-9), and monocyte chemoattractant protein (MCP)-1, in a sample of young and middle-aged men and women with a recent MI, and compare the results with a sample of healthy community controls of age and gender distribution similar to the MI cases. An additional objective is to examine whether such associations are observed in both African American and non-African American groups and whether there is any variation of effect based on race. Our hypotheses are that subjects with MI will show an increased inflammatory response with poor sleep quality compared to controls, and that African Americans, particularly those with MI, will show an increased inflammatory response with poor sleep quality compared to Whites.

2. Methods

2.1 Study design

The Myocardial Infarction and Mental Stress 2 Study includes early onset MI cases and community controls without a history of coronary heart disease (CHD). The MI cases were recruited from the pool of patients who were admitted with a documented history of MI in the previous 8 months at Emory-affiliated hospitals in

Atlanta, Georgia, and who were between 18-60 years of age at the time of screening. The diagnosis of MI (type 1) was verified by medical record review based on standard criteria of a troponin level increase and ECG changes.[23] Controls were recruited in the Atlanta area from a community-based study of individuals without established CHD. Controls were considered for inclusion in the study if they were between 18 and 60 years of age, and had no past history of MI, unstable or stable angina pectoris, congestive heart failure, or stroke. Controls were frequency matched for age and sex to the MI cases, with the goal of achieving ≈50% women and a similar mean age in both samples.

Subjects were excluded if they had a severe comorbid medical or psychiatric disorder that could interfere with study results, such as cancer, renal failure, severe uncontrolled hypertension, current alcohol or substance abuse, or schizophrenia; if they were pregnant or breastfeeding; or if they were currently using immunosuppressant or psychotropic medications other than antidepressants. MI patients were also excluded if they had unstable angina, acute MI or decompensated heart failure within the previous week; if they weighed over 450 pounds (due to weight bearing limits of the nuclear stress test equipment); and if it was deemed to be unsafe by study cardiologists to hold antiischemic medications for 24 hours before the testing.

Clinical information including previous cardiovascular events, risk factors for CHD, sociodemographic, and psychosocial data were collected from all study participants. Both MI and control participants underwent a standardized mental stress test and vascular testing following published methodology, and these methods are

described elsewhere.[24] The present analysis focuses only on baseline levels of inflammatory biomarkers IL-6, CRP, MCP-1, and MMP-9 prior to stress testing in the MIMS2 study population.

2.2 Assessment of sleep quality

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-administered validated 19-item scale that assesses overall sleep-quality and sleep-related symptoms experienced during the previous 1 month.[25] The 19 items yield 7 component scores that reflect the frequency of a variety of sleep problems. The sum of the 7 components yields a global score that ranges from 0 to 21, with higher scores indicating poorer sleep quality. The individual components include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction.[25]

2.3 Measurement of inflammatory biomarkers

Inflammatory biomarkers were measured from venous blood samples collected at rest, including IL-6, high-sensitivity CRP, MCP-1, and MMP-9. Venous blood was collected into ice-cooled citrate tubes and immediately centrifuged at 4 °C; obtained plasma was snap-frozen at -70 °C until further processing. The MesoScale system (Meso Scale Diagnostics Rockville, Maryland) was employed using the SECTOR Imager 2400 to quantitate IL-6, CRP, MCP-1, and MMP-9 according to the protocols supplied by the manufacturer. The Mesoscale multiplex assay system uses electrochemiluminescence for high sensitivity and broad dynamic range. Lower limits of detection for the experiment were: IL-6: 0.06 pg/mL, CRP: 1.33 $\times 10^{-6}$ mg/L, MCP-1: 0.09 pg/mL, and

MMP-9: 0.011 ng/mL. The inter-assay coefficient of variations for midpoint standards were 2.1% for IL-6, 5.3% for CRP, 2.4% for MCP-1, and 1.8% for MMP-9.

2.4 Other measurements

Demographic information was obtained using standardized questionnaires. Previous medical history (diabetes, hypertension, previous MI and medication use (e.g., aspirin, beta blockers) were obtained by study nurses or physicians through medical history, clinical examinations and by reviewing medical records. Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II), a 21-item self-administered scale.[26] PTSD symptoms were assessed using the civilian version of the PTSD Symptom Checklist (PCL-C) a 17-item scale.[27] Cohen's Perceived Stress Scale, a 10-item survey of general stress validated in multiethnic populations[28] and the Spielberger's State-Trait Anxiety Inventory, a 40-item questionnaire to measure anxiety as an emotional state or a personality trait was also administered.[29] Height and weight were measured during the clinical exam and used to calculate body mass index (BMI, kg/m^2). Angiographic data were obtained from the most recent coronary angiogram in the patient's chart. CHD severity was quantified using the Gensini Score.[30]

2.5 Study participants

Of the 313 MI patients in the MIMS2 dataset, 25 patients had missing overall PSQI scores. Among the remaining 288 patients, 30 patients had missing rest plasma samples, due to technical difficulties for blood draw or assays problems. Of the 112 control participants, 7 had missing overall PSQI scores. Among the remaining 105 controls, 8 had missing rest plasma samples. The proportion of participants with

missing samples was slightly higher among MI patients (10.4%) compared to control patients (7.6%), but there was no significant difference in PSQI score between those with and those missing samples within each study group . Thus, a total of 258 MI participants and 97 control participants were included in the final analysis. The Emory Institutional Review Board approved this study protocol and written informed consent was obtained from all study participants.

2.6 Statistical Analysis

Descriptive statistics were stratified by study group (MI cases and controls), as well as by race within each study group, and differences in study variables were calculated using t-tests or Mann-Whitley Wilcoxon tests for continuous variables and chi-square tests for categorical variables. Given that all inflammatory biomarkers had skewed distributions, natural log transformations were used in all analyses, and results are presented as geometric means.

Spearman correlation coefficients were calculated between the overall PSQI score and inflammatory biomarker levels, by study group and by race within each study group. Multivariable linear regression analyses were conducted before and after adjusting for possible confounding factors considered *a priori*, including demographic factors (sex, age, years of education), and lifestyle and clinical risk factors known to affect inflammation (ever smoking, BMI, diabetes, hypertension, aspirin use, statin use, and antidepressant use). These analyses were stratified by study group. We also tested for interactions between total PSQI score and study group, total PSQI score and race, and the three-way interaction between total PSQI score, study group, and race in

overall models. Since inflammatory biomarker data were log-transformed, results were expressed as percent differences of the non-transformed values using the formula: $[(\exp^{\beta})-1] \times 100$ (%), where β is the regression coefficient and $\exp^{\beta}$ returns the exponential value of the parameter.

An additional analysis also considered unadjusted and adjusted results for the individual PSQI subscales and inflammatory biomarkers by study group. The significance level for main effects and interaction effects was set at $p<0.05$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1 Descriptive characteristics

In the analytical sample, MI cases were less likely to be married, less educated, more likely to be African American, and more likely to have an annual income of less than $25,000 compared to controls (Table 1). As expected, all CHD risk factors, including diabetes, hypertension, and dyslipidemia, were higher among MI cases compared to controls. Resting systolic and diastolic blood pressure, were also higher among MI cases than controls. MI cases had a worse psychosocial risk profile than controls, with higher symptom scale scores for depression, PTSD, and perceived stress (all $p<0.001$). However, there was no difference in the proportion of patients taking anti-depressants between MI cases and controls.

Differences in study variables by race tended to be more pronounced among MI cases than among controls (Table 2). Among MI cases, African American patients were

more likely to be female, less likely to be married, and more likely to have an annual income of less than $25,000 (all $p<0.01$). African American patients in both groups were less educated compared to their White counterparts. African American controls, compared to White controls, had a higher BMI, but all the other CHD risk factors except dyslipidemia, as well as resting blood pressure, tended to be higher among African Americans than Whites in both groups. There were no differences in psychosocial risk profiles by race among controls. However, African American MI cases had higher symptom scale scores for depression and PTSD than White MI cases. African American MI cases were also more likely to be taking antidiabetic medications and have a history of MI and congestive heart failure compared to White MI cases.

3.2 Sleep characteristics by study group and race

The overall PSQI score and virtually all PSQI subscale scores were higher (denoting more sleep disturbance) in the MI cases than in controls (Table 3). When sleep characteristics were assessed by race among MI cases and controls separately (Table 4), among MI cases, African Americans had significantly higher overall PSQI scores compared to Whites (8.85 vs. 6.77, $p=0.0004$), and higher scores on the sleep quality, sleep latency, sleep duration, sleep efficiency, and sleep disturbance subscales. Among controls, there were no significant differences in overall PSQI score by race, or for any of the subscales except for sleep duration; however, for all subscales African Americans tended to show worse sleep. African Americans in both study groups had significantly higher sleep duration subscale scores compared to Whites, indicating shorter sleep (MI cases: 1.18 vs. 0.69, $p=0.002$; controls: 1.03 vs. 0.41, $p=0.0005$).

3.3. *Inflammatory biomarker levels by study group and race*

Overall, baseline mean inflammatory biomarker levels were similar between MI cases and controls, except for IL-6 levels, which were higher among MI cases compared to controls (1.7 pg/ml vs. 1.0 pg/ml, $p<0.0001$) (Table 5, Figures 1-4). Differences in mean inflammatory biomarker levels were also assessed by race within each study group (Table 6). African Americans in both study groups had significantly higher CRP levels compared to Whites (MI cases: 3.3 mg/L vs. 1.9 mg/L, $p=0.004$; controls: 4.8 mg/L vs. 2.5 mg/L, $p=0.01$). However, whites in both study groups had higher MMP-9 levels compared to African Americans, a difference that was significant among the MI cases (73.9 ng/ml vs. 53.0 ng/ml, $p=0.0001$).

3.4 Correlation between overall PSQI score and inflammatory biomarkers by study group and race

Spearman correlation coefficients were calculated to examine the relationship between overall PSQI score and each inflammatory biomarker among MI cases and controls separately (Table 7). Among MI cases, there was a statistically significant, weak to moderate correlation between overall PSQI score and IL-6 ($r=0.14$, $p=0.03$), CRP (0.21, $p=0.0007$), and MCP-1 (0.24, $p<0.0001$), but not MMP-9. Among controls, all the correlation coefficients between the overall PSQI score and inflammatory biomarker were smaller than in the MI group. When examined by race, except for MCP1, which was correlated with sleep disturbance only among African Americans, similar

correlations were observed both in African Americans and White/Other MI cases (Table 8).

3.4 Associations between overall PSQI score and inflammatory biomarkers by study group and race

The associations between overall PSQI score and individual inflammatory biomarkers by study group were evaluated by assessing overall PSQI score and inflammatory biomarkers as continuous variables (Table 9). Unadjusted analyses among MI cases showed that a 5-point increase in overall PSQI score was associated with 10.7% higher IL-6 level (p=0.03), a 44% higher CRP level (p=0.0005), and a 9.5% higher MCP-1 level (p<.0001). Unadjusted analyses among control patients showed no significant associations between overall PSQI score and any of the inflammatory biomarkers. Among MI cases, after adjustment for demographic factors of sex, age, years of education, and race, we found a 5-point increase in overall PSQI score was associated with a 27.7% higher CRP level (p=0.02), and a 7.5% higher MCP-1 level (p=0.0008). After further adjustment for lifestyle and clinical risk factors, the association between overall PSQI score and elevated CRP was attenuated. However, the association between overall PSQI score and elevated MCP-1 remained statistically significant, with results showing that for each 5-point increase in overall PSQI score, MCP-1 was 7.1% higher (p=0.003) among MI cases. We also assessed the interaction between overall PSQI score, study group, and race in separate models. We found that the PSQI score*study group, PSQI score*race, and PSQI score*study group*race interaction terms were not significant for any of the inflammatory biomarker relationships assessed.

Associations between scores on each of the 7 PSQI subscales (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, needs medications to sleep, and sleep issues cause dysfunction) and individual inflammatory biomarkers were also examined by study group, with progressive adjustment for demographic, then lifestyle and clinical risk factors (Table 10). These results were mixed in terms of statistically significant associations between PSQI subscale scores and individual inflammatory biomarkers across unadjusted and adjusted models; however, the majority of associations were not statistically significant.

Discussion

This is the first study examining sleep and inflammation in post-MI patients with a healthy control group as a comparison. We found that, among men and women with a recent MI, a number of biomarkers, including IL-6, CRP, and MCP-1, were associated with poorer sleep, although the association weakened somewhat after adjustment for demographic, lifestyle, and clinical risk factors. The associations tended to be stronger in the MI patients than in a healthy control group, but were overall similar by race. The inflammatory biomarker MCP-1 showed the most robust association with sleep among the MI patients, which was minimally affected by adjustment for other factors. These results suggest that poor sleep quality is associated with elevated levels of inflammation which, for some biomarkers but not others, could be in part mediated by other risk factors associated with poor sleep.

The relationship between sleep and cardiovascular disease has been previously examined in the literature. Several studies have found that short sleep is associated with increased cardiovascular event rates and mortality, and some of these studies also described an adverse risk for long sleep.[2–10] One of the hypothesized mechanisms linking sleep and cardiovascular disease suggests that inadequate sleep may increase production of several inflammatory biomarkers, inducing systemic inflammation and thereby increasing cardiovascular disease risk.[4,7,10,16] Several studies have demonstrated that experimental sleep disturbance results in increased levels of cardiovascular inflammatory biomarkers IL-6 and CRP.[3,4,16,18–21] However, the studies examining the relationship between sleep quality specifically and these biomarkers, as well as with MCP-1 and MMP-9 are limited and have yielded mixed results. A cross-sectional study conducted among Taiwanese adults revealed no statistically significant associations between overall PSQI score and IL-6 and CRP.[31] Another study conducted among adults with type 2 diabetes found a significant correlation between overall PSQI score and IL-6, but no significant correlation between PSQI score and CRP.[32] A cross-sectional study conducted among healthy post-menopausal women found that higher PSQI scores were associated with elevated levels of high-sensitivity CRP.[18] Our results are most consistent with this study conducted in post-menopausal women, as we found statistically significant positive correlations between PSQI score and IL-6, CRP, and MCP-1, among patients with a prior MI.

We found that patients with a prior MI had higher mean PSQI scores, or worse sleep quality compared with controls, which is consistent with literature findings

highlighting a high prevalence of insomnia among patients with coronary heart disease (CHD), as well as worse PSQI scores among patients with heart failure.[16,33,34] When we stratified by race within each study group, we found that African American patients with a prior MI had the highest mean overall PSQI score, as well as the highest mean score on the sleep duration subscale. Statistical testing of within study group differences by race were significant for overall PSQI score and the sleep duration subscale, suggesting African Americans have worse sleep quality and shorter sleep duration compared to Whites, consistent with previous reports.[2,12,17,21,22] We also found that African Americans, regardless of prior history of MI, had higher levels of IL-6 and CRP compared to their White counterparts, and that this difference was statistically significant for CRP. This is consistent with the literature suggesting that African Americans have elevated levels of IL-6 and CRP compared to Whites.[35,36] Together, these findings suggest that African Americans with a prior MI are particularly vulnerable to poor sleep quality, and that African Americans, regardless of cardiovascular disease history, have higher systemic inflammation compared to Whites.

There were statistically significant positive correlations between the overall PSQI score and IL-6, CRP, and MCP-1, but only among participants with a prior MI. When we further stratified by race to assess within study group correlations, we found that the magnitude of the correlation between PSQI score and CRP was similar among African Americans and White participants within each study group, and that the correlation was stronger in the MI group. Although we were not able to detect a significant interaction between overall PSQI score and study group, regression analyses

showed the percent increase in IL-6, CRP, and MCP-1 with each 5-point increase in overall PSQI score tended to be higher among participants with a prior MI. For MCP-1 specifically, the percent increase with each 5-point increase in overall PSQI score was statistically significant after adjustment for demographic, lifestyle, and clinical risk factors among patients with a prior MI, races combined. This finding is important, as it suggests that patients with history of cardiovascular disease may disproportionately experience elevated levels of MCP-1 as a consequence of poor sleep quality. Existing data on the association between sleep quality and this particular inflammatory biomarker is limited. Some studies have demonstrated increased levels of MCP-1 among patients with obstructive sleep apnea syndrome (OSAS) compared to controls, but studies of poor routine sleep and elevated MCP-1 are scarce.[37] While these results suggest that MCP-1 may be an inflammatory biomarker indicating poor sleep quality, particularly among those with a prior MI, more research is needed to support these findings.

There are several limitations to the findings of this investigation. One of the main limitations is the cross-sectional design, so it is not possible to evaluate a causal relationship between overall PSQI score and elevated levels of inflammatory biomarkers. Second, the number of patients with a prior MI (n=258) was much higher than the number of healthy controls (n=97), which could impact the power for significance testing, particularly with regards to assessing interaction between overall PSQI score, study group, and race. Additionally, the PSQI is a self-report measure of sleep quality over the previous month, and may be subject to recall bias and imprecise

assessments of sleep duration and quality. Despite these limitations, there are a number of strengths in this study, including the large number of African American and female participants, the availability of a healthy control group matched for age and sex, and a comprehensive panel of biomarkers evaluated.

In summary, we found that worse sleep quality is positively associated with cardiovascular inflammatory biomarker MCP-1 in a well-characterized cohort of patients with a prior MI and healthy controls. Other biomarkers, especially CRP, were also related to sleep quality, especially among MI patients, although the association tended to weaken after adjustment for demographic, lifestyle, and clinical risk factors. Elevated levels of IL-6, CRP, MCP-1, and MMP-9 are hypothesized to play a role in the progression of atherosclerosis and predict future cardiovascular events.[38–41] Given the role of inflammatory biomarkers in the progression of CVD, identifying whether poor sleep quality is a potential cause of elevated levels could help lead to public health interventions geared towards improving sleep quality in order to reduce cardiovascular disease risk. Our results are consistent with the hypothesis that systemic inflammation may link inadequate or poor sleep with CVD, especially post-MI. Given race-related sleep disparities, it is crucial to prioritize enrollment of minority populations. Finally, exploring mechanisms between poor sleep quality, inflammatory response, and cardiovascular events could help identify novel risk pathways that may help with cardiovascular disease prevention.

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Table 1. Characteristics of MIMS-2 Study Participants, by Study Group.

	MI Group (n=258)	Control Group (n=97)	*p*-value
Total Demographics, n			
Age, years, mean (SD)	50.62 (6.72)	49.12 (9.32)	0.5
Female, n (%)	129 (50.0)	50 (51.55)	0.8
Married, n (%)	107 (41.47)	52 (53.61)	0.04
African American, n (%)	166 (64.34)	39 (40.21)	<.0001
Years of Education, years, mean (SD)	13.71 (2.85)	16.47 (2.68)	<.0001
Income <$25,000, n (%)	90 (37.97)	7 (7.53)	<.0001
Cardiovascular Risk Factors			
Lifetime History of Smoking, n (%)	140 (54.26)	28 (28.87)	<.0001
BMI, kg/m^2, mean (SD)	31.57 (7.40)	29.03 (6.17)	0.0013
Diabetes, n (%)	81 (31.40)	7 (7.22)	<.0001
Hypertension, n (%)	211 (81.78)	30 (30.93)	<.0001
Dyslipidemia, n (%)	208 (80.62)	31 (31.96)	<.0001
Psychosocial Risk Factors			
Beck Depression Inventory, mean (SD)	12.01 (10.48)	6.48 (7.57)	<.0001
PTSD Symptom Checklist, mean (SD)	31.85 (14.87)	24.46 (11.13)	<.0001
Perceived Stress Scale, mean (SD)	16.21 (8.61)	10.77 (6.50)	<.0001
State Anxiety, mean (SD)	35.84 (13.11)	30.51 (10.00)	0.0008
Trait Anxiety, mean (SD)	37.49 (12.26)	32.07 (9.93)	<.0001
Medications			
Aspirin, n (%)	212 (82.49)	8 (8.33)	<.0001
β-Blocker, n (%)	222 (86.38)	5 (5.21)	<.0001
Statins, n (%)	219 (85.21)	14 (14.58)	<.0001
ACE Inhibitors, n (%)	111 (43.19)	13 (13.54)	<.0001
Antidiabetics, n (%)	72 (28.02)	7 (7.29)	<.0001
Antidepressants, n (%)	42 (16.34)	16 (16.67)	0.9
Clinical Characteristics (patients with MI only)			
ST-segment elevation MI, n (%)	72 (27.91)		
Maximum troponin, mean (SD)	26.19 (49.42)		
History of MI before index MI, n (%)	52 (20.23)		
History of congestive heart failure, n (%)	22 (8.53)		
History of revascularization, n (%)	208 (80.62)		
LV ejection fraction %, mean (SD)	50.65 (11.71)		
Log transformed Gensini CAD severity score, mean (SD)	3.07 (1.45)		
SPECT summed rest score, mean (SD)	3.56 (6.16)		

Resting Hemodynamics			
Systolic blood pressure, mm Hg, mean (SD)	134.36 (21.55)	120.32 (12.93)	<.0001
Diastolic blood pressure, mm Hg, mean (SD)	84.00 (12.56)	77.36 (9.06)	<.0001

Abbreviations: SD: Standard Deviation; BMI: Body Mass Index; PTSD: Posttraumatic Stress Disorder; MI: Myocardial Infarction; CAD: Coronary Artery Disease; ACE: Angiotensin Converting Enzyme.

Table 2. Characteristics of MIMS-2 Study Participants, by Study Group and Race.

	MI Group			Control Group		
	African-American Participants (n=166)	White Participants (n=77)	*p*-value	African-American Participants (n=39)	White Participants (n=54)	*p*-value
Total Demographics, n						
Age, years, mean (SD)	50.01 (7.27)	52.16 (5.39)	0.06	50.56 (6.42)	48.51 (10.68)	1.0
Female, n (%)	94 (56.63)	29 (37.66)	0.006	23 (58.97)	26 (48.15)	0.3
Married, n (%)	47 (28.31)	49 (63.64)	<.0001	18 (46.15)	33 (61.11)	0.2
Years of Education, years, mean (SD)	13.14 (2.18)	14.86 (3.36)	<.0001	15.67 (2.18)	16.96 (2.93)	0.02
Income <$25,000, n (%)	71 (48.30)	17 (22.67)	0.0002	3 (7.89)	3 (5.77)	0.7
Cardiovascular Risk Factors						
Lifetime History of Smoking, n (%)	95 (57.23)	43 (55.84)	0.8	12 (30.77)	15 (27.78)	0.8
BMI, kg/m^2, mean (SD)	32.37 (7.68)	30.45 (6.80)	0.06	32.08 (6.43)	26.92 (5.11)	<.0001
Diabetes, n (%)	63 (37.95)	15 (19.48)	0.004	5 (12.82)	2 (3.70)	0.1
Hypertension, n (%)	148 (89.16)	53 (68.83)	<.0001	15 (38.46)	13 (24.07)	0.1
Dyslipidemia, n (%)	135 (81.33)	60 (77.92)	0.5	12 (30.77)	16 (29.63)	0.9
Psychosocial Risk Factors						
Beck Depression Inventory, mean (SD)	13.32 (10.88)	9.79 (8.61)	0.02	6.97 (7.76)	6.31 (7.66)	0.7
PTSD Symptom Checklist, mean (SD)	34.23 (15.75)	27.58 (11.15)	0.002	24.45 (10.79)	24.57 (11.73)	0.7
Perceived Stress Scale, mean (SD)	16.84 (8.70)	15.01 (8.27)	0.1	10.18 (6.14)	10.89 (6.68)	0.6
State Anxiety, mean (SD)	36.41 (13.18)	35.46 (12.63)	0.7	29.79 (9.58)	30.91 (10.30)	0.7
Trait Anxiety, mean (SD)	38.35 (12.48)	36.33 (11.48)	0.2	31.74 (9.89)	32.22 (10.06)	0.8
Medications						
Aspirin, n (%)	130 (78.31)	67 (88.16)	0.07	4 (10.26)	4 (7.55)	0.6

β-Blocker, n (%)	147 (88.55)	64 (84.21)	0.3	3 (7.69)	2 (3.77)	0.4
Statins, n (%)	136 (81.93)	68 (89.47)	0.1	5 (12.82)	8 (15.09)	0.8
ACE Inhibitors, n (%)	78 (46.99)	26 (34.21)	0.06	7 (17.95)	5 (9.43)	0.2
Antidiabetics, n (%)	55 (33.13)	13 (17.11)	0.01	5 (12.82)	2 (3.77)	0.1
Antidepressants, n (%)	25 (15.06)	16 (21.05)	0.2	4 (10.26)	12 (22.64)	0.1
Clinical Characteristics (patients with MI only)						
ST-segment elevation MI, n (%)	41 (24.70)	26 (33.77)	0.1			
Maximum troponin, mean (SD)	22.50 (44.07)	31.58 (56.40)	0.6			
History of MI before index MI, n (%)	40 (24.24)	9 (11.69)	0.02			
History of congestive heart failure, n (%)	21 (12.65)	1 (1.30)	0.004			
History of revascularization, n (%)	128 (77.11)	67 (87.01)	0.07			
LV ejection fraction %, mean (SD)	50.25 (12.00)	51.23 (11.04)	0.8			
Log transformed Gensini CAD severity score, mean (SD)	2.90 (1.52)	3.32 (1.28)	0.06			
SPECT summed rest score, mean (SD)	3.67 (5.98)	3.22 (6.19)	0.2			
Resting Hemodynamics						
Systolic blood pressure, mm Hg, mean (SD)	138.53 (22.15)	127.47 (18.52)	0.0002	124.07 (12.78)	117.80 (12.45)	0.02
Diastolic blood pressure, mm Hg, mean (SD)	86.87 (12.72)	79.09 (10.81)	<.0001	80.42 (7.97)	75.54 (9.00)	0.008

Abbreviations: SD: Standard Deviation; BMI: Body Mass Index; PTSD: Posttraumatic Stress Disorder; MI: Myocardial Infarction; CAD: Coronary Artery Disease; ACE: Angiotensin Converting Enzyme.

Table 3. Sleep Characteristics of MIMS-2 Study Participants by Study Group.

	MI Group (n=258)	Control Group (n=97)	*p*-value
Sleep Scores			
Overall PSQI Score, mean (SD)	8.08 (4.10)	5.90 (3.87)	<.0001
Subscale Scores			
Sleep Quality, mean (SD)	1.34 (0.89)	1.02 (0.74)	0.002
Sleep Latency, mean (SD)	1.36 (1.04)	1.07 (1.04)	0.02
Sleep Duration, mean (SD)	1.01 (1.12)	0.65 (0.87)	0.01
Sleep Efficiency, mean (SD)	0.84 (1.12)	0.39 (0.78)	0.0003
Sleep Disturbance, mean (SD)	1.76 (0.75)	1.38 (0.60)	<.0001
Needs Medications to Sleep, mean (SD)	0.80 (1.19)	0.70 (1.18)	0.4
Sleep Issues Cause Dysfunction, mean (SD)	0.96 (0.82)	0.68 (0.73)	0.002

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; MI: Myocardial Infarction.

Table 4. Sleep Characteristics of MIMS-2 Study Participants, by Study Group and Race.

	MI Group			Control Group		
	African-American Participants (n=166)	White Participants (n=77)	*p*-value	African-American Participants (n=39)	White Participants (n=54)	*p*-value
Sleep Scores						
Overall PSQI Score, mean (SD)	8.85 (4.24)	6.77 (3.32)	0.0004	6.72 (4.14)	5.44 (3.69)	0.1
Subscale Scores						
Sleep Quality, mean (SD)	1.48 (0.94)	1.14 (0.70)	0.02	1.15 (0.84)	0.94 (0.66)	0.3
Sleep Latency, mean (SD)	1.51 (1.09)	1.10 (0.93)	0.007	1.05 (1.12)	1.07 (1.01)	0.8
Sleep Duration, mean (SD)	1.18 (1.17)	0.69 (0.95)	0.002	1.03 (0.99)	0.41 (0.69)	0.0005
Sleep Efficiency, mean (SD)	1.00 (1.19)	0.60 (0.94)	0.02	0.56 (0.97)	0.30 (0.63)	0.2

Sleep Disturbance, mean (SD)	1.85 (0.78)	1.60 (0.63)	0.01	1.41 (0.59)	1.37 (0.62)	0.6
Needs Medications to Sleep, mean (SD)	0.84 (1.23)	0.75 (1.14)	0.8	0.82 (1.25)	0.67 (1.17)	0.4
Sleep Issues Cause Dysfunction, mean (SD)	0.99 (0.86)	0.88 (0.71)	0.5	0.69 (0.83)	0.69 (0.67)	0.7

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; MI: Myocardial Infarction.

Table 5. Geometric Mean Inflammatory Biomarker Levels of MIMS-2 Study Participants by Study Group.

	MI Group (n=258) Geometric Mean (95% CI)	Control Group (n=97) Geometric Mean (95% CI)	*p*-value
IL-6 *(pg/ml)*	1.7 (1.5, 1.8)	1.0 (0.9, 1.2)	<.0001
CRP *(mg/L)*	2.6 (2.2, 3.1)	3.2 (2.5, 4.1)	0.2
MCP-1 *(pg/ml)*	123.1 (119.0, 127.4)	121.9 (114.7, 129.7)	0.8
MMP-9 *(ng/ml)*	59.1 (54.8, 63.8)	58.8 (52.8, 65.5)	0.9

Abbreviations: IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

Table 6. Geometric Mean Inflammatory Biomarker Levels of MIMS-2 Study Participants by Study Group and Race.

	MI Group			Control Group		
	African-American Participants (n=166) Geometric Mean (95% CI)	White Participants (n=77) Geometric Mean (95% CI)	*p*-value	African-American Participants (n=39) Geometric Mean (95% CI)	White Participants (n=54) Geometric Mean (95% CI)	*p*-value
IL-6 *(pg/ml)*	1.7 (1.5, 1.8)	1.6 (1.4, 1.9)	0.7	1.2 (1.0, 1.5)	0.9 (0.8, 1.1)	0.02
CRP *(mg/L)*	3.3 (2.7, 4.1)	1.9 (1.4, 2.6)	0.004	4.8 (3.2, 7.1)	2.5 (1.8, 3.4)	0.01
MCP-1 *(pg/ml)*	126.5 (121.5, 132.0)	117.8 (111.1, 124.8)	0.06	129.5 (118.1, 142.0)	115.7 (106.1, 126.3)	0.08
MMP-9 *(ng/ml)*	53.0 (48.4, 58.1)	73.9 (63.8, 85.5)	0.0001	53.0 (44.2, 63.7)	63.3 (54.9, 73.0)	0.1

Abbreviations: IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

Table 7. Spearman Correlation Coefficients between Overall PSQI Score and Individual Inflammatory Biomarkers, by Study Group.

Inflammatory Biomarkers	MI Group		Control Group	
	r	p-value	*r*	p-value
IL-6 *(pg/ml)*	0.14	0.03	0.03	0.8
CRP *(ng/ml)*	0.21	0.0007	0.03	0.8
MCP-1 *(pg/ml)*	0.24	<.0001	0.17	0.09
MMP-9 *(pg/ml)*	-0.07	0.3	-0.13	0.2

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

Table 8. Spearman Correlation Coefficients between Overall PSQI Score and Individual Inflammatory Biomarkers, by Study Group and Race.

	MI Group				Control Group			
	African-American Participants (n=166)		White Participants (n=77)		African-American Participants (n=39)		White Participants (n=54)	
Inflammatory Biomarkers	*r*	p-value	*r*	p-value	*r*	p-value	*r*	p-value
IL-6 *(pg/ml)*	0.10	0.2	0.21	0.07	0.13	0.4	-0.10	0.5
CRP *(ng/ml)*	0.14	0.08	0.16	0.2	-0.07	0.7	0.03	0.8
MCP-1 *(pg/ml)*	0.27	0.0003	0.06	0.6	0.14	0.4	0.11	0.4
MMP-9 *(pg/ml)*	-0.04	0.6	0.07	0.6	-0.01	1.0	-0.16	0.2

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

Table 9. Unadjusted and Adjusted Percent Difference in Inflammatory Biomarkers for Each 5-point increase in Overall PSQI Score.

Inflammatory Biomarker (Outcome)	MI Group % Difference	p-value	Control Group % Difference	p-value	p-value for interaction term: PSQI score*study group	p-value for interaction term: PSQI score*race	p-value for interaction term: PSQI score*study group*race
IL-6 (pg/mL)							
Unadjusted	10.7	0.03	9.4	0.3	0.9	0.8	0.2
Adjusted Model 1	7.1	0.2	4.7	0.6	0.9	0.9	0.2
Adjusted Model 2	2.1	0.7	-2.9	0.8	1.0	1.0	0.4
CRP (ng/ml)							
Unadjusted	44.0	0.0005	13.9	0.4	0.2	0.9	0.8
Adjusted Model 1	27.7	0.02	-4.0	0.8	0.4	0.7	0.6
Adjusted Model 2	19.5	0.07	-23.1	0.1	0.05	0.5	0.1
MCP-1 (pg/ml)							
Unadjusted	9.5	<.0001	8.0	0.06	0.7	0.2	0.8
Adjusted Model 1	7.5	0.0008	7.8	0.09	0.8	0.3	0.8
Adjusted Model 2	7.1	0.003	6.0	0.2	0.5	0.4	1.0
MMP-9 (pg/ml)							
Unadjusted	-5.7	0.4	-4.7	0.3	0.9	0.9	0.4
Adjusted Model 1	0.3	1.0	-2.4	0.8	0.9	0.8	0.4
Adjusted Model 2	-4.2	0.4	-4.7	0.6	0.9	0.9	0.5

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

[a]Model 1 adjusted for sex, age, years of education, race.

[b]Model 2 adjusted for model 1 covariates + smoking, body mass index (continuous), diabetes, hypertension, aspirin use, statin use, and anti-depressant use.

Table 10. Associations between PSQI Subscale Scores and Inflammatory Biomarkers (Continuous) in MIMS-2 population.

	Unadjusted Model		Adjusted Model 1[a]		Adjusted Model 2[b]	
Subscale/Inflammatory Biomarker	Regression Coefficient (95% CI)		Regression Coefficient (95% CI)		Regression Coefficient (95% CI)	
	MI Group	Control Group	MI Group	Control Group	MI Group	Control Group
Sleep Quality						
IL-6 (pg/ml)	0.06 (-0.03, 0.14)	-0.06 (-0.24, 0.12)	0.03 (-0.05, 0.12)	-0.08 (-0.27, 0.11)	-0.01 (-0.09, 0.08)	-0.14 (-0.33, 0.05)
CRP (ng/ml)	0.23 (0.04, 0.42)	-0.02 (-0.36, 0.31)	0.15 (-0.04, 0.34)	-0.15 (-0.51, 0.21)	0.07 (-0.11, 0.25)	-0.32 (-0.66, 0.02)
MCP-1 (pg/ml)	0.04 (0.01, 0.08)	0.02 (-0.07, 0.12)	0.03 (-0.01, 0.07)	0.02 (-0.07, 0.12)	0.03 (-0.01, 0.07)	0.01 (-0.08, 0.09)
MMP-9 (pg/ml)	0.01 (-0.08, 0.09)	-0.07 (-0.22, 0.07)	0.05 (-0.04, 0.14)	-0.05 (-0.21, 0.12)	0.01 (-0.09, 0.10)	-0.06 (-0.23, 0.11)
Sleep Latency						
IL-6 (pg/ml)	0.03 (-0.04, 0.11)	0.01 (-0.11, 0.13)	0.01 (-0.06, 0.08)	0.00 (-0.13, 0.13)	0.00 (-0.07, 0.07)	-0.01 (-0.13, 0.12)
CRP (ng/ml)	0.16 (0.00, 0.32)	-0.01 (-0.24, 0.23)	0.09 (-0.07, 0.25)	-0.06 (-0.30, 0.18)	0.11 (-0.04, 0.25)	-0.11 (-0.34, 0.11)
MCP-1 (pg/ml)	0.05 (0.02, 0.08)	0.02 (-0.03, 0.08)	0.04 (-0.01, 0.07)	0.02 (-0.04, 0.08)	0.04 (0.00, 0.07)	0.02 (-0.03, 0.08)
MMP-9 (pg/ml)	-0.05 (-0.12, 0.02)	-0.03 (-0.14, 0.07)	-0.01 (-0.09, 0.06)	-0.03 (-0.14, 0.08)	-0.02 (-0.10, 0.05)	-0.06 (-0.17, -0.05)
Sleep Duration						
IL-6 (pg/ml)	0.06 (-0.01, 0.13)	0.19 (0.04, 0.33)	0.04 (-0.02, 0.01)	0.14 (-0.03, 0.32)	0.04 (-0.02, 0.10)	0.08 (-0.11, 0.26)
CRP (ng/ml)	0.21 (0.06, 0.36)	0.24 (-0.04, 0.53)	0.13 (-0.02, 0.25)	0.01 (-0.33, 0.35)	0.12 (-0.01, 0.26)	-0.18 (-0.52, 0.15)
MCP-1 (pg/ml)	0.05 (0.02, 0.08)	0.09 (0.02, 0.16)	0.05 (-0.02, 0.08)	0.09 (0.01, 0.17)	0.04 (0.01, 0.07)	0.08 (-0.01, 0.16)
MMP-9 (pg/ml)	0.02 (-0.05, 0.08)	-0.06 (-0.19, 0.07)	0.04 (-0.03, 0.01)	-0.01 (-0.16, 0.15)	0.03 (-0.04, 0.10)	-0.02 (-0.18, 0.15)
Sleep Efficiency						
IL-6 (pg/ml)	0.08 (0.02, 0.15)	0.10 (-0.07, 0.26)	0.05 (-0.01, 0.02)	0.07 (-0.10, 0.24)	0.04 (-0.02, 0.10)	0.01 (-0.16, 0.19)
CRP (ng/ml)	0.26 (0.11, 0.41)	0.01 (-0.31, 0.33)	0.17 (-1.02, 1.25)	-0.12 (-0.45, 0.20)	0.15 (0.02, 0.29)	-0.29 (-0.60, 0.02)
MCP-1 (pg/ml)	0.04 (0.01, 0.07)	0.03 (-0.05, 0.11)	0.02 (-0.01, 0.05)	0.03 (-0.05, 0.11)	0.02 (-0.01, 0.05)	0.01 (-0.07, 0.10)
MMP-9 (pg/ml)	-0.01 (-0.08, 0.06)	-0.10 (-0.24, 0.03)	0.02 (-0.05, 0.09)	-0.07 (-0.22, 0.08)	0.01 (-0.06, 0.08)	-0.08 (-0.24, -0.07)
Sleep Disturbance						
IL-6 (pg/ml)	0.08 (-0.02, 0.18)	0.13 (-0.09, 0.34)	0.06 (-0.05, 0.16)	0.12 (-0.10, 0.35)	-0.01 (-0.10, 0.09)	0.11 (-0.11, 0.34)
CRP (ng/ml)	0.24 (0.02, 0.47)	0.19 (-0.22, 0.60)	0.14 (-0.09, 0.37)	0.11 (-0.32, 0.54)	0.04 (-0.17, 0.24)	0.09 (-0.31, 0.50)
MCP-1 (pg/ml)	0.05 (0.00, 0.09)	0.10 (-0.01, 0.20)	0.03 (-0.01, 0.08)	0.11 (0.00, 0.21)	0.02 (-0.02, 0.07)	0.09 (-0.01, 0.20)
MMP-9 (pg/ml)	-0.03 (-0.13, 0.07)	0.07 (-0.11, 0.25)	0.00 (-0.10, 0.11)	0.12 (-0.07, 0.32)	-0.03 (-0.14, -0.08)	0.12 (-0.08, -0.32)

Needs Medications to Sleep						
IL-6 (pg/ml)	0.03 (-0.03, 0.09)	0.02 (-0.09, 0.13)	0.03 (-0.04, 0.09)	-0.01 (-0.13, 0.10)	0.01 (-0.05, 0.07)	-0.04 (-0.15, 0.08)
CRP (ng/ml)	0.05 (-0.09, 0.19)	0.09 (-0.12, 0.30)	0.02 (-0.11, 0.16)	0.03 (-0.18, 0.24)	-0.01 (-0.13, 0.12)	-0.04 (-0.24, 0.17)
MCP-1 (pg/ml)	0.02 (-0.01, 0.05)	0.03 (-0.03, 0.08)	0.01 (-0.01, 0.04)	0.02 (-0.04, 0.07)	0.01 (-0.02, 0.04)	0.01 (-0.04, 0.07)
MMP-9 (pg/ml)	-0.05 (-0.12, 0.01)	0.02 (-0.07, 0.12)	-0.05 (-0.11, 0.02)	0.03 (-0.07, 0.13)	-0.07 (-0.13, -0.00)	0.02 (-0.08, -0.13)
Sleep Issues Cause Dysfunction						
IL-6 (pg/ml)	-0.01 (-0.10, 0.08)	0.03 (-0.15, 0.21)	-0.01 (-0.10, 0.08)	0.03 (-0.15, 0.20)	-0.06 (-0.15, -0.02)	-0.07 (-0.26, -0.11)
CRP (ng/ml)	0.11 (-0.09, 0.32)	0.06 (-0.28, 0.40)	0.09 (-0.11, 0.30)	0.04 (-0.30, 0.38)	0.02 (-0.17, 0.21)	-0.22 (-0.55, 0.11)
MCP-1 (pg/ml)	0.06 (0.02, 0.10)	0.06 (-0.02, 0.14)	0.06 (0.02, 0.10)	0.07 (-0.02, 0.15)	0.05 (-0.01, 0.10)	0.04 (-0.04, 0.13)
MMP-9 (pg/ml)	-0.04 (-0.13, 0.05)	-0.09 (-0.24, 0.06)	-0.04 (-0.14, 0.05)	-0.07 (-0.23, 0.08)	-0.08 (-0.17, -0.02)	-0.09 (-0.25, -0.08)

Abbreviations: PSQI: Pittsburgh Sleep Quality Index; CI: Confidence Interval; IL-6: interleukin-6; CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; MMP-9: matrix metallopeptidase-9.

[a]Model 1 adjusted for sex, age, years of education, race.
[b]Model 2 adjusted for model 1 covariates + smoking, body mass index (continuous), diabetes, hypertension, aspirin use, statin use, and anti-depressant use.

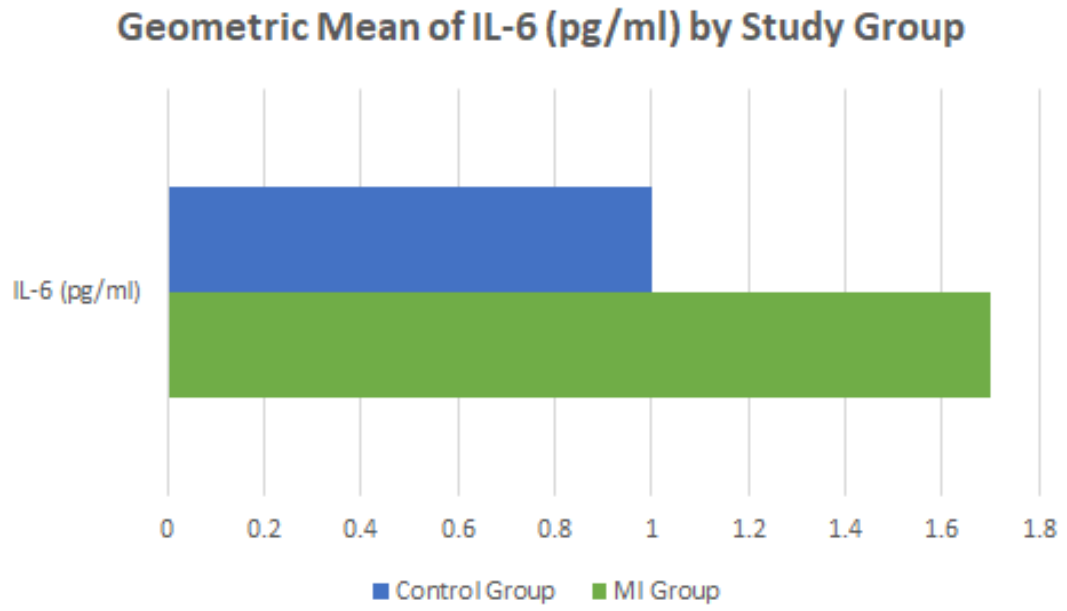

Figure 1. Geometric Mean of IL-6 (pg/ml) by Study Group.

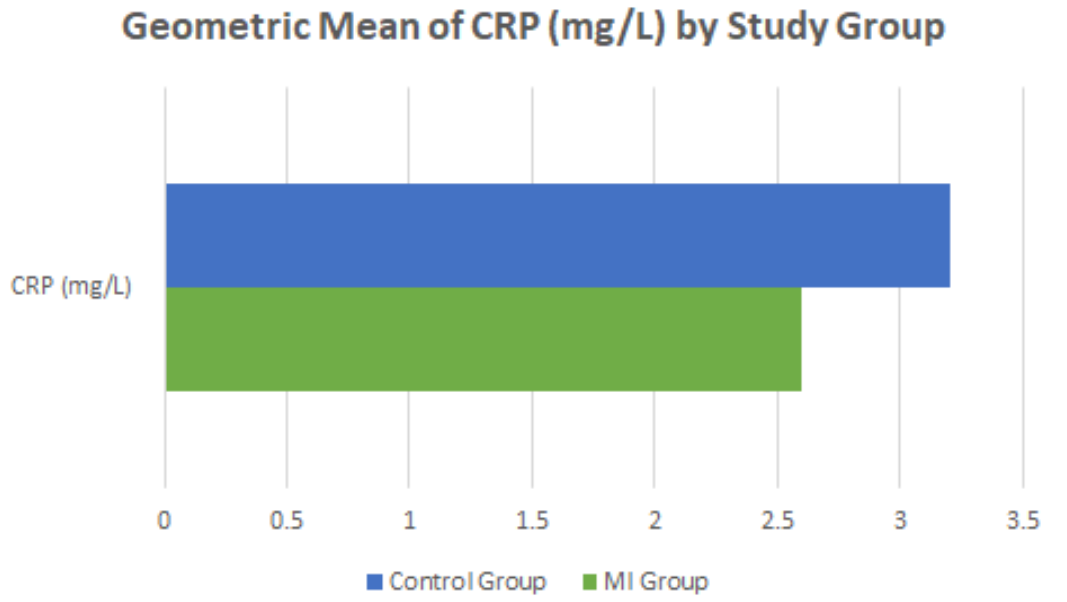

Figure 2. Geometric Mean of CRP (mg/L) by Study Group.

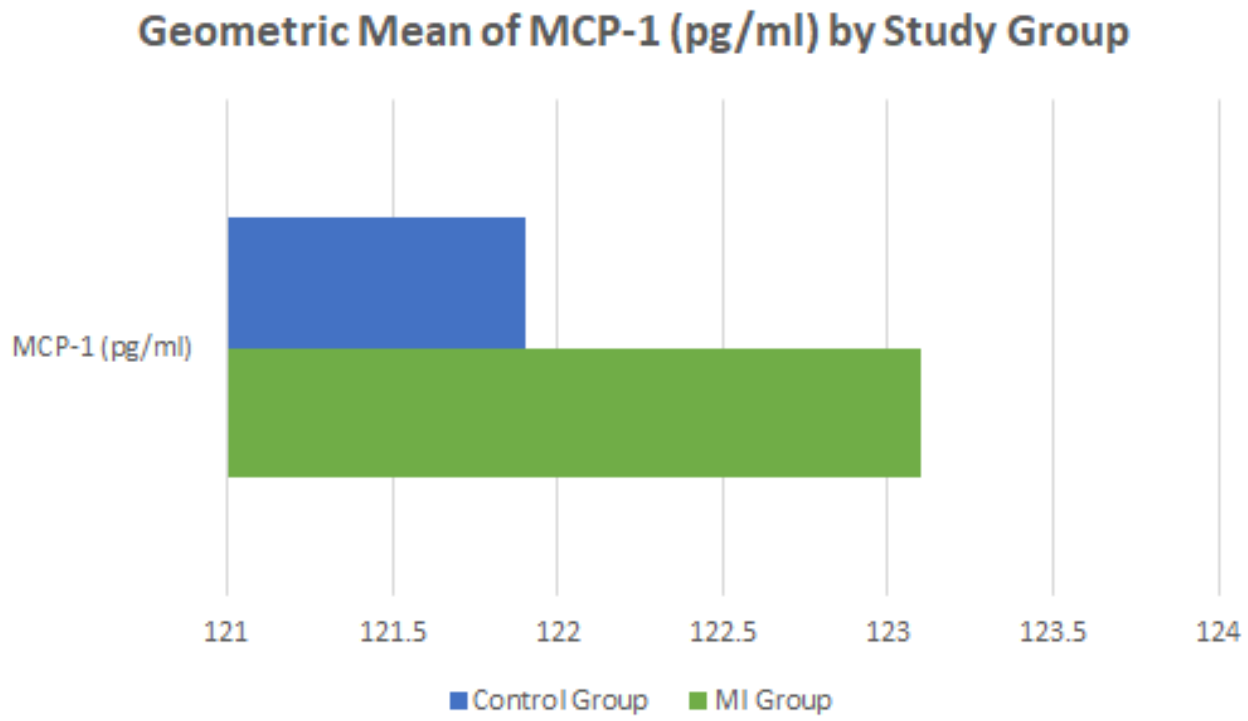

Figure 3. Geometric Mean of MCP-1 (pg/ml) by Study Group.

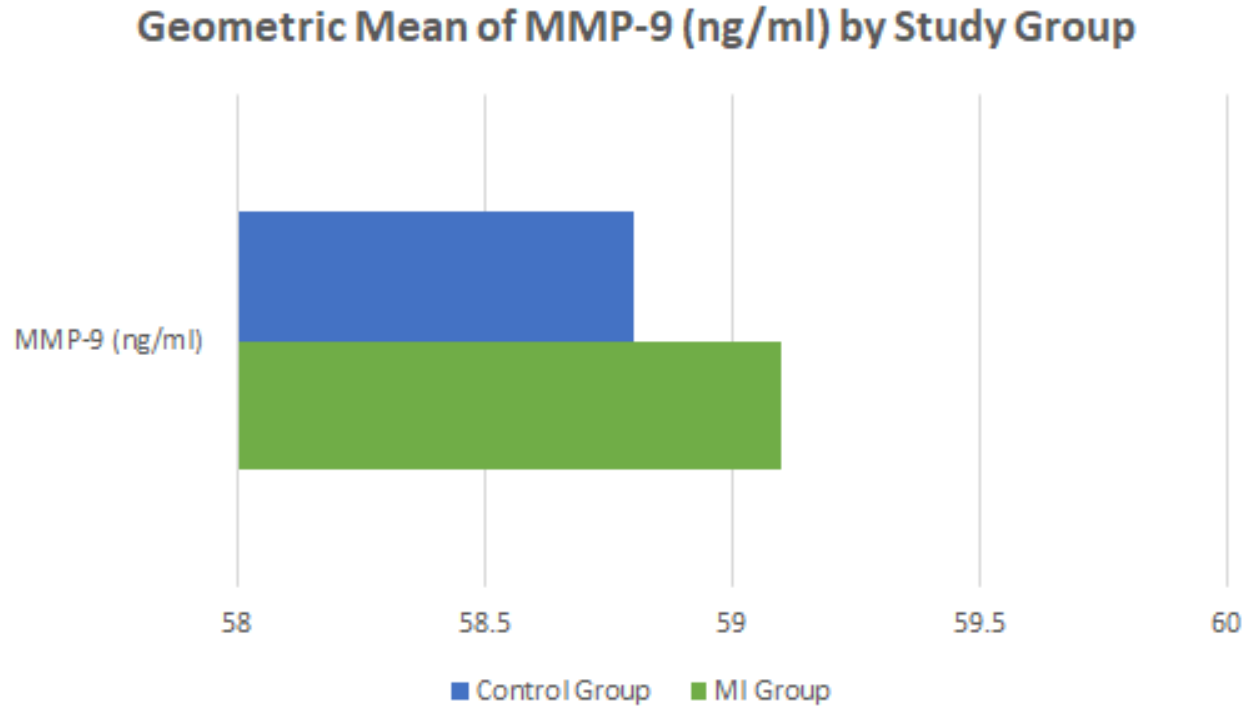

Figure 4. Geometric Mean of MMP-9 (ng/ml) by Study Group.