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Association of Systemic Inflammation with Mental Health Symptoms in Post-Myocardial Infarction Populations

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Master of Public Health

Epidemiology

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2017

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Abstract

Association of systemic inflammation with mental health symptoms in post-myocardial infarction populations

By Peter Toyokazu Buto

Background: Adverse mental health conditions including depression, PTSD, and anxiety are prevalent among patients who survive myocardial infarctions (MI) and are associated with worsened outcomes. The mechanisms underlying these associations, however, are still not well understood. Inflammatory pathways are one proposed pathway by which mental health my affect cardiovascular outcomes. In an exploratory analysis, we examined the bidirectional association between mental health symptoms and inflammatory biomarkers in a younger post MI population. We further examined how this association may differ between females and males as well as between Black and non-Black individuals.

Methods: Participants included individuals with early onset MI between the ages 18 and 60. Mental health scores for depression, PTSD, perceived stress, and anxiety as well as inflammatory biomarkers, interleukin-6 (IL-6) and C-reactive protein (CRP), were collected at baseline and six-month follow up. Exploratory analysis examined changes in mental health symptoms as a function of inflammatory markers at baseline and changes in inflammatory markers as a function of mental health symptoms at baseline. We then focused on one direction: PTSD subscales as the outcome of inflammatory markers at baseline.

Results: Among 244 patients in the study (mean age: 50.8, 48.4% female, 64.3% Black), the average IL-6 level at rest was 1.7 pg/mL and average CRP was 2646.6 ng/mL. Mental health scores at baseline did not predict changes in inflammatory biomarkers. Inflammatory biomarkers at baseline did not show a significant association with most of the mental health scales, however, both IL-6 and CRP were significantly associated with changes in re-experiencing PTSD symptoms. This association was more pronounced in Black individuals and females, however, the magnitudes only significantly differed by race (but not sex).

Conclusion: MI patients with higher levels of inflammation at baseline exhibited greater changes in re-experiencing PTSD symptoms over a six month follow-up period, suggesting a mechanistic link between PTSD and cardiovascular health through inflammation.

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Association of systemic inflammation with mental health symptoms in post-myocardial infarction populations

Background:

Cardiovascular disease (CVD) is the leading cause of death in the world and has been found to be associated with adverse mental health symptoms among people globally.[1] Depression is prevalent in populations with coronary heart disease (CHD), a subgroup of CVD, and has been found to contribute to both onset and poorer prognosis of CVD.[2,3] A meta-analysis by Roest et al. reported substantial evidence also for anxiety following a myocardial infarction (MI) leading to worsening cardiovascular outcomes.[4] Lastly, post-traumatic stress disorder (PTSD) was also found to be associated with poorer cardiovascular outcomes.[5,6] The exact mechanisms underlying the association between mental health and cardiovascular disease, however, have yet to be well elucidated.

Mechanisms Linking Coronary Heart Disease and Mental Health

Many adverse behaviors (e.g., smoking, alcohol consumption, and binge eating) associated with poor mental health are also known risk factors for poor cardiovascular health.[2] Adjustment for these behavioral factors and other traditional cardiovascular risk factors (e.g., age, diabetes, cholesterol levels, etc.), did not eliminate associations between mental health conditions and cardiovascular outcomes in many studies.[2,3,7] Regardless of their age, diabetes status, or cholesterol levels, people with adverse mental health also tended to have a higher risk of CVD.

The biological pathways between mental and cardiovascular health are complex and suspected to be bidirectional and multifactorial. Heart conditions negatively impact one's mental health, while adverse mental health increases one's risk of developing a heart condition.[8] Genetic studies have found little correlation between depression and the genes associated with coronary heart disease,[9] suggesting that this pairing may be driven more by external causes than genetic or intrinsic causes.

Coronary Heart Disease and Inflammation

Though the mechanisms connecting mental health and cardiovascular disease are far from being clarified, inflammation has been implicated. Inflammation has been associated with the progression of coronary artery disease and cardiac events.[7] Higher levels of C-reactive protein (CRP), a marker of inflammation, have been found to be predictive of future coronary events (including death) independent of other CHD risk factors.[8,10]

When exposed to a stressor, the autonomic nervous system activates the immune function signaling the start of inflammation.[11] Cytokines such as interleukin-6 (IL-6) can initiate this physiological response, inducing production of CRP and stimulating the immune system.[12] Cytokines and other immunological factors (e.g., macrophages and leukocytes) initiate cycles of inflammation and lipid modification/deposition, the latter of which is facilitated by presence of traditional risk factors for CHD such as hypercholesterolemia and hypertension.[11]

In advanced stages of coronary artery disease, these same immunologic factors have been implicated in forming and activating thrombi, thus increasing the risk of coronary events.[11] Elevated leukocyte counts in particular were associated with increased risk of death or reinfarction in patients that had a past acute MI.[13]

Inflammation and Mental Health

Systemic inflammation, however, has also been associated with adverse mental health symptoms independent of CVD. Epidemiological evidence has found high levels of inflammatory markers in drug-naïve patients with depression compared to healthy controls.[2] In a study of over 4,000 Medicare eligible individuals, Kop et al. (2002) reported depression to be associated with both inflammation (as measured by CRP) and coagulation, even after adjustment for traditional risk factors.[14]

In another prospective cohort study among men free of CHD at baseline, Empana et al. (2005) reported a significant association between depression and IL-6 and CRP, two measures of

systemic inflammation. Inflammation, however, did not mediate the association between history of depression and CHD.[15]

Similar associations were evident, though not as strong, when examined for PTSD. Lima et al. (2018) reported minor differences in inflammation at resting state among patients with a recent MI who had PTSD compared to those without PTSD, although those with PTSD sustained higher inflammatory response during mental stress.[16]

Miller and Raison (2016) argue that modern humans may have developed an adaptational bias towards inflammation, as it enhances the probability of survival and reproduction from an evolutionary perspective.[17] When faced with the threat of physical harm or an infectious agent, the body would activate immunological and inflammatory cycles in anticipation of foreign invasion. By priming the body to recover and recuperate when presented with an immediate threat to life, people were able to recover more quickly.[17]

As a consequence, the body also reacts to psychological stress in a similar manner as it would to a pathogen, initiating a cascade of inflammatory processes.[12,13] As exposure to psychosocial stressors increase, both the risk of inflammation and the risk of cardiovascular complications increase.

This adaptational bias may have also resulted in vulnerability to depression as continuous systemic inflammation takes a toll on the body, especially when frequently presented with non-life threating stressors.[17] Chronic inflammation has been associated with depression and tends to co-occur with other inflammation-related disorders including asthma, chronic pain, and CHD among other[12].

Depression severity and duration has a dose-response relationship with an altered immune system response[11]. Psychosocial risk factors often cluster; for example, social events such as job loss, socioeconomic disadvantage, and depression often co-occur[7]. Consequently, inflammatory and immunological responses are often dysregulated and can lead to worsening of psychological disturbances.

Inflammation may not be associated so much with the presence or absence of adverse mental health in general, but rather with particular symptoms, especially with regards to severity and quality.[17] Somatic (as opposed to cognitive-affective) symptoms of mental health are of particular concern. When examining the association between depression and anxiety with inflammation among ACS patients, Steptoe et al. (2013) found a significant association only between inflammation and incident somatic depression, but not other subtypes of depression.[18] Physical presentation of psychosocial risk factors are the strongest drivers for individuals to see their providers and have been associated with greater treatment resistance.[19] MI patients who experienced somatic depressive symptoms were also found to have worse cardiovascular outcomes compared to those with cognitive depressive symptoms.[20,21] Consistent with these data, among a large prospective cohort study, Steptoe et al. (2013) reported among those without a history of depression, inflammation predicted severity of somatic symptoms at three weeks follow up but not cognitive. The converse, however, was noted at 6 month follow-up: inflammation predicted cognitive affective depression symptoms at 6 month follow-up, but not somatic depression symptoms.[18] These findings contributes to the unclear directionality between inflammation and mental health.

Inflammation and Mental Health: Longitudinal Pathways

Due to the association of CHD with both adverse mental health and inflammation, the direct relationship between mental health and inflammation has often been obfuscated and may also be bidirectional. Matthews et al. (2010), using adjusted regression models, reported that elevated CRP levels at baseline predicted elevated depression symptoms at follow up; however, they also found the opposite to be true: higher scores on a depression scale at baseline predicted elevated CRP levels at follow up.[22] Indeed, some evidence suggests that inflammation predisposes one to poorer mental health. Induced inflammation in controlled animal experiments provokes depressive symptoms similar to what would be expected in humans.[8] Similarly, Mendelian randomization studies have found genetic predisposition to inflammation to be associated with

depression, suggesting a causal relationship between inflammatory markers and depression.[9] Whether such relationships also exist for PTSD and other mental health disturbances is unknown. However, there is also evidence for the opposite pathway, i.e., adverse mental health leading to an increase in inflammation. Kop et al. (2002) found depression to be significantly associated with inflammation and coagulation among Medicare eligible individuals from four communities. Specifically, depression at baseline had been associated with an increase in white blood cell counts and CRP after adjustment for traditional risk factors.[14] The direction of this association continues to be equivocal and even less is known about other mental health factors such as PTSD. More studies are required to understand these causal directions.

Possible Effect Modification in Subgroups

Though it has been largely established that the prevalence rates of adverse mental health and systemic inflammation are higher in females and people of color[23,24] than their counterparts, there continues to be little research in these subpopulations. Differences between males and females that may contribute to differential effects of inflammation include age and hormonal status. As hormonal factors are altered throughout the life course, different processes (such as menarche and menopause) may impact inflammatory processes[24].

Miller argues that females may have developed a more sensitive response to the behavioral effects of inflammation, observing that women tend to express more depressive symptoms for similar levels of inflammatory markers[17]. Psychosocial stressors that induce a response similar to what a pathogen may have induced, may also induce anhedonia in women.[17] Hodes et al. (2016) highlight that sex differences in immune systems between males and females may contribute to a greater incidence of depression in females.[25] Higher levels of depression prevalence have been observed in women at nearly twice the rate compared to men. This disparity is even more stark among populations with CHD;[19] women in particular have higher inflammatory response to induced stress.[26]

Racial minorities have also been found to have higher levels of inflammation even after adjustment for potential confounders. Longitudinal data from the Coronary Artery Risk Development in Young Adults (CARDIA) study found increased depressive symptoms, particularly somatic symptoms, to be positively associated with increased CRP among Black participants but not White participants.[27] As there is significant variation in the lived experiences between and within races, O'Connor et al. (2009) suggest examining a possible role for racism as an effect modifier.[24]

Black women in particular may experience a double burden of exposure and disease with identities that intersect both disadvantaged populations (by gender and race). In a longitudinal cohort study of nearly 2,000 individuals, Beydoun et al. (2020) found that levels of inflammation were associated with depression and differed by both sex and race/ethnicity.[23] The disparity in both outcomes obligate further research in these subpopulations to examine strata specific effects by sex and race. Few studies have examined the association of mental health and inflammation in post-MI populations, much less stratified by sex, race, and the combination of the two.

This study examines potential longitudinal relationships between systemic inflammation and mental health disorders among patients recently hospitalized for a myocardial infarction (MI), using data collected at baseline and at a 6 month-follow up. Currently, little information is available on the longitudinal associations between mental health-symptoms and inflammation in this population. We focused on two inflammatory biomarkers that have shown established relationships both with CHD and with mental health: IL-6 and CRP. We further examined specific symptom dimensions (e.g., somatic vs affective/cognitive depressive symptoms, or re-experiencing vs other PTSD symptoms) and if results differ by race or sex, as these groups have shown differences in vulnerability towards these health problems.

Methods:

Study Design and Sample

This study is a longitudinal epidemiological analysis on the association between inflammatory markers and mental health scores among a younger cohort of patients who recently experienced an MI. It is part of the larger 2018 Myocardial Infarction and Mental Stress 2 (MIMS2) study, examining study evaluating whether young women with a recent MI are more susceptible to MI due to psychological stress relative to men of similar age.[28]

Participants for the MIMS2 study included early onset MI patients admitted to an Emory-affiliated hospital in Atlanta, Georgia between the ages of 18 and 60 at time of screening. Cases were recruited from those who had a documented history of MI in the past 8 months. Diagnosis of MI was verified by medical record review based on standard criteria of troponin level increase together with symptoms of ischemia and ECG changes or other evidence of myocardial necrosis.

Exclusion criteria extended to subjects with severe comorbid medical or psychiatric disorders (e.g., cancer, renal failure, sever uncontrolled hypertension, current alcohol/substance abuse, or schizophrenia) that could interfere with the study results. Additionally, participants were excluded if they were pregnant or breast feeding, or if they were using immunosuppressant or psychotropic medications other than anti-depressants. MI patients were excluded if they had unstable angina, acute MI or decompensated heart failure within the previous week, if they weighed over 450 pounds, and if it was deemed unsafe to withhold anti-ischemic medications for 24 hours before testing by study cardiologists.

Of 313 CHD patients in the MIMS2 dataset, 32 did not return at 6 months follow up. Of the 281 participants with information at both baseline and 6-month follow-up, 27 were missing data for both inflammatory markers at baseline and an additional 10 were missing information on PTSD scores at baseline. Therefore, the analytical sample included 244 participants. This

research was approved by the Emory University Institutional Review Board. Written informed consent was obtained from all patients in enrolled in the study. Further details about the study design and sample have been provided elsewhere.[28]

Measurements

Demographic information including age, sex, race, marital status, income, and education were obtained using standardized questionnaires. Study nurses or physicians obtained previous medical history and medication use through clinical examinations and by reviewing medical records.

Inflammatory biomarkers were measured from blood samples collected at rest. The biomarkers included in this study are Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP). Previous studies from this dataset included other biomarkers as well.[16] Collection times were based on a mix of prior studies and pilot testing.[29] These collections were cooled and centrifuged at 4° Celsius. To quantitate the biomarkers, the MesoScale system (Meso Scale Diagnostics, Rockville, Maryland) was employed using the SECTOR Imager 2400 per manufacturer protocols allowing for a lower limit detection limits of $1.33*10^{-6}$ mg/L for hsCRP and 0.06 pg/mL for IL-6.

History of psychiatric disorders within the past month were assessed using the Structured Clinical Interview for DSM-IV (SCID). In addition to history of psychiatric disorders, various mental health surveys were administered to all participants. Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II), as a 21-item self-administered scale.[30] PTSD symptoms were assessed using the civilian version of the PTSD Checklist (PCL-C), a 17-item scale.[31] This scale was subdivided into three different DSM-IV PTSD Symptom clusters: re-experiencing, avoidance and numbing, and arousal. Perceived stress was evaluated using the Perceived Stress Scale.[32] Anxiety symptoms were evaluated via the State-Trait anxiety Inventory

(STAI), a 40-item self-administered scale. Patients returned for a follow-up visit six months after their baseline visit where measures were repeated using identical protocols.

Both biomarkers of inflammation and mental health scores were separately examined as exposure and outcome in exploratory analyses. Following the results of the initial analyses, IL-6 and CRP were included in the model as predictors of mental health outcomes, specifically PTSD symptoms subscales.

Statistical Analysis

We compared the descriptive characteristics of the 281 who were present at both baseline and follow up to the 32 who did not return at 6 months. Next, we calculated descriptive statistics for the overall analytic sample as well as within strata of IL-6 values dichotomized by the median log transformed value. The geometric means of non-log transformed biomarker levels were calculated. Differences in biomarkers between follow up and baseline were approximately normally distributed. We calculated means and standard deviations for continuous variables which were then compared using Satterthwaite t-tests. The number of participants and respective proportions were calculated for categorical variables and compared using chi-square values.

To examine the direction of the association between mental health factors and inflammation, we analyzed the association between changes in the concentration of two inflammatory biomarkers, IL-6 and CRP, and mental health scores for depression, PTSD, perceived stress, and anxiety between baseline and six-month follow up in both directions using generalized linear models.

Initially, we examined the change in overall psychological scale scores, such as the PCL-C (total PTSD symptom score) or the BDI-II (total depressive symptom score) as the dependent variable in a linear regression that examined the natural log of IL-6 (or CRP) as the independent variable, controlling only for PCL-C (or BDI-II) at baseline. We also examined the relationship in

the other direction – with changes in non-log transformed IL-6 (or CRP) as the dependent variable in a linear regression that modeled with PCL-C (or BDI-II) at baseline as the independent variable, controlling only for non-log transformed IL-6 (or CRP) at baseline. A similar procedure was used for the other psychological scales. These preliminary analyses revealed that only PTSD was significantly associated with inflammation in either direction.

Following this exploratory analysis, we focused on the PTSD subscales as the outcome of inflammation at baseline. We used linear mixed models which estimated the effects of linear combinations of regression coefficients for the inflammatory marker and time. This approach tends to be more robust in handling longitudinal observational studies with incomplete measurements at follow-up.[33]

For each type of regression, we modeled four equations progressively adjusting for confounding factors decided *a priori*: 1) demographics (age, race, sex, and years of education), 2) clinical severity (ejection fraction and type of MI, i.e., ST-Elevation Myocardial Infarction (STEMI) or non-STEMI), 3) cardiac risk factors (BMI, smoking history, history of diabetes, history of hypertension, and prior history of MI), and 4) medications (anti-depressants, aspirin, beta-blockers, statins). Each set of covariates was added to those of the previous model.

These analyses were then repeated in sub populations by sex, race (dichotomized as Black and non-Black), and a combination of sex and race. Interaction terms were tested to evaluate whether the measures of association in each stratum were significantly different from one another. The significance level for main effects and interaction effects were set at $p < 0.05$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results:

Descriptive Characteristics

We compared baseline covariates between those who contributed data at both baseline and 6-month follow up and those who only had baseline data. Baseline characteristics were largely similar between the two groups with few exceptions. Those that did not return at 6-month follow up tended to be younger and had completed fewer years of education on average (12.1) compared to those whom visited at both baseline and 6-month follow up (13.8). Furthermore, those who only attended the baseline visit were less likely to have a history of high cholesterol (62.5%) compared with those who attended both visits (82.2%).

Table 1 shows the results of descriptive analyses stratified by median IL-6 value. Out of the 244 post-MI patients in our analysis, 122 (50.0%) had log transformed values of baseline IL-6 less than or equal to the median value of 0.48. Those with low IL-6 levels were largely similar to those with high IL-6 levels in terms of age and income; however, there were some other key demographic differences. Those with higher IL-6 levels, were more likely to be female (59.0%) compared to those with lower levels (37.7%). Individuals with higher IL-6 levels were also less likely to be married (34.4%) compared to those with lower levels. Those with higher levels also were completed fewer years of school (13.4), on average, compared to those with lower levels (14.3).

Both groups had similar prevalence rates of depression and PTSD as well as similar mental health scores. Those with higher IL-6 levels did, however, have a higher average somatic depression score at baseline (6.6) compared to those with lower levels (5.1).

Cardiovascular risk factors differed in a few ways. Those with high IL-6 levels were more likely to have greater mean BMI (34.2) compared to those with lower IL-6 levels (28.9). They were also more likely to have ever smoked (63.9%) compared to those with lower levels (45.9%). Lastly,

those with higher levels had higher rates of diabetes (41.0%) compared to those with lower levels (24.6%).

Clinical characteristics including rates of history of prior MI, type of MI, and ejection fraction were similar between the two groups. History of congestive heart failure, however, was higher in those with higher levels of IL-6 (13.5%) compared to those with lower levels (4.3%). Medication use was also largely similar between the two groups with the exception of anti-depressant use. Those with higher levels of IL-6 were more likely to use antidepressants (21.5%) compared to those with lower levels of IL-6 (10.7%).

Bidirectional Exploratory Analysis Between Mental Health Scores and Inflammatory Biomarkers

Bivariate analyses revealed no significant associations between the levels of systemic inflammatory biomarkers at baseline and the change in various mental health scale scores overtime, with the exception of PTSD (Table 2a). For PTSD, only changes in re-experiencing PTSD symptoms were significantly associated with both CRP and IL-6 at baseline. A one unit increase in the natural log of CRP at baseline was associated with a 0.59-point increase in re-experiencing PTSD symptoms between baseline and follow-up. Similarly, a one unit increase in the natural log of IL-6 at baseline was associated with a 0.89-point increase in re-experiencing PTSD symptoms between baseline and follow-up.

For the opposite direction examining the association between mental health scores at baseline and changes in inflammatory marker levels over time (Table 2b), only re-experiencing PTSD symptoms at baseline were associated with changes in CRP levels overtime. A one-unit higher score in the participant's re-experiencing PTSD score at baseline was associated with a 426 unit increase in the change in CRP levels. The mixed model analyses yielded similar results. As preliminary findings provided little evidence to suggest associations between mental health scores

at baseline and changes in inflammatory markers, the rest of the analysis focused on associations between changes in PTSD and inflammatory biomarkers at rest.

Associations Between Baseline Inflammatory Markers & PTSD Symptoms – Multivariate Mixed Models Analysis

Table 3 lists the results of adjusted linear mixed models examining the association between inflammatory markers at baseline and changes in PTSD overall score and PTSD subscales. Models were conducted progressively adjusting for demographic factors, clinical severity, cardiac risk factors, and medications. The associations between overall PTSD score as outcome with either IL-6 and CRP at baseline were not significant for any of the models. When examining subscales, however, both IL-6 and CRP measured at baseline were associated only with changes in the re-experiencing PTSD subscale in models adjusted for more than just demographic factors (Table 3).

Stratified Analysis

Table 4 shows the results of stratified analysis. When stratified by race, baseline IL-6 was significantly associated with changes in both the overall PTSD score and re-experiencing symptoms among the Black stratum but not among the non-Black stratum (Table 4a). Race significantly interacted with IL-6 measured at baseline on the change in re-experiencing PTSD symptoms.

CRP was only significantly associated with a change in re-experiencing symptoms (but not the overall PTSD score) at baseline among those who identified as Black but not those who identified as non-Black (supplemental materials). Race significantly interacted with baseline CRP in association with changes in re-experiencing symptoms as the outcome of interest.

When stratified by sex, IL-6 at baseline was only found to be significantly associated with re-experiencing symptoms of PTSD among females but not males (Table 4b). CRP measured at baseline produced similar patterns to IL-6 measured at baseline when stratified by sex

(Supplemental). However, none of the interaction terms for sex with inflammatory markers were significantly associated with changes in PTSD scores or any of its subscales.

Stratifying by both sex and race, IL-6 at baseline was found to be significantly associated with changes in both overall PTSD score and re-experiencing symptoms only among Black females (Table 5). Similarly, baseline CRP yielded only a significant association with a change in re-experiencing symptoms among Black females, but not in any other strata.

Discussion:

This study sought to examine the association between inflammation and mental health symptoms in a younger population of MI patients. Specifically, we used regression models to investigate possible bidirectional associations between IL-6 and CRP (inflammatory markers) and several mental health subscales including depression, PTSD, perceived stress, and anxiety. This study showed that both IL-6 and CRP measured at baseline are significantly associated with a longitudinal increase in re-experiencing PTSD symptoms among a population of younger MI patients in the US. This association was found to be significant among females but not males and among Black individuals but not non-Black individuals. These findings were found to be independent of clinical and behavioral risk factors associated with inflammation. Though there is not yet consensus in the literature, findings are consistent with prior reports of increases in inflammation being associated with changes in mental health.

Research has implicated inflammation as an important mechanism linking mental health outcomes with increased CHD risk.[2,14–16,18,22] Many of these studies, mostly cross-sectional, found associations between depression and inflammation. In contrast, the present study did not find a significant association between inflammatory biomarkers and changes in depression scores in either direction. This may be influenced by our study population, which was comprised of a younger post-MI population whereas other studies have largely been conducted in older populations with CHD or in general populations.

Few studies have specifically examined the association between inflammation and PTSD. Lima et al. recently found that acute mental stress was associated with a larger increase in IL-6 among patients with PTSD compared to those without PTSD.[16] While in the present study we were not able to examine inflammatory responses to stress longitudinally, we found further evidence for the interconnection of PTSD with inflammation. Specifically, we found that a reverse direction

is also true, indicating that elevated IL-6 measured at baseline can worsen PTSD symptoms over time.

The reason why higher inflammation is related to an increase in re-experiencing PTSD symptoms after an MI requires further study. Each of the PTSD subscales (hyperarousal, re-experiencing, and avoidance/numbing symptoms) have each previously been described to have somatic components.[34] Previous studies have found inflammation to be associated with somatic symptoms of mental health, particularly depression.[18,20,21] In this sample, it is possible that re-experiencing symptoms may have been more somatic in nature compared to the other two subscales that lead to the association found in this study.

Previous studies examining PTSD particularly focused on it as a driving factor for increasing inflammation due to the effect it may have on the sympathetic nervous system as exemplified by Lima et al.[16] This is the first study looking at the other direction. We did find that the association was stronger in the opposite direction. Specifically, we found that, among PTSD symptom subtypes, baseline inflammatory levels were most robustly associated with changes in re-experiencing symptoms. This finding is consistent with other mental health factors, such as depression, where a bidirectional association has been established. The specific mechanism should be further investigated.

Stratified analyses revealed that inflammatory markers were significantly associated with changes in PTSD symptoms among females and Black individuals but not in males or White Individuals. Female and Black populations experienced effects greater in magnitudes than male and non-Black populations. The magnitudes of these effects differed significantly between racial categories, but not between sexes.

Previous studies have found that women and Black individuals have poorer mental health and higher levels of inflammation compared to their respective counterparts.[23,24] These adverse health outcomes may be partially explained by clustering of psychosocial stressors experienced

by these populations, namely sexism and racism.[7,23] Black women, in particular, could be doubly exposed to sexism and racism that may put them at increased risk of adverse health outcomes like those observed in this study.

Strengths and Limitations:

This study has some limitations. First, the current study lacks long-term follow-up data. Second, we focus on post-MI patients, a high-risk group with elevated prevalence rates of PTSD, thus the results may not be generalizable to non-MI populations. Third, many analyses were conducted, including associations between four different outcomes (i.e., PTSD score, re-experiencing symptoms, hyperarousal symptoms, and avoidance symptoms), with two different sets of exposures (i.e., CRP and IL-6 at baseline and follow-up), therefore potentially increasing Type 1 statistical error. However, it is reassuring that both inflammatory markers at baseline and follow up were consistently found to be associated with changes in re-experiencing PTSD symptoms.

Despite these limitations, our study has notable strengths. No previous study has examined longitudinal trajectories between inflammation and PTSD. The evidence of the associations between inflammation and changes in PTSD symptoms using two different models (general linear models and mixed linear models) supported one another. While there were a limited number of cases with a PTSD diagnosis in the study, we examined subjects' PCL-C score as continuous measure as well as the subscales to examine type of PTSD symptoms. Thirty-two individuals did not return at six months follow-up, however, a comparison of covariates revealed that those lost to follow up were largely similar to those who remained in the study, suggesting that selection bias is unlikely in our results.

Conclusion

In a cohort of younger survivors of a recent MI, IL-6 and CRP were significantly associated with an increase in re-experiencing PTSD symptoms between baseline and 6 months. When stratified by sex, this association was found to be significant among females but not males. Similarly, when stratified by race, this association was statistically significant among Black individuals but not non-Black individuals. These results are consistent with the possibility that an increased inflammatory response may be on the pathway between an MI and the development of PTSD, especially among Black individuals and women, however, further research is needed to better elucidate the complex relationship. Future studies should focus on the effects of varying distributions of inflammatory biomarkers and mental health scores in specific sub-populations, such as females and Black people. Further research should also examine more specific inflammatory pathways and the response to appropriate therapies. Additionally, researchers could test the clinical utility of specific interventions in prognosis among diverse groups of post-MI patients with PTSD. A finer understanding of the cellular and molecular mechanism between inflammation, mental health, and CHD may better inform prevention and treatment of CHD.

Table 1. Baseline Characteristics				
	Total N=244	Low IL-6 n=122	High IL-6 n=122	P-value
	n(%) or Mean(SD)			
Demographics				
Age, Years	50.8 (6.5)	50.8 (6.4)	50.8 (6.7)	0.991
Female	118 (48.4)	46 (37.7)	72 (59.0)	0.001*
Menopausal	63 (54.8)	27 (58.7)	36 (52.2)	0.491
Black Race	157 (64.3)	75 (61.5)	82 (67.2)	0.350
Married	101 (41.4)	59 (48.4)	42 (34.4)	0.027*
Income < 25K	87 (39.0)	39 (33.9)	48 (44.4)	0.107
Education, Years	13.8 (2.8)	14.3 (2.7)	13.4 (2.8)	0.013*
Psychosocial Risk Factors				
Current Depression Diagnosis	40 (16.6)	17 (14.1)	23 (19.2)	0.286
Beck Depression Inventory (BDI)	12.3 (10.5)	11.0 (9.6)	13.6 (11.1)	0.051
BDI – Somatic Score	5.9 (4.1)	5.1 (3.8)	6.6 (4.3)	0.004*
BDI – Cognitive-Affective Score	6.4 (7.0)	5.8 (6.4)	6.9 (7.5)	0.223
Current PTSD Diagnosis	31 (12.9)			
PTSD Score	32.4 (15.0)	31.9 (14.5)	32.8 (14.6)	0.620
PTSD – Reexperiencing Score	9.0 (4.8)	9.1 (5.1)	9.0 (4.5)	0.883
PTSD – Hyperarousal Score	10.3 (5.1)	9.9 (5.0)	10.7 (5.1)	0.209
PTSD – Avoidance Score	13.0 (.64)	12.9 (6.4)	13.1 (6.3)	0.778
Perceived Stress Scale Score	16.3 (.86)	15.6 (8.2)	16.9 (9.0)	0.275
State Anxiety Score	36.0 (13.0)	35.3 (12.8)	36.7 (13.3)	0.403
Cardiovascular Risk Factors				
BMI	31.5 (7.4)	28.9 (5.9)	34.2 (7.8)	<0.001*
Alcohol, No. Drinks per Week	2.9 (5.9)	3.3 (5.4)	2.5 (6.4)	0.358
Ever Smoker	134 (54.9)	56 (45.9)	78 (63.9)	0.005*
History of Hypertension	200 (82.0)	95 (77.9)	105 (86.1)	0.096
History of High Cholesterol	198 (81.2)	99 (81.2)	99 (81.2)	1.000
History of Diabetes	80 (32.8)	30 (24.6)	50 (41.0)	0.006*
Clinical Characteristics				
Congestive Heart Failure	21 (8.6)	5 (4.1)	16 (13.1)	0.012*
Ejection Fraction	50.3 (12.1)	41.5 (10.7)	49.1 (13.2)	0.127
Prior MI	47 (19.3)	24 (19.8)	23 (18.9)	0.846
STEMI	67 (27.5)	36 (29.5)	31 (25.4)	0.473
Medications				
Beta Blockers	207 (85.2)	104 (82.3)	103 (85.1)	0.979
Statins	203 (83.5)	105 (86.1)	98 (81.0)	0.286
Aspirin	198 (81.5)	103 (84.4)	95 (78.5)	0.235
ACE Inhibitors	113 (46.5)	55 (45.1)	58 (47.9)	0.656
Antidepressants	39 (16.1)	13 (10.7)	26 (21.5)	0.021*
Inflammatory Markers				
IL-6 at Rest (pg/mL)**	1.7 (0.1)	1.0 (0.0)	2.7 (0.1)	-
CRP at Rest (ng/mL)**	2646.6 (233.4)	1510.0 (164.3)	4638.9 (552.4)	-

* P-value less than 0.05

** Geometric mean, p-value not included as stratified by inflammation.

Table 2a: Bivariate general linear regression on change in outcome			
	Change in Outcome (f/u – bl)		
	Beta	**95% CI**	**P-val**
Baseline Predictor	**Total Depression (BDI-II)**		
Natural log of CRP	0.41	(-0.28,1.10)	0.242
Natural log of IL6	-0.39	(-1.94,1.17)	0.624
	Cognitive-Affective Depression Subscale		
Natural log of CRP	0.17	(-0.31,0.64)	0.494
Natural log of IL6	-0.20	(-1.27,0.89)	0.710
	Somatic Depression Subscale		
Natural log of CRP	0.29	(-0.01,0.58)	0.055
Natural log of IL6	-0.07	(-0.74,0.59)	0.825
	Overall PTSD Score (PSC-C)		
Natural log of CRP	0.68	(-0.26,1.63)	0.156
Natural log of IL6	1.98	(-0.12,4.08)	0.065
	Re-experiencing PTSD Symptoms Subscale		
Natural log of CRP	0.59	(0.25,0.92)	0.001*
Natural log of IL6	0.89	(0.13,1.65)	0.028*
	Hyperarousal PTSD Symptoms Subscale		
Natural log of CRP	0.19	(-0.14,0.51)	0.264
Natural log of IL6	0.82	(0.10,1.54)	0.026*
	Avoidance and Numbing Symptoms Subscale		
Natural log of CRP	0.00	(-0.43,0.44)	0.989
Natural log of IL6	0.28	(-0.69,1.25)	0.567
	Perceived Stress Scale		
Natural log of CRP	-0.12	(-0.68,0.45)	0.684
Natural log of IL6	-0.19	(-1.48,1.09)	0.765
	Total Anxiety Score		
Natural log of CRP	-0.14	(-1.09,0.81)	0.773
Natural log of IL6	-0.71	(-2.87,1.45)	0.519

*The natural logs of inflammatory markers were used as predictors of changes in mental health scores

Table 2b: Bivariate general linear regression on change in outcome			
	Change in Outcome (f/u – bl)		
	Beta	**95% CI**	**P-val**
Baseline Predictor	**CRP (ng/mL)**		
Depression	161.73	(-4.26,327.72)	0.056
Cognitive-Affective	219.16	(-29.50,467.82)	0.084
Somatic	409.00	(-11.46,829.47)	0.057
PTSD	101.56	(-16.90,220.01)	0.093
Re-Experiencing	426.07	(35.52,816.62)	0.033*
Hyperarousal	121.24	(-219.13,461.60)	0.483
Avoidance	249.71	(-29.62,529.04)	0.080
Perceived Stress Scale	32.02	(-169.20,233.24)	0.754
Anxiety	41.87	(-98.54,182.29)	0.557
	IL6 (pg/mL)		
Depression	0.01	(-0.01,0.03)	0.298
Cognitive-Affective	0.01	(-0.01,0.04)	0.343
Somatic	0.02	(-0.02,0.07)	0.298
PTSD	0.00	(-0.01,0.01)	0.835
Re-Experiencing	0.01	(-0.03,0.05)	0.699
Hyperarousal	0.01	(-0.03,0.05)	0.664
Avoidance	-0.00	(-0.03,0.03)	0.855
Perceived Stress Scale	0.01	(-0.02,0.03)	0.635
Anxiety	0.00	(-0.01,0.02)	0.844

*Difference of non-transformed values of inflammatory markers were evaluated as the outcome

Table 3: Mixed Model Analyses: Inflammation at baseline												
	Outcome											
	Total PTSD Score			**Re-experiencing Subscale**			**Hyperarousal Subscale**			**Avoidance Subscale**		
	Beta	**(95% CI)**	**P-val**	**Beta**	**(95% CI)**	**P-val**	**Beta**	**(95% CI)**	**P-val**	**Beta**	**(95% CI)**	**P-val**
Model 1: Demographics (age, sex, education, Black race)												
IL-6*Visit	1.38	(-0.87,3.63)	0.477	0.77	(-0.02,1.55)	0.056	0.51	(-0.31,1.34)	0.224	0.07	(-0.94, 1.09)	0.891
CRP*Visit	0.32	(-0.69,1.33)	0.533	0.48	(0.14,0.83)	0.007	-0.00	(-0.38,0.37)	0.983	-0.09	(-0.55,0.36)	0.686
Model 2: Demographics + Clinical Severity (Ejection Fraction, STEMI)												
IL-6*Visit	1.95	(-0.37, 4.27)	0.099	0.92	(0.01, 1.74)	0.027	0.70	(-0.16, 1.56)	0.112	0.37	(-0.69, 1.42)	0.492
CRP*Visit	0.23	(-0.81,1.26)	0.666	0.45	(0.09,0.81)	0.014	-0.06	(-0.44,0.33)	0.778	-0.12	(-0.59,0.35)	0.606
Model 3: Demographics + Severity + CV Risk Factors (BMI, SMOKE, DIAB, CHOL, HTN)												
IL-6*Visit	1.99	(-0.33, 4.30)	0.092	0.94	(0.12, 1.75)	0.025	0.71	(-0.15, 1.57)	0.104	0.38	(-0.67, 1.44)	0.473
CRP*Visit	0.21	(-0.83,1.25)	0.689	0.45	(0.09,0.81)	0.014	-0.06	(-0.45,0.32)	0.742	-0.13	(-0.60,0.34)	0.575
Model 4: Demographics + Severity + Risk Factors + Rx (Statins, Aspirin, Antidepressants)												
IL-6*Visit	2.04	(-0.29, 4.37)	0.086	0.95	(0.13, 1.77)	0.024	0.74	(-0.13, 1.60)	0.094	0.40	(-0.66, 1.46)	0.457
CRP*Visit	0.23	(-0.81,1.27)	0.663	0.46	(0.10,0.82)	0.013	-0.05	(-0.44,0.33)	0.784	-0.13	(-0.60,0.34)	0.594

Table 4a: Mixed Model Analyses Stratified by Race: (IL-6 at baseline)*Visit								
	Total PTSD Score				Re-experiencing Subscale			
	Beta	(95% CI)	P-value	Interaction P-value	Beta	(95% CI)	P-value	Interaction P-value
Model 1: Demographics (age, sex, education, Black race)								
Black	3.26	(0.16,6.35)	0.040	0.072	1.50	(0.40,2.61)	0.008	0.028
Non-Black	-0.87	(-3.93,2.20)	0.575		-0.29	(-1.31,0.73)	0.571	
Model 2: Demographics + Clinical Severity (Ejection Fraction, STEMI)								
Black	3.79	(0.63,6.94)	0.019	0.082	1.66	(0.53,2.79)	0.004	0.029
Non-Black	-0.40	(-3.56,2.76)	0.801		-0.22	(-1.28,0.83)	0.674	
Model 3: Demographics + Severity + CV Risk Factors (BMI, SMOKE, DIAB, CHOL, HTN)								
Black	3.85	(0.69,7.01)	0.017	0.069	1.69	(0.56,2.83)	0.004	0.024
Non-Black	-0.43	(-3.59,2.72)	0.784		-0.23	(-1.28,0.83)	0.667	
Model 4: Demographics + Severity + Risk Factors + Rx (Statins, Aspirin, Antidepressants)								
Black	3.84	(0.69,6.99)	0.017	0.085	1.69	(0.56,2.82)	0.004	0.027
Non-Black	-0.16	(-3.40,3.08)	0.920		-0.19	(-1.28,0.89)	0.723	

Table 4b: Mixed Model Analyses Stratified by Sex: (IL-6 at baseline)*Visit								
	Total PTSD Score				Re-experiencing Subscale			
	Beta	(95% CI)	P-value	Interaction P-value	Beta	(95% CI)	P-value	Interaction P-value
Model 1: Demographics (age, sex, education, Black race)								
Female	1.96	(-1.36,5.28)	0.245	0.835	1.26	(0.19,2.33)	0.021	0.356
Male	1.41	(-1.83,4.65)	0.391		0.47	(-0.76,1.70)	0.450	
Model 2: Demographics + Clinical Severity (Ejection Fraction, STEMI)								
Female	2.72	(-0.74,6.18)	0.122	0.706	1.44	(0.32,2.56)	0.012	0.323
Male	1.87	(-1.45,5.18)	0.268		0.63	(-0.64,1.90)	0.326	
Model 3: Demographics + Severity + CV Risk Factors (BMI, SMOKE, DIAB, CHOL, HTN)								
Female	2.78	(-0.68,6.24)	0.114	0.691	1.47	(0.35,2.59)	0.011	0.302
Male	1.84	(-1.47,5.15)	0.273		0.61	(-0.66,1.87)	0.344	
Model 4: Demographics + Severity + Risk Factors + Rx (Statins, Aspirin, Antidepressants)								
Female	2.83	(-0.68,6.33)	0.113	0.706	1.49	(0.36,2.63)	0.011	0.310
Male	1.96	(-1.35,5.27)	0.243		0.64	(-0.62,1.91)	0.316	

Table 5: Mixed Model Analyses: Stratified by Sex and Race – Exposure: (IL-6 at baseline)*Visit						
	Total PTSD Score			**Re-experiencing Subscale**		
	Beta (95%CI)	**P-value**	**Interaction**	**Beta (95%CI)**	**P-value**	**Interaction**
Model 1: Demographics (age, sex, education, Black race)						
Black Females	4.43 (0.16,8.70)	0.042	0.457	2.29 (0.87,3.71)	0.002	0.175
Non-Black Females	-2.40 (-7.37,2.57)	0.331		-0.58 (-1.96,0.79)	0.390	
Black Males	2.75 (-2.04,7.54)	0.255		0.75 (-1.10,2.61)	0.418	
Non-Black Males	-0.22 (-4.51,4.07)	0.918		0.16 (-1.43,1.75)	0.840	
Model 2: Demographics + Clinical Severity (Ejection Fraction, STEMI)						
Black Females	4.96 (0.60,9.33)	0.026	0.542	2.41 (0.95,3.87)	0.002	0.242
Non-Black Females	-1.56 (-6.88,3.76)	0.552		-0.47 (-1.94,0.99)	0.514	
Black Males	3.37 (-1.49,8.24)	0.171		1.02 (-0.86,2.90)	0.280	
Non-Black Males	-0.00 (-4.39,4.38)	0.998		0.17 (-1.47,1.81)	0.835	
Model 3: Demographics + Severity + Cardiovascular Risk Factors (BMI, SMOKE, DIAB, CHOL, HTN)						
Black Females	5.05 (0.67,9.41)	0.024	0.541	2.44 (0.97,3.90)	0.001	0.249
Non-Black Females	-1.47 (-6.79,3.84)	0.575		-0.43 (-1.90,1.04)	0.441	
Black Males	3.42 (-1.45,8.28)	0.165		1.04 (-0.84,2.92)	0.272	
Non-Black Males	-0.14 (-4.52,4.22)	0.945		0.09 (-1.55,1.72)	0.913	
Model 4: Demographics + Severity + Risk Factors + Rx (Statins, Aspirin, Antidepressants)						
Black Females	4.94 (0.58,9.31)	0.027	0.584	2.41 (0.95,3.87)	0.001	0.247
Non-Black Females	-1.08 (-6.69,4.53)	0.696		-0.43 (-1.99,1.12)	0.572	
Black Males	3.47 (-1.37,8.32)	0.157		1.06 (-0.81,2.94)	0.261	
Non-Black Males	0.12 (-4.30,4.54)	0.957		0.17 (-1.48,1.82)	0.837	

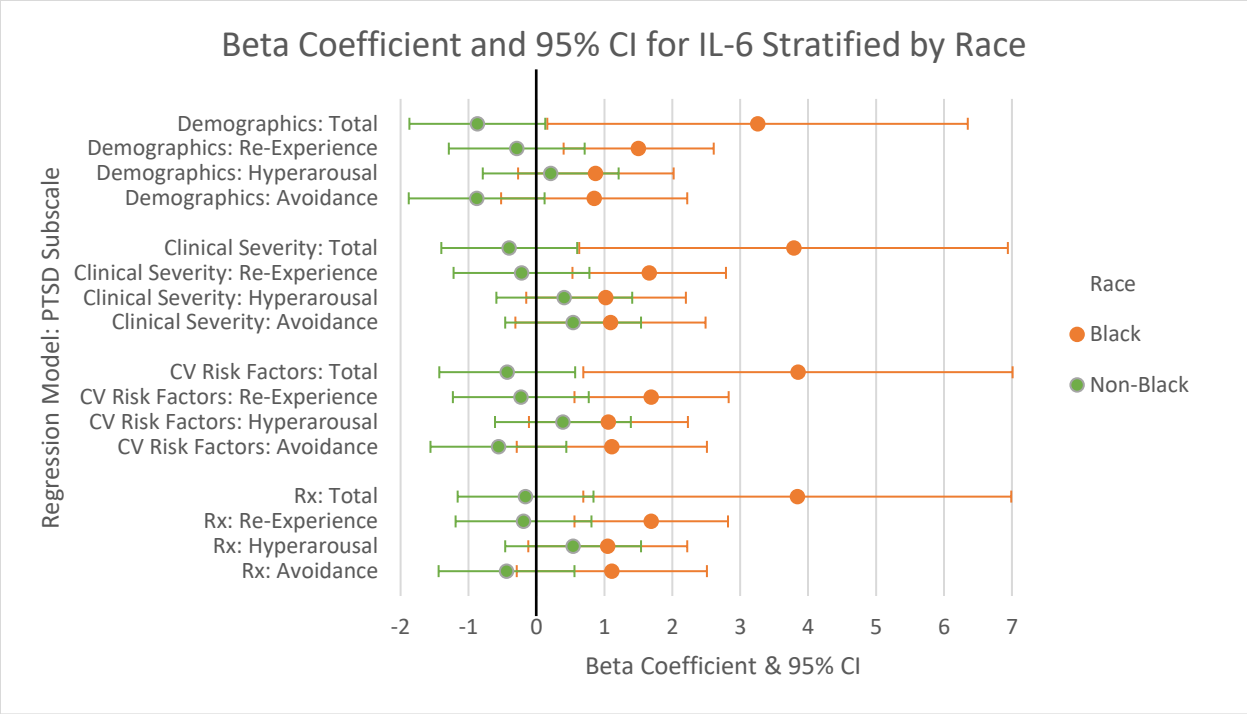

Figure 1: Beta Coefficient and 95% CI Stratified by Race

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