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Factors Associated with Myocardial Infarction Reoccurrence

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Abstract

Background: As recurrent myocardial infarctions (MIR) constitute almost a third of the annual MIs, identifying traditional and novel variables related to MIR is important.

Objective: The aim of this study was to examine modifiable cardiac risks, adiposity, symptoms associated with inflammation (fatigue, depression, sleep) and inflammatory cytokines and MIR by sex and race.

Methods: Using a cross sectional descriptive design, we recruited a convenience sample of adults (N =156) discharged with first MI or had MIR in the last 3 to 7 years. Surveys measured demographics, cardiac risk factors, depression, sleep, and fatigue. Anthropometric measures and cytokines TNFα, IL-6, and hsCRP were obtained. A maximum likelihood regression was calculated to predict MIR.

Results: The sample included 57% men and 30% Black participants, and the mean age was 65 years (SD = 12). The hsCRP was the only cytokine related to symptoms: fatigue (r= .309, p < .001) and depression (r = .255, p = .002). An MIR was not associated with race despite White participants reporting better sleep (t = −3.25 (146), p = .002), lower BMI (t = −3.49 (154), p = .001), and fewer modifiable risk factors (t = −2.05 (152), p = .04). An MIR was associated with being male, higher hsCRP and TNFα levels (p < .001), and higher inflammatory symptoms of fatigue (p = .04), depression (p = .01) and poor sleep (p < .001).

Conclusion: Further examination of biomarkers to understand the mechanisms associated with inflammatory symptoms of fatigue, depression, and poor sleep and MIR is needed.

Keywords

myocardial infarction recurrence; cytokines; fatigue; sleep; depression

Heart disease is a leading cause of death and disability in the United States, and the prevalence of myocardial infarction (MI) is greater than that of heart failure and stroke. Despite positive secondary prevention strategies post MI, including statin use and lifestyle changes, 32% of the annual MIs are recurrent.[1] Unfortunately, MI recurrence (MIR) differs

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by race and sex. More women (21%) ≥45 years of age will have a MIR or fatal coronary heart disease (CHD) within five years compared to men (17%). Blacks have a higher proportion of MIR than Whites with the highest proportional difference in the 65 to 74 years of age range (30% Black males to 12% White males; 30% of Black females to 17% White females).[1] Because an MI is associated with morbidity, such as heart failure,[2] understanding those at highest risk for MIR is important to employ interventions to prevent or delay MIR.

Differences in MIR by sex and race may be related to dissimilarities in modifiable cardiac risk factors. Women have higher body mass index (BMI) and higher dyslipidemia than men.[3] Compared to Whites, Black adults have more diabetes (13% vs. 9%);[4] hypertension (40% vs. 28%);[5] and obesity (36% vs. 24%).[6] However, 8 to 41% of persons experiencing an MI have no risk factors.[7] Thus, modifiable risk factors alone may not identify those at risk for MIR.

In addition to traditional modifiable risk factors, inflammation is associated with an increased risk for CHD. The primary cause of CHD is atherosclerosis, an inflammatory disease[8] involving low density lipoproteins (LDL) that contribute to the development of foam cells via macrophages. This process results in further inflammation affecting LDL movement and the binding of LDL to endothelium leading to the production of cytokines (e.g. interleukins [IL] and tumor necrosis factor [TNF]). An increase of one standard deviation from baseline of IL-6 and TNFα is associated with an MI or CHD related death.[9] Statins are effective in reducing LDL and the resultant inflammatory cascade.[10] Yet, only 40% of women (n = 34,589) and 34% of men (n = 87,869) have hyperlipidemia.[7] Thus, a large proportion of persons post MI may have unattenuated inflammation. Examining inflammation and correlates of inflammation may be important in understanding risk for MIR.

Obesity contributes to inflammation. Adipocytes produce adipokines which increase inflammation. Increased adipocytes result in a higher production of cytokines, chemokines, and acute phase proteins, specifically, IL-1β, IL-6, and TNFα.[11] Interleukin 6 and hsCRP are strongly correlated with body mass index[12] and waist circumference.[13]

Inflammation may be an important clinical indicator of post MI symptomology that would affect secondary prevention behaviors, such as participation in physical activity, as well as indicate those at highest risk for MIR. Symptomology associated with inflammation includes increased fatigue, depression, and poor sleep. This symptom cluster, deemed sickness syndrome, is associated with a brain-mediated response to inflammation.[14,15]

Pro-inflammatory cytokines have catabolic influence on skeletal muscle,[16] and prolonged exposure may contribute to fatigue in adults. Fatigue that persists post MI is a significant problem as up to 77%[17] report fatigue 6 to 12 months post MI. Both men and women report similar levels of fatigue post MI,[17] and these levels are comparable to cancer fatigue.[18,19] Thus, fatigue post MI may be associated with inflammation.

Although depression and fatigue are related,[17,20] research indicates that they are distinct.[21,22] The connections between depression and cardiovascular disease (CVD) are not fully understood. Both the SADHART (testing sertraline compared to placebo), ENRICHD

(testing cognitive behavioral-therapy combined with SSRI when indicated compared to usual care), and other trials have demonstrated a decrease in depression following intervention, but there was no benefit for cardiac morbidity or mortality.[23] Depression in adults has been associated with inflammatory markers,[24] specifically IL-6, and hsCRP, but inflammation explained a small portion of depression and CVD incidence.[25] Examining depression as a component of sickness syndrome associated with inflammation and MIR is important.

Poor sleep, including disturbed sleep, prolonged and shortened sleep, and insomnia may also be associated with MIR. About 50 to 70 million Americans suffer from sleeping issues.[26] Sleep disturbances activate inflammation pathways and increase IL-6, hsCRP, and/or TNFα.[27–29] Women with long sleep durations have higher hsCRP after adjusting for covariates, and higher hsCRP levels were associated with less than five hours of sleep in Black adults.[30] More Black adults report short sleep duration (<7 hours) than White adults (46% vs. 33%).[31] Insomnia symptoms, especially difficulty initiating sleep, are associated with acute MI in both men and women and may increase the risk of MI by 27 to 45%.[32] Those with insomnia had about twice the incidence (2.25 versus 1.08 per 1000 person-years) of acute MI as those without insomnia. However, little is known about poor sleep and MIR.

Identifying specific variables or groups of variables related to MIR that are amenable to monitoring and secondary prevention interventions are important in reducing the number of recurrent MIs. The purpose of this study was to examine modifiable cardiac risks, adiposity, inflammatory symptoms of fatigue, depression, poor sleep, and inflammatory cytokines in those with and without MIR by race (White and non-White) and sex. Research questions were: (1) Are there differences by sex and race in cardiac risks, adiposity [waist hip ratio, BMI], fatigue, depression, sleep and inflammatory cytokines [TNFα, IL-6, hsCRP], in those who have MIR and those without MIR?; and (2) Which factors (modifiable cardiac risks, adiposity [waist hip ratio, BMI], fatigue, depression, sleep and inflammatory cytokines [TNFα, IL-6, hsCRP]) are most strongly related to MIR?

Methods

Design

We used a cross-sectional descriptive design to address the research questions. A convenience sample of 156 participants were recruited from two medical centers that are part of different healthcare systems in the southeastern United States. Both medical centers served as regional referral centers for underserved and high minority populations. Participants included English speaking adults over the age of 25 discharged within the last 3 to 7 years with a medical diagnosis of MI. We excluded those who took antidepressant medication for depression for less than 3 months, scored 6 or above on the Abbreviated Mental Test, had major surgery requiring an overnight hospital stay within the last six months, and self-reported having a diagnosis of multiple sclerosis, HIV/AIDS, chronic fatigue syndrome, or rheumatoid arthritis. In this region, 19% of discharges with a diagnosis of MI were Black. To obtain adequate representation, we oversampled to achieve a minimum of 30% Black participants. Institutional Review Board approval was obtained from the university and both medical centers.

Measures

Cardiac risk.—Data were collected 3 to 7 years after discharge from the hospital with either a first MI or a recurrent Ml. Because the hospital medical record may not accurately reflect current comorbidities 3 to 7 years after discharge, self-reported comorbidities were measured by adapting and combining the Chronic Disease Score[33,34] and the Charlson Comorbidity Index.[35] The Chronic Disease Score tool lists 17 chronic (comorbid) conditions, including conditions found associated with cardiac risk in the literature. To capture all pertinent comorbidities, we added five from the Charlson Comorbidity Index that were not listed on the Chronic Disease Score that included: peripheral vascular disease, cerebrovascular disease, liver disease, hemiplegia, and renal disease. These data were collected and recorded on the investigator developed Demographic Health Status (DHS) form which also included questions related to physical activity and smoking. In addition, height and weight were measured using standardized equipment and procedures. Cardiac risk was calculated by summing the presence of the following modifiable risk factors: hypertension, hyperlipidemia, current smoker, diabetes, obesity (BMI ≥ 30), and low physical activity (range from 0 to 6).

Adiposity.—Adiposity was determined using two measures: waist hip ratio (WHR) and BMI. We used girth and hip measurements to calculate the WHR using the formula: waist circumference/hip circumference. A Gulick tension tape measure was used to assess circumferences. We calculated BMI using the formula: weight in kilograms/height in meters squared.

Fatigue.—Fatigue was measured using the Revised Piper Fatigue Scale (RPFS).[36] This 22-item tool measures four dimensions of fatigue on a 0 to 10 Likert scale. A total fatigue score was calculated by adding scores for the 22 items and dividing by 22. Scores range from 0 to 10 with higher scores reflecting more fatigue. Reliability and validity for this scale are moderate to strong.[36] In this study, we noted a Cronbach alpha of .95 for the total fatigue score.

Depression.—Depression was measured using the Center for Epidemiologic Studies Depression Scale (CES-D).[37,38] The CES-D was chosen as the depression measure because (a) it is a 20-item scale (4 possible responses, 0 to 3, for each question and total possible scores of 0–60) with only one question that may be related to fatigue, tiredness, or energy: “I could not ‘get going’”; (b) it is suitable for both men and women and minorities; and (c) it has good internal consistency and acceptable test-retest reliability. A score ≥ 16 indicates a high level of depression. Cronbach’s alpha for this study was .90.

Sleep.—We used the Pittsburgh Sleep Quality Index (PSQI) to measure sleep. This tool is a self-rated questionnaire with 19 items yielding seven sleep components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction. The sum of the components provides a global score with higher scores indicating worse sleep quality. Global PSQI score greater than five had 89.6% sensitivity and 86.5% specificity in identifying poor and good sleepers.[39] The global

score test-retest reliability is .87 and is valid in those with primary insomnia.[40] In this study, internal consistency was .75 for the global score.

Inflammation.—Two cytokines (IL-6, TNF-α) were analyzed using ELISA kits from R&D Systems, Inc., Minneapolis, MN, and hsCRP was measured in plasma using ELISA kit Quantikine Colorimetric Sandwich #DHSCRP00. The minimum detectable concentration for this assay is 0.010 ng/ml with a precision inter-assay of <6.5%, and intra-assay variation of <5.5% according to the manufacturer's product information.

Procedures

Site collaborators, employees of the medical centers, obtained a list of all adults discharged within a medical diagnosis of MI according to ICD codes 3 to 7 years prior to data collection (2011–2014) and meeting the inclusion criteria. The site collaborator contacted those on the list by telephone to explain the study and ascertain interest. Those agreeing to be contacted by study personnel (N = 178) were screened by telephone for eligibility, and a time for data collection was scheduled for those who were eligible. Fourteen refused to participate due to family caregiving responsibilities, traveling, or hospitalizations and eight met the exclusion criteria. Data were collected at a location convenient for the participant to minimize barriers such as transportation and facilitate recruitment. After completing informed consent, the DHS form, including the PSQI, were completed. Next, the anthropometric measures were assessed, and a venous blood sample was collected. Timing of this was scheduled to allow for observation of abnormal bleeding as many participants were prescribed medication that affected clotting. Specimen collection, preparation, and handling followed standard guidelines. Venous blood samples were centrifuged at ~1200 × g in a portable centrifuge, plasma was transferred in aliquots into ~6 prelabeled cyrovials and placed on ice in a portable refrigerator until stored. All samples were stored in a −20C freezer until analyses. Lastly, participants completed the RPFS and the CES-D. At the completion of all study components, participants received a monetary incentive of $50.

Data Analyses

Descriptive statistics were used to characterize the sample. Missing data were addressed using standard substitution or imputation methods. Distributions were assessed for normality, with transformation and truncation used as appropriate. A P value of .05 was used for statistical significance. The researchers used the "lavaan" package within the R statistical software. A maximum likelihood (ML) regression was used to calculate a multivariate regression path analysis to predict MIR, sex, and race from modifiable cardiac risk factors, adiposity, BMI, fatigue, depression, sleep, TNFα, IL-6, and hsCRP. There is no overall test of model fit for ML regression. A ML multiple regression allows for all the residuals to covary and allows for more accurate estimates.

Results

The final sample (N = 156) was comprised of 57% men (n = 89), 30% Blacks (n = 46), and 68% Whites (n = 106). Four participants identified as "other race." Ages ranged from 34 to 92 (M = 65; SD = 12). Most were married (n = 96; 62%), and 51% had a high school

education or less. Almost a third (31%) had an average annual household income of $20,000 or less. Most of the sample (65%; $n = 102$) had experienced only one MI. Over half of the sample continued to experience fatigue (56%) post MI, 14% had no depression, and 34% had a PSQI score < 5 indicating good sleep. The hsCRP was the only cytokine significantly associated with the symptoms of fatigue ($r = .309$; $p < .001$) and depression ($r = .255$; $p = .002$). Whites reported better sleep ($t = -3.35$ (146); $p = .002$), had lower BMI ($t = -3.49$ (154); $p = .001$), and fewer modifiable cardiac risk factors ($t = -2.05$ (152); $p = .04$). The only variable to differ by sex was WHR, with women having higher WHR than men ($t = 5.35$; (154); $p < .001$) (see Table 1).

A ML multiple regression analysis was calculated to predict MIR, sex, and race from the variables (see Figure 1). Three paths were significant by race: modifiable cardiac risk factors ($p = .01$), BMI ($p < .001$), and PSQI ($p = .01$). Only WHR was significant by sex ($p < 001$). The inflammatory symptoms of fatigue ($p = .04$), depression ($p = .01$) and sleep ($p < .001$) all significantly related to MIR with depression having the highest influence ($\beta = 2.58$). Two cytokines, TNFα ($p < .001$) and hsCRP ($p < .001$), also influenced MIR. Male sex was associated with MIR ($\beta = -.48$), but race was not associated with recurrence. All regression coefficients are summarized in Table 2.

Discussion

The proportion of those in this study with MIR recurrence was similar to the national proportions of 33%.[1] The association of male sex to MIR may be related to men having their first MI at younger ages than women. Lundblad and colleagues[41] noted that although the trend for experiencing a recurrent MI is decreasing in both men and women over time, compared to women, a greater proportion of men experience MIR. These differences may be attributed to modifiable cardiac risk factors that account for over 90% of MI risk.[42] Interestingly, in our study there was a difference in adiposity (WHR) but not modifiable cardiac risk factors by sex.

Increased adiposity is associated with inflammation. Our finding of significant sex differences in WHR, with women having a higher WHR, is similar to a recent study.[43] However, in this study increased abdominal obesity after having a MI was noted in both sexes. A greater waist circumference was independently associated with a recurrent cardiovascular event especially in men. This study along with others have suggested the use of both BMI and WHR to identify those at highest risk.[43–45] However, these studies had measures for risk of coronary artery disease, not specifically MIR. These results support the multiple measures of adiposity to understand risk of MIR.

Race did not contribute to MIR in this sample. Differences were noted by race in modifiable cardiac risk factors, BMI, and sleep with the greatest association of race with BMI. Yet, these differences did not yield differences in MIR. Similarly, another study did not find differences in MIR by race but did note that cardiovascular risks of hypertension, hypercholesterolemia, and current smoking all significantly contributed to MIR.[46] A recent study[47] noted that 1- and 5-year mortality rates were higher for Blacks compared to Whites, but reported that these differences were a marker for other factors such as socioeconomic,

psychosocial, and health status. Of these factors, socioeconomic status was the strongest differentiator between Blacks and Whites. Thus, results from this study should be used with caution as there was a smaller proportion of non-White participants and socioeconomic status was not included in the model.

The three symptoms associated with inflammation were all associated with MIR. The strongest association was with depression. Because we did not ascertain disease severity or onset of depression in this sample, it is difficult to understand the pathology of depression post MI. Following an MI, depression has been associated with an increased risk of cardiovascular events and death.[48] Further, data from studies suggest depression may be related to obesity,[49,50] inflammation,[51,52] and insufficient sleep.[53,54] Similarly, in the current study, MIR was significantly related to depression, inflammation, and sleep, whereas obesity was only significantly associated with race. Research to understand the relationships of obesity to inflammation and depression as a risk for MIR is warranted.

Poorer sleep was also associated with MIR, and we found significant associations between sleep by race and MIR. These results were supported by previous studies noting sleep disturbance by race. Grandner et al.[30] reported that non-White participants who obtained less than 5 hours of sleep and 8 hours of sleep had greater levels of hsCRP. Consequently, poorer sleep was associated with inflammation and increased cardiovascular risk. Although there was no association with sleep and hsCRP in this study, both were significantly related to MIR. Alcántara et al.[55] found that shorter sleep, less than 7 hours of sleep, was associated with a 1-year risk of recurrent acute coronary syndrome including MI. While the current study addressed poor sleep with MIR, most studies focus on sleep and primary MIs. Further research is needed to understand sleep and other symptoms associated with inflammation and MIR.

Fatigue was prevalent in this study 3 to 7 years post MI with 56% continuing to report fatigue. Most studies of fatigue and MI do not address MI recurrence.[56–58] In contrast to our findings, Johansson et al.[59] reported that fatigue did not correlate with a previous MI. While the presence of fatigue as a prodrome to an MI has been identified for women,[60,61] little is known about fatigue and MIR. Furthermore, because the current study sample was comprised of 57% men and being a male was associated with MIR, additional research is needed to understand fatigue as a prodrome to MIR.

All of the symptoms associated with sickness syndrome - fatigue, depression, and poor sleep[14] were significant in our model with MIR. Only two of the cytokines, hsCRP and TNFα, were associated with MIR. Downstream hsCRP was the only cytokine associated with the symptoms of depression and fatigue. The association of hsCRP to MIR 3 to 7 years post MI is consistent with a study reporting that concentrations of hsCRP over 4 years is similar to concentrations of total cholesterol over the same time period and is as predictive of cardiovascular events as cholesterol.[62] The association of TNFα with MIR after primary MI in our study is similar to findings from a study examining TNFα in those post MI without clinical evidence of heart failure. In this study, investigators[63] found that TNFα collected on average nine months after MI was associated with increased risk of recurrent cardiac events, and those with TNFα in the highest level had a 3 fold increased

risk for recurrent MI. While we know inflammatory cytokines are associated with risk of cardiovascular events and a one standard deviation higher baseline level for IL-6 and TNFα is associated with 10 to 25% higher risk of MI or death,[9] no studies were found examining the relationship of inflammation to symptoms of fatigue, depression and poor sleep to MIR.

Pharmacological interventions to attenuate inflammation post MI have had mixed results. The CANTOS trial[64] testing the efficacy of Canakinumab, a IL-1B blocker, in reducing cardiovascular events has demonstrated a reduction in events independent of lipid levels in reducing hsCRP. However, the Cardiovascular Inflammation Reduction Trial testing the efficacy of methotrexate in reducing cardiovascular events post MI did not note a benefit in reducing hsCRP, IL-6, or IL-1β nor in affecting cardiovascular outcomes.[65] Most recently a trial to test the effect of colchicine[66] on reducing cardiovascular events 2 years post MI noted a reduction in stroke and hospital visits compared to placebos. Differences in these results may be related to the complexity of the inflammatory cascade, the heterogeneity in post MI pathology, and the length of follow up.[67,68]

This study provides important preliminary understanding of symptoms of inflammation and biomarkers of inflammation in relation to MIR. Further examination of biomarkers to understand the mechanisms associated with inflammatory symptoms of fatigue, depression, and poor sleep as related to MIR are needed.[69] Results of this study supported inflammation as important in MIR 3 to 7 years post MI. The symptoms associated with inflammation were also significantly related to MIR. In fact, symptoms related to MIR were more important than modifiable cardiac risks. Our findings noted the continuation of fatigue, depression, and poor sleep 3 to 7 years post MI. In addition to increasing associations with MIR, this is concerning as these symptoms may affect quality of life and participation in physical activity at levels to provide cardiovascular benefit.

Limitations

While the symptoms of sickness syndrome - fatigue, depression, and poor sleep- were all related to MIR in this study, findings should be interpreted with caution as these data were cross sectional. Further, other variables not collected in this study may have influenced the findings. Despite these limitations, this study provides support for clinicians to examine symptoms associated with inflammation when identifying those who may be at risk for MIR.

Conclusion

The purpose of this study was to examine factors associated with MIR by sex and race. The symptoms of sickness syndrome including fatigue, depression, and poor sleep along with two biomarkers, TNFα and hsCRP, and being male were all related to MIR. In our sample, symptoms related to MIR were more important than modifiable cardiac risks. These findings suggest addressing other factors associated with MIR. To affect the proportion of MIR, additional research is needed to understand the importance of inflammation and the symptoms of fatigue, depression and poor sleep in identifying those at highest risk for a recurrent cardiovascular event and developing targeted interventions to delay or prevent MIR.

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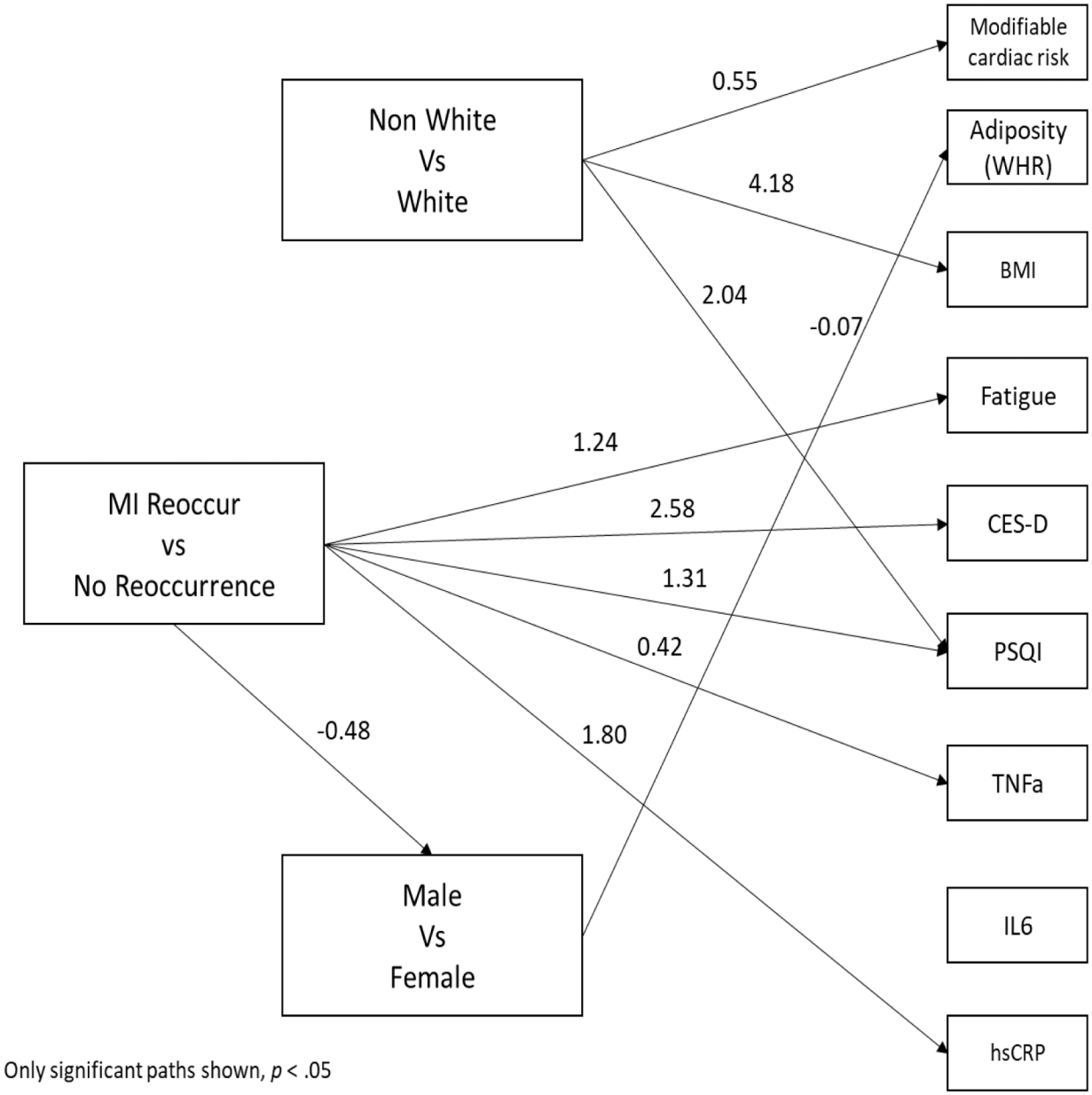

Figure 1.
ML Multiple Regression to Predict MIR, Sex, and Race from the Variables

Table 1.

Results of Descriptives and Differences of Variables by Sex and Race (N = 156)

Variables	Descriptives		Sex (Female vs Male)			Race (Other vs White)		
	M	*SD*	*t*	df	*p* value	*t*	df	*p* value
Modifiable Cardiac Risk	3.03	1.22	−.371	152	.711	−2.048	152	.044*
Adiposity (WHR)	38.11	43.4	5.35	154	<.001*	−.024	154	.981
BMI	31.10	7.34	−.468	154	.641	−3.49	154	.001*
RPFS	47.7	55.06	.127	154	.899	−1.561	154	.122
CES-D	8.86	9.81	−1.73	153	.086	−1.622	153	.108
PSQI	6.97	3.86	−1.39	146	.165	−3.25	146	.002*
TNFα	1.64	1.96	−.498	149	.619	−.329	149	.743
IL-6	3.18	2.38	−1.34	149	.182	−1.579	149	.118
hsCRP	5.14	7.56	−.275	149	.784	−.257	149	.797

Note:

* $p < .05$

Table 2.

Results of ML Multiple Regression by MIR, Sex, and Race

Variables	MI Reoccur Vs No Reoccurrence			Female vs Male			Other vs White		
	β	***SE***	***p***	***β***	***SE***	***p***	***β***	***SE***	***p***
Modifiable Cardiac Risk	0.04	0.12	0.73	−.046	0.21	0.828	0.55	0.21	0.01*
Adiposity (WHR)	0.00	0.01	0.70	−0.07	0.02	0.00*	0.02	0.02	0.32
BMI	0.42	0.64	0.48	0.51	1.20	0.67	4.18	1.28	<.001*
RPFS	1.24	0.60	0.04*	−0.08	0.98	0.94	0.92	1.12	0.41
CES-D	2.58	1.05	0.01*	3.25	1.72	0.06	2.05	1.86	0.27
PSQI	1.31	0.40	<.001*	1.08	0.66	0.10	0.55	0.21	0.01*
TNFα	0.42	0.09	<.001*	0.31	0.53	0.55	0.13	0.53	0.81
IL6	0.20	0.24	0.40	0.49	0.49	0.32	0.72	0.46	0.12
hsCRP	1.80	0.63	<.001*	1.04	1.69	0.54	0.03	2.10	0.99
MI Reoccur	---	---	---	−0.48	0.23	0.04*	0.10	0.24	0.69

Notes. N = 156, Male is coded as 0, Female is coded as 1, White is coded as 0, Other is coded as 1