Effects of Gender-Specific Differences, Inflammatory Response, and Genetic Variation on the Associations Among Depressive Symptoms and the Risk of Major Adverse Coronary Events in Patients With Acute Coronary Syndrome

Jennifer Sanner, PhD, RN^{1,*}, Megan L. Grove, MS^{2,*}, Erica Yu, PhD, RN, ANP¹, F. Gerard Moeller, MD³, Stanley G. Cron, MSPH⁴, Eric Boerwinkle, PhD^{2,5}, Alanna C. Morrison, PhD², and Lorraine Frazier, PhD, RN, MS, FAHA, FAAN¹

Abstract

Depressive symptoms independently contribute to major adverse coronary events (MACEs), with the biological immune response to depression being a likely mediator of this relationship. To determine whether genetic- and/or gender-specific phenotypic differences contribute to associations among depressive symptoms, inflammatory response, and risk of MACE in patients with acute coronary syndrome (ACS), we conducted a prospective study of 1,117 ACS patients to test a gender-specific model in which depressive symptoms (Beck Depression Inventory-II [BDI-II]) are associated with risk of MACE. Cox proportional hazards models were used to model time to incident MACE and determine whether single-nucleotide polymorphisms (SNPs) in specific inflammatory protein-coding genes and depressive symptoms interact to influence levels of inflammatory proteins or risk of MACE. Females had significantly higher high-sensitivity C-reactive protein and monocyte chemoattractant protein-1 levels. Depression status differed by gender (29.9% of females and 21.1% of males had BDI-II scores indicative of depression [$p = .0014$]). Depressive symptoms were associated with MACE; however, the interaction between these symptoms and gender was not significant. SNPs and depressive symptoms did not interact to influence inflammation or MACE. More females than males had BDI-II scores indicative of depression, yet the association between positive depressive symptom status and MACE did not vary by gender. Nor did the SNPs interact with depressive symptoms to influence inflammation or MACE. It remains of interest to identify a high-risk subgroup of ACS patients with genetic polymorphisms that result in immunoinflammatory dysregulation in the presence of depressive symptoms.

Keywords

depression, major adverse coronary events, gender, inflammation, genetics

Comorbid depression is common in patients with acute coronary syndrome (ACS). Researchers have identified an association between the risk of cardiac mortality and morbidity and depressive symptoms even after adjusting for potentially confounding variables including cardiac disease severity (Feng et al., 2016; Meijer et al., 2013). Biological mechanisms, including immunoinflammatory dysregulation, likely act as mediators in the association between depressive symptoms and major adverse coronary events (MACEs; Aydin Sunbul, Sunbul, & Gulec, 2017). The potential role of inflammatory triggers as promoters of MACE suggests that the investigation of depressive symptom-related inflammatory response will be a fruitful area for research in the vulnerable ACS population.

The heightened expression of inflammatory proteins, including E-selectin (SELE), monocyte chemoattractant

¹ The University of Texas Health Science Center at Houston, Cizik School of Nursing, Houston, TX, USA

² Human Genetics Center, Department of Epidemiology, Human Genetics, and Environmental Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA

³ The Virginia Commonwealth University, Richmond, VA, USA

⁴ Center for Nursing Research, The University of Texas Health Science Center at Houston, Cizik School of Nursing, Houston, TX, USA

⁵ Human Genome Sequencing Center, Baylor College of Medicine, Houston, TX, USA

*These authors contributed equally to this work.

Corresponding Author:

Jennifer Sanner, PhD, RN, The University of Texas Health Science Center at Houston, Cizik School of Nursing, 6901 Bertner Ave., Suite 580 D, Houston, TX 77030, USA.

Email: jennifer.e.sanner@uth.tmc.edu

protein-1 (MCP-1), high-sensitivity C-reactive protein (hs-CRP), and interleukin 6 (IL-6), among some individuals with depressive symptoms may contribute pathologically to the risk of subsequent MACE in a high-risk subgroup of patients with ACS and comorbid depressive symptoms (Eyre et al., 2016; Frazier, Vaughn, Willerson, Ballantyne, & Boerwinkle, 2009; Howren, Lamkin, & Suls, 2009; Leonard, 2018). Specifically, immuno-inflammatory dysregulation may mediate the association between depressive symptoms and risk of MACE in patients with ACS. For example, in a study of 490 patients who had undergone coronary stenting, investigators discovered that as levels of hs-CRP and MCP-1 increased, so did the risk for subsequent MACE (Frazier et al., 2009). Patients in Frazier et al.'s study who reported feelings of sadness or depression over the majority of the past year were almost twice as likely to develop MACE as were patients who did not report such feelings. When the investigators removed inflammatory protein levels from the analysis, reported feelings of sadness or depression were of great significance in predicting MACE over the 24-month period following the coronary stenting ($p = .0176$), suggesting that inflammatory proteins partially mediate the relationship between depressive symptoms and risk for MACE.

While some studies have indicated a link between depressive symptoms and immunoinflammatory dysregulation, which patients with depressive symptoms in the context of ACS are at heightened risk of depressive symptom-related inflammatory response and subsequent MACE remains unclear. For example, in a study of patients with stable cardiovascular disease (CVD), women without depressive symptoms had substantially lower cardiovascular risk compared to men without depressive symptoms; however, cardiovascular risk in women became similar to that in men as the frequency of depressive symptoms increased (Guimaraes et al., 2017). One possible explanation for this finding involves gender-specific immunoinflammatory dysregulation in response to increasing depressive symptom severity (Birur, Amrock, Shelton, & Li, 2017). Gender-specific knowledge is necessary to determine the role of gender-specific contributors to cardio-vascular health and disease.

Although authors have proposed many inflammatory protein pathways that might mediate the association between depressive symptoms and subsequent MACE in patients with ACS, our aim in the present study was to focus on those proteins (SELE, MCP-1, hs-CRP, and IL-6) that have been shown by extensive research to be involved with both coronary plaque rupture and depressive symptoms (Danner, Kasl, Abramson, & Vaccarino, 2003; Lespérance, Frasure-Smith, Thérioux, & Irwin, 2004; Miller, Freedland, Duntley, & Carney, 2005; Pace et al., 2006) and to have polymorphisms in or near the protein-coding gene that influences protein levels (Connelly et al., 2008; Ray, Camp, Bennett, Francis, & Crossman, 2002; Srikanth Babu et al., 2012). The purpose of the present study was to determine whether gender-specific phenotypic and genetic differences exist in the associations among

depressive symptoms, inflammatory response, and risk of MACE in patients with ACS. We hypothesized that inherent variations in inflammatory protein levels and risk of MACE in response to depressive symptoms are gender-specific and genetically influenced in patients with ACS. Our hope was that our findings might explain why some, but not all, patients with ACS and comorbid depressive symptoms develop MACE. Given a gene–environment (inflammatory response–depressive symptoms) interaction effect on inflammatory protein levels and risk of MACE, measurement of genetic variation in related inflammatory protein-coding genes among ACS patients with depressive symptoms may allow for the identification of a genetic marker(s) for those with depressive symptoms who are at an increased risk of subsequent MACE. The discovery of a relationship among depressive symptoms, inflammatory response, and MACE in certain at-risk patients with ACS would provide the rationale for changing nursing practice to target this high-risk subgroup for individualized depression interventions using inflammatory proteins as a therapeutic target.

Material and Method

Design and Sample Selection

The Committee for the Protection of Human Subjects, which serves as the institutional review board for the University of Texas Health Science Center at Houston, approved this research (protocol #HSC-SN-08-0173). All participants provided written informed consent to participate in genetic studies, and we followed ethical standards to protect human subjects in the conduct of this research in a manner consistent with the declaration of Helsinki.

We recruited participants for this study from two large, tertiary care, teaching facilities in the Texas Medical Center, which is located in southeast Houston. Patients hospitalized with confirmed ACS based on discharge diagnosis were eligible for the study, which is a substudy of the TexGen cohort described elsewhere (Virani et al., 2012). Researchers collected interview and clinical data upon study entry at the time of hospitalization, and annual follow-ups of outcomes included telephone interviews as well as mailed surveys. Enrollment began in 2007, and the final date of longitudinal data collection was in 2013.

Investigators defined ACS as hospitalization for chest pain or symptoms suggestive of ACS, with new transient or persistent ST segment electrocardiogram changes and ultimate disposition as acute myocardial infarction (AMI), unstable angina, or angina requiring revascularization. Nonfasting, venous blood samples were collected during hospitalization at a time that, if possible, was convenient for the research participant (e.g., along with scheduled clinical blood draws). However, because several factors can increase inflammatory protein levels in patients with ACS including clinical interventions, it was important that researchers collect venous blood samples prior to any clinically invasive cardiac intervention (Wu et al.,

2016). Inflammatory protein levels are also affected by numerous acute and chronic inflammatory conditions (e.g., infections [Woods, 2000], malignancies [Smith & Missailidis, 2004], active inflammatory diseases [Playford & Ghosh, 2005], and dialysis [Memoli et al., 2004]); thus, patients with such conditions noted in the electronic health records or determined by self-report were excluded from enrollment. Patients being treated with immunosuppressants or systemic steroids or who had undergone antibiotic therapy within the past 2 months were also excluded. A total of 1,199 consenting patients with ACS met the criteria described above.

Laboratory Measurements and Quality Control

Detailed laboratory methods are provided in the Online Supplementary Appendix A: Supplementary Methods. Briefly, we selected single-nucleotide polymorphisms (SNPs) in the following four inflammatory protein-coding genes: interleukin 6 (*IL6*), C-reactive protein (*CRP*), selectin E (*SELE*), and C-C motif chemokine ligand 2 (*CCL2*). We used a combined approach to identify common variation in the genes of interest with a focus on SNPs with previous evidence from genome-wide association studies, those that tagged common haplotypes, and those that demonstrated putatively functional significance.

DNA isolated from whole blood samples was used for genotyping with the MassARRAY[®] system (Agena Biosciences, San Diego, CA, USA) as instructed by the manufacturer (<http://agenabio.com/>). Quality control analyses are described in Online Appendix A. The final genetic data set consisted of 1,198 individuals and 131 SNPs. A list of all SNPs genotyped are detailed in the Supplementary Table S1. The SNP counts by gene and functional prediction are described in Supplementary Table S2.

We measured levels of the following four inflammatory proteins in plasma by parameter human enzyme-linked immunosorbent assay at the Atherosclerosis Clinical Research Laboratory at the Baylor College of Medicine: SELE, MCP-1, hs-CRP, and IL-6.

Phenotypes

Depressive symptoms. To measure depressive symptoms, we used the Beck Depression Inventory-II (BDI-II; Steer, Rissmiller, & Beck, 2000), which the research nurse administered within 5 days of hospital admission for ACS when patients were stable. The BDI-II is a self-report instrument used to assess the existence and severity of depressive symptoms as listed in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (American Psychiatric Association, 2000; Steer et al., 2000). The instrument asks a respondent to score each of 21 statements on a scale of 0–3, as it relates to the way they have felt for the past 2 weeks, which captured depressive symptoms during the time period that corresponded to the current episode of ACS. The total BDI-II score is the sum of the scores on all items and ranges from 0 to 63. We considered a BDI-II score <14 to be negative for depression and scores of 14

and greater positive for depression, as similarly categorized by Frasure-Smith et al. (2007) in patients with ACS.

MACEs

We defined MACE as any of the following outcomes or events occurring after discharge for the baseline ACS event: cardiovascular, sudden, or unknown cause of death; stroke; AMI; or readmission for subsequent angina requiring revascularization interventions (i.e., coronary stent or cardiac bypass surgery). We defined the follow-up time interval as the time between hospitalization for the initial or baseline ACS event and the end of follow-up, which for cases was the date of the first MACE and for noncases was December 31, 2013, the date of death, or the date of last contact if lost to follow-up. Of the 1,198 ACS patients with genotype information, we excluded five due to their having a body mass index (BMI) greater than 58 kg/m², which was greater than four standard deviations from the mean. Of the remaining 1,193 individuals, 1,117 had information available on MACE outcomes, and 212 reported a defined MACE.

Statistical Analysis

Males and females were compared for age, weight, height, BMI, and BDI-II score using a *t* test for independent samples. The Wilcoxon's rank sum test was used to test for biomarker differences by gender since the biomarker data did not follow a normal distribution. The χ^2 test was used to compare depressive symptom status, obesity, the MACE variable (yes/no), statin use, and individual MACEs (i.e., death, stroke, AMI, or readmission with angina revascularization) between males and females.

Cox proportional hazards models were used to model time to incident MACE. To evaluate whether depressive symptom status predicts risk of MACE, the first analytic model included an indicator variable for depressive symptom status, age, gender, and statin use. Gender-specific contributors are well known in CVD phenotypes, age was shown to be statistically significant in our own sample between men and women, and Sexton and colleagues (2015) previously reported that statins may reduce short-term adverse clinical outcomes in patients with ACS; thus, we included these three variables as covariates in all models. Conversely, we did not include BMI as a covariate in our analytical models, as it was not a significant predictor of MACE in the present study (data not shown). A Kaplan-Meier plot was used to show the relationship between depressive symptom status and MACE. To evaluate the relationship between inflammatory protein levels and MACE, each inflammatory protein was evaluated in a Cox proportional hazards model that adjusted for age, gender, and statin use.

Linear regression was used to evaluate whether SNPs in inflammatory protein-coding genes are related to the level of those proteins. The model included a given SNP (modeled as the additive effect of the rare allele), age, gender, statin use, and race. Due to differences in allele frequencies among racial groups and because we conducted pooled analyses,

self-reported race coded as non-Hispanic White or other was included as a covariate in all genetic models. An additional linear regression model included the same covariates listed for the model above plus depressive symptom status and the SNP $\times$ Depressive Symptom Status interaction term. Given that we tested 131 SNPs, we used a Bonferroni correction in these multiple linear regression models for the level of significance, which was defined as p value = .00038 (derived by $\alpha = .05$ divided by 131 tests).

Finally, Cox proportional hazards models were used to determine whether specific genetic polymorphisms in inflammatory protein-coding genes and depressive symptom status interacted to influence risk of subsequent MACE in ACS patients. These models included the SNP (modeled as the additive effect of the rare allele), the indicator variable for depressive symptom status, age, gender, statin use, race (coded as non-Hispanic White or other), and the SNP $\times$ Depressive-Symptom Status interaction term. A two-sided p value of .00038 was also used to assess statistical significance in the Cox proportional hazards models. All other statistical tests were two-tailed with an α level of .05. Analyses were performed using R (www.r-project.org) or STATA Version 10 (College Station, TX, USA).

Results

Sample Characteristics

We have shown the descriptive characteristics of the 1,117 participants with ACS for whom we had genetic and MACE data available stratified by gender (Table 1). There were statistically significant differences by gender in BDI-II score, age, weight, and height, with females being older and having higher BDI-II scores. Females had significantly higher hs-CRP and MCP-1 values. There was also a significant difference in depressive symptom status by gender, with 29.9% of females and 21.1% of males having a BDI-II score ≥ 14 . Significant differences in proportions by race group ($p = .0008$) were also noted, with participants as a whole comprising 123 (11.0%) Hispanics, 663 (59.2%) non-Hispanic Whites, 208 (18.6%) African Americans, and 123 (11.0%) Asians.

Depressive Symptoms

After adjusting for age, gender, and statin use, we found that a positive depressive symptom status (BDI-II ≥ 14) was associated with subsequent MACE (Table 2). Participants with a BDI-II score ≥ 14 had twice the risk of subsequent MACE as those with lower scores (hazard ratio [HR] = 2.03; 95% confidence interval [CI] = [1.53, 2.70]; $p < .0001$). Figure 1 shows the Kaplan–Meier curve for this relationship. Although BDI-II scores were significantly higher in females than in males ($p = .0002$, Table 1), the interaction effect between positive depressive symptom status and gender was not significant in this model ($p = .644$), indicating that the association between positive depressive symptom status and subsequent MACE did not vary by gender.

Table 1. Descriptive Characteristics of Participants With Acute Coronary Syndrome (ACS; $N = 1,117$) by Gender.

Characteristic	Men $n = 766$ Mean (SD)	Women $n = 351$ Mean (SD)	p^a
Age (years)	61.4 (11.5)	64.6 (13.1)	.0001**
BMI (kg/m ²)	29.8 (5.3)	30.4 (7.2)	.1937
Body weight (lb)	206.6 (41.3)	175.6 (43.9)	<.0001**
Height (cm)	69.7 (3.0)	63.7 (2.9)	<.0001**
BDI-II score	8.7 (7.9)	10.9 (9.7)	.0002**
Inflammatory protein levels			
SELE (ng/mL)	35.8 (17.0)	36.6 (19.9)	.9481
MCP-1 (pg/mL)	229.0 (157.9)	241.9 (129.1)	.0062*
hs-CRP (mg/L)	12.7 (27.4)	15.0 (30.0)	<.0001**
IL-6 (pg/mL)	7.4 (7.0)	7.8 (7.0)	.1141
	n (%)	n (%)	
Obesity, yes	334 (43.7)	165 (47.1)	.2859
Depressive symptom status, BDI-II score ≥ 14	162 (21.1)	105 (29.9)	.0014*
MACE, yes	147 (19.2)	65 (18.5)	.7903
Deceased	42 (5.5)	24 (6.8)	.3728
Stroke	22 (2.9)	9 (2.6)	.7712
AMI	45 (5.9)	13 (3.7)	.1290
Readmission angina revascularization ^b	38 (5.0)	19 (5.4)	.7498
Statin use	401 (52.4)	192 (54.9)	.4361

Note. AMI = acute myocardial infarction; BDI-II = Beck Depression Inventory-II; BMI = body mass index; SELE = E-selectin; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; MACE = major adverse coronary event; MCP-1 = monocyte chemoattractant protein-1.

^a p Value for a test of equality of means or proportions between men and women.

^bRevascularization interventions included stent replacement, angioplasty, or cardiac bypass surgery.

*Significant at $p \leq .01$. **Significant at $p \leq .001$.

Table 2. Association of Depressive-Symptom Status With Subsequent MACE in Participants Who Had Been Hospitalized With ACS.

Model	N	Hazard Ratio	CI	p Value Depression	p Value Interaction
Age, gender, statin use	1,116	2.03	[1.53, 2.70]	<.0001*	
Age, gender, statin use, Depression $\times$ Gender	1,116	2.45	[1.05, 5.70]	.038	.644

Note. BDI-II score was dichotomized for depressive symptom status, with <14 considered negative and ≥ 14 positive. ACS = acute coronary syndrome; MACE = major adverse coronary event; CI = confidence interval.

*Significant at $p \leq .001$.

Inflammatory Response

There were no significant differences in inflammatory protein marker levels by depressive symptom status, either among the entire sample or among the 212 individuals with subsequent MACE (data not shown). We investigated the association

Figure 1. Kaplan–Meier curve demonstrating the relationship between depressive symptom status and major adverse coronary event (MACE) after adjustment for age, gender, and statin use. Those individuals who had been hospitalized for an acute coronary syndrome and had a positive depressive symptom status (i.e., score on the Beck Depression Inventory-II ≥ 14) had twice the risk of subsequent MACE as those with lower scores.

Table 3. Association of Inflammatory Protein Levels With Subsequent MACEs in Participants Who Had Been Hospitalized With ACS.

Inflammatory Protein	N	Hazard Ratio	CI	p Value
SELE	1,194	1.00	[0.99, 1.01]	.853
MCP-I	1,194	1.00	[1.00, 1.00]	.078
hs-CRP	1,193	1.00	[1.00, 1.01]	.025*
IL-6	1,118	1.00	[1.01, 1.04]	.010**

Note. Covariates in Cox regression models for each inflammatory protein level included age, gender, and statin use. ACS = acute coronary syndrome; SELE = E-selectin; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; MACE = major adverse coronary event; MCP-I = monocyte chemoattractant protein-I; CI = confidence interval.

*Significant at $p \leq .05$. **Significant at $p \leq .01$.

between inflammatory protein markers and MACE using a model that adjusted for BDI-II score, age, gender, and statin use, with separate analyses for each inflammatory protein marker. Higher levels of hs-CRP (HR = 1.00; 95% CI = [1.00, 1.01]; $p = .025$) and IL-6 (HR = 1.02; 95% CI = [1.00, 1.04]; $p = .010$) were associated with an increased risk of subsequent MACE (Table 3). However, we found that none of the inflammatory protein markers significantly interacted with depressive symptom status in these models, indicating that the association between the inflammatory protein markers and subsequent MACE did not vary by depression status (data not shown).

SNPs

After adjusting for age, gender, statin use, and race, we found that none of the SNPs were significantly associated with levels of any of the inflammatory proteins when using our corrected

p value for multiple testing. We report SNPs with a p value of $<.05$ in Supplementary Table S3. Additional linear regression models including depressive symptom status and SNP $\times$ Depression Multiplicative interaction term determined that the selected SNPs in inflammatory protein-coding gene regions and depressive symptoms did not interact to influence the level of circulating inflammatory proteins (Supplementary Table S4). Furthermore, Cox proportional hazards models that adjusted for the same variables indicated that none of the SNPs significantly interacted with depressive symptom status to affect the risk of subsequent MACE (data not shown).

Discussion

We designed this prospective study to investigate whether genetic- and gender-specific phenotypic differences influence the relationships among depressive symptoms, inflammatory response, and risk of subsequent MACE in patients with ACS. Female patients with ACS in this study reported more depressive symptoms than males. Similarly, researchers in other recent studies have reported a higher prevalence of depressive symptoms in females compared to males with established CVD (Doyle et al., 2015).

We also observed in the present study that depressive symptoms were associated with the risk for subsequent MACE. Researchers in previous studies have reported a similar relationship between elevated levels of depressive symptoms identified by screening instruments and negative CVD outcomes (Angst & Merikangas, 1997; Penninx et al., 2001). Indeed, studies have shown, not only that an increased risk of CVD is associated with a diagnosis of major depressive disorder or elevated depressive symptoms reaching diagnostic significance (O'Brien et al., 2015) but also that the presence of even minimal depressive symptoms not meeting diagnostic criteria for major depression negatively impacts prognosis to a degree comparable to the mortality rates seen in patients with major depression (Cuijpers et al., 2013).

Despite the fact that more females than males had depressive symptom screening scores indicative of depression, the interaction between depressive symptoms and gender was not significantly associated with MACE in the present study, indicating that the association between positive depressive symptom status and MACE did not vary by gender. Researchers in other studies have also found that, while females were more likely to report depressive symptoms than males, females and males experienced comparable CVD-related outcomes (Farmer et al., 2017). Conversely, in a similar sample of patients with ACS, investigators likewise reported a higher prevalence of depression in females when compared to males but found that the association between depression and MACE was worse for men (Doyle et al., 2015). They also found, however, that severity of cardiac disease accounted for this increased risk. In spite of these findings, many studies have suggested that the association between depressive symptoms and poor prognosis is independent of severity of cardiac disease (Meyer et al., 2015; Schopfer, Regan, Heidenreich, & Whooley, 2016).

Researchers have discovered immunoinflammatory dysregulation in some patients with ACS and reported depressive symptoms; however, studies have produced conflicting results (Annie et al., 2005; Azar, Nolan, & Stewart, 2012; Miller et al., 2005). In a study of hs-CRP and IL-6 in healthy individuals, researchers observed higher hs-CRP levels in women with depressive symptoms than in men with depressive symptoms (Azar et al., 2012). They observed no significant differences with respect to IL-6. In contrast, investigators in a more recent study found elevated IL-6 levels in females with depressive symptoms compared to men with these symptoms (Birur et al., 2017). In another study, among 65 patients with ACS, those in the highest tertile for depressive symptoms had a 50% increase in CRP levels ($r = .27, p = .03$), a well-known biomarker linked to CVD (Miller et al., 2005). On the other hand, Miller et al. found no association between depressive symptoms and levels of IL-6 ($r = .05, p = .72$), a biomarker known to increase the expression of CRP. However, the researchers in that study measured the inflammatory protein levels at only one time point, which was more than 3 months after the ACS event. In a similar study, investigators also found no difference in IL-6 levels between 57 patients with depressive symptoms after AMI and 46 AMI patients without depressive symptoms (Annie et al., 2005). However, the study had insufficient power to detect a difference between the groups, and the authors did not control for statin use in the analysis, which decreases inflammatory protein levels.

Our findings in the present study support and extend Lespérance and Frasure-Smith's proposal (Lespérance et al., 2004) that transient increases of inflammatory protein levels, potentially activated by depressive symptoms in patients after an ACS event, are sufficient to initiate an inflammatory cascade that could contribute to the instability and rupture of a moderate atherosclerotic plaque resulting in MACE (Mann, 2003). However, the possibility of bidirectional associations between heightened inflammatory states and depressive symptom severity emphasizes the complexity of this relationship (Shaffer et al., 2011). Evidence for the role of the inflammatory process in the development of depressive symptoms points to cytokine mechanisms by which the immune system can also influence the brain and behavior (Capuron & Miller, 2011). The elucidation of the mechanisms by which the immune system influences the development of depressive symptoms suggests a variety of therapeutic targets to inhibit inflammatory processes (e.g., pro-inflammatory cytokines such as IL-1 and IL-6) and manage neuropsychiatric disorders. Given the extensive growth in knowledge in the field of psychoneuroimmunology, it is likely that increases in the understanding of brain-inflammatory system interactions will have broad applicability for the development of novel mind-body interventions targeting individuals struggling to live well within the confines of disease states associated with inflammation and comorbid psychological distress.

While we did find, in the present study, that higher levels of hs-CRP and IL-6 were associated with an increased risk of subsequent MACE, none of the inflammatory protein markers

that we measured interacted significantly with depressive symptom status to affect the risk of MACE, indicating that the association between the inflammatory protein markers and subsequent MACE did not vary by depressive symptom status. Additionally, we found that none of the SNPs in inflammatory protein gene-coding regions significantly interacted with depressive symptom status or MACE. These findings do not support the idea that the prognostic effect of depressive symptoms can be explained by immunoinflammatory dysregulation. There is evidence from previous studies, however, that depressive symptoms and inflammatory response likely interact in complex pathways to influence cardiovascular risk, perhaps partially by overlapping risks, and that measures of immunoinflammatory dysregulation may serve as prognostic factors in some, but not all, individuals with depressive symptoms (Frasure-Smith et al., 2007; Granville Smith, Parker, Cvejic, & Vollmer-Conna, 2015).

Our study has both strengths and limitations. The sample size was adequate, and the sample was racially diverse; however, we conducted the study in a single academic medical center, potentially limiting the generalizability of our findings. Although we would have liked to have evaluated the impact of major depressive disorder and inflammatory response on MACE, we did not obtain a definitive diagnosis of depression. However, we did use a validated depressive symptom screening instrument that has been used frequently in the ACS population. Evidence suggests that the use of depression-screening assessment tools in patients hospitalized for acute CVD conditions effectively predicts risk (Beach et al., 2013; Pedersen et al., 2009; Thombs et al., 2008). Additionally, we assessed inflammatory protein levels only once during the time of hospitalization for the ACS event, which was during the same time frame in which we administered the screening tool for depressive symptoms; therefore, we cannot infer cause-and-effect relationships between symptoms of depression and inflammatory protein levels. Replication studies to confirm our findings are needed.

Conclusions

The current study underscores the complex relationship between depressive symptoms and prognosis in patients with ACS and increases our understanding of biological changes within illness. Given our confirmatory finding of an association between depressive symptoms and subsequent MACE in a subgroup of ACS patients, it remains of interest, in this era of personalized healthcare, to identify a well-defined, high-risk subgroup of ACS patients with genetic polymorphisms that result in immunoinflammatory dysregulation in the presence of depressive symptoms. Even without that specific knowledge, however, knowing the potential effect of depressive symptoms on the risk of subsequent MACE may help patients with ACS and symptoms of depression to better understand their CVD risk factors, and this understanding may create an opportunity for nurses to initiate personalized depression interventions and prevention strategies to promote cardiovascular health.

Authors' Note

Jennifer Sanner and Megan L. Grove contributed equally to this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of NCATS or NIH.

Author Contribution

J. Sanner contributed to conception, design, acquisition, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. M. Grove select item contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. E. Yu select item contributed to acquisition and interpretation, critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy. F. Moeller contributed to conception, design, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. S. Cron contributed to analysis, critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy. E. Boerwinkle contributed to conception and design, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. A. Morrison contributed to conception, design, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. L. Frazier contributed to conception, design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Supplemental Material

Supplementary material is available for this article online.

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