



# **Association of Somatic and Cognitive Depressive Symptoms and Biomarkers in Acute Myocardial Infarction: Insights from the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status Registry**

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## Association of Somatic and Cognitive Depressive Symptoms and Biomarkers in Acute Myocardial Infarction: Insights from the TRIUMPH Registry

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### Abstract

**Background**—Somatic depressive symptoms and certain biomarkers are each associated with worse acute myocardial infarction (AMI) prognosis, but the relationship between depressive symptom domains and inflammatory, neurohormonal, and coagulation markers is unknown.

**Methods**—We examined the relationship between depressive symptoms and 1-month biomarker levels (hs-CRP, NT-proBNP, white blood cell, platelet counts) in 1265 AMI patients from the 24-center TRIUMPH study. Depressive symptoms (PHQ-9) were assessed during index hospitalization and categorized as somatic or cognitive. Using median regression models, the upper quartile of somatic and cognitive depression scores and each biomarker were compared with the lower 3 quartiles, adjusting for site, demographics, and clinical characteristics.

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#### Data Access and Responsibility

- Dr. Smolderen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
- The views in this article are those of the authors and do not necessarily reflect the views of the Department of Veterans Affairs.

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*Study Concept and design:* Smolderen, Spertus, Chan.

*Acquisition of Data:* Spertus, Chan.

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*Statistical Analysis:* Reid.

*Study Supervision:* Smolderen, Spertus, Reid, Buchanan, Vaccarino, Lichtman, Bekelman, Chan.

**Results**—High scores for somatic depression were present in 355 (28.1%), and in 382 (30.2%) of patients for cognitive depression. Although hs-CRP values were higher in patients with somatic symptoms, this association was attenuated after adjustment ( $B_{\text{per SD increase}}=0.02$ , 95% CI: 0.00; 0.05,  $P=.07$ ). WBC count was independently associated with somatic depressive symptoms ( $B_{\text{per SD increase}}=0.28$ , 95% CI: 0.12; 0.44,  $P<.001$ ). Cognitive depressive symptoms were not associated with hs-CRP or WBC count. Neither dimension was associated with NT-proBNP or platelet levels. For each biomarker, the depression dimensions explained <1% of their variation.

**Conclusions**—Neither somatic nor cognitive depressive symptoms were meaningfully associated with hs-CRP, NT-proBNP, WBC or platelet counts 1 month after AMI, suggesting that the association between depression and long-term outcomes may be unrelated to these biomarkers. Future research should explore other biomarkers to better illuminate pathways by which depression adversely impacts AMI prognosis.

### Keywords

Depressive Symptoms; Myocardial infarction; Inflammation; Neurohormones; Coagulation; Mechanisms

### Introduction

A substantial proportion of acute myocardial infarction (AMI) patients experience clinically relevant depressive symptoms, which have been associated with a worse cardiovascular prognosis (1, 2). Recent studies suggest that the higher mortality and readmission risk in depressed patients after AMI is more strongly associated with the somatic symptoms of depression (e.g., loss of energy, sleep disturbances, and fatigue), (3-5) rather than the cognitive symptoms of depression (e.g., negative mood, hopelessness, and loss of interest), even after adjustment for AMI severity(3, 5). Other studies have linked various inflammatory biomarkers (high-sensitivity C-Reactive Protein [hsCRP] and white blood cell [WBC] count), neurohormonal biomarkers (Pro-Brain Natriuretic Peptide [NT-proBNP]), and markers of blood coagulation (platelet count) with worse outcomes after AMI (6-9). Despite prior research that has identified associations between depressive symptoms and each of these biomarkers in cardiac disease, findings are not conclusive (10-13). Specifically, the relationship between depressive symptoms and these biomarkers remains poorly understood in patients who recently experienced an AMI (10-13). Defining a strong relationship between depression and various biomarkers could provide important insights into potential pathways by which depression is associated with increased mortality and readmission after AMI.

Accordingly, we examined the relationship between depressive symptoms and these established biomarkers associated with worse AMI outcomes. Given prior work showing that the association between depression and mortality after AMI is attributable to somatic depressive symptoms, and not cognitive depressive symptoms, (4, 5, 14, 15) we hypothesized that only the somatic symptoms of depression would be positively associated with elevated biomarker levels. Demonstrating a strong correlation between somatic depressive symptoms and any of the proposed AMI biomarkers could illuminate a potential mechanism for the association of somatic depressive symptoms with long-term outcomes in AMI patients and could identify novel targets for attenuating the adverse prognosis of depressed AMI patients.

## Methods

### Participants and Study Design

This is an *a priori* defined sub-study of the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health Status (TRIUMPH) study, which is a large prospective, geographically diverse, multi-site AMI registry, with a focus on evaluating racial differences in patients with AMI (16). Participants in this observational registry were consecutively enrolled between April 11, 2005 and December 31, 2008 from 24 U.S. hospitals and were eligible for inclusion if they were aged  $\geq 18$  years, had elevated cardiac enzymes (creatinine kinase-MB or Troponin-I) within 24 hours of hospital admission and supporting evidence suggestive of AMI, including prolonged ischemic symptoms or electrocardiographic ST changes. Patients were excluded if they were transferred to the participating hospital from another facility after more than 24 hours, were incarcerated, refused participation, were unable to provide consent, or did not speak English or Spanish. Patients were also excluded from our analyses if they expired or were discharged prior to being contacted by the investigators for study enrolment.

Per sub-study protocol, laboratory tests were obtained at the 1-month follow-up. Of the 1333 patients who initially consented for 1-month phlebotomy and follow-up in this sub-study, we excluded 68 patients (5.1%) who did not complete a baseline assessment of depressive symptoms or undergo phlebotomy at 1-month for biomarker levels. The final study cohort was comprised of 1265 patients. The study protocol was approved by the local institutional review board at each participating center and all participants provided written informed consent.

### Data Collection

Standardized patient interviews were performed by trained research staff between 24 and 72 hours after AMI admission and were supplemented by detailed information obtained from chart abstraction. Patient data included demographic information (age, sex, and race), socio-economic factors (marital status, education, access to health care insurance, and employment status), and clinical variables (hypercholesterolemia, hypertension, peripheral arterial disease, diabetes mellitus, prior AMI, prior angina, prior coronary artery bypass surgery [CABG] or percutaneous coronary intervention [PCI], prior stroke, chronic renal failure, chronic lung disease, chronic heart failure, non-skin cancer, smoking status, body mass index, family history of coronary artery disease, and history of depression or current treatment for depression). Data on AMI severity were also obtained and included type of AMI (ST-elevation vs. non-ST elevation), left ventricular ejection fraction  $< 40\%$ , Killip class, number of coronary arteries with  $\geq 70\%$  stenosis, and systolic blood pressure and heart rate at AMI presentation.

Trained phlebotomists collected blood samples at 1 month following the index AMI in patients' homes or through their primary care practice. After collection, blood samples were immediately spun, refrigerated, and transferred to a central laboratory (Clinical Reference Laboratory, Lenexa, KS) where they were analyzed within 24 hours. Additionally, at 1-month follow-up, information on patients' current medications was updated through patient interviews.

**Assessment of Depressive Symptoms**—The standardized and validated 9-item Patient Health Questionnaire (PHQ-9) was used to assess symptoms of depression during the index AMI admission (17). The PHQ-9 quantifies the frequency of depressive symptoms over the past 2 weeks based on 9 criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (18). Items are answered along a 4-point Likert scale

ranging from “0” (not at all) to “3” (nearly every day) and responses are summed to create a score between 0 and 27 points.

Consistent with prior studies (5, 19), we derived depressive symptom dimension scores, with 4 PHQ-9 items assigned to somatic depressive symptoms (items on sleep, fatigability, appetite, and psychomotor agitation/retardation) and 5 PHQ-9 items assigned to cognitive depressive symptoms (items on lack of interest, depressed mood, negative feelings about self, concentration problems, and suicidal ideation). Prior to this study's analyses, we replicated the anticipated factor structure (5, 19) using confirmatory factor analysis in our population sample (20). Model fit indices supported this factor structure: the comparative fit index was 0.97, whereas the Tucker-Lewis Index was 0.98 (values >0.90 indicate good fit for both measures) (20). We accordingly calculated sum scores of the two dimensions for our analyses. The correlations between both dimensions among patients with a PHQ-9  $\geq$  10 were -0.16, suggesting that these domains quantify unique aspects of depression. The Cronbach's alpha coefficients were 0.69 for somatic symptoms and 0.79 for cognitive symptoms, indicating good internal consistency.

**Assessment of 1-Month Biomarkers**—Biomarker levels were obtained at 1-month follow-up ( $\pm$  10 days) to avoid the transient increases that may acutely occur in all patients during an AMI (21-23). These included markers of inflammation (hs-CRP and WBC count), left ventricular hemodynamics (NT-proBNP), and blood coagulation (platelet count). Hs-CRP is an acute phase protein that is released by the liver and provides a stable biomarker for low-grade systemic inflammation. Levels of hs-CRP have been shown to be highly predictive of vascular risk in AMI patients (6, 24, 25). Concentrations of hs-CRP (mg/L) were measured with the Roche Tina-quant high-sensitivity assay (26, 27). WBC count is a non-specific marker of inflammation and has been consistently found to be a strong prognostic indicator in patients with a recent AMI (7). WBC levels were evaluated with the ADVIA 120 BASO reagent.

NT-proBNP is a neurohormone that is primarily stimulated through increased myocardial stretch secondary to ischemia-induced left ventricular systolic/and or diastolic dysfunction. NT-proBNP has been shown to be strongly associated with both short- and long-term mortality and heart failure incidence after AMI (8, 28-31). The Roche Elecsys NT-proBNP assay was used to measure NT-proBNP (pg/mL).

Platelet counts, as marker of coagulation, play a prominent role in the response-to-injury hypothesis of atherosclerosis (32) and elevated levels are known to be associated with worse prognosis in AMI patients (9, 33). Platelet counts ( $\times 10^3/\mu\text{L}$ ) were analyzed by a single optical cytometer after appropriate dilution of the blood sample with ADVIA 120 RBC/PLT reagent. Within- and total precision of the assays used to assess all of the aforementioned AMI biomarkers have all been reported to be <3% and were verified by the core lab (26, 27, 34, 35).

## Statistical Analyses

For descriptive purposes only, and consistent with prior work, (5, 19) we categorized patients in the upper vs. lower 3 quartiles as having or not having somatic and cognitive depressive symptoms. This categorization of patients did not exactly correspond to 25% of the population. Given that discrete, ordinal scale of the PHQ, it was necessary to use the cut-off score that was closest to the segment of patients that contained the upper quartile of the distribution. Baseline comparisons between patients with and without increased somatic or cognitive depressive symptoms were compared using Student's t-tests and the Wilcoxon test for continuous variables and the Chi-square or Fisher's Exact test for categorical variables, as appropriate. Descriptive statistics of the 1-month biomarker data (median, minimum and

maximum values, interquartile range) were similarly described according to the upper quartile vs. the lower 3 quartiles of somatic and cognitive depressive symptom scores.

Because of the skewed nature of the biomarker data, we analyzed the data using median regression. Median regression directly models the biomarker median as a function of the covariates, yielding more robust estimates of central tendency. In these models, results are interpreted as a median change (36). Unadjusted median linear regression models were constructed to evaluate the association between somatic and cognitive depressive symptom scores (entered jointly as continuous variables in the model) and each of the 4 study biomarkers. Multivariable median linear models were then constructed for each biomarker and were adjusted for site, demographics (age, sex, race), socioeconomic status (marital status, education, insurance status, and working status), clinical variables (hypercholesterolemia, hypertension, diabetes mellitus, prior coronary artery disease [prior AMI, prior PCI or prior CABG], prior angina, stroke, chronic renal failure, chronic lung disease, chronic heart failure, non-skin cancer, current smoking, body mass index), AMI severity (ST elevation AMI, left ventricular ejection fraction <40%), and use of statin medications. Before proceeding with the main analyses, non-linear relationships between depression dimensions and biomarkers were assessed by including a quadratic squared term in addition to the main effect in the multi-variable models (37). Additionally, as inflammation markers may be suppressed by the use of statins, we verified the existence of potential interactions with the depressive symptom dimensions in their association with hs-CRP and WBC count (12).

Model results for somatic and cognitive depressive symptoms were presented as a standard deviation (SD) increase in each depressive symptom measure, which was 3 points for both somatic and cognitive depressive symptoms. Finally, to assess the importance of any statistically significant relationship between depressive symptoms and a biomarker, we calculated Pearson product-moment correlations and the proportion of explained variance ( $R^2$ , expressed as percentages) between the somatic and cognitive depressive symptom scores and each biomarker.

Two sets of sensitivity analyses were performed for each of the 4 biomarker models. First, multivariable median linear regression models were constructed with each of the somatic and cognitive depressive symptom scores separately entered in the models. Second, unadjusted and multivariable median linear regression models were replicated modeling the full PHQ-9 (i.e., combining both somatic and cognitive depressive symptoms into an overall depression score, with estimates presented per standard deviation increase of 5 points) as the independent variable and each biomarker as the dependent variable, to assess depression as a homogeneous entity rather than within its discrete symptom domains.

Covariate data were >90% complete for our models with 9% missing 1 covariate and 0.5% missing 2 covariates. The rate of missing data for individual covariates was low; the covariate that was most frequently missing was BMI, which was missing in <5% of patients. Covariate missingness was assumed to be missing at random (37). All tests were conducted with SAS Version 9.1.3 (SAS Institute, Cary, NC) and R version 2.11.1 (38). Tests for significance were 2-tailed with alpha levels of 0.05.

## Results

Of 1265 patients, 355 (28.1%) were found to have increased somatic depressive symptoms (cut-off score for upper quartile of somatic depressive symptoms  $\geq 4$ ) and 382 (30.2%) were found to have increased cognitive depressive symptoms (cut-off score for upper quartile of cognitive depressive symptoms  $\geq 2$ ). Table 1 compares patient characteristics between those with and without increased somatic depressive and cognitive depressive symptoms. Patients

with either increased somatic or cognitive depressive symptoms were more likely to be younger, female, unmarried, and smokers. They also were more likely to have higher rates of diabetes mellitus, prior percutaneous coronary intervention, and chronic lung disease at the time of their AMI. In addition, patients with increased somatic symptoms were more likely to be uninsured and to have a higher BMI. Compared with those without cognitive depressive symptoms, patients with increased cognitive symptoms were more likely to be unemployed and to have a history of peripheral arterial disease, AMI, and angina.

### Distribution of Biomarker Data by Depression Dimensions

Unadjusted median hs-CRP values were higher in patients with increased somatic depressive symptoms (median for the upper quartile of 0.25; interquartile range [IQR]: 0.11-0.65 vs. median for the lower 3 quartiles of 0.21 [IQR: 0.09-0.50];  $P=.02$ ). In contrast, unadjusted median hs-CRP values were not different between the cognitive depressive symptom groups (median for the upper quartile of 0.22 [IQR: 0.09-0.53] vs. median for the lower 3 quartiles of 0.23 [IQR: 0.10-0.53];  $P=.83$ ) (Figure 1, upper left graph). Similarly, median WBC levels were higher in patients with increased somatic symptoms (median for the upper quartile of 6.90 [IQR: 5.50-8.50] vs. the lower 3 quartiles of 6.50 [IQR: 5.30-7.80];  $P=.009$ ) whereas no differences between median WBC values were noted for the cognitive depressive symptom comparison (median for the upper quartile of 6.80 [IQR: 5.20-8.30] vs. median for the lower 3 quartiles of 6.55 [IQR: 5.40-7.90];  $P=.46$ ) (Figure 1, upper right graph). For NT-proBNP and platelet count, there were no significant differences between those with and without either somatic or cognitive depressive symptoms (Figure 1, bottom).

### Unadjusted and Adjusted Model Results

There was an unadjusted positive association between somatic depressive symptoms and hs-CRP (unadjusted B per SD increase = 0.04, 95% confidence interval [95% CI]: 0.01; 0.07,  $P<.0001$ ), but not for cognitive depressive symptoms (unadjusted B per SD increase = -0.02, 95% CI: -0.04; 0.01,  $P=.18$ ). However, the relationship between somatic depressive symptoms and hs-CRP was attenuated after multivariable adjustment (adjusted B per SD increase = 0.02, 95% CI: 0.00; 0.05,  $P=.07$ ). Somatic depressive symptoms were also associated with higher WBC counts (unadjusted B per SD increase = 0.23, 95% CI: 0.02; 0.44,  $P=.03$ ), which persisted after multivariable adjustment (adjusted B per SD increase = 0.28, 95% CI: 0.12-0.44,  $P<.001$ ). Cognitive depressive symptoms were not associated with WBC levels in the unadjusted model, (unadjusted B = -0.09, 95% CI: -0.29; 0.11,  $P=.39$ ) (Figure 2, upper left graph), but an unexpected negative association was observed for the association between cognitive depressive symptoms and WBC count in the multivariable model (adjusted B = -0.23, 95% CI: -0.40; -0.06,  $P<.01$ ) (Figure 2, upper right graph).

There were no significant associations between either of the depression dimensions and NT-proBNP and platelet levels (Figure 2, bottom). There was also no evidence of an interaction between the depression dimensions and statin medication use. In addition, there was no evidence of non-linearity in the relationship between the depression dimensions and each biomarker (data not shown).

Finally, the correlations between each depression dimension and each biomarker are presented in Table 2. There were small, statistically significant correlations between somatic and cognitive depressive symptoms and hs-CRP, WBC, and NT-proBNP levels, cognitive depressive symptoms and platelet count, and overall depressive symptoms and hs-CRP and platelet count. However, each depressive symptom domain explained less than 1% of the total variance for each biomarker (see Table 2).

## Sensitivity Analyses

When each of the depression dimensions were separately included in the regression models, we replicated the unadjusted relationship between somatic symptoms and hs-CRP ( $B = 0.03$ , 95% CI 0.01-0.05,  $P=.01$ ). When we repeated our analyses using the overall PHQ-9 score, we did not find statistically significant associations between the overall depression score and each of the 1-month AMI biomarkers (Figure 3).

## Discussion

In this large observational multi-center AMI registry, we evaluated whether established prognostic AMI biomarkers, including markers of inflammation, left ventricular hemodynamics, and coagulation could potentially serve as candidate mediators for the previously reported associations of somatic depressive symptoms and long-term AMI outcomes. Despite significant associations between somatic depressive symptoms and increased levels of hs-CRP and WBC levels, neither somatic, cognitive nor overall depressive symptom scores were able to account for >1% of the variance for each of the biomarkers we studied. Our results suggest that these prognostic biomarkers are unlikely to play a mediating role in the association between overall or somatic depression and worse AMI prognosis.

The current findings provide important insights into ongoing efforts to explore the association of depressive symptoms and post-AMI outcomes. First, this is the largest AMI registry to evaluate the association between depressive symptoms and a number of important prognostic AMI biomarkers, thereby providing greater statistical power than prior studies (10). Second, we examined depression as separate somatic and cognitive symptom domains and as an overall entity, thereby allowing us to explore whether results of prior studies were confounded by considering depression as a homogeneous concept. Finally, this study examined the previously-unexplored relationship between depression and NT-proBNP in an AMI population.

The depression-inflammation hypothesis (39-41) presents an appealing theory that has been hypothesized to partly explain the association between depression and adverse outcomes in AMI (39, 40). Activation of the innate immune system can induce depressive-like symptoms in humans that has been called the “sickness syndrome”. In certain medical conditions in which the innate immune system is chronically activated, including coronary artery disease, disproportionate activation and deregulation of inflammatory processes occurs in patients with affective disorders (39, 40). However, most studies have reported negative findings or have only found a very small effect size for the association between depression, inflammation, and cardiac disease (12, 42, 43). A recent meta-analysis (10) did find a positive association between depression and inflammatory cytokines, but effect sizes in studies involving coronary artery disease patients were very small (effect size of 0.18 for hs-CRP and effect size of 0.10 for interleukin-6). Importantly, there was considerable heterogeneity in study design and biomarkers evaluated in this meta-analysis.

The lack of a robust relationship between the depression symptom domains and inflammatory biomarkers evaluated in this study challenges the hypothesis that inflammatory pathways mediate the association between depression and worse outcomes after AMI. Similarly, the lack of an association with NT-proBNP suggests that the association of depression – and particularly somatic depressive symptoms - with long-term AMI prognosis may not be mediated by this biomarker. Although previously suggested to be a plausible mechanism for the association between depressive symptoms and adverse outcomes in cardiac disease (44), increased coagulation, as measured by platelet count, was not associated with either somatic or cognitive depressive symptoms. These findings suggest

that the association between depression and outcomes after AMI are either mediated by other biomarkers not measured in our study, by other pathophysiological mechanisms such as a lack of exercise (45, 46), or that depression is simply a surrogate marker of poor long-term outcomes after AMI.

With neither somatic nor cognitive depressive symptoms explaining a substantial amount of the variation in the 4 biomarkers in this study, future research is needed to explore other pathways which may mediate the association between depressive symptoms and worse outcomes after AMI. Candidate mechanisms that have been suggested previously include biological mechanisms such as decreased heart rate variability (19, 47) and behavioral factors such as medication adherence and physical inactivity (45). Recently, others have proposed that there may be a common genetic liability underlying both depression and cardiovascular disease (i.e., depression and cardiovascular disease could be different manifestations of the same underlying genetic substrates) (48, 49).

Our findings should be interpreted in the context of the following potential limitations. Because of the study's cross-sectional and observational design, the possibility of residual confounding by unmeasured factors remains. We were limited in the range of inflammatory markers that were included in our study, as we did not measure some of the more proximal biomarkers (e.g. interleukin-6 or tumor necrosis factor-alpha) in the inflammatory pathway that have been previously related to somatic symptoms of depression in animal models and patients undergoing immunotherapy (41); therefore, we cannot exclude the possibility that these other biomarkers may have had stronger associations with the examined depression dimensions. Because the relationship between inflammation and depression is complex, future studies are needed to better understand the neurobiological mechanisms underlying depression in the context of a chronic illness like atherosclerosis. Although the somatic depression subscale of the PHQ-9 has been validated and used before, (5, 19) its relatively limited Cronbach's alpha requires probably further efforts of validation to improve its psychometric properties. In addition, Depressive symptoms were self-assessed, and we did not assess patients for major depression according to the DSM-IV criteria. However, the 9-item Patient Health Questionnaire is a validated depression instrument (50) that has been shown to be highly prognostic of outcomes after AMI (1).

In conclusion, we did not find any robust or clinically meaningful relationships between somatic or cognitive depressive symptoms and several prognostic AMI biomarkers, including hsCRP, WBC, NT-proBNP and platelet counts. Somatic depressive symptoms – as well as cognitive and overall depressive symptoms – explained only a very small proportion of the variance in the investigated biomarkers. This suggests that the association between depression after AMI and long-term outcomes may not be mediated by these biomarkers.

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### Funding Sources

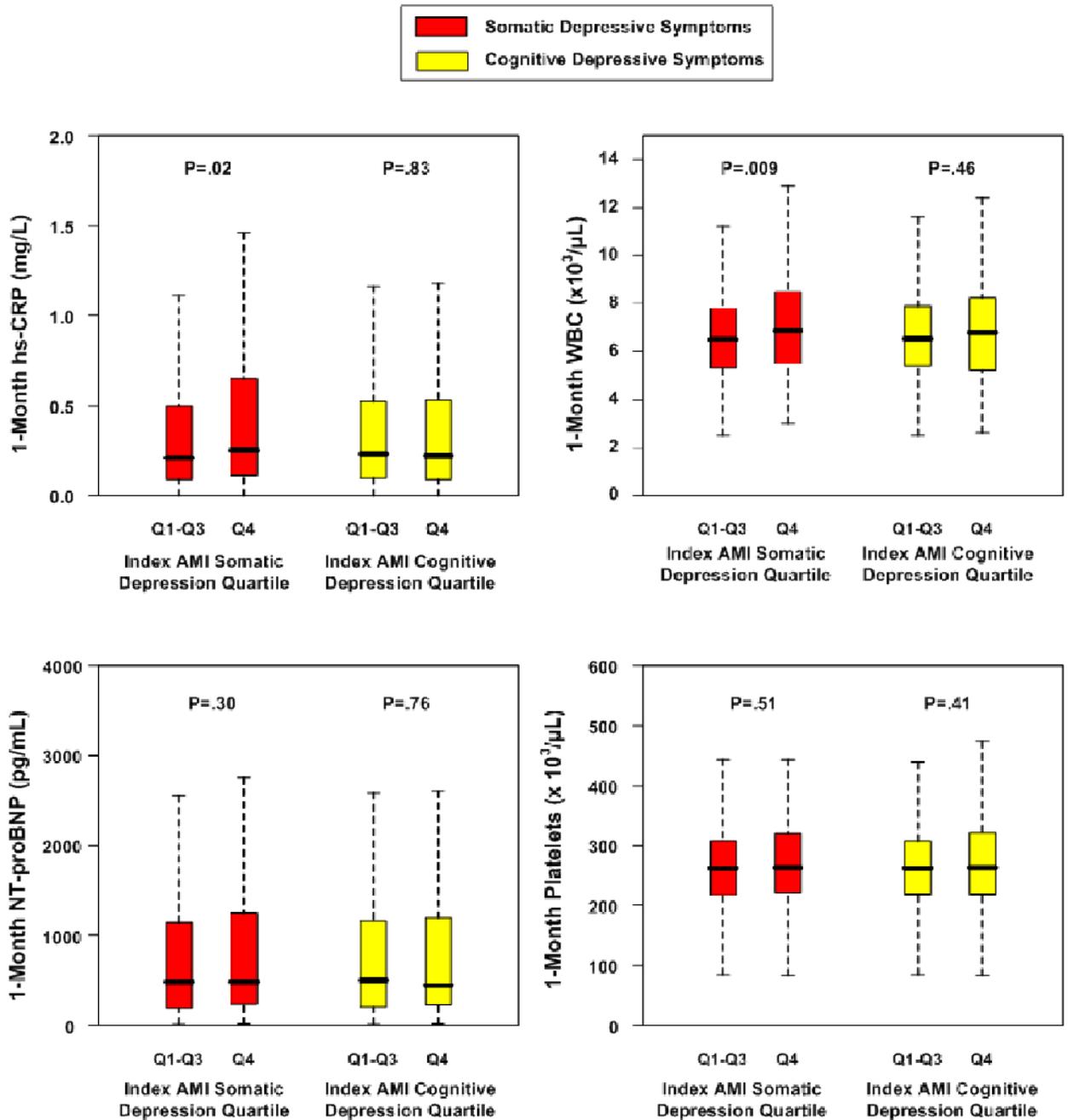
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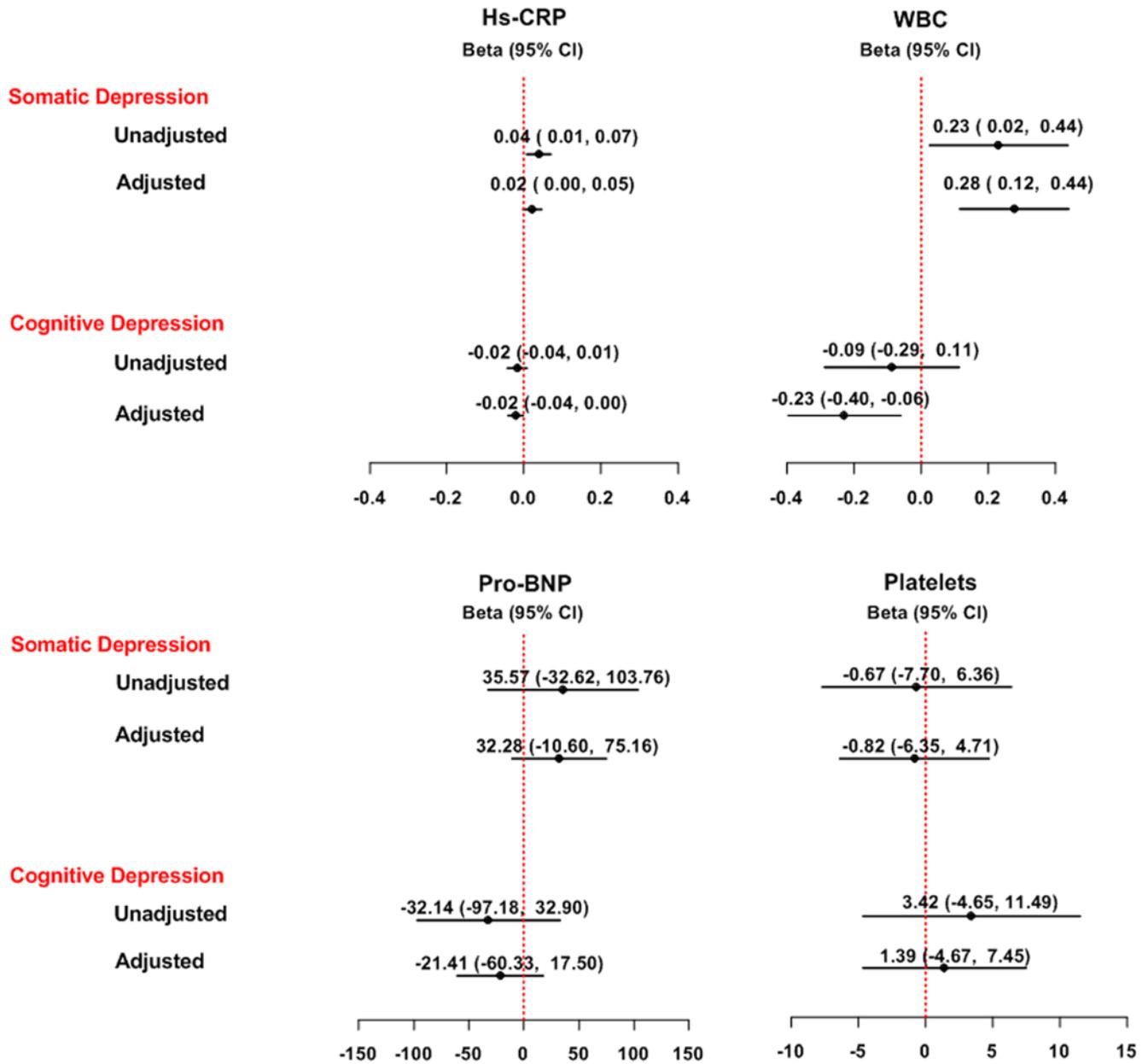
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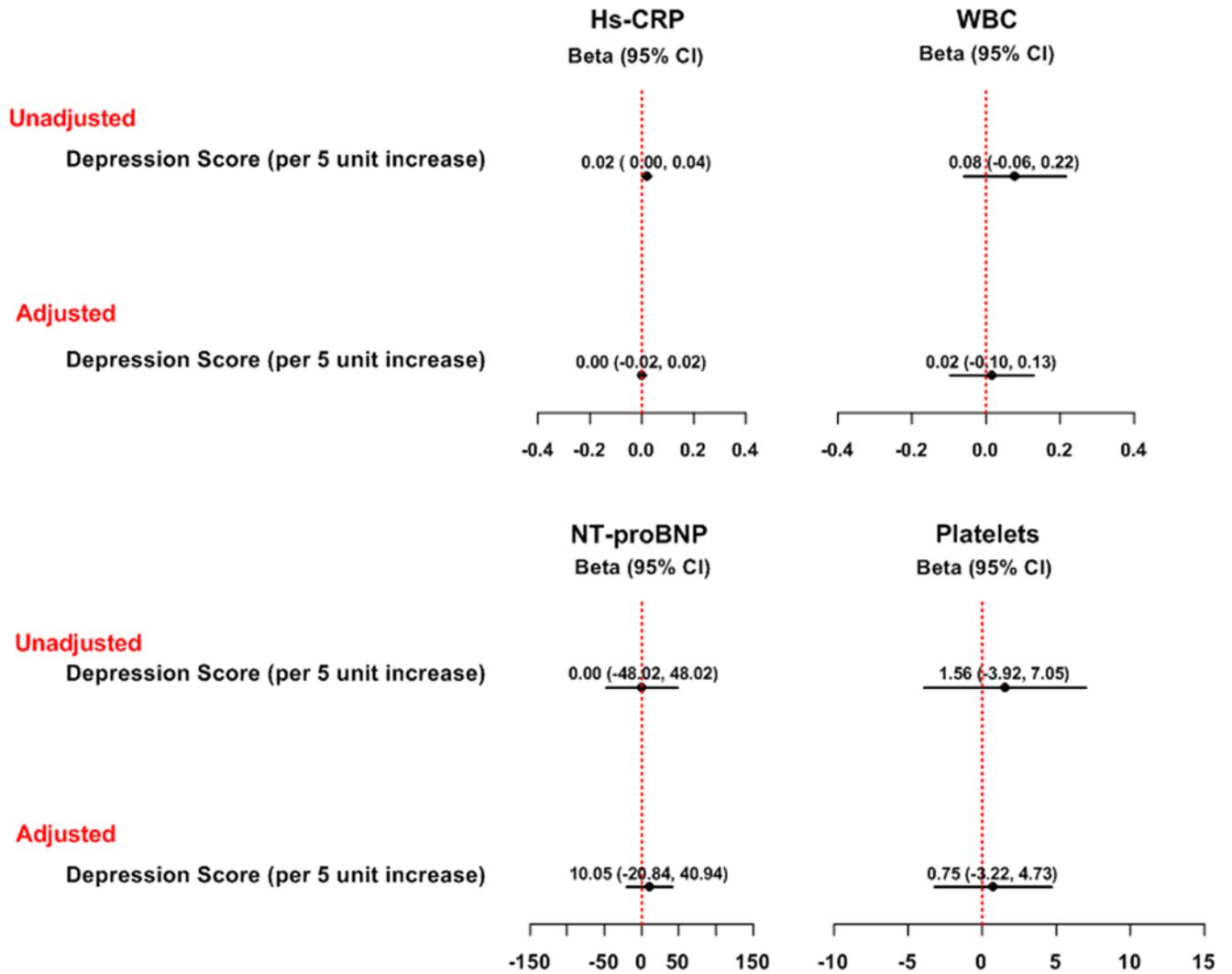


**Figure 1. – Distribution of Biomarker Data by Depression Dimensions (lower three quartiles [Q1-Q3] vs. highest quartile [Q4])**  
 Median (horizontal line), 1<sup>st</sup> to 3<sup>rd</sup> quartile (box), minimum and maximum (whiskers). The highest quartile in each depression dimension indicates increased depressive symptoms.



**Figure 2. – Unadjusted and Adjusted Median Regression Results for the Association Between Depression Dimensions and Biomarkers**

Estimates for depression dimensions are provided per SD increase (1SD=3points). Multivariable models adjusted for site, age, sex, race, marital status, education, insurance status, and working status, hypercholesterolemia, hypertension, diabetes mellitus, prior coronary artery disease [prior AMI, prior PCI or prior CABG], prior angina, stroke, chronic renal failure, chronic lung disease, chronic heart failure, non-skin cancer, current smoking, body mass index, ST elevation AMI, left ventricular ejection fraction <40%, and use of statin medications. Abbreviations: PHQ, patient health questionnaire.



**Figure 3. – Unadjusted and Adjusted Median Regression Results for the Association Between Overall PHQ-9 Depression Scores and Biomarkers**

Estimates for depressive symptoms are provided per SD increase (1SD=5points).

Multivariable models adjusted for site, age, sex, race, marital status, education, insurance status, and working status, hypercholesterolemia, hypertension, diabetes mellitus, prior coronary artery disease [prior AMI, prior PCI or prior CABG], prior angina, stroke, chronic renal failure, chronic lung disease, chronic heart failure, non-skin cancer, current smoking, body mass index, ST elevation AMI, left ventricular ejection fraction <40%, and use of statin medications. Abbreviations: PHQ, patient health questionnaire.

**Table 1**  
**Patient Characteristics of the Depression Dimension Groups.\*†**

	PHQ Somatic Symptoms			PHQ Cognitive Symptoms		
	Highest Quartile (score ≥4) n=355	Lower 3 Quartiles (score <4) n=910	P Value	Highest Quartile (score ≥2) n=382	Lower 3 Quartiles (score <2) n=883	P Value
<i>Demographics, No. (%)</i>						
Age, years	58.7±11.6	60.1±11.8	.05	58.2±11.3	60.4±11.9	.003
Female sex	159 (44.8)	251 (27.6)	<.001	162 (42.4)	248 (28.1)	<.001
Race			.65			.67
White/Caucasian	268 (75.5)	664 (73.0)		284 (74.3)	648 (73.4)	
Black/African American	71 (20.0)	202 (22.2)		83 (21.8)	190 (21.5)	
Other	16 (4.5)	44 (4.8)		15 (3.9)	45 (5.1)	
<i>Socioeconomic factors, No. (%)</i>						
Married	181 (51.1)	550 (60.4)	.003	192 (50.4)	539 (61.0)	<.001
Greater than high school education	178 (50.1)	531 (58.4)	.008	199 (52.1)	510 (57.8)	.06
Having no insurance	79 (22.6)	144 (16.1)	.007	75 (20.0)	148 (17.0)	.21
Working full- or part-time	164 (46.5)	472 (52.3)	.06	168 (43.3)	468 (53.4)	.003
<i>Medical history, No. (%)</i>						
Hypercholesterolemia	185 (52.1)	449 (49.3)	.38	202 (52.9)	432 (48.9)	.20
Hypertension	248 (69.9)	589 (64.7)	.08	266 (69.6)	571 (64.7)	.09
Peripheral arterial disease	23 (6.5)	39 (4.3)	.11	26 (6.8)	36 (4.1)	.04
Diabetes mellitus	127 (35.8)	221 (24.3)	<.001	124 (32.5)	224 (25.4)	.009
Prior CAD	120 (33.8)	274 (30.1)	.20	144 (37.7)	250 (28.3)	<.001
Prior AMI	84 (23.7)	174 (19.1)	.07	93 (24.3)	165 (18.7)	.02
Prior CABG	40 (11.3)	103 (11.3)	.98	51 (13.4)	92 (10.4)	.13
Prior PCI	80 (22.5)	159 (17.5)	.04	96 (25.1)	143 (16.2)	<.001
Prior angina	51 (14.4)	125 (13.7)	.77	66 (17.3)	110 (12.5)	.02
Prior stroke	18 (5.1)	45 (4.9)	.93	19 (5.0)	44 (5.0)	.99
Chronic renal failure	19 (5.4)	51 (5.6)	.86	21 (5.5)	49 (5.5)	.97
Chronic lung disease	43 (12.1)	43 (4.7)	<.001	44 (11.5)	42 (4.8)	<.001
Chronic heart failure	29 (8.2)	53 (5.8)	.13	31 (8.1)	51 (5.8)	.12

	PHQ Somatic Symptoms			PHQ Cognitive Symptoms		
	Highest Quartile (score $\geq 4$ ) n=355	Lower 3 Quartiles (<4) n=910	P Value	Highest Quartile (score $\geq 2$ ) n=382	Lower 3 Quartiles (score <2) n=883	P Value
Cancer (other than skin)	30 (8.5)	71 (7.8)	.70	29 (7.6)	72 (8.2)	.74
Smoked within last 30 days	162 (45.9)	307 (33.9)	<.001	174 (45.8)	295 (33.6)	<.001
Body Mass Index	30.7 $\pm$ 7.0	29.3 $\pm$ 5.8	<.001	30.1 $\pm$ 6.6	29.5 $\pm$ 6.0	.14
<i>Clinical characteristics index AMI admission, No. (%)</i>						
ST-elevation AMI	156 (43.9)	443 (48.7)	.13	168 (44.0)	431 (48.8)	.11
Ejection fraction <40%	62 (17.5)	144 (15.8)	.47	64 (16.8)	142 (16.1)	.76
Killip class			.36			.55
I (No heart failure)	314 (90.5)	833 (92.2)		339 (90.6)	808 (92.2)	
II (Heart failure)	30 (8.6)	56 (6.2)		29 (7.8)	57 (6.5)	
III (Pulmonary edema)	3 (0.9)	12 (1.3)		6 (1.6)	9 (1.0)	
IV (Cardiogenic shock)	0 (0)	2 (0.2)		0 (0.0)	2 (0.2)	
Diseased vessels (>75% stenosis)			.28			.67
0	27 (8.1)	68 (7.9)		33 (9.4)	62 (7.3)	
1	132 (39.4)	387 (44.8)		148 (42.0)	371 (43.8)	
2	91 (27.2)	228 (26.4)		92 (26.1)	227 (26.8)	
3	85 (25.4)	181 (20.9)		79 (22.4)	187 (22.1)	
Systolic blood pressure, mm Hg	142.5 $\pm$ 30.8	143.7 $\pm$ 29.7	.50	141.7 $\pm$ 30.2	144.1 $\pm$ 29.9	.20
Heart rate, beats per minute	82.7 $\pm$ 23.0	79.7 $\pm$ 19.5	.02	82.0 $\pm$ 22.6	80.0 $\pm$ 19.7	.11
<i>Depressive symptoms, No. (%)</i>						
Depression index AMI admission (PHQ-9 $\geq$ 10)	215 (60.6)	12 (1.3)	<.001	221 (57.9)	6 (0.7)	<.001
PHQ-9 Score	11.8 $\pm$ 5.0	2.6 $\pm$ 2.5	<.001	11.5 $\pm$ 5.0	2.5 $\pm$ 2.4	<.001

\* Depression dimensions were defined by the highest score quartile for somatic and for cognitive depressive symptoms.

<sup>†</sup> Plus-minus values are means  $\pm$  standard deviation.

Abbreviations: PHQ, patient health questionnaire; CAD, coronary artery disease; AMI, acute myocardial infarction; BMI, body mass index (kilograms/meters<sup>2</sup>); CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary interventions; PHQ, patient health questionnaire; STEMI, ST-segment elevation.

**Table 2**  
**Correlations ( $R^2$ ) Between Depressive Symptoms and Biomarkers**

	Hs-CRP		WBC		NT-proBNP		Platelets	
	Correlation	% Variance Explained						
PHQ Somatic Symptoms	0.08**	(0.64%)	0.06*	(0.36%)	0.06*	(0.36%)	0.05	(0.25%)
PHQ Cognitive Symptoms	0.04	(0.16%)	0.02	(0.04%)	0.02	(0.04%)	0.08**	(0.64%)
Overall PHQ-9	0.06*	(0.36%)	0.05	(0.25%)	0.04	(0.16%)	0.07*	(0.49%)

\*\*\* $P \leq .001$ ;

\*\* $P \leq .01$ ;

\* $P \leq .05$ .

Abbreviations: AMI, acute myocardial infarction; PHQ, patient health questionnaire.

$R^2$  equals the squared correlations calculated between the depressive symptoms and each biomarker and are expressed as percentages.