Published in final edited form as:

Psychosom Med. 2015 September ; 77(7): 808–815. doi:10.1097/PSY.0000000000000216.

Inflammation markers and Major Depressive Disorder in Patients with Chronic Heart Failure: Results from the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) study

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Abstract

Background—Major Depressive Disorder (MDD) and Chronic Heart Failure (CHF) have in common heightening states of inflammation, manifested by elevated inflammation markers such as C-reactive protein (CRP). This study compared inflammatory biomarker profiles in CHF patients with MDD to those without MDD.

Methods—The study recruited patients admitted to inpatient care for acute heart failure exacerbations, after psychiatric diagnostic interview. Patients with Beck Depression Inventory (BDI) scores < 10 and with no prior history of depression served as the non-depressed reference group (n = 25). MDD severity was defined as: Mild (BDI 10–15; n = 48); Moderate (BDI 16–23; n = 51); and Severe (BDI ≥ 24; n = 33). A Bio-Plex assay measured 18 inflammation markers. Ordinal logistic models were used to examine the association of MDD severity and biomarker levels.

Results—Adjusting for age, sex, statin use, BMI, LVEF, tobacco use, and NHYA class the MDD overall group variable was significantly associated with elevated interleukin (IL) -2 (p = .019), IL-4 (p = .020), IL-6 (p = .026), interferon (INF)- γ (p = .010), monocyte chemoattractant protein (MCP-1) (p = .002), macrophage inflammatory protein (MIP-1 β) (p = .003) and tumor

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Clinical trials registry: clinicaltrials.gov NCT00078286

Disclosures: Dr. O'Connor reports receiving funding from the following: Actelion Pharmaceuticals Ltd., Amgen, Inc., Biscardia, LLC, Cardiology Consulting Associates, Faculty Connection, GE Healthcare, Ikaria, Neurotronik/Interventional Autonomics Corporation, Novella Clinical, Inc., Pfizer Inc., Pozen, and Roche Diagnostics. The other authors do not have any conflicts of interest to disclose.

necrosis factor (TNF)- α ($p = .004$). MDD severity subgroups had a greater probability of elevated IL-6, IL-8, IFN- γ , MCP-1, MIP-1 β , and TNF- α compared to none-depressed group. The non-depressed group had greater probability of elevated IL-17 ($p < 0.001$) and IL-1 β ($p < 0.01$).

Conclusions—MDD in CHF patients was associated with altered inflammation marker levels compared to CHF patients who had no depression. Whether effective depression treatment will normalize the altered inflammation marker levels requires further study.

Keywords

Heart Failure; Depression; Inflammation markers

INTRODUCTION

Chronic heart failure (CHF) is a common manifestation of cardiovascular diseases, affecting approximately 6 million people in the United States and nearly 25 million worldwide. The lifetime risk of CHF is one in five.¹ Total direct and indirect costs due to CHF in the United States were estimated at \$39.2 billion in 2010.² The adjusted one-year mortality rate has decreased only marginally from 31.7% in 1999 to 29.6% in 2008.³ Major Depressive Disorder (MDD) may be present in up to 40% patients with CHF.⁴ In CHF patients, MDD is an independent risk factor for reduced quality of life, adverse health outcomes and elevated risk of mortality.^{5–12}

In recent years, our understanding of CHF pathogenesis has expanded beyond the traditional hemodynamic model. Emerging studies have demonstrated that inflammatory cytokines and other aspects of the immune system play significant roles in CHF development and progression.^{13,14} It is postulated that myocardial injury leads to activation of the inflammatory cascade. This activation has lasting effects on the circulatory system leading to the development and subsequent worsening of CHF. This hypothesis has received support from multiple lines of inquiry, and suggests that various inflammatory cytokines play roles in the etiology and progression of CHF.

It has become increasingly clear that inflammatory cytokines also play a role in MDD as demonstrated by a number of studies that reported positive associations between severity of depressive symptoms and various markers of inflammation.^{15–20} The exact causal nature of these associations has not been fully delineated, but they do show promise in elucidating mechanisms whereby MDD contributes to elevated morbidity and mortality of cardiovascular diseases.

The common associations between inflammatory processes and both CHF and MDD make cytokines a critical area of study for understanding the co-morbidity of these two conditions.²¹ The association between depressive symptoms and cytokines in CHF has been examined in prior studies but with mixed findings.^{22–24} While one study found that depressive symptoms were associated with elevated IL-6 and CRP,²³ this relationship was not found in two other studies.^{22,24} The same study that did not find a relationship between depression and IL-6 found that higher BDI score is associated with elevated TNF- α .²⁴ Thus far, most studies have limited measurement of inflammation markers to upstream cytokines

such as CRP and IL-6, emerging studies have demonstrated that novel cytokines can play an important role that had been previously under-recognized.^{25,26} The present study attempted to replicate the prior studies and also examined additional inflammation markers in CHF patients with MDD, using data collected from the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) study.^{27–29} We hypothesized that patients with CHF and MDD will have elevated inflammation markers compared to those with CHF and no MDD.

METHODS

Study Population

This study consisted of CHF patients who were enrolled during inpatient hospital admissions in a tertiary academic medical center to the SADHART-CHF study between October 13, 2004 and March 3, 2008. SADHART-CHF is a National Institute of Mental Health (NIMH) sponsored, prospective, randomized, double-blind, placebo-controlled study that was designed to assess the safety and efficacy of sertraline in the treatment of CHF patients with MDD. Patients aged 45 years or older with a diagnosis of CHF of any etiology, left ventricular ejection fraction (LVEF) $\geq$ 45%, New York Heart Association (NYHA) class II, met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for MDD, and provided signed informed consent were eligible for enrollment. Main exclusion criteria included significant cognitive impairment, alcohol or drug dependence within the previous year, psychoses, bipolar disorder, severe personality disorder, active suicidal ideation, life-threatening comorbidity (estimated 50% mortality within 1 year), and current use of antipsychotic or anti-depressant medications. Detailed methods of the SADHART-CHF study have been previously published.^{27–29}

Depression Evaluation

All patients completed the Beck Depression Inventory (BDI) as the first step of depression screening. Patients whose BDI scores were $\geq$ 10 were administered the Diagnostic Interview Schedule, a structured psychiatric interview, which was used to establish MDD diagnosis. Patients whose BDI scores were $<$ 10 and who had no prior history of MDD via the Diagnostic Interview Schedule interview were enrolled into the non-depressed group ($n = 40$) for the biomarker substudy. Classification and severity of MDD were determined by a priori cut-offs. Mild MDD was defined as having a BDI score from 10–15. Moderate was score between 16–23. Severe was score $\geq$ 24. The BDI scores were treated in the above four categories and not analyzed as a continuous variable.

Collection of Blood Samples

The biomarker substudy was approved by the Duke Institutional Review Board at the beginning of October 2004 as an add-on to the SADHART-CHF trial. Participation in this substudy was voluntary and refusal to participate had no effect on patients' participation in the parent study.

Blood samples were collected using a Vacutainer system (Ref# 367983) containing clot activator and gel serum separator. The samples were centrifuged using a Sorvall Model RT 7

Plus Centrifuge at a g-force of 1864 (3000 rpm for 10 minutes at a fixed angle of 34°). The resulting serum was aliquoted in cryogenic vial tubes (Fisher Scientific microtube 2 mL Catalog#: NC9739217) and frozen at -80°C. Once all samples were collected, the tubes were marked with a unique number to blind them and were sent to the laboratory for assays. Blood samples used for this study were collected at the baseline prior to the SADHART-CHF trial intervention.

Assessment and Quantification of Inflammation markers

InterleukinIL-1 β (IL-1 β) (Range (R) 3.2–3,261pg/ml; Limit of Detection (LOD) 0.6pg/ml), IL-2 (R 2.1–17,772pg/ml; LOD 1.6pg/ml), IL-4 (R 2.2–3,467pg/ml; LOD 0.7pg/ml), IL-5 (R 3.1–7,380pg/ml; LOD 0.6pg/ml), IL-6 (R 2.3–18,880pg/ml; LOD 2.6pg/ml), IL-7 (R 3.1–6,001pg/ml; LOD 1.1pg/ml), IL-8 (R 1.9–26,403pg/ml; LOD 1.0pg/ml), IL-10 (R 2.2–8,840pg/ml; LOD 0.3pg/ml), IL-12p70 (R3.3–13,099pg/ml; LOD 3.5pg/ml), IL-13 (R 3.7–3,137pg/ml; LOD 0.7pg/ml), IL-17 (R4.9–12,235pg/ml; LOD 3.3pg/ml), granulocyte colony-stimulating factor [G-CSF] (R2.4–11,565pg/ml; LOD 1.7pg/ml), granulocyte-macrophage colony-stimulating factor [GM-CSF] (R 63.3–6,6039pg/ml; LOD 2.2pg/ml), Interferon [IFN]- γ (R 92.6–52,719pg/ml; LOD 6.4pg/ml), monocyte chemoattractant protein [MCP]-1 (R 2.1–1,820pg/ml; LOD 1.1pg/ml), macrophage inflammatory protein [MIP]-1 β (R 2.0–1,726pg/ml; LOD 2.4pg/ml), and TNF- α (R 5.8–95,484pg/ml; LOD 6.0 pg/ml) were measured using a Bio-Plex assay, which employed a bead-based sandwich immunoassay technique. A monoclonal antibody specific for each cytokine of interest was coupled onto a particular set of beads with a known internal fluorescence, and several combinations of cytokine antibody coated beads could be included and thus multiple cytokines are measured simultaneously. The assays were performed according to the manufacturer's instructions using a BioPlex-kit (BioRad, Hercules, CA, USA) in the Dermatology Diagnostic Immunology Laboratory headed by Russell Hall MD. C-reactive protein (CRP) levels were determined using the Quantikine ELISA CRP immunoassay (R&D Systems, Minneapolis, MN, Mean Detectable Dose (MDD) 0.01 ng/ml).

Briefly, 50 ml of standard or test sample along with 50 ml of mixed beads were added into the wells of a pre-wet 96-well microtiter plate. After 1 h incubation and washing, 25 ml of detection antibody mixture were added and the samples were incubated for 30 min and then washed. Finally, 50 ml of streptavidin-PE was added and after 10 min incubation and washing, the beads were resuspended in 125 ml of assay buffer and analyzed employing a BioPlex suspension array system (BioRad Laboratories) and the BioPlex manager software (version 3.0). A minimum of 100 beads per region were analyzed. Using a 5th order polynomial regression analysis, a curve fit was applied to each standard curve according to the manufacturer's manual and sample concentrations were interpolated from the standard curves.³⁰

Statistical Analysis

Demographics were compared between the four groups (the MDD severity groups and the none-depressed group) using a one-way analysis of variance (ANOVA) for age and separate chi-square tests for gender, race, and statin use.

Visual inspection of the cytokine value distributions revealed that several cytokines had a large number of values (i.e. >50%) that were below the level of detection, thus creating difficulties in using parametric approaches in data analysis. For example, IL-2 and GM-CSF levels were not quantifiable in 86% of patients. Other cytokines with a large number of values beneath the detection threshold included IL-17 (78%), IL-4 (78%), IFN- γ (78%), IL-10 (65%), G-CSF (63%), IL-13 (57%), and IL-12 (54%). Therefore, we chose to model the cytokine data as ordinal outcomes using ordinal logistic regression. Prior to analysis, the data for each cytokine were recoded into six groups. Values that fell below the limit of detection were assigned to the smallest ordinal group. The remaining values, those above the limit of detection, were then divided into five equally sized groups based on their respective quintiles. In the event that no values fell below the limit of detection, data were split into six equally sized percentile groups. An advantage to using a smaller number of categories rather than the continuous scores is that the estimates of the regression coefficients of the covariates and their standard errors are close to those for the ungrouped data. It also avoids estimating a large number of nuisance parameters (i.e. the y-intercept for each level of the criterion variable) at the expense of degrees of freedom. The ordinal logistic models contained the four-group depression variable and age, sex, statin use, body mass index (BMI), tobacco use, NYHA class, and LVEF as covariates. Separate models were fitted for each cytokine measure. Type I error was controlled for this multiple testing process by applying the Hommel procedure,^{31,32} which is a more appropriate method than the Bonferroni correction when dealing with correlated outcomes (i.e. cytokines).

We also fitted a multivariate analysis of covariance (MANCOVA) to model the association between depression status and the 18 inflammation markers. Values of inflammatory markers that were beneath the detection threshold were assigned a value of zero for this analysis. The MANCOVA included age, sex, statin use, BMI, tobacco use, LVEF and NYHA class as covariates. The Wilk's Λ statistic was used to judge significance. To locate the sources responsible for the global differences reflected by the MANCOVA, analysis of covariance (ANCOVA) were used evaluate the association of the depression variables with each cytokine. Statistical analyses were performed using SAS, version 9.3 (SAS Incorporated, Cary, NC).

RESULTS

Subject Characteristics

Blood samples were collected from a total of 175 CHF patients; 135 with MDD and 40 in the none-depressed group. Due to limited blood volume following the metabolomics and the lipidomics studies^{33,34}, adequate blood sample volume suitable for this inflammatory biomarker study was only available for 157 of the 175 subjects. Two subjects were missing data for important covariates resulting in a final sample size of 155: 130 from the MDD groups (Mild: n = 48; Moderate: n = 49; and Severe: n = 33) and 25 from the none-depressed group.

The baseline characteristics of these subjects are described in Table 1. The patients in the none-depressed group tended to be older (65.60 ± 11.70 vs. 59.79 ± 9.67 , $p = 0.010$), consisted of more men (80% vs. 70%; $p = 0.31$), were less likely to use statin medication

(52% vs. 75%; $p = 0.018$), had a lower BMI (26.79 ± 4.55 vs. 32.17 ± 8.95 $p = .004$), lower LVEF (24.60 ± 9.67 vs. 29.35 ± 10.28 ; $p = 0.034$) and lower NYHA class (2.52 ± 0.87 vs. 2.81 ± 0.67 ; $p = 0.064$), and was less likely to smoke (76% vs 72%; $p = 0.41$), compared to those in the MDD groups.

Inflammatory Biomarker Profiles

Overall, the analysis showed that the inflammatory biomarker profiles of CHF patients with MDD were different from the non-depressed group (Table 2 and Table 3). The MANCOVA evaluating the main effect of the depression variable was significant $F(54, 379.226) = 3.30$, $p < .001$ when the cytokines are considered simultaneously. ANCOVAs showed significant associations between the depression variable and IL-1 β ($p = .006$), IL-4 ($p = .006$), IL-6 ($p = .026$), IL-17 ($p < .001$), IFN- γ ($p = .004$), MIP-1 β ($p = .014$), and TNF- α ($p = .003$). These associations essentially parallel those of our shown by our primary analysis using logistic regression in that there was pattern for MDD patients, particularly those with severe MDD, to show higher levels of IL-4, IL-6, IFN- γ , MIP-1 β , and TNF- α and lower levels of IL-1 β and IL-17.

Analyses of the six-level ordinal inflammation marker variables showed parallel results (Table 3). After adjusting for age, sex, statin use, BMI, LVEF, tobacco use, and NYHA class, the ordinal logistic regression models (Table 3) demonstrated that overall MDD status was significantly associated with IL-1 β ($p = .011$), IL-2 ($p = .019$), IL-4 ($p = .021$), IL-6 ($p = .026$), IL-17 ($p < .001$), INF- γ ($p = .010$), MCP-1 ($p = .004$), MIP-1 β ($p = .003$), and TNF- α ($p = .004$) when compared to the non-depressed group. Examination of the odds ratios (OR) of each MDD severity subgroup comparing to the non-depressed group showed the tendency of MDD patients, particularly those with severe MDD, to have a greater probability of elevated levels of IL-6, IL-8, IFN- γ , MCP-1, MIP-1 β , and TNF- α . Conversely, the none-depressed group had a tendency to have a greater probability of elevated IL-17 and IL-1 β .

Using the Hommel adjusted p-values, the effects for IL-17 ($p = .002$) and MIP-1 β ($p = .045$) were significant and the effects for MCP-1 ($p = .056$) and TNF- α ($p = .056$) were marginally significant. After adjustment for the other variables in the model, female sex was associated with a greater probability of elevated IL-1 β (OR = 2.56, $p = .016$), IL-6 (OR = 3.13, $p = .001$), and IFN- γ (OR = 2.86, $p = .052$); statin use was associated with a greater probability of elevated IL-2 (OR = 4.00, $p = .019$) and IFN- γ (OR = 2.50, $p = .050$) and a lower probability of G-CSF (OR = 0.43, $p = .050$); current smokers had a higher probability of IL-6 (OR = 1.76, $p = .014$) and IL-8 (OR = 2.00, $p = .003$); and lower LVEF was associated with a higher probability of elevated levels of IL-1 β (OR = 1.04, $p = .019$), IL-7 (OR = 1.04, $p = .019$), IL-10 (OR = 1.04, $p = .031$), IL-12p70 (OR = 1.03, $p = .047$), and IFN- γ (OR = 1.08, $p = .024$). Although higher CRP was shown with greater depressive symptoms, i.e., none-depressed: 12.01 ± 9.21 ; Mild: 12.58 ± 11.34 , Moderate: 16.47 ± 12.84 , and Severe: 16.17 ± 13.52 ; there was no statistical significance among the four groups.

DISCUSSION

This study demonstrated associations between MDD and altered level of inflammatory markers in CHF patients with acute heart failure exacerbations. Logistic regression analysis, adjusted for age, sex, statin use, BMI, LVEF, tobacco use, and NYHA class, suggested elevations in multiple inflammation markers, i.e. IL-6, IL-8, IFN- γ , MCP-1, MIP-1 β , and TNF- α , and lower levels of IL-17 and IL-1 β in MDD relative to non-depressed CHF patients. The results of the MANCOVA generally confirmed those findings. The overall pattern of these associations may help explain the well-established link between high levels of depressive symptoms and worsening prognosis in patients with CHF.

Our study findings are in line with previous studies that found an association between MDD and elevated IL6, and TNF- α .^{16,24} In a meta-analysis of 24-studies, Dowlati and colleagues found that IL-6 and TNF- α were both elevated with MDD in medically healthy and non-medicated depressed subjects.³⁵ The current study demonstrated a statistically significant association of MDD and elevated IL-6 and TNF- α , extending earlier observations with medically healthy subjects to those with CHF.

It is important to note that our study sample consisted of inpatients with CHF exacerbations and therefore direct comparison with other CHF and depression studies may be limited by methodological differences. In separate outpatient CHF studies, Johansson et al. found that BDI score was associated with TNF- α but not IL-6 or IL-1 β ,²² while Dekker did not find any relationship between inflammation markers (CRP, IL-6, TNF- α , etc.) and depressive symptoms.²³ In an inpatient CHF sample, Dekker et al. found that BDI score was associated with elevated TNF- α but not IL-6 or IL-1 β .²⁴ However, the study did not adjust for statin use, LVEF, and other clinical variables used in the present study.

We did not find a significant association between MDD and CRP levels in our population, though we did observe the higher levels in patients with moderate and severe MDD. This finding is at variance with previous reports, such as the one from the National Health and Nutrition Examination Study (NHANES) III study which reported that CRP elevation was significantly associated with MDD severity in a dose response manner.³⁶ However, the NHANES population consisted of “noninstitutionalized” men and woman ages 18–39 years with MDD but no predominant medical disorders. The current study population was comprised of an older population with significant history of CHF who were hospitalized for acute heart failure exacerbations. Even in the non-depressed group, the mean CRP level was elevated (12.01 ± 9.21 mg/L) suggesting that within the context of acute exacerbation, the acute phase reactant, CRP, may be less sensitive to the condition of MDD. This is still somewhat surprising given our finding that MDD was associated with a greater likelihood of elevated IL-6, a cytokine that stimulates CRP production.

As compared with prior CHF studies, our findings are consistent with previous findings that showed elevated IL-6²² and elevated TNF- α ²⁴ in patients with MDD compared to CHF patients without MDD. The finding that IL-17 was significantly lower in the MDD groups is intriguing and has not been reported previously. IL-17 was discovered in 1995 as a T-cell cytokine that acts as a potent mediator in delayed-type reactions by increasing chemokine

production in various tissues to recruit monocytes and neutrophils to the site of inflammation, similar to IFN- γ .³⁷ IL-17 is a pro-inflammatory cytokine that responds to the invasion of the immune system by extracellular pathogens and induces destruction of the pathogen's cellular matrix. IL-17 acts synergistically with TNF- α and IL-1.^{38,39} While most of the cytokines we studied are associated with an elevated risk for cardiovascular disease, IL-17 has been shown to have a protective function in coronary heart disease, with studies showing lower levels of IL-17 to be associated with an elevated risk of death and recurrent myocardial infarction.^{25,26} It is, however, important to note that only 34 out of 157 patients had discernable levels of IL-17.

This study had a number of limitations that might affect the inferences we can draw regarding the association between depression severity and cytokine levels. We tested associations between depression severity and a large number of cytokines ($N = 18$), which could have resulted in type 1 errors. We controlled for the multiple testing problem by employing the Hommel correction. However, a potential cost of utilizing a correction for multiple testing in studies with low power is an increase in the likelihood of false negative findings. Residual confounding is another potential limitation of this study. In our analysis, we found that depression severity was associated with cytokines independent of a number of potential confounders including age, sex, BMI, statin usage, smoking status, NYHA class, and resting LVEF. Still, there are other important co-morbidities (eg. diabetes) and disease severity variables (eg. BNP) that would be useful to examine as possible confounders or even mediators of associations between cytokines and depression severity. However, issues related to small sample size and availability of additional covariate data could not allow these possibilities to be properly tested. Ultimately, the associations described in this paper will require replication in larger samples before definitive conclusions be drawn regarding the association between depression severity and inflammatory markers in CHF patients.

The study contained a relatively small sample size that was partially attributed to the large number of SADHART-CHF subjects who did not participate in this ancillary study. Another limitation of the study is the cross-section design which precludes the ability to examine the evolution of depressive symptoms relative to changes in inflammatory biomarker levels or vice versa. In fact, the relationship between depression and inflammation could be bidirectional and this study is unable to examine this complex phenomenon.

In summary, our study demonstrated that CHF patients with MDD had an altered inflammatory biomarker profile compared to CHF patients with no MDD. The ability to differentiate inflammatory biomarker profiles in acutely ill patients with comorbid MDD may lead to better understanding of the pathophysiology of MDD and ultimately to novel targets for monitoring MDD progression and treatment.

Acknowledgments

Funding Sources: The SADHART-CHF study was funded by the National Institute of Mental Health (NIMH), Bethesda, Maryland. Sertraline was supplied by Pfizer, Inc., New York, New York. Pfizer had no other role in any aspect of the study.

We would also like to thank Jennifer L. Wilson, BA for here editorial assistance.

Abbreviations

BDI	Beck Depression Inventory
BMI	body mass index
CHF	Chronic heart failure
CRP	C-reactive protein
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
IFN-γ	interferon gamma IL, Interleukin
MCP-1	monocyte chemoattractant protein
MCP-1β	macrophage inflammatory protein
TNF-α	tumor necrosis factor
NYHA	New York Heart Association class
LVEF	left ventricular ejection fraction
SADHART-CHF	Sertraline Against Depression and Heart Disease in Chronic Heart Failure
MDD	Major Depressive Disorder
NIMH	National Institute of Mental Health

References

1. Bui AL, Horwich TB, Fonarow GC. Nat Rev Cardiol. 2011; 8:30–41. [PubMed: 21060326]
2. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics, 2010 update: a report from the American Heart Association. Circulation. 2010; 121(7):e46–e215. [PubMed: 20019324]
3. Chen J, Normand SLT, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008. JAMA. 2011; 306(15): 1669–1678. [PubMed: 22009099]
4. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48:1527–37. [PubMed: 17045884]
5. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med. 2001; 161:1849–1856. [PubMed: 11493126]
6. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, Krumholz HM, Spertus JA. Cardiovascular Outcomes Research Consortium. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. J Am Coll Cardiol. 2003; 42:1811–1817. [PubMed: 14642693]

7. Rozzini R, Sabatini T, Frisoni GB, Trabucchi M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med.* 2002; 162:362–363. [PubMed: 11822939]
8. Penninx B, Beekman ATF, Honig A, Deeg DJH, Schoevers RA, van Eijk JTM, van Tilburg W. Depression and cardiac mortality—results from a community-based longitudinal study. *Arch Gen Psychiatry.* 2001; 58:221–227. [PubMed: 11231827]
9. Rozzini R, Sabatini T, Frisoni GM, Trabucchi M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med.* 2002; 162:362–363. [PubMed: 11822939]
10. Vaccarino V, Kasl SV, Abramson J, Krumholz HR. Depressive symptoms and risk of functional decline and death in patients with heart failure. *J Am Coll Cardiol.* 2001; 38:199–205. [PubMed: 11451275]
11. Rumsfeld JS, Havranek E, Masoudi FA, Peterson ED, Jones P, Tooley JF, Krumholz HM, Spertus JA. Cardiovascular Outcomes Res C. Depressive symptoms are the strongest predictors of short-term declines in health status in patients with heart failure. *J Am Coll Cardiol.* 2003; 42:1811–1817. [PubMed: 14642693]
12. Angermann CE, Gelbrich G, Stork S, Fallgatter A, Deckert J, Faller H, Ertl G. MOOD-HF Investigators. . Rationale and design of a randomised, controlled, multicenter trial investigating the effects of selective serotonin re-uptake inhibition on morbidity, mortality and mood in depressed heart failure patients (MOOD-HF). *Eur J Heart Fail.* 2007; 9:1212–22. [PubMed: 18029292]
13. Givertz MM, Colucci WS. New targets for heart-failure therapy: endothelin, inflammatory cytokines, and oxidative stress. *Lancet.* 1998; 352(Suppl 1):34–8. [PubMed: 9800749]
14. Seta Y, Shan K, Bozkurt B, Oral H, Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. *J Cardiac Failure.* 1996; 2:243–9. [PubMed: 8891862]
15. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. *Am J Cardiol.* 2002; 90:1279–1283. [PubMed: 12480034]
16. Suarez EC. C-reactive protein is associated with psychological risk factors of cardiovascular disease in apparently healthy adults. *Psychosom Med.* 2004; 66(5):684–691. [PubMed: 15385692]
17. Suarez EC, Krishnan RR, Lewis JG. The Relation of Severity of Depressive Symptoms to Monocyte-Associated Proinflammatory Cytokines and Chemokines in Apparently Healthy Men. *Psychosom Med.* 2003; 65(3):362–368. [PubMed: 12764208]
18. Kop WJ, Gottdiener JS, Tangen CM, Friend LP, McBurnie MA, Walston J, Newman AP, Hirsch C, Tracy RP. Inflammatory and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol.* 2002; 89:419–424. [PubMed: 11835923]
19. Dentino AN, Pieper CF, Rao KMK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatric Soc.* 1999; 47:6–11.
20. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009; 65(9):732–741. [PubMed: 19150053]
21. Pasic J, Levy WC, Sullivan MD. Cytokines in depression and heart failure. *Psychosom Med.* 2003; 65:181–193. [PubMed: 12651985]
22. Johansson P, Lesman-Leegte I, Svensson E, Voors A, van Veldhuisen DJ, Jaarsma T. Depressive symptoms and inflammation in patients hospitalized for heart failure. *Am Heart J.* 2011; 161:1053–9. [PubMed: 21641350]
23. Dekker RL, Moser DK, Chung ML2, Heo S3, Wu JR4, Dunbar SB5, Pressler SJ6, Lennie TA2. Depressive symptoms and inflammation markers in patients with heart failure. *Eur J Cardiovasc Nurs.* 2014; 13(5):444–50. [PubMed: 24062026]
24. Ferketich AK, Ferguson JP, Binkely PF. Depressive symptoms and inflammation among heart failure patients. *Am Heart J.* 2005; 150:132–6. [PubMed: 16084159]
25. Troitskaya M, Baysa A, Vaage J, Sand KL, Maghazachi AA, Valen G. Interleukin-17 (IL-17) expression is reduced during acute myocardial infarction: Role on chemokine receptor expression in monocytes and their in vitro chemotaxis towards chemokines. *Toxins.* 2012; 4:1427–1439. [PubMed: 23202375]

26. Simon T, Taleb S, Danchin N, Laurans L, Rousseau B, Cattani S, Montely JM, Dubourg O, Tedgui A, Kotti S, Mallat Z. Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction. *Eur Heart J*. 2013; 34:570–577. [PubMed: 22956509]
27. Jiang W, O'Connor C, Silva SG, Kuchibhatla M, Cuff MS, Callwood DD, Zakhary B, Henke, Arias RM, Krishnan R. SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with CHF (SADHART-CHF): a randomized, double-blind, placebo-controlled trial of sertraline for major depression with congestive heart failure. *Am Heart J*. 2008; 156:437–44. [PubMed: 18760123]
28. O'Connor CM, Jiang W, Kuchibhatla M, Silva SG, Cuffe MS, Callwood DD, Zakhary B, Stough WG, Arias RM, Rivelli SK, Krishnan R. SADHART-CHF Investigators. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHARTCHF trial. *J Am Coll Cardiol*. 2010; 56:692–699. [PubMed: 20723799]
29. Jiang W, Krishnan R, Kuchibhatla M, Cuff MS, Martzberger C, Arias RM, O'Connor CM. SADHART-CHF Investigators. Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF study). *Am J Card*. 2011; 107:545–551. [PubMed: 21295172]
30. Hall RP, Benbenisty KM, Mickle C, Takeuchi F, Streilein RD. Serum IL-8 in patients with dermatitis herpetiformis is produced in response to dietary gluten. *J Invest Dermatol*. 2007; 127:2158–2165.
31. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika*. 1988; 75:383–386.
32. Blakesley RE, Mazumdar S, Dew MA, Houck PR, Tang G, Reynolds CF 3rd, Butters MA. Comparisons of methods for multiple hypothesis testing in neuropsychological research. *Neuropsychology*. 2009 Mar; 23(2):255–64. [PubMed: 19254098]
33. Steffens DC, Jiang W, Krishnan KRR, Karoly ED, Mitchell MW, O'Connor CM, Kaddurah-Daouk R. Metabolomic differences in heart failure patients with and without major depression. *J Ger Psychol*. 2010; 23(2):138–146.
34. Jiang W, Oken H, Fiuzat M, Shaw LK, Martzberger C, Kuchibhatla M, Kaddurah-Daouk R, Steffens DC, Baillie R, Cuffe M, et al. Plasma omega-3 polyunsaturated fatty acids and survival in patients with chronic heart failure and major depressive disorder. *J Cardiovasc Transl Res*. 2012; 5(1):92–99. [PubMed: 22042636]
35. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010; 67:446–457. [PubMed: 20015486]
36. Ford DE, Erlinger TP. Depression and C-Reactive Protein in US Adults: Data from the third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2004; 164(9):1010–1014. [PubMed: 15136311]
37. Kubly, Janis; Kindt, Thomas J.; Goldsby, Richard A.; Osborne, Barbara A. Kubly Immunology. San Francisco: W.H. Freeman; 2007. p. 396
38. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nogales KE, Tian S, Cardinale I, Chimenti S, Krueger JG. Integrative responses to IL-17 and TNF- α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J Invest Dermatol*. 2011; 131(3):677–87. [PubMed: 21085185]
39. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. *N Engl J Med*. 2009; 361(9):888–98. [PubMed: 19710487]

Table 1

Baseline participant characteristics

		Overall (n=155)	None-Depressed (n=25)	Mild (n=48)	Moderate (n=49)	Severe (n=33)	Test statistic; p value
Age							
(years)	Mean	60.73 ± 10.43	65.60 ± 11.70	60.75 ± 10.58	58.12 ± 8.08	60.88 ± 11.37	$F_{(3,151)} = 2.95$; $p = 0.035$
Gender							$\chi^2 = 12.01$; $p = 0.007$
Male	N (%)	111 (71%)	20 (80%)	35 (73%)	40 (78%)	16 (48%)	
Female	N (%)	46 (29%)	5 (20%)	13 (27%)	11 (22%)	17 (52%)	
Race							$\chi^2 = 9.40$; $p = 0.15$
White	N (%)	83 (54%)	12 (48%)	28 (58%)	22 (45%)	21 (64%)	
Black	N (%)	60 (39%)	12 (48%)	17 (36%)	24 (49%)	7 (21%)	
Other	N (%)	12 (7%)	1 (4%)	3 (6%)	3 (6%)	5 (15%)	
Tobacco Use							$\chi^2 = 2.91$; $p = 0.41$
No	N (%)	42 (27%)	6 (24%)	17 (35%)	10 (20%)	9 (27%)	
Yes	N (%)	113 (73%)	19 (76%)	31 (65%)	39 (80%)	24 (73%)	
NYHA Class							$\chi^2 = 20.03$; $p = 0.17^*$
I	N (%)	3 (28%)	3 (12%)	0 (0%)	0 (0%)	0 (0%)	
II	N (%)	53 (72%)	9 (36%)	20 (42%)	13 (27%)	11 (33%)	
III	N (%)	77 (72%)	10 (40%)	23 (48%)	26 (53%)	18 (55%)	
IV	N (%)	22 (72%)	3 (12%)	5 (10%)	10 (20%)	4 (12%)	
Statin Use							$\chi^2 = 9.41$; $p = 0.024$
No	N (%)	44 (28%)	12 (48%)	7 (15%)	15 (31%)	10 (30%)	
Yes	N (%)	111 (72%)	13 (52%)	41 (85%)	34 (69%)	23 (70%)	
LVEF (%)	Mean	28.59 ± 10.30	24.60 ± 9.67	31.15 ± 10.76	27.86 ± 10.77	28.97 ± 8.57	$F_{(3,151)} = 2.40$; $p = 0.070$
BMI (kg/m²)	Mean	31.31 ± 8.63	26.79 ± 4.55	34.20 ± 8.07	32.12 ± 9.73	32.21 ± 9.32	$F_{(3,151)} = 2.82$; $p = 0.041$
BDI	Mean	16.55 ± 7.95	4.74 ± 2.12	12.83 ± 1.55	19.06 ± 2.37	27.76 ± 4.25	$F_{(3,151)} = 392.42$; $p < 0.001$

Values are mean (SD) or %. Statistical tests examined associations of demographic and clinical variables to severity of depressive symptoms. Chi-square or *Fisher exact tests were used for categorical variables, and *t* tests were used for continuous variables. NYHA = New York Heart Association class; LVEF = left ventricular ejection fraction; BMI = body mass index; BDI = Beck Depression Inventory.

Table 2

Cytokine levels based on depression severity.

	Non-depressed (n = 25)		Mild (n = 48)		Moderate (n = 49)		Severe (n = 33)	
	Median (25th, 75th)		Median (25th, 75th)		Median (25th, 75th)		Median (25th, 75th)	
CRP	9862.67 (4572.84,17678.03)		8004.30 (4243.48,16997.82)		13377.50 (4151.60,29744.65)		15076.77 (3773.71,29518.74)	
IL-1β	0.34 (0.12,0.50)		0.00 (0.00,0.29)		0.01 (0.00,0.22)		0.00 (0.00,0.52)	
IL-2	0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)	
IL-4	0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.23)	
IL-5	0.21 (0.00,1.28)		0.00 (0.00,0.35)		0.00 (0.00,0.28)		0.00 (0.00,0.47)	
IL-6	4.51 (2.84,7.15)		5.68 (2.42,13.48)		7.64 (3.00,18.32)		8.73 (4.85,20.28)	
IL-7	0.29 (0.00,4.37)		0.69 (0.00,4.50)		1.16 (0.00,3.38)		3.25 (0.00,4.63)	
IL-8	7.28 (5.31,13.76)		7.96 (5.09,14.79)		11.98 (6.35,17.58)		13.29 (8.00,21.23)	
IL-10	0.00 (0.00,0.00)		0.00 (0.00,0.39)		0.00 (0.00,0.95)		0.00 (0.00,0.24)	
IL-12p70	0.85 (0.00,4.60)		0.00 (0.00,0.85)		0.00 (0.00,1.47)		0.21 (0.00,2.97)	
IL-13	0.17 (0.00,0.52)		0.00 (0.00,0.14)		0.00 (0.00,0.21)		0.00 (0.00,0.63)	
IL-17	19.96 (0.00,58.11)		0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)	
G-CSF	0.00 (0.00,1.25)		0.00 (0.00,0.02)		0.00 (0.00,2.74)		0.00 (0.00,4.15)	
GM-CSF	0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)	
IFN-γ	0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,0.00)		0.00 (0.00,4.94)	
MCP-1	22.52 (8.95,27.05)		45.88 (28.0,74.79)		33.36 (18.25,65.88)		35.90 (21.34,53.83)	
MIP-1β	83.64 (51.07,132.82)		122.19 (101.16,165.12)		121.65 (89.45,152.26)		145.50 (98.55,171.10)	
TNF-α	2.65 (0.00,5.24)		0.00 (0.00,4.98)		0.00 (0.00,2.36)		3.82 (0.00,23.55)	

Overall MANCOVA $F(54, 379.226) = 3.30, p < .001$ adjusted for age, sex, statin use, BMI, tobacco use, LVEF and NHYA class

* Values are unadjusted. CRP is expressed in ng/mL. All other cytokines are expressed as pg/mL. CRP = C-reactive protein; IL = Interleukin; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN- γ = interferon gamma; MCP-1 = monocyte chemoattractant protein; MCP-1 β = macrophage inflammatory protein 1 β ; TNF- α = tumor necrosis factor.

** Values of inflammatory markers that were beneath the detection threshold were assigned a value of zero.

Table 3

Ordinal Regression Models

	Mild			Moderate			Severe			Overall Depression effect		
	Odds Ratio (95% CI)	p value		Odds Ratio (95% CI)	p value		Odds Ratio (95% CI)	p value		$\chi^2(3df)$	p value	
CRP	0.73 (0.28, 1.81)	0.48		1.21 (0.48, 3.01)	0.69		1.08 (0.41, 2.87)	0.87		2.19	0.53	
IL-1 β	0.21 (0.08, 0.57)	0.003		0.24 (0.09, 0.64)	0.005		0.46 (0.17, 1.29)	0.14		11.24	0.011	
IL-2	5.23 (0.76, 35.82)	0.09		2.01 (0.27, 15.01)	0.50		6.89 (0.97, 49.10)	0.05		5.47	0.019	
IL-4	0.94 (0.24, 3.64)	0.93		0.63 (0.16, 2.42)	0.50		3.23 (0.88, 11.93)	0.08		9.73	0.021	
IL-5	0.45 (0.16, 1.26)	0.13		0.37 (0.13, 1.01)	0.06		0.76 (0.26, 2.23)	0.62		4.16	0.20	
IL-6	1.95 (0.76, 5.00)	0.17		1.97 (0.78, 4.99)	0.15		4.59 (1.67, 12.61)	0.003		9.23	0.026	
IL-7	1.37 (0.52, 3.56)	0.52		0.77 (0.30, 2.00)	0.60		2.32 (0.85, 6.39)	0.10		6.81	0.078	
IL-8	1.08 (0.43, 2.75)	0.87		1.90 (0.76, 4.77)	0.17		2.45 (0.91, 6.58)	0.08		5.77	0.12	
IL-10	4.08 (1.08, 15.39)	0.04		3.77 (1.03, 13.82)	0.05		3.17 (0.80, 12.61)	0.10		4.66	0.20	
IL-12p70	0.35 (0.13, 0.96)	0.04		0.41 (0.15, 1.08)	0.07		0.81 (0.29, 2.24)	0.69		6.49	0.090	
IL-13	0.68 (0.25, 1.85)	0.45		0.38 (0.14, 1.05)	0.06		0.70 (0.24, 2.00)	0.50		3.91	0.27	
IL-17	0.02 (0.005, 0.01)	<0.001		0.015 (0.003, 0.07)	<0.001		0.07 (0.02, 0.27)	<0.001		35.73	<0.001	
G-CSF	0.59 (0.19, 1.81)	0.35		1.35 (0.46, 3.94)	0.58		2.05 (0.67, 6.32)	0.21		7.20	0.066	
GM-CSF	1.80 (0.32, 10.29)	0.51		1.80 (0.33, 9.85)	0.50		2.58 (0.44, 15.06)	0.29		1.13	0.77	
IFN- γ	1.55 (0.39, 6.25)	0.54		0.44 (0.11, 1.84)	0.26		3.45 (0.88, 13.57)	0.08		11.29	0.010	
MCP-1	6.26 (2.35, 16.69)	<0.001		3.79 (1.47, 9.76)	0.006		3.36 (1.23, 9.16)	0.018		13.52	0.004	
MIP-1 β	4.23 (1.64, 11.23)	0.003		3.42 (1.33, 8.79)	0.01		6.75 (2.42, 18.81)	<0.001		13.88	0.003	
TNF- α	0.90 (0.33, 2.44)	0.83		0.62 (0.23, 1.68)	0.35		3.12 (1.10, 8.82)	0.03		13.44	0.004	

Odds ratios for the association between depression subgroups with elevated (upper quintile) inflammation markers are adjusted for age, sex, statin use, body mass index, tobacco use, New York Heart Association class, and left ventricular Ejection fraction. CRP = C-reactive protein; IL = Interleukin; GM-CSF = granulocyte-macrophage colony-stimulating factor; G-CSF = granulocyte colony-stimulating factor; IFN- γ = interferon gamma; MCP-1 = monocyte chemoattractant protein; MCP-1 β = macrophage inflammatory protein [MIP]-1 β ; TNF- α = tumor necrosis factor.