Inflammation, Obesity, and Metabolic Syndrome in Depression: Analysis of the 2009–2010 National Health and Nutrition Examination Survey (NHANES)

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ABSTRACT

Objective: To describe the rates of elevated inflammation, obesity, and metabolic syndrome (MetS) within a large cohort of individuals with depression and to examine the interrelationships of inflammation and MetS in depressed individuals.

Method: Analyses were conducted on study participants from the 2009–2010 National Health and Nutrition Examination Survey (NHANES) with Patient Health Questionnaire (PHQ-9) depression scores ≥ 10 to (1) examine the relationship of inflammation (C-reactive protein; CRP) with demographic and clinical characteristics and (2) examine the prevalence of MetS criteria within CRP groups.

Results: 5,579 participants provided PHQ-9 data; of those, 606 had PHQ-9 scores ≥ 10 and were included in further analysis. Of the 606 depressed participants, 585 participants had valid CRP data; 275 participants (47.01%) had CRP levels ≥ 3.0 mg/L, while 170 (29.06%) had CRP levels ≥ 5.0 mg/L. Elevated inflammation was significantly correlated with body weight, waist circumference, body mass index, insulin, 2-hour glucose tolerance, and self-report general health (*P* values < .05). 112 subjects (41.18%) met American Heart Association/National Heart, Lung, and Blood Institute criteria for MetS. Those with elevated CRP were more likely to meet criteria for MetS (odds ratios of 2.81 for those with CRP levels ≥ 3.0 mg/L and 1.94 for those with CRP levels ≥ 5.0 mg/L).

Conclusions: Over 29% of depressed individuals had elevated levels of CRP, and 41% met criteria for MetS. Individuals with elevated inflammation are more likely to be obese and meet criteria for MetS. These results highlight the significant inflammatory and metabolic burden of individuals with depression.

J Clin Psychiatry 2014;75(12):e1428–e1432

Submitted: *January 21, 2014; accepted April 23, 2014 (doi:10.4088/JCP.14m09009).*
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Major depressive disorder (MDD) is a chronic, recurring disorder that results in significant emotional and socioeconomic burden.[1,2] This burden is due, in part, to the lack of a clear understanding of biological subgroups and shortcomings of available treatments to match subtypes of depression. Many patients with MDD do not receive adequate care, and, among those who do, a significant portion fail to achieve remission.[3–5] These poor outcomes underscore the need for novel treatment options for patients with MDD. To this end, recent research has aimed to identify specific biomarkers indicative of reliable subtypes in the hopes that patients can ultimately be matched to treatments most likely to elicit a positive treatment response.

Inflammation has been implicated in the etiology of MDD. Proinflammatory cytokines, specifically interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1 beta (IL-1β), are elevated in patients with MDD compared to healthy controls.[6,7] Furthermore, studies of interferon-α–induced MDD in hepatitis C and cancer patients implicate inflammation in the development and recurrence of MDD.[8] Research also indicates an effect of antidepressant medications on inflammatory cytokines. A meta-analysis by Hannestad et al[9] reports reductions in IL-6 and IL-1β following antidepressant treatment, while other studies have reported correlations between reductions in IL-1β and reductions in depressive symptoms. Importantly, elevated baseline levels of inflammation are predictive of treatment nonresponse to a variety of antidepressant medications.[10–14]

The role of inflammation in MDD treatment response suggests MDD in the presence of inflammation may be a distinct subtype of MDD requiring a targeted treatment approach. While previous epidemiologic work has shown a relationship between inflammation and MDD, the rates of inflammation among those with MDD have not been well characterized. Inflammation accompanying MDD may also be related to important demographic and clinical characteristics that may impact treatment selection and response. For example, there is a bidirectional relationship between MDD and metabolic syndrome (MetS),[15–17] and it has been proposed that inflammation is the underlying link between MDD and MetS.[18]

The purpose of this article is to describe the rates of elevated inflammation among those with depression using the 2009–2010 National Health and Nutrition Examination Survey (NHANES) (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm). Furthermore, we will describe the clinical characteristics, including the presence of MetS, of those with depression and elevated inflammation.

METHOD

Study Sample

The 2009–2010 NHANES data were used for the analysis. The NHANES, conducted by the National Center for Health Statistics, is a stratified, multistage probability sample of the civilian noninstitutionalized US population. Adults, aged 18 and older, were included for this analysis.

Clinical Points

- This study highlights the significant prevalence of inflammation, obesity, and metabolic syndrome (MetS) in persons with major depressive disorder (MDD).
- The high rates of inflammation, obesity, and MetS most likely contribute to the elevated risk of developing medical comorbidities in persons with MDD.

Measures

Depression was assessed using the Patient Health Questionnaire (PHQ-9).[19] Only those with significant depressive symptoms were included in the analysis. Based on previous research, a cutoff of ≥ 10 was used to identify those with significant depressive symptoms. C-reactive protein (CRP) was assessed via a high sensitivity assay with latex-enhanced nephelometry. Glucose concentrations for fasting glucose and the 2-hour glucose tolerance test were determined by a hexokinase method. Insulin concentration was measured by Mercodia Insulin ELISA (Uppsala, Sweden), a 2-site enzyme immunoassay. Triglycerides were assessed enzymatically using a 2-reagent, end point reaction that is specific for triglycerides. Reported blood pressure was the average of 3 consecutive blood pressure readings collected following 5 minutes of quiet rest.

Demographic information and medical history were assessed through self-report questionnaires, and a physical examination was conducted to ascertain height, body weight, and waist circumference.

Metabolic syndrome classification was based on the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition.[20] The AHA/NHLBI definition for MetS requires the presence of at least 3 of the following 5 cardiovascular disease risk factors: (1) impaired fasting glucose (IFG) ≥ 100 mg per deciliter (mg/dL) or pharmacologic treatment for IFG, (2) low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men or < 50 mg/dL in women) or pharmacologic treatment for an abnormal HDL cholesterol level, (3) triglycerides ≥ 150 mg/dL or pharmacologic treatment for hypertriglyceridemia, (4) a waist circumference ≥ 102 cm in men or ≥ 88 cm in women, and (5) blood pressure ≥ 130/85 mm Hg or pharmacologic treatment for hypertension.

Analysis

Pearson correlations were calculated to examine the relationship of CRP with demographic and clinical characteristics. C-reactive protein levels were examined as a continuous variable and then dichotomized using cutoffs of 3 mg/L and 5 mg/L. Continuity-adjusted χ^2 tests examined the prevalence of MetS criteria within CRP groups. Since the analysis was conducted on a small subsample of the total sample, analyses were conducted with and without the population weighting. No substantive differences in the 2 approaches were observed; therefore, only the unweighted results are reported. Odds ratios were calculated to quantify the association of CRP with MetS and individual MetS criteria.

Table 1. Sample Characteristics of Depressed Patients With Valid C-Reactive Protein Data

Variables	n	%	Mean	SD
Age, y	585		48.74	15.88
Gender	585			
Female, %	332	56.75		
Race	585			
White, %	247	42.22		
African American, %	110	18.80		
Mexican American, %	127	21.71		
Other Hispanic, %	67	11.45		
Other, %	34	5.81		
Body mass index, kg/m^2	581		30.43	8.24
Waist circumference, cm	565		101.28	18.53
C-reactive protein, mg/L	585		4.77	6.52
≥ 3.0 mg/L, %	275	47.01		
≥ 5.0 mg/L, %	170	29.06		
Fasting glucose, mg/dL	275		109.80	39.45
Fasting insulin, uU/mL	271		15.93	12.51
2-Hour glucose tolerance, mg/dL	202		124.42	54.37
Systolic blood pressure, mm Hg	565		120.26	18.85
Diastolic blood pressure, mm Hg	564		70.17	12.53
High-density lipoprotein cholesterol, mg/dL	581		50.79	15.40
Triglyceride, mg/dL	273		144.97	178.86

RESULTS

In total, 5,579 participants provided PHQ-9 data; of those, 606 (10.86%) had PHQ-9 scores ≥ 10 and were included in further analysis. Demographic and clinical characteristics of the sample are reported in Table 1. No substantive differences in analyses with and without the population weighting were observed; therefore, only the unweighted results are reported.

Proportion of Depressed Sample With Elevated Inflammation

C-reactive protein was dichotomized using 2 established criteria. A cutoff of ≥ 3.0 mg/L is typically used to signify high-risk of cardiovascular disease.[21] However, a recent study by Raison et al[26] suggests that a cutoff of ≥ 5.0 mg/L might predict treatment response in depression, so both criteria were employed. Of the 606 depressed participants, 585 participants had valid CRP data; 275 participants (47.01%) had CRP levels ≥ 3.0 mg/L, while 170 (29.06%) had CRP levels ≥ 5.0 mg/L. Mean CRP levels did not differ in patients taking antidepressant or antipsychotic medications compared to those not taking medications ($t = -0.67$; $P = .50$).

Relationship of Inflammation With Demographic and Clinical Characteristics

Pearson correlation coefficients were calculated to examine the relationship of elevated inflammation with demographic and clinical characteristics (Table 2). Elevated inflammation was not significantly correlated with gender, race, or age (P values > .05). CRP was positively correlated with body weight, waist circumference, and body mass index (BMI) (P values < .0001). C-reactive protein also had significant correlations with insulin ($P = .04$) and 2-hour glucose tolerance ($P = .03$),

as well as self-report general health ($P = .02$). As expected given these significant correlations, individuals with elevated CRP levels had significantly higher body weight, waist circumference, BMI, and insulin (P values < .0001).

Inflammation and MetS

Of the 272 depressed participants with complete data for determination of MetS status, 112 subjects (41.18%) met criteria for MetS. Though the collection of samples was random, the subsample that provided a fasting blood sample had a significantly lower BMI ($P = .04$) and waist circumference ($P = .02$). The subsample did not differ in PHQ-9 score or mean CRP level.

Those with elevated CRP were more likely to meet criteria for MetS. Metabolic syndrome was present in 53.79% of those with CRP greater than or equal to 3.0 mg/L compared to 29.29% of those with CRP less than 3.0 mg/L (OR = 2.81) and in 52.38% of those with CRP greater than or equal to 5.0 mg/L compared to 36.17% among those with CRP less than 5.0 mg/L (OR = 1.94). Individuals with elevated inflammation were also more likely to meet a greater number of MetS criteria (Figure 1) and had greater prevalence of individual MetS symptoms, specifically elevated glucose, low HDL cholesterol, and high waist circumference (Table 3).

DISCUSSION

Our results highlight the prevalence of inflammation among those with depression. While previous research has demonstrated a relationship between depression and inflammation, the current analysis is the first to characterize inflammation within a depressed sample and to describe the clinical characteristics associated with elevated inflammation among those with depression. Approximately half of those with PHQ-9 scores indicative of significant depression had CRP levels greater than or equal to 3.0 mg/L, and nearly 30% had CRP levels greater than or equal to 5.0 mg/L. Furthermore, inflammation was associated with markers of obesity, insulin resistance, and MetS.

Our results also build upon an existing literature highlighting the association between depression and MetS. Previous research suggests a bidirectional relationship between MetS and MDD, as the presence of MDD predicts future incidence of MetS[16]; and, conversely, current MetS is associated with future onset of MDD.[15] This would suggest that rates of MetS are higher in those with MDD. In fact, our results indicate that the rate of MetS is over 41% in those with depression, while estimates of the prevalence of MetS in the general population range from 27.9% to 34.1%.[22]

The implications of the prevalence of inflammation and MetS in MDD are substantial. These factors help to explain the high rates of medical comorbidities and poor health outcomes in persons with depression.[23,24] Furthermore, inflammation and MetS are also associated with poorer treatment outcomes for MDD.[10–14,25] Major depressive disorder is a heterogeneous disease, and it is postulated that the biological underpinnings are equally varied. As a result, there are multiple treatment targets, and effective treatment of MDD most likely requires several treatment options. Therefore, effective treatment of MDD will require

Table 2. Pearson Correlations of C-Reactive Protein (CRP) With Clinical Characteristics

Variables	n	CRP
Weight	583	0.29*
Body mass index	581	0.33*
Waist circumference	565	0.33*
Fasting glucose	275	0.01
Insulin	271	0.13
2-Hour glucose tolerance	202	0.14
Systolic blood pressure	565	0.11#
Diastolic blood pressure	564	0.05
High-density lipoprotein cholesterol	581	−0.09
Triglyceride	273	0.002

*$P < .0001$. #$P < .01$.

Figure 1. Metabolic Syndrome Criteria by C-Reactive Protein (CRP) Status

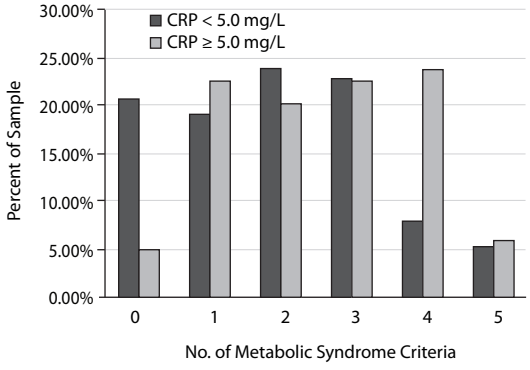

Table 3. Relationship of C-Reactive Protein (CRP) With Metabolic Syndrome

Variables	Total Sample (N = 272)	CRP < 3.0 mg/L (n = 140)	CRP ≥ 3.0 mg/L (n = 132)	χ^2	P	OR (95% CI)	CRP < 5.0 mg/L (n = 188)	CRP ≥ 5.0 mg/L (n = 84)	χ^2	P	OR (95% CI)
Metabolic syndrome	112 (41.18%)	41 (29.29%)	71 (53.79%)	15.84	< .0001	2.81 (1.71, 4.63)	68 (36.17%)	44 (52.38%)	5.65	.0175	1.94 (1.15, 3.27)
Glucose	140 (51.47%)	55 (39.29%)	85 (64.39%)	16.16	< .0001	2.79 (1.71, 4.57)	85 (45.21%)	55 (65.48%)	9.67	.0031	2.30 (1.35, 3.92)
High-density lipoprotein cholesterol	112 (41.18%)	42 (30.00%)	70 (53.03%)	13.94	.0002	2.63 (1.60, 4.33)	65 (34.57%)	47 (55.95%)	10.09	.0015	2.40 (1.42, 4.06)
Triglyceride	86 (31.62%)	40 (28.57%)	46 (34.85%)	0.96	.326	1.34 (0.80, 2.23)	56 (29.79%)	30 (35.71%)	0.69	.4065	1.31 (0.76, 2.26)
Waist circumference	163 (59.93%)	65 (46.43%)	98 (74.24%)	20.74	< .0001	3.33 (1.99, 5.55)	103 (54.79%)	60 (71.43%)	6.02	.0141	2.06 (1.19, 3.59)
Blood pressure	79 (29.04%)	41 (29.29%)	38 (28.79%)	0.00	1.00	0.98 (0.58, 1.65)	56 (29.79%)	23 (27.38%)	0.07	.7954	0.89 (0.50, 1.58)

identification of specific MDD "subtypes" that are then matched to the appropriate treatment. Given that previous research suggests that elevated inflammation and presence of MetS are associated with poorer treatment response, these factors might be indicative of 1 specific biological "subtype" of MDD.

Recent research has begun to identify potential novel treatment options for depression in patients with elevated inflammation. A recent study by Raison et al[26] suggests the TNF-α antagonist infliximab, a TNF antagonist, may be efficacious in those with elevated inflammation. In a randomized controlled trial in treatment-resistant depression, infliximab resulted in a better treatment response in patients whose baseline CRP levels were greater than 5.0 mg/L.[26] Furthermore, genetic transcription factors related to glucose and lipid metabolism were predictive of treatment response to infliximab.[27] Similarly, a trial examining exercise augmentation in nonresponders to selective serotonin reuptake inhibitors (SSRIs) observed favorable findings in treating patients with elevated inflammation. Specifically, elevated pretreatment levels of TNF-α were predictive of improved remission rates.[28] Higher BMI was also associated with better treatment outcomes following the exercise intervention.[29]

Continued research is necessary to better characterize this potential biological subtype of MDD. Results of a recent latent class analysis of the Netherlands Study of Depression and Anxiety cohort identified 2 classes of severe depression based on depressive symptom profiles: melancholic and atypical.[30] Atypical depression was characterized by increased weight, increased appetite, and leaden paralysis. Atypical depression was also related to elevations in multiple inflammatory markers (CRP, IL-6, and TNF-α), higher BMI, and prevalence of MetS.[31] The association between obesity and atypical depressive symptoms has also been reported elsewhere.[32] Therefore, it is possible that the potential biological "subtype" of MDD, characterized by inflammation and MetS, may overlap with the clinical "subtype" of MDD, characterized by atypical depressive symptoms. A limitation of the current analysis is that we are unable to assess the relationship of atypical depressive symptoms with inflammation and MetS in this sample because the PHQ-9 does not assess for atypical depressive symptoms.

While the NHANES data provide a large, nationally representative sample, there are limitations of the data collection methods that could influence our results. First is the identification of depression using the PHQ-9. The PHQ-9 has been validated as a screening tool with acceptable sensitivity and specificity[19]; however, it is not a diagnostic tool. Though our findings may not reflect the exact portion of individuals with MDD that also have high inflammation and MetS, our results do highlight the significant portion of individuals with elevated depressive symptoms that also have elevated inflammation and MetS. Second, only a subset of the sample provided fasting blood samples for allowing classification of MetS, and those who provided samples had significantly lower BMI and waist circumference. While these differences potentially bias our findings, the fact that those who provided fasting samples had lower BMI and waist circumference would suggest that the high rate of MetS observed in our sample might in fact underestimate the true prevalence of MetS in those with MDD.

Another important topic for future research is to identify factors that may affect the relationship of inflammation and MetS with depression. Previous research indicates that psychiatric medications may be in part responsible for higher rates of MetS in persons with MDD.[33,34] Our analyses support these findings, as the use of psychiatric medications was associated with higher BMI and waist circumference. However, levels of CRP were not higher in those taking psychiatric medication. Similarly, diet and exercise are clearly linked to MetS and inflammation,[35,36] and engaging in physical activity may affect the relationship between inflammation and depressive symptoms.[37] Though examination of these factors is beyond the scope of the current analysis, identification of these and other factors that may influence the relationship of inflammation and MetS with depression is an important area for future research.

The current analysis highlights prevalence of elevated inflammation in a depressed sample along with the links among inflammation, obesity, insulin resistance, and metabolic symptoms. Previous research suggests that these biological markers may be associated with atypical depressive symptoms. Furthermore, these biological and psychological symptoms may be indicative of treatment resistance of depression. Future work should continue to characterize the clinical and biological characteristics that may distinguish specific MDD subtypes and to identify efficacious treatment options for those subtypes.

Drug name: infliximab (Remicade).

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Potential conflicts of interest: **Dr Bernstein** serves on the Joint Research Committee of the National Council of State Boards of Nursing and is a stock shareholder in Merck, Bristol-Myers Squibb, and DuPont de Nemours. **Dr Trivedi** is or has been an advisor/consultant to Abbott Laboratories, Abdi Ibrahim, Akzo (Organon Pharmaceuticals), Alkermes, AstraZeneca, Axon Advisors, Bristol-Myers Squibb, Cephalon, Cerecor, Concert Pharmaceuticals, Eli Lilly, Evotec, Fabre Kramer Pharmaceuticals, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Global Services, Janssen Pharmaceutica Products, Johnson & Johnson PRD, Libby, Lundbeck, Meade Johnson, MedAvante, Medscape, Medtronic, Merck, Mitsubishi Tanabe Pharma Development America, Naurex, Neuronetics, Otsuka Pharmaceuticals, Pamlab, Parke-Davis Pharmaceuticals, Pfizer, PgxHealth, Phoenix Marketing Solutions, Rexahn Pharmaceuticals, Ridge Diagnostics, Roche Products, Sepracor, Shire Development, Sierra, SK Life and Science, Sunovion, Takeda, Tal Medical/Puretech Venture, Targacept, Transcept, VantagePoint, Vivus, and Wyeth-Ayerst Laboratories. In addition, he has received research support from Agency for Healthcare Research and Quality (AHRQ), Corcept Therapeutics, Cyberonics, National Alliance for Research on Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), and Solvay Pharmaceuticals.

Funding/support: The National Institute of Mental Health of the US National Institutes of Health under Award Number K01MH097847 (to Dr Rethorst).
Role of the sponsor: The National Institutes of Health had no role in the design of the study, data collection, data analysis, or manuscript preparation.
Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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