Depression and C-Reactive Protein in US Adults

Data From the Third National Health and Nutrition Examination Survey

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Background: The biological mechanisms by which depression might increase risk of cardiovascular disease are not clear. Inflammation may be a key element in the development of atherosclerotic cardiovascular disease. Our objective was to determine the association between major depression and elevated C-reactive protein (CRP) level in a nationally representative cohort.

Methods: We estimated the odds of elevated CRP level (>0.21 mg/mL) associated with depression in 6914 non-institutionalized men and women (age, 18-39 years) from the Third National Health and Nutrition Examination Survey (NHANES III).

Results: The prevalence of lifetime major depression was 5.7% for men and 11.7% for women. The prevalence of elevated CRP level was 13.7% for men and 27.3% for women. A history of major depression was associated with elevated CRP level (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.20-2.24). The association between depression and CRP was much stronger among men than among women. Results were adjusted for age, African American race, body mass index, total cholesterol, log triglycerides, diabetes, systolic blood pressure, smoking status, alcohol use, estrogen use in women, aspirin use, ibuprofen use, and self-reported health status. Compared with men without a history of depression, CRP levels were higher among men who had a more recent (within 1 year) episode of depression (adjusted OR, 3.00; 95% CI, 1.39-6.48) and who had recurrent (≥2 episodes) depression (adjusted OR, 3.55; 95% CI, 1.55-8.14).

Conclusion: Major depression is strongly associated with increased levels of CRP among men and could help explain the increased risk of cardiovascular disease associated with depression in men.

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O ver the past 20 years, evidence from observational studies has increasingly indicated that depression is a marker for increased risk for subsequent coronary artery disease (CAD). The studies have addressed the risk of depression both before and after the development of clinical CAD. In addition, several recent studies have found that depression increases risk for strokes. The underlying biological mechanism by which depression might increase risk for CAD has not been elucidated. Proposed biological mechanisms have included alterations in the hypothalamic-pituitary system, platelet function, and heart rate variability. Mediating factors that return toward normal when the depression remits would be of particular interest.

Inflammation has been proposed as an underlying process associated with atherosclerosis. Most recently, C-reactive protein (CRP) has been used as a marker of underlying low-grade inflammation. The availability of highly sensitive assays for detecting minor elevations in CRP level has improved our ability to detect relationships between inflammation and subsequent disease. A meta-analysis based on 14 prospective studies found that the risk ratio for CRP levels in the top third compared with the lower third was 1.9 for the development of coronary heart disease. A few studies have suggested that depression may be associated with increased production of proinflammatory cytokines such as interleukin (IL) 1, IL-6, and interferon (IFN-γ). High levels of cytokines do not appear to decrease when reassessed 5 weeks after initiating therapy for depression. A study of 24 inpatients with depression treated with amitriptyline found that CRP levels were elevated before treatment, decreased slightly with treatment, and did not predict responsiveness to treatment. This study was limited by small numbers of patients with severe depression followed up for a short time.
We completed an analysis of a nationally representative sample of young adults to assess if CRP levels are related to major depression. Young adults have lower rates of medical comorbidity that could confound any association between depression and CRP levels. We hypothesized that CRP levels would be higher in those with current major depression and intermediate for those with past major depression and less chronic depression.

METHODS

STUDY POPULATION

The Third National Health and Nutrition Examination Survey (NHANES III) is a national probability survey of Americans conducted between 1988 and 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. This survey used a complex, multistage, stratified, cluster sampling design to obtain a representative sample of the noninstitutionalized civilian US population. A detailed description of survey methods and data collection procedures has been published elsewhere.18

The Diagnostic Interview Schedule (DIS) depression questionnaire was administered to 8773 male and female participants aged 18 to 39 years. Of these, 8435 completed the questionnaire. For this analysis, participants were excluded if they were missing measurements for CRP (n=1255) or other covariates (n=266), leaving 6914 (3154 men and 3760 women) for this analysis. The DIS was not administered to anyone older than 39 years.

MEASUREMENTS

C-reactive protein was measured using latex-enhanced nephelometry. Pooled controls had a coefficient of variation between 3.2% and 16.1% throughout the period of data collection.19 Since 74.1% of individuals had CRP levels below the detection limit for this assay (0.22 mg/dL), we treated CRP as a categorical variable: undetectable (<0.22 mg/dL) or detectable (≥0.22 mg/dL).

Major depression was measured with the DIS. The DIS is a well-established highly structured interview designed to produce diagnoses of specific mental disorders according to the DSM-III criteria of the American Psychiatric Association. The DIS consists of close-ended (mostly yes/no) questions following structured probe protocols and is designed for administration by interviewers with 1 to 2 weeks of training.19 For this analysis, the 56 depressive episodes occurring within 6 months of the death of a loved one were not excluded. Current major depression was defined as an episode present in the past year. Respondents were also asked how many episodes of depression and major depression (≥95% confidence interval [CI], 1.20-2.24). In stratified

RESULTS

The prevalence of lifetime major depression for this sample was 8.7%, with a prevalence of 5.7% for men and 11.7% for women. Men and African Americans were less likely to have lifetime depression. There were no significant differences between those with and without a diagnosis of lifetime depression by body mass index, total cholesterol, log triglycerides, smoking, and diabetes. We used self-reported health status as a proxy for the many health conditions that might be associated with chronic inflammation. Because of the known influence of sex and estrogen use on serum levels of CRP and the sex differences in the prevalence of major depression, all analyses were stratified by sex. Tests for a statistical interaction between sex and depression categories were conducted by entering an interaction term for sex and measures of depression in multivariate models. Tests for trend were conducted by entering categorical variables as continuous variables in logistic regression models. To account for the complex survey design and to obtain results generalizable to the US noninstitutionalized population, we used STATA software (Stata Corp, College Station, Tex) and applied NHANES III weights in all analyses. P<.05 was considered statistically significant. All reported P values are 2 sided.

The prevalence of elevated CRP levels was 13.7% for men and 27.3% for women. Overall, there was a significant association between lifetime history of major depression and elevated CRP levels (odds ratio [OR] = 1.64; 95% confidence interval [CI], 1.20-2.24). In stratified
Many factors have been associated with elevated CRP levels, which might act as confounders. Since it is nearly impossible to account for all health conditions that might be associated with higher risk of inflammation, we adjusted for self-reported health status. Even after adjusting for all health conditions that might possibly account for elevated CRP levels, no associations between depression and CRP levels in women were found.

Additional analyses were completed to assess potential associations between levels of CRP and major depression in women. Changing the threshold for elevated CRP level did not reveal any associations. There was no significant correlation between number of depressive symptoms and CRP levels in women. Excluding women using estrogen or progesterone medications who were pregnant did not substantially alter the results.

Because of the association of tobacco smoking and depression, we completed stratified analyses by smoking status for men. The adjusted OR for elevated CRP level in men who had an episode of major depression not active in the past year was significantly associated with elevated CRP levels (OR = 3.00; 95% CI, 1.39-6.48 [P = .006]) after adjusting for all the factors listed above. The OR for elevated CRP level in men who had an episode of major depression not active in the past year was intermediate. There were no associations between depression status and CRP levels in women.

Another measure of chronicity of depression is the number of episodes of major depression. For men, recurrent major depression was strongly associated with elevated CRP levels after adjusting for potential confounders (OR = 3.55; 95% CI, 1.55-8.14 [P = .003]). Single episodes of major depression were not associated with elevated CRP levels. No associations between recurrent major depression and CRP were found for women (Table 3).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lifetime History of Major Depression</th>
<th>No History of Major Depression</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>29.4 (0.5)</td>
<td>28.3 (0.2)</td>
<td>.03</td>
</tr>
<tr>
<td>Female, %</td>
<td>67.7 (2.7)</td>
<td>48.7 (0.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African American, %</td>
<td>9.7 (1.4)</td>
<td>12.6 (0.8)</td>
<td>.02</td>
</tr>
<tr>
<td>BMI</td>
<td>25.8 (0.5)</td>
<td>25.4 (0.1)</td>
<td>.42</td>
</tr>
<tr>
<td>Smoking status, %†‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>48.9 (3.1)</td>
<td>37.6 (1.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Former</td>
<td>11.3 (1.9)</td>
<td>12.1 (0.7)</td>
<td>.66</td>
</tr>
<tr>
<td>Never</td>
<td>39.7 (2.6)</td>
<td>50.3 (1.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>19.7 (5.4)</td>
<td>12.6 (1.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>185.3 (2.5)</td>
<td>185.8 (1.0)</td>
<td>.83</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>149.1 (3.3)</td>
<td>155.4 (1.8)</td>
<td>.61</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>118.0 (5.9)</td>
<td>119.9 (2.3)</td>
<td>.76</td>
</tr>
<tr>
<td>Diabetes, %‡</td>
<td>2.4 (0.9)</td>
<td>12.0 (2.2)</td>
<td>.28</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112.0 (0.8)</td>
<td>113.7 (0.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71.5 (0.6)</td>
<td>71.9 (0.5)</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); LDL, low-density lipoprotein; SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

*Values are mean or percentage (SE).†Current smokers were defined by a self-reported history of current smoking or a serum cotinine level of 10 ng/mL or greater (=56.8 nmol/L). Ex-smokers and never smokers were defined by self-report.
‡Diabetes was defined by a self-reported history or a fasting plasma glucose level of 126 mg/dL or greater (=7.0 mmol/L) or a 2-hour postchallenge glucose level of 200 mg/dL or greater (=11.1 mmol/L).

Table 2 Odds Ratios of Elevated C-Reactive Protein Level by Recent History of Major Depression in Men and Women*†

<table>
<thead>
<tr>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Severe depression &lt;1 year</td>
<td>3.00 (1.39-6.48)</td>
</tr>
<tr>
<td>Severe depression &gt;1 year</td>
<td>1.95 (0.81-4.69)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Severe depression &lt;1 year</td>
<td>0.76 (0.44-1.33)</td>
</tr>
<tr>
<td>Severe depression &gt;1 year</td>
<td>1.39 (0.80-2.42)</td>
</tr>
</tbody>
</table>

*Adjusted for age, African American race, body mass index, total cholesterol, log triglycerides, diabetes, systolic blood pressure, smoking status, alcohol use, estrogen use in women, aspirin use, ibuprofen use, and self-reported health status. P value for trend = .01 (men) and .70 (women); P value for interaction (<1 year) = .01.
In this large, nationally representative database, we found that major depression was associated with elevations of CRP level in men. The association was present even after accounting for multiple potential confounders. The findings were indicative of a graded association between CRP level and depression when the data were analyzed by the time since the depression was active or by the number of episodes of depression. There was no indication of any association between CRP level and depression in women. These results in young adults are complementary to a study of adults older than 65 years in whom CRP level was positively associated with depressive symptoms, particularly exhaustion, in both men and women.

Owing to the cross-sectional nature of the data, causality is difficult to determine. Depression may be causing the elevated CRP level, an inflammatory state may be causing the depression, or both the depression and elevated CRP level may be due to another unmeasured disease process. Inflammation, particularly at a low level, is a ubiquitous, fundamental biological phenomenon that may affect several processes. The sample is relatively young, decreasing the probability that other common chronic diseases account for the relationship between depression and CRP levels.

There were clear differences between men and women in the relationship between depression and CRP. Despite a higher prevalence of depression and elevated CRP level in women than in men, there was no association between the two in women. Even altering the threshold for major depression and elevated CRP level did not reveal any associations for women. We hypothesized that CRP levels might vary by the hormonal environment. Excluding women who were pregnant or using oral contraceptive agents did not change the results. It is of interest that CRP levels vary with the menstrual cycle. One study found that median CRP levels increase by 44% at mid-cycle and 31% in the luteal phase. While one might expect that women with depression would be in a similar phase of the menstrual cycle as women without depression, it is possible that women with depression are more likely to have menstrual cycle abnormalities owing to stress. The data set contained no information on date of last menses, so this hypothesis could not be tested. Studies on depression and subsequent CAD have not found that there are differences by sex. Both men and women have a similar relative risk of CAD related to depression. Understanding these sex differences should be a research priority because of the high burden of suffering related to depression in women. It also should be noted that sex differences might not be present in older adulthood when women are postmenopausal.

There are several aspects of this study that should be considered in the interpretation of the results. These data are cross sectional. Therefore, even though we tried to illuminate possible temporal relationships between depression and CRP by considering the recency of the depressive episodes, longitudinal data would be preferred for understanding the temporal relationship between these complex biological processes. It is also important to note that although the DIS is a well-validated method of measuring major depression in community surveys, it does not replace a structured clinical interview. This is particularly true in the determination of number of episodes of depression and lifetime history of depression. The strengths of the present study include the national representation of the sample, the ability to measure episodes of major depression and not simply depressive symptoms, and the young age of the adults in the sample in whom the effect of chronic diseases on underlying inflammation are less likely than in older adults. Finally, obesity and tobacco smoking, the most important recognized factors affecting CRP levels, were measured carefully and included in the analysis. Using this same NHANES III data set, recent major depression is associated with nearly the same adjusted OR for elevated CRP level as obesity in young men. The OR for obesity and elevated CRP level was substantially higher for women. Data suggest that reduction of obesity and depression is associated with normalization of CRP levels.

Inflammation may be another possible mechanism for how depression may act as a risk factor for atherosclerotic vascular disease. The data also suggest that the inflammatory state may return toward normal when the depression resolves. One study has found that men with high levels of CRP are more likely to benefit from aspirin therapy to reduce cardiovascular events. Statin therapy has also been found to not only decrease lipid levels, but CRP levels as well. If future studies confirm the association between depression and CRP level for men and possibly women, new approaches to lower the risk for cardiovascular disease in individuals with depression should be evaluated. While it is unlikely that inflammation is the only mechanism by which depression might increase risk for cardiovascular disease, future studies need to evaluate this possibility.

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REFERENCES