Effect of Negative Emotions on Frequency of Coronary Heart Disease (The Normative Aging Study)

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Negative emotions, such as depression and anxiety, have been associated with the development of coronary heart disease (CHD). In multivariate models, negative emotions have predicted CHD outcomes, such as nonfatal myocardial infarction and CHD mortality. Few studies, however, have investigated this relation while controlling for variables associated with the metabolic syndrome or those indicative of sympathetic nervous system activity. We prospectively examined the relation between negative emotions and incident CHD in older men (mean 60.3 ± 7.9 years) participating in the Normative Aging Study (NAS). Four hundred ninety-eight men who completed the Minnesota Multiphasic Personality Inventory (MMPI) and who participated in a subsequent laboratory assessment were included in the study. All men were not on medication and free of diagnosed CHD and diabetes. Negative emotions were measured by the MMPI Welsh A scale, which is comprised of 39 items measuring symptoms of depression and anxiety. Negative emotion score, sociodemographic characteristics, health behaviors, components of the metabolic syndrome, and stress hormones were used to predict incident CHD over a 3-year follow-up period. During follow-up, 45 CHD events were observed. In unadjusted logistic regression analyses, negative emotions significantly predicted the incidence of CHD (odds ratio [OR] 1.06, 95% confidence interval [CI] 1.01 to 1.10, p = 0.02). After adjusting for potential covariates, negative emotions continued to predict the incidence of CHD (OR 1.06, 95% CI 1.01 to 1.12, p = 0.02). A linear, dose-response relation was observed (chi-square 10.8, degree of freedom 2, p = 0.005): participants who had the highest level of negative emotions experienced the greatest incidence of CHD.

METHODS
Participants: The NAS is a longitudinal study designed to examine biomedical and psychosocial changes involved in the normal aging process. This study involved a cohort of 2,280 men living in the greater Boston area who were between 21 and 80 years of age at enrollment (1961 to 1970). Study participants were predominantly white, high school
educated, and free of any chronic medical conditions, such as cardiovascular disease, cancer, or diabetes mellitus. The NAS study timeline involved regular examinations every 3 (>52 years old) or 5 (<52 years old) years depending on the participants’ age. After 1986, however, all men were examined at 3-year intervals. Additional details about the sample and admission criteria have been described elsewhere.7

To be included into the present study, NAS participants were required to meet the following criteria: (1) completion of the Minnesota Multiphasic Personality Inventory (MMPI) in 1986; (2) completion of a comprehensive laboratory-based physiologic assessment within 3 years after administration of the MMPI; and (3) no use of cardiac (e.g., antihypertensives, lipid-lowering agents) or diabetic medications at the MMPI baseline assessment. Among the 1,081 participants who provided a complete MMPI, 307 participants were excluded for taking cardiac and/or diabetic medications and 276 were excluded for missing laboratory measurements, resulting in a final study sample of 498 men.

Procedures: Participants were instructed to refrain from eating or drinking after midnight and to avoid smoking after 8 P.M. the night before the medical examination. Urine samples were collected at home and returned at the next day examination to measure epinephrine and norepinephrine. The examination included blood pressure measurement, blood work (12-hour fasting serum levels of glucose, insulin, and lipids), an anthropometric evaluation including body mass index and waist-to-hip ratio, and assessment of health behaviors (diet, alcohol intake, and smoking) by standardized questionnaires. The first blood sample was drawn at 8 A.M. to measure fasting insulin and glucose. Another blood sample was taken 2 hours after the participant orally consumed a 100-g glucose load to obtain post-challenge insulin and glucose concentrations. Sociodemographic data, including educational attainment, were obtained at entry into the study.

Measurements: The diagnostic criteria for myocardial infarction, angina pectoris, and ischemic heart disease were adapted from those used in the Framingham Heart Study.8 A diagnosis of myocardial infarction was made when supported by unequivocal electrocardiographic changes (i.e., pathologic Q waves), by a diagnostic elevation of serum glutamic-oxaloacetic transaminase and lactic dehydrogenase, and concurrent chest discomfort commonly evidenced in patients with myocardial infarction. Angina pectoris was diagnosed when participants reported experiencing recurrent chest discomfort lasting ≥15 minutes during periods of exertion that was remedied by rest or use of nitroglycerin. A classification of ischemic heart disease was defined as a horizontal or downsloping ST-segment depression of >1 mm measured via a 12-lead electrocardiogram, without meeting established criteria for myocardial infarction or angina pectoris.

Negative emotion: Negative emotion was measured by the MMPI Welsh A scale9 from the MMPI Form AX.10 The A scale contains 39 items measuring a variety of affective and cognitive manifestations of psychological maladjustment, such as dysphoric mood, anxiousness, social inhibition, pessimistic outlook, and distorted thought processes. Internal consistency as measured by Cronbach’s α was 0.91, indicating good scale cohesion.

Blood lipids: Serum samples were analyzed for total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Serum cholesterol was assayed enzymatically (SCALVO Diagnostics, Wayne, New Jersey). The HDL cholesterol fraction was measured in the supernatant after precipitation of LDL cholesterol and very LDL fractions with dextran sulfate and magnesium, using the Abbott Biochromatic Analyzer 100 (Abbott Laboratories, South Pasadena, California). Triglycerides were measured using the Dupont ACA discrete clinical analyzer (Dupont Company, Biomedical Products Department, Wilmington, Delaware). LDL cholesterol was estimated using Friedewald’s formula.11

Fasting and post-challenge serum insulin and glucose: Two blood samples were analyzed to obtain fasting and post-challenge insulin and glucose values. Serum insulin concentration was determined by a solid-phase iodine-125 radioimmunoassay (Diagnostic Products Corporation, Los Angeles, California). Serum glucose concentration was measured in duplicate on an autoanalyzer using the hexokinase method.12

Stress hormones: Each participant was instructed to collect 24-hour urine samples at home and to return them at examination. A questionnaire documenting urine collection times, missed collections, spilled urine, and medication use was completed by study participants. Urinary catecholamine levels, including epinephrine and norepinephrine, were measured by high-performance liquid chromatography with electrochemical detection on the basis of Smedes et al’s method13 as modified by Macdonald and Lake.14 The intra-assay coefficients of variation for urine samples (corrected for recovery) were 4% to 6%, and the interassay coefficient of variations were 6% to 7%.

Blood pressure: Blood pressure was measured using a standard mercury sphygmomanometer with a 14-cm cuff. Systolic and diastolic blood pressures were measured to the nearest 2 mm Hg. Both left and right arm pressures were measured in a sitting position, followed by right arm pressures taken in a supine position, followed 30 seconds later by a second reading of right arm pressures taken in a standing position. The palpatory method was used to check auscultatory systolic readings.

Anthropometric measurements: Weight was measured to the nearest 0.5 lb on a standard hospital scale with the participant dressed in undershorts and socks. It was later converted to kilograms. Height was measured to the nearest 0.1 in with the participant standing in bare feet against a wall, and this value was then converted to meters. Body mass index was computed as kilogram per squared meters. Abdomen circumference was measured in centimeters at the level of the
umbilicus with the participant standing. Hip circumference was measured in centimeters at the greatest protrusion of the buttocks. Waist-to-hip ratio was calculated by dividing abdomen circumference by hip circumference.

**Health behaviors:** Assessed behavioral risk factors included alcohol consumption, tobacco use, and dietary intake. Dietary data were obtained by means of a semiquantitative food-frequency questionnaire,\(^15\) which was mailed to each participant and completed before the examination. The food-frequency questionnaire lists food items with serving sizes and elicits information on frequency of intake during the past year. Nutrient scores were computed by multiplying the frequency of intake by the nutrient content of the food items. Macronutrients examined in the present analyses were total energy intake (kilocalories per day) and alcohol drinks per year. Information was also obtained on the number of cigarettes smoked per week.

**Sociodemographic risk factors:** Age in years was recorded at the time of the MMPI administration. Education attainment was divided into 4 categories: less than high school, high school graduate, some college or college graduate (2 years of technical school or 4 years of college), and postgraduate studies (some postgraduate education or postgraduate degree).

**Data analysis:** Variables with non-normal distributions (i.e., triglycerides, serum insulin concentration, cigarettes smoked per week, drinks per year) were transformed with a natural log function. Bivariate correlations were used to examine the relation between negative emotions and its potential correlates, including sociodemographic, behavioral, and physiologic risk factors. To examine the prospective relation between negative emotions and incident CHD while controlling for potential confounding variables, a series of hierarchical logistic regressions were applied to predict CHD (1 = yes; 0 = no). Next, we examined whether the relation between negative emotions and CHD was moderated by any behavioral or physiologic risk factors. No association was observed between negative emotions and HRV. However, a significant correlation was found between negative emotions and norepinephrine (\(r = 0.11, p = 0.01\)).

**RESULTS**

**Sample characteristics:** Sociodemographic, behavioral, and physiologic characteristics of study participants are listed in Table 1. Study participants were older men (mean age 60 ± 7.83 years), and, generally, of at least high school education. The average negative emotions score was 6.92 ± 6.78 (range 0 to 35). Approximately 88% of the sample consumed alcohol (defined as >1 drink/year) and 10.4% were active cigarette smokers. Study participants, on average, consumed 2,008 calories per day, had 551 alcoholic beverages per year (1.51 drinks/day), and smoked 2.7 cigarettes/day (0.14 packs). For those who reported drinking alcohol and smoking cigarettes, they consumed 1.7 alcoholic beverages and 1.3 packs of cigarettes per day. In terms of anthropometric and physiologic risk factors, study participants had an average waist-to-hip ratio of 0.98 and a body mass index of 26.3. Mean systolic blood pressure was 127 mm Hg and diastolic blood pressure 78 mm Hg for the sample. HDL cholesterol and post-challenge insulin were 49.3 mg/dl and 59.5 μU/ml, respectively.

Among 498 men, 43 experienced ≥1 episode of CHD during the 3-year follow-up (CHD incidence 11.1%). These included 24 cases of myocardial infarction, 23 cases of angina pectoris, and 12 cases of ischemic heart disease.

**Association between negative emotion and other risk factors:** Correlations between negative emotions, sociodemographic characteristics, health behaviors, components of the metabolic syndrome, and stress hormones are shown in Table 2. Bivariate correlations indicated that negative emotions were negatively correlated with education (\(r = -0.18, p < 0.01\)) and positively with CHD incidence (\(r = 0.11, p < 0.05\)), cigarette smoking (\(r = 0.09, p < 0.05\)), daily caloric intake (\(r = 0.09, p < 0.05\)), waist-to-hip ratio (\(r = 0.11, p < 0.01\)), epinephrine (\(r = 0.11, p < 0.05\)), and norepinephrine (\(r = 0.14, p < 0.01\)) concentrations. No association was observed between negative emotions and alcohol consumption, body mass index, lipids, blood pressure, or post-challenge insulin and glucose.

**Coronary heart disease incidence associated with negative emotion:** Hierarchical logistic regression analyses were conducted to examine the association between negative emotions and incidence of CHD (see Table 3). In the first model, negative emotions were entered alone and significantly predicted the development of CHD (OR 1.06, 95% CI 1.01 to 1.10, \(p = 0.02\)). Next, negative emotions were adjusted for sociodemographic characteristics, including age and education. The association between negative emotions

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**Table 1: Descriptive Statistics of Study Variables (n = 498)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>60.45 ± 7.83</td>
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<tr>
<td>Negative emotion</td>
<td>6.92 ± 6.78</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.29 ± 3.18</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.98 ± 0.048</td>
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<tr>
<td>Drinks/yr</td>
<td>5.51 ± 2084.15</td>
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<tr>
<td>No. of cigarettes/d</td>
<td>2.73 ± 8.95</td>
</tr>
<tr>
<td>Daily caloric intake (kcal/d)</td>
<td>2,007.53 ± 621.58</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>49.27 ± 12.20</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>159.54 ± 34.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>127.39 ± 15.40</td>
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<tr>
<td>Post-challenge glucose (mg/dl)</td>
<td>109.80 ± 36.49</td>
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<tr>
<td>Post-challenge insulin (μl/ml)</td>
<td>59.50 ± 59.26</td>
</tr>
<tr>
<td>Epinephrine (μg/24 h)</td>
<td>6.96 ± 3.97</td>
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<tr>
<td>Norepinephrine (μg/24 h)</td>
<td>45.82 ± 18.81</td>
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</tbody>
</table>

**Table 2: Correlation Coefficients among Study Variables (n = 498)**

- **Correlation Coefficients:**
  - Negative emotion vs. sociodemographic characteristics: Age (\(r = -0.18, p < 0.01\))
  - Negative emotion vs. health behaviors: Cigarette smoking (\(r = 0.09, p < 0.05\)), Daily caloric intake (\(r = 0.09, p < 0.05\)), Waist-to-hip ratio (\(r = 0.11, p < 0.01\)), Epinephrine (\(r = 0.11, p < 0.05\)), Norepinephrine (\(r = 0.14, p < 0.01\))

**Table 3: Hierarchical Logistic Regression Models for CHD Incidence**

- **First Model:** Negative emotions entered alone (OR 1.06, 95% CI 1.01 to 1.10, \(p = 0.02\))
- **Second Model:** Negative emotions adjusted for sociodemographic characteristics, including age and education
and CHD incidence was slightly attenuated, but remained significant (OR 1.05, 95% CI 1.00 to 1.10, p = 0.05). Health behaviors were added to the next model without any attenuation of negative emotions’ association with the development of CHD (OR 1.05, 95% CI 1.00 to 1.10, p = 0.04). In the next model, components of the metabolic syndrome were added and, again, negative emotions remained a significant predictor of CHD (OR 1.06, 95% CI 1.01 to 1.11, p = 0.02). In this model, HDL concentration also emerged as a significant predictor of a lower incidence of CHD (OR 0.95, 95% CI 0.91 to 0.99, p = 0.02). In the final model, which adjusted for sociodemographic characteristics, health behaviors, components of the metabolic syndrome, and stress hormones, the association between negative emotions and CHD incidence was...
corresponded to the unadjusted model (OR 1.06, 95% CI 1.01 to 1.12, p = 0.02). A significant association between HDL cholesterol and CHD incidence was also observed in this model (OR 0.95, 95% CI 0.91 to 0.99, p = 0.03).

These results suggested that while controlling for other risk factors, a 1-point increase in the negative emotion scores corresponded to a 6% increase in the risk of developing CHD during the 3-year follow-up. Alternatively, 1 SD increase in the negative emotion scores represented a 51% increase in the CHD risk. This relation appears to be independent of sociodemographic characteristics, health behaviors, components of the metabolic syndrome, and stress hormone levels.

To examine the relation between severity of negative emotions and the development of CHD, subjects were divided into 3 groups based on a tertile split of negative emotions scores: low negative emotions (score <3; n = 240), medium negative emotions (score 3 to 7; n = 258), and high negative emotions (score >7; n = 276). The distribution of CHD events observed across levels of negative emotions included 5 events in the low negative emotions group (2.1%), 15 events in the medium negative emotions group (5.8%), and 24 events in the high negative emotions group (8.7%). Chi-square analyses indicated that the development of CHD was significantly associated with the severity of negative emotion (chi-square 10.8, degree of freedom 2, p = 0.005). Specifically, a linear, dose-response relation was observed, such that participants in the high negative emotions group had the greatest incidence of CHD (see Figure 1).

We also examined whether the relation between negative emotions and the development of CHD was moderated by other sociodemographic characteristics, health behaviors, components of the metabolic syndrome, or stress hormones. In all moderation analyses, none of the interaction terms reached significance, suggesting that the relation between negative emotions and CHD incidence was not influenced by changes in other risk factors.

**Subtypes of negative emotion and coronary heart disease incidence:** To better understand the association between negative emotions and CHD incidence, we examined whether specific subtypes of negative emotions were more strongly related to the development of CHD than others. Principal component analysis with varimax rotation was conducted on negative emotions items to identify the major components underlying negative emotion. According to the Eigen values and scree plot, a 3-factor solution was selected, explaining 33% of total variance in the items. The first factor was named “depressed mood” as it was represented by items assessing mood disturbance associated with depression (e.g., feeling blue, diminished self-worth, feeling tired, and loneliness). The second factor was composed of items tapping social embarrassment, awkwardness, and nervousness, and was thus named “social anxiousness.” The third factor consisted of items measuring cognitive difficulties and distortions commonly presented by depressed and anxious patients (e.g., indecisiveness, mental dullness, and hopelessness), and was named “cognitive interference.” Based on these results, 3 subscales of negative emotion (depressed mood, social anxiousness, and cognitive interference) were constructed.

Additional logistic regression analyses were conducted in which each negative emotion subscale was used in separate models to predict CHD along with sociodemographic and physiologic risk variables. The results indicated that social anxiousness (OR 1.18, 95% CI 1.03 to 1.36, p = 0.02) and cognitive distortion (OR 1.16, 95% CI 1.01 to 1.34, p = 0.03) significantly predicted CHD incidence, whereas depressed mood had only a marginal association with the incidence of CHD (OR 1.13, 95% CI 0.98 to 1.31, p = 0.10).

**DISCUSSION**

The results of this study indicate that negative emotions, such as depression and anxiety, were associated with an increased risk of developing CHD in a sample of healthy, older men. Specifically, a 1 SD increase in the negative emotion score resulted in a 51% increase in the risk of developing CHD over the 3-year follow-up period. This association remained significant even while controlling for relevant covariates, including components of the metabolic syndrome (post-challenge insulin and glucose, body mass index, waist-to-hip ratio, and serum lipids) and markers of sympathetic nervous system activity (epinephrine and norepinephrine). These findings extend prior research examining the relation between negative emotions and incident CHD by providing additional evidence that negative emotions are independent risk factors for the development of CHD even after controlling for traditional risk factors, as well as those associated with the metabolic syndrome and sympathetic nervous system activity.

In this study, we also examined whether certain subtypes of negative emotions were more strongly related to CHD incidence. Our data suggested that social anxious-
ness and cognitive interference significantly predicted the development of CHD, such that every 1 SD increase corresponded to a 52% and 50% increase in the risk of developing CHD, respectively. Depressed mood, however, which has been reported in a number studies to be an independent risk factor for cardiac morbidity and mortality, was only marginally related to CHD incidence. Although our findings are somewhat inconsistent with previous studies, the marginal relation between depression and the development of CHD may be due to a number of study limitations, including sample selection (i.e., male population, inclusion of participants with only complete laboratory measures), combination of hard and soft events in our measure of CHD incidence, and the small number of total events observed in this study. In contrast, it is plausible that when depressed mood is isolated from other aspects of the depressive experience, its impact on the development of CHD is weakened. Future studies examining specific components of depression (i.e., dysphoric mood, cognitive interference, vital exhaustion) and their association with CHD risk would be useful, because such investigations would offer important insights into the mechanisms underlying the relation between depression and CHD.