Longitudinal Association Between Depressive Symptoms and Incident Type 2 Diabetes Mellitus in Older Adults

The Cardiovascular Health Study

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Background: Prospective studies indicate that a single self-report of high depressive symptoms is associated with an increased risk of developing type 2 diabetes mellitus.

Methods: We tested whether a single report of high depressive symptoms, an increase in depressive symptoms, or persistently high depressive symptoms over time were associated with the development of diabetes in adults 65 years and older. Participants from the Cardiovascular Health Study completed the 10-item Center for Epidemiological Studies–Depression Scale (CES-D) annually from 1989 to 1999. A single report of high depressive symptoms (CES-D score, ≥8), an increase in symptoms during follow-up (≥5 from baseline), and persistently high symptoms (2 consecutive scores ≥8) were each studied in relation to incident diabetes, defined by initiation of diabetes control medications among participants who were free from diabetes at baseline (n=4681).

Results: The mean CES-D score at baseline was 4.5 (SD, 4.5). The incidence rate of diabetes was 4.4 per 1000 person-years. Following adjustment for baseline demographic characteristics and measures of physical activity, smoking, alcohol intake, body mass index, and C-reactive protein during follow-up, each measure of depressive symptoms was significantly associated with incident diabetes (high baseline CES-D score: hazard ratio, 1.6 [95% confidence interval, 1.1-2.3]; CES-D score increase: hazard ratio, 1.5 [95% confidence interval, 1.1-2.2]; and persistently high symptoms: hazard ratio, 1.5 [95% confidence interval, 1.1-2.3]).

Conclusion: Older adults who reported higher depressive symptoms were more likely to develop diabetes than their counterparts; this association was not fully explained by risk factors for diabetes.

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Most previous studies1-8 indicate that the relative risk of developing type 2 diabetes mellitus is elevated in persons who report high depressive symptoms or clinical depression compared with those with fewer symptoms or without a clinical diagnosis. With the exception of 2 studies3,6 that included a measure of clinical depression, high depressive symptoms are typically defined based on a single self-reported survey. Given the episodic nature of depression and depressive symptoms, a single self-report of symptoms may not fully characterize the association between depressive symptoms and diabetes. Similarly, measurements of correlates of depressive symptoms and diabetes (eg, cigarette smoking, physical inactivity, and body mass index [BMI]) taken at a single point (typically at baseline) do not permit an accurate assessment of their role in the development of diabetes.

In the present study, we tested the hypothesis that high depressive symptoms were associated with the development of diabetes in older adults (those ≥65 years). Our approach differed from prior studies in 3 ways. First, using depressive symptoms characterized annually, we studied the relationship of a single high report of depressive symptoms, an increase in depressive symptoms during follow-up, and persistently high symptom scores with the development of diabetes. Second, we tested whether any observed association was independent of known correlates of depression and diabetes by statistically adjusting for health behaviors, BMI, and inflammatory markers measured repeatedly during follow-up. Third, to our knowledge, this is the only study of a population of older adults.
who, according to national surveys, have a high prevalence of diabetes and depression.

METHODS

STUDY POPULATION

The Cardiovascular Health Study (CHS) is a prospective, population-based, cohort study of cardiovascular disease in adults 65 years and older. In 1989 and 1990, 5201 men and women were recruited from a random sample of Medicare-eligible residents in 4 US communities.11 A supplemental cohort of 687 predominantly African American men and women was recruited during 1992 and 1993 from 3 of the same communities using the same sampling and recruitment methods. Details of the study design, sampling, and recruitment have been published previously.11,12

DATA COLLECTION

The CHS participants were examined yearly from baseline through 1999. Further details about data collection instruments and examination schedules were published.13 Data collected by standardized interview included sociodemographic characteristics (ie, age, race, sex, marital status, and educational attainment) and health behaviors (ie, physical activity, smoking, and alcohol intake). Medication use was assessed at baseline and annually by a medication inventory.14 Clinical measures included height (measured in 1989-1990, 1992-1993, and 1996-1997), weight (measured annually), and waist circumference (measured in 1989-1990, 1992-1993, 1996-1997, and 1998-1999). Body mass index was calculated as weight in kilograms divided by the height in meters squared. Venipuncture was conducted following an overnight fast. Plasma and serum samples were frozen at −70°C and shipped to the CHS Central Laboratory (University of Vermont, Burlington) for analysis. Serum glucose was assayed according to standard methods.15 C-reactive protein level was measured using an ultrasensitive enzyme-linked immunosorbent assay.15 Fasting serum glucose level was measured during the annual examinations in 1989-1990, 1992-1993, and 1996-1997.

MEASUREMENT OF DEPRESSIVE SYMPTOMS

Depressive symptoms were evaluated annually using the 10-item version of the Center for Epidemiological Studies—Depression Scale (CES-D).16 The CES-D is a self-reported measure of depressive symptoms experienced during the previous week. Previous research has compared the validity of the 10- with the 20-item CES-D and found that the 10-item version shows good predictive accuracy (κ = 0.97, P < .001) in an elderly population and repeatability comparable to other surveys (r = 0.71). Questions focus on mood (5 items), irritability (1 item), concentration (1 item), and sleep (1 item). Items are coded on a scale of 0 (rarely or none of the time [<1 day]) to 3 (most or all of the time [5-7 days]) points, for a maximum of 30 points.

The CES-D is not a diagnostic instrument for clinical depression. Higher scores on the CES-D indicate a higher burden of depressive symptoms. Scores above both 8 and 10 on the 10-item scale have been used to indicate high depressive symptoms. Scores above both 8 and 10 on the 10-item scale have been used to indicate high depressive symptoms.17 We applied a cut point of CES-D scores of 8 and higher based on reports from the baseline clinic examination to indicate high depressive symptoms, hereafter referred to as “depressive symptoms.” We attempted to verify our findings using a CES-D cut point of 10 or higher. To evaluate dose-response for incident diabetes, baseline CES-D scores were categorized into quartiles (≤1, 2-3, 4-6, and ≥7) and continuous scores were studied per standard deviation increase. In accordance with previous research in the CHS,18,19 we defined an increase in depressive symptoms over time as a CES-D score of 3 or higher from baseline, and persistent depressive symptoms as 2 consecutive CES-D scores of 8 or higher. Participants using medications classified as antidepressants (selective serotonin reuptake inhibitors, tricyclic agents, and monoamine oxidase inhibitors) were identified during the medication inventory.

DIABETES ASCERTAINMENT

We classified participants as having new-onset diabetes based on the initiation of insulin or oral hypoglycemic therapy ascertained by annual medication inventory. In an effort to identify undiagnosed diabetes, we created a second incident diabetes definition that included medication use and elevated fasting glucose level (≥126 mg/dL [≥7.0 mmol/L]), measured during 1992-1993 and 1996-1997. If a participant’s diabetes medication use is missing at a given examination, but available at the prior examination, the participant was assumed to have the same medication use as the previously reported year. We excluded observations from participants missing medication use at 2 consecutive examinations.

EXCLUSIONS

To identify a cohort of persons free from diabetes at baseline, we excluded 919 participants with prevalent diabetes and 104 among whom we were unable to determine diabetes status. Also, 8 participants who were missing baseline CES-D scores and 176 who did not participate in the second and third clinic visits were excluded, leaving 4681 participants for this analysis.

STATISTICAL ANALYSIS

Baseline characteristics were calculated for all CHS participants and stratified by CES-D score. Kaplan-Meier curves were used to describe the association between quartiles of baseline CES-D score and incident diabetes. No effect modification was detected between depressive symptoms and selected covariates of interest (ie, sex, race, educational age, and marital status), so we built a series of multivariate Cox proportional hazards models to calculate hazard ratios (HRs) between baseline CES-D scores and incident diabetes. The time to event was calculated as the interval between enrollment date and the earliest of the following: (1) date of clinic examination when new diabetes was ascertained, (2) date of the last clinic visit during which diabetes status could be ascertained (a description of missing data criteria is given in the “Diabetes Ascertainment” subsection of this section), (3) date of death, or (4) date of last follow-up. Logistic regression analysis was used to calculate odds ratios for the association of increases in depressive symptoms or persistently high symptoms with incident diabetes. We included covariates from multiple follow-up examinations and imputed values for missing data using methods for longitudinal data previously validated in the CHS cohort.20 The proportion of values imputed ranged between 6% and 17% for data that were collected yearly (CES-D scores, weight, alcohol intake, and smoking status), and was 71% for physical activity, which was measured only during 1989-1990, 1992-1993, and 1996-1997. Statistical significance was set at P < .05. All analyses were conducted using computer software (Stata, version 9.0; Stata Corp, College Station, Tex).

RESULTS

Baseline demographic and clinical characteristics in this sample of participants are reported in Table 1. Notably, the proportion of participants who were overweight or obese was similar across depressive symptom categories. Figure 1
displays the distribution of depressive symptom scores at baseline: 20.0% of participants had CES-D scores of 8 or higher and 13.2% had scores of 10 or higher. During follow-up, the CES-D scores increased by at least 5 in 47.2% of participants; 37.7% had 2 consecutive CES-D scores of 8 or higher. There was little evidence of dose response in the association between baseline CES-D score and incident diabetes, as displayed using Kaplan-Meier curves (Figure 2). Participants in the uppermost quartile were more likely to develop diabetes than those in the lowest quartile; there was no association between each of the middle quartiles of depressive symptoms and the lowest quartile. Higher depressive symptoms at baseline were associated with incident diabetes (Table 2), and this association persisted with statistical adjustment for baseline demographic characteristics and correlates of depression and diabetes measured during follow-up. The magnitude of association in fully adjusted models was identical when CES-D scores of greater

### Table 1. Baseline Characteristics of the Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Sample</th>
<th>High (≥8)</th>
<th>Low (&lt;8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>72.7 (5.5)</td>
<td>73.0 (5.7)</td>
<td>72.6 (5.5)</td>
<td>.07</td>
</tr>
<tr>
<td>African American race</td>
<td>13.0</td>
<td>18.2</td>
<td>11.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>59.2</td>
<td>70.1</td>
<td>56.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt; High school education</td>
<td>27.0</td>
<td>34.5</td>
<td>25.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>8.7</td>
<td>10.0</td>
<td>8.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married</td>
<td>67.5</td>
<td>58.6</td>
<td>69.7</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>23.8</td>
<td>31.4</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>Life events score†</td>
<td>1.1 (1.2)</td>
<td>1.5 (1.4)</td>
<td>1.0 (1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, total kcal/wk†</td>
<td>1783.7 (2038.9)</td>
<td>1443.7 (1803.9)</td>
<td>1868.3 (2085.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12.1</td>
<td>14.9</td>
<td>11.4</td>
<td>.002</td>
</tr>
<tr>
<td>Former</td>
<td>41.3</td>
<td>37.4</td>
<td>42.2</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>46.7</td>
<td>47.8</td>
<td>46.4</td>
<td></td>
</tr>
<tr>
<td>Total alcohol intake per week, No. of beverages‡</td>
<td>2.7 (7.3)</td>
<td>1.8 (4.9)</td>
<td>2.9 (7.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antidepressant medication use</td>
<td>3.8</td>
<td>7.3</td>
<td>2.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI†</td>
<td>26.3 (4.5)</td>
<td>26.4 (2.9)</td>
<td>26.3 (4.4)</td>
<td>.43</td>
</tr>
<tr>
<td>Weight status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (BMI, ≤24.9)</td>
<td>41.4</td>
<td>41.9</td>
<td>41.2</td>
<td>.15</td>
</tr>
<tr>
<td>Overweight (BMI, 25.0-29.9)</td>
<td>41.6</td>
<td>39.3</td>
<td>42.2</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI, ≥30.0)</td>
<td>17.0</td>
<td>18.8</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm†</td>
<td>93.3 (12.8)</td>
<td>93.4 (13.8)</td>
<td>93.3 (13.8)</td>
<td>.84</td>
</tr>
<tr>
<td>Log of C-reactive protein level, mg/L†</td>
<td>0.87 (1.00)</td>
<td>0.98 (1.06)</td>
<td>0.84 (1.00)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the height in meters squared); CES-D, Center for Epidemiological Studies–Depression Scale.

*Data are given as percentage of each group unless otherwise indicated.
†Data are given as mean (SD) unless otherwise indicated.
‡Percentages do not total 100 because of rounding.
than 10 were used (HR, 1.57; 95% confidence interval, 1.01-2.42). There was no association between antidepressant use at baseline and incident diabetes (HR, 1.20; 95% confidence interval, 0.62-2.34).

Participants whose depressive symptom scores increased by at least 5 during follow-up were significantly more likely to develop diabetes than participants whose scores did not increase (Table 3). Similarly, 2 consecutive CES-D scores of 8 or higher were associated with a greater likelihood of developing diabetes. Statistical adjustment for confounders attenuated the strength of these associations, but they retained statistical significance. Adjusting for baseline CES-D score (<8 or ≥8) did not attenuate the association between an increase in CES-D scores and incident diabetes; however, adjustment for baseline did attenuate the association between 2 consecutive high scores and incident diabetes to marginal statistical significance. When we stratified the analyses by categories of baseline CES-D score, an increase in CES-D scores was only statistically significant in those with low CES-D scores (<8) at baseline (HR, 1.73; 95% confidence interval, 1.12-2.67); by contrast, the association was not significant in those with baseline CES-D scores of 8 or higher (HR, 1.26; 95% confidence interval, 0.54-2.94). Two consecutive high CES-D scores were not associated with incident diabetes in either stratum of baseline CES-D scores.

Repeating all analyses using a definition of incident diabetes that included elevated measured fasting glucose level in addition to medications yielded generally similar results. During follow-up, 234 participants (7.9/1000 person-years) developed diabetes; rates were higher among persons with CES-D scores of 8 or more vs less than 8 (9.4 vs 7.5/1000 person-years). The direction of multivariate HRs was similar, but the findings were not statistically significant (P > .05).

In this sample of older adults, a single report of high depressive symptoms, an increase in symptoms with time, and persistently high symptoms over time are each associated with an excess incidence of diabetes. Furthermore, increasing symptoms with time are associated with incident diabetes beyond initial high depressive symptoms and the association between increasing scores and incident diabetes was strongest among those with initially low baseline scores (CES-D score, <8). These findings were present across demographic strata and persisted with statistical adjustment for known correlates of depression and diabetes, such as BMI, physical activity, cigarette smoking, alcohol intake, and C-reactive protein level.

Because inflammatory markers are associated with the development of diabetes and with depressive symptoms, inflammation is often proposed as a mechanism in the association between depressive symptoms and incident diabetes. However, our findings demonstrating no attenuation of the association following adjustment for C-reactive protein level suggest that other biological mechanisms previously proposed, such as hypothalamic-pituitary-adrenal axis dysregulation and sympathetic nervous system stimulation, may be more salient. Depression is associated with adverse autonomic nervous system functioning and prospective studies demonstrate that autonomic nervous system dysfunction can be detected prior to the development of diabetes. Under conditions of short- and long-term sympathetic activation, pancreatic β-cell functioning is suppressed and insulin secretion declines.

### Table 2. Association Between Depressive Symptoms at Baseline and the Development of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;8</th>
<th>≥8</th>
<th>Per 4.5 Points Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3745</td>
<td>936</td>
<td>4681</td>
</tr>
<tr>
<td>No. of events</td>
<td>108</td>
<td>39</td>
<td>147</td>
</tr>
<tr>
<td>Rate per 1000 person-years</td>
<td>3.9</td>
<td>6.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Model*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 [Reference]</td>
<td>1.59 (1.10-2.30)</td>
<td>1.18 (1.02-1.37)</td>
</tr>
<tr>
<td>2</td>
<td>1 [Reference]</td>
<td>1.63 (1.12-2.36)</td>
<td>1.19 (1.03-1.39)</td>
</tr>
<tr>
<td>3†</td>
<td>1 [Reference]</td>
<td>1.58 (1.07-2.28)</td>
<td>1.16 (0.99-1.35)</td>
</tr>
<tr>
<td>4</td>
<td>1 [Reference]</td>
<td>1.57 (1.07-2.29)</td>
<td>1.17 (1.00-1.36)</td>
</tr>
</tbody>
</table>

*Data are given as hazard ratio (95% confidence interval). The models are as follows: 1, the crude model; 2, adjusted for age, race, and sex; 3, adjusted for the variables in model 2 plus educational attainment, marital status, physical activity, smoking, alcohol intake, and body mass index; 4, adjusted for the variables in model 3 plus C-reactive protein level.
†Statistical adjustment includes covariates from multiple follow-up examinations.

### Table 3. Association Between Depressive Symptom Scores During Follow-up and the Development of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Increase in CES-D Score by ≥5 Points†</th>
<th>2 Consecutive CES-D Scores ≥8†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.57 (1.13-2.20)</td>
</tr>
<tr>
<td>2</td>
<td>1.70 (1.19-2.43)</td>
</tr>
<tr>
<td>3</td>
<td>1.59 (1.10-2.30)</td>
</tr>
<tr>
<td>4</td>
<td>1.54 (1.06-2.24)</td>
</tr>
<tr>
<td>5</td>
<td>1.63 (1.12-2.37)</td>
</tr>
</tbody>
</table>

*Data are given as odds ratio (95% confidence interval).
†The models are as follows: 1, the crude model; 2, adjusted for age, race, and sex; 3, adjusted for the variables in model 2 plus educational attainment, marital status, physical activity, smoking, alcohol intake, and body mass index; 4, adjusted for the variables in model 3 plus C-reactive protein level; and 5, adjusted for the variables in model 4 plus baseline CES-D score (<8 or ≥8).

COMMENT
At the same time, sympathetic activation causes declines in muscle insulin sensitivity, hepatic glucogenesis, and rate of glucose uptake, all of which could result in the development of a clinically elevated glucose level. Future mechanistic studies of the association between depressive symptoms and diabetes incidence should investigate the role of the autonomic nervous system in depth.

Our primary findings have been described in most but not all, prior studies. However, even those studies reporting a statistically null association between depressive symptoms and incident diabetes trend toward a positive association. Often, the association became nonsignificant following adjustment for factors such as overweight or physical inactivity, which may fall along the causal pathway toward diabetes development. Depressive symptoms are associated with risk factors for diabetes, such as physical inactivity or excess calorie intake, leading to increased BMI or disturbed sleeping patterns. We still observed an association following adjustment for measures of BMI and physical activity collected during study follow-up, suggesting that other mechanisms associated with depressive symptoms contribute to diabetes risk. However, our measure of physical activity was not available at all time points during follow-up, so we relied on imputation for our longitudinal analyses, which may have introduced error.

Population-based studies such as this one commonly rely on self-reported symptom surveys as opposed to diagnostic interviews. An important consequence of the differential assessment of depression across studies is the wide variability in the presence and strength of association between depressive symptoms and incident diabetes. While we are unable to identify clinical depression using the 10-item CES-D, we do report consistent findings using multiple classifications taken from a range of time periods. In addition, we observed that consistently high depressive symptoms are only marginally and nonsignificantly associated with incident diabetes after adjustment for baseline CES-D category. It is possible that increases in depressive symptoms have the greatest influence on the incidence of diabetes, as evidenced by the statistically significant association between increasing symptoms during follow-up and incident diabetes, even after adjustment for baseline symptom score. Further support in favor of this hypothesis was found in our observation that increasing scores were most strongly associated with incident diabetes among those with initially low (CES-D score, <8) symptom scores at baseline.

Consistent with previous research studies, we do not find a graded association between depressive symptoms and diabetes incidence. Rather, there seems to be a threshold of symptoms associated with diabetes risk. Our finding that antidepressant medication use was not associated with the development of diabetes was unexpected because this association has been described in another study. However, few older adults in this cohort reported using antidepressant medications; thus, we may have been underpowered to detect an association. Alternatively, antidepressant medications may have successfully controlled the somatic and behavioral symptoms of depression.

Despite the novel strengths of our study, which include investigation in a cohort of older adults, multiple measurements of depressive symptoms during follow-up, and the ability to adjust for time-varying covariates, our findings must be interpreted in light of some limitations. Incident diabetes in the CHS has commonly been identified as the initiation of hypoglycemic agents or insulin therapy because the medication inventory is conducted annually, whereas fasting glucose level was measured at a few follow-up visits.

It is difficult to determine the impact of this misclassification on our findings, because it is not clear whether depressive symptoms predispose persons to less or more frequent health care visits in order to be diagnosed. In our secondary analysis, we defined incident diabetes with elevated fasting glucose level in addition to medications, which resulted in a slightly weaker association. Thus, it is plausible that persons with higher depressive symptoms were less likely to be under the regular care of a physician and, therefore, less likely to be diagnosed and treated with medications. If so, our primary results may have overestimated the strength of the association, despite effect sizes representing an approximately 50% higher risk of diabetes among persons with higher depressive symptoms, which is consistent with prior studies.

In summary, high depressive symptoms may be related to the development of diabetes in older adults, and this association may not be attributable solely to the adoption of adverse health behaviors or weight gain. The pathophysiologic mechanism for this association remains unclear. Our findings in this population of older adults are of particular public health importance because there are 35 million US adults older than 65 years. An estimated 2 million older adults may have a depressive illness, which is the second highest prevalence of depression across the age range. The highest prevalence of diabetes in the population is among those 65 years or older (15.3%), and nearly 39% of diabetes cases in older adults were diagnosed after the age of 65 years. Thus, findings from this study of a novel and highly prevalent risk factor for diabetes have important implications for a substantial subset of our population.

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Author Contributions: Dr Carnethon had full access to all the data in the study and takes responsibility for the integ-
rity of the data and the accuracy of the data analysis. Study concept and design: Carnethon and Siscovick. Acquisition of data: Arnold and Siscovick. Analysis and interpretation of data: Carnethon, Biggs, Barzilay, Smith, Vaccarino, Bertoni, and Siscovick. Drafting of the manuscript: Carnethon. Critical revision of the manuscript for important intellectual content: Carnethon, Biggs, Barzilay, Smith, Vaccarino, Bertoni, Arnold, and Siscovick. Statistical analysis: Carnethon, Biggs, Arnold, and Siscovick. Obtained funding: Siscovick. Administrative, technical, and material support: Barzilay and Arnold. Study supervision: Barzilay and Vaccarino.

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Previous Presentation: This study was presented at the 46th Annual Meeting of the American Heart Association Council on Epidemiology and Prevention; March 3, 2006; Phoenix, Ariz.

Additional Information: A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

REFERENCES
