Depression Is a Risk Factor for Coronary Artery Disease in Men

The Precursors Study

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Background: Several studies have found that depression is an independent predictor of poor outcome after the onset of clinical coronary artery disease. There are few data concerning depression as a risk factor for the development of coronary artery disease.

Objective: To determine if clinical depression is an independent risk factor for incident coronary artery disease.

Patients and Methods: The Johns Hopkins Precursors Study is a prospective, observational study of 1190 male medical students who were enrolled between 1948 and 1964 and who continued to be followed up. In medical school and through the follow-up period, information was collected on family history, health behaviors, and clinical depression. Cardiovascular disease end points have been assessed with reviews of annual questionnaires, National Death Index searches, medical records, death certificates, and autopsy reports.

Results: The cumulative incidence of clinical depression in the medical students at 40 years of follow-up was 12%. Men who developed clinical depression drank more coffee than those who did not but did not differ in terms of baseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity, or family history of coronary artery disease. In multivariate analysis, the men who reported clinical depression were at significantly greater risk for subsequent coronary heart disease (relative risk [RR], 2.12; 95% confidence interval [CI], 1.24-3.63) and myocardial infarction (RR, 2.12; 95% CI, 1.11-4.06). The increased risk associated with clinical depression was present even for myocardial infarctions occurring 10 years after the onset of the first depressive episode (RR, 2.1; 95% CI, 1.1-4.0).

Conclusion: Clinical depression appears to be an independent risk factor for incident coronary artery disease for several decades after the onset of the clinical depression.

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SEVERAL LINES of evidence suggest that clinical depression may be a risk factor for coronary artery disease (CAD). In patients with known CAD, depression predicts long-term mortality.[1-3] In prospective studies in which c socioeconomic status, traditional cardiovascular risk factors, and preexisting heart disease were controlled for, depressed affect and hopelessness were independent risk factors for fatal and nonfatal CAD.[4,5] Increasing level of depression over time, but not extent of baseline depressive symptoms, was a predictor for cardiovascular events in a sample of older adults participating in a clinical trial.[6] Depressive symptoms were associated with incident CAD in a sample of elderly Danish men and women.[7] However, several studies have not found an association between depression and incident CAD.[8,9]

In most epidemiological studies, depression has been measured with instruments that ascertain the number of self-reported depressive symptoms present in the past week, which can vary greatly from week to week. In contrast, an episode of major or clinical depression requires that a number of symptoms be present simultaneously for several weeks. The largest study (to our knowedge) in which a structured interview was used to diagnose major depression found an association with self-reported myocardial infarction, but data on levels of cholesterol or blood pressure were not collected.[10] Also, deaths due to cardiovascular disease (CVD) were not assessed. The Johns Hopkins Precursors study has collected data on episodes of clinical depression, CAD risk factors, and CAD for more than 35 years and provides a unique opportunity to determine if individuals

PATIENTS AND METHODS

The Johns Hopkins Precursors Study was designed by Dr Caroline Bedell Thomas in 1946.[11] All students who entered The Johns Hopkins Medical School classes from 1948 to 1964 were enrolled in the study. In medical school, participants underwent a standardized medical examination and completed questionnaires about their personal and family history, health status, and health behaviors. The cohort has been followed up since graduation with annual mailed questionnaires, with an average response rate of 90% (range, 87%-94%) over every 5-year period.[12] Self-reports of cardiovascular parameters have been verified for a subsample of the cohort and found to be extremely accurate.[13]

The main results are based on data from 1190 men. Those who did not provide personal information in medical school (n = 48), those reporting clinical depression at baseline (n = 11), and those who died in medical school or were unavailable for follow-up (n = 26) were excluded from this analysis. An exploratory analysis is presented for the small number of eligible women (n = 121) in the cohort.

Cardiovascular risk factors have been assessed in multiple ways throughout the study. Exercise, serum cholesterol levels, smoking, blood pressure, diabetes, and history of parental myocardial infarction were assessed in medical school by questionnaire, examination, and blood tests. Changes in all these risk factors, including a family history of premature CAD, have been measured with specific questions on subsequent questionnaires and review of medical records, when available.

Incidence of clinical depression has been measured on the mailed surveys with direct questions concerning the occurrence of depression and associated treatment.[14] Self-reports of depression were confirmed by a committee of 5 physician reviewers who were unaware of the study hypothesis. The self-report of clinical depression was not confirmed if there was a comment that the symptoms resolved in 2 weeks or less or that the symptoms were exclusively related to grief. Strict adherence to *Diagnostic and Statistical Manual of Mental Disorders, Third Edition,* criteria,[15] which have been modified several times during the long follow-up of the study, was not possible. As a result, the term *major depression* is not used. The validity of the diagnosis of clinical depression was assessed with questions covering treatment of the depression. Use of antidepressant medication has been assessed multiple times and lifetime history of receiving care from a mental health specialist for "an emotional problem" was assessed on the 1988 questionnaire.

Cardiovascular disease end points have been assessed with reviews of annual questionnaires, National Death Index searches, medical records, death certificates, and autopsy reports. Events are verified with medical records. All of the outcomes are reviewed and *International Classification of Diseases, Ninth Revision (ICD-9)*[16] codes are assigned by a committee of internists using standardized criteria modified from the Lipids Research Clinic Study.[17] This analysis is based on outcomes verified through 1995.

Cardiovascular disease was categorized as follows. The most specific category, myocardial infarction, included myocardial infarction (410 and 412) and sudden death (427.5 and 798.2). Coronary heart disease (CHD) included all events in the myocardial infarction codes, as well as angina pectoris (413), chronic ischemic heart disease (411), and other types of symptomatic coronary disease that did not meet these criteria but required coronary artery bypass surgery or percutaneous transluminal coronary angioplasty (414). The broadest category, CVD, included events resulting from CHD as well as hypertensive heart and renal disease (402 to 404), congestive heart failure (428), and cerebrovascular disease (430 to 438).

Multivariate relationships were assessed with Cox proportional hazards models to take full advantage of the long period of observation. Several models are presented to assess whether potential confounders influenced the risk of CAD associated with clinical depression. Clinical depression, hypertension, and diabetes were included as time-dependent variables. This technique assesses whether these independent variables were present for a given individual at multiple times over follow-up. Changes in smoking status, coffee drinking, and alcohol intake over follow-up were also accounted for through the use of time-dependent covariates. The baseline serum cholesterol level was used to assess the contribution of lipids in the main analysis. A time-dependent covariate based on report of hyperlipidemia requiring treatment with diet or medication was also created. The potential for misclassification of the timing of clinical depression and CHD was assessed by excluding cases in which the CHD event occurred within 2 years of the first report of a depressive episode. To assess the duration of elevated risk from clinical depression, additional Cox models were also developed incorporating a lag period of 10 years. Two-tailed test α levels of $<.05$ were used to define statistical significance.

who have had an episode of clinical depression are at increased risk for the development of CAD.

RESULTS

The mean age of the 1190 men at graduation from medical school was 26 years. The median follow-up was 37 years. In 1995, the average age of the cohort was 66 years, with a range of 55 to 88 years. The sample is 98% white. One hundred thirty-two men reported an episode of clinical depression during follow-up, with a median age of 46 years at onset of the first episode. The cumulative incidence of depression in these men at 40 years of follow-up was 12%, with no evidence for a secular trend in incidence. Treatment for clinical depression reflects usual care between 1950 and 1995. A minority of men (23%) reported no treatment for clinical depression, with 33% reporting use of antidepressant medications and 44% reporting psychotherapy with or without use of benzodiazepines or other sedatives.

Men who later developed clinical depression over follow-up were slightly older when they graduated from medical school (27 vs 26 years; $P = .03$) and reported drinking significantly more cups of coffee at baseline, but otherwise did not differ (**Table 1**). Clinical depression was associated with an almost 2-fold increased risk for subsequent CHD in unadjusted analysis (**Table 2**). It has been suggested that the relationship between clini-

Table 1. Baseline Characteristics of 1190 Men in The Johns Hopkins Precursors Study

Characteristics	Total Sample (N = 1190)	Lifetime Occurrence of Depression		*P*
		Yes (n = 132)	No (n = 1058)	
Mean (SD)				
Age, y	26 (2.4)	27 (3.0)	26 (2.4)	.02
Systolic blood pressure, mm Hg	116 (8.9)	115 (8.1)	116 (9.1)	.83
Diastolic blood pressure, mm Hg	70 (6.7)	69 (6.1)	70 (6.7)	.19
Cholesterol, mmol/L [mg/dL]	192 [4.96] (29.2) [0.76]	192 [4.96] (33.3) [0.86]	192 [4.96] (28.7) [0.74]	.99
Body mass index, kg/m^2	23 (2.6)	23 (2.8)	23 (2.6)	.84
Coffee, cups per day	2 (1.8)	3 (1.9)	2 (1.8)	.01
No. (%)				
Smoker	557 (51)	65 (53)	492 (51)	.57
Physical training during past month	182 (18)	17 (16)	165 (19)	.50
Premature parental myocardial infarction*	105 (9)	10 (8)	95 (9)	.59
Drinks alcohol	940 (89)	106 (91)	834 (89)	.40

**Collected at baseline and during follow-up. Defined as myocardial infarction before the age of 55 years in men and 65 years in women.*

cal depression and CHD may be a result of higher rates of tobacco smoking and use of other psychoactive substances among depressed individuals. However, the association between clinical depression and CHD did not change when time-dependent smoking, alcohol use, and coffee consumption were added to bivariate models. Likewise, adjusting for body mass index, family history of premature parental myocardial infarction, baseline serum cholesterol level, and time-dependent report of hyperlipidemia requiring treatment had no effect on the association between clinical depression and CHD in bivariate models (data not shown). In a model containing the strongest traditional risk factors (baseline serum cholesterol level and time-dependent smoking, hypertension, and diabetes), the risk of CHD associated with clinical depression remained statistically significant (relative risk [RR], 1.7; 95% confidence interval [CI], 1.0-2.9).

Stratified analysis for baseline tobacco smokers and nonsmokers was completed. Baseline smokers had a higher RR for CHD associated with clinical depression (RR, 2.11; 95% CI, 1.24-3.62) than did baseline nonsmokers (RR, 1.03; 95% CI, 0.57-2.89) in univariate analysis. Similar results were found when a time-dependent smoking variable was added or a complete multivariate model was developed. A formal test of the interaction of clinical depression and smoking on CHD was not statistically significant. However, statistical power was limited, with only 45 cases of CHD in baseline nonsmokers.

The results presented above are based entirely on the men in the study cohort. An exploratory analysis was undertaken for the 12 cases of CVD reported in 119 women in the study cohort. The RR for clinical depression was statistically significant (RR, 4.04; 95% CI, 1.17-13.97) in a univariate analysis. The small number of cases made the results of multivariate analysis uninterpretable.

In **Table 3**, the relationship of clinical depression with several cardiovascular outcomes and mortality is presented. In multivariate analysis, men who reported clinical depression were at significantly greater risk for CHD (RR, 2.12; 95% CI, 1.24-3.63) and myocardial infarction (RR, 2.12; 95% CI, 1.11-4.06). Clinical depression was not associated with cerebrovascular accidents but was associated with a greater risk of total mortality according to both unadjusted and adjusted analyses. Clinical depression was significantly related to CVD mortality in unadjusted analyses, with a trend toward increased CVD mortality in adjusted analyses. The association of clinical depression with CVD mortality was stronger than the association of clinical depression with other causes of death, exclusive of suicide. The RR for sudden death associated with clinical depression (RR, 2.75; 95% CI, 0.6-13.1) was slightly, but not significantly, higher than the RR for CVD (RR, 1.8; 95% CI, 1.1-2.8). As expected, the risk for suicide was dramatically higher in the men with clinical depression.

Several analyses were completed to better understand the relationship between major depression and CHD. The median time from first episode of major depression to first CHD event was 15 years, with a range of 1 to 44 years. To limit the possibility that respondents might have actually had the CHD event before the onset of clinical depression, an analysis was completed in which all cases of CHD occurring within 2 years of the first report of major depression were censored. The RR of CHD associated with clinical depression did not change. In multivariate analyses, clinical depression was still an independent risk factor for CHD (RR, 2.1; 95% CI, 1.1-4.0) 10 years after the onset of depression. Similar to many cardiovascular risk factors, the magnitude of the association with clinical depression decreased slightly for cardiovascular events occurring after the age of 65 years.

Tricyclic agents, which were the antidepressants most commonly used by the majority of this cohort, are known to have cardiac effects, and use of these therapeutic agents may explain the apparent association between clinical depression and myocardial infarction. The RR for clinical depression was slightly higher for those reporting treatment with psychotherapy with or without sedatives (RR, 2.33; 95% CI, 1.17-4.65) than for those reporting treatment with antidepressant medications (RR, 1.89; 95% CI, 0.77-4.65) or those reporting no treatment (RR, 0.94; 95% CI, 0.13-6.8). However, in this analysis, it was not possible to control for the underlying severity of the initial

Table 2. Relative Risk of Subsequent Coronary Heart Disease Associated With Clinical Depression in Cox Proportional Hazards Analysis*

Adjusting Variables	Relative Risk	95% CI
None	1.8	1.1-2.8†
Smoking, time dependent	1.8	1.1-2.8‡
Alcohol, time dependent	2.0	1.2-3.2‡
Coffee, time dependent	1.7	1.1-2.7‡
Baseline serum cholesterol level, time-dependent smoking, incident hypertension, and incident diabetes	1.7	1.0-2.9‡

**Based on 163 events. CI indicates confidence interval.*
†P≤.01.
‡P≤.05.

Table 3. Univariate and Multivariate Relative Risks (RRs) and 95% Confidence Intervals (CIs) Associated With Clinical Depression

	No.	Univariate RR (95% CI)	Multivariate RR* (95% CI)
All events			
Cardiovascular disease	234	1.28 (0.82-1.99)	1.52 (0.92-2.51)
Coronary heart disease	163	1.79 (1.13-2.84)	2.12 (1.24-3.63)
Myocardial infarction	103	1.98 (1.14-3.44)	2.12 (1.11-4.06)
Cerebrovascular accident	63	0.95 (0.38-2.38)	0.93 (0.33-2.65)
Fatal events			
Cardiovascular disease	34	2.42 (1.06-5.90)	1.80 (0.56-5.75)
Suicide	17	14.27 (5.18-39.33)	. . .
Other	102	1.49 (0.79-2.81)	1.43 (0.67-3.04)
Total	**153**	2.31 (1.49-3.59)	2.45 (1.44-4.15)

**Adjusted for graduation age, baseline serum cholesterol level, premature parental myocardial infarction, physical activity, time-dependent smoking, incident hypertension, and incident diabetes. Ellipses indicate insufficient number of cases to calculate a value.*

clinical depression, and the small number of individuals in the various treatment categories limits our ability to draw firm conclusions.

COMMENT

Several studies have demonstrated that individuals who develop major depression after a myocardial infarction have decreased survival. This report provides new evidence that men with clinical depression are at moderately increased risk for developing CAD even after multiple cardiovascular risk factors are carefully adjusted for. The risk is greater for myocardial infarction than for CVD in general. None of the possible confounders proposed by other investigators, such as tobacco smoking, substantially altered the association between clinical depression and onset of CAD.

This is one of the few studies addressing development of CAD that has assessed clinical depression, and not the level of depressive symptoms, based on a single questionnaire. The measurement of clinical depression in this study appears valid in that it was strongly related to treatment. Moreover, the lifetime rate of clinical depression (12%) is almost identical to the rate found in a sample of white men 45 to 54 years of age who were representative of the US population (12.8%).[18] The one difference in the pattern of clinical depression found in this sample compared with other community samples is the relatively late age at onset of the first episode. This difference may be because men who develop clinical depression in adolescence or early adulthood are less likely to be admitted to medical school. This selection of men who are less likely to be depressed at baseline should not affect the generalizability of the association.

Several explanations have been suggested for the association between depression and atherosclerotic heart disease.[19] Confounding by traditional cardiac risk factors is not supported by the data from this or other studies. Our results support earlier data that the increased risk from clinical depression persists for more than 10 years after the onset of the depression.[3] This finding would suggest that clinical depression may have an impact on the progression of underlying atherosclerosis. There also was no evidence that most of the excess deaths in men with clinical depression were the result of sudden death, as has been reported for phobic anxiety.[20] However, uncertainty of the duration of the depressive episodes hinders our ability to make firm conclusions about the mechanism of the association. The leading biological explanation appears to relate to altered autonomic tone as manifested by less heart rate variability, a characteristic associated with CAD mortality in several studies.[21-23] Sympathetic nervous system activity is increased in patients with major depression and may be playing a role as well.[24] We found no differences in baseline resting heart rates for the study participants who eventually developed clinical depression or CVD. Increased platelet reactivity has also been reported in a small sample of young patients with major depression who were not taking any medications.[25] Individuals with clinical depression may be less adherent to medical care recommendations, even though they are more likely to use general medical services. Higher levels of nonadherence to medications has been reported for elderly patients with CAD and depression, but it is not clear if this finding would explain an increased risk of incident CAD.[26] Several studies have reported an association between tricyclic antidepressant therapy and CAD, but, to our knowledge, none have been able to separate the level of severity of the depression from the use or duration of use of the antidepressant medication.[27,28] The dramatic increase in the use of selective serotonin reuptake inhibitor antidepressants may allow a more informative investigation of the possible impact of antidepressant therapy on CAD.

Our data provided some evidence that lifetime smokers have a greater risk for the development of CVD as a result of clinical depression than do lifetime nonsmokers. Similar results have been found in other studies. A strong interaction between smoking and both depressed affect and hopelessness on risk of fatal and nonfatal ischemic heart disease was found in the National Health Examination Follow-up Study.[4] With a different chronic disease, depressed mood as measured by the Center for Epidemiologic Studies Depression Scale was associated with a much higher risk of cancer for smokers than nonsmokers in a community sample.[29]

This analysis has several strengths including the prospective design, the long period of follow-up, the careful assessment of cardiac risk factors, and the use of clinical depression, and not just depressive symptoms, as the measure of depression. When depression is measured by symptom count, the classification is less reliable and may be more influenced by the presence of physical illness.[30] Also, while effective treatment strategies for clinical depression are available, management in cases in which only a few depressive symptoms are reported is not clear. Nonetheless, like all studies, our findings need to be interpreted with several reservations in mind. The subjects were men with a limited range of education and income. Therefore, the results should be generalized with caution. The high socioeconomic status of this sample might protect the participants from some of the adverse consequences of depression and lead to a conservative estimate of the risk related to depression. Also, the diagnosis of clinical depression was based on self-report and was not confirmed by a structured clinical interview. Finally, it is possible that not all participants with clinical depression were excluded at baseline. The long period between baseline measurements and incident CAD suggests this would have little impact on the observed association.

This study adds to the growing body of literature that depression is an independent risk factor for CAD. Future research needs to address the extent to which treatment of depression either decreases or increases this risk.

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