ORIGINAL ARTICLE

Depression and History of Attempted Suicide as Risk Factors for Heart Disease Mortality in Young Individuals

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Context: Although depression is associated with increased cardiovascular morbidity and mortality, there is virtually no information on whether it also increases the risk in young populations.

Objectives: We sought to determine the association of unipolar and bipolar depression and a history of attempted suicide with mortality due to ischemic heart disease (IHD) and cardiovascular disease (CVD) in young US adults and to examine potential sex differences.

Design: Longitudinal epidemiologic study.

Setting: Nationally representative sample of US adults.

Participants: A total of 7641 US adults aged 17 to 39 years from the 1988-1994 Third National Health and Nutrition Examination Survey.

Main Outcome Measures: Cardiovascular disease and IHD mortality. Unipolar/bipolar depression and a history of attempted suicide were assessed via the Diagnostic Interview Schedule.

Results: After a median follow-up of 14.9 years, a total of 51 subjects (0.67%) died of CVD causes and 28 (0.37%) died of IHD. Depression (538 individuals [7.04%]) and history of attempted suicide (419 [5.48%]) were each associated with an increased risk of IHD death, with adjusted hazard ratios of 3.70 (95% CI, 1.32-10.35) for depression and 7.12 (2.67-18.98) for a history of attempted suicide. Women with depression or a history of attempted suicide had a 3-fold adjusted risk of CVD (adjusted hazard ratio, 3.20 [95% CI, 1.12-9.17]) and a 14-fold adjusted risk of IHD (14.57 [2.65-80.10]). Corresponding figures for men were 2.37 (0.85-6.58) and 3.52 (1.05-11.76).

Conclusion: In adults younger than 40 years, depression and history of attempted suicide are significant independent predictors of premature CVD and IHD mortality in both sexes.

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ALTHOUGH MAJOR DEPRESSIVE disorder has been associated with increased risk of ischemic heart disease (IHD) in multiple studies, virtually no investigations have focused on young populations.[1] Ischemic heart disease begins in youth,[2] and the value of a life-course approach to early detection of IHD risk is increasingly recognized as fundamental for risk assessment and prevention.[3] Depression and other psychiatric disorders are highly prevalent in young people, with more than one-half of persons aged 18 to 44 years affected by a psychiatric disorder of some type.[4] Therefore, the impact of psychiatric conditions on risk of cardiovascular disease (CVD) could be particularly significant in younger populations, who may also be more vulnerable to the adverse effects of psychological stressors on health than older populations.[5,6]

Depression, hopelessness, aggression, and impulsivity may lead to attempted suicide.[7] A recent study[8] has shown that suicide is highly comorbid with IHD; patients with myocardial infarction (MI) and psychiatric illness were found to have a nearly 6-fold increased rate of suicide after MI compared with those with only psychiatric illness. Although MI may be a trigger for suicide, underlying suicidality may also be a risk factor for MI. History of attempted suicide may therefore be a CVD risk factor, although this has not been previously examined.[7]

Young adults, in general, have a substantially higher prevalence of mood disorders compared with elderly subjects, and women have 50% higher odds of a mood or an anxiety disorder compared with men.[4] This is also a group for which considerable gaps in our understanding of the IHD pathophysiologic mechanism exist.

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In more than half of young women who die of IHD, only 1 or no traditional risk factor is present, and smoking is the only conventional risk factor found to be consistently associated with IHD mortality in this group.[9] Therefore, the investigation of psychosocial risk factors is especially warranted in young women, who, after developing IHD, have accelerated mortality compared with men[10] as well as twice the prevalence of depression.[11]

In this study, we examined whether a clinical diagnosis of unipolar or bipolar depression according to the *DSM-III* criteria and a history of attempted suicide are associated with IHD and total CVD mortality in young adults and explored sex differences in these associations. The Third National Health and Nutrition Examination Survey (NHANES III) is ideally suited to answer these questions because a clinical diagnosis of depression and a history of attempted suicide were measured in a large, nationally representative sample of persons aged 17 to 39 years, with subsequent linkage to the National Death Index. In addition, a comprehensive array of CVD risk factors and other characteristics were thoroughly assessed, allowing for rigorous analysis of possible confounders.

METHODS

STUDY DESIGN

Study participants included US adults aged 17 to 39 years who participated in the 1988-1994 NHANES III and underwent the mental health survey. The NHANES is a continuous survey of the US civilian, noninstitutionalized population designed to obtain nationally representative estimates on diet and health indicators.[12] Participants are selected from a complex, multistage sampling design. The study protocol for NHANES III was approved by the institutional review board at the National Center for Health Statistics. Signed informed consent was obtained from all participants.

A total of 7968 people aged 17 to 39 years were examined in NHANES III. Those with a history of MI (n=18), missing depression and history of attempted suicide data (n=303), and missing mortality data (n=6) were excluded. The final sample for analysis included 7641 subjects.

BASELINE MEASUREMENTS

A history of or current unipolar/bipolar depression was measured with the Diagnostic Interview Schedule,[13] which is a standardized clinical instrument based on *DSM-III* criteria and uses a structured interview format.[14] A history of attempted suicide was also queried during administration of the Diagnostic Interview Schedule with the question, "Have you ever attempted suicide?"

Via interview, information was obtained on age, sex, years of education, self-identified race, ethnicity, family income, cigarette use, alcohol consumption, cocaine use, leisure-time physical activity during the preceding month, medication use, and medical history. Blood pressure was determined by the average of 3 measurements in the examination centers and 3 measurements during the interview. Hypercholesterolemia was defined as a total cholesterol level of more than 240 mg/dL (to convert to millimoles per liter, multiply by 0.0259); obesity, as a body mass index of at least 30 (calculated as weight in kilograms divided by height in meters squared); and hypertension, as a blood pressure of at least 140/90 mm Hg and/or current administration of antihypertensives. Total and high-density lipoprotein cholesterol levels were measured using commonly available reagents (catalogue No. 816302 from Boehringer Mannheim, Indianapolis, Indiana). Binge drinking was quantified as the number of days in the past year when the respondent drank 5 or more drinks per day and was analyzed as a continuous measure. A person was considered inactive if he or she did not do any leisure-time physical activity. Socioeconomic status was determined by the poverty to income ratio, which is the ratio of the midpoint of the observed family income category to the official poverty threshold, scaled to family size; it was analyzed as a continuous variable. Years of education was also analyzed as a continuous variable. A person was considered to have a lifetime history of smoking if he or she had smoked 100 or more cigarettes in his or her lifetime. Because race/ethnicity was associated with CVD and overall mortality in previous studies, we included variables for white non-Hispanic, black non-Hispanic, and Mexican-American race or ethnicity in the analyses.[15] Use of antidepressants was not included as a risk factor because only 5.72% of those with depression or a history of attempted suicide reported such use, and no CVD events occurred in that subgroup.

Mortality data through December 31, 2006, were available for NHANES III participants 17 years or older via use of the National Death Index. Death certificate data were also available to determine the primary cause of death. A complete description of the probabilistic matching methods used to ascertain mortality can be found elsewhere.[16] Ischemic heart disease was identified by *International Classification of Diseases, 10th Revision* (*ICD-10*) codes I20 through I25, which included acute MI, other acute IHD, atherosclerotic CVD, and other forms of chronic IHD. Cardiac deaths from hypertensive causes (*ICD-10* codes I11 and I13) were also included because of recent guidelines on secondary IHD, which indicate that cardiac death from hypertensive causes may relate to ischemia.[17] Total CVD deaths were identified by *ICD-10* codes I00 to I99, which, in addition to the aforementioned, included endocarditis, myocarditis, heart failure, cerebrovascular diseases, atherosclerosis, and other circulatory and heart diseases. Total non-CVD mortality was analyzed as a secondary outcome to determine whether the relative risks for CVD or IHD due to depression were specific to the cardiovascular system or part of a general mortality effect. Suicide (*ICD-10* codes U03, X60-X84, and Y87.0) was excluded from total mortality outcomes because the association of depression and history of attempted suicide with suicide mortality is well established.[18]

DATA ANALYSIS

We used commercially available statistical software (SAS, version 9.2 [SAS Institute, Cary, North Carolina] and SUDAAN, version 10 [Research Triangle Institute, Research Triangle Park, North Carolina]) for all analysis, which accounted for the complex survey design. Missing data were accounted for through multiple imputation.[19] For most variables, less than 1% of data were missing; exceptions included income (8.45% missing) and high-density lipoprotein cholesterol levels (6.19% missing). Sample weights (which take into account oversampling for race/ethnicity, age, and nonresponse) were not taken into account in regression analyses because of extreme variability in the weights when dealing with a small number of outcomes. To minimize bias, we tested for possible depression-race interaction (none was found) and adjusted for race/ethnicity in our analyses.[20] Subjects with non-CVD/IHD deaths were censored at the time of death.

The Framingham risk score (FRS) was based on age, sex, hypertension, diabetes mellitus, total and high-density lipoprotein cholesterol level, and smoking history, as described else-

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where[21]; subjects younger than 30 years were counted as 30 years of age for point scoring. Despite this approximation, the C statistic for the FRS as a lone predictor for IHD was very good in this young population (0.77). We used the FRS in place of the individual risk factors (age, total and high-density lipoprotein cholesterol levels, diabetes, systolic/diastolic blood pressure, and smoking) to minimize statistical bias due to the small number of IHD deaths.[22] As a test of robustness of this substitution, analyses that adjusted for individual risk factors were also performed and yielded similar results (data not shown).

We fitted Cox proportional hazards models to test for the association of depression and history of attempted suicide with the study outcomes. Unipolar and bipolar depression were analyzed together because of the small number of individuals with bipolar depression (n=122). Depression and a history of attempted suicide were analyzed in separate models because of significant overlap. In sex-stratified analyses, depression and a history of attempted suicide were combined as a unified predictor given that they likely share similar pathophysiologic features.[23] The proportional hazards assumption was checked using Schoenfeld residuals and log-log survival plots. In addition to the core model that included sex, race/ethnicity, and the FRS for women and men, sensitivity analysis that included individual socioeconomic and lifestyle-related risk factors was also performed to demonstrate the robustness of depression and history of attempted suicide as predictors.[24,25] Covariates to be included in sensitivity analysis were chosen on the basis of theoretical plausibility, prior empirical findings, or demonstrated associations with depression or attempted suicide and mortality in this sample; they included income, education, body mass index, alcohol intake, sedentary lifestyle, and cocaine use.

Finally, we calculated the population-attributable risk (PAR) for depression and attempted suicide, as well as for traditional risk factors that were positively associated with IHD in this young population (smoking, hypertension, diabetes mellitus, and obesity), using the following formula[26]:

PAR = [(Proportion of Exposed Cases) × (Relative Risk − 1)]/Relative Risk

The formula determined the proportion of deaths that could be prevented if the exposure was not present. The unweighted proportion of cases exposed was calculated, and adjusted relative risks were derived from a model that included all these risk factors.

RESULTS

BASELINE CHARACTERISTICS

The mean age of the sample was 28.1 years, with women constituting 54.47%. Of 7641 participants, 416 (5.44%) had a lifetime history positive for unipolar depression, 122 (1.60%) had a lifetime history positive for bipolar depression, and 419 (5.48%) reported previous attempted suicide. Considerable overlap existed between depression and attempted suicide; of 821 people with any of these conditions, 136 had both. Of those who had a history of attempted suicide, 101 of 309 women (32.69%) and 35 of 110 men (31.82%) had a history of depression. These frequencies translate into more than 10 million people (15.2% of women and 7.6% of men) aged 18 to 39 years in the United States who had major depressive disorder, bipolar disorder, and/or a history of attempted suicide in 1990.

Factors related to higher rates of depression were older age, female sex, white race, smoking, cocaine use, and morbid obesity (**Table 1**). Factors associated with higher rates of attempted suicide were female sex, less education, poverty, sedentary behavior, smoking, and cocaine use.

MORTALITY

After a median follow-up time of 14.9 (interquartile range, 13.6-16.5) years, there were 261 total deaths (3.42%), of which 246 (3.22%) were for reasons other than suicide, and 51 (0.67%) from CVD. Of these, 28 (0.37%) were from IHD, 8 were from cerebrovascular causes, and 15 were from other CVD causes.

Depression and a history of attempted suicide were related to CVD mortality (**Table 2**), which occurred in 51 people, of whom 4 had attempted suicide, 4 had depression, and 2 had both. After adjusting for age, sex, and race/ethnicity, the hazard ratio (HR) for depression was 2.38 (95% CI, 0.93-6.08) and for history of attempted suicide was 3.21 (1.36-7.56). Further adjustment for traditional risk factors caused only minimal change in the estimates for depression (HR, 2.21 [95% CI, 0.86-5.69]) and history of attempted suicide (3.21 [1.33-7.76]). Similarly, sensitivity analysis adding socioeconomic and lifestyle factors to the model showed modest (<10%) decreases in effect size.

Depression and history of attempted suicide also showed significant associations with IHD mortality. Of the 28 people who died of IHD, 4 had attempted suicide, 3 had depression, and 2 had both. After adjustment for sex, race, and traditional risk factors, a history of attempted suicide was associated with more than 7 times higher risk of IHD (HR, 7.12 [95% CI, 2.67-18.98]), and depression was associated with an almost 4-fold higher risk (HR, 3.70 [1.32-10.35]; Table 2). Addition of socioeconomic and lifestyle factors to the model had only a modest effect on the association. Additional sensitivity analyses that included medical history (asthma, chronic obstructive pulmonary disease, arthritis, gout, cancer, and thyroid disease) did not significantly alter the findings (data not shown). Similarly, when subjects who were taking antidepressants were excluded (n=32), the HR of IHD for depression was only minimally changed (<10%).

In sex-stratified analyses, the adjusted HR for IHD death for depression and history of attempted suicide as a combined risk factor was higher in women (7 IHD deaths; HR, 14.57 [95% CI, 2.65-80.10]) than in men (21 IHD deaths; 3.52 [1.05-11.76]), with $P=.13$ for the interaction with sex (**Table 3**). A smaller sex difference was found for CVD mortality, with an adjusted HR of 3.20 (14 deaths [95% CI, 1.12-9.17]) in women and 2.37 (37 deaths [0.85-6.58]) in men, with $P=.62$ for the interaction with sex. History of depression and/or attempted suicide occurred in 5 women and 5 men who died of CVD. Of these, all 5 women and 4 of the 5 men died of IHD causes.

For non-CVD mortality, depression and a history of attempted suicide were significant predictors in men only (n=3491), with an adjusted relative risk of 2.49 (95% CI, 1.19-5.21) for depression, and $P=.02$ for the sex-depression interaction (**Figure 1**). The results were similar for a history of attempted suicide (HR, 2.58 [95% CI,

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Table 1. Baseline Prevalence of Unipolar and Bipolar Depression and History of Attempted Suicide According to the Level of Other Baseline Factors

Factor	No. of Subjects[a]	Depression		Attempted Suicide	
		Prevalence, % (n=538)	*P* Value[b]	Prevalence, % (n=419)	*P* Value[b]
Overall	7641	7.04		5.48	
Age, y					
<30	4472	6.35	.01	5.64	.49
30-39	3169	8.02		5.27	
Sex					
Male	3479	4.50	<.001	3.16	<.001
Female	4162	9.20		7.42	
Race/ethnicity					
White	2182	9.43	<.001	5.96	.39
Black	2530	6.01		4.90	
Hispanic	2610	6.25		5.56	
Other	319	5.33		6.27	
<High school educational level	2698	6.45	.13	7.15	<.001
Economic status below poverty level[c]	2053	7.89	.08	7.50	<.001
Health behaviors					
Sedentary lifestyle	1286	7.93	.17	7.08	.01
Never smoker	4506	5.70	<.001	3.86	<.001
Past smoker	892	8.62		6.05	
Current smoker	2242	9.10		8.52	
History of cocaine use	297	11.11	.01	13.47	<.001
History of binge drinking	2624	8.46	.07	5.68	.53
BMI					
Normal weight	3875	6.97	.01	5.11	.052
Overweight	2172	6.45		5.39	
Obese	940	6.60		5.74	
Morbidly obese	643	10.09		7.78	

Abbreviation: BMI, body mass index.
[a]The following categories may include fewer than 7641 individuals because of missing data (n missing): educational level (46), economic status (646), smoking behavior (1), sedentary behavior (35), cocaine use (7), and BMI (11).
[b]Calculated as χ^2 test comparing depression prevalence in those with and without the characteristic.
[c]Based on a poverty to income ratio of less than 1.

Table 2. Hazard Ratios Relating Unipolar and Bipolar Depression and History of Attempted Suicide to CVD and IHD Mortality Before and After Adjustment for Covariates[a]

	CVD Mortality (51 Deaths)		IHD Mortality (28 Deaths)	
	Depression	Attempted Suicide	Depression	Attempted Suicide
No. exposed/total population	538/7641	419/7641	538/7641	419/7641
Unadjusted	1.84 (0.74-4.61)	2.38 (0.97-5.87)	3.04 (1.08-8.55)	4.92 (1.84-13.16)
Adjustments[b]				
Sex and race	2.38 (0.93-6.08)	3.21 (1.36-7.56)	3.98 (1.43-11.12)	6.82 (2.75-16.91)
FRS[c]	2.21 (0.86-5.69)	3.21 (1.33-7.76)	3.70 (1.32-10.35)	7.12 (2.67-18.98)
Additional separate covariates				
Income	2.21 (0.86-5.65)	2.96 (1.20-7.28)	3.70 (1.33-10.26)	6.53 (2.40-17.76)
Educational level	2.28 (0.89-5.85)	3.10 (1.28-7.51)	3.78 (1.35-10.53)	7.00 (2.60-18.80)
BMI	2.01 (0.78-5.19)	3.25 (1.37-7.74)	3.20 (1.12-9.15)	7.04 (2.61-18.96)
Alcohol intake	2.17 (0.84-5.64)	3.15 (1.27-7.84)	3.71 (1.32-10.45)	7.19 (2.61-19.77)
Sedentary lifestyle	2.20 (0.86-5.66)	3.19 (1.33-7.63)	3.66 (1.31-10.21)	6.99 (2.37-18.31)
Cocaine use	2.19 (0.87-5.53)	3.18 (1.34-7.59)	3.72 (1.35-10.28)	7.26 (2.78-18.99)
All additional covariates	1.99 (0.79-5.04)	2.90 (1.19-7.08)	3.23 (1.16-9.02)	6.69 (2.42-18.52)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FRS, Framingham risk score; IHD, ischemic heart disease.
[a]Unless otherwise indicated, data are expressed as hazard ratio (95% CI).
[b]Adjustments are inclusive of previous rows unless otherwise indicated.
[c]The FRS involves age, smoking, systolic blood pressure, diastolic blood pressure, total and high-density lipoprotein cholesterol levels, and diabetes mellitus as categorical measures.

1.28-5.20]). For women, the relative risks for non-CVD mortality were all nonsignificant, with an estimate less than 1.

The PAR for IHD for subjects with depression/attempted suicide and conventional IHD risk factors is shown in **Figure 2** for men and women. The PAR for

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Table 3. Sex-Stratified Hazard Ratios Relating Depression and History of Attempted Suicide to CVD and IHD Mortality Before and After Adjustment for Covariates[a]

	CVD Mortality		IHD Mortality	
	Women (14 Deaths)	Men (37 Deaths)	Women (7 Deaths)	Men (21 Deaths)
No. exposed/total population	591/4162	230/3479	591/4162	230/3479
Unadjusted	3.46 (1.21-9.90)	2.34 (0.85-6.45)	15.70 (2.85-86.58)	3.56 (1.08-11.72)
Adjustments[b]				
Sex and race	3.58 (1.24-10.32)	2.40 (0.86-6.73)	16.11 (2.94-88.33)	3.59 (1.08-11.98)
FRS[c]	3.20 (1.12-9.17)	2.37 (0.85-6.58)	14.57 (2.65-80.10)	3.52 (1.05-11.76)
Additional separate covariates				
Income	3.10 (1.08-8.89)	2.28 (0.81-6.40)	14.13 (2.55-78.19)	3.36 (1.01-11.16)
Educational level	3.13 (1.08-9.04)	2.42 (0.88-6.63)	14.35 (2.58-79.86)	3.51 (1.07-11.84)
BMI	3.08 (1.08-8.83)	2.18 (0.78-6.07)	13.88 (2.41-76.80)	3.03 (0.88-10.48)
Alcohol intake	3.13 (1.07-9.21)	2.34 (0.83-6.59)	14.72 (2.63-82.47)	3.54 (1.05-11.97)
Sedentary lifestyle	3.19 (1.12-9.13)	2.85 (0.85-6.49)	14.52 (2.65-79.62)	3.45 (1.06-11.25)
Cocaine use	3.19 (1.12-9.08)	2.35 (0.88-6.28)	14.66 (2.70-79.53)	3.59 (1.11-11.64)
All additional covariates	2.89 (1.00-8.40)	2.11 (0.79-5.65)	13.58 (2.42-76.24)	2.99 (0.91-9.81)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; FRS, Framingham risk score; IHD, ischemic heart disease.
[a] Unless otherwise indicated, data are expressed as hazard ratio (95% CI).
[b] Adjustments are inclusive of previous rows unless otherwise indicated.
[c] The FRS involves age, smoking, systolic blood pressure, diastolic blood pressure, total and high-density lipoprotein cholesterol levels, and diabetes mellitus as categorical measures. Sex interaction in the adjusted CVD model is $P=.62$ and in the IHD model is $P=.13$.

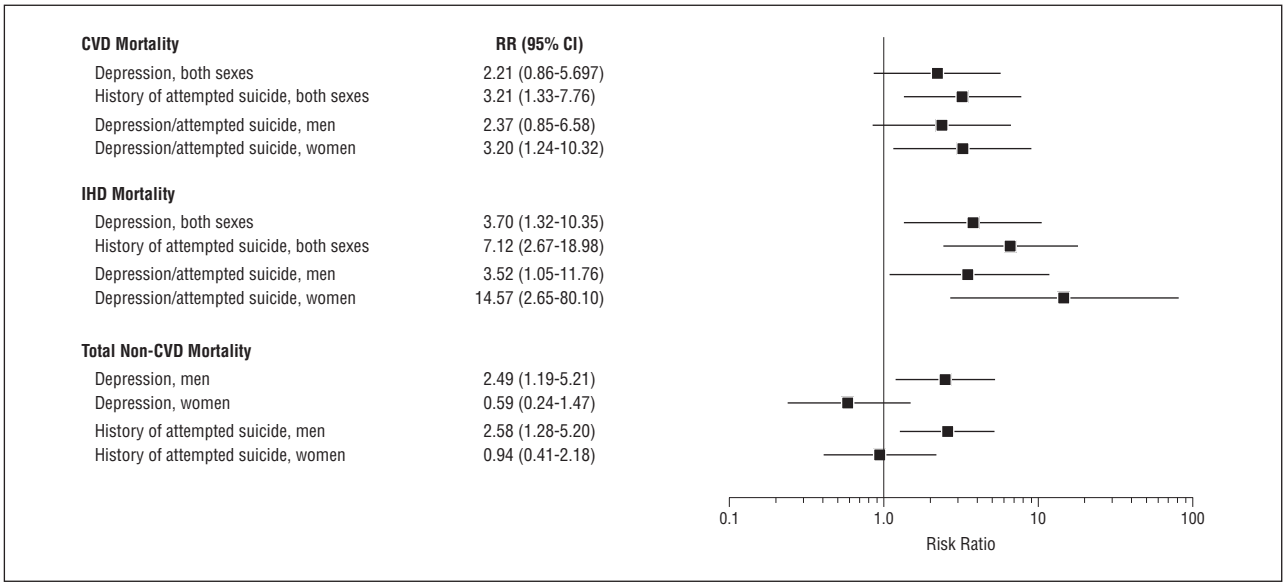

Figure 1. Adjusted relative risks (RRs) of unipolar and bipolar depression and a history of attempted suicide for death from cardiovascular disease (CVD), ischemic heart disease (IHD), and other causes. Relative risks are based on hazard ratios in a multivariate model adjusted for Framingham risk score (calculated from age, smoking status, blood pressure, total and high-density lipoprotein cholesterol levels, diabetes mellitus, race/ethnicity, and sex).

depression/attempted suicide is highest (65%) in women and is higher than for any conventional risk factor.

COMMENT

This is, to our knowledge, the first population-based study to examine the relationship between a clinical diagnosis of depression and mortality due to CVD and IHD in a cohort of young adults. In addition, it is the first study to examine a history of suicide attempts along with depression as a marker for future CVD and IHD mortality. Because previous studies have included middle-aged and older populations, the dramatic impact of depression and suicidality (as measured by attempted suicide) on IHD mortality in younger individuals has gone unrecognized. Our results are supported by other studies that show increased cardiac susceptibility to psychosocial stress in younger vs older populations[5,6,27] and further underscore the importance of stress reduction in young adults. Young women may also be at particular risk given that 5 of 7 IHD deaths (as opposed to 4 of 21 in young men) involved depression and/or attempted suicide.

Although several studies have examined the relationship between depression and CVD mortality,[1] our study differs in many substantial ways. First, we examined a clinical diagnosis of unipolar or bipolar depression, which

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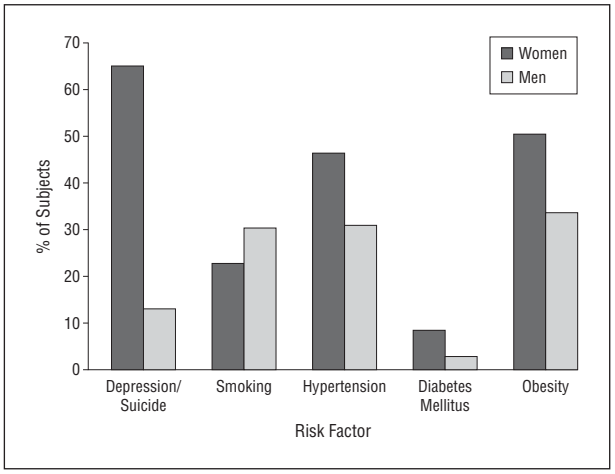

Figure 2. Population-attributable risk of ischemic heart disease mortality due to depression and a history of attempted suicide and traditional risk factors. Risk is based on hazard ratios in a multivariate model that included depression/attempted suicide, age, race/ethnicity, smoking, hypertension, hyperlipidemia, diabetes mellitus, and obesity.

may be a more robust risk indicator for IHD mortality compared with depressive symptom scales, which were the focus of most previous population studies.[28] Second, we examined young individuals, whereas much of the previous data come from older populations with comorbidities and a larger burden of IHD risk factors.[1] Because our young sample is considerably healthier than the older populations included in previous studies, the potential for unaccounted confounding factors is less, adding validity to our findings. Third, along with depression, we considered a history of attempted suicide, a related factor that may help capture mood and personality disturbances in young individuals at a population level that may have been missed by the Diagnostic Interview Schedule and that was never examined before with respect to cardiovascular risk.[29]

Although we did not find significant sex interaction with regard to CVD and IHD mortality, we did find significant sex differences in non-CVD mortality that were in the opposite direction. Specifically, women with depression/attempted suicide were at higher risk for CVD and IHD mortality but not for non-CVD mortality, whereas men showed more consistent associations across types of mortality. Although the reasons for this are not clear, it implies that the increased risk associated with depression/attempted suicide in women is specific to IHD, whereas in men it reflects a more general mortality risk. Our findings are consistent with previous studies that, albeit in different populations, have noted higher risks associated with depression among women than men,[30,31] although such sex differences are also subject to debate.[32]

We found that a history of attempted suicide was at least as predictive of CVD/IHD mortality as depression. Although suicidality is a symptom of depression, people with a history of attempted suicide may be affected by other psychiatric disorders in addition to depression, which may also increase CVD risk.[29] Patients with increased suicidality exhibit changes in the brain that are consistent with a state of severe, enduring stress, including increased serotonin binding sites in the brain in those who completed suicide.[33] It is possible that a history of attempted suicide is a marker of severe depression and hopelessness or is an index of multiple adverse psychological risk factors that synergistically increase CVD risk. In addition, the increased suicide rate found in patients with MI by Larsen et al[8] may, in part, be owing to increased prevalence of antecedent suicidality in patients with MI. A history of attempted suicide, therefore, is likely a very important and underrecognized risk factor for IHD in addition to depression.

Depression is thought to increase the risk of IHD through several stress-related physiological mechanisms that may also occur in people with a history of attempted suicide. For example, heart rate variability, an indicator of poor autonomic function and a risk factor for IHD,[34] is lower in persons with depression compared with those without depression.[35] Depression is also associated with increased cortisol secretion,[36] which has potential adverse cardiovascular effects, including decreased glucose intolerance and increased visceral adiposity.[37] Lifestyle factors may also play a role in mediating the relationship between depression and IHD,[38] although our study showed a significant risk of depression and a history of attempted suicide even after thorough adjustment for health behaviors. Therefore, direct physiological effects of depression may play a greater role than lifestyle factors in this young population.

LIMITATIONS

Although we did not use sample weights, we attempted to minimize this limitation by controlling for the sampling factors of race/ethnicity in our analysis. Each risk factor was measured only at inception of the cohort and is subject to change over time; therefore, this may increase random error. However, this problem would only bias the estimates toward the null. The utility of a history of attempted suicide as a preventable risk factor is limited by the understanding of its underlying cause, although 2 primary causes, hopelessness and impulsivity (even without an intent to die), are amenable to psychotherapy.[39] A history of attempted suicide may be misclassified because it was ascertained from a single question and subject to recall bias. Questions regarding the use of cocaine, alcohol, and tobacco may be subject to recall bias as well. The cause of death was ascertained by death certificate data and may also be subject to misclassification owing to missing information. However, such misclassification more frequently occurs in elderly individuals.[40] Also, it is likely that these causes of misclassification are equally distributed in exposed and unexposed individuals, again biasing the study estimates toward the null.

Possibly the most important limitation of this study is the low event rate given the young age of our population. This limited the power of our analysis and caused wide CIs. As a result, the sex interaction was not statistically significant, and despite large numerical differences in HRs, we cannot make definite conclusions about sex differences. Although bias is possible in multivariate models because of few outcomes, a ratio of 5 outcomes per predictor has been shown to suffice for accu-

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rate (<10% bias) estimation of relative risk.[22] The number of covariates was also minimized in our analysis by using the FRS rather than individual CVD risk factors. In addition, we performed a series of sensitivity analyses, including a diverse array of adjustment factors, and our results remained robust. Because of this, we believe that our analyses are unbiased and our results are valid; nonetheless, further study is necessary. We believe that the identification of risk factors for CVD in younger adults is so important for prevention that this area should not be neglected on the basis of low event rates alone. This practice may especially limit our understanding of preventable risk factors for women, who notoriously have lower event rates than men until elderly age. On the other hand, women remain a group for whom more knowledge about CVD risk factors and pathophysiologic mechanisms is needed.

In conclusion, our study uncovers a profound role of psychological factors on premature CVD deaths in young individuals. Although young men and women with depression or a history of attempted suicide are at increased risk of CVD, women with these risk factors may be especially susceptible to death from IHD. Given the high impact of premature death on families and the workforce, more research and more preventive and therapeutic efforts are warranted to uncover the causes and mitigate the consequences of these adverse effects. Our data also suggest that more research should take a life-course approach to identify risk factors for IHD early in life.

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REFERENCES

1. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763-2774.
2. McGill HC Jr, McMahan CA, Zieske AW, Tracy RE, Malcom GT, Herderick EE, Strong JP. Association of Coronary Heart Disease Risk Factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102(4):374-379.
3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121(4):586-613.
4. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):768]. *Arch Gen Psychiatry*. 2005;62(6):593-602.
5. Barefoot JC, Brummett BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. *Psychosom Med*. 2000;62(6):790-795.
6. Williams RB Jr, Barefoot JC, Haney TL, Harrell FE Jr, Blumenthal JA, Pryor DB, Peterson B. Type A behavior and angiographically documented coronary atherosclerosis in a sample of 2289 patients. *Psychosom Med*. 1988;50(2):139-152.
7. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1999;56(7):617-626.
8. Larsen KK, Agerbo E, Christensen B, Søndergaard J, Vestergaard M. Myocardial infarction and risk of suicide: a population-based case-control study. *Circulation*. 2010;122(23):2388-2393.
9. Daviglus ML, Stamler J, Pirzada A, Yan LL, Garside DB, Liu K, Wang R, Dyer AR, Lloyd-Jones DM, Greenland P. Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA*. 2004;292(13):1588-1592.
10. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction: National Registry of Myocardial Infarction 2 participants. *N Engl J Med*. 1999;341(4):217-225.
11. Mallik S, Spertus JA, Reid KJ, Krumholz HM, Rumsfeld JS, Weintraub WS, Agarwal P, Santra M, Bidyasar S, Lichtman JH, Wenger NK, Vaccarino V; PREMIER Registry Investigators. Depressive symptoms after acute myocardial infarction: evidence for highest rates in younger women. *Arch Intern Med*. 2006;166(8):876-883.
12. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802-813.
13. Robins LN, Helzer JE, Croughan J, Ratcliff KS. National Institute of Mental Health Diagnostic Interview Schedule: its history, characteristics, and validity. *Arch Gen Psychiatry*. 1981;38(4):381-389.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
15. Thomas AJ, Eberly LE, Davey Smith G, Neaton JD, Stamler J. Race/ethnicity, income, major risk factors, and cardiovascular disease mortality. *Am J Public Health*. 2005;95(8):1417-1423.
16. National Center for Health Statistics; Office of Analysis and Epidemiology. The Third National Health and Nutrition Examination Survey (NHANES III) linked mortality file: mortality follow-up through 2006: matching methodology. May 2009. http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhanes3_final.pdf. Accessed January 7, 2011.
17. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50(22):2173-2195.
18. Gibb SJ, Beautrais AL, Fergusson DM. Mortality and further suicidal behaviour after an index suicide attempt: a 10-year study. *Aust N Z J Psychiatry*. 2005;39(1-2):95-100.
19. US Department of Health and Human Services (DHHS); National Center for Health Statistics. Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994). Multiple Imputed Data Set. CD-ROM, Series 11, No. 7A. http://www.cdc.gov/nchs/nhanes/nh3data.htm#7a. Accessed May 23, 2010.
20. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health*. 1991;81(9):1166-1173.
21. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837-1847.
22. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165(6):710-718.
23. Sher L. Combined dexamethasone suppression–corticotropin-releasing hormone stimulation test in studies of depression, alcoholism, and suicidal behavior. *ScientificWorldJournal*. 2006;6:1398-1404.

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24. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med*. 2000; 343(1):16-22.
25. Skodova Z, Nagyova I, van Dijk JP, Sudzinova A, Vargova H, Studencan M, Reijneveld SA. Socioeconomic differences in psychosocial factors contributing to coronary heart disease: a review. *J Clin Psychol Med Settings*. 2008;15(3):204-213.
26. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health*. 1998;88(1):15-19.
27. Barefoot JC, Brummett BH, Clapp-Channing NE, Siegler IC, Vitaliano PP, Williams RB, Mark DB. Moderators of the effect of social support on depressive symptoms in cardiac patients. *Am J Cardiol*. 2000;86(4):438-442.
28. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001;58(3):221-227.
29. Bolton JM, Robinson J. Population-attributable fractions of Axis I and Axis II mental disorders for suicide attempts: findings from a representative sample of the adult, noninstitutionalized US population. *Am J Public Health*. 2010;100(12): 2473-2480.
30. Mallik S, Krumholz HM, Lin ZQ, Kasl SV, Mattera JA, Roumains SA, Vaccarino V. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. *Circulation*. 2005;111(3):271-277.
31. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosom Med*. 2002;64(1):6-12.
32. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study: National Health and Nutrition Examination Survey. *Arch Intern Med*. 2000;160 (9):1261-1268.
33. Arango V, Ernsberger P, Marzuk PM, Chen JS, Tierney H, Stanley M, Reis DJ, Mann JJ. Autoradiographic demonstration of increased serotonin 5-HT_2 and β-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*. 1990;47(11):1038-1047.
34. Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, Rautaharju P, Heiss G. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study: the ARIC Study: Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1997;145(8):696-706.
35. Vaccarino V, Lampert R, Bremner JD, Lee F, Su S, Maisano C, Murrah NV, Jones L, Jawed F, Afzal N, Ashraf A, Goldberg J. Depressive symptoms and heart rate variability: evidence for a shared genetic substrate in a study of twins. *Psychosom Med*. 2008;70(6):628-636.
36. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression? results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2003;158(12):1139-1147.
37. Björntorp P. Neuroendocrine abnormalities in human obesity. *Metabolism*. 1995; 44(2)(suppl 2):38-41.
38. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008;300(20):2379-2388.
39. Gonda X, Fountoulakis KN, Kaprinis G, Rihmer Z. Prediction and prevention of suicide in patients with unipolar depression and anxiety. *Ann Gen Psychiatry*. 2007;6:23.
40. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med*. 1998; 129(12):1020-1026.

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