Depression and the Metabolic Syndrome in Young Adults: Findings From the Third National Health and Nutrition Examination Survey

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Objective: Previous reports have suggested that depression may lead to the development of cardiovascular disease through its association with the metabolic syndrome; however, little is known about the relationship between depression and the metabolic syndrome. The aim of this study was to establish an association between depression and the metabolic syndrome in a nationally representative sample. **Methods:** The Third National Health and Nutrition Examination Survey is a population-based health survey of noninstitutionalized US citizens completed between 1988 and 1994. Three thousand one hundred eighty-six men and 3003 women, age 17 to 39, free of coronary heart disease and diabetes, completed the depression module from the Diagnostic Interview Schedule and a medical examination that provided clinical data needed to establish the presence of the metabolic syndrome, as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults. **Results:** Women with a history of a major depressive episode were twice as likely to have the metabolic syndrome compared with those with no history of depression. The relationship between depression and metabolic syndrome remained after controlling for age, race, education, smoking, physical inactivity, carbohydrate consumption, and alcohol use. Men with a history of depression were not significantly more likely to have the metabolic syndrome. **Conclusions:** The prevalence of the metabolic syndrome is elevated among women with a history of depression. It is important to better understand the role depression may play in the effort to reduce the prevalence of the metabolic syndrome and its health consequences. **Key words:** depression, the metabolic syndrome, the Third National Health and Nutrition Examination Survey.

ATP III = Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III); **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **DSM III-R** = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; **HPA** = hypothalamic-pituitary-adrenal; **MDE** = major depressive episode; **NHANES III** = The Third National Health and Nutrition Examination Survey; **OR** = odds ratio.

INTRODUCTION

Major depressive disorder is the most prevalent psychiatric illness in the United States, affecting more than 12% of men and more than 21% of women in their lifetime (1). Previous studies indicate that prevalence of major depression has increased during the past century, although these trends may, in part, be explained by methodological problems (eg, 2). Depression has been associated with a variety of diseases; specifically it has been implicated in the development of cardiovascular disease (CVD) and all-cause mortality (eg, 3,4). However, little is understood about mechanisms that may account for poor health outcomes associated with depression.

Previous reports have speculated that depression may be linked to adverse health outcomes through an association with the metabolic syndrome (5–7). The metabolic syndrome, characterized by elevated abdominal obesity, triglycerides, blood pressure, fasting glucose, and low high-density lipoprotein (HDL) cholesterol, has an estimated prevalence of more than 21% in the US population (8,9); with obesity and sedentary behavior on the rise, the prevalence of the metabolic syndrome is likely to grow even higher in coming years. The metabolic syndrome is an important risk factor for the development of cardiovascular disease (CVD) and all-cause mortality (10–12). It was highlighted as a secondary target of therapy in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III or ATP III; (13)), and it will likely be an increasingly important focus in disease prevention.

Despite the body of research implicating depression and the metabolic syndrome as risk factors for CVD, there are few data examining the relationship between depression and the metabolic syndrome. Raikkonen and colleagues (14) noted that depressive symptoms, assessed with the Beck Depression Inventory, were associated with the presence of the metabolic syndrome in middle-aged women, as well as with the development of the metabolic syndrome over 7.4 years. However, because of the sample used, the authors were not able to examine this relationship in men. Furthermore, to our knowledge no studies have examined the relationship between major depressive illness and the metabolic syndrome in men and women.

We believe it is important to better characterize the association between depression and the metabolic syndrome, so as to help inform treatment efforts aimed at reducing the prevalence of the metabolic syndrome, as well as to direct future research efforts aimed at understanding mechanisms through which depression may be linked to CVD. Thus, the objective of this study was to establish an association between major depressive illness and the metabolic syndrome in a nationally representative cross-sectional sample of men and women.

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METHODS

The Third National Health and Nutrition Examination Survey (NHANES III), completed between 1988 and 1994, is a population-based health survey of noninstitutionalized US citizens conducted by the National Center for Health Statistics of the Center for Disease Control and Prevention. The study was conducted at 89 locations, using a stratified, multistage probability design similar to previous NHANES surveys (15,16). By design, black and Mexican American citizens were oversampled to produce reliable health estimates for these minority groups (17).

Participants completed household surveys conducted by trained study staff, which included questions about demographic, psychosocial, and health history. Participants completed standardized medical examinations at mobile centers, which included measurements of height, weight, waist-circumference, blood pressure, and plasma lipid and glucose levels. Interviews were conducted in both English and Spanish. The study protocol has been described in detail previously (17).

Measures

Depression

A subsample of participants, aged 17 to 39 years, completed the depression module from the Diagnostic Interview Schedule (18), originally developed for the National Institute of Mental Health's Epidemiologic Catchment Area research study (19). The interview yielded data on the lifetime prevalence of a major depressive episode (MDE) based on criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R*) (20). In analyses presented here, depression status was treated as a dichotomous variable according to whether or not a study participant had ever had a major depressive episode. The Diagnostic Interview Schedule also yielded information about number of episodes, age of first episode, and the presence of a current episode.

The Metabolic Syndrome

Consistent with the operational definition outlined in the ATP III report, the metabolic syndrome was defined as having 3 or more of the following: (1) High blood pressure: ≥130/85 mm Hg or antihypertensive medication use; (2) High triglycerides: ≥150 mg/dL; (3) Low HDL cholesterol: <40 mg/dL in men or <50 mg/dL in women; (4) High fasting glucose: ≥110 mg/dL or antidiabetic medication use; or (5) Abdominal obesity: waist circumference >102 cm in men or >88 cm in women. Blood pressure readings were taken from seated participants 3 times during the household interview and 3 times at the mobile examination center; we report the mean of all available readings. Serum triglycerides were measured enzymatically after hydrolyzation to glycerol (Hitachi 704 Analyzer; Hitachi, Tokyo, Japan). HDL cholesterol was measured after the precipitation of other lipoproteins with a heparin–manganese chloride mixture (Boehringer-Mannheim Diagnostics, Indianapolis, Indiana). Serum glucose was measured using a modified hexokinase enzymatic method (Cobas Mira assay; Roche, Basel, Switzerland). Waist circumference was measured to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and above the top of the iliac crest from participants at minimal respiration. Laboratory procedures have been described in detail previously (21).

Other Variables

Education was treated as a dichotomous variable: less than or greater than or equal to 12 years of completed schooling. Smoking status was a dichotomous variable based on lifetime use of 100 or more cigarettes. Given our focus on lifetime history of depression, former and current smokers were not distinguished. Physical inactivity was defined as no leisure-time physical activity in the past month, based on questions about exercise, sports, and hobbies adapted from the 1985 National Health Interview Survey (17). Percent of dietary energy from carbohydrates was derived from a 24-hour dietary recall interview designed for NHANES (22,23). Alcohol use was defined as having had at least 12 drinks in the past year. Body mass index was calculated from height and weight measurements, with the formula: weight (kg)/height $(m)^2$. Coronary heart disease (CHD) history was based on self-report of physician diagnosis of a prior myocardial infarction. Diabetes was defined according to fasting glucose >126 mg/dL, antidiabetic medication use, or self-reported physician diagnosis.

Data Analysis

Logistic regression models were used to examine the relationship between depression and the metabolic syndrome by gender. In univariate analyses, lifetime prevalence of a major depressive episode was entered as an independent variable and presence of the metabolic syndrome was entered as the dependent variable. In multivariate analyses, age, race, education, smoking status, physical inactivity, percent of dietary energy from carbohydrates, and alcohol use were added as covariates. Obesity was not included in the model because it correlates with waist circumference, which is a component of the metabolic syndrome. We tested for the presence of first-order interactions between depression and gender, depression and age, depression and race, and depression and education in evaluating the relationship with the metabolic syndrome.

To examine the relationship between depression and each component of the metabolic syndrome, we conducted a series of logistic regression analyses with depression status entered as the independent variable and each component of the metabolic syndrome, as defined above, entered in turn as dependent variables: high blood pressure or antihypertensive medication, high triglycerides, low HDL cholesterol, high serum glucose or antidiabetic medication, and large waist circumference. We also used linear regression to examine the relationship between depression status and the number of components of the metabolic syndrome present (0–5, 0 = no components, 5 = all components).

We excluded individuals from the analyses if they (1) had CHD or diabetes, as defined above; (2) did not have data available on depression status; (3) did not have data available on more than 2 of the 5 potential components of the metabolic syndrome; (4) consumed food or beverage other than water during the 6 hours before blood draw; or (5) were pregnant at the time of or had been pregnant during the 12 months before the survey. Analyses were conducted using SUDAAN, version 7.11 (Research Triangle Institute, Research Triangle Park, NC), a software program that adjusts for the NHANES III sampling design in calculating population level variance estimates.

RESULTS

Of the 7981 NHANES III participants who were between the ages of 17 and 39 years and therefore eligible for the psychiatric interview, 250 had CHD or diabetes, 314 had incomplete depression diagnostic data, 314 had fewer than 3 components of the metabolic syndrome available due to incomplete data or failure to fast before blood draw, and 873 were pregnant or had been pregnant during the 12 months before the examination. Three thousand one hundred eighty-six men (87.3%) and 3003 women (69.3%) were retained for analyses. The characteristics of this sample are outlined in Table 1.

As anticipated, women were more likely than men to have reported a depressive episode (population weighted lifetime prevalence for women: 13.4%; for men: 6.1%; $\chi^2 = 36.39$, $p < .0001$). The prevalence of the metabolic syndrome in this sample was 7.8%, with men and women experiencing similar rates (population weighted prevalence for women: 7.1%; men: 8.4%; $\chi^2 = 1.04$, $p = .31$). However, men were more likely to have higher blood pressure ($\chi^2 = 61.49$, $p < .0001$), triglycerides ($\chi^2 = 42.80$, $p < .0001$), and glucose ($\chi^2 = 7.94$, $p = .007$), whereas women were more likely to have low HDL ($\chi^2 = 12.60$, $p = .001$) and large waist circumferences ($\chi^2 = 46.31$, $p < .0001$). These findings are similar to previous reports from NHANES III of this age cohort (8,9).

TABLE 1. Sample Characteristics by Lifetime History of a Major Depressive Episode (MDE)

Characteristic	Women		Men	
	MDE (n = 368)	No MDE (n = 2635)	MDE (n = 177)	No MDE (n = 3009)
Age, mean (SE)	29.77 (0.59)†	28.66 (0.26)	28.25 (0.79)	28.27 (0.17)
Race,[a] %				
White	14.79*	85.21	6.34	93.66
Black	9.30	90.70	5.27	94.73
Mexican-American	11.71	88.29	6.95	94.45
Other	7.88	92.12	5.62	94.38
Education <12 y, %	18.94	21.04	28.30	23.84
Ever smoked,[b] %	53.74**	41.99	63.55*	51.03
No physical activity,[c] %	12.52	15.88	14.54	9.41
% Diet carbohydrates, mean (SE)	51.47 (0.81)	51.07 (0.37)	46.84 (1.67)	48.50 (0.45)
Alcohol in past year,[d] %	70.94†	63.40	83.96	81.81
Body Mass Index, mean (SE)	25.99 (0.53)*	24.84 (0.20)	25.26 (0.39)	25.59 (0.14)
Systolic BP, mean (SE)	109.10 (0.92)	108.84 (0.29)	118.65 (1.26)	118.45 (0.34)
Diastolic BP, mean (SE)	70.69 (0.52)***	68.70 (0.29)	75.12 (1.19)	73.88 (0.27)
Triglycerides, mean (SE)	104.10 (6.93)	95.24 (2.69)	114.53 (10.76)	129.55 (4.23)
HDL, mean (SE)	52.77 (1.24)†	54.59 (0.52)	48.79 (2.13)	46.01 (0.47)
Glucose, mean (SE)	88.21 (0.73)	88.20 (0.37)	91.92 (1.02)	93.11 (0.31)
Waist circumference, mean (SE)	85.40 (1.15)**	82.24 (0.52)	89.96 (1.36)	89.74 (0.33)
Metabolic syndrome,[e] %	12.28*	6.28	11.72	8.21

[a] Race differences appear to be attributed to black women reporting lower incidence of depression than white women ($\chi^2 = 7.98$, $p = .01$).
[b] Lifetime use of 100+ cigarettes.
[c] No leisure-time physical activity in past month.
[d] 12 drinks in past year.
[e] Defined as outlined in ATP III.
% refers to population-weighted proportions: *** $p \leq .001$, ** $p \leq .01$, * $p \leq .05$, † $p \leq .10$.

In logistic regression models, history of a depressive episode was associated with the metabolic syndrome in women, and this relationship remained after controlling for a variety of demographic and behavioral risk factors, as outlined in Table 2. The direction of the association between depression and the metabolic syndrome was the same in men, although not statistically significant; in addition, the depression by gender interaction in the full sample was not statistically significant ($\chi^2 = 0.18$, $p = .67$). The relationship between depression and the metabolic syndrome was homogenous across age (median split), race, and education level for both women and men (Women: age × depression, $\chi^2 = 3.57$, $p = .06$, depression × race, $\chi^2 = 1.17$, $p = .76$, depression × education, $\chi^2 = 0.05$, $p = .82$; Men: depression × age $\chi^2 = 2.39$, $p = .12$, depression × race $\chi^2 = 2.72$, $p = .44$, depression × education, $\chi^2 = 0.25$, $p = .62$); although the interaction between age and depression did reach marginal significance among women, such that the presence of the metabolic syndrome appeared to be most closely associated with history of depression in the younger women (<28 years). Post-hoc analyses indicated that among participants with a history of depression, neither number of depressive episodes (Women: $\chi^2 = 5.29$, $p = .15$; Men $\chi^2 = 5.36$, $p = .15$), age of first episode (Women: $\chi^2 = 0.64$, $p = .42$; Men $\chi^2 = 0.70$, $p = .40$), nor the presence of a current episode (Women: $\chi^2 = 0.86$, $p = .35$; Men $\chi^2 = 1.34$, $p = .25$) were significantly associated the presence of the metabolic syndrome.

To determine whether history of a major depressive episode was associated with individual components of the metabolic syndrome, we examined the relationship between depression and each of the syndrome's 5 criteria. As outlined in Table 3, depression in women was associated with high blood

TABLE 2. Logistic Regression Models for the Presence of the Metabolic Syndrome in Those with a Lifetime History of a Major Depressive Episode (MDE) Compared to Those Without a History of MDE

Model	Women		Men	
	Wald χ^2	OR (95% CI)	Wald χ^2	OR (95% CI)
Unadjusted	8.20**	2.09 (1.20–3.65)	0.66	1.48 (0.56–3.96)
Demographic[a]	6.27**	2.00 (1.15–3.50)	0.72	1.50 (0.58–3.88)
Complete[b]	4.39*	1.96 (1.03–3.73)	0.81	1.51 (0.60–3.77)

[a] Model adjusted for age, race.
[b] Model adjusted for age, race, education, ever smoked, no physical activity, % dietary energy from carbohydrates, alcohol in past year.
** $p \leq .01$, * $p \leq .05$.

TABLE 3. Logistic Regression Models for Each Component of the Metabolic Syndrome Adjusted for Age, Race, Education, Ever Smoked, No Physical Activity, % Dietary Energy from Carbohydrates, and Alcohol Use in Past Year

Dependent variable	Women			Men		
	MDE,[a] %	No MDE, %	OR (95% CI)	MDE, %	No MDE, %	OR (95% CI)
High BP	12.48	6.18	2.26 (1.38–3.72)***	25.14	17.40	1.63 (0.84–3.17)
High triglycerides	16.28	9.68	1.89 (0.99–3.58)*	20.69	25.86	0.66 (0.33–1.34)
Low HDL	45.03	38.17	1.34 (0.92–1.93)[b]	26.70	31.08	0.77 (0.43–1.40)
High glucose	1.08	1.46	0.48 (0.07–3.24)	3.78	2.77	1.35 (0.41–4.48)
Large waist circumference	33.13	27.09	1.35 (0.91–1.99)[b]	15.93	14.14	1.14 (0.60–2.16)

[a] Major depressive episode.
[b] We observed a trend toward increased rates of low HDL ($p = .11$) and large waist circumference ($p = .12$) among women with a history of MDE.
*** $p \leq .001$, * $p \leq .05$.

pressure and high triglyceride level. We also observed a trend toward increased rates of low HDL ($p = .11$) and large waist circumference ($p = .12$). Depression in women was also associated with the number of the metabolic syndrome components present, even after controlling for all demographic and behavioral risk factors (MDE m = 1.04, se = 0.08, no MDE m = 0.79, se = 0.04, Wald F = 6.76, $p = .01$). In fact, we observed a graded relationship between depression and number of the metabolic syndrome components present, such that women with 4 to 5 characteristics of the metabolic syndrome were most likely to have reported a prior depressive episode (Figure 1). By contrast, depression in men was not significantly associated with any components of the metabolic syndrome (Table 3), nor with the number of components present (MDE m = 0.86, se = 0.16, no MDE m = 0.84, se = 0.04, Wald F = 0.01, $p = .92$).

DISCUSSION

This is the first study to examine the relationship between depression and the metabolic syndrome, as defined by the ATP III guidelines, in a nationally representative sample of young adults. The results presented here demonstrate that young women with a history of at least 1 major depressive episode were more than twice as likely to have the metabolic syndrome compared with those with no history of depression. Specifically, depression appeared to be most closely associated with high blood pressure and high triglyceride level. The relationship between depression and the metabolic syndrome, as well as its components, was independent of age, race, education, smoking, physical inactivity, carbohydrate intake, and alcohol use.

Although in women we found a strong association between depression and the metabolic syndrome, in men the association was much weaker and did not reach statistical significance. Depression was also not associated with any individual components of the metabolic syndrome in men, and in fact the direction of the relationship appeared to be reversed for triglyceride and HDL cholesterol levels. These findings suggest that there may be important gender differences in the role depression plays in the metabolic syndrome; perhaps the

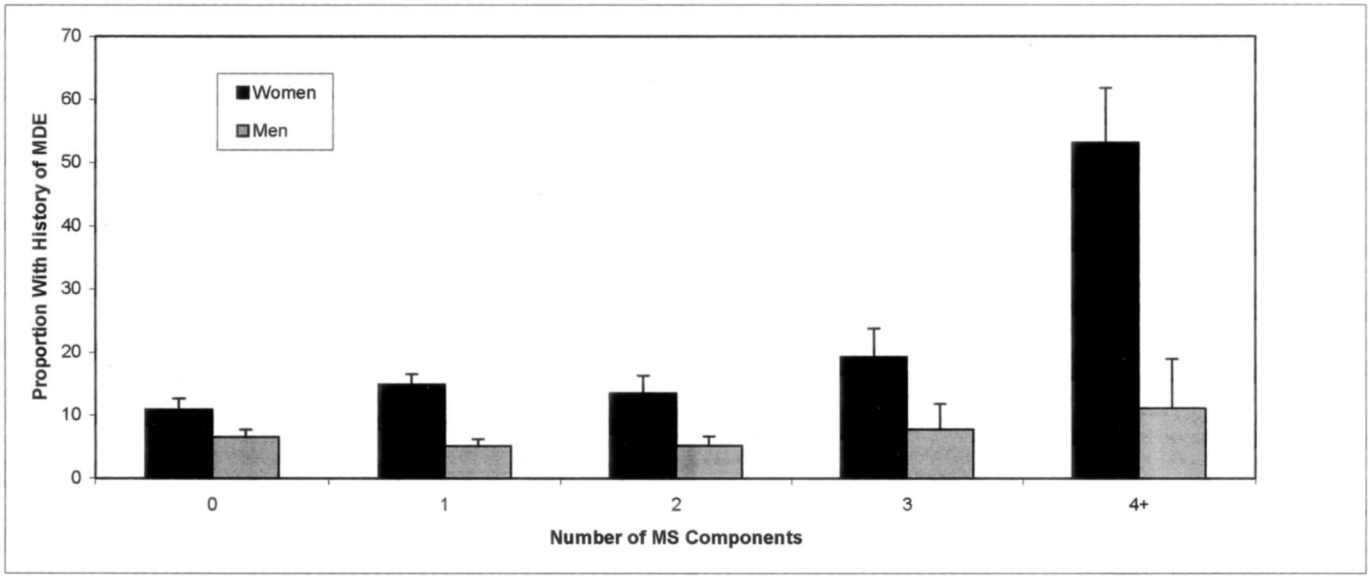

Figure 1. Relationship between history of a major depressive episode (MDE) and number of components of the metabolic syndrome (MS) present. Number of persons with a history of a MDE by number of metabolic syndrome components present: Women—0 components, $N = 133$, 1 component, $N = 127$, 2 components, $N = 60$, 3 components, $N = 39$, 4 to 5 components, $N = 9$; Men—0 components, $N = 90$, 1 component, $N = 48$, 2 components, $N = 25$, 3 components, $N = 8$, 4 to 5 components, $N = 6$. SEM represented with error bars.

health risks linked to depression are more critical to women, at least those risks pertaining to the metabolic syndrome. While we did have sufficient statistical power to detect an association in men despite the limited number of cases of depression in this group, gender differences should be interpreted with caution given the absence of an interaction between depression and gender in predicting the metabolic syndrome.

Possible Mechanisms

Depression has been prospectively associated with the development of CVD, and it is plausible that depression is also associated with the development of the metabolic syndrome, when the metabolic syndrome is characterized as an intermediate medical condition that frequently precedes the clinical manifestations of CVD. A number of mechanisms have been proposed to explain the relationship between depression and CVD development, and many of these mechanisms may be relevant to the relationship between depression and the metabolic syndrome as well. Depressed individuals more often engage in deleterious health behaviors than nondepressed individuals: smoking, eating an unhealthy diet, leading a sedentary lifestyle, and being noncompliant with medical treatment (eg, 24–27). These behaviors may lead to the development of the metabolic syndrome and ultimately to CVD. However, it is unlikely that health behaviors account for the entire relationship between depression and disease. Consistent with previous literature examining the relationship between depression and CVD, we found that depression was associated with the metabolic syndrome in women, even after controlling for smoking status, physical inactivity, and carbohydrate and alcohol consumption.

Depression has also been associated with a number of physiological alterations, and it is plausible that these alterations help account for the relationship between depression and the metabolic syndrome. First, depression has been associated with autonomic nervous system changes, including elevated heart rate and reduced heart rate variability (28–31), and autonomic changes may, in turn, lead to the development of the metabolic syndrome. This is consistent with previous reports that both elevated heart rate and reduced heart rate variability are associated with the metabolic syndrome, CVD, and total mortality (32–34). Second, depression has been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (35,36), which has also been implicated in the development of the metabolic syndrome and CVD (32,37). Finally, depression has been associated with altered inflammatory and hemostatic markers, such as heightened platelet aggregation, fibrinogen, and white blood cell count (7,35,38). Inflammatory and hemostatic processes have been recognized as important in the metabolic syndrome, CVD, and total mortality, and it is plausible that depression may be linked to these health outcomes through inflammatory or hemostatic processes.

Although we outline a number of mechanisms that may explain how depression could lead to the development of the metabolic syndrome, the data presented here are cross-sectional and therefore we cannot determine whether depression preceded the development of the metabolic syndrome. However, the strong association between history of depression and current metabolic syndrome among women is consistent with this hypothesis and with previous findings (14). Regardless of whether depression is a cause, consequence, or simple marker for the metabolic syndrome, the association has important clinical ramifications. As noted above, depressed individuals are less likely to comply with medical treatment, yet doing so is especially important in this group. The metabolic syndrome is associated with the development of CVD and ultimately mortality; medical compliance and lifestyle modification are critical to preventing these complications. Thus, even if depression is not associated with the development of the metabolic syndrome, it is likely that depression is associated with subsequent complications among those with the metabolic syndrome. Given that depression is common among patients with the metabolic syndrome, health care professionals should take special care to assess the psychological status of these patients and develop treatments that take into account the added difficulties patients with depression may pose. Although depression is common in medical patients, it often goes untreated or undertreated. However, failure to recognize and treat depression in patients with the metabolic syndrome may have deleterious physiological as well as psychological consequences.

We acknowledge several limitations of these findings. First, although it is impressive that NHANES III researchers conducted a comprehensive well-validated psychiatric interview on depression status in a large nationally representative sample, the measure is self-reported and is therefore subject to various biases, including recall bias. Although certainly a concern, we do note that our rates of depression are somewhat lower than we might have expected based on other national samples (1), and therefore overreporting, at least, is less likely to be problematic here. Second, a complete psychiatric interview was not conducted and therefore we are unable to compare the relative importance of depression and related disorders, such as anxiety, in the metabolic syndrome. Other psychiatric disorders have been implicated in the development of CVD and mortality, and although not as prevalent as depression, they may also play an important role in the metabolic syndrome (eg, 39–41). Third, the psychiatric interview was conducted with adults age 17 to 39 only. Therefore, we cannot determine the importance of depression in older adults. While 1 study supported a relationship between depressive symptoms and the metabolic syndrome in women age 42 to 50 (14), we found the strongest association in the youngest women. One advantage of examining the relationship between depression and the metabolic syndrome in young adults is that we are better able to assert that the relationship is unlikely to be attributed to CVD, given the low prevalence of CVD in this age group. An association between depression and the metabolic syndrome, before the development of CVD, is consistent with the hypothesis that depression is linked to the develop-

ment of CVD through its association with the metabolic syndrome. Finally, as noted earlier, these data are cross-sectional, and therefore we cannot determine the direction of the relationship between depression and the metabolic syndrome, or make causal inferences.

In sum, young women with a history of a major depressive episode have higher rates of the metabolic syndrome compared with those with no history of depression, whereas men with a history of depression do not appear to have higher rates. Given the substantial health consequences the metabolic syndrome poses to our population, prevention and treatment efforts are of great national interest. In addition, possible trends toward increased rates of the metabolic syndrome, as well as depression, suggest that prevention and treatment efforts will be an increasingly pressing public health concern in future years. Our findings here highlight the importance of better understanding the role of depressive illness, especially among women, in the metabolic syndrome.

Future research should examine the prospective relationship between major depression and the metabolic syndrome, to better characterize the nature of the relationship we have highlighted here. Interventions aimed at treating either depression or the metabolic syndrome will also yield important information about the causal relationship between these 2 conditions. Finally, whatever the nature of the relationship between depression and the metabolic syndrome, future research should examine whether depression confers additional medical risks among patients with the metabolic syndrome, and, if so, treatment efforts should target this at-risk group.

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