# A Longitudinal Relationship Between Depressive Symptoms and Development of Metabolic Syndrome: The Coronary Artery Risk Development in Young Adults Study

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## ABSTRACT

**Objective:** Despite variability in the burden of elevated depressive symptoms by sex and race and differences in the incidence of metabolic syndrome, few prior studies describe the longitudinal association of depressive symptoms with metabolic syndrome in a diverse cohort. We tested whether baseline and time-varying depressive symptoms were associated with metabolic syndrome incidence in black and white men and women from the Coronary Artery Risk Development in Young Adults study.

**Methods:** Participants reported depressive symptoms using the Center for Epidemiologic Studies Depression Scale at four examinations between 1995 and 2010. At those same examinations, metabolic syndrome was determined. Cox proportional hazards models were used to examine the associations of depressive symptoms on the development of metabolic syndrome in 3208 participants without metabolic syndrome at baseline.

**Results:** For 15 years, the incidence rate of metabolic syndrome (per 10,000 person-years) varied by race and sex, with the highest rate in black women (279.2), followed by white men (241.9), black men (204.4), and white women (125.3). Depressive symptoms (per standard deviation higher) were associated with incident metabolic syndrome in white men (hazard ratio = 1.25, 95% confidence interval = 1.08–1.45) and white women (hazard ratio = 1.17, 95% confidence interval = 1.00–1.37) after adjustment for demographic characteristics and health behaviors. There was no significant association between depression and metabolic syndrome among black men or black women.

**Conclusions:** Higher depressive symptoms contribute modestly to the onset of metabolic syndrome among white adults.

**Key words:** depressive symptoms, metabolic syndrome, race, longitudinal.

## INTRODUCTION

Metabolic syndrome is an established risk factor for coronary heart disease and diabetes (1). Prior studies have described an association of depression or elevated depressive symptoms with high blood pressure (2–5), large waist circumference (5–9), elevated fasting blood glucose (6,8), and increased diabetes risk (10,11)—each of which is a component of the metabolic syndrome. However, findings on the relationship between depression and metabolic syndrome are less consistent. Cross-sectional studies report

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**CARDIA** = Coronary Artery Risk Development in Young Adults,
**CES-D** = Center for Epidemiologic Studies Depression Scale,
**HDL** = high-density lipoprotein, **METs** = metabolic equivalents

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both positive (4,6,8,9,12) and no association (2–4,13,14) with metabolic syndrome. By contrast, longitudinal studies do report a significant positive association (7,13,14). However, some of these studies were restricted to females, and the majority were conducted predominately in one race/ethnic group (90% white) (13,14).

Demographic differences are observed in the prevalence of metabolic syndrome, with rates higher among blacks (15,16). Although the risk factors for metabolic syndrome are well characterized (17–19), the contribution of depressive symptoms is understudied. Population screening studies estimate that the prevalence of major depressive disorder and elevated depressive symptoms is higher in women as compared with men (20,21). Several studies suggest that blacks have higher depressive symptoms compared with whites (22–25). Despite demographic differences in rates of metabolic syndrome by race and depression, few prior studies have had adequate sample size and longitudinal follow-up to test the hypothesis that elevated depressive symptoms are associated with incident metabolic syndrome within population subgroups.

## METHODS

### Participants

We tested our hypotheses in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a multicenter, longitudinal investigation of cardiovascular disease risk starting in young adulthood. The study began in 1985 to 1986 with 5115 black and white adults between the ages of 18 and 30 years. Participants were recruited from four metropolitan areas (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Participants were reexamined 2, 5, 7, 10, 15, 20, and 25 years after study initiation. The sample for our analysis began at the 10-year follow-up examination in 1995 to 1996 which is the first visit when both depressive symptoms and metabolic syndrome components were available. Participants were then followed up through 2010 for changes in depressive symptoms and outcomes. The 10-year follow-up examination will now be referenced as baseline throughout. The institutional review boards for the protection of human subjects for the participating study sites provided approval for the study, and written informed consent was obtained for all participants.

There were 3950 participants completed the examination in 1995 to 1996. We excluded participants from our analysis sample for the following reasons: pregnancy ($n = 28$), unable to determine metabolic syndrome status ($n = 68$), prevalent metabolic syndrome ($n = 429$), unable to determine metabolic syndrome incidence over follow-up ($n = 216$), or missing depressive symptoms at our baseline examination ($n = 1$). Our final analysis sample included 3208 participants. When we compared the characteristics of participants who were free from metabolic syndrome at baseline (1995–1996) but who were excluded for the other reasons above ($n = 217$), we observed that excluded participants were slightly younger (34.2 versus 34.9 years, $p = .003$), more likely to be black (64.1 versus 46.8%, $p < .001$), and more likely to be current smokers (42.6% versus 23.9%, $p < .001$).

### Measures

#### Depressive Symptoms

Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (26). The 20-item CES-D measure was used to generate a single score to assess the participant's mood during the previous week. The possible range of scores is 0 to 60, and scores ≥ 16 have been correlated with major depressive disorder (26). To capture the potential for depressive symptoms to vary over time, we studied the influence of multiple measures of CES-D for four examination years (1995–1996, 2000–2001, 2005–2006, and 2009–2010) using longitudinal modeling. Our primary measure of depressive symptoms was the continuously measured CES-D score, and our secondary measure categorized the CES-D score to compare those with elevated depressive symptoms (CES-D ≥ 16) to those without elevated depressive symptoms.

### Metabolic Syndrome

Participants fasted for at least 12 hours and blood was drawn according to standardized protocols across field centers (27). Glucose (28) and lipids (high-density lipoprotein [HDL] cholesterol and triglycerides) (29,30) were determined at a central laboratory (27). After a 5-minute rest, blood pressure was measured from participants in the seated position three times; the average of the last two measurements was used. Waist circumference was determined as the average of two waist circumference measures at captured at the minimum abdominal girth (nearest 0.5 cm) from participants standing upright.

Metabolic syndrome was defined using modified National Cholesterol Education Program–Adult Treatment Panel III criteria (31). Participants were identified as having metabolic syndrome if they had at least three of the following cardiovascular risk factors: a) fasting glucose ≥100 mg/dl or diabetes medication, b) waist circumference >88 cm (women) or >102 cm (men), c) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or hypertension medicine, d) triglycerides ≥150 mg/dl, or e) HDL cholesterol <50 mg/dl in women or <40 mg/dl in men (32). We excluded participants who had metabolic syndrome at the baseline examination for our study in order to determine incident metabolic syndrome. Incident metabolic syndrome was determined at the time that participants first met the above criteria at any of the following examinations: 2000–2001, 2005–2006, and 2009–2010.

### Covariates

We selected covariates that demonstrated an association with both depressive symptoms and metabolic syndrome in prior studies. Education (years), smoking status ("never," versus "former," versus "current"), and alcohol intake ("none" versus "≤2 drinks/day or last month's maximum ≤4 drinks in 1 day for males or ≤1 drink/day or last month's maximum ≤3 drinks in 1 day for females" versus " >2 drinks/day or last month's maximum >4 drinks in 1 day for males or >1 drink/day or last month's maximum >3 drinks in 1 day for females") were determined using self-reported questionnaires. Physical activity was assessed by an interviewer-administered questionnaire, which assessed the amount of time spent in 13 different activities of either heavy (>5 metabolic equivalents [METs]) or moderate (3–4 METs) intensity during the last year (33). A medical history questionnaire was used to quantify self-reported antidepressant medication use. Covariates were measured at each of the follow-up examinations (2000–2001, 2005–2006, and 2009–2010).

### Data Analysis

We made an a priori decision to stratify our findings by race and sex given that the relationship between depression and metabolic syndrome components has varied by race and sex (7,34,35). However, we did test for the presence of interactions between the main effect (depressive symptoms) and race from a sex-pooled model as well as sex from a race-pooled model.

The distribution of covariates in 1995–1996 (baseline) is presented using means for continuous variables and proportions for categorical variables. $t$ Tests and $\chi^2$ tests were used to compare the covariates by race within sex categories. Follow-up time was determined between baseline

(1995–1996) and the visit at which incident metabolic syndrome was identified. Among participants who did not experience metabolic syndrome, follow-up time was calculated through the last clinic examination date they attended. Person-years were calculated as a product of the number of participants by their follow-up time and used in the denominator of our calculation of event rates per 10,000 person-years. After testing and confirming that the proportional hazards assumption was met using log-log survival plots, we modeled the association between depressive symptoms and metabolic syndrome in unadjusted and multivariable adjusted models. Because metabolic syndrome was identified at only three follow-up examinations, there is the potential for events to have the same survival time (heavily "tied" data). We handled ties using the Efron method which outperforms other methods in simulation models (36). Our first multivariable model included demographic characteristics from 1995 to 1996 including age and education and our second multivariable model additionally adjusted for physical activity, alcohol intake, smoking status, and antidepressant use which are also measured at baseline. Diabetes development was not included as a time-dependent covariate. Our findings are presented as hazard ratios and 95% confidence intervals. To account for the potential for depressive symptoms to vary over time, we repeated our analyses using time varying CES-D. In those Cox proportional hazards models, we used time-varying covariates to adjust for physical activity, alcohol intake, smoking status, and antidepressant use measured at each follow-up examination (2000–2001, 2005–2006, and 2009–2010). All analyses were repeated using categorically elevated depressive symptoms. Statistical significance was determined by a $p$ value < .05 (two tailed). Version 9.3 of the SAS software package (SAS Institute, Cary, NC) was used for all analyses.

## RESULTS

### Sample Characteristics

Participants were aged 28 to 40 years at the time of the 10-year follow-up examination in 1995 to 1996. The distribution of cardiovascular disease risk factors stratified by race and sex is presented in Table 1. Among men, black participants were younger, were nearly twice as likely to be current smokers (36% in black men and 20% in white men), and had higher systolic and diastolic blood pressure. Black men had a higher mean depressive symptom score and were more likely to report elevated depressive symptoms (CES-D ≥ 16) compared with white participants. Black women were younger but had less favorable measures of physical activity, cigarette smoking, fasting glucose, waist circumference, and blood pressure than did white women. Mean depressive symptom scores and the proportion with elevated depressive symptoms were higher among black as compared with white women.

Over 10 years of follow-up, the rate of metabolic syndrome was markedly higher in black women (279.2 per 10,000 person-years) compared with white women (125.3 per 10,000 person-years), whereas rates of metabolic

**TABLE 1.** Baseline Characteristics of CARDIA Participants ($n$ = 3208)

| Characteristic | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Black ($n$ = 634) | White ($n$ = 796) | $p$ | Black ($n$ = 868) | White ($n$ = 910) | $p$ |
| Age, y | 34.2 (3.7) | 35.4 (3.4) | <.001 | 34.4 (3.9) | 35.6 (3.4) | <.001 |
| Physical activity, exercise unit (y) | 424.3 (273.3) | 446.2 (324.7) | .175 | 219.4 (208.5) | 311.5 (237.7) | <.001 |
| Smoking, $n$ (%) | | | <.001 | | | <.001 |
| Never | 351 (55.6) | 500 (63.0) | | 536 (62.4) | 514 (56.7) | |
| Former | 53 (8.4) | 138 (17.4) | | 98 (11.4) | 239 (26.4) | |
| Current | 227 (36.0) | 156 (19.7) | | 225 (26.2) | 154 (17.0) | |
| Alcohol use, $n$ (%) | | | <.001 | | | <.001 |
| None | 133 (21.1) | 101 (12.7) | | 255 (30.0) | 108 (11.9) | |
| Moderate | 269 (42.6) | 409 (51.5) | | 436 (51.1) | 538 (59.3) | |
| Heavy | 229 (36.3) | 285 (35.9) | | 163 (19.1) | 262 (28.9) | |
| Antidepressant use, $n$ (%) | 5 (0.8) | 17 (2.1) | .0398 | 53 (1.6) | 53 (5.8) | <.001 |
| CES-D | 11.1 (8.1) | 8.8 (6.7) | <.001 | 12.6 (9.3) | 9.4 (7.4) | <.001 |
| CES-D ≥ 16, % | 143 (22.8) | 104 (13.2) | <.001 | 263 (31.3) | 154 (17.1) | <.001 |
| Fasting glucose, mg/dl | 91.3 (10.9) | 91.6 (8.6) | .5326 | 87.6 (8.8) | 86.8 (8.5) | .060 |
| Waist circumference, cm | 87.8 | 88.2 | .499 | 84.1 | 75.7 | <.001 |
| Systolic blood pressure, mm Hg | 114.7 (11.5) | 110.3 (9.9) | <.001 | 108z.8 (12.5) | 102.4 (9.1) | <.001 |
| Diastolic blood pressure, mm Hg | 75.5 (9.9) | 72.3 (8.1) | <.001 | 72.1 (9.6) | 67.7 (8.1) | <.001 |

CARDIA = Coronary Artery Risk Development in Young Adults; CES-D = Center for Epidemiologic Studies Depression Scale; SD = standard deviation; METs = metabolic equivalents.

The continuous variables are presented as means (SD). Physical activity was assessed by an interviewer-administered questionnaire, which assessed the amount of time spent in 13 different activities of either heavy (>5 METs) or moderate (3–4 METs) intensity during the last year. Alcohol use ("none" versus "≤2 drinks/day or last month's maximum ≤4 drinks in 1 day for males or ≤1 drink/day or last month's maximum ≤3 drinks in 1 day for females" versus ">2 drinks/day or last month's maximum >4 drinks in 1 day for males or >1 drink/day or last month's maximum >3 drinks in 1 day for females"). $t$ Tests and $\chi^2$ tests were used to compare the covariates by race within gender categories.

syndrome were lower in black men (204.4 per 10,000 person-years) versus white men (241.9 per 10,000 person-years).

Before modeling the relationship of baseline depressive symptoms with incident metabolic syndrome, we confirmed that there was a significant interaction between depressive symptoms and race ($\chi^2 = 9.03$, $p < .003$). Although sex did not modify the association ($\chi^2 = 2.15$, $p = .14$) further, we present stratified results given the a priori objective to present stratified findings. Elevated depressive symptoms, measured per standard deviation higher score, are associated with significant elevations in the metabolic syndrome incidence in white men and women (Table 2). For the white men, these results seem to be driven by the positive association between elevated depressive symptoms and high triglycerides or low HDL (Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A296). For the white women, these results seem to be driven by the positive association between elevated depressive symptoms and high fasting glucose or taking diabetes medication (Table S1). These findings persisted, though attenuated, after additional statistical adjustment for antidepressant medication use, total physical activity, alcohol intake, and smoking status. In parallel, categorically elevated depressive symptoms as defined by CES-D ≥ 16 were associated with significantly higher metabolic syndrome incidence in white men and women, although the findings were only statistically significant in crude models

among the men and in demographic adjusted models for women. Among black participants, there was no association of either continuously determined depressive symptoms or categorically elevated depressive symptoms with incident metabolic syndrome.

In a secondary analysis where we allowed depressive symptoms to vary over time using time-varying covariates, we again found a significant positive association between depressive symptoms and incident metabolic syndrome among white men and women (data not shown). There was again no association of time-varying depressive symptoms with incident metabolic syndrome in black women or men.

## DISCUSSION

We report for the first time a positive association of elevated depressive symptoms with metabolic syndrome in white, but not black, middle-aged adults. Our observation persisted after statistical adjustment for relevant health behaviors and was consistent whether we used a single measure of depressive symptoms at baseline or allowed depressive symptoms to vary over time. There was no evidence of heterogeneity in this association by sex. To our knowledge, ours is the first longitudinal study to highlight that the relationship of depressive symptoms with metabolic syndrome incidence may be driven by the strength of association among white adults.

**TABLE 2.** Event Rates and Cox Proportional Hazards Analysis of Baseline Depressive Symptoms With Incident Metabolic Syndrome (1995–1996)

| | Men | | Women | |
|---|---|---|---|---|
| | Black ($n = 634$) | White ($n = 796$) | Black ($n = 868$) | White ($n = 910$) |
| Events, $n$ | 160 | 242 | 302 | 153 |
| Events, % | 25.2 | 30.4 | 34.8 | 16.8 |
| Rate per 10,000 PY | 204.4 | 241.9 | 279.2 | 125.3 |
| Continuous depressive symptoms, HR (95% CI) | | | | |
| M1: unadjusted | 0.95 (0.81–1.11) | **1.31 (1.14–1.51)** | 1.04 (0.95–1.14) | **1.24 (1.07–1.44)** |
| M2[a] | 0.98 (0.83–1.15) | **1.26 (1.10–1.45)** | 0.99 (0.90–1.09) | **1.20 (1.03–1.39)** |
| M3 | 1.02 (0.86–1.21) | **1.25 (1.08–1.45)** | 0.99 (0.90–1.10) | 1.17 (1.00–1.37) |
| Categorical depressive symptoms, HR (95% CI; CES-D < 16 is reference) | | | | |
| M1: unadjusted | 0.92 (0.63–1.35) | **1.50 (1.07–2.10)** | 1.16 (0.91–1.47) | **1.66 (1.15–2.40)** |
| M2: | 1.06 (0.72–1.56) | 1.34 (0.96–1.89) | 1.00 (0.78–1.28) | **1.49 (1.03–2.16)** |
| M3 | 1.09 (0.73–z1.64) | 1.27 (0.90–1.80) | 1.00 (0.77–1.29) | 1.40 (0.95–2.05) |

PY = person-years; HR = hazard ratio; CI = confidence interval; CES-D = Center for Epidemiologic Studies Depression Scale; HDL = high-density lipoprotein; SD = standard deviation.

Metabolic syndrome was measured between Year 15 and Year 25 and is composed of at least three of the following cardiovascular risk factors: a) fasting glucose ≥100 mg/dl or diabetes medication, b) waist circumference >88 cm (women) or >102 cm (men), c) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or hypertension medicine, d) triglycerides ≥150 mg/dl, e) HDL cholesterol <50 mg/dl in women or <40 mg/dl in men.

M2: adjusted for age and education; M3: M2 + total physical activity, alcohol use, smoking status, and antidepressant use.

Continuous depressive symptoms should be interpreted as 1-SD unit. Baseline is Year 10.

Bold font indicates that the hazard ratio is statistically significant at the .05 level.

Our findings are consistent with existing longitudinal studies carried out in American and Israeli adults (7,13,14). Because prior longitudinal studies did not compare the burden of depressive symptoms or major depressive disorder by race/ethnicity, it is not known whether depressive symptom reporting in whites was also was relatively lower in those populations, as it was in ours. Although the burden of depressive symptoms was not particularly high among white participants, one pathway by which elevated symptoms may be associated with metabolic syndrome is through adverse health behaviors. Participants who are experiencing depression may be less likely to adhere to healthy life-style recommendations (37–39), thus placing themselves at risk for developing metabolic syndrome components and the metabolic syndrome. Among women, we observed that our associations were attenuated to borderline significance when we adjusted for health behaviors such as physical activity, alcohol intake, smoking status, and antidepressant use. These observations suggest one pathway by which depressive symptoms could be associated with incident metabolic syndrome.

It is equally plausible that depression and/or the behaviors adopted to cope with depression act by inducing physiologic changes that increase risk for metabolic syndrome. For example, dysregulation of the autonomic nervous system and hyperactivity of the hypothalamic-pituitary-adrenal axis (40,41) may lead to the development of insulin resistance (42)—an underlying features of the metabolic syndrome. Elevated cortisol, a consequence of an activated hypothalamic-pituitary-adrenal axis and indicator of chronic stress, may play a role in the association. Vogelzangs et al. (9) found that when both depression and high cortisol levels are present, the odds of metabolic syndrome increases. Muhtz et al. (5) revealed that elevated cortisol partially mediated depressive symptoms' association with several components of metabolic syndrome.

Our finding that there was no association between depressive symptoms and the development of metabolic syndrome among black men and women was unexpected. Two studies have found elevated depressive symptoms and major depressive disorder are associated with incident diabetes in multiracial samples, but they did not test whether the associations were differential by race/ethnicity (43,44). It is possible that the metabolic syndrome is a unique disease phenotype in black versus white adults. In particular, the syndrome is most commonly composed of elevations in hypertension, diabetes, and obesity in blacks and less commonly includes dyslipidemia. Given prior studies demonstrating that elevated depressive symptoms are associated with incident hypertension (34) and diabetes (45–47) in blacks and prevalent obesity in blacks (35), we would have expected these relationships to underlie a significant finding in our study. Hypertension, diabetes, and obesity are so highly prevalent among US blacks that the origins of disease may lie in behavioral or other social factors that, when compared with depressive symptoms, are much more strongly associated with metabolic disorders. Alternatively, our measure of depressive symptoms, the CES-D, may not capture the aspects of depressive symptoms that are directly associated with the somatic changes that could predispose to metabolic syndrome. These hypotheses to explain the null association warrant testing in future studies, and our findings should be verified in other data sets using different measures of depressive symptoms.

One limitation of our study is that we were unable to account for the potential influence of diet because diet assessment in CARDIA did not coincide with the baseline assessment in our analysis (1995–1996). Excess energy intake with weight gain may account for the association of depression and the development metabolic syndrome in our study. However, because adults who are experiencing elevated depressive symptoms may be just as likely to overeat as to undereat, it is not clear how this adjustment would have affected our findings. Another limitation of this study is that there is a 5-year window between study visits. However, for it to bias the association, we would have to hypothesize that one group (those with or without elevated depressive symptoms) would have been more likely to develop metabolic syndrome at a visit versus in between a visit. There is no reason for us to assume this differential development of metabolic syndrome by our exposure variable; thus, the influence on our effect estimates would not lead to a bias away from the null. We used survival analysis and defined time using discrete intervals to account for heavily "tied" data (events could happen at only three time points during the study). When we compared our findings using logistic regression analysis (had metabolic syndrome versus did not), our results were similar. Statistical adjustment for potential confounders may not have accounted for all of the observed effect, and residual confounding may remain.

A strength of our study is the relatively large sample size with equal numbers of black and white adults. In addition, we were able to confirm that the association was the same whether a single measure of depressive symptoms was used or if depressive symptoms were permitted to vary over time as they do clinically (48).

In conclusion, depressive symptoms may contribute to the development of metabolic syndrome in white adults. Our findings add to the growing body of research highlighting the adverse health effects of elevated depressive symptoms in some population subgroups. Future studies should investigate the contribution of stress-related biological mechanisms (i.e., elevated cortisol) that may underlie the association of depressive symptoms and metabolic syndrome.

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