# Depressive Symptoms, Race, and Glucose Concentrations

## The role of cortisol as mediator

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**OBJECTIVE** — This study examined the associations of depressive symptoms with glucose concentrations and morning cortisol levels in 665 African-American and 4,216 Caucasian Vietnam-era veterans.

**RESEARCH DESIGN AND METHODS** — Glucose level was measured as a three-level variable (diabetes, impaired glucose, and normal). Depressive symptoms were measured by the Obvious Depression Scale (OBD) from the Minnesota Multiphasic Personality Inventory.

**RESULTS** — Regression models showed significant race × OBD interactions in relation to glucose concentration ($P < 0.0001$) and cortisol ($P < 0.0001$). The OBD was positively associated with glucose concentration and cortisol in both racial groups. However, the magnitude of those associations was larger for African Americans. Further analyses suggested that cortisol partially mediated the race difference in the relation of depressive symptoms to glucose concentrations.

**CONCLUSIONS** — These results suggest that enhanced hypothalamic pituitary adrenal activity plays an important role in the relation of depressive symptoms to dysregulated glucose metabolism and may partially explain the differential effects of depressive symptoms on glucose levels in African-American and Caucasian male subjects.

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Evidence from cross-sectional and prospective studies suggests that depressive symptoms negatively influence glucose metabolism (1,2). While there is conflicting evidence supporting a relationship of depressive symptoms to glucose control in those with established diabetes (3), there have been more consistent findings of a relationship of depressive symptoms to the risk of developing diabetes (e.g., 4–6). One recent study by Everson et al. (6) reported a significant race difference in the relation of depressive symptoms to incident diabetes. This study included 1,318 Caucasian and 696 African-American women without diabetes from the SWAN (Study of Women's Health Across the Nation) study who were examined annually over a 3-year period. Among African Americans, higher levels of depressive symptoms predicted an increased risk of incident diabetes. In contrast, depressive symptoms were not significantly associated with incident diabetes among Caucasian participants. That study only included women, so it is important to examine whether a similar interaction exists for men.

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**Abbreviations:** AOVS, Agent Orange Validation Study; OBD, Obvious Depression Scale; PTSD, Posttraumatic stress disorder; VES, Vietnam Experience Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.



It is also important to explore possible mediators of the association between depressive symptoms and glucose metabolism. Depressive symptoms have been associated with measures of adiposity (7) that have been associated with altered glucose metabolism. However, the previous study by Everson et al. (6) controlled for central adiposity, suggesting that some other mechanism is responsible. Another possible mechanism involves cortisol, a hormone that plays an important role in metabolic control by stimulating hepatic glucose production. Cortisol has been shown to be responsive to emotional stress (8), and higher levels have been observed in depressed individuals (9,10). Thus, elevated levels of fasting glucose among individuals with high levels of depressive symptoms may reflect enhanced cortisol activity in response to chronic stress.

This study examined the relation of depressive symptoms to glucose levels in a large sample of Caucasian and African-American Vietnam-era veterans. We did not study diagnosed depression because previous studies suggest that the health risk of depressive symptoms is best represented by a continuum of severity with a graded association with health outcomes (11). We hypothesized that depressive symptoms would be positively associated with glucose levels and that these relations would be stronger among African Americans. Further analyses examined whether morning cortisol levels mediated any observed associations of depressive symptoms to glucose levels.

## RESEARCH DESIGN AND METHODS

— The sample for this study was a combination of two similar, but independent, studies of U.S. Army Vietnam-era veterans. The first sample was comprised of 525 African-American and 3,654 Caucasian participants in the Vietnam Experience Study (VES) (12,13), a multidimensional assessment of the health of Vietnam-era veterans that was conducted from 1985 to 1986. The study population included male Vietnam-era veterans who entered military service in

the U.S. Army for the first time between 1 January 1965 and 31 December 1971, served only one term of enlistment in the Army, had at least 16 weeks of active service time, earned a military occupational specialty other than "trainee" or "duty soldier," and had a pay grade no higher than E-5 at separation from active duty. From a random sample of 48,000 military records, 17,867 were identified as eligible for a telephone survey and a medical examination. The telephone survey was administered to 15,288 subjects (85.6% of those eligible), and a random sample of the respondents ($n$ = 6,443) were invited to attend a medical examination. Of 4,462 subjects (69% of those invited) that participated, 525 were African American, 3,654 were Caucasian, and 283 were other races (i.e., Hispanic, Asian, Pacific Islander, American Indian, or Alaskan Native).

The second sample was comprised of U.S. Army Vietnam-era veterans that participated in the Agent Orange Validation Study (AOVS) (14), an investigation conducted from 1986 to 1987 to examine the efficacy of using military records to identify veterans who had been exposed to the herbicide Agent Orange. The study population for the AOVS was the same as that of the VES, except that the participants who were Vietnam veterans must have served in Vietnam during 1967 and 1968 in an Army combat battalion in which information on daily location was known. After a review of 14,473 military records, 9,727 were deemed eligible and 994 were selected for the study. Of those selected, 871 completed a telephone survey identical to the one administered in the VES. In addition, 200 U.S. Army veterans, matched on age and race, who did not serve in Vietnam were included in the study as a referent group. These veterans were interviewed as a part of the VES but did not attend the medical examination. Of 1,071 veterans that completed the telephone survey, 775 (72% of those invited) attended the medical examination. Of those, 143 were African American, 574 were Caucasian, and 58 were other races. Because the procedures used in both studies were essentially identical, the samples were combined for data analysis. Participants were excluded from the analyses if they were taking prednisone ($n$ = 14), a medication known to have a strong influence on cortisol levels, at the time of the examination. An additional participant was excluded because of missing BMI data. The final sample was comprised of 4,216 Caucasians and 665 African Americans. Our analyses only focused on Caucasians and African Americans because of the small number of participants representing the other race/ethnic groups.

Participants in the VES and AOVS were invited to attend a 3-day medical and psychological examination at Lovelace Medical Foundation. On the 1st day, participants attended an orientation session and signed a consent form. At this time, they were asked to maintain an overnight fast, with only drinking water permitted, beginning at 7 P.M. that evening. On the 2nd day, blood specimens were obtained in the morning and then the participants attended a series of medical examinations. During the 3rd day, participants completed a psychological examination that included the administration of the Minnesota Multiphasic Personality Inventory (15). More detailed descriptions of the study design of the VES (12,13) and the AOVS (14) have been published previously.

### Depressive symptoms

The 40-item Obvious Depression Scale (OBD) from the Minnesota Multiphasic Personality Inventory was used to measure depression (16). The OBD is a measure of depressive symptoms (e.g., I am blue most of the time) that is more appropriate for nonclinical samples than the widely known D scale. Obvious indicators of depression have been shown to be more highly correlated with several criterion measures than the more subtle items (17–19). Also, unpublished data from a community sample showed that the OBD was correlated with the Beck Depression Inventory (20) similarly in African Americans ($r$ = 0.65) and Caucasians ($r$ = 0.64). It has also predicted myocardial infarction and all-cause mortality in a population sample (11). For the participants with missing items ($n$ = 153 or 3.13% of the sample), we multiplied the mean of the completed items by the number of items making up the scale. None of the participants were missing more than six (15%) items on the OBD. The mean OBD score for this study was (means ± SD) 9.98 ± 6.04. These scores are high compared with scores from a large national sample of African-American and Caucasian men of similar ages (8.01 ± 4.20) (21).

### Posttraumatic stress disorder

The presence of posttraumatic stress disorder (PTSD) was assessed by the Diagnostic Interview Schedule. The Diagnostic Interview Schedule is a structured interview used to assess the occurrence of psychiatric conditions according to DSM-III. Those participants that met diagnostic criteria for PTSD within the past year were coded as having PTSD.

### Socioeconomic position

Socioeconomic position was indexed by education (number of years) and household income. Household income was measured by a categorical item that asked participants to indicate their level of household income from one (<$5,000) to seven (>$50,000). This information was collected as a part of the telephone interview.

### Place of service

Place of service was indexed by a dichotomous variable (Vietnam, Non-Vietnam). This information was abstracted from participants' military records.

### BMI

BMI was calculated as weight in kilograms (kg) divided by the square of height in meters ($m^2$).

### Blood chemistry

Fasting glucose was determined from serum samples by using a standard adaptation of the glucose oxidase-peroxidase-chromogen–coupled system for glucose determination in biological fluids. Cortisol levels were determined by using a standard double-antibody radioimmunoassay system (Leeco Diagnostics). Coefficients of variation for these measures based on 5% of the sample were acceptable (i.e., <10%) throughout the study.

### Glucose concentrations

Because some of the participants were taking medication that affected glucose levels (e.g., insulin), we chose to model glucose concentration as a three-level variable (diabetes, impaired glucose, and normal). Participants were classified as having diabetes if they were taking medication for diabetes, were on a special diet for diabetes, or had a fasting glucose level ≥126 mg/dl. The remaining participants were classified as glucose impaired if their fasting glucose was <126 and ≥100 mg/dl or normal if their fasting glucose levels were <100 mg/dl.

**Table 1—*Selected characteristics of Caucasian and African-American participants***

| | Caucasians | African Americans | *P* |
|---|---|---|---|
| *n* | 4,216 | 665 | |
| OBD scores | 9.86 ± 6.01 | 10.76 ± 6.20 | <0.0005 |
| Age (years) | 38.08 ± 2.50 | 38.32 ± 2.73 | <0.03 |
| Education (years) | 13.33 ± 2.35 | 13.01 ± 1.96 | <0.0007 |
| Income (% >40,000 USD) | 23.09 | 13.76 | <0.0001 |
| Place of service (% Vietnam) | 60.71 | 61.65 | 0.48 |
| PTSD (%) | 7.05 | 7.63 | 0.09 |
| BMI (kg/m$^2$) | 26.91 ± 4.49 | 26.73 ± 4.86 | 0.49 |
| Cortisol (μg/dl) | 18.44 ± 5.57 | 18.45 ± 6.02 | 0.49 |
| Glucose concentrations (%)* | | | |
| Diabetes | 1.64 | 4.06 | <0.009 |
| Impaired | 16.88 | 18.35 | |
| Normal | 81.48 | 77.59 | |

Data are means ± SD or percent. *Participants were classified as having diabetes if they were taking medication for diabetes, were on a special diet for diabetes, or had fasting glucose ≥126 mg/dl. The remaining participants were classified as being glucose impaired if their fasting glucose was <126 and ≥100 mg/dl or normal if their fasting glucose was <100 mg/dl.

### Data analysis

Ordinal logistic regression was used for analyses in which glucose level was the dependent variable, and general linear models were used for analyses in which cortisol level was the dependent variable. All models included age and BMI as covariates. Interactions between the depressive symptoms and race were examined by adding OBD × race product terms to regression models.

To test the mediation hypothesis (22), we included the cortisol variable in the OBD/glucose model. The degree of mediation was estimated by the reduction in the regression coefficient associated with the OBD × race interaction term after introduction of cortisol to the regression model.

**RESULTS** — Sample characteristics are presented in Table 1. Initial analyses indicated that in comparison to the Caucasian participants, African-American participants were slightly older, less well-educated, had lower incomes, had higher OBD scores, and were slightly more likely to meet criteria for the diagnosis of PTSD; however, they were equally likely to have served in Vietnam while in the Army. African-American participants were also more likely to have impaired glucose or diabetes (22.4 vs. 18.50% in Caucasians) but were similar to Caucasian participants in terms of BMI and morning cortisol levels. Further analyses revealed that BMI was significantly and negatively related to morning cortisol levels ($r = -0.09$, $P < 0.0001$) but not to depression scores ($r = 0.00$, NS). The magnitude of these correlations was similar in both racial groups.

The race × OBD interaction was a significant predictor of glucose concentrations [$\chi^2(1) = 10.10$, $P < 0.002$]. Higher levels of depressive symptoms were associated with a greater likelihood of having impaired glucose or diabetes for both groups, but this relation was stronger among African Americans ($P < 0.0001$) than among Caucasians ($P < 0.03$). To further illustrate this interaction, we present the unadjusted prevalence of abnormal glucose levels (i.e., glucose impaired or diabetes) by race and OBD tertile in Fig. 1.

Analyses of cortisol levels also revealed a significant race × OBD interaction [$F(1, 4,875) = 9.14$, $P < 0.003$]. For African Americans, depressive symptoms were positively and significantly associated with cortisol levels ($P < 0.002$). This relation was significant for Caucasians ($P < 0.02$) but was much smaller in magnitude. To illustrate this effect, we used logistic regression to estimate the odds of having high (i.e., upper quartile of the distribution) levels of cortisol associated with the interquartile range of depression scores. The corresponding odds ratios were 1.32 for African Americans and 1.06 for Caucasians.

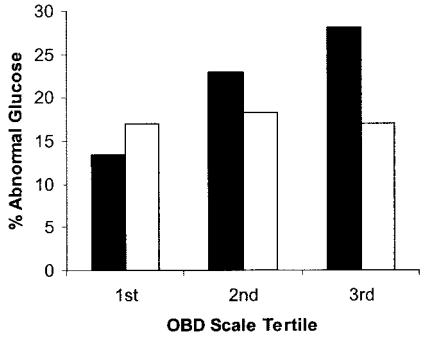


**Figure 1—*Prevalence of abnormal glucose levels by race and OBD tertile. Participants were classified as having abnormal glucose levels if they were classified as having impaired glucose or diabetes.* ■*, African Americans;* □*, Caucasians.***

Cortisol levels were also positively associated with glucose concentration [$\chi^2(1) = 220.29$, $P < 0.0001$], and this association was similar for Caucasians and African Americans ($P > 0.50$). There was evidence that cortisol partially mediated the differential relation of depressive symptoms to glucose concentrations in African Americans and Caucasians. When cortisol was added to the OBD/glucose concentrations model, the race × OBD interaction was still significant [$\chi^2(1) = 5.98$, $P < 0.02$]; however, the regression coefficient associated with the interaction term was reduced by 20.4%. Separate analyses for each racial group revealed that cortisol reduced the regression coefficient associated with the OBD by 20.5% for African Americans and by 18.8% for Caucasians. Thus, the stronger effect of depressive symptoms on glucose in African Americans is likely due, in part, to the stronger association of depressive symptoms and cortisol seen in that group rather than a difference in the physiological impact of cortisol on glucose.

We also fitted a series of models to examine the possibility that other variables (i.e., place of service [Vietnam/Non-Vietnam], diagnosis of PTSD, education, or household income) might account for the race differences in the relation of depressive symptoms to glucose and cortisol. In general, controlling for those variables had little effect on those associations. For example, place of service only reduced the effect by <2% for both variables, whereas adjustment for PTSD, education, and household income did not decrease the race × depressive symptoms regression coefficients for glucose and cortisol. Thus, confounding with those variables does not appear to explain the differential relation of depressive symptoms to glucose and cortisol in African Americans and Caucasians.

**CONCLUSIONS** — In the present study, depressive symptoms were more strongly associated with an index of glu-

cose metabolism in African Americans than Caucasians. This is consistent with the study by Everson et al. (6), which reported a stronger relation between depressive symptoms and incident diabetes among African-American female subjects and extends those findings to male subjects. Consideration of these racial differences may also help explain inconsistent findings, perhaps due to power constraints, in the literature on depressive symptoms and glycemic control in diabetic subjects (3).

Data from large-scale epidemiological studies suggest that African Americans are more likely than their Caucasian counterparts to develop type 2 diabetes (23). Those differences do not seem to be fully accounted for by traditional risk factors for diabetes, such as elevated adiposity (23). The present study suggests that depression may help explain some of this disparity in diabetes incidence. That is, African Americans exhibited somewhat higher levels of depressive symptoms, a phenomenon seen in other studies (24). Thus, the disease burden associated with depressive symptoms may be greater in African Americans. Depressive symptoms also had a larger impact on glucose metabolism in African Americans.

Our results also suggest that cortisol may, in part, account for the race difference in the relation of depressive symptoms to glucose concentrations. Cortisol was associated with the OBD for both ethnic groups, but this effect was much stronger among African Americans and partially explained the pattern of depression/glucose associations observed in this study. This finding is consistent with previous literature suggesting that depressive symptoms are associated with dysregulation of the hypothalamic-pituitary-adrenal axis (9,10), although the extent and exact nature of this relationship is not well established (25). It is not clear why depressive symptoms were more strongly associated with cortisol levels in African Americans. Although African Americans had significantly higher depression scores than Caucasians, the difference was small, suggesting that this relation was not simply due to African Americans experiencing more severe depressive symptoms. One possibility is that the associations found in this study reflect differences in coping strategies among African Americans and Caucasians. For example, it has been hypothesized that African Americans are more prone to self-medicate with alcohol and nicotine in response to stress (26). Though such strategies may be effective in reducing subjective levels of distress, they may result in activation of the hypothalamic-adrenal cortex, resulting in elevated levels of cortisol.

Cortisol levels did not completely account for the race difference in the relation of depressive symptoms to glucose, suggesting that other mechanisms are involved. One possibility is that other stress hormones, such as catecholamines and growth hormone, play a role in that association. For example, norepinephrine may contribute to increased levels of glucose by inhibiting secretion of insulin from the pancreas, while epinephrine and growth hormone can impact hepatic glucose production. Although there is no direct evidence to suggest that those stress hormones played a role in the associations observed in this study, several lines of evidence suggest they may be plausible mechanisms (27–29).

It must be remembered that the cross-sectional design of this study does not allow us to make causal inferences. It could be argued that high depression scores are the consequence of being diagnosed with diabetes. However, we also found that depressive symptoms were associated with a greater likelihood of having impaired glucose, suggesting that the association observed in this study is not just a response to a clinical diagnosis. This study only had male participants, so it is important to examine the role of cortisol in the relation of depressive symptoms to glucose metabolism in Caucasian and African-American female subjects. This study also has a number of strengths, including its large sample size and its considerable variability in levels of glucose concentrations and depressive symptoms.

In summary, these findings suggest that depressive symptoms have a stronger impact on glucose metabolism in African Americans. Furthermore, these results suggest that cortisol accounts for ~20% of that race difference. Similar comparisons should be made in relation to other determinants of glucose metabolism. Such interactions may have implications for the development of differential preventive strategies for diabetes in African Americans and Caucasians.

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