

Depressive symptoms, race and glucose concentrations: the role of cortisol as mediator

Stephen H. Boyle PhD, Richard S. Surwit PhD, Anastasia Georgiades PhD, Beverly H. Brummett PhD, Michael J. Helms BS, Redford B. Williams MD & John C. Barefoot PhD.

Department of Psychiatry and Behavioral Medicine  
Duke University Medical Center  
Durham NC, USA

Corresponding author:  
Stephen H. Boyle PhD  
Email: shboyle@duke.edu  
Behavioral Medicine Research Center  
Duke University Medical Center  
Department of Psychiatry  
Box 2969  
Durham, NC

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**Abstract**

**Objective** - This study examined the associations of depressive symptoms with glucose concentrations and morning cortisol levels in 665 African American and 4216 Caucasian Vietnam era veterans.

**Research Design and Methods** - Glucose level was measured as a three level variable (Diabetes, impaired glucose, normal). Depressive symptoms were measured by the obvious depression (OBD) scale from the MMPI.

**Results** - Regression models showed significant race X OBD scale interactions in relation to glucose concentration ( $p < .0001$ ) and cortisol ( $p < .0001$ ). The OBD scale 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 Americans and Caucasian males.

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 reported a significant race difference in the relation of depressive symptoms to incident diabetes (6). This study included 1318 Caucasian and 696 African American women without diabetes from the SWAN study who were examined annually over a three 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 if a similar interaction exists for men.

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 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 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**

### **Subjects**

The sample for this study was a combination of two similar, but independent studies of US Army Vietnam-era veterans. The first sample was comprised of 525 African American and 3654 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 US Army for the first time between January 1, 1965 and December 31, 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 (85.6 % of those eligible) and a random sample of the respondents (N = 6443) were invited to attend a medical examination. Of those 4462 (69% of those invited) that participated, 525 were African American; 3654 were Caucasian, and 283 were other races (i.e. Hispanic, Asian, Pacific Islander, American Indian, Alaskan Native).

The second sample was comprised of US 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 that 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, 9727 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 US 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 the 1071 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 data on body mass index. The final sample was comprised of 4216 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.

### **Procedures**

Participants in the VES and AOVS were invited to attend a three day medical and psychological examination at Lovelace Medical Foundation. On the first 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 7PM that evening. On the second day, blood specimens were obtained in the morning and then the participants attended a series of medical examinations. During the third day, participants completed a psychological examination that included the administration of the Minnesota Multiphasic Personality Inventory (MMPI, 15). More detailed descriptions of the study design of the VES (12-13) and the AOVS (14) have been published previously.

### **Measures**

**Depressive symptoms.** The 40-item Obvious Depression Scale (OBD) from the MMPI 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 scale was correlated with the Beck Depression Inventory (20) similarly in African Americans ( $r = .65$ ) and Caucasians ( $r = .64$ ). It has also predicted myocardial infarction (MI) 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  $> 6$  (15 %) items on the OBD scale. The mean OBD score for this study was 9.98 ( $SD = 6.04$ ). These scores are high compared to scores from a large national sample of African American and Caucasian men of similar ages (Mean = 8.01,  $SD = 4.20$ ) (21).

**Post traumatic stress disorder (PTSD).** The presence of PTSD was assessed by the Diagnostic Interview Schedule (DIS). The DIS 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.

**Socio-economic position (SEP).** SEP 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 1 ( $< \$5000$ ) to 7 ( $> \$50,000$ ). 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.

**Body mass index (BMI).** BMI was calculated as weight (kg) divided by height ( $m^2$ ).

**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 biologic fluids. Cortisol levels were determined by using a standard double antibody radioimmunoassay system (Leeco Diagnostics, INC). 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, normal). Participants were classified as having diabetes if they were taking medication for diabetes, on a special diet for diabetes or had a fasting glucose level  $\geq 126$  mg/dL. The remaining participants were classified as "glucose impaired" if their fasting glucose was  $< 126$  mg/dL and  $\geq 100$  mg/dL or "normal" if their fasting glucose levels were  $< 100$  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 body mass index as covariates. Interactions between the depressive symptoms and race were examined by adding OBD X race product terms to regression models.

To test the mediation hypothesis (22), we included the cortisol variable in the OBD scale/glucose model. The degree of mediation was estimated by the reduction in the regression coefficient associated with the OBD X 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, but 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 body mass index and morning cortisol levels. Further analyses revealed that BMI was significantly and negatively related to morning cortisol levels ( $r = -.09$ ,  $p < .0001$ ), but not to depression scores ( $r = .00$ , NS). The magnitude of these correlations was similar in both racial groups.

The race X OBD scale interaction was a significant predictor of glucose concentrations ( $\chi^2(1) = 10.10$ ,  $p < .002$ ). 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 ( $p < .0001$ ) than among Caucasians ( $p < .03$ ). To further illustrate this interaction we present the prevalence of abnormal glucose levels (i.e. glucose impaired or

diabetes) by race and OBD scale tertile in Figure 1.

Analyses of cortisol levels also revealed a significant race X OBD scale interaction ( $F(1,4875) = 9.14$ ,  $p < .003$ ). For African Americans, depressive symptoms were positively and significantly associated with cortisol levels ( $p < .002$ ). This relation was significant for Caucasians ( $p < .02$ ), 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 American and 1.06 for Caucasians.

Cortisol levels were also positively associated with glucose concentration ( $\chi^2(1) = 220.29$ ,  $p < .0001$ ) and this association was similar for Caucasians and African Americans ( $p > .50$ ). 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 scale/glucose concentrations model, the race X OBD scale interaction was still significant ( $\chi^2(1) = 5.98$ ,  $p < .02$ ), 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 scale 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 did not decrease the race X 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 glucose metabolism in African Americans, as compared to Caucasians. This is consistent with the study by Everson et al (6) that reported a stronger relation between depressive symptoms and incident diabetes among African American females and extends those findings to males. 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 diabetics (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 scale 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 females. 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 about 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.

## References

1. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D: Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute twin study. *Psychosom Med* 65: 490-497, 2003.
2. Suarez EC: Sex differences in the relation of depressive symptoms, hostility, and anger expression indices of glucose metabolism in nondiabetics. *Health Psychol* 25: 484 – 492, 2006
3. Van Tilburg MAL., Georgiades A, and Surwit RS: Depression in Type 2 Diabetes. In. *Type 2 Diabetes Mellitus: Evidence-Based Approach to Practical Management*. Feinglos M, Bethel MA, Eds. Humana Press. 2007
4. Carnethon MR, Kinder LS, Fair JM, Stafford RS, Fortmann SP: Symptoms of depression as a risk factor for incident diabetes: findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971 – 1992. *Am J Epidemiol* 158:416 – 423, 2003
5. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H: Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care* 22: 1071 – 1076
6. Everson-Rose SA, Torrens JI, Meyer PM, Kravitz HM, Powell LH, Bromberger JT, Pandey D, Matthews KA: Depressive symptoms, insulin resistance and risk of diabetes in women at midlife. *Diabetes Care* 27: 2856 – 2862, 2004
7. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA: Pathways linking depression, adiposity, and inflammatory markers in healthy young. *Brain Behav Immun* 17: 276 – 285, 2003
8. Earle TL, Linden W, Weinberg J: Differential effects of harassment on cardiovascular and salivary cortisol stress reactivity and recovery in women and men. *J Psychosom Res* 46: 125 – 141, 1999
9. Linkowski P, Mendlewicz J, Leclercq R, Brasseur M, Hubain P, Golstein J, Copinschi G, Van Cauter E: The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. *J Clin Endocrinol Metab* 61: 429 – 438, 1985
10. Mortola JF, Liu JH, Gillin JC, Rasmussen DD, Yen SS: Pulsatile rhythms of adrenocorticotropin (ACTH) and cortisol in women with endogenous depression: Evidence of increased ACTH pulse frequency. *J Clin Endocrinol Metab* 65: 962 – 968, 1987
11. Barefoot JC, Schroll M: Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*, 93: 1976 – 1980, 1996
12. The Centers for Disease Control Vietnam Experience Study: Health status of Vietnam veterans. I. Psychosocial characteristics. *JAMA*, 259: 2701-2707, 1988
13. The Centers for Disease Control Vietnam Experience Study: Health status of Vietnam veterans. II. Physical Health. *JAMA*, 259: 2708-2714, 1988
14. The Centers for Disease Control Veterans Health Studies: Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in US Army Vietnam-era veterans. *JAMA*, 260: 1249 – 1254, 1988
15. Dahlstrom WG, Welsh GS, Dahlstrom LE: *An MMPI Handbook Volume II: Research Applications*. University of Minnesota Press, 1960
16. Wiener DN: Subtle and obvious keys for the MMPI. *J Consult Clin Psychol*, 12: 164 – 170, 1948
17. Burgess P, Campbell I, Zylinderberg A: Face validity vs. item subtlety in the MMPI D scale. *Journal of Clinical Psychology*, 40: 499 – 504, 1984
18. Burkhart B, Gynther M, Fromuth M: The relative predictive validity of the subtle and obvious items on the MMPI Depression Scale. *Journal of Clinical Psychology*, 36: 748 – 751, 1980
19. Nelson LD, Cicchetti D: Validity of the MMPI Depression Scale for outpatients. *Psychol Assess*, 3: 55 – 59, 1991
20. Beck AT, Steer RA, Garbin MG: Psychometric properties of the Beck Depression Inventory: twenty – five years of evaluation. *Clin Psychol Rev*, 8: 77 – 100, 1988
21. National Computer Systems. *Manual for the MMPI-II: An administrative and interpretive guide*. Minneapolis: University of Minnesota Press. 1989

22. Baron RM, Kenny DA: The moderator-mediator distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*, 6: 1173 – 1182, 1986
23. Brancati FL, Kao WHL, Folsom AR, Watson RL, Szklo M: Incident Type 2 diabetes in African American and white adults: The Atherosclerosis Risk in Communities Study. *JAMA*, 283: 2253 – 2259, 2006
24. Jackson-Triche ME, Greer SJ, Wells KB, Rogers W, Camp P, Mazel R: Depression and health-related quality of life in ethnic minorities seeking care in general medical settings. *J Affective Disorders*, 58: 89 – 97, 2000
25. Antonijevic IA: Depressive disorders-is it time to endorse different pathophysiologies? *Psychoneuroendocrinology*, 31: 1 – 15, 2006
26. Jackson JS, Knight KM: Race and self regulatory health behaviors: The role of the stress response and the HPA axis in physical and mental health disparities. In: *Social Structure, Aging and Self-Regulation in the Elderly*. Cartensen LL, Schaie KW, Eds. New York: Springer. 2006
27. Wyatt RJ, Portnoy B, Kupfer DJ, Snyder F, Engleman K: Resting plasma catecholamine concentrations in patients with depression and anxiety. *Arch Gen Psychiatry*, 24: 65 – 70, 1971
28. Light KC, Kothandapani RV, Allen MT: Enhanced cardiovascular and catecholamine responses in women with depressive symptoms. *Int J Psychophysiol*, 28: 157 – 166, 1998
29. Dinan TG: Psychoneuroendocrinology of depression. Growth hormone. *Psychiatr Clin North Am*, 21: 325 – 339, 1998

**Table 1.** Selected characteristics (Means or %) of Caucasian and African American participants.

	Race		P
	Caucasians (N = 4216)	African Americans (N = 665)	
OBD scores	9.86 (6.01)	10.76 (6.20)	<.0005
Age (years)	38.08 (2.50)	38.32 (2.73)	<.03
Education (years)	13.33 (2.35)	13.01 (1.96)	<.0007
Income (% > 40,000)	23.09	13.76	<.0001
Place of Service (% Vietnam)	60.71	61.65	.48
PTSD(%)	7.05	7.63	.09
BMI (kg/m <sup>2</sup> )	26.91 (4.49)	26.73 (4.86)	.49
Cortisol (µg/dL)	18.44 (5.57)	18.45 (6.02)	.49
Glucose Concentrations * (%)			
Diabetes	1.64	4.06	< .009
Impaired	16.88	18.35	
Normal	81.48	77.59	

\* Participants were classified as having diabetes if they were taking medication for diabetes, on a special diet for diabetes or had fasting glucose (FG) of  $\geq 126$  mg/dL. The remaining participants were classified as being “glucose impaired” if their FG was  $< 126$  mg/dL and  $\geq 100$  mg/dL or “normal” if their FG was  $< 100$  mg/dL.

**Figure 1.** Prevalence of abnormal glucose levels by race and Obvious Depression (OBD) Scale tertile. African Americans are represented by black bars and Caucasians are represented by white bars. Participants were classified as having abnormal glucose levels if they were classified as having impaired glucose or diabetes.

