Author's response to reviews

Title: The Association of Depression and Anxiety with Glycemic Control among Mexican Americans with Diabetes Living Near the U.S.-Mexico Border

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Version: 3 Date: 10 January 2014

Author's response to reviews: see over
January 10, 2014

Dear Dr. Pafitis:

Thank you for your invitation to resubmit our manuscript, *The Association of Depression and Anxiety with Glycemic Control among Mexican Americans with Diabetes Living Near the U.S.-Mexico Border*, to BMC Public Health. We have revised the document as suggested by the reviewer, and we believe the resulting manuscript is much improved as a result. The reviewer suggestions and concerns are summarized below, followed by our response and the corresponding changes made to the manuscript. We are happy to make additional changes to the manuscript as needed.

Sincerely,

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**EDITOR COMMENT**
1. Please format the Authors' Contributions in your manuscript.

   **Response:** Contributor names have been replaced with initials (pg. 17).

**REVIEWER CONCERNS**
1. The reliability of the method used for determination of HbA1c (GLYCO-Tek) should be reported providing some data on comparisons with the methods currently recommended by IFCC.

   **Response:** We have provided references describing the GLYCO-Tek affinity column method as well as the validity of the method in relation to other methods (pg. 7).

   “Glycosylated hemoglobin was measured on frozen whole blood using the GLYCO-Tek® Affinity column method [Helena Laboratories, Beaumont, TX; 42] or by High Performance Liquid Chromatography. The validity of affinity chromatography for the determination of glycosylated hemoglobin has been demonstrated in comparison with other methods [43].”
2. A major remark on this study concerns the statistical analyses performed by authors. In Methods section is stated that authors performed a series of linear regression models correcting for several covariates. How did the authors know that the effect is linear? Data with quartiles should be provided and, if the case, patients should be categorized on the basis of CESD.

Response: To evaluate linearity, we examined scatterplots of the predicted values by the residuals. We looked for a roughly rectangular shape (without curvature). Relationships appeared linear for both depression and anxiety with all dependent variables (BMI, waist circumference, physical activity, fasting glucose, and HbA1c). The pattern was similarly indicative of linear relationships when the dependent variables were examined by quartiles of depression and anxiety. We have added a note about the scatterplots to the statistical analyses section (pg. 7):

“Scatterplots of predicted values by residuals were examined to evaluate and confirm linearity.”

3. In the results section R², Adjusted R² and significance levels of each model is not reported.

Response: R² and model p-values have been added to the text, which now reads as follows (pgs. 9-10):

**Depression, Modifiable Factors, and Glycemic Control**

After controlling for covariates (i.e., age, gender, years of education, assessment language, birth country), linear regression analyses correcting for design effects indicated that depression (as measured by the CES-D) was significantly and positively associated with BMI, \( p = .054 \) (model R² = .03) and waist circumference, \( p = .005 \) (model R² = .06), and negatively associated with physical activity (METs), \( p = .007 \) (model R² = .03; additional analyses indicated that results remained significant even after controlling for physical activity measure). Depression was also significantly and positively associated with fasting glucose, \( p = .007 \) (model R² = .13), after controlling for all previously mentioned covariates as well as medication status. The positive association between depression and HbA1c (controlling for all covariates including medication status) approached significance, \( p = .08 \) (model R² = .07; see Table 3). Analyses indicated good fit for each model (all \( p \)'s < .05).

**Anxiety, Modifiable Factors, and Glycemic Control**

After controlling for covariates (i.e., age, gender, education, assessment language, birth country), linear regression analyses correcting for design effects indicated that anxiety (as measured by the SAS) was positively associated with BMI, \( p = .001 \) (model R² = .04) and waist circumference, \( p < .001 \) (model R² = .08), and negatively associated with physical activity (METs), \( p = .049 \) (model R² = .03; additional analyses indicated that results remained significant even after controlling for physical activity measure). Similarly, anxiety was positively associated with HbA1c, \( p = .047 \) (model R² = .07), after for controlling for all previously mentioned covariates and medication status. The positive association between anxiety and fasting glucose approached significance, \( p = .073 \) (model R² = .13), after controlling for all covariates and medication status (see Table 4). Analyses indicated good fit for each model (all \( p \)'s < .05).
4. In Table 3 and 4 only unstandardized coefficients [B] and no Standard Error have been reported. Furthermore, these Tables are definitely not clear. For example: In Table 3 (reporting the associations between depression and indicators of glycemic control), how an association expressed with a B of -5.292 (p<.01) between birth country and waist circumference, should be interpreted?

Response: Standard errors have been added to Tables 3 and 4. The presentation of the unstandardized coefficients in combination with the coding of the independent variables (which is noted in the left column) allow for easy interpretation of the findings in Tables 3 and 4. In the example the reviewer mentions (from Table 3), birth country is coded as 1= U.S. and 2 = Mexico (noted in the left column) and waist circumference (cm) is a continuous variable. Thus, as birth country goes from U.S. to Mexico, waist circumference decreases by 5.292 cm (i.e., unstandardized coefficient = -5.292). Those born in Mexico have significantly lower waist circumference than those born in the USA (p ≤ .01).

5. In addition, the last three paragraphs of the results section are not clearly explained. What kind of analyses did authors perform to obtain results on moderation/interaction? Why authors chose to make sub-analyses dividing patients in two groups using the median of the variables taken into consideration?

Response: This is an important omission. Thus, we have added text to describe the analyses used to evaluate possible interactions in the Statistical Analyses section (pg. 8):

“Interactions between study covariates with depression and/or anxiety were examined to determine whether any of the variables functioned as moderators of the relations between depression/anxiety and diabetes-related outcomes (i.e., BMI, waist circumference, physical activity, fasting glucose, and HbA1c). Interaction terms were created by multiplying depression and anxiety with each of the covariates. Interaction terms were evaluated for significance by including them individually in linear regression models along with either depression or anxiety and all covariates. When an interaction term was found to be significant, the relationship between depression or anxiety with diabetes-related outcomes were further examined within either the natural groupings of the moderating variable (i.e., gender, assessment language, birth country) or the groups created by a median split for continuous variables (i.e., age, years of education).”

6. Finally, a p#.10 it is not usually worth to be considered an “approached significance”.

Response: We agree with the reviewer that p = .10 is probably not normally worth noting. However, in this case the p-values were actually less than .10, with p = .08 for the relationship between depression and HbA1c, and p = .07 for the relationship between anxiety and fasting glucose (see pgs. 9-10). We wanted to show a consistent pattern of relationships between depression and anxiety with measures of glycemic control, so we thought it was important that readers know the relationships approached significance. In addition, the fit for the entire model (with covariates) in each of these cases was also significant (information about model fit has been added to pgs. 9-10 at the reviewers request – see comment #3).

7. Background (2nd par): Several longitudinal studies have been performed to investigate the bidirectional association between diabetes and depression, and some meta-analyses, combining
these studies, have been recently published. This point should be expanded, discussing the fact that diabetes may cause depression, thus influencing the rates of depression in diabetic subjects found in cross-sectional studies.

Response: The second paragraph of the introduction (pgs. 3-4) has been expanded to emphasize the bi-directional relationship of depression and diabetes (including the citation of several recently published papers) and now reads as follows:

“Research suggests that the relationship between depression and diabetes is bi-directional, and that depression may influence the management of diabetes among those already diagnosed [8-10]. Specifically, diabetes is more common among those who are depressed than those who are not depressed [10, 11]. Conversely, depression is more common among those with diabetes than those without [10, 12, 13]. Further, Mexican Americans with diabetes are more likely than other racial/ethnic groups to report symptoms of depression [14]. In fact, rates of clinically significant depressive symptoms have been reported to be as high as 40% among individuals of Mexican origin with diabetes who live on either side of the South Texas border [15]. The presence of depression in diabetes is noteworthy because depression may influence glycemic control among individuals with diabetes through physiological and behavioral pathways [for reviews, see 8, 9, 12, 16].”

8. Materials and Methods (4th par): Physical Activity was assessed using two different instruments. This should be reported in the discussion section as it could be a limitation of the study. In addition, authors should confirm the results obtained on physical activity performing a multivariate model including the questionnaire used for the assessment.

Response: The reviewer makes a good point. As such, we have re-run the physical activity models controlling for the physical activity measure and the findings remain significant (for CES-D, $p = .010$; for SAS anxiety, $p = .050$). To address the reviewer’s concerns, we have provided additional detail about the measurement of physical activity in the current study (pgs. 6-7). We have added notes in the results section (both depression and anxiety sections; pg. 9-10) to indicate that we conducted additional analyses controlling for the specific physical activity measure, and that this issue did not substantially impact the findings. Finally, we have addressed this concern in the discussion section (pg. 15).

Pgs. 6-7

“Physical Activity. Intensity and duration of physical activity during the last 7 days was assessed using validated instrumentation of either the International Physical Activity Questionnaire (IPAQ) [35, 36] or the Godin Leisure-Time Exercise Questionnaire [37, 38]. While the physical activity questionnaire changed in response to broader study design modifications, both measures assess moderate and vigorous physical activity and allow for the calculation of metabolic equivalent values (METS) using instrument-specific scoring recommendations [39, 40]. METs were used as a continuous variable in the analysis. Participants who reported > 600 MET adjusted minutes in the 7 day period were considered to have met national physical activity guidelines [41]. The physical activity assessment of some participants ($n = 92$) was not concurrent with the other measures (i.e., was not completed on the same date), and instead occurred during a later participant visit. However, additional analyses controlling for the physical activity assessment (IPAQ vs. Godin vs. delayed assessment) did not substantially change the results of the physical activity models.”
Pgs. 9-10
“…additional analyses indicated that results remained significant even after controlling for physical activity measure."

Pg. 15
“Finally, it is notable that the physical activity measure (from which METs were calculated) changed during the course of the study (i.e., IPAQ to Godin) and some participants completed the physical activity assessment after a delay (i.e., assessment not completed concurrently with other measures) which may have impacted the findings. However, please note that depression and anxiety remained significantly related to physical activity (METs) even after controlling for the specific physical activity measure (Godin vs. IPAQ vs. delayed assessment).”

9. Table 2: Numbers of different groups should be added in each column.
Response: We have added the number of participants in each group (depressed vs. non-depressed; anxious vs. non-anxious). However, the number of participants reflected in each row may be reduced when there are missing data for that specific variable. This caveat has been noted at the bottom of the table.

10. Results (2nd par): Physical activity appears to be negatively associated with depression.
Response: The reviewer is correct. We have corrected this error for the relationships of depression and anxiety with physical activity (pg. 9).

11. Discussion (2nd par): This paragraph, as an overall, appears to be redundant as it almost repeats what already reported in the results section.
Response: The purpose of this paragraph was to summarize our findings and to place them in the context of other research. As such, we report which of our findings are similar to other research and which findings differ. Throughout this paragraph, we reference 5 other studies. We believe this summary and comparison is important and may be useful and of interest to readers. However, based on the reviewer’s comment, we have removed a sentence that stated a finding without placing it in the context of other research (to avoid redundance). We are happy to remove the remainder of the paragraph if the reviewer and editor think that would be appropriate. The revised paragraph now reads as follows (pg. 12):

“Depressed and anxious participants differed from those who were not depressed or anxious in a variety of ways. Similar to nationally representative samples [44, 45], depressed/anxious Mexican Americans with diabetes were of greater age, more likely to be female, and less educated than their non-depressed/anxious counterparts; they also had greater BMI and waist circumference, and engaged in less physical activity. In contrast with other research focused on anxiety disorder prevalence [e.g., 46], anxious participants were more likely than non-anxious participants to have been born in Mexico than the U.S., and preferred to complete their study assessments in Spanish. Perhaps this finding may be understood in the context of research indicating that acculturative stress
is associated with greater anxiety and depression among Mexican Americans [47]. In addition, Breslau et al. [48] found that immigration from Mexico predicted the subsequent onset of anxiety. Plausibly, the higher levels of anxiety among Mexican-born participants may have been related to acculturative stress, though more research will be needed to understand potential links between nativity, acculturative stress, and anxiety.”