

Author's response to reviews

Title: Racial and ethnic disparities in the control of cardiovascular risk factors in southwestern American veterans: the Diabetes Outcomes in Veterans Study

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Author's response to reviews:

Dear BioMed Central Editorial Team:

We appreciate having the opportunity to revise our manuscript. We thank the reviewers for their thoughtful comments and believe that the revised manuscript is much improved. We have summarized and addressed each of the reviewers' comment below. Text revisions are in bold.

We were asked by the editor to document any ethics and consent approval obtained for this study in the Methods section. We added the following:

P 5, P 1: The institutional review board of each study site approved the protocol.

P 6, 2: At the entry visit, research coordinators explained the project, answered questions, and obtained informed consent.

We have changed the manuscript title and extensively revised the abstract to more clearly reflect our study objectives.

Reviewer 1

Compulsory Revisions:

1)Page, 4, paragraph 1. It is not clear that supposed physiological differences by race and ethnicity among diabetics are particularly relevant to this paper. Focus more clearly on what is and what is not known regarding racial and ethnic disparities in risk factor control among diabetics and specifically how this study addresses that gap in knowledge.

RESPONSE: We have deleted the comment about physiological differences. We now emphasize in the abstract and background that the strength of our study is the ability to evaluate racial/ethnic differences in glycemic control and treatment intensity by controlling for multiple potential confounders--sociodemographic and clinical factors as well as the patient's physical, cognitive, and psychosocial capacity for risk factor management.

P 4, P 2: The purpose of this study was to examine the association between race and ethnicity and control of cardiovascular disease risk factors, adjusted for socioeconomic, clinical, and behavioral factors, in a large cohort of insulin-treated veterans with type 2 diabetes.

2)Page 5, paragraph 2. It is possible that minority patients were in the process of having their regimen changed more often than majority patients, but these differences were missed by misclassification of subjects as truly on stable regimens. Recent data show that African American and Hispanic VA patients are seen significantly less often than non-Hispanic white patients. This creates a potential bias in misclassification for study eligibility as suggested above, but also represents a plausible explanation for the findings. Since most dosage changes occur at visits, fewer visits over 8 years could result in differences in insulin dosage of the order of magnitude that were observed. This major limitation should be acknowledged

in the discussion.

RESPONSE: The reviewer has rightly pointed out that we should not have characterized our sample as being on "stable medication regimens." The patients were considered "stable" in that their A1c taken at time of interview would have reflected their last medication adjustment. It takes 8 to 10 weeks for A1c to equilibrate. We did not believe that subjects had necessarily reached a steady-state dose as far as their providers were concerned.

We have changed the definition in the methods section (P 5, P1) to now read:

...their diabetes medication regimen had been relatively unchanged in the preceding 2 months (the dose of all oral agents remained unchanged, no oral agents were added to the treatment regimen, and the total daily insulin dose was increased by no more than 10 units or 15%, whichever was less), thus ensuring that their A1c had equilibrated at the current insulin dose.

This clarification notwithstanding, we appreciate the reviewer's suggestions about potential mechanisms for the observed disparity. We believe it is unlikely that minority patients, particularly given that their average duration on insulin was the same as non-Hispanic whites, were in the process of having their doses changed more rapidly. Moreover, from the prospective data collected in DOVES, we found that insulin doses did not change significantly in the subsample of subjects who completed the 26-week follow-up. In fact, the week-26 dose was an average of 3.8 units less for African Americans and 3.9 units greater for NHW, compared to baseline. We have added these lines to the Results section (P 9, P4):

At follow-up, the treatment patterns remained essentially the same. Overall, 63% of each minority group and 70% of the non-Hispanic whites returned for the 26-week follow-up visit. For non-Hispanic whites, Hispanics, and African Americans, the mean (SD) daily insulin units were 71.1 (51.2), 63.1 (36.9), and 51.4 (26.6), respectively ($p=0.14$). Among patients with a baseline A1c [greater than or equal to] 8.0%, the mean (SD) daily insulin units at follow-up also differed significantly ($p=0.04$): non-Hispanic whites = 80.3 (51.3), Hispanics = 63.0 (34.0), and African Americans = 47.8 (23.1).

We do not have data on number of visits patients had since being started on insulin and cannot rule out the possibility that minority subjects were seen less often by providers. Although such a scenario could certainly contribute to our findings, we do not see that less frequent visits would "explain" differences in insulin treatment intensity. Less frequent visits would likely be a marker for other underlying explanatory factors that affect access to care and treatment, such as geographic barriers, cultural differences, fear of parenteral treatment, socioeconomic barriers, or lack of transportation among others. We acknowledge lack of visit data as a limitation--and have added the following to the discussion (P 12, P 3):

Another possibility for the difference in treatment intensity is that minority patients had fewer clinic visits. We were unable to assess this because we did not have data on the number of clinic visits since being started on insulin. However, it is unlikely that an effect from fewer visits would persist over an average of 8 years of insulin treatment. Additionally, given the equal access to VA health care shared by all veterans, the frequency of clinic visits would not likely be an explanation for differential treatment, but rather a marker for confounding socioeconomic or psychological factors.

3)Page 5, paragraph 2. Why was a 2-month period used to define "stable"? Was this definition empirically based? A rationale should be provided.

RESPONSE: See response to comment 2 above.

4)Page 5, paragraph 2. If the authors have access to number of visits either from subject self-report or electronic health records, they should assess whether differences in number of visits for diabetes explains their findings.

RESPONSE: See response to comment 2. We agree that this would be a useful covariate, but we do not have these data. This is listed as a study limitation--see response to comment 2 (P 12, P 3).

5)Page 6, paragraph 3. The study fails to adequately control for provider effects. Failure to increase insulin in response to suboptimal glucose control represents what is termed "clinical inertia". It is possible that a substantial number of minority patients were seen by a provider with greater clinical inertia. Ideally, this would be assessed using random effects models that include facility and physician level variables, but the sample is probably too small. This should be acknowledged as a limitation.

RESPONSE: We agree that glycemic control and treatment intensity reflects provider (and health care system) factors as well as patient factors. Our research focus was on patient-centered factors and we lacked the sample size to perform hierarchical modeling to evaluate the influence of provider and hospital. Given the relatively small sample size and the fact that we randomly sampled patients from 3 hospitals, we believe it unlikely that a single provider would have unduly influenced our findings. However, we have acknowledged this as a limitation (P 14, P1).

Although provider effects are an important determinant of diabetes control, we did not have sufficient power to model this factor in our analyses.

6)Page 7, paragraph 2. "Baseline A1C" needs to be clearly defined? Does it refer to the most recent A1C level available at the time of study enrollment regardless of how long ago it was done or did all subjects undergo A1C levels at enrollment for the purposes of the study? It sounds like the latter but this needs to be clearer.

RESPONSE: We clarify that the "baseline" A1c was obtained at entry into the study (P 7, P 1):

Baseline physiologic measurements made upon entry to the study included hemoglobin A1c (A1c), blood pressure, height, weight, smoking status and blood lipids.

7)Page 11, paragraph 3. As noted study limitations need to be more clearly acknowledged. This also applies to the absence of findings of differences in BP control and lipids.

RESPONSE: In addition to limitations addressed above, we added the following to the discussion of lipid and blood pressure results (P 13, P 3):

Our study may have been underpowered to detect small differences in lipids, blood pressure, and other risk factors. However, the finding of comparable control across racial/ethnic groups suggests that subjects did not face substantial access barriers and that providers were addressing these cardiovascular risk factors. However, glycemic control and insulin treatment requires more motivation and patient education than other aspects of cardiovascular disease risk factor control.

8)Page 13, paragraph 2. The African American subsample size is small and findings are of questionable generalizability. Specifically, the authors should be more cautious in drawing firm conclusions based on a selected sample of 35 African Americans from SW VAs. Without knowledge of the characteristics of the larger population of diabetics within these medical centers or participation bias by race or ethnicity, it is difficult to generalize these findings to all diabetics within these medical centers much less to diabetics within the VA nationally. More caution is needed in the interpretation of their findings in both the abstract and discussion sections.

RESPONSE: We agree with the reviewer's comment and have modified the abstract and body conclusion sections to reflect more caution.

Abstract conclusion:

Further research with larger sample sizes and more geographically diverse populations are needed to confirm our findings.

Conclusion (P 14, P 2):

In summary, insulin-treated veterans who are minorities may have an increased risk of poor glycemic control and receiving lower doses of insulin. African-Americans in this sample were the most likely patients to experience this problem, while Hispanics had an intermediate risk. No racial or ethnic differences were found for the control of other cardiovascular disease risk factors. The disparities in glycemic control and treatment intensity could not be explained by the socioeconomic barriers, attitudes, level of knowledge, depression, cognitive dysfunction, or social support rated by the instruments in this study. Further research with larger sample sizes and more geographically diverse populations are needed to confirm our findings and to elucidate the reasons for any observed disparities.

Minor Compulsory Revisions

1)When during the prospective DOVES was this cross-sectional analysis done? In other words, were data all data derived from baseline assessments?

RESPONSE: All data were derived from baseline assessments. We have added this sentence after description of prospective design (P 6, P2):

All measures in this report were collected at the two baseline visits, scheduled two weeks apart, with the exception of insulin doses measured at a 26-week follow-up visit.

2)How were alcoholism and substance abuse assessed? What morbidities that might affect glucose homeostasis were considered?

RESPONSE: Diagnosed active alcoholism and substance abuse assessed during chart review screening by nurse coordinators of potentially eligible subjects (methods section clarified). We have revised the discussion of the subject eligibility criteria in the methods section (P 5, P2):

We excluded patients for having less than one year expected survival; alcoholism or substance abuse listed as an active problem in the electronic medical record; history of diabetic ketoacidosis or type I diabetes; or co-morbidities affecting glucose homeostasis: diabetes resulting from pancreatitis or pancreatic resection; cirrhosis, chronic active hepatitis, hemochromatosis, Wilson's disease or other liver disease; endocrinopathies such as pituitary adenoma, Cushing's or Addison's disease; hereditary or acquired forms of insulin resistance; glucocorticoid treatment; immunosuppression or treatment with immunosuppressant drugs; or chronic infectious diseases (e.g. osteomyelitis or refractory skin ulcers).

Discretionary Revisions

1)Abstract-background. Why not mention previous work documenting disparities in diabetic control and associated CVD risk factors?

RESPONSE: Abstract background was revised:

Racial/ethnic disparities in cardiovascular disease complications have been observed in diabetic patients.

2)Abstract-methods. It is helpful to distinguish primary from secondary outcomes variables rather than lumping them all together.

RESPONSE: The methods section was revised:

We collected medical record and patient survey data on diabetes control and management, cardiovascular disease risk factors, comorbidity, demographics, socioeconomic factors, psychological status, and health behaviors. We used analysis of variance and multivariate linear regression to determine the effect of race/ethnicity on glycemic control, insulin treatment intensity, lipid levels, and blood pressure control.

3)Page, 4, paragraph 2. It is not clear why disparities in SES make the SW an appropriate region. Ideally, variation by SES would be modest (as it probably is in the VA) in order to more clearly isolate race and ethnicity effects.

RESPONSE: Although the Southwest has substantial SES variation, the reviewer is correct that this is less of a factor on veterans, particularly regarding access to health care. The sentence was rewritten (P 4, P2):

The American Southwest is an appropriate region in which to evaluate ethnic and racial differences in diabetes care because of the high prevalence of disease and the large minority populations.

4)Page 7, paragraph 2. Use of a subject flow diagram might help readers to better understand how the sample was constructed.

RESPONSE: We believe that the current description is self-explanatory and that a figure is probably unnecessary.

5)Was any consideration given to over-sampling minorities to increase their numbers in the total sample?

Although race and ethnicity are not available through pharmacy records, minorities could be oversampled through a combination of use of Hispanic surnames and sampling from neighborhoods (based on geocoded addresses) that include large proportions of African Americans and Hispanics. Use of this approach would also provide some indication of differential study enrollment by race and ethnicity.

RESPONSE: We did not consider over-sampling minorities--in part because the race/ethnicity data were not reliably available from the VA electronic medical record and because our primary concern in sampling was to obtain a random selection of insulin-treated patients with type II diabetes. We implemented this strategy to minimize selection bias.

6) Do the authors have any data from other sources, such as VA EHR data, on all medical center patients with a diagnosis of type II? It would be helpful to compare characteristics of the entire diabetic population in these medical centers with the study sample as a means of assessing generalizability.

RESPONSE: We agree that comparing our study cohort with the regional population of veterans with type II diabetes would increase generalizability, but these data are not available.

7) Why was metformin assessed separately from other OHAs?

RESPONSE: Metformin was found to be an independent predictor in several steps of the modeling process, and was retained as a borderline predictor due to its unique mechanism of action. At the time of this study, glitazone use was relatively unusual in these centers, so that "other orals" were almost all sulfonylureas.

8) Page 11, paragraph 2. Some of the barriers proposed are not well supported by the data. There were no differences in number of injections per day by race or ethnicity. There is not evidence (to my knowledge) that glucose monitoring is associated with improved diabetic control. It is not clear how cultural barriers related to images of wellness would affect insulin dose.

RESPONSE: See discretionary comment 9, below. We have previously published data suggesting that glucose monitoring is in fact associated with improved glycemic control (Murata GH et al. *Diabetes Care* 2003; 26: 1759-1763.). Several other studies--usually ones that linked monitoring with behavioral changes--also have demonstrated a benefit for glucose testing: Karter AJ et al. *Am J Med.* 2001;111:1-9. Rutten G et al. 1990. *Fam Pract* 7:273-278. Muchmore DB et al. 1994. *Acta Diabetol* 31:215-219.

Culturally-based images of wellness can present obstacles to insulin treatment, especially initiation. In our qualitative work, we have encountered beliefs among minority groups that taking insulin is the harbinger of severe complications, and insulin is considered to be the cause of these complications--often because of experience in family or close friends of a major event such as amputation that they link temporally to initiation of insulin.

9) Page 12, paragraph 1. The authors' cite 14 year old data suggesting that African American diabetics report less frequent glucose monitoring, but there is no evidence (to my knowledge) that glucose monitoring is associated with improved glucose control. While patient-provider interaction is clearly a possibility, it is notable that none of the patient level variables that might be mitigated by patient-provider race or ethnicity concordance such as language preference or attitudes were predictive of insulin dose in the multivariate model. This might be acknowledged. I agree that competing demands can affect management of diabetes, but it is not clear from these data why minorities might have greater competing demands.

RESPONSE: See response to discretionary revision 8 regarding the benefits of glucose monitoring. The comment about competing demands was revised (P 14, P 1):

Providers often address multiple acute and chronic conditions during medical encounters; this may present a barrier for consistently providing preventive services and optimal disease management for diabetes, particularly if minority patients have more comorbidity than non-Hispanic white patients [40, 41].

10) It also might be worthwhile to note in the paper the need for future research to examine physician stereotypes. For example, it is possible that many physicians stereotype minority patients as at greater risk for hypoglycemia (in the absence of any evidence). This area warranting study based on other work on physician stereotyping.

RESPONSE: This is certainly a key question of our current research. We have added this sentence to discussion: (P 13, P 1)

Possibly, some providers perceive a higher hypoglycemia risk for minority patients that may affect treatment intensity. This hypothesis requires further evaluation.

Reviewer 2

1)p. 5: Some comment on rationale for some of the eligibility criteria would be useful, e.g., what do "living arrangements conducive to self-care" mean, what were considered "co-morbidities that affect glucose homeostasis" and why was it a requirement that their diabetes medication regimen be "stable" in the preceding two months?

RESPONSE: "Living arrangements conducive to self-care" essentially meant not being homeless. The study arose from a prospective study that required SMBG four times per day for eight weeks, which was not considered feasible for homeless veterans. We have added to the methods section (P 6, P 1):

Patients were also excluded if they were homeless, which would have interfered with the intensive self-monitoring of blood glucose component of the DOVES prospective study.

We have expanded the discussion of eligibility criteria (see response to Reviewer 1 minor compulsory revision 2, above).

We have revised the discussion of stable medication regimens (see response to Reviewer 1 compulsory revision 2, above).

2)p.6: What does it mean that 'psychological instruments were given in random order'?

RESPONSE: We shuffled in a random way the order in which each patient was presented with the various instruments in visit two. This was done to avoid any possible systematic influence of the experience of answering earlier instruments on the later ones, as well as effects such as fatigue falling on the same instruments.

We have changed the word "given" to "administered" in the methods section

3)p.9: The description of how insulin doses were determined should be clearer here. As the authors note, VA electronic pharmacy records do not accurately record actual insulin doses. Were patient reports supplemented with medical record review? Please include some references about the validity of patient self-report for insulin doses.

RESPONSE: Insulin doses were collected via structured interviews with nurses, in which the number of units of each insulin type and at each dosing time were queried. Enumerating each dose time and type may have provided somewhat higher validity than asking patients directly for their units per day, by obliging them to reflect more carefully on their routines. However, nurses did not question the accuracy of the dosing unless there was reason to believe the patient was confused. These measures were not supplemented with review of provider notes, which would be the only place dose adjustments would be recorded. We acknowledge that this was a subjective measure chosen by default because both pharmacy and medical notes were not practical sources. We are not aware of any report on the validity of this approach.

We have added more detail to the methods section on the collection of data on insulin dose (P 6, P 2).

Research coordinators conducted structured interviews with study subject to collect data about medical treatment, including insulin dose, number of injections, types of preparations, and the dose, type, and frequency of oral medications. Research coordinators then ascertained the number of units of each insulin type at each daily dosing time and summed them to determine total insulin units per day.

4) p. 10: Their discussion of possible factors contributing to lower insulin doses (e.g., differences in blood glucose self-monitoring, etc.) is excellent.

We hope that our revisions have satisfactorily addressed the reviewers' concerns.

Sincerely,

