Author's response to reviews

Title: Changes in Glycemic Control from 1996 to 2006 among Adults with Type 2 Diabetes: A Longitudinal Cohort Study

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Author's response to reviews: see over
March 3, 2010

Re:
MS: 1645227323308397
Changes in Glycemic Control from 1996 to 2006 among Adults with Type 2 Diabetes: A Longitudinal Cohort Study
Karen J Blumenthal, Mary E Larkin, Gail S Winning, David M Nathan and Richard W Grant

Dear Dr. Graham,

Thank you for the opportunity to revise our manuscript. We thank the reviewers for their helpful comments. Below we provide a point-by-point summary of our responses to the reviewer comments. We have also highlighted using blue font the corresponding changes in the revised manuscript. As requested, we have also added an Authors’ contributions section before the Acknowledgments and Reference list.

Sincerely,

Richard W Grant MD MPH
Corresponding author
Review #1
We were grateful that this reviewer found our manuscript to be “well-written paper with useful information” with “important findings” to others in the field.

Minor Essential Revisions:
1. Pg3, second paragraph: NHANES is National Health and Nutrition Examination Survey. Since NHANES was a cross-sectional study the fact that mean age remained constant doesn’t necessarily imply that aging was counterbalanced by younger age of diagnosis. It could mean that the age at diagnosis is not changing and the mean age of death is not changing.
   The reviewer raises a good point. We have revised this sentence in the new introduction.
2. Pg5, line 14: one usually measures CVs of quality controls, not standards (or calibrators).
   In this case, CVs were measured using standards as referenced in refs #2 & #15.
3. The authors should use either “loss to follow-up” or preferably “lost to follow-up” throughout but not both.
   We now use “lost to follow-up” throughout the revised manuscript.
4. Pg10, line 7: It might be clearer to say “10-year decline in HbA1c” (so that decline doesn’t imply decline in glycemic control).
   This has been changed in the revised manuscript as suggested by the reviewer.
5. Figure 1: The graph needs axis labels (HbA1c for x-axis and mean change in HbA1c (1996 to 2006) for y-axis). Also, the value label for the 9-10% bar is partly missing and <=11.0% should be >=11.0%.
   Figure 1 has been revised to include axis labels and to correct missing/incorrect bar labels.
6. Figure 2 and legend: loss or lost to follow-up?
   Fixed to read “lost to follow-up”.

Review #2
This reviewer also found that our study was “an article of importance in the field”.

Minor Essential Revisions: May wish to expand comments re: loss to follow-ups. Do these detract from your conclusions & how? This number plus those who died ((64%) of initial patients.

As suggested, we have expanded our comments in the discussion section to more fully address the implications of the loss to follow up rate.
Reviewer #3
The secular review of changes in glycemic control from 1996-2006 constitutes a tantalizing paper lacking in closure and completeness. While the paper provides some answers to the “what” question, it lacks sufficient speculation and concern with the “why” question. Apparently patients with type 2 diabetes were recruited in large number from MGH and its satellites. In this report, focus was upon Type 2 patients who were evaluated in 1996 and again in 2006. What occurred within the ten-year interval seemed almost irrelevant so long as the patients remained accessible in the bookend periods of 1996 and 2006. Did the patients continue to receive evaluations, instruction, and adjustments, during the intervening ten years? What motivated or prompted this study?

We agree that answering the “why” question would be of tremendous interest. However, this is beyond the scope of the present study. We were able to study a very large number of patients (4944 in 1996 and 1772 in 2006) by creating an extensive database using electronic clinical care data sources. Thus, we did not “recruit” patients, a process which would have been prohibitively expensive and also would have introduced a patient-level selection bias that would not be reflective of usual care practices for the population. We were motivated to conduct an “epidemiology of care” analysis designed to provide much-needed patient-level longitudinal trend data. Our goal was to assess whether trends reported using national cross-sectional data held true at the patient level.

Even though as discussed on Page 6, the improvement in glycemic control seemed to fit a regression toward the mean model, the authors dismissed this possible outcome simply because all patients were included in the overall analyses. I am not convinced with that argument although it has some appeal. I think ‘playing’ with various subgroups at baseline and follow up could have more exhaustively tested this possibility of regression toward the mean, but this strategy was not pursued.

Fundamentally, regression to the mean is a bias that results from random variation in measurement. With random variation, subjects selected because they are in the extreme of the population distribution may be found to be closer to the mean when re-measured. In our study, we report changes in HbA1c levels over a 10-year period that were substantially larger (e.g. 3.2% in the highest baseline A1c group) than can be explained by random variation. In other words, patients with HbA1c levels of 10% don’t randomly fluctuate to 8.0% when re-tested. For these 2 reasons (i.e. we did not select outliers but measured all patients and then re-measured 10 years later, and HbA1c random variation is orders of magnitude smaller than the variation we report), we do not believe regression to the mean can explain our results.

However, one of the major weaknesses with the study was the failure to perform zero order correlations among the potentially relevant confounding variables. This analytic strategy could have been followed by linear multiple regression analyses thereby controlling for the variables needing control including cholesterol and triglycerides. Thus, the evaluation for general improvement in glycemic control over the decade could have been more critically assessed.

We did address correlations between potentially relevant confounding variables in our regression model building strategy. This has been clarified in the revised statistical methods section of the manuscript.
Also, the predictive utility of “English” as the critical language partly responsible for improving glycemic control raises several questions. Is English a proxy for Educational level? Was there any examination of the use of translators in the treatment program?

We agree that English may have been a proxy for educational level. Educational attainment was not an available variable from our clinical care data and thus we cannot directly test that hypothesis. However, we have revised the discussion to reflect this point. Translators are generally available (either directly or via phone-based translation) at the practices in our system, although we cannot evaluate to what extent the individuals in our analysis used these services.

Why was continuous HbA1c not the primary dependent variable? Why not establish a statistical ‘moderator’ approach rather than simply utilizing a series of independent variables?

We agree that there are several different approaches to the statistical analysis of longitudinal data. In our experience, the use of independent variables in logistic or linear regression models - as is widely done in many clinical research studies - provides robust results.

It seems as if there were an aversion to an attempt to ‘explain’ and to provide a why rather than just a what model. I think this strategy is unfortunate since there is such a potential wealth of data in this study including possibly vital information on causal factors associated with mortality in diabetes.

We agree that further research in this area is necessary. We used large electronic databases of clinical care data to provide novel longitudinal data for a large cohort of usual care patients. This approach is well-suited for proving a broad view of care trends. Other methods, such as individual patient recruitment and enrollment into prospective research studies with patient-level surveys, will need to be employed to better understand the “Why” of our findings.