Author’s response to reviews

Title: Hypoglycaemic events in Patients with Type 2 Diabetes in the United Kingdom: Associations with Patient-Reported Outcomes and Self-Reported HbA1c

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Author’s response to reviews: see over
Dear Dr. Beverly and Ms. Nolasco,

Thank you for the opportunity to revise and resubmit our manuscript to BMC Endocrine Disorders. My coauthors and I have revised our manuscript in response to the reviewers’ suggestions, and include a point-by-point response to their comments below.

Sincerely,
Jeff Vietri

Please find our responses to reviewer feedback presented in **bold** font below each comment.

**Reviewer's report**
**Title:** Hypoglycaemic events in Patients with Type 2 Diabetes in the United Kingdom: Associations with Patient-Reported Outcomes and Self-Reported HbA1c
**Version:** 3  **Date:** 6 October 2013
**Reviewer:** John Zrebiec

**Reviewer's report:**
This is an important subject that has been extensively discussed in regard to type 1 diabetes, but relatively few studies have focused on type 2 diabetes. It’s importance is underlined by the National Job Analyses of Certified Diabetes Educators (CDE’s), conducted every 5 years by the National Certification Board for Diabetes Educators in the United States. Consistently, CDE’s rank teaching patients about preventing and treating hypoglycemia as their #1 priority. My guess is that if a similar survey were conducted in the United Kingdom, the results would mirror those in the U.S.

This manuscript is very well-written with research objectives that are well-defined. The data that the authors attempted to capture seemed pertinent and specific to the research questions they proposed to study. The paper itself is thoughtful and well-organized. I thought the authors described the limitations of the study (p16) quite straightforwardly, including that the data is based upon self-report. The reference list is solid and the tables are well-presented and easy-to-understand. There are no major compulsory revisions needed, but there are some discretionary explanations that might be considered based upon the following comments.

**Thank you.**

There are a few spelling and grammatical errors that I assume the authors will correct, but if needed, I can point them out. The most troublesome one was the term “impaired patient reported outcomes.” The wording makes it difficult to
understand whether it is the patient that is impaired or the outcomes are impaired?

The manuscript has undergone additional editing for clarity, readability, and elimination of ambiguous passages such as the one mentioned above, which now reads "impairment in patient-reported outcomes."

It was unclear whether the Light Speed chronic ailment panel received a fee for participation in that panel which might potentially affect their response?

We have added this information to the method section: Respondent were informed that they would receive a small incentive for completion of each assessment point, either in the form of points that could be exchanged for merchandise or monetary payment. Incentives increased from approximately £2.50 for the baseline survey to £12.75 for the final assessment to discourage attrition.

The authors note that only 34% of the baseline sample completed the last follow-up and only 9% completed all follow-up (p6). If my calculations are correct that is 604 and 160 respondents, respectively. I would suggest including these numbers in addition to the percentage, rather than force readers to do the math.

We have added the exact numbers to this passage, which now reads: However, attrition over the duration of the study resulted in only 34% (n=451) of the baseline sample reporting at the last follow-up, and only 12% (n=155) of baseline respondents completed all follow-up waves. Additionally, the 9% figure was an error and has been corrected to 12%.

Household jobs and shopping were noted to be the most common circumstance (22.1%) for HE (p12), and this finding might be highlighted again in the discussion because the majority of health care professionals believe that the most common reason is exercise.

We have added the following passage to the discussion: Another interesting finding was the location of the HEs, which were most commonly reported as happening in the context of household jobs or relaxing rather than during physical activity such as exercise or playing sports which might be expected to result in low blood glucose levels. Unfortunately, this is likely due to lack of physical activity among the sample; less than half of the sample reported one or more days in the previous month during which they exercised for 20 minutes or more, and items asking about the context of the HE referred only to the most recent episode to maximize the accuracy of the recall. If individuals exercise infrequently, they have limited opportunities to have an HE during exercise.

Predictably, adherence to insulin was significantly lower among those experiencing HE, but only marginally lower with adherence to oral medication (p13). In the discussion, I would like to hear the author’s hypothesis for the difference between the treatment groups.
We have added the following text to the discussion: the relationship between HEs and adherence was not observed in oral medications, perhaps because patients understand the potential for insulin to cause hypoglycaemia, and perhaps due to the injectable mode of administration, which is more aversive than swallowing a pill and also enables dose reduction. Those who had experienced HE were noted to have “a greater likelihood of reporting behaviors that would raise their blood glucose levels” (p14). However, there was not any specific description of what those primary behaviors were and that was the most frustratingly missing piece in the paper.

We have added a passage in the section on the HFS-II that includes mention of each of the behaviors, whereas the initial version included these only in Table 4 of the results. The passage now reads: Behaviour subscale items include items that would not necessarily contribute to poorer glycaemic control (e.g., avoiding being alone) and five behaviors that would: eating large snacks, keeping blood glucose (BG) above 150, keeping BG higher than normal in social situations, keeping BG higher than normal during important activities, and reducing insulin dose. These items were included in the behavioral subscale and total scale scores, but also analyzed separately, dichotomized as never engaging in that behaviour versus engaging in the behaviour during the recall period.

I think your assumption at the bottom of page 15 that “those who experience Hes would be expected to adjust their regimen to prevent Hes, raising their HbA1c in the process” overlooks complex variables. For example, this reviewer conducts a specialty program about preventing severe hypoglycemia and the majority of patients with long-standing diabetes were historically indoctrinated to keep their BG as low as possible in order to avoid long-term complications from the disease, and will tolerate significant low BG rather than run higher. Of course, your sample only had a mean duration of 9.6 years with diabetes.

This passage is in the midst of a discussion of why the relationship between HEs and HbA1c might be complex, we felt a slight adjustment of the passage to imply greater uncertainty in the relationship would be sufficient, and we cite previous research that has suggested this as a possibility. The passage now reads: However, those who experience HEs may adjust their regimen in an attempt to prevent subsequent HEs [42, 43].

The paper raises many questions that are worthy of further study, including how come 27.7% did not test blood glucose during an HE? How is it that 5.5% rated a normal blood glucose reading as an HE? How did 13.2% explain the HE as caused by stress rather than behavior? Are fears of hypoglycemia different between those who self-managed episodes versus those who required assistance from others?

These and many other interesting questions remain about the psychology of individuals with type 2 diabetes coping with hypoglycemic events; we have opted not to add any beyond those further directions included in the original paper in order to retain a single focused recommendation. However, we hope that this paper will serve as an impetus for
researchers to generate studies to seek answers to such questions which have important implications for clinical practice

Congratulations, I look forward to reading the article in print.

Thank you for your helpful comments.

Reviewer's report
Title: Hypoglycaemic events in Patients with Type 2 Diabetes in the United Kingdom: Associations with Patient-Reported Outcomes and Self-Reported HbA1c
Version: 3 Date: 10 October 2013
Reviewer: Linda Gonder-Frederick

Reviewer's report:
This is a well-written and well-organized report on the impact of hypoglycemic episodes on individuals with type 2 diabetes in the U.K. The authors have taken a comprehensive perspective and investigated a broad range of outcome variables ranging from quality of life to clinical status, which adds to the significance of the paper as a contribution to the hypoglycemia literature. There are, however, several questions that need to be addressed to improve the manuscript and help the reader understand the study and findings.

Major Compulsory Revisions

1. As the authors note, the study was planned as a longitudinal prospective project, with participants completing outcome measures on six separate occasions. Compliance to the longitudinal protocol was poor and by the sixth assessment, only 34% of participants responded, with only 9% of participants completing all six assessments. While the authors note this as problematic, they have chosen to report the findings on the 9% of participants who completed the protocol as a guide to future research. Although this is the prerogative of the authors, what is missing is methodological detail on how the follow-up assessments were conducted, and this needs to be included in the Methods section.

We agree that the attrition is the greatest limitation of the study and limits our ability to draw conclusions from the longitudinal data, although attrition is likely to have resulted in an under-estimate of HE. The method section now includes additional information on the fielding of the follow-up surveys. The following text was added:

Respondents were informed that they would receive a small incentive for completion of each assessment point, either in the form of points that could be exchanged for merchandise or monetary payment. Incentives increased from approximately £2.50 for the baseline survey to £12.75 for the final assessment to discourage attrition. Respondents were notified of the availability of the questionnaire via email at the opening of each assessment point and had one week to complete the questionnaire, and all those who completed the baseline were invited to participate in each follow-up. Up to four reminder emails were sent over the course of the week the survey was available.
For example, what type of reminders did participants receive and how many?

This is addressed in the passage above.

What was the level of contact with participants for follow-up data collection?

This is addressed in the passage above.

Why do the authors think that the compliance rate for the entire protocol was so low?

This seems better addressed in the discussion, where we have added the following: The use of the online survey panel also limited follow-up reminders to email which, along with the limited response window, likely contributed to the relatively low response rate for the follow-up waves.

This type of information is needed to evaluate the study methods/findings and to help other researchers planning similar longitudinal studies. The other alternative the authors could consider is leaving out the follow-up data, although this may not be appropriate given that several statistically significant findings emerged even with the reduced power.

Related to this point, the Results section (paragraph 1) needs to describe the number of respondents who completed each follow-up assessment.

Our preference is to retain the longitudinal data findings as they serve as important observations from which future research can be considered. However, acknowledging the reduction in patient data from baseline, the results present baseline comparisons first (showing that worse HbA1c, greater diabetes-related healthcare resource use, greater fear of hypoglycaemia, and impaired health outcomes were associated with HE in the four weeks prior to baseline) followed by the longitudinal data. It is the cumulative nature of the observations that allows us to categorise patients into HE vs no HE for the latter analyses and as stated in the results, “this analysis included only a small and self-selected subsample of the baseline survey respondents, but is included here to facilitate hypothesis generation for future research.” The number of respondents in each follow-up is presented with the baseline sample size at the opening of the Results section, which reads: A total of 1,329 respondents completed the baseline survey; follow-up surveys were completed by 836, 759, 765, 511, and 451 respondents.

2. The method for soliciting potential respondents is also unclear, even though the authors do go to a great deal of trouble to describe this in detail. However, several issues remain unclear. For example, what is the purpose of the SEU NHWS survey?

The introduction of the 5EU NHWS now reads: “The 5EU NHWS is a proprietary survey of adults (≥18 years) conducted by Kantar Health in France, Germany, Italy, Spain, and
United Kingdom (UK), which collects data approximately every 18 months to provide timely patient-reported information on a broad range of health conditions.”

Why were respondents who indicated that a family member had type 2 diabetes invited to participate in the study?

The original description has been amended to reflect that the panel respondents indicated they had diabetes. The original description was confused because fielding coordinators from the panel company indicated that family members of the panel member without diabetes may have access to the contact email, and so require the inclusion of screening questions confirm the age and gender of the respondent match those of the targeted panelist.

How many of the potential respondents did have type 2 diabetes and of these how many declined to participate?

Respondents provided consent prior to completing the screening questions, so we cannot provide these figures. We have added additional details to this passage to help illustrate the flow of participants through the screening process.

3. Table 2 should be described as “Clinical” characteristics and not “Patient” characteristics in the first paragraph of the Results section.

This change has been made.

4. In the fourth paragraph of the discussion, the statement regarding individuals who maintain low blood glucose who are “closer to hypoglycemia” should be rewritten to reflect that individuals with lower glycosylated hemoglobin measures are indeed at higher risk for hypoglycemia according to several studies and give representative references.

The following text has been added: and previous research has demonstrated that individuals with lower glycosylated hemoglobin levels are indeed at greater risk of HEs. Several representative references are now included.

5. What do the authors think are the clinical implications of their findings?

To the discussion we have added: The findings underscore the importance of considering risk of HEs when planning a patient’s treatment regimen, ensuring patients are educated about HEs, and encouraging regular testing of blood glucose.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: My research program has received licensing fees from Eli Lilly for the use of the Hypoglycemia Fear Survey-II.