Author’s response to reviews

Title: Prevalence of diabetes and pre-diabetes in rural Tehri Garhwal, India: Influence of diagnostic method

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Author’s response to reviews:

Dr Grace Joshy,

Associate Editor

BMC Public health

Dear Dr Joshy,

Re: Prevalence of diabetes and pre-diabetes in rural Tehri Garhwal, India: Influence of diagnostic method

Thank you for your review of our manuscript. We outline the comments of the reviewers below, together with a point-by-point response to each item. Page and line number references are based on our manuscript in word format.
Thank you for the opportunity to respond to these comments

Yours sincerely

Amanda Thrift

Matthew Kelly (Reviewer 1):

Please note that page and line number references are based on our manuscript in word format.

1. In the methods it is mentioned that anthropometric measurements were taken of the participants. But no results from these measurements are presented. Is there a reason for this? In describing your study population it would be interesting information for the reader to know.

We have included height, weight, BMI, waist, hip and waist-hip ratio of participants in Table 2, but these refer only to the people with diagnoses of diabetes status using both HbA1c and glucose-based measurements. To address this deficiency, we have now included the characteristics of participants in a new online Supplementary Table 2.

2. Further to this point, did you do any assessment of interaction between anthropometric measurements and the diabetes diagnosis?

Please see new Supplementary Table 2. These data demonstrate notable differences in characteristics, including anthropometry, according to diabetic status. Clearly, individuals with a normal HbA1c result were younger, had a lower BMI and a smaller WHR compared to those who were pre-diabetic or diabetic. This is now mentioned in the revised Results (page 8, lines 21-25)

“There were notable differences in most of the anthropometric measures between individuals who were non-diabetic and those who were either pre-diabetic or diabetic according to HbA1c.
Kruskal-Wallis tests (set at 0.05 significance level) show that those with pre-diabetes or diabetes were progressively heavier, with greater BMI, waist and hip circumference, and waist-hip ratio.”

3. The description of the study population in the methods section is too brief. How did you randomly select villages? Within the selected villages, were all adults recruited? Or was there a random sample of households in each sample village? How did you recruit the villagers? Through local health staff? We need to know a little more about how recruitment actually happened.

We recruited each village randomly using random number generation, from a total list of 58 villages on the western side of Chamba. Adults in the village were approached by health workers, and a nurse, for potential participation. As we had no access to a census in the region, participants were recruited on a voluntary basis. We have added the following to the methods on page 5-6:

“We randomly selected five villages from 58 villages located on the west side of Chamba, in the mountainous Tehri District in the Garhwal region of the state of Uttarakhand in northern India (May to July 2015), using random number generation. We undertook a cross-sectional survey of adults in each village for between 8 and 10 days, with the aim of obtaining approximately 100 participants per village. As we did not have a census for each village, randomization of individual participants was not possible. Health staff, including a nurse and health workers recruited participants following full informed consent.”

4. In the follow-up study using FBG you only tested the people who were assessed as pre-diabetic, or diabetic using the initial methodology. I was wondering why this was? If you tested all participants again then you may identify individuals who were negative under the first method, but positive using FBG. This would contribute to the methodological assessment. I realise the study has already been conducted and you can't go back and do that. But, a justification as to why should be included in the Methods section.

Our aim was to develop a protocol for testing and following up residents at risk of cardiovascular events. Our concern over the high level of diagnosis of pre-diabetes at the initial survey led us to speculate that this large prevalence may have been attributable to a high prevalence of anemia in the region. We have added this detail to the introduction and methods. We agree that this is a
Introduction, page 5, lines 13-15: “Based on our initial finding of relatively high prevalence of both diabetes and pre-diabetes, we then aimed to test the hypothesis that HbA1c over-diagnoses diabetes and pre-diabetes when compared to FBG.”

Methods, page 8, lines 1-2: “The high prevalence of pre-diabetes at the initial survey prompted us to consider that anemia may have contributed to this surprising finding.”

Discussion (limitations), page 16, lines 15-18: “Furthermore, because we did not follow-up people who were categorized as having a normal HbA1c at baseline, we will have missed detecting anyone who was negative for diabetes and pre-diabetes at the first assessment, but who were then positive using the glucose-based definition. This may mean that the differences that we observed are overestimated.”

5. The same as point 4 applies to the anemia testing. Why was that only carried out in the second round?

See response to point 4 above.

6. In the results, first paragraph, you describe median household income. Is that per week, per month?

The income specified is monthly, and further details are now provided in the results and methods (and copied below):

Methods, page 7, lines 15-16: Age, weight, height, waist, hip, body mass index (BMI) and monthly income per capita (household monthly income/household size) are presented as medians and quartiles (Q1, Q3).
Results, page 8, lines 17-18: The median monthly income per capita (household monthly income divided by household size) was 1,000 rupees (500 – 3,000 rupees, n=400 due to missing values for the number of people in the household).

Joanne Thandrayen (Reviewer 2):

Please note that page and line number references are based on our manuscript in word format.

1. Page 6, sub-heading "Initial Survey (time 1)"; It would be appropriate to report that one missing case in this section rather than later (Page 7, Line 47). The reference to Figure 1 where readers can see the "499" is in this section.

These are in fact two different cases. The missing case in baseline (which reduced the total sample size to 499) was due to a missing value in HbA1c whereas the case mentioned in the Methods section was excluded from analysis of differences in proportions of diabetes/pre-diabetes between time 1 and time 2 because of taking up treatment after initial assessment of diabetes status in time 1. We have clarified this in the methods (and results and copied below):

Methods, page 6, lines 12-13: “Screening for diabetes and pre-diabetes was undertaken in 499 participants, using HbA1c measured by the Afinion Analyzer (Alere, Oslo; Figure 1).”

Results, page 8, lines 18-19: “One person had missing information on HbA1c (Figure 1).”

2. Page 6, sub-heading "Clinical definitions": Perhaps use these mathematical definitions instead for FBG (100 mg/dL ≤FBG ≤ 125 mg/dL) and PBG (140 mg/dL ≤PBG ≤ 200 mg/dL). They are more in line with their opposites of FBG > 125 mg/dL and PBG > 200 mg/dL respectively.

The above mathematical definitions have been used as suggested.
Clinical definitions, page 7, line 7: “Pre-diabetes was also defined as 100 mg/dL ≤FBG ≤ 125 mg/dL or 140 mg/dL ≤PBG ≤ 200 mg/dL.”

3. Page 7, Line 32: It is not clear what the authors meant by "same procedures". Did they mean "crude prevalence" and/or "Chi-square" test. The latter is a test of association. It's not a test to obtain percentages.

Thank you. This sentence lacked clarity, we have now reworded this to the following:

Methods (Statistical analysis), page 7, lines 20-22:

“Similarly, we compared age specific percentages of diabetes and pre-diabetes based on the FBG and/or PBG obtained in Time 2 using Pearson’s Chi-square test.

4. Page 7, Line 45: It would facilitate the reading to specify the n and % for FBG.

We have added in the number of observations and percentage stated as suggested (and copied below):

Methods (Statistical analysis), page 8, lines 5-6: “In the majority of cases, FBG was used (n = 117, 84%), but in those instances where this was unavailable (n=23, 16%), PBG was used.”

5. Page 7, Line 47: "We excluded one case..."; please see comment 1 above.

We have clarified that this is a different case to that outline in point 1, above, by stating:

“If we excluded one case who began treatment for diabetes between time 1 and time 2 (Figure 1).” Methods (Statistical analysis), page 8, lines 6-7.
6. Page 9, Line 16: Space missing between HbA1c and FBG/PBG.

The space has been inserted (and copied below):

Page 9, Line 19: “…anthropometric variables between the times of measurement of HbA1c and FBG/PBG”

7. Page 9, Line 26: It is not necessary to specify "exact McNemar's" before the p-value. It is understood that the p-value belongs to McNemar's test as the test statistic value was provided.

“Exact McNemar’s” has been deleted as suggested.

Results section, page 10, line 4: “This corresponds to a 48.6% greater percentage of pre-diabetes using HbA1c than by FBG/PBG (95% CI: 39.3% to 57.7%) (McNemar’s chi-square = 66.1; p<0.001).”

8. Page 9, Line 54: The word "outcomes" is not appropriate for p-values. Perhaps rephrase as the "p-values were based on the Wilcoxon's...".

Page 10, legend to table 2: We have amended this as suggested, i.e. “p-values were based on Wilcoxon’s signed-rank test”

9. Page 10, Lines 33 & 34: Please see comment 2 above.

The mathematical definitions of pre-diabetes have been changed as suggested.

Legend to Table 3, page 11, lines 8-10: “aTested at time 1; pre-diabetes was defined as 5.7% ≤ HbA1c ≤ 6.4%; diabetes was defined as HbA1c ≥6.5%
bTested at time 2; pre-diabetes was defined as $100 \text{ mg/dL} \leq \text{FBG} \leq 125 \text{ mg/dL}$ or $140 \text{ mg/dL} \leq \text{PBG} \leq 200 \text{ mg/dL}$; diabetes was defined as FBG >125 mg/dL or PBG >200 mg/dL.”

10. Page 10, Line 47: Colon missing after 95%CI. Also see comment 7 above.

Results, page 11, line 15: colon inserted and “exact McNemar’s” deleted as suggested.

11. Page 10, Line 54: The authors commented on "with and without moderate to severe anemia...". However this is not reflected in the column headings of Table 4. Perhaps use something along those lines in the column headings. No anemia (including mild anemia), Anemia (moderate/severe anemia).

Results, page 12, Table 4: The headings have been amended as suggested. We have changed the legend in line 9 to : “Moderate/severe anemia was defined as Hb≤11.4 g/dL.”

12. Page 10, Line 56: The word "thus" doesn't appear to be necessary here.

Page 11, line 18: The word “thus” has been deleted as suggested.

13. Page 11, Line 36: Please see comment 2 above.

Results, page 12, line 11. The mathematical definitions of pre-diabetes based on FBG have been changed as suggested (and copied below):

Legend to Table 4: “Pre-diabetes was defined as $5.7 \% \leq \text{HbA1c} \leq 6.4$” and “Pre-diabetes was defined as $100 \text{ mg/dL} \leq \text{FBG} \leq 125 \text{ mg/dL}$ or $140 \text{ mg/dL} \leq \text{PBG} \leq 200 \text{ mg/dL}$.”

14. Page 12, Line 29: Space missing between Hb and diagnosed...
The space has now been inserted (and copied below):

Page 13, line 10: “…while in other studies HbA1c diagnosed smaller percentages of diabetes than did FBG [22, 26].”

15. Page 13, Line 18: Extra dash between Hb and diagnosed...

We have re-phrased this to the following to ensure that there was no requirement for a hyphen:

Discussion, page 14, lines 6-8. “The presence of a large proportion of individuals diagnosed as having pre-diabetes based on HbA1c but with normal glucose-based results may have important prognostic implications.”

16. It would be appropriate to include a table showing the distribution of the "499", "117" and "23" across the 5 villages. Perhaps the authors could add this in the Supplementary Material section.

We have added a new Supplementary Table 1 that incorporates these details, and have added a sentence in the results section to highlight this (Page 8, lines 19-20):

“There was a similar number of people recruited to each village (Supplementary Table 1).”