Author’s response to reviews

Title: Type 1 diabetes-associated cognitive impairment and diabetic peripheral neuropathy in Chinese adults: results from a prospective cross-sectional study

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Author’s response to reviews:

Dear Handling Editor,

We are submitting a revised manuscript entitled “Type 1 diabetes-associated cognitive impairment and diabetic peripheral neuropathy in Chinese adults: results from a prospective cross-sectional study” (BEND-D-18-00214R2).

The editor and reviewers provided highly constructive suggestions and we made changes accordingly. A point-by-point description made as they relate to the reviewers’ suggestions follows:

Reviewer reports:

Baqiyyah Conway (Reviewer 2): The authors have adequately addressed most of my concerns. I just have a few minor comments:
1. In the Methods section, page 4, please be more specific about where in the supplementary materials the cutoff points for NCV are listed. Which table(s)?

Ans: We added “see Tables 1-5 in the supplementary materials” after the sentence “the cut off points for NCV measures are listed in the supplementary materials”(Methods section, line 31, page 4).

2. Please indicate in the title of Table 3 whether the data in the table are from univariate or multivariate analysis.

Ans: We revised the title of Table 3 as “The association between multiple factors and cognitive impairment in T1DM patients from multivariate analysis” in Results section, page 8.

Anna Shalimova (Reviewer 3):

1. According to the description of healthy controls, ‘… as persons like, they can have biochemical examination of blood such as serum lipids, hepatic and renal function, and fasting glucose, also including tumor markers, thyroid function and so on by the same detecting instruments as T1DM patients. Additionally, patients can have a CT or X-ray scan of any part of the body as indicated, even including MRI examinations…’. However, it does not confirm that all possible causes of cognitive impairment were excluded from this group, since individuals from the control group could receive certain diagnostic procedures or could not receive them.

In continuation of this, I agree with the opinion of reviewer Baqiyah Conway, according to which it would be more correct to additionally present logistic regression data for healthy individuals (even considering their young age).

Ans: The description of “…..as persons like, they can have biochemical examination of blood such as serum lipids, hepatic and renal function, and fasting glucose, also including tumor markers, thyroid function and so on by the same detecting instruments as T1DM patients. Additionally, patients can have a CT or X-ray scan of any part of the body as indicated, even including MRI examinations…” provides detailed descriptions of the healthy examination center, according to the suggestions from Baqiyah Conway to provide more information about the healthy examination center.

However, for healthy controls, we used standard diagnostic procedure to exclude as many causes of cognitive impairment as possible. Therefore, we added “For each healthy control included in the study, a standard diagnostic procedure was given. This procedure includes biochemical blood examinations such as serum lipids, hepatic and renal function, glucose tests, tumor markers, and
thyroid function as well as cranial CT scan and detailed history inquiry to exclude those with hypothyroidism, DM, tumor, hepatic and renal diseases, neurological illness, or peripheral neuropathy.” in Methods section, line 15-19, page 4.

We carried out a logistic regression analysis for healthy individuals including potential confounders: sex, age, educational levels, fasting glucose levels, serum uric acid concentrations, C peptide, creatinine ratio, and HAb1C. No confounder has been shown to be associated with cognitive impairment in healthy controls, which may be due to the small number of healthy controls. Therefore, we did not show the results in the manuscript.

2. Taking into account the fact that educational level is associated with cognitive impairments (and it is also confirmed in the results of this work, p = 0.029 in the table 3), I consider the group of people with educational level ≤6-year education' to be excluded from the study (especially given the fact that there are only 2 such patients in the main group and 1 in the control group). In my opinion, it is incorrect to include in one group of persons with such a different educational level. I also believe that it is necessary to conduct an additional comparison between patients of the main and control groups, taking into account their educational level (within '7 to ≤12-year education' and ' > 12-year education' groups). If such a comparison has already been made, should indicate whether there was a difference between the groups.

Ans: We deleted the persons with the educational level “≤6-year education” and conducted the comparison between patients of the main and control groups with their educational level within '7 to ≤12-year education' and ' > 12-year education' and similar results of a difference between the groups have been found. Therefore, we added “For educational level is associated with cognitive impairment and there were few patients in educational level ≤6-year education group, 3 patients in the group were excluded from the study.” in the Results section, line 13-14, page 6. New results have been shown in the Results section, including” The type 1 diabetes group scored lower on both the MMSE and MoCA compared with control subjects(28.4±1.7 vs. 29.1±1.0, P=0.005; 25.9±2.7 vs. 27.1±2.4, P=0.017, respectively). Based on the MoCA scores, there were 26 (38.2%) patients with cognitive impairment in T1DM group and 5 (10.6%) controls in healthy control group, with a significant difference between the two groups (P=0.001)” in line 16-19, page 6. “For MoCA scales, scores on attention and concentration, memory, language, visuospatial and executive abilities, and abstraction of T1DM patients were significantly lower than those of healthy controls.” in line 23, page 6 and line 1-2, page 7. Table 2 on page 7 and Table 3 on page 8 have been revised according to the new results.