Dear Editor-in-Chief

Thank you for your positive response and the constructive comments from the Reviewers. We followed closely the Reviewers' comments and the Journal's guidelines for authors in revising our manuscript. In the revised manuscript, we highlighted all amendatory material with red color, except for adjustments of style. Our point-by-point responses to the Reviewers' concerns and suggestions are listed below. We hope that our detailed responses are satisfactory.

REVIEWER 1

Q1. Title. The title reflects the main subject of the manuscript. It may be considered suitable. **Response**: We appreciate the Reviewer's comment.

Q2. Abstract. The abstract summarizes and reflects the work described in the manuscript. **Response**: We are grateful for the Reviewer's comment.

Q3. Key Words. Key words may not match with the words used in the title of the manuscript. So, some other suitable key words may be provided. **Response:** We revised the lists of keywords based on the Reviewer's suggestion.

Q4. Background. The manuscript adequately describes the background, present status and significance of the study. In addition, it may also include the prevalence of dementia in T2DM case in respect to age group. **Response**: We are grateful for the Reviewer's comment.

Q5. Methods. The manuscript does not describe the methods in adequate detail. The following information may be provided in this section. o Information regarding sample size determination is lacking. **Response**: Because a secondary database was used in our study, we did not perform sample size calculation. That being said, as long as the major finding (adding CHM was associated with a decrease in the risk of dementia in T2DM patients) is statistically

significant, the statistical power is should not be a concern. This is evidenced by a post hoc analysis that we performed in response to the Review's comment using the G*POWER 3.1 analytical software, which showed the power as 0.999.

Q5.1. The definition of case: diagnostic criteria of type 2 diabetes mellitus and dementia.

• 20–70 years of age group subject were included, but the subjects were classified into two groups only i.e. ≤ 50 years and >50 years. ≤ 50 years subjects may further be classified into different age groups to report the prevalence of dementia in T2DM patients.

Response: As suggested by the Reviewer, we reexamined the outcomes of interest after separating all enrollees into the following age groups: 20-40 years, 41-60 years, and over 60 years. Collectively, we noted that the results of the reanalysis, which took into account the new age stratifications, were essentially the same as those reported in the original analysis. CHM use was found to lower subsequent risk of dementia by 49% in T2DM persons (adjusted OR= 0.51; 95% CI= 0.48–0.53). Please refer to the revised content (Page 9), as well as updated Tables and Figure 2. We also made changes to other related contents in the revised manuscript.

Q5.2. When the cases were included in this study and up to what duration the data regarding cases were followed retrospectively in the National Health Insurance database.

Response: T2DM cases were recruited from the national claim data between 2001 and 2010, and all were followed up until the end of 2013. In response to the Reviewer's comment, we remarked this issue in the Method section.

Q5.3. The statement 'All enrolled subjects were followed until the earliest dementia incident, death, withdrawal, or the end of this study, whichever came first'. The direction of follow up of the subjects in the cohort is not clear. In case of case control study, the direction of follow up (case to exposure) may be retrospective.

Response: To avoid any unnecessary confusion, these statements were removed.

Q5.4. The time line in the given below sentences may be clarified to avoid confusion about the study. The present study focused on subjects 20–70 years of age with T2DM who had at least three outpatient diagnoses or a single inpatient visit of 250 made by the doctors

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who specialized in endocrinology between 2001 and 2010. The case of this study was defined as having the first diagnosis of dementia occurring during 2002–2013.

Response: While we excluded subjects who had suffered from dementia before the onset of T2DM, to meet causal inference, we also excluded those with a time interval (between the date of T2DM diagnosis and dementia) of less than one year. Therefore, cases of this study had their first diagnosis of dementia during 2002–2013. In response to the Reviewer's comment, we added the information on further exclusion and re-wrote the description.

Q5.5. Assessment of CHM exposure: the term dose-response is not suitable. As the classification was based on duration of CHM exposure not on the dose.

Response: As suggested by the Reviewer's comments, this term has been replaced with the "exposure–response relationship" throughout the paper to avoid any misunderstandings.

Q5.6. The criteria for classifying of the subjects on income may be given.

Response: As requested by the Reviewer, we briefly delineated this point.

Q6. Results The outcomes of the study may be modified as suggested in the methods section. Average time period for development of dementia in T2DM may also be reported.

Response: We carefully modified the paragraphs based on the Reviewer's comments. Additionally, we provided additional information regarding average time period for development of dementia in the two groups.

Q7. Discussion. The manuscript interprets the findings adequately and appropriately. the following key points need concise, clear and logical explanation. Specifically, for those who received CHM treatment for more than two years, the risk of dementia would be reduced by nearly 80%. The integration of CHM would reduce the chance of dementia by nearly 50%. How are these conclusions drawn?

Response: As suggested by the Reviewer, we amended the related sentences in the main document, indicating the conclusions were drawn on the basis of multi-variate analysis.

Q8. Illustrations and tables. The figures, diagrams, and tables are of sufficient good quality and appropriately illustrative, with labeling of figures using arrows, asterisks, etc, and the legends are adequate and accurately reflective of the images/illustrations shown.

Response: We appreciate the Reviewer's comment.

Q9. Biostatistics. The manuscript meets the requirements of biostatistics.

Response: We thank the Reviewer for the approval.

Q10. References. The manuscript appropriately cites the latest, important and authoritative references in the Introduction and Discussion sections.

Response: We appreciate the Reviewer's comment.

Q11. Quality of manuscript organization and presentation. The manuscript is well, concisely and coherently organized and presented. The style, language and grammar need improvement.

Response: The manuscript has been carefully edited for spelling and grammar by a professional editor who is a native English speaker and member of the American Medical Writers Association, as well as the author of nearly 200 English-language refereed articles.

Q12. Ethics statements. The manuscript meets the requirements of ethics.

Response: We are grateful for the Reviewer's comment.

REVIEWER 2

Q1. Please consider the following comments: 1. Please present a concise and self-explanatory tiltle conveying the most important findings of this study. Suggestion: "Reduced risk of dementia in patients with type 2 diabetes mellitus using Chinese herbal medicine: a nested case-control study" **Response:** We concur with the Reviewer's concern and modified the title of manuscript. Please refer to the Title shown in Page 1.

Q2. A graphical abstract that will visually summarize the main findings of the manuscript is highly recommended.

Response: We add the graphic abstract as suggested by the Reviewer but are not sure it

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fits the journal's format.

Q3. Abstract: I would like the authors to make as much effort for this section as for the rest of the manuscript. Please present the abstract in 200 words (preferably 200–220 words, max. 250) according to the guidelines of the journal, focusing on proportionally presenting the background, methods, results, and conclusion (without the headings of subsections). The background should include the general background (one to two sentences), the specific background (two to three sentences), and "the current issue addressed to this study" (one sentence), leading to the objectives. The methods should clarify the authors' approach, such as study design and variables, to solving the problem and/or making progress on the problem. The results should close with a single sentence putting the results in a more general context. The conclusion should open with one sentence describing the main result using such words as "Here we show", which should be followed by statements such as the potential and the advance this study has provided in the field, and finally a broader perspective (two to three sentences) readily comprehensible to a scientist in any discipline.

Response: After carefully reviewing earlier literature [1], and the Guidelines for authors (https://www.wjgnet.com/bpg/GerInfo/200), we rewrote the related segments in the Abstract and reduce the word count to 221 as suggested.

Q4. Keywords: Please list as many keywords as allowed by the journal and choose them from Medical Subject Headings (MeSH) and use as many as possible in the title and in the first two sentences of the abstract.

Response: We updated the list of keywords. There are five keywords covered, including type 2 diabetes mellitus, dementia, Chinese herbal medicine, nested case-control study, and odds ratio.

Q5. Introduction: The authors need to fully expand this section with several paragraphs made up of about 1000 words, introducing information on the main constructs of this protocol, which should be understood by a reader in any discipline, and making it persuasive enough to put forward the main purpose of the current research the authors have conducted and the specific purpose the authors have intended by this protocol. I

would like to encourage the authors to present the introduction starting with the general background, proceeding to the specific background, and finally the current issue addressed to this study, leading to the objectives. Those main structures should be organized in a logical and cohesive manner. In this regard, the following works, but not limited to, may enhance the value of this manuscript

Response: We appreciate the Reviewer's valuable comments. We made an effort to address these concerns in the Introduction. The first paragraph illustrates the current epidemiological reports regarding T2DM and the corresponding economic burdens triggered by T2DM. The second paragraph displays the links between T2DM and subsequent dementia incidents from a molecular perspective, and further highlights the consequences, after dementia onset, for T2DM subjects. This, in a nutshell, is the reason that implementation of effective disease management in improving clinical manifestations of T2DM should be stressed.

In view of a growing body of evidence manifesting that abnormal inflammatory responses may be involved in the pathogenesis of T2DM and dementia [2, 3], use of CHM may, therefore, be a useful approach to prevent or delay onset of dementia among such groups. To our knowledge, no study has been done to explore the long-term effect of CHM use in reducing the risk of dementia among T2DM patients. These research gaps have driven the implementation of our study. We believe the revisions are in accordance with the rules of funnel writing style.

Q6. Methods: I recommend citing more references to ensure the reliability and integrity of the evidence in the study design the authors built and the methodology they have decided to apply.

Response: In accordance with the Reviewer's suggestion, we deliberately rewrote the Methods section and cited more references.

Q7. Results: Please refrain from describing statistical values in the body of the text; tables should be used instead. I recommend the authors present figures in color. I suggest closing this section with a paragraph that puts the results into a more general context.

Response: We endeavor to refrain from describing statistical values in the Results section based on the Reviewer's suggestion and modified the closing paragraph to put the results

into a more general context.

Q8. Discussion: The discussion section lacks a clear and structured organization. I would like the authors to begin this section with an introduction and then provide a summary of the previous section. Then, I expect the authors to develop arguments clarifying the potential of this study as an extension of the previous work, the implication of the findings, how this study could facilitate future research, the ultimate goal, the challenge, the knowledge and technology necessary to achieve this goal, the statement about this field in general, and finally the importance of this line of research. It is particularly important to present its limits, its merits, and the potential translation of this study into clinical practice.

Response: We appreciate the Reviewer's comment, and we revise the Discussion section to closely meet the requirement as requested. First, we briefly highlighted the crosswalk between diabetes and dementia and then summarized the main findings of our study. Afterwards, we incorporated findings from previous research to describe those commonly prescribed herbal products that are reported to probably reduce dementia risk. We believe this could pave the way for a more detailed exploration for future pharmacological survey. Finally, we remarked on the potential limitations of this study in generalizing our findings to other patients in other nations.

Q9. Conclusion: I believe that presenting this section with 150–200 words would benefit from a single paragraph that presents some thoughtful and in-depth considerations by the authors as experts in order to convey the main message. The authors should make an effort to explain the theoretical implications as well as the translational application of their research. In order to understand the significance of this field, I believe it would be necessary to discuss theoretical and methodological avenues in need of refinement as well as future research directions.

Response: We rewrote the Conclusion section to closely meet the requirement suggested by the Reviewer.

Q10. References: Please cite more references. An original article like this typically cites 60–70 references. Overall, the manuscript contains two figures, three tables, and 39 references. I believe that the manuscript has merits in its rigorous methodology, which

enhances the validity and reliability of the findings. The study used a nested case-control design, which allowed for a more efficient and cost-effective way of investigating the association between Chinese herbal medicine and dementia risk. The study also used strict criteria for selecting the participants and controlling for potential confounding factors. Additionally, the study provides valuable insights into the potential benefits and risks of using Chinese herbal medicine for patients with type 2 diabetes and its impact on dementia risk. The findings of this study have important implications for healthcare providers and patients with diabetes who are considering using Chinese herbal medicine.

Response: As suggested by the Reviewer, we carefully reviewed the contents regarding the Methods and Discussion sections, and we strived to incorporate several references to strengthen the implications of this study. Please refer to the updated References list.

1. Li PI, Guo HR: **Long-term quality-of-care score for predicting the occurrence of acute myocardial infarction in patients with type 2 diabetes mellitus**. *World J Diabetes* 2023, **14**(7):1091–1102.

2. Cholerton B, Baker LD, Montine TJ, Craft S: **Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach**. *Diabetes spectrum : a publication of the American Diabetes Association* 2016, **29**(4):210–219.

3. Saedi E, Gheini MR, Faiz F, Arami MA: **Diabetes mellitus and cognitive impairments**. *World J Diabetes* 2016, **7**(17):412–422.