Peer Review Comments and Author Responses

Reviewer 1

1. *I recommend the use of PRISMA guidelines to standardize the headings and subheadings in the text.*

Thank you so much, I took PRISMA as guidance to my writing.

2. *I would recommend rewriting the introduction section. Starting with the actual information (use of statins, development of a new onset of type 2 diabetes, lack of knowledge on the relationship between statins and the incidence of type 2 diabetes in these patients) …*

Appreciated, I spent long time to write this section!

This included: definition of diabetes, incidence, timelines of statin initiation, indication, actions, adverse effects, what reported by studies? Clear and unclear, controversy, lack of knowledge, then aims and objective

3. *The selection of terms (keywords and MeSh terms) is not clear; please clarify.*

While MeSH searching is not always essential, it can be beneficial if my keyword search yields an overwhelming number of irrelevant results. By using MeSH terms, I can refine my search and retrieve more relevant articles. It's particularly helpful when dealing with complex topics or when traditional keyword searches are too broad. So, while not always necessary, MeSH searching can be a valuable tool in certain situations to improve the precision of my literature search.

4. *Incidence? Prevalence? Please, I recommend improving this sentence, it is not clear as it is stated.*

Thanks! I removed it. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease, with rapidly growing incidence. The International Diabetes Federation Diabetes Atlas reported a 537 million adults aged 20 to 79 years had diabetes worldwide in 2021, and the number is estimated to rise to 783 million by 2045 (International Diabetes Federation, 2021).

5. *First time mentioning this abbreviation, please state it completely before the abbreviation.*

I strongly agree! Thank you

6. *It is not clear the connection between this information and the systematic review Some sentences are not clear, and the connection between the information is lacking. Remove this.*

Very appreciated! I considered your observations.

7. *May I ask how statin improved lifestyle (mechanics of action) after cardiovascular events? This sentence is not clear, please clarify.*

I mean quality of life if use for primary or/and secondary prevention of CVD and atherosclerosis. **Li et al**. (2018) found strong clinical evidence supporting the efficacy of statins in reducing all-cause mortality and CV events in patients at risk of CVDs. I deleted the confusing words.

8. *First time FBG is used in the text. Please add the complete words before the abbreviation.*

Thank you! Done!

9. *I recommend to add the reference for his statement here.*

I wrote the introduction with references.

10. *It is not clear what the main objective of this manuscript is. I would recommend stating clearly the primary and secondary objectives in the rationale section.*

Great comment! Thank you once again! I wrote the end of my introduction as follows: Studies demonstrated that atorvastatin did not worsen insulin sensitivity in patients with diabetes, whereas one study suggested that patients treated with atorvastatin may be at a lower risk of developing NOT2DM (Angelidi et al., 2018). Research indicates that statin use in patients with concomitant risk factors for diabetes is associated with NOT2DM, although the precise mechanisms behind this association remain unclear (Hadjiphilippou & Ray, 2019). However, research on statin therapy has yielded conflicting findings regarding the association between statin use and the risk for incident NOT2DM. Questions regarding their adverse effects and beneficiaries are controversial and have remained unresolved. Therefore, extensive studies are needed to elucidate both the association between NOT2DM, statin use and the underlying mechanisms (Park et al., 2014). These observations prompted me to undertake a systematic review aimed at examining the literature relating to statins use and their association with the development of NOT2DM. The primary objectives were to assess and explore: (1) the potential association between statins use and the development of NOT2DM; (2) the magnitude, extent, and incidents of new onset diabetes due to statin use; and the secondary objective was (1) to explore the underlying mechanism(s).

11. *Why only these 2 terms were included in the literature review?*

I added 3 terms instead of 2 as follows:

Two authors Musa Basheer Mansour and Sara Elsheikh Ahmedana (MBM and SEA) independently performed a comprehensive literature search for relevant systematic reviews of studies reporting the data on statin use and incidence of NOT2DM and the possible underlying mechanism. We applied the Boolean operators “AND” and “OR,”

12. I did not find “statin use” or “incidence of NOT2DM” as MeSH terms.

Me too!

While MeSH searching is not always essential, it can be beneficial if my keyword search yields an overwhelming number of irrelevant results. By using MeSH terms, I can refine my search and retrieve more relevant articles. It's particularly helpful when dealing with complex topics or when traditional keyword searches are too broad. So, while not always necessary, MeSH searching can be a valuable tool in certain situations to improve the precision of my literature search.

13. *I suggest avoid the use of “/ “ Avoid the use of “/ “*

Corrected and avoided.

14. *This paragraph is not suitable for methods. If you want to justify why the article was not included, probably you should add it in results. But not in methods.*

I agree. I removed it.

15. *In the text, it is unclear if observational studies were included or excluded in the analysis. However, in the tables, I understood all the articles included were population-based longitudinal studies (prospective or retrospectives).*

Only 7 observational studies were included in this review. I re-wrote the design and refine my tables.

16. *The study design is not clear in the table one (I was expecting all information being extracted from randomized clinical trials because the authors described that observational studies were excluded. But it looks like the data come from population base studies. (Observational studies)*

Only 7 observational studies were included in this review. I wrote the design and I refined my tables.

17. *It is not clear what the study design is for each study.*

I wrote the design of each one.

18. *The figure is not adequate, arrows are out of place.*

Managed.

19. *I understood you did not include this study in the systematic review because it is an observational study. Why it is described here?*

Managed, only 7 observational studies were included in this review.

20. *It is not clear the main outcome of each study.*

I wrote the outcomes of each study.

21. *The results did not report forest plots, publication bias, or risk of bias assessment. There was no assessment of heterogeneity. The statistical method to find the pooled effect is not described.*

Forest plots' this graphical representation commonly used in meta-analyses to display the results of multiple studies. I used simple tables and figures shows confidence interval, odd ratios, hazard ratios and the average of the 7 studies.

22. *I was expecting the forest plot and a table with confidence interval and weight for each study.*

Forest plots' this graphical representation commonly used in meta-analyses to display the results of multiple studies.

23. *The odds ratio and hazard ratio were interpreted as "risk," which is not necessarily adequate in this case.*

Thank you for your observation! We are looking for association between statin use and NOT2DM. Confidence intervals are one of the most useful tools in epidemiological studies. Both the OR and RR (Hazard ratio) have confidence intervals as a measure of uncertainty. The included studies were 7 observational articles in this review.

24. *The text flow and formatting would require improvement.*

Appreciated! I considered this in my writing.

25. *Why this study was included? I understood that development of NOT2DM was not the outcome in the study. It is unclear why the manuscript published by Anyanwagu et al. (2017) was included in this analysis. Please clarify.*

The participants with known T2DM on statin were not included therefore, I removed this study by Anyanwagu et al. (2017) from the review, previously 8 studies were included in this review, now, they were 7 studies.

26. *It is difficult to assess the quality of the discussion because the methods and results are unclear and require improvement.*

Thank you so much! Considered!

Reviewer 2

27. *The authors describe through evidence synthesis an association between the use of statin and new onset type 2 diabetes. While the manuscript is informative in respect to background related to both variables, statin and diabetes, it can be improved for clarity, structure, and managing of density of information.*

Overall, the manuscript provides interesting information that can be useful for future research, however, it can be improved for clarify.

28. *General suggestions*

Data reporting: Data were reported median without (IQR) and means without SD's. Please use appropriate descriptive statistics i.e. mean (SD) or median (IQR), depending on data, also to two decimal places. For example, where "average" in HR table 5 refers to means, please specify. Using "mean" and "average" interchangeably may mislead the reader.

Great point,

Yes, you are correct! I used to 'mean' instead of 'means' or 'average.' I removed the right column of tables 4 and 5 to avoid any confusion for the reader. I agree that the removed column requires the interquartile range (IQR) for the upper and lower limits of the confidence interval (CI), which isn't necessary here. I corrected table 5, adjusting the average of HR."

29. *General suggestions*

The authors describe an FDA warning early 2012 and conduct their review from early 2012 as well. Extending the review period to include earlier evidence may provide a broader understanding and capture data lead to the FDA determination for this warning.

Thank you so much!

I wrote this again, it was happened in US FDA (Feb 2012) and subsequently in China FDA (Nov.2012), Both reported that as demonstrated by (Li, 2018).

Reviewer 3

30. *General suggestions*

The keywords used for the data search are missing. Please provide all keywords to ensure manuscript's reproducibility.

Appreciated!

I used;' MeSH' and I search for keywords

31. *Key points: Improve structure and order.*

Done.

32. *Key points: Cleary define objective, statistical methods used, and inclusion criteria*.

Thank you, I wrote it again!

33. *Consider further elaborating on the impact of confounders the discussion section; reference previous research that showed similar and different findings and draw conclusions accordingly; indicate implication on clinical practice cautiously; carefully address the impact of limitations on the interpretation of the findings and conclusions made.*

Potential confounding variables (age, BMI, lifestyle factors) appropriately addressed in analysis Confounders and pre-existing risk factors such as blood pressure, age, obesity, high total cholesterol level, gender, comorbidities, smoking, alcohol consumption, poor exercising and ethnicity augmented the risk of T2DM (Sattar et al., 2014; Waters et al., 2011; Waters et al., 2013). Great points! Already considered!

34. *Title*

Consider restructuring the title to improve clarity e.g., use one colon instead of two

True! I considered this.

35. *Abstract*

Abbreviations: The abstract has few abbreviations that were introduced but not used. Minimize unnecessary abbreviations in the abstract. Also make sure to define all abbreviations in the manuscript body as well. Consider limiting abbreviations that are not used frequently (at least three times) in the manuscript.

Great! Done.

36. *Abstract*

Methods and Results: Please clearly specify the objective of the review. The reader should be able to understand the aim of the study clearly without the need to read the methods section. For instance, if the aim to evaluate association, specify whether you're assessing risk factors, incidence rates etc.

My understanding aims are general statement, the focus of the study based on my title. While the objectives are the statement of intent - what I hope to achieve by the end of the research (the action(s) I will take in order to achieve the aims.

Aims and Objectives: to undertake a systematic review aimed at examining the literature relating to statins use and their association with the development of diabetes. The primary objectives were to assess and explore: (1) the potential association between statins use and the development of new onset diabetes; (2) the magnitude, extent, and incidents of new onset diabetes due to statin use; and the secondary objective was to explore the underlying mechanism(s).

37. *Introduction*

Consider providing a concise introduction that provides focused information related to the research question without digressions into broader topics.

Great comment! Thank you once again!

I think the introduction for this topic is challenging to us because many research were published about statin and NOT2DM. I tried to write it briefly as follows:

Diabetes definition, incidence, cause. Statin timelines, action, its uses, adverse effects, what already known, controversy, gaps, then my end of the and justification

I wrote the end of my introduction as follows: Studies demonstrated that atorvastatin did not worsen insulin sensitivity in patients with diabetes, whereas one study suggested that patients treated with atorvastatin may be at a lower risk of developing NOT2DM (Angelidi et al., 2018). Research indicates that statin use in patients with concomitant risk factors for diabetes is associated with NOT2DM, although the precise mechanisms behind this association remain unclear (Hadjiphilippou & Ray, 2019). However, research on statin therapy has yielded conflicting findings regarding the association between statin use and the risk for incident NOT2DM. Questions regarding their adverse effects and beneficiaries are controversial and have remained unresolved. Therefore, extensive studies are needed to elucidate both the association between NOT2DM, statin use and the underlying mechanisms (Park et al., 2014). These observations prompted me to undertake a systematic review aimed at examining the literature relating to statins use and their association with the development of NOT2DM. The primary objectives were to assess and explore: (1) the potential association between statins use and the development of NOT2DM; (2) the magnitude, extent, and incidents of new onset diabetes due to statin use; and the secondary objective was (1) to explore the underlying mechanism(s).

38. *Introduction*

When citing previous publications, please ensure presenting findings accurately reflecting the investigators evidence and conclusion. For example, the statement "Studies showed statin use in patients with concomitant risk factors for diabetes was associated with NOT2DM, but the mechanisms are unclear (Park et al., 2014)" should attribute to a single study instead of studies (a review remains a single study). A clearer representation would be "Park et al suggest a possible association between statin use and incident diabetes in at-risk patients, noting unclear mechanism."

Great! I considered these remarks.

39. *Introduction*

The statement "(JUPITER) showed Rosuvastatin associated with a 27% expanded risk of NOT2DM than placebo" is not clear. The original article indicates 270/8,901cases of diabetes in the rosuvastatin group, and 216/8,901 in the placebo group. Please provide additional information whether the data from the same original article or if you have made the calculations independently; please note that there few publications, including FDA's

statement that have reported varied increased risk from 25% to 28%. This inconsistency indicates possible miscalculations.

JUPITER trial demonstrated significant cardiovascular benefits with rosuvastatin therapy, it also highlighted the potential for statin use to modestly increase the risk of new-onset diabetes. In analysis limited to the 486 participants who developed diabetes during follow-up (270 on rosuvastatin vs. 216 on placebo group, P=0.01). Hazard ratio (95%CI) for incident diabetes associated with rosuvastatin as compared to control was 1.26 (1.02–1.56) for those aged 50 to 69 years and 1.25 (0.90–1.74) for those aged 70 and over, Specifically, the trial reported a 27% increase in physician-reported diabetes among participants receiving rosuvastatin compared to those receiving placebo (p=0.01). However, it's important to note that the absolute risk of developing diabetes with statin therapy was relatively low, with approximately 3% of participants in the rosuvastatin group and 2.4% in the placebo group developing diabetes over the trial period (Ridker et al., 2012) (*Carter, A. A. et al 2013*).

40. *Methods*

In section 2.3, it was suggested that observational and clinical designs were included "Articles written for academic and clinical practice and relevant to the title and research question included observational studies, randomized clinical trials and meta-analyses." However, this is contradicting section 2.5 where the following was stated "This systematic review had a specific focus on randomized controlled trials (RCTs). As explained by Harrison et al. (2016) RCTs contain the strongest and most reliable evidence to apply when analysing the impact of interventions such as drug treatment." Please determine the study design included and reason it.

Thank you, I refined it. Effect size is not included.

The 2 reviewers [MBM and SEA] independently assessed qualities of the extracted studies and summarized data of the selected studies in tabulated forms for outcomes of interest and performed methodological and quality assessments based on review question, citations, country of the study, aim, population characteristics, design, setting, sample size, sample technique, data source, measures, analysis, confounder variable and key observations for systematic review. Reviewer results were compared, and we discussed, resolved disagreements, and discrepancies in data extraction. The relevant authors might be contacted as needed for more data obtaining, missing or/and ambiguous data.

41. *Methods*

It is not clear why authors used HR and OR for ES. Authors should elaborate in the statistical methods section.

I wrote it in detail in result section included CI, HR(RR), and OR in tables and figures.

42. *Results*

Please use PRISMA flowchart for clarity or similar flowchart structure.

Great point!

Done

43. *Results*

In the result section, it was reported "Internet searches generated 13 additional studies." It is not clear how these searched were conducted. Please provide more details on the methods used to conduct the search and identify the studies.

Thanks, I correct it.

We generated 13 additional studies from other sources such as universities sites, Academia, research gate.

44. *Results*

"Non-randomized studies were excluded as they can often allocate an intervention's impact in a non-random way." This statement is redundant. It was suggested that non-RCT do meet the inclusion criteria. It is enough to mention in the results section the reason for exclusion, which is non-RCT. "However, the systematic reviews offered valuable information that aided the identification of areas with adequate evidence supporting or objecting statins as an intervention and places where more evidence is required" This statement contradict previous statement about included study design. Please specify clearly the included study design(s).

Thank you so much! I agree! Great point and suggestion!

I refined it. The 2 authors demonstrated in (Figure 1) a total of 66 studies were identified in the initial search. 53 studies collected from PubMed, Wiley, Google Scholar, Science Direct, and we generated 13 additional studies from other sources such as universities sites, Academia, and research gate. After removing duplicates, a total of 61 studies remained. These were then screened and a total of 40 studies that availed only abstracts, RCTs and non-RCTs were excluded. Twenty-one full texts remained, and 14 were excluded for including participants younger than 18 years. Finally, 7 studies were included in the synthesis.

Reviewer 4

45. *First, I found writing issues (Punctuation, incomplete sentences, wordy sentences, and grammar issues) Please review the article again. Use the same font and format the article.*

Managed.

46. *INTRODUCTION*

1.1 Background: Type 2 diabetes mellitus (T2DM) increases worldwide add reference.

Type 2 diabetes mellitus (T2DM) is a chronic endocrine and metabolic disease, with rapidly growing incidence and prevalence. The International Diabetes Federation Diabetes Atlas reported a 537 million adults aged 20 to 79 years had diabetes worldwide in 2021, and the number is estimated to rise to 783 million by 2045 (International Diabetes Federation, 2021).

46. *Study Selection/Eligibility Criteria: Articles that their participants are nondiabetic adults aged >18 years using statin. We excluded studies with participants less than 18 years*

I think you meant more and equal to 18 years old diabetic individuals, people with T1DM??

Be more specific when you write diabetic individuals? T1DM needs also the full term.

Included studies were required to meet the following criteria: (1) Nondiabetic adults (aged ≥18 years) using statin; (2) Assessing and measuring the risk and or incidence of NOT2DM; and (3) Only observational studies**.** We excluded studies involving, pregnant populations, diabetic participants, nondiabetic participants (aged <18 years) using statin, abstracts, conference, posters, presentations and commentaries or editorials.

47. *Association between Statins Therapy and NOT2DM Development: The included studies reported a significant association between statin and NOT2DM even though the conditions contributing to NOT2DM risk differed. For instance, Lee et al. (2018) found that statin therapy raised NOT2D chances, but risk appeared more common among normotensive participants and hypertensive females. Lee et al. (2018) described NOT2DM as a sophisticated disease with several risk factors such as high levels of FBG and triglyceride, BMI, and hypertension. Add reference. These risk factors were proven in RCTs that involved atorvastatin. Add reference with hypertension, however, several clustering elements beyond statins contribute to the development of NOT2DM. Statin had no connection to NOT2DM among hypertensive men. Add reference.*

Lee et al. (2018) demonstrated these risk factors were proven in RCTs that involved atorvastatin. Lee et al. (2018) found with hypertension, however, several clustering elements beyond statins contribute to the development of NOT2DM. Lee et al. (2018) reported statin had no connection to NOT2DM among hypertensive men.

48. *When you mention older patients, please define what you consider old?*

The relationship was more significant among **older** patients. I mean over the age of 40 years.

49. *Possible Mechanisms in Statins Use and Development of NOT2DM:*

Patients on statin therapy with a BMI below 24 were identified to face higher diabetes risks than individuals with 28 and beyond. Although the findings were like those of research on postmenopausal females, Li et al. (2018) recommended further investigations to examine the influence of weight on statin related NOT2DM.

The study found that patients with a BMI <24 had a higher risk (HR: 1.65) for developing NOT2D) compared to those with a BMI >28 or higher (HR: 1.44). Similar results were observed in a study involving postmenopausal women, although the reasons behind these findings remain unclear. Further research is needed to confirm the impact of weight on statin related NOT2D. Nevertheless, these findings suggest the importance of considering statin prescription carefully, especially for younger patients with a normal BMI.

50. Limitations. *Firstly, this SR includes articles published in the English language that may exclude some articles Secondly, the number of articles is relatively small because are free.*

Grammar correction are…

51. *Can you provide the exact number of participants included in your systematic review?*

    Of the 2,567,888 adult patients, 861,925 nondiabetic patients on statin use and 1,705,963 were diabetic on statin or non-statin users.

52. *Did you consider that that some of the articles accessed may contain the same data and this may bias the result?*

No, the 2 reviewers independently selected the articles according to eligibility criteria. We search for evidence of incidence of type 2 diabetes from the selected studies.

53. *I would consider add strengths of the study too.*

    Strength

    We followed a predefined protocol to minimize bias in study selection, data extraction, and analysis. Furthermore, we included studies that based on a transparent and reproducible process under comprehensive rigorous search strategies to identify all relevant studies to the risk of selection bias. Additionally, we addressed critical appraisal to help the readers to evaluate the reliability and validity of the evidence of this review and consider the strength of the overall conclusions.

54. *CONCLUSIONS AND RECOMMENDATIONS*

Conclusion

The systematic review found a significant level of risks of statin on NOT2DM incidence. We have presented the most current research outlining possible mechanisms through which statins may cause. We can conclude that statins may cause NOT2DM, but the benefits of statins exceed the related risks, and its use remains one of the most important agents to treat individuals with dyslipidaemia and CVD. The use of statins should not be discouraged in anticipation of the risk of NOT2DM. And the balance between continuity and intermission of statins should be considered because discontinuity could be more harmful. Therefore, periodic follow-up and assessment of risks of NOT2DM in statins users is very helpful. In addition to that, clinicians should follow the guidelines when prescribing statins and must consider the advantages and disadvantages for patients below 50 years. Many treatment

plans for instance, statin dose reduction, switching from one type of statins to another or switching to non-statin hypolipidemic agents, may be beneficial.

Add references where applicable.

Thank you so much! My understanding, conclusion requires no reference, but I added it to the reference.

Cleveland Clinic Journal of Medicine. (2021). Title of the article. Cleveland Clinic Journal of Medicine, 88(7), 381-387. https://doi.org/10.3949/ccjm.88a.20165

55. *Tables and figures:*

All abbreviations used in tables and figures should be defined in the table note or figure caption, respectively, even though the abbreviations will also be defined in the text if they are used there.

I agree! Appreciated and added.

56. *Maybe the tools could be itemized in order to make it clear, maintaining the conceptual explanation and implementation.*

Two different tools were applied to appraise the studies for review. The Critical Appraisal Skills Programme. (2018). CASP (Qualitative) Checklist. JBI Critical Appraisal Checklist for Qualitative Research Lockwood, C., Munn, Z., & Porritt, K. (2015).

Critical Appraisal Skills Programme. (2018). CASP (Qualitative) Checklist. Retrieved from https://casp-uk.net/casp-tools-checklists/

Lockwood, C., Munn, Z., & Porritt, K. (2015). Qualitative research synthesis: Methodological guidance for systematic reviewers utilizing meta-aggregation. International Journal of Evidence-Based Healthcare, 13(3), 179–187.

57. *I believe that use "subjects" fits better.*

Subjects.

58. *I believe the use expression could be more adequate, for example ">18 years old".*

Subjects who are >18 years old.

59. *I believe it would be interesting to explain how it was done, using which method/ too.*

Managed.