Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTERS TO THE EDITOR

Authors' response: Meta-analysis of statin and outcomes of coronavirus disease 2019 (COVID-19)

Dear Editor,

We would like to thank the authors of the recent letter "Meta-analysis of statin and outcomes of coronavirus 1 disease 2019 (COVID-19): reconsideration is needed" for sharing their concerns after reading our manuscript [1,2]. Their careful reading gives us the opportunity to clarify several aspects of the article.

First, regarding Tandaju et al. [1] concerns of our previous publication [3] in the *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* journal with the same topics with our latest publication in this journal, we feel that it still reasonable to update the meta-analysis regarding statin and outcomes from COVID-19. Several reasons can be proposed to justify our action in updating the meta-analysis. Tandaju et al. [1] have mentioned that the search date between the first and second publications was only 3 months, however in our opinion, three months was already enough to perform an updated meta-analysis in the case of COVID-19. All the evidences and information regarding COVID-19 are highly dynamic where new evidences keep appearing each days because COVID-19 is a new disease so that rigorous researches were performed around the world. For example, during the early course of the pandemic in March 2020, chloroquine phosphate and hydroxychloroquine sulfate were advocated as the therapeutic agents for COVID-19 patients, and the Food and Drug Administration (FDA) have issued their emergency use authorization (EUA) [4]. However, one months later, the FDA issued a caution against its use and finally on June 2020, the FDA rescinded its EUA for hydroxychloroquine from the Strategic National Stockpile [4]. In the cases of our articles, the first article only include 8 studies [3], while our latest article already involved 35 studies [2]. All of these show how dynamic the evidences regarding COVID-19 are and three months is an enough time to conduct another meta-analysis. Our first article [3] did not involve the risk of COVID-19 outcome because, at that time, the number of studies that contain information regarding the risk of COVID-19 outcome was still minimal. Moreover, at that time, we were still learning on how to perform meta-regression analysis, therefore we couldn't include meta-regression in our first article. Our first article in *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* [3] was submitted as short communication to give preliminary results of evidence, whereas our latest article in this journal [2] was submitted as full text with higher number of included studies (different data), more outcomes of interest (different question), and also include meta-regression analysis (different methodological approach), making them two different articles and cannot be categorized as text-recycling nor self-plagiarism. To be noted, our latest article [2] is still in language editing process and hasn't undergone page proof process, therefore we surely will cite our previous article in the latest one.

Second, regarding the different databases in our search strategy, we think that two databases for our search strategy are already enough and still acceptable. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which we have used in our latest article, there is no minimum number in the search database used [5]. Even, the PRISMA checklist only mentioned "Present full electronic search strategy for at least one database …" [5]. In our latest article, we have used 2 different databases (PubMed and Europe PMC), which we believe already cover all potentially eligible articles.

Third, regarding Tandaju et al. [1] concern of inclusion of various study designs in article, we think that it is still methodologically valid and not prohibited by PRISMA guidelines to include various study designs in systematic review and meta-analysis. Inclusion of various study designs will results in the increment of heterogeneity and should be mentioned in the limitation of the study. To support our arguments, we provide the example of two recent highly citable meta-analysis (study by Sze S et al. [6] and Cevik M et al. [7]) in top-rank journals which combine various study designs in their analysis. Again, Tandaju et al. [1] did not comment on these papers. Moreover, in our latest article, we

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only combine observational studies (cohort and case−control) in the forest plot analysis and used random-effect models to overcome the inter-study variability and heterogeneity. If we found there are some randomized clinical trial to be included in our analysis, we surely will provide subgroup analysis for different study designs.

Fourth, we think that combining the "risk of COVID-19" outcome as composite poor outcomes, together with severity and mortality is still possible and will not affect the meta-analysis and meta-regression results. Even though studies with "risk of COVID-19" outcome have a higher number of participants when compared to the studies with "severity" and "mortality" outcomes, but as you can see in Figure 2 (forest plot analysis) of our latest article, the weight given for each of the included studies were almost the same (ranging from 1 to 2%) and no studies were given dominant weight in the analysis. That can be happened because we use random-effect models which not only consider the number of participants but also elaborate the standard error or variance in each of the included studies. In the subgroup analysis, each of the outcome of interest also showed a non-significant results, the same as overall results estimates when the three outcomes were combined, therefore inclusion of "risk of COVID-19" outcome will not affect the results from meta-analysis. Considering the "risk of COVID" outcome in our study which also include the number of control patients without COVID-19 and to reduce the confusion from the readers, we decided to only provide the data regarding total number of participants from each of the included studies in Table 1, including the one from Holman et al. [8] Moreover, regarding the inclusion of study by Huh et al. [9] and Vila-Corcoles et al. [10] in our study, we feel that there is no problem with that because the outcome of interest in our study were one of the followings: "risk of COVID-19" or "severe COVID-19" or "mortality from COVID-19" and there is no overinflated estimate in our study. Again, for their concerns regarding the inclusion of "risk of COVID-19" outcome studies with large sample size which they afraid will affect the meta-analysis results, we have already provided the rebuttals in above statements.

Fifth, Tandaju et al. [1] have mentioned that the numbers on Figure 1 and 'Results' section in our article do not add up. For Figure 1, there must be some error during uploading process of our manuscript which made the lines are disappeared and some text were missing. We will try to reupload Figure 1 during Page Proof process. For the number of studies in 'Results' section, we think that all calculations were already correct. Here is the full statement from our article "After evaluating 55 full-texts for eligibility, 10 full-text articles were excluded because they do not have the outcome of interest (risk of COVID-19, severe COVID-19, and mortality), 7 full-text articles were excluded because they do not have the control/comparison group, 3 full-text articles were excluded because the articles were not in English, and finally, 35 studies with a total of 11,930,583 sample sizes were included in the meta-analysis." If you calculate, 35 + 10 (do not have outcome of interest) + 7 (do not have comparison group) + 3 (were not in English) = 55 studies.

Sixth, for the "cardiovascular disease" in the meta-regression analysis, we think that "coronary heart disease", "heart failure", "arrhythmia" still belong to the same disease category which is "cardiovascular disease". Some of the authors have combined these disease into one category "cardiovascular disease", while others provide overall number of patients with "cardiovascular disease" and also listed the number of disease such as "coronary heart disease" and "heart failure" under that category [12,13]. Do Tandaju et al. [1] think that "coronary heart disease" and "heart failure" are not "cardiovascular disease"? If they say so, then under what categories do these disease belong into?

Seventh, we think that our latest article was already in line with PRISMA guidelines. You can check the PRISMA checklist and compare it to the content of our article. For the review protocol or registration number which does not exist in our study, we think that is still acceptable. Review protocol is not mandatory for meta-analysis study. PRISMA checklist itself only stated "Indicate if a review protocol exists …". They used the word "if" which shows it is not mandatory [5]. Moreover, several previously published meta-analysis with high citation index in Scopus Q1 indexed journals also do not have registration number [9,10]. For methodological checking, we think that the reviewers must also check on the methodology of the study before giving recommendations.

Finally, for the risk of bias, we have provided risk of bias assessment by using Newcastle Ottawa Scale (NOS) for observational studies. Moreover, it is not common to provide justification for each point of assessment in NOS because we think that each points of assessment in NOS was already clear enough if you look at the description or its manual book and by giving statements regarding justification for each points will make the manuscript become lengthy. Reviewers can also check the score given to each point of assessment to see if it matched or not. PRISMA guidelines only stated "Present data on risk of bias of each study …" [5] and there is no statement that we must also provide justification in the text for each points given, therefore by providing the methods for risk of bias assessment and the data of risk of bias assessment results are already enough. Previously published meta-analysis studies which use NOS for their risk of bias assessment [11] or which use other methods of assessment [6,7,9,10] also do not provide statements regarding justifications behind each points given.

We would like to express our gratitude to Tandaju et al. [1] for their concerns and their point of views regarding our article. We hope that our response in this letter can help in answering their concern from our article. We also would like to express our gratitude to the Editors for letting us to respond to Tandaju et al. [1] letter on our article. We hope that this authors' respond can give more insight into clear methodology about systematic review and meta-analysis.

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Declaration of competing interest

The authors declare no conflict of interest.

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