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## ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: A systematic review and meta-analysis of observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Mahamat-Saleh, Yahya; Fiolet, Thibault; Rebeaud, Mathieu Edouard; Mulot, Matthieu; Guihur, Anthony; El Fatouhi, Douae; Laouali, Nasser; Peiffer-Smadja, Nathan; Aune, Dagfinn; Severi, Gianluca</td>
</tr>
</tbody>
</table>

## VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Xu, Zhenghao Zhejiang Chinese Medical University, School of Basic Medical Science</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>03-Jul-2021</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

This is a systematic literature review and meta-analysis of observational studies to investigate the association between diabetes, hypertension, body mass index (BMI), or smoking with the risk of death in patients with COVID-19. Their results suggest that diabetes, hypertension, obesity, and smoking are major contributors to COVID-19 mortality accounting for nearly 30% of COVID-19 deaths. This is a very interesting and meaningful study. I only have some minor suggestions

1. As most systematic literature reviews and meta-analysis studies, three databases are needed. I suggest they add the Cochrane library (https://www.cochranelibrary.com/) as the third database.

2. “Our meta-analysis is, to the best of our knowledge, the first to estimate the proportion of COVID-19 death attributable to diabetes, hypertension, obesity and smoking” This may be true but not science. Please remove it.

3. Is there any difference between Asia, Europe, and America?

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Dwivedi, Alok Texas Tech University, Division of Biostatistics &amp; Epidemiology, Department of Biomedical Sciences</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVIEW RETURNED</td>
<td>08-Jul-2021</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

The authors have performed a systematic review and meta-analysis of observational studies to examine the association between diabetes (DM), hypertension (HTN), body mass index (BMI) or smoking with the risk of death in patients with COVID-19. A total of 186 studies were included in this study. Overall, it is a nice study summarizing the contributors to COVID-19 mortality.
The main strengths of this study are the large sample size with a large number of studies, subgroup analyses, and an exploration of a non-linear relationship between BMI and mortality. There are several concerns that need to be addressed to improve the quality of the manuscript:

1. The authors concluded that the consider factors (diabetes, hypertension, body mass index (BMI) or smoking) are the major contributors to COVID-19 mortality. However, a recent meta-analysis by Thakur et al, 2021 showed that chronic kidney disease, cardiovascular disease, and cardiovascular accident had the highest mortality related to COVID-19 while the other factors such as diabetes, hypertension, and obesity are the most common comorbidities for COVID-19 patients. I would strongly suggest to expanding discussion by considering Thakur et al study (Thakur, B., Dubey, P., Benitez, J. et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep 11, 8562 (2021). https://doi.org/10.1038/s41598-021-88130-w).

2. All the estimated associations had high heterogeneity. The range of association between diabetes and mortality was 1.28-2.47, 1.08-2.64 between hypertension and mortality, 0.97-2.50 between obesity and mortality, and 1.16-2.56 between smoker and mortality. If we consider no heterogeneity in the estimates then the associations between considered factors and COVID-19 mortality might change. It would be appropriate to make conclusions after exploring thoroughly heterogeneity in estimates and final conclusion should be based on estimates with low heterogeneity in estimates (I² <50%). One way is to produce estimates after removing outlier studies identified through funnel plots. If we remove studies not included in the funnel 95% confidence limits, what would be the association between each considered factor and mortality?

3. Since the authors have considered only four major factors associated with COVID-19 mortality, it would be difficult to conclude that these are the major contributors to COVID-19 mortality.

4. While exploring the non-linear relationship between BMI and COVID-19 mortality, the authors have used relative risk estimates reporting 5 unit increase or 1 SD increase or categorized BMI with different reference ranges across different studies. It is unclear that how different forms of BMI were included in the pooled analyses. Please expand the statistical analyses section for readers to understand the conversion of all estimates on the same format from different studies. Moreover, I do not see any studies reporting estimates for BMI>=50, however, the non-linear curve was drawn up to BMI 50.

5. Several studies were excluded in the sensitivity analysis. However, any rationale was not included in the footnotes of figures or tables.

6. In Table 1, the exposure category for smoking needs to be specified.

7. In Table 2 footnote, the authors mentioned: “within each cancer type”. Please correct it.
8. Some studies were based on the elderly population, subgroup analyses may be performed separately for elderly and non-elderly populations.
9. Most of the studies were based on hospitalized patients except for a few studies that were based on ICU admitted patients. Sensitivity analyses may be performed accordingly.
10. Although the authors have performed subgroup, influence, and sensitivity analyses, the discussion was not provided based on heterogeneous findings (such as geographical differences in the associations) and geographical differences in the treatments for managing COVID-19 (Dubey, P., Thakur, B., Reddy, S. et al. Current trends and geographical differences in therapeutic profile and outcomes of COVID-19 among pregnant women - a systematic review and meta-analysis. BMC Pregnancy Childbirth 21, 247 (2021). https://doi.org/10.1186/s12884-021-03685-w)

REVIEWER
Herbison, Peter
University of Otago, Preventive and Social Medicine

REVIEW RETURNED
09-Aug-2021

GENERAL COMMENTS
This study was a lot of work that was carefully done and reported well.

I have a couple of minor comments. While very good, there were a few places where the English might be improved. For example, some singular words that should be plural. And it is no surprise to get such high I squared values. There are many more included studies than a typical meta-analysis and I squared increases with the number of studies. Is it worth mentioning this in the discussion?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Zhenghao Xu, Zhejiang Chinese Medical University

Comments to the Author:

1. This is a systematic literature review and meta-analysis of observational studies to investigate the association between diabetes, hypertension, body mass index (BMI), or smoking with the risk of death in patients with COVID-19. Their results suggest that diabetes, hypertension, obesity, and smoking are major contributors to COVID-19 mortality accounting for nearly 30% of COVID-19 deaths. This is a very interesting and meaningful study. I only have some minor suggestions

Response: First of all, we would like to thank Prof. Zhenghao Xu for his careful and interesting comments and suggestions that allow us to improve the paper. We’ve taken into consideration each comment and suggestion, and the manuscript has been modified accordingly. We agree with this summary.

2. As most systematic literature reviews and meta-analysis studies, three databases are needed. I suggest they add the Cochrane library (https://secure-web.cisco.com/1h8slRik-P-toMATUvSJDH7zEYYyaN1FZNs5HB1Vab6NnDdfuFk-t4xGMVVXqL8cUPPPZ3Rdt9TQR5AJmkRhrBZxr37p55-
Response: Yes, indeed, we initially performed a literature search for relevant observational studies of diabetes, hypertension, BMI and smoking and COVID-19-related mortality using only the two major databases (PubMed and Embase). Since almost all observational studies/epidemiological studies were generally identified by the PubMed and Embase search, we thought that it was sufficient to perform the search on PubMed and Embase as we have done previously with other meta-analysis (Kvaskoff et al 2021, Hum Reprod Update).

However, as requested by the reviewer, we additionally conducted the search in Cochrane library using the same specific key terms.

We identified 2,111 publications from Cochrane library search. After removing duplicates among the PubMed, EMBASE, and Cochrane Library databases (n=1547), 564 publications were screened by reviewing titles, abstracts, and key terms related to diabetes, hypertension, obesity, smoking or COVID-19 death. All the 564 publications were not eligible because they were trial protocol, reviews, irrelevant exposure/outcome or because of insufficient data. Finally, no new articles were identified from Cochrane library database in addition to the previous search performed on PubMed and Embase databases.

As requested by the reviewer, we’ve have included the search in Cochrane library in the manuscript and re- phrased the sentence in Methods section on page 6 as follow:

“PubMed (MEDLINE), Cochrane library and Embase databases were searched to identify relevant articles published in English from December 2019 to 14th November 2020”

In addition, we re-phrased the sentences in Results section on page 9 as follow:

“A total of 6,007 records were identified in MEDLINE, Cochrane library and in EMBASE (Figure 1). A total of 4,665 publications were excluded after reading title and abstract or because of duplicates. Among 1,342 full-text articles retrieved, 994 were excluded as not meeting the inclusion criteria, leaving a total of 348 publications. Of these, 162 articles were not eligible because they lacked sufficient data, reported no risk estimate or irrelevant data, because they had identical populations or were retracted. Finally, a total of 186 observational studies were included in this meta-analysis”

We also added the following statement in the Abstract section on page 3.

“Relevant observational studies were identified by searches in the PubMed, Cochrane library and Embase databases through November 14, 2020”

Finally, we updated the flow-chart of study selection by including Cochrane library search (see Figure 1).

3. “Our meta-analysis is, to the best of our knowledge, the first to estimate the proportion of COVID-19 death attributable to diabetes, hypertension, obesity and smoking” This may be true but not science. Please remove it.

Response: As requested by the reviewer, we have deleted it.

4. Is there any difference between Asia, Europe, and America?
Response: Thank you very much. Indeed, we have conducted stratified analyses by geographic location to see if there is any difference across country where the research was conducted.

As previously mentioned in the Results section on page 10, we observed that the positive association between the four exposures and COVID-19 mortality persisted in subgroup analysis by geographic location. While heterogeneity within subgroup analysis was still present, there was no evidence of heterogeneity between subgroups.

Although, previous studies reported a geographical difference in the prevalence of diabetes, hypertension and obesity associated with mortality rates among COVID-19 patients (Thakur et al, 2021), we found no difference in findings between Asia, Europe, North America, South America, Australia and Africa. P-values for heterogeneity between regions with meta-regression analysis were 0.10, 0.33, 0.07 and 0.21 for diabetes, hypertension, BMI and smoking, respectively, suggesting no difference between subgroups.

Reviewer: 2

Dr. Alok Dwivedi, Texas Tech University

Comments to the Author:

1. The authors have performed a systematic review and meta-analysis of observational studies to examine the association between diabetes (DM), hypertension (HTN), body mass index (BMI) or smoking with the risk of death in patients with COVID-19. A total of 186 studies were included in this study. Overall, it is a nice study summarizing the contributors to COVID-19 mortality. The main strengths of this study are the large sample size with a large number of studies, subgroup analyses, and an exploration of a non-linear relationship between BMI and mortality. There are several concerns that need to be addressed to improve the quality of the manuscript:

Response: We would like again to thank Prof. Alok Dwivedi for their very constructive comments and suggestions, which have greatly helped to improve our manuscript. We agree with this summary.

2. The authors concluded that the consider factors (diabetes, hypertension, body mass index (BMI) or smoking) are the major contributors to COVID-19 mortality. However, a recent meta-analysis by Thakur et al, 2021 showed that chronic kidney disease, cardiovascular disease, and cardiovascular accident had the highest mortality related to COVID-19 while the other factors such as diabetes, hypertension, and obesity are the most common comorbidities for COVID-19 patients. I would strongly suggest to expanding discussion by considering Thakur et al study (Thakur, B., Dubey, P., Benitez, J. et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep 11, 8562 (2021). https://doi.org/10.1038/s41598-021-88130-w).

Response: As suggested, we have now re-phrased the conclusion part of this manuscript stating that diabetes, hypertension, obesity and smoking are the major contributors to COVID-19 mortality. The sentence now reads as follows:

“Our findings suggest that diabetes, hypertension, obesity and smoking were associated with higher COVID-19 mortality, contributing to nearly 30% of COVID-19 deaths”

Thank you to the Reviewer for suggesting this reference (Thakur, B et al 2021) pointing that chronic kidney disease, cardiovascular disease, and cardiovascular accident had the highest mortality related to COVID-19. In contrast, this paper was published after our meta-analysis was submitted.
Indeed, the systematic literature review and meta-analysis conducted by Thakur and colleagues (Thakur et al. 2021) included 120 studies with 125,446 patients showed that cerebrovascular accident (44%), chronic kidney or other renal diseases (44%), cardiovascular disease (40%) and lung disease (33%) patients had a higher COVID-19 mortality while the most prevalent comorbidities were diabetes (32%), hypertension (30%), obesity (27%), and cardiovascular disease (16%). The authors found that the mortality among those with underlying medical diseases was high in mostly elderly and predominantly male patients. In addition, they observed that COVID-19 mortality among all comorbidities was highly variable across geographic regions with the highest mortality observed in studies from Latin America and Europe. However, in our study, there were no evidence of heterogeneity in findings between Asia, Europe, North America, South America, Australia, and Africa.

As suggested by Prof. Alok Dwivedi, we have now considered this reference in the manuscript and added the following sentence in the Discussion on page 16.

“Although we found that diabetes, hypertension, BMI and smoking were associated with greater COVID-19 mortality, a recent meta-analysis suggested that mortality was more frequently observed in COVID-19 patients with cardiovascular disease, cerebrovascular accident, and chronic kidney disease (Thakur et al., 2021). The authors observed that COVID-19 mortality among all comorbidities was high in European and Latin American patients compared to the US patients. It is possible that geographical differences in therapeutic practice of COVID-19 such as the use of antibiotics, antivirals and others drugs may partly explain the greater COVID-19 death in some regions (Dubey, P et al. 2021), while there was no evidence of heterogeneity in findings across geographic location in our study. The review also suggested that COVID-19 mortality among those with underlying medical diseases was high in mostly elderly patients. However, we did not perform subgroup analysis by age because this information was lacking in most of the included studies”.

3. All the estimated associations had high heterogeneity. The range of association between diabetes and mortality was 1.28-2.47, 1.08-2.64 between hypertension and mortality, 0.97-2.50 between obesity and mortality, and 1.16-2.56 between smoker and mortality. If we consider no heterogeneity in the estimates then the associations between considered factors and COVID-19 mortality might change. It would be appropriate to make conclusions after exploring thoroughly heterogeneity in estimates and final conclusion should be based on estimates with low heterogeneity in estimates (I² <50%). One way is to produce estimates after removing outlier studies identified through funnel plots. If we remove studies not included in the funnel 95% confidence limits, what would be the association between each considered factor and mortality?

Response: Given this meta-analysis included more studies than a typical meta-analysis, I² and heterogeneity were high as they increase with the number of studies. It is important to note that there was no publication bias detected in our study, whereas study heterogeneity was high for all exposure and this persisted in all subgroup and influence analyses. However, the heterogeneity appeared to be driven to a larger extent by differences in the strength of the associations, than differences in the direction of the effect, as the vast majority of studies reported significant or nonsignificant positive associations between these exposures and increased mortality, and relatively few studies reported risk estimates in the direction of an inverse association.
We have already discussed this in the Discussion section on page 13.

Thank you to the reviewer for this comment suggesting exclusion of outlier studies identified through funnel plots. We have performed these analyses but this latter did not influence overall association and the heterogeneity still high even after exclusion of several studies. Therefore, we decided to not include these analyses in this manuscript as the results are not significantly changing overall association and the heterogeneity still is not reduced. Also, we are limited by the number of words in the manuscript.

4. Since the authors have considered only four major factors associated with COVID-19 mortality, it would be difficult to conclude that these are the major contributors to COVID-19 mortality.

Response: We agree with this reviewer’s comment. We have re-phrased this sentence of the manuscript. The sentence now reads as follows:

“Our findings suggest that diabetes, hypertension, obesity and smoking were associated with higher COVID-19 mortality, contributing to nearly 30% of COVID-19 deaths”

5. While exploring the non-linear relationship between BMI and COVID-19 mortality, the authors have used relative risk estimates reporting 5 unit increase or 1 SD increase or categorized BMI with different reference ranges across different studies. It is unclear that how different forms of BMI were included in the pooled analyses. Please expand the statistical analyses section for readers to understand the conversion of all estimates on the same format from different studies.

Response: Yes, indeed, we presented results using both linear and nonlinear dose-response models.

For linear dose-response analysis, we used the method described by Greenland and Longnecker to compute the linear trend from the natural logs of the RRs and CIs across categories of BMI (Greenland S and Longnecker MP, 1992). When continuous risk estimates were not provided in the articles, dose–response associations and 95% CIs were derived from categorical data using generalized least-squares for trend estimation, which required the RRs and CIs associated to at least three categories of BMI, number of cases, and noncases. The mean or median BMI level in each category was assigned to the corresponding relative risk for each study, and for studies that reported the exposures in ranges we used the midpoint of the upper and the lower cut-off point.

When upper and lower categories were open ended or had extreme upper or lower values, we used the width of the adjacent category to calculate an upper or lower bound. When studies reported analyses by the World Health Organisation (WHO) categories of overweight and obesity we used a BMI of 15 as a lower bound for the underweight category (<18.5) and 18.5 as the lower bound for the normal weight category (<25), consistent with definition of normal weight by the WHO.

For studies that reported continuous risk estimates, for example for a 1 unit increment or any others SD increment, we converted risk estimates into 5 unit increments. We then pooled SRRs and 95% CIs for a 5-unit increment in BMI for each study using random effects models to estimate an overall relative risk.
We have already mentioned this in the Methods section on page 8.

“We further performed a dose-response analysis for the associations between BMI and COVID-19 mortality using the method described by Greenland and Longnecker analysis to compute the linear trend from the natural logs of the RRs and CIs across categories of BMI (Greenland S and Longnecker MP, 1992). We calculated summary RRs and 95% CIs for a 5-unit increment in BMI using random effects models. This method required mean or median of BMI, RRs and 95% CIs for at least three categories. The mean or median BMI level per category was used if provided in the publication, and if not, the midpoint of the upper and lower boundaries was estimated as a range in each category. When the highest and lowest categories were open-ended, we used the width of the adjacent interval to estimate the upper and lower boundaries for the category”

Regarding non-linear dose response analysis, we examined a potential non-linear dose-response relation between BMI in relation to COVID-19 mortality by using fractional polynomial models as described by Bagnardi et al 2004. We determined the best fitting second order fractional polynomial regression model, defined . For this purpose, we included all categories of BMI (even the underweight categories) to model the association between BMI and COVID-19 mortality across the full BMI range and used the method of Hamling and colleagues to convert risk estimates when the lowest category was not the reference category (Hamling J et al 2008). Only studies which presented more than two categories could be included in the nonlinear analysis. The analyses were re-scaled so the reference category was a BMI of 23. It is important to note that studies that provided continuous risk estimates were excluded from nonlinear dose response analysis.

Since we are limited by number of words, we did not include all these details in the manuscript. However, we have now added the following short statement in the Methods section on page 8 to make this section more clear for reader.

“To explore the potential nonlinear dose-response relation between BMI and mortality among patients with COVID-19, we used fractional polynomial models (Bagnardi et al 2004). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. Only studies which presented more than two categories were included in the nonlinear analysis”

6. Moreover, I do not see any studies reporting estimates for BMI>=50, however, the non-linear curve was drawn up to BMI 50.

Response: We agree with reviewer. There was no study that reported relative risk estimates for BMI more than 50. The maximum BMI level was 45.

As requested by the reviewer, we have now replaced the old figure by this new figure.
7. Several studies were excluded in the sensitivity analysis. However, any rationale was not included in the footnotes of figures or tables.

**Response:** Sorry – but we did not exclude several studies at one time in the sensitivity analysis. However, we excluded one study at a time to ensure that the results were not simply due to one large study or a study with an extreme result as described in the methods section on page 8:

"We conducted sensitivity analyses excluding one study at a time to clarify whether the results were driven by one large study or a study with an extreme result"

Overall, our findings persisted in sensitivity analyses excluding one study at a time, suggesting that no individual study explained the result and that the findings were robust to the influence of single studies.

8. In Table 1, the exposure category for smoking needs to be specified.

**Response:** Done!

9. In Table 2 footnote, the authors mentioned: “within each cancer type”. Please correct it.

**Response:** Many thanks for the remark – this was a mistake from our part. We have now corrected the sentence.
10. Most of the studies were based on hospitalized patients except for a few studies that were based on ICU admitted patients. Sensitivity analyses may be performed accordingly.

Response: Thank you for the suggestion.

From the 186 studies included in this meta-analysis, only five studies were based on ICU admitted patients (Dennis et al. 2020, Grasselli et al. 2020, Haasse et al. 2020, Alharthy et al. 2020 and Wang et al. 2020). Of these, three studies reported results of the association between diabetes and COVID-19 mortality, two studies reported results for hypertension, two studies for smoking and one study evaluated the association between BMI and COVID-19 mortality.

As suggested by the reviewer, we have now performed stratified analyses comparing hospital based patient’s studies versus ICU admitted patient’s studies. Our meta-regression analysis showed that patient admission unit did not influence the magnitude of the overall association. The SRR for diabetes patients compared to those without diabetes was 1.55 (95% CI=1.45-1.66, I²=92%, n=142) in non-ICU admitted patient’s studies and 1.22 (95% CI=1.14-1.30, I²=0.0%, n=3 studies) in ICU admitted patient’s studies although there was no indication of heterogeneity across this parameter (P\text{heterogeneity}=0.24). The SRR for hypertension patients versus those without hypertension was 1.43 (95% CI=1.31-1.56, I²=90%) and 0.98 (95% CI=0.82-1.17, I²=0%) among non-ICU admitted patient’s studies and ICU admitted patient’s studies, respectively, with no evidence of heterogeneity (P\text{heterogeneity}=0.28).

As requested by the reviewer, we have added this in the Table (Table 2), although there was very few studies based on ICU admitted patients.

Regarding analyses for smoking and BMI, our meta-regression analysis showed that this parameter did not alter the overall estimate too. However, since there was very few studies (one study for BMI and two for smoking) based on ICU admitted patients, we decided to not include the results in the Table.

11. Some studies were based on the elderly population, subgroup analyses may be performed separately for elderly and non-elderly populations.

Response: Because we did not have access to the original data of each article and because most of study did not report patient’s ages or age-stratified analyses, unfortunately, we were not able to conduct analyses stratified by patient’s age category or for elderly patient’s studies vs. non-elderly patient’s studies.

12. Although the authors have performed subgroup, influence, and sensitivity analyses, the discussion was not provided based on heterogeneous findings (such as geographical differences in the associations) and geographical differences in the treatments for managing COVID-19 (Dubey, P., Thakur, B., Reddy, S. et al. Current trends and geographical differences in therapeutic profile and outcomes of COVID-19 among pregnant women - a systematic review and meta-analysis. BMC Pregnancy Childbirth 21, 247 (2021). https://doi.org/10.1186/s12884-021-03685-w)

Response: Thank you for the suggestion. Indeed, we agreed that geographical differences in therapeutic practice of COVID-19 such as the use of antibiotics, antivirals, oxygen therapy, immunosuppressants, and hydroxychloroquine may explain heterogeneity between studies as reported by Dubey, P et al 2021. However, information about therapeutic practice of COVID-19 was
not reported in the original data; therefore, we were unable to perform a stratified analysis by therapeutic profile of the patients.

As suggested by the reviewer, we have now discussed geographical differences in the associations and included the suggested reference in the Discussion section on page 16.

Please refer to response #2 for the comment #2 to Dr. Alok Dwivedi.

Reviewer: 3

Prof. Peter Herbison, University of Otago

Comments to the Author:

This study was a lot of work that was carefully done and reported well. I have a couple of minor comments. While very good, there were a few places where the English might be improved. For example, some singular words that should be plural. And it is no surprise to get such high I squared values. There are many more included studies than a typical meta-analysis and I squared increases with the number of studies. Is it worth mentioning this in the discussion?

Response: Many thanks, Prof. Peter Herbison, for these comments. We have modified the manuscript according reviewer’s comments.

As requested, we have added the following statement in the Discussion section on page 14.

“Given this meta-analysis included more studies than a typical meta-analysis, $I^2$ and heterogeneity were high as the likelihood of divergent findings increases with increasing number of studies”

Associate Editor’s comments to Author:

1. Please be clear in the Conclusion of the Abstract that you only looked at these four factors (diabetes, hypertension, BMI, smoking) and that other factors may also be contributors to Covid mortality.

Response: As proposed by the reviewers, we have now modified the conclusion part and stated that diabetes, hypertension, obesity and smoking were associated with higher COVID-19 mortality and contributed to nearly 30% of COVID-19 deaths.

Here is the corrected sentence:

“Our findings suggest that diabetes, hypertension, obesity and smoking were associated with higher COVID-19 mortality, contributing to nearly 30% of COVID-19 deaths”

2. Please provide sub-headings in the Discussion to help guide the reader.

Response: Thank you. Done!
| GENERAL COMMENTS | I have no further comments. Thank you very much! |
| REVIEWER         | Dwivedi, Alok  |
|                  | Texas Tech University, Division of Biostatistics & Epidemiology, Department of Biomedical Sciences |
| REVIEW RETURNED  | 19-Sep-2021 |
| GENERAL COMMENTS | The authors have addressed all the concerns that have improved the quality of the manuscript. I do not have any further comments. |