PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Contribution of the Elevated Thrombosis Risk of Males to the Excess Male Mortality Observed in COVID-19: An Observational Study
AUTHORS	Cohen, Kenneth; Anderson, David; Ren, Sheng; Cook, David

VERSION 1 – REVIEW

REVIEWER	Gasparyan, Armen Yuri Dudley Group NHS Foundation Trust (Teaching Trust of the University of Birmingham)), Departments of Rheumatology and Research & Development
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	This is a large observational study of thrombosis due to COVID-19. It highlights the role of male gender in thrombogenesis due COVID-19. There are some comments: 1. Methods. Please provide details of inclusion and exclusion criteria. Why subjects above 40 years, and not younger, were included in this study? Did the authors exclude subjects with background inflammatory, neoplastic and hematological disorders? 2. Ethics approval/waiver protocol number and date should be reported. 3. Discussion. Mechanisms of thrombosis could be better interpreted in view of the following highly relevant studies: https://pubmed.ncbi.nlm.nih.gov/32654082/ https://pubmed.ncbi.nlm.nih.gov/34364927/

REVIEWER	Pripp, Are Oslo University Hospital, Department of Biostatistics, Epidemiology & Health Economy
REVIEW RETURNED	17-Oct-2021

GENERAL COMMENTS	Statistical review: Thank you for an interesting manuscript with useful statistical analysis. It is well written, but I have some concerns about the explanation and presentation of the statistical methods and results. Minor comment: Provide SD for age in table 1. Major comments: Make it clear which variables you used for estimation of adjusted odds ratio in table 2. How did you estimate "proportion mediated (explained)" in table 2 and 3? Please provide a more detailed

	description with formulas and preferable with software codes. For example, these could be presented in an appendix or as supplementary information. If you provide software codes, it is much easier for readers to replicate your findings and use your methods in other studies. Why did you use "one-tailed p-values" (statistical methods)? I think the usual "two-tailed p-values" are more appropriate and would correspond to the presented confidence intervals.

VERSION 1 – AUTHOR RESPONSE

The 3 comments from reviewer 1 have been incorporated into the new manuscript version. Additional responses to comments from reviewer 2 include:

- Question 1: Age and co-morbidities were adjusted in estimating adjusted odds ratios in Table 2. Age was treated as a binary variable (age > 65 or not). All co-morbidities (based on Charlson co-morbidity scores) can be found in Supplementary materials Table e3. We added one sentence in the Methods section to make this more clear.
- Question 2: We included an additional reference on how to estimate the “proportion mediated” in the manuscript and included our R codes for mediation analysis in the Supplementary Materials. As rigorous explanation of how to estimate the proportion mediated is fully handled by the R package “mediation” and is thoroughly explained in the two papers cited, we believe it may be better for readers who are interested in this method to refer to these papers rather than providing additional detail in the Supplementary Materials.
- Question 3: This is because all three associations described in Figure 1/Table 2 (male and higher risk of mortality, male and higher risk of thrombosis and thrombosis and higher risk of mortality) are one-directional and well-supported by the literature we discussed in the Introduction section. As we only wanted to test whether these hypotheses were true with respect to the directions supported by the literature, we decided to use one-sided tests and one-tailed p-values to provide greater power. In these hypotheses tests, the null hypotheses were odds ratios <=1, and alternative hypotheses were odds ratios > 1. However, it did not make sense to use one-sided confidence intervals, because confidence intervals quantify uncertainty around point estimates (estimated odds ratios), not uncertainty around an odds ratio equal to one – which is what hypothesis tests do. Confidence intervals and hypothesis tests quantify two different kinds of uncertainties, so it was not necessary to pair hypotheses tests and confidence intervals based on whether they were one- or two-sided. Besides, given the small p-values shown in Table 2, even if we use two-sided p-values, the conclusions would not be changed since all associations were still very statistically significant under 0.05 significance level.

This manuscript has not been published nor is it being considered for publication elsewhere.
Thank you for your attention,

VERSION 2 – REVIEW

REVIEWER	Pripp, Are Oslo University Hospital, Department of Biostatistics, Epidemiology & Health Economy
REVIEW RETURNED	05-Dec-2021

GENERAL COMMENTS	The authors have revised the statistical analysis. I have no further comments or suggested revisions.

VERSION 2 – AUTHOR RESPONSE

- We felt that the following comment from reviewer 1 was not fully addressed in your response letter or revised manuscript:

1. Methods. Please provide details of inclusion and exclusion criteria. Why subjects above 40 years, and not younger, were included in this study? Did the authors exclude subjects with background inflammatory, neoplastic and hematological disorders? Thank you for this comment. When we broadened the data set to include the new cohort of 60,877 subjects, we reduced the age inclusion to 18 years and older. We did not have any exclusions for comorbidities or underlying diseases, including those listed above.

Reviewer: 2

Dr. Are Pripp, Oslo University Hospital

Comments to the Author:

The authors have revised the statistical analysis. I have no further comments or suggested revisions.

Reviewer: 2

Competing interests of Reviewer: None