NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

QRESEARCH

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10th December 2021

Dr Nerys Astbury
University of Oxford

Dear Dr Astbury

Reference	OX141
Title	Obesity and SARS-CoV-2 infection: Quantifying the burden of obesity on severe COVID-19 outcomes and on the healthcare system: analysis of a community-based cohort of people in England
Chief Investigator(s)	Dr Nerys Astbury, Dr Carmen Piernas-Sanchez, Prof Susan Jebb, Prof Paul Aveyard
Date Application submitted	15.09.2021
Date Application re-reviewed	06.12.2021
Decision	Revise and Resubmit

Thank you for submitting your application to QResearch.

Reviewed documents

The documents reviewed were

Document	version	Date
Application Form		15.09.2021
Letter from applicants in response to first review		05.11.2021
Lay Summary		17.09.2021
Data Specification		17.09.2021

Reviewing Members of the Committee

The members of the scientific committee who took part in the review are listed on the attached sheet.

Comments and Recommendations from the Scientific Committee:

- Thank you for providing a sample size calculation, however I have some queries.
  1. The sample size is very large. I have managed to replicate it a part of it, but am unsure if the 4:6

(2:3) ratio has been applied correctly. The total number I get for both groups is closer to 2.5m (1.5m in group 1 and 1m in group 2). Please can this be re-checked.

2. The sample size is also based on very small COVID-19 event rates informed by the first wave, however, sadly a higher proportion of event was seen in the second wave. Could the research team revisit their estimated proportions for the calculation.
3. The sample size is based on detecting a hazard ratio of 1.1 but is based on proportions of events alone and does not account for time to event – such as the median survival time and the follow up time. By accounting for this the research team may be able to reduce their required sample size substantially. The research team may find this website particularly useful https://sample-size.net/sample-size-survival-analysis/
4. I would be happy to have a meeting with the research team if you would like to discuss the sample size further

- Health economic review:
  1. The applicants should acknowledge that framing the study population around individuals with at least one BMI measure in the electronic records is likely to result in some selection biases. The BMI categories for the proposed economic analysis (18·5 to <25 kg/m2, 25 to <30 kg/m2, 30 to <35 kg/m2, and ≥35 kg/m2) could be further disaggregated (for example: 18·5 to <20 kg/m^2, 20 to <22·5 kg/m^2, 22·5 to <25 kg/m^2, 25 to <27·5 kg/m^2, 27·5 to <30 kg/m^2, 30 to <35 kg/m^2, 35 to <40 kg/m^2, and 40 kg/m^2 or more), at least for the purposes of a secondary analysis.
  2. It is worth considering to use cluster-robust standard errors in economic models to account for the lack of independence between hospital admissions of a given individual across the period(s) of follow-up.
- Missing data and biases
  1. The authors state that there are socio-demographic differences between people with a recorded BMI and those without a recorded BMI. Surely then, applying BMI as an inclusion criterion is introducing a selection bias. What's more, even if completeness of BMI is made a selection criterion there are other variables with missing values, such as ethnicity, smoking and alcohol consumption. Why would multiple imputation not be applied to these?
  2. I agree the fact that completeness of BMI fails the missing at random assumption makes accounting for missingness more complicated, but I don't think applying it as a selection criterion satisfies the underlying concern relating to analysis and I don't think it inherently justifies a complete case analysis of the remaining variables.
- Other (minor) comments:
  1. There are basic spelling and grammatical mistakes throughout the document, please could this be addressed.
  2. Please could it be clarified if results are added to GP records? And does the research team propose to access contact tracing? How would this data allow them to determine the existence of an asymptomatic case that had not been tested?
  3. Please provide a reference for this statement - "In Europe, most countries have aimed to halt the spread of the virus by restricting social interactions, resulting in nationwide lockdowns, with significant decreases in nations' gross domestic product measured in billions of euros."
  4. In the response to reviewer's document the authors indicated that the economic analysis was born from PPI for a previous project. I would recommend including mention of this in the background to this project as it strengthens the case for the proposed economic analyses.
  5. What are the proposed dates of each of the pandemic "waves"?
  6. Based on the author's response it seems that by "individual attributable fraction" they mean "attributable risk percent" (AR%). Given the latter is a more commonly used and understood term I would recommend switching to it in the proposal.

7. The study period states the study begins on 24 January 2020. In the response to reviewer's comments the authors indicated this had been changed, please could this be clarified in the proposal.
8. The censoring dates listed at the beginning of this section are not complete. The list should also include de-registration from practice and final date of available data.
9. "Using the modelled data from aim 1, we will first calculate the attributable risk, interpreted as the number of additional cases/10,000 persons of severe COVID-19 in each age group (18-39; 40-59; 60-79, 80+) at each BMI level". This should explicitly state that the attributable risk relates to the number of additional cases due to the primary exposure, in this case BMI. Please could this be added.
10. "HES data comprises inpatient stay, medical/surgical procedures as well as the use of adult critical care services." The response in the "datasets" section did not mention procedures.
11. "...by BMI category (18·5 to <25 kg/m2, 25 to <30 kg/m2, 30 to <35 kg/m2, and =35 kg/m2)". Presumably >=35 kg/m2? Please could you clarify.
12. "There is no need to adjust for treatments for obesity related or non-obesity related disease". Please explain why this is not necessary.
13. The study title on the lay summary does not mention COVID. The study title on the application form is different and does mention COVID.
14. In the lay summary, I wonder if the term 'quantify' could be replaced with 'work out'?
15. On p4 of the lay summary, should "sheltering" say "shielding"?
16. Page 4 of the lay summary states "when a vaccine eventually becomes available" – this needs updating.
17. The application mentions that the analysis will include waist circumference, but my experience suggests this is very poorly recorded in GP data.
18. Waist circumference has also been deleted from the proposal.
19. Page 6, 15 lines form bottom: "adjusting for non-obesity related" should read "adjusting for non-obesity related"
20. The research team have pointed out changes in their response but there is no updated lay summary attached in the email so can't confirm that the changes were made in the document.

How to respond:

If you wish to respond please reply to this letter addressing each comment from the committee, sending the reply to qresearch@phc.ox.ac.uk. Please do not contact reviewers directly; any correspondence with reviewers should be made via QResearch@phc.ox.ac.uk. Please also update your application form in QWeb to match any alterations and clarifications made in your letter. If you're able to respond to this letter by return, I should be able to review and hopefully approve before the end of the year.

Dr Paula Dhiman
Chair of QResearch Scientific Committee

Enclosures:
List of names and professions of members who took part in the review
Completed peer review forms

Copy to: Prof Julia Hippisley-Cox, Chief Investigator of QResearch.

Reviewing Members of the Committee

Name	Profession
Dr Paula Dhiman	Senior Researcher in Medical Statistics
Dr Brian McMillan	Clinical Senior Lecturer, GP
Professor Stavros Petrou	Professor of Health Economics
Professor Julia Hippisley-Cox	Professor of Clinical Epidemiology & General Practice
Professor Paul Aveyard	Professor of Behavioural Medicine
Dr Mike Walton	GP, Chair of the QResearch Advisory Board
Ms Madhurima Bhadra	Lay Member
Dr Rebecca Harmston	Lay Member
Dr Franco De Crescenzo	DPhil Candidate, Honorary Psychiatrist
Ms Jennifer Camaradou	Lay Member
Dr Hui Guo	Senior Lecturer in Biostatistics
Dr Koen Pouwels	Senior Researcher in Health Economics
Ms Polly Kerr	Patient and Public Involvement Manager
Dr Tom Ranger	Epidemiologist