PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations of obesity, physical activity level, inflammation and cardiometabolic health with COVID-19 mortality: a prospective analysis of the UK Biobank cohort
AUTHORS	Hamrouni, Malik; Roberts, Matthew; Thackray, Alice; Stensel, David; Bishop, Nicolette

VERSION 1 – REVIEW

REVIEWER	Christensen, Rebecca University of Toronto
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	The authors present a large prospective analysis looking at whether physical activity may be an effect modifier for the association between obesity and death in covid-19 patients. They also examine whether the inclusion of several biomarkers can attenuate the relationship between physical activity and all-cause mortality in covid-19 patients. The authors also make a strong argument regarding why this prospective design is necessary and an important strength of this study, despite the data being almost 10 years old. Overall, it was a very good paper, but I had some questions regarding the methods and analytic approach. Abstract Please elaborate on how you define high physical activity in the abstract as this is your main exposure Methods The authors appear to have used age at baseline, however, age at time of covid-19 assessment or death is likely more appropriate. Can the authors explain why they did not recalculate age? Please specify the exact number of covid-19 deaths in the underweight population. Please specify the sample size (n=1255) in the main paper? Also, is there a reason why you did not just collapse underweight with normal weight? There is data available on updated medical history through linkage such as cancers. Is there a reason why the authors did not update comorbidities? Given the importance of physical activity as the exposure, it would be beneficial to provide more explanation regarding how IPAQ classifies people into low, medium or high. What are the specific MET cut-offs used, for example? It is interesting that you included mortality in anyone with covid-19 rather than covid-19 specific mortality. Can you please explain your rationale for this? We know that physical activity can modify

	the association between obesity and the risk of cardiovascular disease, and several other conditions that people who had covid-19 could die from. I would be interested in seeing your analysis restricted just to those where covid-19 was the primary cause of death. I would also be interested in knowing what the primary cause of death was in those who had covid-19 listed as a contributory cause. Results It would be great if you could describe some of the differences evident in Table 1. Consider incorporating standardized differences to describe these differences given the large sample size. Placement of the main BMI results under the title “Associations of physical activity level with covid-19 across BMI categories” seems weird. I recommend creating its own section. I understand that you are focusing on p-values, but you are reporting a 1.56 odds ratio and a lower bound of a confidence interval of 0.98. If your sample size was slightly bigger you would see a significant effect. It seems illogical to not mention the borderline significance. There are similar issues with the overweight interpretation of low activity. Your biomarker analysis within those with obesity should also report the impact for those with moderate physical activity (i.e. no effect).

REVIEWER	Pou, Sonia Alejandra CONICET Cordoba, Research Institute of Health Sciences
REVIEW RETURNED	10-Aug-2021

GENERAL COMMENTS	This manuscript deals with an interesting topic and adds to a growing body of literature focusing on lifestyle-related factors and mechanisms underlying COVID-19 mortality, which is relevant for public health planning. However, the following issues need to be resolved before the paper could be published: Major comments: - One concern is the at least 10-year time period between baseline biomarker measurement and COVID-19 mortality. Blood levels are largely affected by changes in diet, stress, health status, physical activity level, and nutritional status. In addition, the variation of these last two exposure variables could affect the classification of individuals in the study. Although the authors include this issue as a limitation of the study, if possible, it would be very informative to examine and report the concordance of biomarkers levels at recruitment and a repeat assessment moment in a subsample of participants UK Biobank cohort. This information would allow assessing the magnitude of the changes. Also, I suggest reinforcing the reference of the baseline or pre-pandemic status of the variables throughout the manuscript. - The study hypotheses would be clarified if the authors included an illustration (path diagram) explaining the role of each variable used.

	- I have serious doubts about the way the authors describe their OR results. In this study, this measure of association informs if the odds of dying are greater (or lower) for those participants in a category of the exposure variable compared to the reference category, exclusively. At times, the wording is confusing and seems to refer to increased risk based on the comparison between different categories rather than with the reference category. Please revise this point and rewrite it where necessary. - The authors refer that “the analysis was based on a whole population-level approach outlined for the UK Biobank cohort,[18] whereby individuals who died from COVID-19 were compared with the remaining population as controls.” This sentence introduces confusion because the studied sample is not representative of the whole population, nor is it a case-control study. The mentioned approach should be better outlined or removed. In addition, I recommend avoiding the term “control population” (in Table 1) because it is more related to a case-control design. - Page 8, lines 12 to 17: The authors indicate that “the cohort was stratified by BMI category to assess how associations of physical activity level with COVID-19 mortality differed across BMI categories.” However, a unique reference group is illustrated (high physical activity with normal BMI) in Figure 1. Therefore, It seems that several logistic regression models have not been adjusted in a stratified manner (for each category of nutritional status), as the authors state. I think that a logistic regression model has been carried out with an interaction term (BMI category * physical activity level). Please, describe in detail the implemented modeling strategy. Minor comments: Introduction - Page 5, line 17: I recommend replacing the term COVID-19 “burden” to COVID-19 “morbimortality” (or morbidity or mortality if corresponding) because the term “burden” often refers to the population level and no the individual one as in this case. Methods: - Please clarify is the touchscreen questionnaire was self-administrated or administrated by trained interviewers and the year for which the Townsend deprivation index was calculated. - Page 8, line 6 (and Table 1 in the Results section): Discrete (quantitative) variables must also be mentioned. - Page 8, lines 37 to 41: Do you mean individuals with a positive SARS-CoV-2 test result who did not die by COVID-19? - Page 9, lines 5 to 8: I suggest rewrite the sentence about significance level as follows: “Statistical significance was accepted at the alpha 0.05 level, and the corresponding 95% confidence intervals were calculated” - What is the rationality of including the number of cancers as an adjustment variable in models if Table 1 showed null frequency? Consider including a general variable called “number of illnesses”, without distinguishing cancer or non-cancer illnesses. In that case, Table 1 should be corrected. Results:

	- As I mentioned, the “control population” term could be replaced by, for example, population without COVID-19 mortality (Table 1). - I recommend adding data about BMI categories and physical activity levels in Table 1. - It would be useful for the reader to find a table with the estimated ORs and their CI for the associations of physical activity level with COVID-19 mortality (independent of BMI), and of BMI categories with COVID-19 mortality (independent of the physical activity level), supporting the text described in lines 6 to 25 of page - How did the authors estimate the percentage of effects attenuation reported on lines 19 to 21 (page 13)? Please, clarify in the method section. - Table 3: N cases are referred to the number of deaths (cases of death)? In epidemiology, the term case is frequently used to refer occurrence of disease rather than death. Please, replace the term to avoid confusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Rebecca Christensen, University of Toronto

Comments to the Author:

Abstract

Please elaborate on how you define high physical activity in the abstract as this is your main exposure

We have now added the MET-minute thresholds for IPAQ PA levels to the abstract.

Page 3, lines 17-19 of updated manuscript: Physical activity level was assessed using the International Physical Activity Questionnaire (high: ≥3000 MET-minutes/week, moderate: ≥600 MET-minutes/week, low: not meeting either criteria)…

Methods

The authors appear to have used age at baseline, however, age at time of covid-19 assessment or death is likely more appropriate. Can the authors explain why they did not recalculate age?

We originally only reported baseline age as this was cohesive with all the other confounding variables being from the same timepoint (baseline assessment). We cannot use age at time of COVID-19

assessment as that only applies to those that died from COVID-19. However, we have now crudely recalculated current age using year and month of birth (UK Biobank do not provide day of birth for anonymity purposes, so we made this the first of the month for all participants for the purpose of calculating current age) and the date March 1st, 2020. We have added this value to Table 1 alongside baseline age. The statistical results remain the same whether using baseline age or current age as a covariate, so baseline age is still the variable used as a covariate in the statistical models in the revised manuscript.

Page 6, lines 26-28 of updated manuscript: Current age was estimated as age on March 1st, 2020.

Please specify the exact number of covid-19 deaths in the underweight population. Please specify the sample size (n=1255) in the main paper? Also, is there a reason why you did not just collapse underweight with normal weight?

There were only two deaths in this population, which we have now specified alongside the sample size in the revised manuscript. We did not collapse underweight and normal weight into the same group because being underweight may be a risk factor for COVID-19 severity and mortality (Kim et al., 2020)*. Therefore, we did not want to give the impression that they were a comparable population to normal weight individuals in regard to COVID-19 risk (even if collapsing them into the same group does not affect results due to the small sample size).

Page 6, lines 37-39 of updated manuscript: Individuals who were underweight (n = 1255) were not included in the analysis due to limited cases of COVID-19 deaths (n = 2).

*https://doi.org/10.3390/ijerph17249336

There is data available on updated medical history through linkage such as cancers. Is there a reason why the authors did not update comorbidities?

We did not add this initially as we were only presenting the data for confounding variables, exposures and outcomes. However, using Hospital Episode Statistics, we have now added this data.

Page 7, lines 6-17 of updated manuscript: Co-morbidities were assessed at baseline and updated over the follow-up period using participant linkage with hospital episode statistics (occurrences of specific ICD-

10 codes in hospital admission data up until February 27th, 2021). Listed co-morbidities include cardiovascular diseases (ischaemic heart disease, hypertensive disease, pulmonary heart disease and cerebrovascular disease), respiratory diseases (asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema and bronchiectasis), diabetes mellitus, liver disease, kidney disease and cancer.

The comorbidity data can be found in Table 2, and the main differences are briefly described in text.

Page 10, lines 23-27 of updated manuscript: Regarding co-morbidities, individuals who died from COVID-19 had a higher prevalence of the listed cardiovascular and respiratory diseases, as well as diabetes, liver disease, kidney disease and cancer (Table 2).

Given the importance of physical activity as the exposure, it would be beneficial to provide more explanation regarding how IPAQ classifies people into low, medium or high. What are the specific MET cut-offs used, for example?

Thank you for the suggestion, we have now added the MET-minute thresholds for the different physical activity levels.

Page 7, lines 31-37 of updated manuscript: High and moderate physical activity level were classed as achieving ≥3000 and ≥600 MET-minutes per week of any combination of walking, moderate-intensity or vigorous-intensity activity, respectively. Individuals who did not meet such criteria were considered to have a low physical activity level.

It is interesting that you included mortality in anyone with covid-19 rather than covid-19 specific mortality. Can you please explain your rationale for this? We know that physical activity can modify the association between obesity and the risk of cardiovascular disease, and several other conditions that people who had covid-19 could die from. I would be interested in seeing your analysis restricted just to those where covid-19 was the primary cause of death. I would also be interested in knowing what the primary cause of death was in those who had covid-19 listed as a contributory cause.

Originally, we wanted our analysis to be sensitive to instances where COVID-19 was a contributory cause

of death. However, upon reading your comment and confirming that COVID-19 listed as a secondary cause on the death certificate does not necessarily mean it was implicated in death, we realise we do not want to give the impression that our findings may be driven by the association of physical activity with different diseases and medical conditions that may be present in individuals who had COVID-19 when they died. Thank you for highlighting this. We have now restricted our analysis to COVID-19 as a primary cause of death and have updated all of the statistical analyses. The results are mostly similar, with the exception of glucose no longer exhibiting a significant association with COVID-19 mortality, individuals who are overweight now being at significantly higher risk than individuals with normal weight (independent of PA level), and lowly physically active individuals with overweight now being at significantly higher risk than highly active individuals with a normal BMI. There are now 397 COVID-19 deaths featured in the analysis (as opposed to 438 in the previous manuscript).

Page 8, lines 16-20 of updated manuscript: COVID-19 mortality was determined from the presence of ICD-10 codes U07.1 (virus identified in laboratory testing) or U07.2 (clinical or epidemiological diagnosis) as the primary cause on the death certificate.

Results

It would be great if you could describe some of the differences evident in Table 1. Consider incorporating standardized differences to describe these differences given the large sample size.

Thank you for the suggestion. we have now described the differences in Table 1.

Page 10, lines 14-23 of updated manuscript: Participants who died from COVID-19 were more likely to be older, male, current or former smokers, as well as have obesity, a low physical activity level, and lower educational attainment. Additionally, the Townsend deprivation index, the number of illnesses, and the number of treatments and medications taken was higher for participants who died from COVID-19.

Regarding standardized differences, we have opted to just provide a brief description of the differences for consistency across the data, as most of the data is categorical and the continuous/discrete variables are non-normally distributed, meaning that standardised differences would only be available/valid for a

handful of outcomes (after data transformation).

Placement of the main BMI results under the title "Associations of physical activity level with covid-19 across BMI categories" seems weird. I recommend creating its own section.

Thank you for the recommendation, this has now been made into a separate section (page 13, lines 3-8 of updated manuscript).

I understand that you are focusing on p-values, but you are reporting a 1.56 odds ratio and a lower bound of a confidence interval of 0.98. If your sample size was slightly bigger you would see a significant effect. It seems illogical to not mention the borderline significance. There are similar issues with the overweight interpretation of low activity.

We have rewritten the results section to highlight when there is a higher risk (even if non- significant).

Page 14, lines 19-27 of updated manuscript: Whilst moderately active individuals with overweight (1.52, 0.97 – 2.38) were at higher risk compared to the reference group, this did not reach statistical significance. The COVID-19 mortality risk was still higher in highly active individuals with obesity (1.61, 0.98 – 2.64) and overweight (1.51, 0.96 – 2.35) compared to the reference group; however, these associations were also non-significant.

Also, we have added a paragraph in the discussion that highlights that highly active individuals with obesity may still be at higher risk compared to highly active individuals with a normal BMI (based on the magnitude of the odds ratio and the lower 95% CI approaching 1). Thank you for raising this issue; it is definitely an important consideration when interpreting our findings.

Pages 18, 19; lines 53-60, 3-6 of updated manuscript: However, a high physical activity level may not completely negate the higher COVID-19 mortality risk associated with obesity. Although the COVID-19 mortality risk in highly active individuals with obesity was not significantly higher compared to highly active individuals with a normal BMI, the magnitude of the odds ratio (1.61) and the lower 95% confidence

interval approaching 1.00 (0.98) suggests that the former may still be at elevated risk of COVID-19 mortality. Therefore, weight-loss may still be necessary to further lower the COVID-19 mortality risk in highly active individuals with obesity.

Your biomarker analysis within those with obesity should also report the impact for those with moderate physical activity (i.e. no effect).

Thank you for the suggestion. We have added that there was no significant difference in risk between highly and moderately active individuals with obesity (page 16, lines 12-15), which was absent from the previous manuscript. However, the reason we did not provide the percentage attenuation in risk of COVID-19 mortality for moderately active individuals with obesity when including biomarkers to the model is because there was no notable difference in risk between them and highly active individuals with obesity. Calculating this value from the reduction in the effect estimate upon biomarker adjustment (1.21 > 1.17) would yield a percentage attenuation of 19% [(21-17)/21 × 100 = 19%]. We believe that presenting this may lead to confusion in interpreting the biomarker analysis as we would be looking at the attenuation of an effect estimate that was not significantly/notably different from the reference group.

Reviewer: 2

Prof. Sonia Alejandra Pou, CONICET Cordoba, National University of Cordoba

Comments to the Author:

Major comments:

One concern is the at least 10-year time period between baseline biomarker measurement and COVID-19 mortality. Blood levels are largely affected by changes in diet, stress, health status, physical activity level, and nutritional status. In addition, the variation of these last two exposure variables could affect the classification of individuals in the study. Although the authors include this issue as a limitation of the study, if possible, it would be very informative to examine and

report the concordance of biomarkers levels at recruitment and a repeat assessment moment in a subsample of participants UK Biobank cohort. This information would allow assessing the magnitude of the changes.

Thank you for the suggestion. However, repeat assessment with full biomarker data is only available for the first follow up assessment (2012-2013) for UK-Biobank participants. The most recent assessment with incomplete biomarker data is 2014, and, therefore, is still several years before the COVID-19 pandemic. We believe that using such data would not be a valid way to address how biomarkers may have changed between baseline and the start of the pandemic (considering the repeat assessment is so far away from the start of the pandemic), but also that attempting to address this question (quantification of how biomarkers may change over time) is beyond the scope/purpose of our paper.

For clarity, below we have provided the biomarker levels at baseline assessment and the repeat assessment in a subsample of participants with available data (6,671 of the 259,397 individuals included in the analysis).

Also, I suggest reinforcing the reference of the baseline or pre-pandemic status of the variables throughout the manuscript.

Thank you for the suggestion. We have reiterated the baseline/pre-pandemic status of variables throughout the manuscript, particularly in the discussion.

The study hypotheses would be clarified if the authors included an illustration (path diagram) explaining the role of each variable used.

Thank you for the recommendation, this has now been added (Figure 1).

I have serious doubts about the way the authors describe their OR results. In this study, this measure of association informs if the odds of dying are greater (or lower) for those participants

in a category of the exposure variable compared to the reference category, exclusively. At times, the wording is confusing and seems to refer to increased risk based on the comparison between different categories rather than with the reference category. Please revise this point and rewrite it where necessary.

We apologise for the confusion. We have rewritten several sections to correct this by ensuring that direct comparisons are made with the reference group exclusively.

Page 3, lines 33-40 of the updated manuscript: Compared to highly active individuals with a normal BMI (reference group), the odds ratio (95% confidence intervals) for COVID-19 mortality was 1.61 (0.98 – 2.64) for highly active individuals with obesity, 2.85 (1.78 – 4.57) for lowly active individuals with obesity, and 1.94 (1.04 – 3.61) for lowly active individuals with a normal BMI.

Page 18, lines 34-43 of the updated manuscript: Our results suggest there may have been a disproportionate amount of attention drawn to obesity compared to physical inactivity as a risk factor during the pandemic. Indeed, we found that lowly active individuals with a normal BMI were at significantly higher risk of COVID-19 mortality compared to highly active individuals with a normal BMI (reference group), whereas highly active individuals with obesity were not.

Additionally, we have removed the following sentence: Not only were highly active individuals

with obesity at lower risk compared to their less active counterparts, but they were also at lower risk than individuals with a normal BMI who had low levels of physical activity.

The authors refer that "the analysis was based on a whole population-level approach outlined for the UK Biobank cohort,[18] whereby individuals who died from COVID-19 were compared with the remaining population as controls." This sentence introduces confusion because the studied sample is not representative of the whole population, nor is it a case- control study. The mentioned approach should be better outlined or removed. In addition, I recommend avoiding the term "control population" (in Table 1) because it is more related to a case-control design.

Thank you for the recommendation, we have removed this sentence to avoid confusion. We have also avoided using the term 'control population' and have used 'individuals who did not die from COVID-19'

instead.

Page 8, lines 12 to 17: The authors indicate that "the cohort was stratified by BMI category to assess how associations of physical activity level with COVID-19 mortality differed across BMI categories." However, a unique reference group is illustrated (high physical activity with normal BMI) in Figure 1. Therefore, It seems that several logistic regression models have not been adjusted in a stratified manner (for each category of nutritional status), as the authors state. I think that a logistic regression model has been carried out with an interaction term (BMI category * physical activity level). Please, describe in detail the implemented modelling strategy.

We apologise for not making this clear. There were no interaction terms. The sentence you mention refers to the logistic regression that included all BMI/PA level combinations with highly active individuals with a normal BMI as the reference group. We have changed the wording to make this clearer.

Page 8, lines 37-42 of updated manuscript: Next, we assessed the risk of COVID-19 mortality for the different combinations of physical activity level (low, moderate, high) and BMI category (normal, overweight, obesity), with highly active individuals with a normal BMI as the reference group.

Minor comments:

Introduction

Page 5, line 17: I recommend replacing the term COVID-19 "burden" to COVID-19 "morbimortality" (or morbidity or mortality if corresponding) because the term "burden" often refers to the population level and not the individual one as in this case.

Thank you for the clarification, this has now been changed (page 5, line 17 of updated manuscript).

Methods:

Please clarify is the touchscreen questionnaire was self- administrated or administrated by trained interviewers and the year for which the Townsend deprivation index was calculated.

We have now addressed both of these points in the methods section.

Page 6, line 41-42 of updated manuscript: … was assessed via self-report using a touchscreen questionnaire…

Page 6, lines 54-56 of updated manuscript: Townsend deprivation index was calculated for each participant using national census output for their postcode at the time of recruitment

Page 8, line 6 (and Table 1 in the Results section): Discrete (quantitative) variables must also be mentioned.

We have now mentioned discrete variables in the methods section and in Table 1.

Page 8, lines 28-31 of updated manuscript: Participant demographics were presented as median and interquartile range for continuous and discrete variables (due to non-normal distribution) and number and percentage for categorical variables.

Page 8, lines 37 to 41: Do you mean individuals with a positive SARS-CoV-2 test result who did not die by COVID-19?

Yes, thank you for pointing this out. We have updated this sentence.

Page 9, lines 16-21 of updated manuscript: As there may be similar risk factors for severe and fatal COVID-19, sensitivity analysis was conducted to determine whether exclusion of individuals with a positive SARS-CoV-2 test result from an inpatient setting[20] who did not die from COVID-19 altered results.

Page 9, lines 5 to 8: I suggest rewrite the sentence about significance level as follows: "Statistical significance was accepted at the alpha 0.05 level, and the corresponding 95% confidence intervals were calculated"

Thank you for the suggestion, the sentence has been rewritten accordingly.

Page 9, lines 44-47 of updated manuscript: Statistical significance was accepted at the alpha level of 0.05, and the corresponding 95% confidence intervals were calculated.

What is the rationality of including the number of cancers as an adjustment variable in models if Table 1 showed null frequency? Consider including a general variable called "number of illnesses", without distinguishing cancer or non-cancer illnesses. In that case, Table 1 should be corrected.

Thank you for the suggestion, this has been updated throughout the manuscript. The null frequency for this variable in the original manuscript was due to a very low occurrence of cancers within the sample, such that when both values were rounded they were 0.

Results:

As I mentioned, the "control population" term could be replaced by, for example, population without COVID-19 mortality (Table 1).

We have replaced control population with 'No COVID-19 mortality' in Table 1.

I recommend adding data about BMI categories and physical activity levels in Table 1.

This has now been added to be Table 1.

It would be useful for the reader to find a table with the estimated ORs and their CI for the associations of physical activity level with COVID-19 mortality (independent of BMI), and of BMI categories with COVID-19 mortality (independent of the physical activity level), supporting the text described in lines 6 to 25 of page

This has now been added. Table 3 shows the associations of BMI category with COVID-19 mortality independent of physical activity level, and Table 4 shows the associations of physical activity level with COVID-19 mortality independent of BMI.

How did the authors estimate the percentage of effects attenuation reported on lines 19 to 21 (page 13)? Please, clarify in the method section.

We have now clarified this in the methods section.

Page 8, 9; lines 54-60, 3-8 of updated manuscript: The degree to which cardiometabolic and/or inflammatory biomarkers may explain the association between physical activity level and COVID-19 mortality in individuals with obesity was ascertained from the percentage change in the effect estimate upon their inclusion in the biomarker-adjusted models, in line with previous studies.[18,19] Percentage change was calculated from the change in value divided by the original value, multiplied by 100 (using odds ratios expressed as percentages).

Table 3: N cases are referred to the number of deaths (cases of death)? In epidemiology, the term case is frequently used to refer occurrence of disease rather than death. Please, replace the term to avoid confusion.

Thank you for the clarification, we have changed this to 'N deaths/N total' for all the relevant tables.

VERSION 2 – REVIEW

REVIEWER	Christensen, Rebecca University of Toronto
REVIEW RETURNED	28-Sep-2021

GENERAL COMMENTS	Strengths and Limitations Self-reported physical activity estimates are known to be biased in individuals with excess weight. Mainly, there is thought to be overreporting by these individuals. How might this impact your results? This seems especially pertinent as you are looking specifically at the impact of obesity in relation to physical activity. Another limitation that appears to be missed is that you likely underestimated the burden of comorbid conditions as you only used hospital data to ascertain comorbidities. As several of these conditions are more likely to occur in individuals with excess weight, what impact would this have on your findings? Results Please update the footnote for table 1 to include an explanation on how to interpret the Townsend index

REVIEWER	Pou, Sonia Alejandra CONICET Cordoba, Research Institute of Health Sciences

REVIEW RETURNED	16-Sep-2021

GENERAL COMMENTS	The authors have successfully addressed my previous comments. I consider that this work is suitable for publication.

VERSION 2 – AUTHOR RESPONSE

Further amendments have now been made based on the additional limitations of our paper raised by reviewer 1, which can be found in red font in our marked copy of the manuscript.

"Self-reported physical activity estimates are known to be biased in individuals with excess weight. Mainly, there is thought to be overreporting by these individuals. How might this impact your results? This seems especially pertinent as you are looking specifically at the impact of obesity in relation to physical activity".

Thank you for highlighting this. We have now pointed out this limitation in our discussion and have explained how it could influence our results (page 21, lines 40-57).

"Another limitation that appears to be missed is that you likely underestimated the burden of comorbid conditions as you only used hospital data to ascertain comorbidities. As several of these conditions are more likely to occur in individuals with excess weight, what impact would this have on your findings?"

Similarly, we have also added to our discussion how the issues raised by the reviewer could impact our findings (page 22, lines 1-33). Also, both limitations raised by the reviewer are now mentioned in our conclusion (page 22, lines 50-54).

"Please update the footnote for table 1 to include an explanation on how to interpret the Townsend index"

Table 1 has been updated accordingly.

VERSION 3 – REVIEW

REVIEWER	Christensen, Rebecca University of Toronto
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	The authors have done a commendable job addressing all of the concerns I have raised. I have no further recommendations.