PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Active living environments, physical activity, and premature cardiometabolic mortality in Canada: a nation-wide cohort study
AUTHORS	Mah, Sarah; Sanmartin, C; Riva, Mylene; Dasgupta, Kaberi; Ross, Nancy

VERSION 1 – REVIEW

REVIEWER	Ralph Stewart Auckland City Hospital, New Zealand
REVIEW RETURNED	29-Jan-2020

GENERAL COMMENTS	This study addresses an interesting and important question. A criticism is the focus on age/sex defined subgroups without presenting data for the overall cohort. In my view it is important to first report associations for the whole population, and then by age and sex. This is particularly important given that this is the only study to report an association between favourable living environments and CM death. Suggest results for whole population are presented Suggest some justification is given for the the 3 variables used to define an active environment with relevant references. Consider including the data in supplementary table S2 in the main manuscript. While walking is greater in the areas with higher ALS this did not have much impact on overall physical activity except in elderly women. This many explain why there was no clear association with premature CM death for these groups. ICD-10 E codes include many endocrine and metabolic causes of death unlikely to be influenced by physical activity. Consider restricting to deaths related to diabetes and obesity.

REVIEWER	Pedro Saint-Maurice National Cancer Institute
REVIEW RETURNED	18-Feb-2020

GENERAL COMMENTS	This manuscript examined cross-sectional associations between living environment and physical activity (PA) and then prospectively, if each living environment and PA were associated with mortality risk, after adjusting for a few potential confounders. The study includes a large sample size (~250 000 individuals) followed through 5-6 years, on average. I found this study interesting but question the novelty of the idea considering all the limitations (some acknowledged by the authors). The additional information on living environment is the most novel piece of the manuscript however it is not clear this information as collected can be used for the purpose that the authors had in mind. My major concerns are described below:

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

	1 – The most novel piece in the study is the add-on information on living environment and the extent to what individuals living in active living environments are more active and likewise, have a lower risk of premature mortality. However, in this study it is not possible to determine if individuals that were more active in active living environments did accumulate more activity in these neighborhoods or were simply, individuals that were already active among other characteristics (e.g., higher income, high SES, etc) and therefore, more likely to live in such environments. This is an important limitation and the authors should elaborate more on this possibility. Maybe conduct sensitivity analysis stratified by confounders and see if associations hold. 2 – The authors should include more information on the measure of walking and total PA used in the study. An assessment of walking in the previous 3 months is very challenging so I wonder what format was used to obtain this information and the extent to what facilitated vs. complicated recall. The same is true for total PA. I'm guessing that most of the information reported included exercise, some sort of structured high intensity activity. That is the information that is most likely recalled when questions are rather vague and aimed at medium/long-term recall (e.g. 3 months). If this is true, this is likely a poor measure of overall physical activity. 3 - Also related to my comment above. It was not clear to me how energy expenditure was calculated. The authors indicate MET.hours or MET.min were divided by 365 to get to cal/kg/day. Shouldn't the number be divided by approximately 90 days considering your assessment was of the last three months? The actual kcal/kg/day don't look right to me. Please clarify by showing your math/calculations. Please share the same calculations that support the following statement: "This cuttof (1.44 kcal/kg/day) is equivalent to the recommended 150 minutes or more per week of moderate to vigorous exercise" 4 – Still related to kcal/kg/day, please explain why did you choose this metric as opposed to MET.min or MET.hours that have a direct link to meeting not meeting the guidelines? What about just using duration since most of your results are focused on walking? 5 – From figure 2 looks like the differences between least vs more active living environments ranges from 0.2 to 0.4 kcal/kg/day. How meaningful is this? This range looks irrelevant if you were to re-calculate this back to METs. Please clarify. It is also not clear the trend between walking and environment is linear. Add p trend to figure 2. Also, please add table 1 with descriptives and n deaths by level of active living environment. This will clarify how walking and potential demographics/confounders are distributed and might affect your results. 6 – I'm not totally familiar with the literature in walking and active environments but looks like there are a few already published studies on this topic. The discussion starts by mentioning this is the "…first study to examine associations between active living environments and premature cardiometabolic health". Probably not an accurate statement or maybe very nuanced considering the at least couple of papers published on environment walkability and mortality. Consider removing.

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

	Additional comments: 1 – Add n individuals and n deaths to Figure 3 to show sample size and outcomes for each category of walking. 2 – In Figure 4, show results stratified for all categories of active environment. 3 – How much the walking associations with mortality changed if you were to adjust for active living environment in your models? This might help understand the extent to what the association between walking and mortality is explained by neighborhood. 4- Also interesting that your full vs reduced models (Table S2) barely differ. This might indicate greater amounts of either residual or unmeasured confounding, or both. Only a limited list of confounders was included in the models and there is no information on SES or income, likely great predictors of residential location. Please comment.

VERSION 1 – AUTHOR RESPONSE

Overview

Comment 1 (R1): This study addresses an interesting and important question.

Comment 2 (R2): This manuscript examined cross-sectional associations between living environment and physical activity (PA) and then prospectively, if each living environment and PA were associated with mortality risk, after adjusting for a few potential confounders. The study includes a large sample size (~250 000 individuals) followed through 5-6 years, on average. I found this study interesting but question the novelty of the idea considering all the limitations (some acknowledged by the authors). The additional information on living environment is the most novel piece of the manuscript however it is not clear this information as collected can be used for the purpose that the authors had in mind.

We thank the reviewers for their time and careful consideration of this study. Below is our response to their comments, which contain the following typographical conventions:

Reviewer comments are categorized under headings in bold.

2. Comments are numbered and underlined
(and are ordered by category, not the order presented by reviewers).

3. Comments from the first and second reviewer are labelled (R1) and (R2), respectively.

4. Our direct responses are indented and in italics.

5. References and changes to the manuscript are indented and highlighted.

Study population

Comment 3 (R1): A criticism is the focus on age/sex defined subgroups without presenting data for the overall cohort. In my view it is important to first report associations for the whole population, and

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

then by age and sex. This is particularly important given that this is the only study to report an association between favourable living environments and CM death. Suggest results for whole population are presented.

We understand and agree with the reviewer on the general importance of overall estimates for the whole population in any study. However, we defined premature cardiometabolic death uniquely based on sex and middle versus older age groups. Estimates for the four groups would be difficult to combine without a common endpoint. If we chose a common endpoint understood as an overall cut-off for premature death (for example, age 75 years), we would exclude older age groups from this cohort, since the maximum follow-up time for individuals in our study is 12 years. If we chose a common endpoint that ensured inclusion of all individuals in the cohort (age 85 years), our focus would shift away from premature death, and would include men age 81-85 years – a group that had not originally been included in the study.

In sum, we wanted to know whether living in an active living environment might mitigate chronic-disease deaths that are premature in mid-life and later life and could be avoidable through the physical activity pathway. We excluded the very elderly, as most of these deaths are driven by old age. We excluded younger age groups, because the number of cardiometabolic deaths in those under the age of 45 years were very low in our study population, and these tend to be driven by additional factors and pre-existing conditions.

Study framing

Comment 4 (R2): How much the walking associations with mortality changed if you were to adjust for active living environment in your models? This might help understand the extent to what the association between walking and mortality is explained by neighborhood.

The reviewer poses an interesting suggestion that points to the theoretical framing we used for this study. The socioecological model has been applied to wide range of health research. The key strength of this model over other health behavior theories is that, in addition to intra-individual factors such as personal beliefs, motivations, and selfefficacy, it argues that individual-level behavior is shaped and conditioned by environmental factors. Therefore, we chose to model the active living environment as being upstream of the health behavior (walking and physical activity) that would in turn, impact cardiometabolic health. Modeled this way, we treat walking and physical activity as the potential mediators of the relationship between the active living environment (the primary exposure of interest) and cardiometabolic mortality. We know that, within this framework, adjusting for walking/physical activity as a mediator could introduce bias into our models. Therefore, we chose to successively assess each part of the pathway between environment, physical activity, and health, as summarized in supplementary figure S1.

Exposure measures

Comment 5 (R1): Suggest some justification is given for the 3 variables used to define an active environment with relevant references.

The extent to which a neighbourhood encourages active living is also referred to in the literature as "walkability." The concept is widely understood and measured to be a combination of density, diversity, and design, and while limitations to the number of cited works for this journal prohibit us from extensively justifying the validity of these 3 variables, we cite the original paper that proposed

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

these three constructs (below), as well as multiple previous studies that have demonstrated links between these three constructs, physical activity, and health.

However, we omitted population density in the introduction of our manuscript and have made the following correction. We thank the reviewer for drawing our attention to this issue.

Page 4, line 22:

> "Active living environments, also widely known as 'walkable environments', are places that are easy to navigate with well-connected walking paths and have a number and variety of destinations[3]. These neighbourhoods are understood to encourage active living – the kind of neighbourhood-based activity that tends to be 'built-in' to one's daily life."

Modified to:

> "Active living environments, also widely known as 'walkable environments', are places that are easy to navigate with well-connected walking paths, have a number and variety of destinations, and are more densely populated[3]. These neighbourhoods are understood to encourage active living – the kind of neighbourhood-based activity that tends to be 'built-in' to one's daily life."

Physical activity measures

Comment 6 (R2): The authors should include more information on the measure of walking and total PA used in the study. An assessment of walking in the previous 3 months is very challenging so I wonder what format was used to obtain this information and the extent to what facilitated vs. complicated recall. The same is true for total PA. I'm guessing that most of the information reported included exercise, some sort of structured high intensity activity. That is the information that is most likely recalled when questions are rather vague and aimed at medium/long-term recall (e.g. 3 months). If this is true, this is likely a poor measure of overall physical activity.

As detailed in the Canadian Community Health Survey's Derived Variable Specifications, the variables that are used to calculate average daily energy expenditure and are available in the Canadian Community Health Survey are:

- The number of times over the last 3 months respondents took part in an activity
- The average length of time spent doing this activity on each occasion. Times were assigned an average duration value for the calculation at: 13 minutes or 0.2167 hour, 23 minutes or 0.3833 hour, 45 minutes or 0.75 hour, and 60 minutes or 1 hour.

Briefly, these values were multiplied by 4 (3 months x 4 = 12 months), multiplied by a standard MET value for the activity type (eg. a MET value of 3 kcal/kg/hr was used for walking), and then divided by 365 days to yield a daily average energy expenditure associated with the activity. Daily energy expenditure for overall leisure time physical activities was calculated by adding all daily energy expenditure values associated with unique activity types together. This method has been used extensively in the CCHS as well as other Canadian health surveys such as the National Population Health Survey.

We understand that readers could benefit from a brief description and citation of this derivation, and have therefore made the following augmentation:

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Beginning on page 6, line 48:

> "We assessed the average daily energy expenditure related to walking and to leisuretime physical activity, which we refer to as "walking and "physical activity," respectively. Daily energy expenditure was calculated based on respondents' self-reported activities in the last three months from baseline survey response. Frequency and time spent walking were multiplied by an assigned metabolic equivalents (MET) value of three for walking and divided this number by 365 days to yield daily energy expenditure in kcal/kg/day."

Modified to:

> "We approximated average daily energy expenditure related to leisure-time walking and to leisure-time physical activity for each respondent, which we refer to as "walking and "physical activity," respectively. Daily energy expenditure for leisure time physical activity is available as a derived variable in the CCHS and has been described previously[21].
> Average daily energy expenditure for walking was derived using the same method.
> Briefly, the calculation is based on respondents' self-reported activities in the last three months from baseline survey response. Frequency and time spent walking were multiplied by an assigned metabolic equivalents (MET) value of three for walking. We then divided this number by 365 days to yield daily energy expenditure in kcal/kg/day."
>
> We also included the following citation:
>
> 21. Statistics Canada. Canadian Community Health Survey (CCHS) Annual Component, 2009-2010 Common Content: Derived Variable (DV) Specifications. Ottawa: Statistics Canada, 2011.

Comment 7 (R2): Also related to my comment above. It was not clear to me how energy expenditure was calculated. The authors indicate MET.hours or MET.min were divided by 365 to get to cal/kg/day. Shouldn't the number be divided by approximately 90 days considering your assessment was of the last three months? The actual kcal/kg/day don't look right to me.

We apologize for the lack of clarity in how average daily energy expenditure was derived. We hope the answer to comment 6 addresses these concerns.

Comment 8 (R2): Please clarify by showing your math/calculations. Please share the same calculations that support the following statement: "This cut-off (1.44 kcal/kg/day) is equivalent to the recommended 150 minutes or more per week of moderate to vigorous exercise"

This is a method that is based on the CCHS procedure for calculating average daily energy expenditure, and similar cut-offs have been used in the literature. We have added the calculation as a supplementary figure (S2) to the appendix. We also included reference to this figure on page 8, line 18:

> "This cut-off is equivalent to the recommended 150 minutes or more per week of moderate to vigorous exercise[25], which we applied to walking alone, and to overall physical activity."

Modified to:

> "This cut-off is equivalent to the recommended 150 minutes or more per week of moderate to vigorous exercise[25], which we applied to walking alone, and to overall physical activity (Supplementary figure S2 for sample calculations)."

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

Comment 9 (R2): Still related to kcal/kg/day, please explain why did you choose this metric as opposed to MET.min or MET.hours that have a direct link to meeting not meeting the guidelines? What about just using duration since most of your results are focused on walking?

We thank the reviewer for the opportunity to discuss this analytic decision. While deriving MET-minutes or MET-hours could be done, we used the method for deriving average daily energy expenditure that is consistent with the CCHS. This is an approach that has been validated and used extensively for the Canadian context. The reviewer's suggestion of using duration only is reasonable, however we wanted to derive comparable measures for overall physical activity and for walking. Duration of time spent walking and overall physical activity would not be comparable, due to the differences in MET values associated with different activity types. This derivation was also necessary for calculating the proportion of leisure time physical activity energy expenditure attributable to walking, as seen in Figure 2B.

Outcome measures

Comment 10 (R1): ICD-10 E codes include many endocrine and metabolic causes of death unlikely to be influenced by physical activity. Consider restricting to deaths related to diabetes and obesity.

We tested this suggestion, and we were also motivated to return to the ICD-codes and specifically select those conditions that are more likely to be influenced by physical activity, removing conditions that are congenital in nature and/or less likely to be rooted in behavior. Instead of wholesale inclusion of all circulatory (I00-I99) and endocrine, nutritional and metabolic (E00-E99) codes, we re-ran our analyses and included:

- I10-I15 – hypertension
- I20-I25 – Ischaemic heart disease
- I50 – heart failure
- I61-I69 – Cerebrovascular diseases, excluding subarachnoid haemorrhage
- I70-I74 – Select codes for diseases of arteries, arterioles and capillaries
- E11-E14 – diabetes (excluding T1D)
- E65-68 - Obesity and other hyperalimentation
- E78 - Disorders of lipoprotein metabolism and other lipidaemias

This difference in ICD code selection led to a reduction of 740 premature

cardiometabolic deaths, which brought the total number of premature deaths from 4625 to 3885 deaths (16 per cent reduction):

	broad classification	restricted classification	No. of deaths censored	% reduction in no. of deaths
Older women	1750	1465	285	16.3
Older men	1425	1265	160	11.2
Middle-age women	490	385	105	21.4
Middle-age men	960	830	130	13.5

Changes in estimates for associations of walking and premature cardiometabolic mortality, and the active living environment and premature cardiometabolic mortality were minimal as a result of the change in ICD code selection.

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

We have added supplementary figures S5 and S6 and have modified the manuscript text to reflect these changes.

Notably, we have added the following sentences on page 7, after line 14:

> "We also tested a definition for cardiometabolic death based on a restricted set of ICD codes for certain cardiovascular diseases (including I10-15, I21-25, I50, I61-69, I70-74) and metabolic diseases (including E11-E14, E65-68, E78) that have stronger etiologic links to physical inactivity."
>
> Page 11, line 35:
>
> "Associations between overall physical activity and premature cardiometabolic mortality were found for all groups, using both broad and restricted ICD classifications (Supplementary figures S4, S5)."

Page 12, line 5:

> " Restricted ICD-code classification rendered similar results to analyses based on broad ICD-code classification (Supplementary figure S6).

Unfortunately, the longer length of time required to run competing risks models did not permit us to release supporting analyses for competing risks before COVID-19 laboratory closures occurred. However, we note that there was little difference between results of cox proportional hazards models and competing risks models in the previous analysis, and 2) there was little difference between models using the broad classification of cardiometabolic death, and models using the restricted classification. We expect similarly negligible differences for competing risks models using the restricted classification of cardiometabolic death.

Self-selection as a confounder

Comment 11 (R2): The most novel piece in the study is the add-on information on living environment and the extent to what individuals living in active living environments are more active and likewise, have a lower risk of premature mortality. However, in this study it is not possible to determine if individuals that were more active in active living environments did accumulate more activity in these neighborhoods or were simply, individuals that were already active among other characteristics (e.g., higher income, high SES, etc) and therefore, more likely to live in such environments. This is an important limitation and the authors should elaborate more on this possibility. Maybe conduct sensitivity analysis stratified by confounders and see if associations hold.

The reviewer has raised what will be a perennial issue for linked data studies involving human behaviour: whether associations between the built environment and health arise from behavioral responses to the environment, or from individual-level motivations. We acknowledged this limitation in the discussion on page 14, line 27:

> While we were also unable to adjust for residential self-selection, such adjustment has resulted in only minor impacts in some studies examining built environment associations with walking and obesity.

With respect to the other characteristics cited by the reviewer, we note that all models were adjusted for both income and education. The suggestion to conduct sensitivity analyses stratified by

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

confounders is an interesting idea, however we chose our subgroups based on a priori research questions related to premature cardiometabolic death. Further sub-division of these groups by income or education would render such findings susceptible to issues of multiple-testing and diminished sample sizes.

Descriptive statistics

Comment 12 (R2): Also, please add table 1 with descriptives and n deaths by level of active living environment. This will clarify how walking and potential demographics/confounders are distributed and might affect your results.

The reviewer's request for such is understandable. However, there are two main reasons we did not include this cross-tabulation. First, the sample size of each subgroup results in cell counts that are too low to be authorized for release by Statistics Canada. Second, population/death counts in each ALE class are not distributed evenly and are largely driven by population size. We are confident that our current descriptive table as well as our consistent adjustment for these factors in all models will provide sufficient evidence for readers.

We note that a descriptive table for the overall cohort categorized by ALE class could be helpful to readers. While laboratory closures resulting from the coronavirus (COVID-19) prohibit us from releasing further counts and analyses at this time, this information can be made available upon request when facilities re-open.

Analysis

Comment 13 (R2): From figure 2 looks like the differences between least vs more active living environments ranges from 0.2 to 0.4 kcal/kg/day. How meaningful is this? This range looks irrelevant if you were to re-calculate this back to METs. Please clarify. It is also not clear the trend between walking and environment is linear. Add p trend to figure 2.

From a population health level, we would argue that the pattern in mean daily energy expenditure levels among active respondents are meaningful, especially when taken together with the proportion of people that are completely inactive. We note that the trend referenced by the reviewer are among those who report any walking ("walkers") only.

This exploratory component of the analysis was descriptive in nature and was meant to add context to the association between active living environments and mortality, which was our main research question of interest. We chose to describe physical activity levels separately for walkers and non-walkers because we felt it necessary to show the extent to which the trends are driven by levels of complete inactivity versus the physical activity levels among those who are active.

Whilst we understand the desire to include tests of trend, we see several issues with this approach. First, the underlying assumption of linearity for many such tests would be difficult to impose on the relationship between active living environments and walking – which we suspect, is not necessarily linear. Second, conducting a test of trend with five datapoints (means) for each outcome/subgroup is highly susceptible to outliers, as well as the strong possibility that the result is driven by a single ordinal value – which in this case, is likely to be ALE class 5. For these reasons, we believe that measures of correlation and their respective p-values are of limited value to the reader. We trust that

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

readers will visually detect relevant trends in figures 2 and S2 (note that we corrected and updated supplementary figure S2 during the course of this review).

For reference, we have included results of test of trend in the form of a Spearman's rank correlation between the five mean energy expenditure values for each ALE class below.

Reference	Outcome	Subgroup	R_s	P
Figure 2, Figure S2	Walking	Older women	1.0	0.02
Figure 2, Figure S2	Walking	Older men	1.0	0.02
Figure 2, Figure S2	Walking	Middle-age women	0.6	0.35
Figure 2, Figure S2	Walking	Middle-age men	0.9	0.08
Figure S2	Physical activity	Older women	0.1	0.95
Figure S2	Physical activity	Older men	0.1	0.95
Figure S2	Physical activity	Middle-age women	0.1	0.95
Figure S2	Physical activity	Middle-age men	0.9	0.08

Comment 14 (R1): Consider including the data in supplementary table S2 in the main manuscript. While walking is greater in the areas with higher ALS this did not have much impact on overall physical activity except in elderly women. This many explain why there was no clear association with premature CM death for these groups.

We thank the reviewer for this observation, as this was the purpose of including table S2 and we are glad that this finding was clear. For the main body of the paper, we wanted our readers to focus on the associations between active living environments, walking, and cardiometabolic mortality, and felt that the addition of overall physical activity could obfuscate this focus. We are confident that readers will refer to the appendix for our claims about walking versus physical activity.

Comment 15 (R2): In Figure 4, show results stratified for all categories of active environment.

We appreciate the reviewer's attention to detail on this point, as we did not provide an explanation for why we carried out survival analyses using an indicator variable for "less favourable" versus "more favourable" active living environments. For survival analyses of the active living environment, we lacked the power to include ALE as a 5-level measure, as increasingly low numbers of people reside in higher ALE classes, and the deaths in these groups are also very low. We therefore aggregated ALE classes 1-3 and 4-5.

We have added the following sentence at line 38, page 8:

> "Due to low sample sizes and events in ALE class 5, active living environment classes 1 through 3 were aggregated as less favourable, while classes 4 and 5 were aggregated as more favourable for survival analyses."

Comment 16 (R2): Add n individuals and n deaths to Figure 3 to show sample size and outcomes for each category of walking.

We have incorporated the reviewer's suggestion in supplementary figure S5. Unfortunately, we are unable to provide these counts by physical activity group for figures 3 and S4 at this time, as this

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

would require further vetting from the research laboratory. However, counts can be made available upon request when facilities reopen.

Analysis of confounding

Comment 17 (R2): Also interesting that your full vs reduced models (Table S2) barely differ. This might indicate greater amounts of either residual or unmeasured confounding, or both. Only a limited list of confounders was included in the models and there is no information on SES or income, likely great predictors of residential location. Please comment.

We share the reviewer's surprise towards the robustness of association between the active living environment and cardiometabolic mortality. Indeed, neighbourhoods that are favourable for active living may be more powerful than we had expected!

In contrast to previous ecological studies with limited sociodemographic information available, we would argue that this individual-level study accounted for a relatively substantial list of confounders, while also bearing in mind model efficiency and parsimony.

We included seven confounders in models of the active living environment and premature cardiometabolic mortality, and eight confounders in models of walking and premature cardiometabolic mortality. We included age (entered as a continuous variable), education, area-level income, survey cycle, smoking status, obesity, and the presence of two or more chronic conditions. In models of the active living environment and walking/physical activity, we also adjusted for season of survey response to account for potentially lower activity levels during the winter months in Canada. These variables were chosen a priori, because they are strong predictors of cardiometabolic mortality, and could also be associated with living in certain neighbourhoods.

Our objective was to model the relationship between the active living environment and premature cardiometabolic mortality and account for as many individual-level confounders as possible, knowing that even the best models will have unmeasured confounding and measurement error. Even after adjusting for our two proxy measures of SES (education and income), associations with the active living environment persisted.

Discussion

Comment 18 (R2): I'm not totally familiar with the literature in walking and active environments but looks like there are a few already published studies on this topic. The discussion starts by mentioning this is the "…first study to examine associations between active living environments and premature cardiometabolic health". Probably not an accurate statement or maybe very nuanced considering the at least couple of papers published on environment walkability and mortality. Consider removing.

While we appreciate the level of caution regarding the strength of our claims in this paper, our study is indeed the first study to examine the association between active living environments and premature cardiometabolic death (not "health", as stated above). Previous studies have also used ecological approaches. We also draw attention to the strengths of the individual-level linked data analysis used in this study by stating (Line 14, page 12):

"To our knowledge, this is the first individual-level study to examine associations between active living environments and premature cardiometabolic death."

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

VERSION 2 – REVIEW

REVIEWER	Pedro Saint-Maurice National Cancer Institute
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	I appreciate the challenges in addressing some of the concerns I previously stated, given the current situation and limited (or no) access to the RDC. However, there are still a few major concerns that need to be addressed. My concerns below reiterate previous comments I had and that I think were not appropriately addressed in the revised manuscript. Comment 4: Despite that aim 1 does refer to mediation there was still no attempt at testing this mediation hypothesis. Please adjust your active environment-mortality association to walking and provide an estimate of attenuation so that mediation is even plausible. If there is attenuation, then this will provide preliminary support to your mediation hypothesis. Comment 6: There is likely great bias in recalls on medium/long time frames (eg.,3 months); more so when asking about frequency and type of activity. This source of error can potentially lead to systematic bias. There is also the assumption that the previous 3 months represent usual (yearlong) activity. This last is more an issue of stability and also deserves to be mentioned. Please address these in the discussion and how could they potentially affect your results. Comment 13: P trends are a very common approach to demonstrate if there is an overall relation between a given exposure and outcome. If you don't feel comfortable with this test, please present an alternative test to support that there is a non-linear (or linear) and significant association between walking and active environment. For example, it is not clear that this statement is supported by your results: "Among those who reported walking, the highest average daily energy expenditures were reported in the most favourable active living environments (classes 4 and 5)." Also, the distribution of EE looks highly skewed so you might want to consider interpreting the median values instead of means. From your figure 2 seems that you have wide confidence intervals and likely, there is no gradient, considering that mean EE is not statistically significant across ALE levels. I also noticed that in some circumstances, your upper confidence limit might go beyond your max value on the y-axis. For example, CIs for Mean EE for walking at ALE5. This concern also applies to the remaining of the results described in this paragraph and figure S3.

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

VERSION 2 – AUTHOR RESPONSE

Overview

<u>Comment 2</u> (R2): I appreciate the challenges in addressing some of the concerns I previously stated, given the current situation and limited (or no) access to the RDC. However, there are still a few major concerns that need to be addressed. My concerns below reiterate previous comments I had and that I think were not appropriately addressed in the revised manuscript.

We are happy to provide further clarification. Please note:

1. **Reviewer comments are categorized under headings in bold.**
2. <u>Comments are numbered and underlined</u>
   (and are ordered by category, not the order presented by reviewers).
3. Comments from the first and second reviewer are labelled (R1) and (R2), respectively.
4. Our direct responses are indented and in italics.
5. References to specific changes to the manuscript are indented and highlighted.

Analysis

<u>RE: Comment 13</u> (R2): P trends are a very common approach to demonstrate if there is an overall relation between a given exposure and outcome. If you don't feel comfortable with this test, please present an alternative test to support that there is a non-linear (or linear) and significant association between walking and active environment. For example, it is not clear that this statement is supported by your results:
"Among those who reported walking, the highest average daily energy expenditures were reported in the most favourable active living environments (classes 4 and 5)."
Also, the distribution of EE looks highly skewed so you might want to consider interpreting the median values instead of means. From your figure 2 seems that you have wide confidence intervals and likely, there is no gradient, considering that mean EE is not statistically significant across ALE levels. I also noticed that in some circumstances, your upper confidence limit might go beyond your max value on the y-axis. For example, CIs for Mean EE for walking at ALE5. This concern also applies to the remaining of the results described in this paragraph and figure S3.

We would like to clarify that that the whiskers are of box plots, not of confidence intervals, as is noted in the caption for figure 2. To make this clear, we have modified the figure caption with a description of box plots:

Boxes represent the interquartile range (25th to 75th percentile) and the horizontal line represents the median.

In appreciation of the reviewer's comment, we have included tests for trend in the manuscript and figures, and the methods have been updated to reflect these additions on page 9:

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

“Trends across the 5 ALE classes were evaluated by entering the categorical ALE variable as an ordinal variable in a generalized linear model with a log link, adjusted for individuallevel factors.”

We have also modified figure 2 and supplementary figure S3 accordingly:

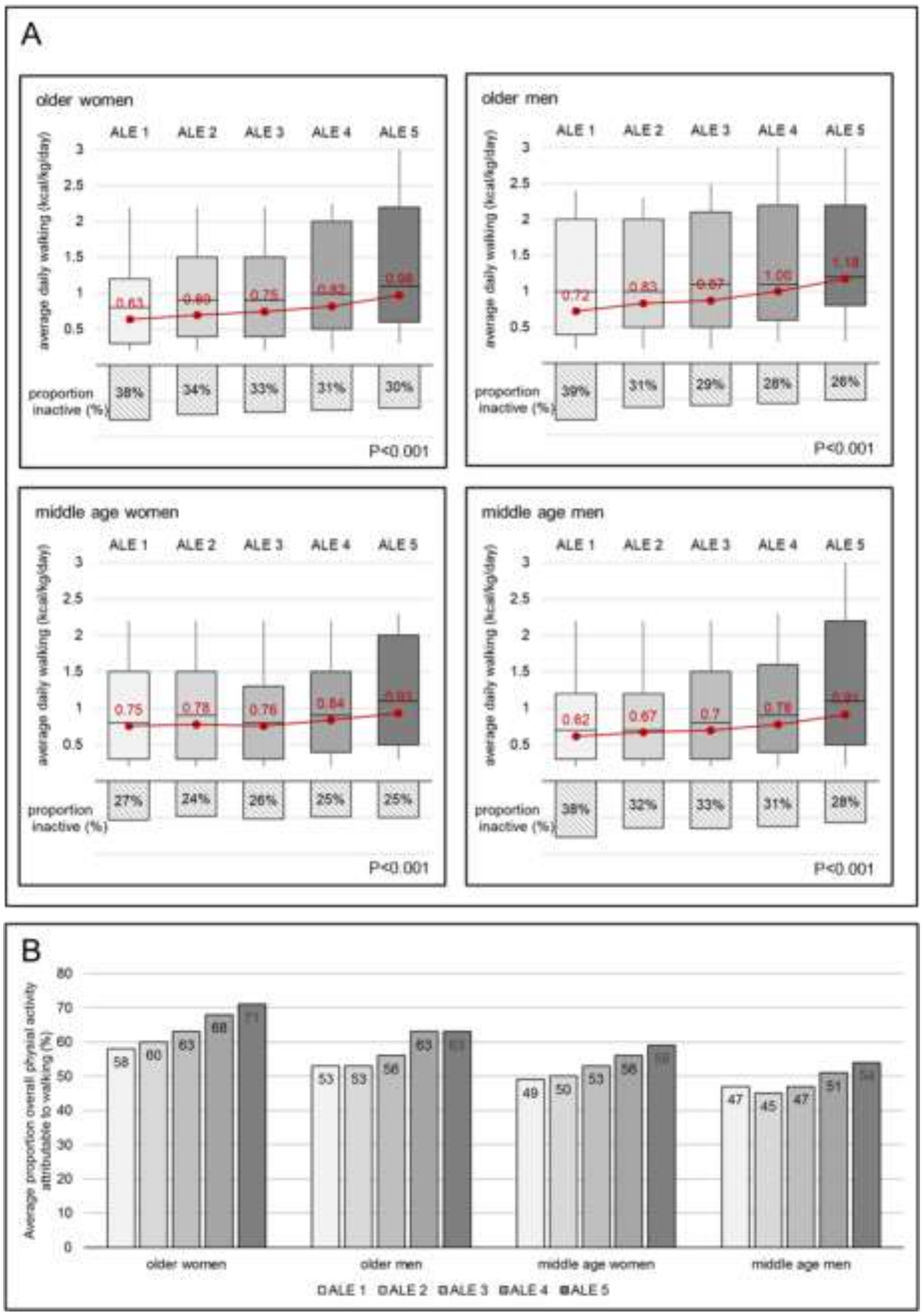
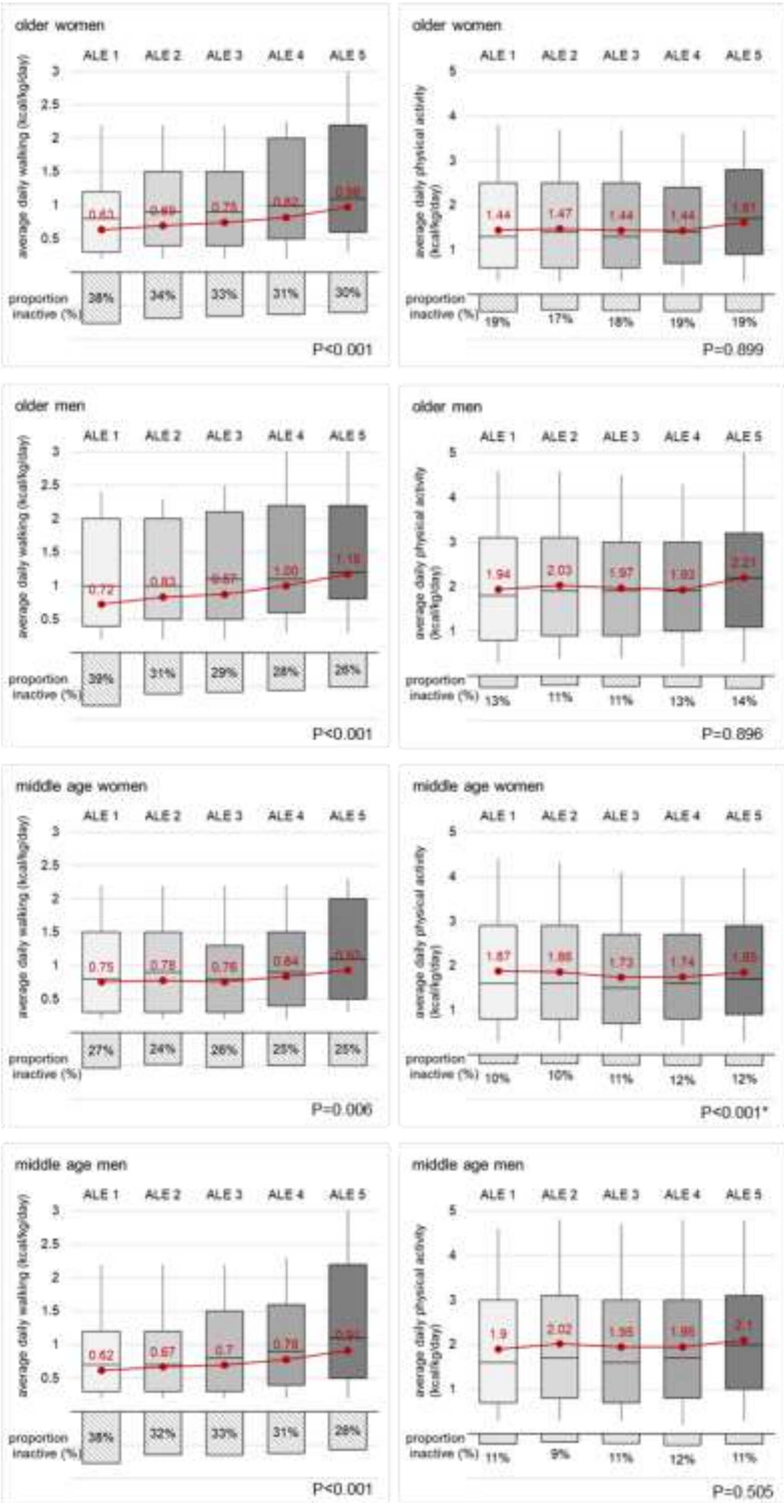


Figure 2. Average daily energy expenditure related to walking.

Data are mean or (%). Active living environment (ALE) 1 represents the least favourable environment, while ALE 5 represents the most favourable environment. Panel (A) contains box plots, mean energy expenditure related to walking, and proportion that report no walking. Boxes represent the interquartile range (25th to 75th percentile) and the horizontal line represents the median. Note that upper and lower limits of the boxplots have been adjusted to represent the 90th and 10th percentile, respectively, for confidentiality purposes. Red markers and trend line represent means in each ALE class with test

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

for trend (P<0.05). Panel (B) shows the proportion of all physical activity that walking accounts for, by active living environment favourability.



Supplementary Figure S3: Average daily energy expenditure related to walking compared with physical activity. Active living environment (ALE) 1 represents the least favourable environment, while ALE 5 represents the most favourable environment. Panel (A) contains box plots, mean energy expenditure related to walking, and proportion that report no walking. Boxes represent the interquartile range (25th to 75th percentile) and the horizontal line represents the median. Note that upper and lower limits of the boxplots have been adjusted to represent the 90th and 10th percentile, respectively, for confidentiality purposes. Red markers and trend line represent means in each ALE class with test for

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

positive trend ($P<0.05$). *Average daily energy expenditure for overall physical activity was inversely graded by ALE class for middle-aged women.

Study framing

RE: Comment 4 (R2): Despite that aim 1 does refer to mediation there was still no attempt at testing this mediation hypothesis. Please adjust your active environment-mortality association to walking and provide an estimate of attenuation so that mediation is even plausible. If there is attenuation, then this will provide preliminary support to your mediation hypothesis.

The reviewer makes an important point and suggestion. Formal mediation analyses of whether the active living environment does indeed operate through certain physical activity pathways is a crucial endeavor. Our approach for this manuscript was to provide the population-level descriptive characteristics of active living environments, physical activity, and cardiometabolic death. We did not frame this manuscript as a formal examination of mediation and have not comprehensively evaluated the necessary components for such an analysis. We feel that simple insertion of our physical activity measures into the models of active living environments and mortality could be misleading, given the complicated and interrelated nature of these constructs.

We take seriously the reviewer's suggestion and will continue to pursue formal mediation analysis for the subject of a future paper.

Physical activity measures

RE: Comment 6 (R2): There is likely great bias in recalls on medium/long time frames (eg.,3 months); more so when asking about frequency and type of activity. This source of error can potentially lead to systematic bias. There is also the assumption that the previous 3 months represent usual (yearlong) activity. This last is more an issue of stability and also deserves to be mentioned. Please address these in the discussion and how could they potentially affect your results.

Acknowledging the importance of the points raised by the reviewer, we have made the following augmentation to the discussion on page 15:

Our study was limited to self-reported physical activity, which is less precise than objective measures[41] and is vulnerable to recall bias, especially over longer time frames[42]. However, such bias is likely to be non-differential with respect to the active living environment – an assignment unknown to study participants at survey response. Moreover, the large sample size afforded by multiple waves of a national survey allowed us to overcome the limitations of self-report measures that would likely have generated estimates biased towards the null, and helped uncover nation-wide physical activity variations that could otherwise be overlooked.

We also added the following references:

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

41. Prince SA, Adamo KB, Hamel ME, et al. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56. doi: 10.1186/1479-5868-5-56

42. Haskell WL. Physical Activity by Self-Report: A Brief History and Future Issues. J Phys Act Health 2012;9:S5-S10. doi: DOI 10.1123/jpah.9.s1.s5

OTHER REVISIONS OF NOTE

Descriptive statistics. Regarding Comment 12 (R2) from the first set of comments from reviewers, we were able to produce a descriptive table for the overall cohort categorized by ALE class could be helpful to readers, having regained partial access to our data laboratory. We made the following addition to the results section of the manuscript on page 11:

"Baseline characteristics of the entire study population stratified by active living environment revealed that the most favourable ALES tended to have the lowest proportion of obese respondents, the highest proportion of highly educated respondents, and the lowest area-level household income on average (Supplementary Table S2).

The following sentence was also added to the discussion on page 13:

"The fact that these associations were robust to adjustment for social class (which, for some measures such as income, were inversely related to active living environment favourability, Supplementary Table S2), speaks to the importance of neighbourhoods in shaping behaviours and health, over and above the sociodemographic composition of the people living in the neighbourhood."

Outcome variable. Regarding Comment 10 (R1) from the first set of responses, our re-analyses were run using only the restricted set of codes recommended by reviewer 1. We have removed supplementary tables S5 and S6 that were added in the first revision, and have modified the methods section to reflect these changes on page 7, line 14:

"The cause of interest was death due to metabolic diseases (ICD 10 codes E11-E14, E65-68, E78) or cardiovascular conditions (I10-15, I21-25, I50, I61-69, I70-74) which we term cardiometabolic mortality."

Additional reference. We added an important reference to the manuscript:

13. Griffin BA, Eibner C, Bird CE, et al. The relationship between urban sprawl and coronary heart disease in women. Health Place 2013;20:51-61

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

VERSION 3 – REVIEW

REVIEWER	Pedro Saint-Maurice National Cancer Institute - USA
REVIEW RETURNED	14-Sep-2020

GENERAL COMMENTS	Thank you for the extra work, more so given the challenges accessing the data and getting back to the physical work space.

BMJ Open: first published as 10.1136/bmjopen-2019-035942 on 20 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.