Author’s response to reviews

Title: Trajectories of physical activity, from young adulthood to older adulthood, and pancreatic cancer risk; a population-based case-control study in Ontario, Canada

Authors:

Jaspreet Sandhu (sandhj16@mcmaster.ca)
Vanessa De Rubeis (derubevg@mcmaster.ca)
Michelle Cotterchio (michelle.cotterchio@cancercare.on.ca)
Brendan Smith (brendan.smith@oahpp.ca)
Lauren Griffith (griffith@mcmaster.ca)
Darren Brenner (darren.brenner@ucalgary.ca)
Ayelet Borgida (Ayelet.Borgida@sinahealthsystem.ca)
Steven Gallinger (sgallinger@rogers.com)
Sean Cleary (cleary.sean@mayo.edu)
Laura Anderson (ln.anderson@mcmaster.ca)

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Author’s response to reviews:

Dear Dr. Linda Gummlich and Dr. Dylan Smith, Editors, BMC Cancer,

Thank you for considering our manuscript. We appreciate the thoughtful reviewer comments and have addressed all comments raised by both reviewers. A point-by-point response is provided below and an updated manuscript (marked with track changes) has been uploaded.

Sincerely,

Laura Anderson, PhD
TECHNICAL COMMENTS:

1. Please include the email addresses for all authors on the title page. The corresponding author should still be indicated.

RESPONSE: We have now included the email addresses for all authors on the title page.

2. Please include a statement in the Authors' contributions section to the effect that all authors have read and approved the manuscript and ensure that this is the case.

RESPONSE: We have now included this in the author’s contributions section (Page 16).

REVIEWER REPORTS:

Dominique Michaud (REVIEWER 1)

There is great interest in whether physical activity at different points during a lifetime is associated with pancreatic cancer risk and few studies have data to address this. Data from studies on adulthood physical activity and pancreatic cancer are inconsistent; measurement error in assessment of physical activity may have contributed to the null findings. Unfortunately, despite having collected data on physical activity at different decades in the cases and controls, the measurement of physical activity is extremely crude in this study (there were no questions on what type of exercise the participants engaged in, just two questions on "moderate" and "vigorous" activity). The findings for the trajectories are null and most odds ratios have very wide confidence intervals - it is unclear if this means there are no associations, or if the PA measures have too much measurement error to detect any associations. So, while the study is novel, it uses poor methodology and is inconclusive. The discussion addresses potential recall bias, but not random measurement error from an oversimplified PA assessment - this should be discussed.
RESPONSE: We have now addressed the potential error associated with the simplified physical activity assessment, “The lack of objective measurement may introduce measurement error due to the simplified nature of the self-reported assessment via questionnaire. The use of an objective measure such as an accelerometers, pedometers or heart-rate monitors may enhance the accuracy and precision of measurement (33). However, other studies that have used similar self-reported measures to assess physical activity, have provided some possible evidence that increased physical activity may be associated with a reduction of risk of pancreatic cancer (35-37).” (Page 16 Paragraph 1).

Authors should include results from a study which reported associations with adolescent and adult physical activity in relation to pancreatic cancer (cohort from Shanghai) published in Cancer Epidemiol Biomarkers Prev. 2018 Apr; 27(4): 479-487.

RESPONSE: Thank you for providing this recommendation. We have now referenced this study in the discussion, “A recent study reported possible differences by sex when studying physical activity in adolescence and adulthood and risk of pancreatic cancer (33). These results are consistent with our current study that suggested possible sex differences. Future studies may want to further research how sex modifies the association between physical activity throughout the life-course and pancreatic cancer” (Page 15 Paragraph 2).

Table 4 includes categories for engaging in moderate activities with the lowest and referent level being at "never/rarely" with very small numbers of case/controls. The next category up "a few times a month" still represents a very low activity level but has more cases and controls. Given the estimates (and confidence intervals) for the moderate exercise analysis are very unstable due to the small numbers in the referent, it would make sense to collapse the two bottom categories. Also, it doesn't seem plausible that exercising "a few times a month" would result in an OR of 0.27 in men - stronger inverse associations than those exercising more. It is also misleading to report the OR of 0.56 from table 4 in the abstract, given the implausible results from this table - I think this is more likely to be a chance finding.

RESPONSE: Thank you for this suggestion, we have now updated Table 4 (Page 23) and updated the results throughout the manuscript. We have also modified this statement in the abstract, “When time periods were evaluated separately, the OR for the association between high moderate activity in the 20s-30s and pancreatic cancer was 0.89 (95% CI: 0.64, 1.25) and some sex differences were observed.” (Page 2 Paragraph 3).
Was smoking duration or dose available and if so could these also be included in the multivariate models?

RESPONSE: We have now corrected the explanation of how smoking was included in the multivariable model, “Smoking was included in the model as a categorized pack-years variable. This variable was derived from the number of years an individual smoked and the average number of cigarettes smoked per day. (Page 8 Paragraph 1). We have also included the distribution of this variable in Table 1. (Page 20 Table 1).

Verena Katzke (REVIEWER 2)

The authors evaluated trajectories of physical activity over time and risk of pancreatic cancer in a case-control study. Despite having identified several trajectories, these were not associated with pancreatic cancer risk. However, physical activity at young age was inversely associated with risk, which was confined to men in sex-stratified analyses. The authors conducted a very interesting research study with a novel approach to capture changes of physical activity comprehensively over one's life course and associated these with risk of pancreatic cancer. Despite the novel approach, the study setting per se is rather weak, given the case-control design and behavioural recall to assess physical activity at three time points in the past.

Abstract

"at" missing in the last sentence of your results section "…20s-30s, but not AT older ages…”

RESPONSE: This correction has been made in the results section of the abstract (Page 2 Paragraph 3).

Background

Page 3, line 46: The WCRF CUP has been updated 2018 for pancreatic cancer, please update your reference accordingly (reference 10).

RESPONSE: We have now consulted the 2018 update for the WCRF, and the citation has now been updated (Page 30 Reference list – reference 10).
Page 3, line 56: you mention that life-course approaches with respect to physical activity had been evaluated for some cancer, hence only provide an overview article on pancreatic cancer. Could you search for some newest articles on cancers and physical activity and add these? This would be much more informative and would show the increasing use of trajectory modelling in the literature.

RESPONSE: This section has now been updated, referencing studies that modelled physical activity trajectories across the life course and adult disease outcomes, “An increasingly utilized approach to understand life-course exposures is the use of trajectory modelling (13-15). Few studies (16-18) have used this approach to understand the impact of physical activity across the life-course and disease outcomes in adulthood.” (Page 4 Paragraph 1).

Methods

Page 5, sample size: Would you be so kind as to draw a flow chart? The sampling is rather confusing.

RESPONSE: We have now included a flow diagram of the sampling for this study, “Figure 1 displays the sampling flow chart” (Page 6 Paragraph 1). Figure 1 can be found on Page 26.

Page 7, measurement of other variables: did the questionnaires capture lifestyle variables before diagnosis, and if yes, how many weeks/months/years? Was this procedure comparable to the assessment of physical activity? And are diabetes and pancreatitis self-reported or had they been validated by a physician? I would appreciate it if you could be more precise here.

RESPONSE: Clarification about measurement of variables has now been added to the methods, “Assessment of all other variables was collected via self-reported mailed questionnaires two years prior to cancer diagnoses for cases or two years earlier for controls” (Page 7 Paragraph 2).

To some extend I do understand that you did not include BMI as a confounder due to the causal pathway problematic. However, I do not see the point in excluding diabetes and pancreatitis. Both are associated with pancreatic cancer, but (1) are they related to physical activity and (2) are they in the causal pathway? I have strong doubts.
RESPONSE: We ran an additional model that included diabetes, BMI and pancreatitis as we hypothesized these as variables that may potentially lie on the causal pathway. However, the results did change in a meaningful way, and therefore we did not present the results. For your interest, the ORs when including BMI, diabetes and pancreatitis in the model were: Group 1: 1.00 (reference); Group 2: 1.14 (0.75, 1.71); Group 3: 1.02 (0.65, 1.62); Group 4: 1.18 (0.59, 2.39); Group 5: 0.74 (0.45, 1.20); Group 6: 1.72 (0.97, 2.03). We have now included this in the methods “Diabetes, pancreatitis and current body mass index (BMI) were not included in the adjusted model as they were hypothesized to potentially be on the causal path between physical activity and pancreatic cancer. A third analyses was run that included these three variables in additional to the potential confounding variables” (Page 8 Paragraph 1) and the results, “None of the ORs changed substantially when BMI, diabetes and pancreatitis were included, in addition to the other variables, in the fully adjusted model (results not shown).” (Page 11 Paragraph 2).

Page 8, trajectories: Please make sure that the reader understands what PROC TRAJ is because this is no standard SAS procedure and cannot be found in the statistical package of SAS. It would also be nice to read more on how trajectories are actually formed. According to the literature, defining trajectories seems to more complex than the way you write it (see possible reference below).

RESPONSE: We have clarified that this package has to be downloaded onto SAS in the methods, “PROC TRAJ, is a statistical package that is available free of charge for download (www.andrew.cmu.edu/user/bjones/) to implement in SAS for group-based trajectory modeling (25). Using this group-based trajectory modelling procedure we identified distinct subgroups (or clusters) among the study population which shared underlying trajectories of physical activity” (Page 8 Paragraph 2).

We have now elaborated and better explained the steps used to generate the trajectories following the framework proposed by Lennon et al. and consulting literature published by Nagin on life-course research using trajectories. “Trajectories were generated by consulting literature by Nagin (26) and following the proposed framework by Lennon et al. (27). We first identified the potential number of trajectories that may fit the model based on previous literature. A recent systematic review noted the most common number of trajectories of physical activity across the life-course were 3-5 (12). We tested models with up to 7 trajectories. The optimal model fit was determined based on the lowest Bayesian Information Criterion (BIC) across the various models. Significance of polynomial terms were also used to assess goodness-of-fit. Next, we calculated the average posterior probability, using a cut-off value of 0.70 (25). It is recommended, all trajectories hold a minimum of 5% group membership (30), however the increasingly active group held 3.6% of the study sample. When decreasing the number of classes within the model, this group remained so we retained all six trajectories. A six-class trajectory was determined to be the best model to fit this data. In accordance with studies of similar methodologies (29) and upon visual inspection, each trajectory was given a name.” (Page 9 Paragraph 1).
Results

Page 10, line 29 on: I would suggest to be more careful in your wording. It reads as if the associations were significant albeit they are not.

RESPONSE: This line has been corrected to ensure readers understand the associations noted are not statistically significant, “For example, the adjusted OR for the association between the ‘high activity in young adulthood with slight decrease in older adulthood’ trajectory and pancreatic cancer among males was 1.35 (95% CI: 0.72, 2.51) and for females the adjusted OR was 0.57 (95% CI: 0.27, 1.21). Similarly, for the “increasingly active” trajectory in males the adjusted OR was 2.53 (5% CI: 0.89, 7.20), whereas in females the adjusted OR was 0.62 (95% CI: 0.24, 1.61). However, none of these sex stratified associations were statistically significant at p<0.05 and confidence intervals were very wide and overlapped 1.0.” (Page 11 Paragraph 2)

Discussion

Page 13 limitations: I would suggest to emphasize in what directions the true associations could have been estimated due to your limitations, i.e. over- or under-estimation.

RESPONSE: This has now been included in the discussion, “Although self-reported recall of physical activity has been found to be a relatively valid measure (35-39), recalling physical activity at earlier periods of life may introduce additional measurement error. Future studies would benefit from prospective assessment of physical activity, which may decrease the risk of bias associated with recall. Further, we cannot rule out the possibility of recall bias leading to differential measurement error which may result in either over- or under-estimation of the true association” (Page 16 Paragraph 1).

Page 14, top: Recall bias does lead to differential misclassification in this study, and not the other way around, as the authors stated.

RESPONSE: Thank you for this suggestion, we have now corrected this wording in the manuscript, “Further, we cannot rule out the possibility of recall bias leading to differential measurement error” (Page 16 Paragraph 1).
Page 14, line 20: not only studies with a larger sample size but also a prospective design would be needed, i.e. prospective cohorts, that assessed physical activity and potential confounders independent of the outcome of interest, i.e. pancreatic cancer (no differential misclassification possible).

RESPONSE: This correction has now been made, “Future studies would benefit from prospective assessment of physical activity, which may decrease the risk of bias associated with recall.” (Page 16 Paragraph 1).

References


RESPONSE: We have now updated this citation to reflect the most updated version of the WCRF and CUP and have corrected the citation in the reference list (Page 30, Reference list – reference 10).

Number 20 lacks details on where to find the proc traj procedure in SAS. It is not a SAS procedure developed by SAS but a procedure developed by Jones and implementable in SAS and can be downloaded. Please add the link.

RESPONSE: The link to the citation has now been added to the reference (Page 30 Reference list – reference 25).

Hannah Lennon et al published an article on latent class trajectory modelling recently, this might be a good and new article to add to your list of references, i.e. in addition to reference 22 or by replacing it. The concept and how to interpret this approach is explained nicely. You may refer to this article for interested readers. (doi: 10.1136/bmjopen-2017-020683)

RESPONSE: Thank you for this suggestion, we have now included reference to this framework in the methods section of the manuscript (Page 9 Paragraph 1).

However, the most well-known author on these concepts is Daniel Nagin, see for example 10.1159/000360229 (doi). It would be good to elaborate on trajectory modelling in your methods section for the less experienced readers.

RESPONSE: We have now included reference to this article by Nagin in the methods (Page 9 Paragraph 1) (Reference 26).