nature portfolio

Peer Review File

A Prospective Study of Physical Activity and Cardiometabolic Diseases in association with Cancer Risk

Corresponding Author: Dr Heinz Freisling

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
I read the manuscript with interesting that investigated associations between physical activity and cancer risk in adults with and without a history of cardiometabolic diseases. It is generally well written. I have a few suggestions for this manuscript.
1. It is not clear to me why participants with CVD or typ2 diabetes at baseline were excluded. Including participants with cardiometabolic diseases, and conducted interaction analysis could also address the research question in this manuscript that whether the association between PA and cancer risk was independent of CMD.
2. It is not easy to understand what is PA-related cancer. How to define PA-associated cancer? Is there any consensus on this definition?
3. In the Introduction part, it is not clear to me why the authors indicated that “Furthermore, there is a lack of recommendations for individuals with cardiovascular diseases (CVD)”, since it was existed regarding the role of PA in the management of CVD.
4. In the Methods part, the authors indicated that “Model 1 was stratified by age”, should it be “…adjusted for…”.
5. This manuscript did not assess the influences of different types of PA on the cancer risk, which should be addressed as a limitation.

Reviewer #2

(Remarks to the Author)
Thank you for the opportunity to review the article by Gebremariam et al. on associations between physical activity and cancer risk in adults with and without a history of cardiometabolic diseases.
Strengths of the study include the use of multiple datasets across several countries, the large sample size which provides strong statistical power, and the clear description of the study methodology.
The authors combined physical activity from various domains, such as household and leisure time. Previous research has shown that leisure-time physical activity, but not occupational physical activity, is beneficially associated with the prevention of type 2 diabetes and cardiovascular disease. This phenomenon is often referred to as the "physical activity paradox." However, this paradox seems to be reversed in cancer prevention, where occupational physical activity appears more beneficial than leisure-time physical activity. For example, in the EPIC Italy study (PMID: 27832394), "In multivariate models, inverse associations with breast cancer risk emerged for increasing level of total (p trend 0.02), leisure time (p trend 0.04), and occupational (p trend 0.007) PA".
I encourage the authors to further analyze physical activity by different domains in their analysis. For example, it would be interesting to see the joint association of occupational physical activity and cardiometabolic disease on cancer risk.

Reviewer #3

(Remarks to the Author)
General comments
The topic of the present study is interesting, and the manuscript is very well written. The statistical analyses are appropriately conducted, and the results are clearly presented. The reviewer has several comments that may help further improve the manuscript.

Specific major comments
-Lines 188-191: Based on IARC (2002) or WCRF/AICR (2007), it is reasonable to assume that colon, breast, and endometrial cancers are generally considered PA-related cancers. However, is it appropriate to treat the other cancers as PA-related cancers? There is no explanation of how the authors defined PA-related cancers.
-Cancer ascertainment and Statistical Analysis: It is unfortunate that the authors did not examine the interaction between PA and CMD for specific cancer types. Because the mechanisms underlying the interaction between PA and CMD may differ by individual cancer type, examining this interaction at least for representative PA-related cancers (e.g., colon, breast, and endometrial cancers) would be of great interest to readers. The Swedish Mammography Cohort (reference 14) appears to show a significant interaction between PA and T2D on a specific cancer (i.e., endometrial cancer).
-Line 220: Is there no data on employment status in EPIC? It is not common to use workplace physical activity data as a covariate instead of employment status; however, there is no adequate explanation for this choice.
-Line 259: An explanation of why the analyses were stratified by age, sex, and recruitment centre (instead of adjusting for these variables) is missing.
-Line 260: It may not be common for height to be included as a covariate, but the explanation for this is missing.
-Line 275: The authors used the term “inactive”. In the results section, words such as “active adults” or “inactive adults” were also used. However, physical inactivity is generally defined as an insufficient level of PA to meet the current PA recommendations for health. It refers to a condition in which an individual does not engage in enough moderate- to vigorous-intensity PA (MVPA) to achieve substantial health benefits—typically, not accumulating at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic activity, or an equivalent combination thereof. Please correct this point and revise it throughout the manuscript.
-Line 329: The interactions between PA and CMD status (all p for interaction > 0.3) were not statistically significant; nevertheless, these results are the main findings of the present study. Therefore, the results of the interaction should not be presented in a supplementary table.
-Lines 354-356: The authors expressed the conclusion that “taken together, these results suggest that being physically active is beneficial for cancer prevention in adults living with or without T2D and/or CVD”. If they conclude so, why did they not use “inactive with cardiometabolic disease” as a reference category (instead of using “active without cardiometabolic disease” as a reference)?

Other comments
-Line 145: The words CVD and T2D should be deleted.
-Lines 192-194: The explanation of the reason for the exclusion of non-melanoma skin cancer is missing.
-Lines 194-199: There is no explanation of how data from individuals who developed cancer multiple times were processed.
-Covariates: It is unclear whether all covariates, including BMI (weight and height) were assessed by a self-reported questionnaire.
-Line 322: UK Baiobank should be expressed as UKB.
-Lines 386- 407: Analysis of joint association, objective diabetes status, and large sample sizes may be strengths that should be mentioned. No data on employment status in EPIC may be a limitation that should be acknowledged.
-Line 435: A period is missing.

Reviewer #4

(Remarks to the Author)
Alem et al. integrated data from the EPIC and UK Biobank, investigated the association between PA and the risk of cancer, and assessed the interaction between PA and cardiometabolic diseases in relation to cancer risk. The results are somehow negative but still very meaningful. But I have several concerns in the background and method:

Major:
Introduction:
Relevant knowledge needs to be updated. ESC and AHA both published PA guidelines for CVD patients in 2021 and 2024, respectively, rendering the research gap mentioned in the introduction no longer valid.

The logical flow needs revision. In the second paragraph, the author mentioned the WHO recommendations for age groups, which are totally irrelevant to the current study hypothesis.

There is conflict between Abstract and Introduction, In the Abstract, the author stated the purpose of this study is to assess “Whether physical activity is associated with the risk of cancer among adults with a cardiometabolic disease.”, but in the introduction, the purpose appears to be “whether CMD is a modifier in the association between PA and cancer”??

There are differences between EPIC and UKB in the definition of physical activity; EPIC does not include work-related activity, while UKB does. I suggest repeating the analysis using only leisure-time physical activity.

Reviewer #5

(Remarks to the Author)
The study addresses an important public health question by examining whether the association between physical activity and cancer risk differs among individuals with and without cardiometabolic diseases. The use of two large prospective cohorts (EPIC and UK Biobank) and individual participant data meta-analysis are notable strengths. One major concern should be addressed.

A central concern pertains to the alignment between the study design, the actual population analyzed, and the language used to describe the findings. The authors excluded participants with prevalent CMD at baseline and modeled CMD as a time-varying exposure based on incident diagnoses during follow-up. Consequently, the analysis specifically evaluates the PA-cancer association in adults who developed an incident CMD after study entry.
However, the Abstract and Discussion consistently generalize these results to "adults living with a CMD." This terminology is misleading, as it implies applicability to the broader population of individuals with CMD, including those with long-standing, prevalent disease. The current language overstates the direct applicability of the findings and is not fully congruent with the study design. This conflation risks misinterpretation by readers and clinicians regarding the specific patient group to which these results pertain.
This methodological choice, while sound for establishing temporal sequence, inherently shapes the interpretation and generalizability of the findings:
1.Limited Clinical Generalizability: The results are most directly relevant to adults newly diagnosed with CMD who were previously free of it. The study does not address whether the benefits of PA are similar in the substantial population managing long-standing CMD, who often have different disease severity, complications, treatment regimens, and established activity patterns.
2.Potential for Healthy-Participant Bias: By excluding prevalent CMD at baseline, the cohort may select for a healthier subset of individuals who developed CMD later in life. Those with severe, early-onset CMD (or who died from it prior to recruitment) are not represented. Therefore, the "CMD" group in this analysis likely represents a comparatively resilient subgroup, potentially biasing the estimated association between PA and cancer risk in this group.

Several minor comments as bellow:
1.Despite adjustment for several covariates, residual confounding cannot be ruled out. Factors such as sedentary behaviors, medication use influence both physical activity levels and cancer risk.
2.The handling of PA outliers (e.g., capping) and the dichotomization of PA at the median for interaction analyses, while common, may introduce bias and oversimplify the exposure-outcome relationship.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This manuscript was improved a lot, but several issues still require clarification.
1. The rationality of conducting this meta-analysis focusing on CMD requires further clarification. For example, the second paragraph discussed about T2D and CVD; however, in the third paragraph, it came to CMD, why not individually T2D or CVD.
2. The language requires copy-editing. For example, "hampering more personalized prevention", "Sub-group" (subgroup), "where we ignored CMD status", "a CMD" versus "CMD" (could be counted?), "a summary HR per 1 SD increment in MET-h/week of NOPA of 0.88", "among women with a CVD with a summary HR per", " Respective results"..., "a ...risk" vs "risk" (risk could be counted or not?)
3. It requires to be checked whether it was correctly expressed "However, the joint associations of PA and T2D on cancer risk were not investigated". There were papers on the topic, e.g., Eur J Epidemiol. 2013;28(12):945-58.
4. What is non-occupational physical activity (NOPA)? This should be explained at the first paragraph of the Introduction, as well as in the Methods, since there were many parts talking about NOPA.
5. The defination of CMD requires to be clarified with reference to published evidence. What disease was regarded as CVD? How to deal with MAFLD or Obesity if refering to CMD?
6. How to assess the significance of the linearity, by which test?
7. I do not know the reason why the authors disscussed individual types of cancer in the Results? What about the other specific types of cancer? Some outcomes were not significant, but were expressed in a positive way. For example, "a suggestively higher risk of breast cancer with a summary HR of 1.27 (95% CI: 0.94, 1.73) " but the P value, I guess, should be >0.05. Please check similar expressions. It seems the results were in part selectively reported.
8. Some conclusions in the Discussion should be corrected. For example, "The inverse association with colorectal cancer was stronger in adults with T2D than in those without...", this was not well supported by the results (i.e., no interactive effect).
9. It was not easy to understand "Our study, therefore, adds evidence that can inform clinical practice and public health recommendations. People living with CVD may be reluctant to engage in regular PA because of uncertain health implications (37, 38)". What was the implication?
10. Resudual confouding effects from other unmeasured factors could not be excluded.
11. How to understand " OPA was positively associated with PA-related cancers among adults with CVD" in the Conclusion?
In general, depite of high amout of work, the results should be presented in a logic and clear manner.

Reviewer #2

(Remarks to the Author)
My comments have been addressed appropriately.

Reviewer #3

(Remarks to the Author)
The authors have, for the most part, adequately addressed all reviewer comments.

Reviewer #4

(Remarks to the Author)
I have no further comments

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for your revisions. I have no further comments.

Point-by-point response to reviewers

TITLE: A Prospective Study of Physical Activity and Cardiometabolic Diseases in association with Cancer Risk.

Dear Reviewers,

We sincerely appreciate your extensive and constructive feedback on our manuscript titled "Physical Activity, Cardiometabolic Diseases, and Cancer Risk: A Prospective Analysis" submitted to Communications Medicine. Your insightful comments provided us with the opportunity to enhance our manuscript. We have addressed the comments, which have greatly improved the clarity, rigor, and overall quality of the paper. We have now submitted the revised manuscript online. Below, you will find our point-by-point responses to each of the comments.

Please note that we have changed the title as per the Editor's suggestion to "*A Prospective Study of Physical Activity and Cardiometabolic Diseases in association with Cancer Risk.*"

Thank you once again for your valuable input.

Response to reviewer #1

Reviewer #1 feedback:

I read the manuscript with interesting that investigated associations between physical activity and cancer risk in adults with and without a history of cardiometabolic diseases. It is generally well written.

Response: We thank the reviewer for the positive feedback.

Comment #1: It is not clear to me why participants with CVD or type 2 diabetes at baseline were excluded. Including participants with cardiometabolic diseases, and conducted interaction analysis could also address the research question in this manuscript that whether the association between PA and cancer risk was independent of CMD.

Response: We appreciate the reviewer's valuable suggestion. We have now rerun the analysis, including the participants with prevalent cardiometabolic diseases (CVD and T2D). The manuscript has been revised to reflect these changes in the methods, analysis, and results sections.

Comment #2: It is not easy to understand what is PA-related cancer. How to define PA-associated cancer? Is there any consensus on this definition?

Response: We agree that the term "physical activity-related cancers" requires further definition. In our manuscript, it refers to cancer types for which the scientific literature provides robust evidence of an association with physical activity. We categorized cancers as physical activity-related based on the

evaluation of the World Cancer Research Fund (WCRF) (1), a literature review by Friedenreich et al. (2) and McTiernan et al. (3), and two large pooled analyses of prospective cohort studies (4, 5). In the table below, we list the cancer types, which we included in our definition of physical activity-related cancers, along with the risk estimates or evaluations from the considered literature. We have added this table to the supplementary material section and described the rationale for our classification in the revised manuscript (Methods, page 8, lines 121-127):

"*The primary outcome of interest was the incidence of PA-related cancers combined, defined as site-specific cancers for which evidence supports an inverse association with PA (1, 3-6): pre- and postmenopausal breast cancer, adenocarcinoma of the oesophagus, endometrial, colon, kidney, gastric cardia, urinary bladder, gallbladder, liver, lung, small intestine, multiple myeloma, myeloid leukemia, rectal, and head and neck cancer. A list of these cancer types, along with corresponding risk estimates or evidence evaluations, is provided in Supplemental Table 2.*"

Supplementary Table 1: List of physical activity-related cancers with risk estimates or evaluation from the considered literature

Cancer Type/Site	Moore et al., 2016 (4); HR (95% CI)	Matthews et al., 2020 (5); HR (95% CI)	McTiernan et al., 2019 (3)	Friedenreich et al., 2021 (2)	World Cancer Research Fund, 2018 (1)
Colon	0.87 (0.80-0.94)	0.84 (0.77-0.92)	Strong	Strong	Strong
Breast: postmenopausal	0.93 (0.90-0.96)	0.92 (0.88-0.97)	Strong	Strong	Probable
Endometrial	0.98 (0.89-1.09)	1.02 (0.91-1.14)	Strong	Strong	Probable
Oesophageal adenocarcinoma	0.62 (0.40-0.97)	0.90 (0.70-1.16)	Strong	Strong	Limited-suggestive
Urinary Bladder	0.88 (0.83-0.94)	0.95 (0.87-1.03)	Strong	Strong	NE
Gastric Cardia	0.85 (0.69-1.04)	0.81 (0.61-1.08)	Strong	Strong	NE
Kidney: renal cell	0.84 (0.77-0.91)	0.90 (0.80-1.01)	Strong	Strong	NE
Lung	0.73 (0.70-0.76)	NE	Moderate	Moderate	Limited-suggestive
Head and neck	0.85 (0.77-0.94)	0.94 (0.83-1.07)	Limited	Limited	NE
Rectum	0.88 (0.81-0.96)	0.93 (0.83-1.05)	Limited	Limited	NE
Liver	0.81 (0.61-1.09)	0.79 (0.64-0.99)	NE	NE	Limited-suggestive
Gallbladder	0.78 (0.57-0.97)	0.76 (0.51-1.14)	NE	NE	NE
Small intestine	0.81 (0.62-1.05)	0.83 (0.59-1.16)	NE	NE	NE
Multiple Myeloma	0.87 (0.77-0.98)	0.83 (0.71-0.98)	NE	NE	NE
Myeloid leukemia	0.85 (0.73-0.97)	0.93 (0.77-1.13)	NE	NE	NE
NE, not evaluated.					

Comment #3: In the Introduction part, it is not clear to me why the authors indicated that "Furthermore, there is a lack of recommendations for individuals with cardiovascular diseases (CVD)", since it was existed regarding the role of PA in the management of CVD.

Response: We acknowledge that physical activity guidance for managing CVD exists in the clinical literature, and we thank the reviewer for raising this point. Our aim, however, was to highlight that the

2020 WHO physical activity recommendations did not include tailored PA recommendations for individuals with CVD – unlike for other chronic conditions (e.g., cancer, hypertension, T2D). Additionally, we aimed to emphasize the lack of evidence-based recommendations on cancer prevention among individuals with CVD, rather than the absence of PA guidance for management of CVD. We have revised the text accordingly for clarity. In the Introduction section, this reads now as follows (page 6, lines 36-48):

"The 2020 physical activity (PA) guidelines from the World Health Organization (WHO) include recommendations for adults with chronic conditions such as cancer, hypertension, or type 2 diabetes (T2D) (7). A caveat is that these recommendations are largely based on extrapolation of evidence from the general population, with limited direct evidence on the role of PA in cancer prevention for individuals with, for example, T2D. Although the guidelines acknowledge that higher levels of PA are associated with improved outcomes in individuals with coronary heart disease, this condition, or other cardiovascular diseases *(CVD), were not included among the chronic conditions subjected to formal evidence review (7). The exercise guidelines of the European Society of Cardiology do recommend at least 150 min/week of moderate-intensity exercise to individuals with cardiac disease, but not specifically for cancer prevention (8). Taken together, PA recommendations for cancer prevention tailored to individuals with CVD or T2D remain limited, hampering more personalized prevention."*

Comment #4: In the Methods part, the authors indicated that "Model 1 was stratified by age", should it be "…adjusted for…".

Response: Thank you very much for your helpful comment. We appreciate that the original phrasing may have confused the distinction between stratification variables and adjusted covariates in our analysis. To clarify, all three models were stratified by age (in 5-year categories), sex, and recruitment centre, allowing the baseline hazard to vary across these key variables, as they influence the baseline risk. To avoid any misunderstanding, we have revised the methods section to explicitly state (page 10, lines 194-197):

"All models were stratified by age (5-year categories), sex (except for the breast cancer analysis), and recruitment centre, allowing the baseline hazard to vary across these strata and thus removing the violated proportional hazards assumption of these variables."

Comment #5: This manuscript did not assess the influences of different types of PA on the cancer risk, which should be addressed as a limitation.

Response: Unfortunately, data about different types of PA other than aerobic exercise was not available in either of the cohorts. As suggested, we have added this limitation in the Discussion section (page 16, lines 383-385):

"Additionally, we were unable to assess the effects of specific types of physical activity beyond aerobic exercise because such information was not collected consistently across the two cohorts."

Reviewer #2 (Remarks to the Author):

Thank you for the opportunity to review the article by Gebremariam et al. on associations between physical activity and cancer risk in adults with and without a history of cardiometabolic diseases. Strengths of the study include the use of multiple datasets across several countries, the large sample size, which provides strong statistical power, and the clear description of the study methodology.

Response: We thank the reviewer for the positive feedback.

Comment #1: The authors combined physical activity from various domains, such as household and leisure time. Previous research has shown that leisure-time physical activity, but not occupational physical activity, is beneficially associated with the prevention of type 2 diabetes and cardiovascular disease. This phenomenon is often referred to as the "physical activity paradox."

However, this paradox seems to be reversed in cancer prevention, where occupational physical activity appears more beneficial than leisure-time physical activity. For example, in the EPIC Italy study (PMID: 27832394), "In multivariate models, inverse associations with breast cancer risk emerged for increasing level of total (p trend 0.02), leisure time (p trend 0.04), and occupational (p trend 0.007) PA".

I encourage the authors to further analyze physical activity by different domains in their analysis. For example, it would be interesting to see the joint association of occupational physical activity and cardiometabolic disease on cancer risk.

Response: Thank you for this thoughtful comment. In agreement with the reviewers' suggestion, we have now analysed non-occupational and occupational physical activity separately. We computed both multiplicative and additive interactions between these two domains of physical activity and cardiometabolic diseases (CMD) in relation to PA-related cancers. Accordingly, we have updated our results, tables, and interpretations.

Reviewer #3 (Remarks to the Author):

General comments

The topic of the present study is interesting, and the manuscript is very well written. The statistical analyses are appropriately conducted, and the results are clearly presented. The reviewer has several comments that may help further improve the manuscript.

Response: We thank the Reviewer for your positive feedback and helpful comments.

Specific **major comments**

Comment #1: Lines 188-191: Based on IARC (2002) or WCRF/AICR (2007), it is reasonable to assume that colon, breast, and endometrial cancers are generally considered PA-related cancers**.** However, is it appropriate to treat the other cancers as PA-related cancers? There is no explanation of how the authors defined PA-related cancers.

Response: Thank you for highlighting this important point. We based our decision to include additional cancer sites as physical activity-related on growing evidence from large, high-quality pooled cohort analyses. These studies have reported inverse associations between physical activity and several other cancers, which we summarize now in a Supplementary Table (please see also our response to comment #2 of Reviewer #1 above). To enhance clarity, we defined physical activity-related cancers now in more detail in the methods section (page 8, lines 121-127):

"The primary outcome of interest was the incidence of PA-related cancers combined, defined as site-specific cancers for which evidence supports an inverse association with PA (1, 3-6): pre- and postmenopausal breast cancer, adenocarcinoma of the oesophagus, endometrial, colon, kidney, gastric cardia, urinary bladder, gallbladder, liver, lung, small intestine, multiple myeloma, myeloid leukemia, rectal, and head and neck cancer. A list of these cancer types, along with corresponding risk estimates or evidence evaluations, is provided in Supplemental Table 2."

Comment #2: Cancer ascertainment and Statistical Analysis: It is unfortunate that the authors did not examine the interaction between PA and CMD for specific cancer types. Because the mechanisms underlying the interaction between PA and CMD may differ by individual cancer type, examining this interaction at least for representative PA-related cancers (e.g., colon, breast, and endometrial cancers) would be of great interest to readers. The Swedish Mammography Cohort (reference 14) appears to show a significant interaction between PA and T2D on a specific cancer (i.e., endometrial cancer).

Response: We thank the reviewer for this thoughtful suggestion. We have now conducted additional analyses for the two cancer sites with the strongest established association with PA: colorectal cancer, and breast cancer (women only). We examined the interaction between non-occupational physical activity and each CMD (CVD and T2D) using the same modelling approach as in the main analysis, by considering additional female-related covariates in the model. We have added the summary of the findings in the results section, and more detailed results are provided in the supplemental tables 7, 12 and 13, and supplementary Figures 10-11. Also, we have analysed the interaction between occupational physical activity and each CMD (CVD and T2D) for these cancers in the UKB, and the results are provided in supplementary Tables 16, 18, and 19.

Comment #3: Line 220: Is there no data on employment status in EPIC? It is not common to use workplace physical activity data as a covariate instead of employment status; however, there is no adequate explanation for this choice.

Response: Thank you for your valid comment. Information on employment status in EPIC is limited, which is why we used occupational PA as a proxy for work-related activity. Occupational PA is one of the core standardized variables from the EPIC physical activity questionnaire; it has been centrally harmonized and validated across centres as a categorical variable. We explained this choice now in the Methods section (page 9, lines 154-156):

"Due to limited employment information in EPIC, we used OPA as a proxy for type of employment (sedentary or standing vs. manual or heavy manual)."

Comment #4: Line 259: An explanation of why the analyses were stratified by age, sex, and recruitment centre (instead of adjusting for these variables) is missing.

Response: We have clarified this point now in the Statistical analysis section (page 10, lines 194-197):

"All models were stratified by age (5-year categories), sex (except for the breast cancer analysis), and recruitment centre, allowing the baseline hazard to vary across these strata and thus removing the violated proportional hazards assumption of these variables."

Comment #5: Line 260: It may not be common for height to be included as a covariate, but the explanation for this is missing.

Response: Thank you for your comment. We have clarified our rationale in the manuscript. Height was included because it may serve as a proxy for early life nutritional status, growth patterns, and hormonal profiles, all of which have been linked to cancer risk in previous epidemiological studies. Adjusting for height helps reduce potential confounding, particularly for cancers such as breast, colorectal, and

endometrial cancers, where adult height has been associated with risk (9, 10). We have added a brief explanation in the methods section to reflect this (page 9, line 158-159):

"Other covariates included height (as a proxy for early life nutrition), and among women, use of hormones for menopause, and menopausal status."

Comment #6: Line 275: The authors used the term "inactive". In the results section, words such as "active adults" or "inactive adults" were also used. However, physical inactivity is generally defined as an insufficient level of PA to meet the current PA recommendations for health. It refers to a condition in which an individual does not engage in enough moderate- to vigorous-intensity PA (MVPA) to achieve substantial health benefits—typically, not accumulating at least 150 minutes per week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic activity, or an equivalent combination thereof. Please correct this point and revise it throughout the manuscript.

Response: Thank you for this important comment. We appreciate the distinction between guideline-based definitions of physical inactivity and study-specific PA classifications. In our analysis, applying the WHO-recommended PA cut-points resulted in too few participants in the "insufficient" group (especially in the EPIC cohort, approximately 85% had PA levels greater than the threshold), leading to unstable modelling. In line with comment #3 of Reviewer #5, we revised the categorization of PA and the terms of PA accordingly. We categorized non-occupational PA based on percentile-based cut-point of the MET-h/week distribution: low (< 20^{th} percentile), moderate (20^{th} – 60^{th} percentile), and high (>= 60^{th} percentile). This approach should be more robust, and population-level prevalence is not critical. The revised labelling should also prevent conflation with guide-based terminology. Results and terminology have been revised throughout the manuscript.

Comment #7: Line 329: The interactions between PA and CMD status (all p for interaction > 0.3) were not statistically significant; nevertheless, these results are the main findings of the present study. Therefore, the results of the interaction should not be presented in a supplementary table.

Response: Thank you for your valid comments. We have included these results in the main manuscript as Table 3.

Comment #8: Lines 354-356: The authors expressed the conclusion that "taken together, these results suggest that being physically active is beneficial for cancer prevention in adults living with or without T2D and/or CVD". If they conclude so, why did they not use "inactive with cardiometabolic disease" as a reference category (instead of using "active without cardiometabolic disease" as a reference)?

Response: Thank you for this valuable comment. We agree that the choice of reference category can influence the interpretability of joint exposure analyses. We chose these with high PA and without

CMDs as the reference because it represents the lowest risk group. We also tried considering the "low PA with CMD" as the reference, but this subgroup was small and produced an unstable estimate. Additionally, we followed Knol and VanderWeele's recommendation to recode preventive exposures so that the joint stratum with the lowest risk of the outcome served as the reference category when estimating additive interaction (11). Nonetheless, regardless of the reference category used, the conclusion remains unchanged: higher non-occupational PA is associated with a lower risk of cancer in individuals with and without CMD.

Comment #9: Line 145: The words CVD and T2D should be deleted.

Response: Thank you for your suggestion. We have removed the words CVD and T2D in this respective sentence.

Comment #10: Lines 192-194: The explanation of the reason for the exclusion of non-melanoma skin cancer is missing.

Response: We have now included the justification for treating non-melanoma skin cancer differently in the methods section (page 8, lines 129-131):

"Non-melanoma skin cancer cases were censored at the diagnosis date but not classified as cancer cases, since it has a distinct biological pathway, and is primarily caused by exposure to ultraviolet radiation (12)."

Comment #12: Covariates: It is unclear whether all covariates, including BMI (weight and height) were assessed by a self-reported questionnaire.

Response: We have added a description that clarified how the covariates were measured in the cohorts, noting that all covariates were questionnaire-based unless otherwise specified and that height and weight were self-reported only in EPIC Oxford and measured elsewhere (page 9, lines 152-153).

"*Unless otherwise specified, covariates were assessed in both cohorts at baseline using self-reported questionnaires.***"**

Comment #13: Line 322: UK Biobank should be expressed as UKB.

Response: We have now consistently used UKB throughout the manuscript.

Comment #14: Lines 386- 407: Analysis of joint association, objective diabetes status, and large sample sizes may be strengths that should be mentioned. No data on employment status in EPIC may be a limitation that should be acknowledged.

Response: We appreciate your helpful comments. We have included these in the strength description and noted the limitation regarding the lack of data on employment status in EPIC as well (page 16, lines 367-370, 383-385):

"The analysis is based on multinational data across six European countries from two large prospective cohort studies, which also allowed us to model the temporal relationship between PA, objective T2D and/or CVD status, and cancer risk. We also assessed multiplicative interaction and joint associations of PA and CMD on cancer risk."

"Additionally, the lack of data on medication use and employment information in the EPIC cohort could have impacted our estimates. However, accounting for these covariates in UKB did not affect estimates."

Comment #15: Line 435: A period is missing.

Response: Apologies for the typo. We have edited accordingly.

Reviewer #4 (Remarks to the Author):

Alem et al. integrated data from the EPIC and UK Biobank, investigated the association between PA and the risk of cancer, and assessed the interaction between PA and cardiometabolic diseases in relation to cancer risk. The results are somehow negative but still very meaningful. But I have several concerns in the background and method.

Response: Thank you for your positive feedback and constructive comments.

Comment #1: Relevant knowledge needs to be updated. ESC and AHA both published PA guidelines for CVD patients in 2021 and 2024, respectively, rendering the research gap mentioned in the introduction no longer valid. The logical flow needs revision. In the second paragraph, the author mentioned the WHO recommendations for age groups, which are totally irrelevant to the current study hypothesis.

Response: Thank you for your comments. We have revised the introduction section. The phrase on the WHO age-specific recommendations has been cut. In page 6, paragraph 1, line 36-48, it now reads as follows:

"*The 2020 physical activity (PA) guidelines from the World Health Organization (WHO) include recommendations for adults with chronic conditions such as cancer, hypertension, or type 2 diabetes (T2D) (7). A caveat is that these recommendations are largely based on extrapolation of evidence from the general population, with limited direct evidence on the role of PA in cancer prevention for individuals with, for example, T2D. Although the guidelines acknowledge that higher levels of PA are associated with improved outcomes in individuals with coronary heart disease, this condition, or other cardiovascular diseases (CVD), were not included among the chronic conditions subjected to formal evidence review (7). The exercise guidelines of the European Society of Cardiology do recommend at least 150 min/week of moderate-intensity exercise to individuals with cardiac disease, but not specifically for cancer prevention (8). Taken together, PA recommendations for cancer prevention tailored to individuals with CVD or T2D remain limited, hampering more personalized prevention."*

Comment # 2: There is conflict between Abstract and Introduction, In the Abstract, the author stated the purpose of this study is to assess "Whether physical activity is associated with the risk of cancer among adults with a cardiometabolic disease.", but in the introduction, the purpose appears to be "whether CMD is a modifier in the association between PA and cancer"??

Response: Thank you for the careful reading and for highlighting the discrepancy between the abstract and introduction sections. We have aligned the study objectives across both sections. On page 6, Line 63-65, the revision reads as follows:

"We examine associations between NOPA and the risk of a composite outcome of 15 PA-related cancers in adults with and without CMD in the European Prospective Investigation into Cancer and Nutrition (EPIC) and UK Biobank (UKB)."

Comment #3: There are differences between EPIC and UKB in the definition of physical activity; EPIC does not include work-related activity, while UKB does. I suggest repeating the analysis using only leisure-time physical activity.

Response: Thank you for the valuable comment. We have now analysed non-occupational and occupational physical activity separately, with non-occupational physical activity as our main exposure. Accordingly, we have updated our results, tables, and interpretations throughout the manuscript.

Reviewer #5 (Remarks to the Author):

The study addresses an important public health question by examining whether the association between physical activity and cancer risk differs among individuals with and without cardiometabolic diseases. The use of two large prospective cohorts (EPIC and UK Biobank) and individual participant data meta-analysis are notable strengths. One major concern should be addressed.

Response: Thank you for your positive feedback and constructive comments.

Comment #1: A central concern pertains to the alignment between the study design, the actual population analyzed, and the language used to describe the findings. The authors excluded participants with prevalent CMD at baseline and modeled CMD as a time-varying exposure based on incident diagnoses during follow-up. Consequently, the analysis specifically evaluates the PA-cancer association in adults who developed an incident CMD after study entry.

However, the Abstract and Discussion consistently generalize these results to "adults living with a CMD." This terminology is misleading, as it implies applicability to the broader population of individuals with CMD, including those with long-standing, prevalent disease. The current language overstates the direct applicability of the findings and is not fully congruent with the study design. This conflation risks misinterpretation by readers and clinicians regarding the specific patient group to which these results pertain.

This methodological choice, while sound for establishing temporal sequence, inherently shapes the interpretation and generalizability of the findings:

1.Limited Clinical Generalizability: The results are most directly relevant to adults newly diagnosed with CMD who were previously free of it. The study does not address whether the benefits of PA are similar in the substantial population managing long-standing CMD, who often have different disease severity, complications, treatment regimens, and established activity patterns.

2.Potential for Healthy-Participant Bias: By excluding prevalent CMD at baseline, the cohort may select for a healthier subset of individuals who developed CMD later in life. Those with severe, early-onset CMD (or who died from it prior to recruitment) are not represented. Therefore, the "CMD" group in this analysis likely represents a comparatively resilient subgroup, potentially biasing the estimated association between PA and cancer risk in this group.

Response: Thank you for your insightful comments. We agree that excluding individuals with prevalent CMD at baseline limited the clinical generalizability of our original analyses and could lead to the interpretational issues highlighted by the reviewer. In response, we have now revised our analysis and have included participants with prevalent cardiometabolic diseases at baseline, in addition to modelling

incident CMD as a time-varying exposure. This modification ensures that our CMD group now reflects the full spectrum of individuals living with cardiometabolic disease, including both newly diagnosed and long-standing cases. All corresponding sections of the methods, results, discussion, and abstract are modified accordingly to reflect this revised analytical approach.

Comment #2: Despite adjustment for several covariates, residual confounding cannot be ruled out. Factors such as sedentary behaviors and medication use influence both physical activity levels and cancer risk.

Response: Thank you for this comment. We agree that residual confounding cannot be completely excluded. We have now additionally adjusted the estimates in UKB for sedentary behaviour and medication use, which were available in that cohort. For the EPIC, these specific variables were not captured in a harmonized and detailed form. However, EPIC includes information on physical activity at work, categorized as sedentary, standing, manual, and heavy manual. This variable is a proxy for occupational sedentary behaviour, and we included it as an adjustment factor in our models. While this does not fully eliminate residual confounding, it strengthens our control for behaviour differences related to activity levels. Results have been updated accordingly.

Comment #3: The handling of PA outliers (e.g., capping) and the dichotomization of PA at the median for interaction analyses, while common, may introduce bias and oversimplify the exposure-outcome relationship.

Response: Thank you for your insightful comment. We acknowledge that managing outliers through capping and dichotomizing at the median for interaction analyses can influence exposure-outcome analyses, though the capping did not alter the median PA value in either cohort since the proportion of capped observations was small and located only at the extreme upper tail of the distribution.

For the joint analysis, we have now categorized non-occupational physical activity (NOPA) using a percentile-based cut-point for the MET-hours per week distribution: low (< 20th percentile), moderate (20th – 60th percentile), and high (≥ 60th percentile), rather than simply dividing it at the median. Our primary analysis focused on the continuous standardized measure of MET-hours per week of NOPA, which produced consistent results across both cohorts.

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Point-by-point response to COMMSMED-25-2617A

TITLE: A Prospective Study of Physical Activity and Cardiometabolic Diseases in association with Cancer Risk.

Response to Reviewer #1 comments:

1. The rationality of conducting this meta-analysis focusing on CMD requires further clarification. For example, the second paragraph discussed about T2D and CVD; however, in the third paragraph, it came to CMD, why not individually T2D or CVD.

Response: We thank the reviewer for this comment. We have revised this sentence to clarify using CMD as an overarching concept while also analysing T2D and CVD separately. CMD is used to reflect shared cardiometabolic risk and clinical relevance, whereas individual analyses of T2D and CVD are presented in the results and discussion. This has now been clarified in the introduction and stated as follows (page 6, lines 46-50).

"Taken together, PA recommendations for cancer prevention tailored to individuals with CVD and/or T2D, here referred to as cardiometabolic diseases (CMD) [reference see manuscript], remain limited, hampering personalized prevention."

2. The language requires copy-editing. For example, "hampering more personalized prevention", "Sub-group" (subgroup), "where we ignored CMD status", "a CMD" versus "CMD" (could be counted?), "a summary HR per 1 SD increment in MET-h/week of NOPA of 0.88", "among women with a CVD with a summary HR per", " Respective results"..., "a ...risk" vs "risk" (risk could be counted or not?)

Response: Thanks for the comments. We have copy-edited the manuscript throughout to improve language clarity, consistency, and adherence to journal style, addressing all examples raised by the reviewer.

3. It requires to be checked whether it was correctly expressed "However, the joint associations of PA and T2D on cancer risk were not investigated". There were papers on the topic, e.g., Eur J Epidemiol. 2013;28(12):945-58.

Response: We have revised the text to clarify that, although some previous studies have examined PA and cancer risk according to diabetes status, formal investigation of joint effects between PA and T2D on cancer risk has been limited. The suggested article did not test a joint PA and T2D effect on thyroid cancer. It examined PA and diabetes as separate exposures in relation to thyroid cancer, rather than a combination of them into joint categories like active/inactive by diabetes status.

4. What is non-occupational physical activity (NOPA)? This should be explained at the first paragraph of the Introduction, as well as in the Methods, since there were many parts talking about NOPA.

Response: We have revised the first paragraph of the introduction to explicitly define NOPA (page 6, lines 35-37).

5. The defination of CMD requires to be clarified with reference to published evidence. What disease was regarded as CVD? How to deal with MAFLD or Obesity if refering to CMD?

Response: We have clarified the definition of CMD in the manuscript as the presence of either cardiovascular disease (CVD) or type 2 diabetes (T2D), in line with previous studies. The specific types of diseases classified as CVD are detailed in the Methods section, specifically on page 9, paragraph 1, and lines 141-145. Obesity and MAFLD were not included in the definition of CMD, as obesity was treated as a covariate.

"*The ascertainment of CVD and T2D has been described previously [reference see manuscript]. Cardiometabolic disease included CVD and T2D, coded using ICD-10. Cardiovascular disease refers to a composite of ischemic heart diseases (I20-I25), and cerebrovascular disease (I60-I69), while T2D was defined as E11."*

6. How to assess the significance of the linearity, by which test?

Response: We have revised the methods section to clarify that non-linearity was formally assessed using likelihood ratio tests comparing Cox models with spline terms to models assuming a linear association (page 11, lines 205-207).

"*Departure from linearity was evaluated using likelihood ratio tests comparing models including spline terms with models assuming a linear association (Supplementary Figures 3, 4, 5, and 6)."*

7. I do not know the reason why the authors disscussed individual types of cancer in the Results? What about the other specific types of cancer? Some outcomes were not significant, but were expressed in a positive way. For example, "a suggestively higher risk of breast cancer with a summary HR of 1.27 (95% CI: 0.94, 1.73) " but the P value, I guess, should be >0.05. Please check similar expressions. It seems the results were in part selectively reported.

Response: Site-specific analyses were added in response to reviewers' suggestions to explore potential heterogeneity across the most common cancers. This is mentioned in the Methods as (page 8, lines 133-135):

"Furthermore, we provided risk estimates for colorectal (C18-C20 and C26.0) and breast cancer (C50), the two most common PA-related cancers."

We have revised the results section to remove interpretive or positive language for non-significant findings and now report effect estimates and confidence intervals without implying statistical significance. We also clarified that no evidence of additive interaction was observed where the corresponding CI included the null value (page 13, lines 288-294).

"For colorectal cancer, compared to adults who had high NOPA without T2D, those with low NOPA and T2D had a summary HR of 1.28 (95% CI: 0.94, 1.75); although the RERI was positive, confidence intervals included the null, providing no clear evidence of additive

*interaction (RERI = 0.23; 95% CI: -0.08, 0.55) (Supplementary **Table 14**). For breast cancer, compared to women with high NOPA without CVD, those with low NOPA and CVD had a summary HR of 1.27 (95% CI: 0.94, 1.73), with no clear evidence of additive interaction (RERI = 0.30; 95% CI: -0.36, 0.95) (Supplementary **Table 15**).”*

8. Some conclusions in the Discussion should be corrected. For example, "The inverse association with colorectal cancer was stronger in adults with T2D than in those without...", this was not well supported by the results (i.e., no interactive effect).

Response: We have removed this sentence from the Discussion and kept this part now more general.

9. It was not easy to understand "Our study, therefore, adds evidence that can inform clinical practice and public health recommendations. People living with CVD may be reluctant to engage in regular PA because of uncertain health implications (37, 38)". What was the implication?

Response: We have revised the text to clarify the clinical and public health implications of our findings as follows (page 15, lines 346-349):

“Our study, therefore, adds evidence by suggesting that higher NOPA levels are associated with similar cancer risk reductions among adults with and without CVD. This is clinically relevant, as people living with CVD may be reluctant to engage in regular PA because of uncertain health implications [references see manuscript].”

10. Residual confounding effects from other unmeasured factors could not be excluded.

Response: We have now acknowledged potential residual confounding in the limitations section as follows (page 16, lines 392-393):

“Nevertheless, other unmeasured factors may also contribute to residual confounding.”

11. How to understand " OPA was positively associated with PA-related cancers among adults with CVD" in the Conclusion?

Response: Since this finding is based on a *post hoc* and exploratory analysis, we removed this statement from the main conclusions.

In general, despite a high amount of work, the results should be presented in a logical and clear manner.

Response: We believe that these revisions, as described above, make the presented results clearer.