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# Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: a dose-response meta-analysis of large prospective studies 

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#### Abstract

Objective To estimate the dose-response associations between non-occupational physical activity and several chronic disease and mortality outcomes in the general adult population. Design Systematic review and cohort-level doseresponse meta-analysis. Data sources PubMed, Scopus, Web of Science and reference lists of published studies.


Eligibility criteria Prospective cohort studies with (1) general population samples $>10000$ adults, (2) $\geq 3$ physical activity categories, and (3) risk measures and Cls for all-cause mortality or incident total cardiovascular disease, coronary heart disease, stroke, heart failure, total cancer and site-specific cancers (head and neck, myeloid leukaemia, myeloma, gastric cardia, lung, liver, endometrium, colon, breast, bladder, rectum, oesophagus, prostate, kidney).
Results 196 articles were included, covering 94 cohorts with > 30 million participants. The evidence base was largest for all-cause mortality ( 50 separate results; 163415543 person-years, 811616 events), and incidence of cardiovascular disease ( 37 results; 28 884209 person-years, 74757 events) and cancer (31 results; 35500867 person-years, 185870 events). In general, higher activity levels were associated with lower risk of all outcomes. Differences in risk were greater between 0 and 8.75 marginal metabolic equivalent of task-hours per week (mMET-hours/week) (equivalent to the recommended $150 \mathrm{~min} /$ week of moderate-tovigorous aerobic physical activity), with smaller marginal differences in risk above this level to 17.5 mMET-hours/ week, beyond which additional differences were small and uncertain. Associations were stronger for all-cause (relative risk (RR) at 8.75 mMET -hours/week: $0.69,95 \%$ Cl 0.65 to 0.73 ) and cardiovascular disease (RR at 8.75 mMET-hours/week: $0.71,95 \% \mathrm{Cl} 0.66$ to 0.77 ) mortality than for cancer mortality (RR at 8.75 mMET -hours/week: $0.85,95 \% \mathrm{Cl} 0.81$ to 0.89 ). If all insufficiently active individuals had achieved 8.75 mMET -hours/week, $15.7 \%$ ( $95 \% \mathrm{Cl} 13.1$ to 18.2 ) of all premature deaths would have been averted.
Conclusions Inverse non-linear dose-response associations suggest substantial protection against a range of chronic disease outcomes from small increases in non-occupational physical activity in inactive adults.

PROSPERO registration number CRD42018095481.

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally, responsible for 17.9 million annual deaths in 2019, ${ }^{1}$ whereas cancers were responsible for 9.6 million deaths in 2017. ${ }^{1}$ Both conditions top the global disease burden with respect to disabilityadjusted life-years. ${ }^{2}$ The relative contribution of various risk and protective factors to the incidence of, and mortality from, these conditions is an ongoing debate.

Higher levels of physical activity (PA) are associated with lower risk of all-cause mortality, CVD and some site-specific cancers. ${ }^{2-8}$ The highest quality evidence for these associations and the population impact of low PA levels comes from disease-specific meta-analyses. However, differing methods used in previous meta-analyses limit comparability of relative risks across different outcomes. The only initiative to consistently consider the population impact across diseases (five in total) is the Global Burden of Disease (GBD) study, which uses estimates of total PA, including occupational activity. ${ }^{9}$ This is problematic as occupational activity is generally poorly measured compared with non-occupational activity and estimates of activity at work often dwarf the non-occupational component. One reason for this is the use of gross metabolic equivalent of task (MET)-hour/week to quantify PA volume. Sedentary office work may be considered to cost approximately 1.25 METs, of which 1 MET represents resting metabolic rate. Non-occupational activity is typically more intense (eg, walking at $4.0 \mathrm{~km} /$ hour is approximately 3 METs), meaning the relative contribution of the resting metabolic rate is smaller. Including low-intensity high-duration activities such as occupational activity without marginalising the resting component can therefore distort the PA exposure dramatically. Furthermore, even when occupational PA is well measured, it remains unclear whether it has similar health benefits to non-occupational activity. ${ }^{10}$ These factors add statistical noise, decreasing the accuracy of the
estimated associations, and may underestimate the contribution of non-occupational PA.
Accurate estimation of the dose-response association between PA and disease outcomes, combined with prevalence estimates, is a prerequisite to assessing the population disease burden of insufficient PA and the potential impact of changes to population levels of PA. Modelling studies that evaluate public health strategies aimed at increasing population activity levels have found that the shape of the dose-response association makes a significant difference when quantifying population health impacts. ${ }^{6}$

Our objective was to quantify dose-response associations between non-occupational PA and several CVD, cancer and mortality outcomes using a novel harmonisation framework to overcome the challenges posed by different PA measurement methods. This framework allowed us to compare studies measuring and reporting PA in a wide variety of ways on the same activity exposure scale of marginal MET-hours per week (mMET-hours/week). This meant we could be more inclusive of the available evidence than previous meta-analyses and we could explore the dose-response relationships between nonoccupational PA and nine site-specific cancers for the first time. To contextualise our results for public health promotion, we generated potential population impact fractions (PIFs) to estimate the proportion of preventable deaths and disease outcomes at different non-occupational PA levels.

## METHODS

The study protocol is available at PROSPERO (registration number CRD42018095481).

## Eligibility criteria

Online supplemental eMethods 1 shows the study inclusion and exclusion criteria. We included prospective cohort studies that followed adults ( $\geq 18$ years) without pre-existing conditions, reported PA at baseline in at least three ordinal exposure levels and reported risk estimates for the examined outcomes. We excluded studies with $<10000$ participants to limit potential bias from small study sizes with positive results; this is the required cohort sample size for outcomes with up to $70 \%$ of subjects in the unexposed group (ie, no or less physically active), expected incidence rate in the unexposed group around $15 \%$ or more, and assumed relative risk of 0.85 , when type I and type II errors are 0.05 and 0.20 , respectively. These are reasonable parameters for the investigated populations, exposure and endpoints. We also excluded studies where the follow-up period was $<3$ years to minimise reverse causality bias, which is in accordance with the findings of Lee et al. ${ }^{11}$

Only articles that examined leisure-time PA, alone or in combination with other domains or specific types of activity, were included. We excluded articles whose measures of PA contained occupational activity that could not be factored out and that investigated individual domains of PA that did not include leisure-time activity (eg, transport-related PA only).

The outcomes of interest were the following:

- All-cause, total CVD and total cancer mortality.
- Total CVD, coronary heart disease, stroke and heart failure incidence (fatal and non-fatal events combined).
- Total and site-specific (head and neck, myeloid leukaemia, myeloma, gastric cardia, lung, liver, endometrial, colon, breast, bladder, rectum, oesophageal, prostate, and kidney) cancer incidence (fatal and non-fatal events combined). These site-specific cancers were selected based on previously reported associations with PA. ${ }^{8}$

Search and selection process
We searched PubMed, Scopus, Web of Science and the reference lists of reviews retrieved from our systematic review, known to the authors or cited in the 2018 US Physical Activity Guidelines Advisory Committee Scientific Report. ${ }^{12}$ Online supplemental eMethods 2 details the systematic search strategy. We considered peer-reviewed articles in any language published in academic journals until February 2019.

Titles and abstracts, and subsequently full texts, were screened independently twice for eligibility (online supplemental eFigure 1). Disagreements were resolved by discussion.

If multiple articles reported results on the same cohort and outcome, we followed specific criteria (online supplemental eMethods 3) to select one.

## Data extraction

Data from each paper were extracted by one reviewer and doublechecked independently by a second reviewer. Disagreements were checked against the full text and resolved by discussion.

We extracted data on publication (first author, year of publication), study characteristics (country, cohort name, sample size, age and sex of participants, and duration of follow-up), PA exposure assessment (instrument, domains of activity and exposure categories) and outcome assessment (defined using the International Classification of Disease 10th revision (ICD-10) codes as reported in the PROSPERO registration and online supplemental eMethods 1). We extracted whether fatal, non-fatal or the combination of fatal and non-fatal events was tallied. We also identified how original study analyses had considered baseline morbidity (exclusion at baseline or statistical adjustment in multivariable regression models) and early incident cases during follow-up.

For each exposure category, we extracted information to quantify PA volume, number of cases, number of participants and/ or person-years of follow-up, and risk estimates with $95 \%$ CIs. Risk estimates from the most adjusted model were used. When available, risk estimates of the most adjusted model without adiposity-related covariates (eg, body mass index (BMI), waist circumference) were retrieved and used in sensitivity analyses. Exposure data were extracted to the level of precision reported in the published study before being harmonised to PA volume in mMET-hours/week. Risk estimates were extracted exactly as reported. Results reported separately by sex or other attributes (eg, age, ethnicity) or for multiple cohorts within an article were treated as separate associations. If the original publication did not fully report information required for the meta-analysis, data were obtained from other publications using the same cohort, imputation procedures (online supplemental eMethods 4 ) or by contacting the authors. We had no control over the methods used to handle confounders and missing data in the original analyses.

## PA exposure harmonisation <br> Overview of harmonisation

A comprehensive data harmonisation was conducted to combine PA data from different sources. We harmonised reported PA exposure levels from all included studies into a common metric of non-occupational PA volume in mMET-hours/week, reflecting the rate of energy expenditure outside of work, above the resting metabolic rate ( 1 MET ). This allows correct equating of PA volume of time spent at different PA intensity levels. ${ }^{13}$ The principles of each aspect of our harmonisation procedure are described in the following sections and presented in a flow chart available in our OSF repository. The last columns of the table on
'Details of included articles and original and harmonized exposures' in the same OSF repository contain the details of how the original PA exposure categories of each study were harmonised to mMET-hours/week values.

## Frequency, duration and intensity assumptions

PA exposures described in studies as frequency and duration measures were converted to weekly duration. If session duration was not provided, we assumed a duration of 0.75 hours/session ( 0.5 hours/session in sensitivity analyses). Categorical frequency data (eg, never, sometimes and often) were converted to weekly duration using assumptions for both frequency (eg, 0,2 and 5 sessions per week) and duration of sessions. When PA intensity was not explicitly described, we considered the reported activities as light, moderate or vigorous based on the description provided and using the Compendium of Physical Activities. ${ }^{14}$ We assigned mMET values of 1.5 for light, 3.5 for moderate and moderate-to-vigorous, and 7.0 for vigorous PA ( 1 mMET less in sensitivity analyses).

## Converting absolute energy expenditure to MET values

For studies reporting energy expenditure without adjustment for body weight (eg, $\mathrm{kJ} /$ day, $\mathrm{kcal} /$ week ), energy expenditure was divided by reported weights to derive MET equivalents (1 $\mathrm{MET}=1 \mathrm{kcal} / \mathrm{kg} /$ hour). If unavailable, body weight was calculated from reported BMI and height. If BMI was reported without height, a mean value from national survey data was used for height.

## Subtracting resting energy expenditure from estimates of PA

To marginalise studies reporting volume of PA in gross units, 1 MET-hour was subtracted for each hour of activity. If the mean duration was not available, we used a conversion equation derived from all remaining studies where both volume and duration were available (online supplemental eMethods 5).

## Isolating the non-occupational component of aggregate PA estimates

Some articles provided aggregated exposures of nonoccupational and occupational PA alongside other behaviours, such as sleep or sedentary time. When quantified information about these behaviours was available, this was subtracted from the point estimate of each exposure category. If no quantifiable data were available, we assumed occupational activity to be 40 hours/week at 1.25 MET (or 0.25 mMET ) or the value of the lowest exposure category and subtracted this from all exposure categories.

## Meta-analytical methods

We conducted a meta-analysis for any outcome with results from at least four cohorts. Where necessary, risk estimates were recalculated to set the least active category as the referent. ${ }^{15}$ For studies reporting only stratified results (eg, sex or ethnicity), we combined stratum-specific risks into overall population estimates using fixed-effect meta-analysis.

We performed a two-stage random-effects meta-analysis. In the first stage, we estimated study-specific dose-response coefficients using generalised least squares to incorporate the correlation within each set of log-relative risks. ${ }^{1617}$ In the second stage, we estimated the pooled coefficients by combining study-specific dose-response coefficients using restricted maximum likelihood, ${ }^{1819}$ with cohorts weighted by the inverse of their variance. We assumed non-linearity of dose-response associations, ${ }^{2-47913}$
and thus modelled them by fitting restricted cubic splines. Given that the volumes of PA reported in most studies were at the lower end of the exposure range and that there is greater uncertainty about the reliability of very high levels of self-reported PA, we set three knots at the 0 th, 37.5 th and 75 th percentiles of person-years rather than persons ( 0 th, 42.5 th and 85 th percentiles in sensitivity analyses). The slope was fixed at the last knot. If the statistical model was unable to converge, we progressively increased the percentile for the upper knot by $1 \%$ until model convergence. Dose-response curves were drawn from 1000 points evenly distributed between 0 mMET -hour/week and the largest PA dose observed in the cohorts included for the outcome of interest.

To investigate the potential effect of study-level confounders on the pooled results across outcomes, we conducted subgroup analyses with the 11 studies that reported results for all all-cause, CVD and cancer mortality outcomes and contrasted them with results from the corresponding main analysis. We also conducted subgroup analysis by sex using studies that reported separate results for men and women.

## Estimation of population health impact

PIFs were calculated for all outcomes based on PA exposure levels in the population of all included cohorts for a given outcome (see formula in online supplemental eMethods 6). ${ }^{20}$ PIFs were calculated for three exposure levels based on the equivalents of the WHO moderate-to-vigorous aerobic PA recommendations for adults ${ }^{21}$ : 8.75 mMET -hours/week (the minimum recommended level, equivalent to 2.5 hours/week of PA at an intensity of 3.5 mMET , such as brisk walking), 17.5 mMET -hours/ week (upper bound of recommended levels for health benefits) and 4.375 mMET -hours/week (half the minimum recommended level). The risk estimates used to calculate PIFs were taken from the dose-response curves, which pooled the most adjusted associations provided by the individual studies.

## Risk of bias assessment

We explored the impact of six potential sources of bias in individual articles and our meta-analytical procedures: how studies had analysed participants with other morbidities, whether they excluded early incident cases during follow-up, duration of follow-up, imputation procedures for missing data, aspects of our approach to exposure harmonisation and separation of occupational PA. For each of these, we contrasted the overall risk estimates between groups of studies with different characteristics. This was done for the five outcomes with the largest number of separate results (all-cause mortality, and total CVD and cancer mortality and incidence), using a fixed PA level of 8.75 mMET -hours/week, relevant to the six sources of bias.

## Software, data and code availability

Analyses were performed using R V.4.0.5 and the dosresmeta package (V.2.0.1). ${ }^{19}$ An interactive interface to visualise the doseresponse associations was developed using the Shiny package (V.1.0.5). Syntax for all analyses and the interactive interface are available at https://github.com/meta-analyses/.

## Patient and public involvement

Patients and the public were not involved in the development of this work.

Marginal MET hours per week


Figure 1 Distribution of marginal MET-hours/week for cohorts included in the all-cause mortality analysis. The exposure distribution for cohorts included in the analysis of other outcomes is available at https://shiny.mrc-epid.cam.ac.uk/meta-analyses-physical-activity/. MET, metabolic equivalent of task.

## RESULTS

## Identified literature

We screened titles and abstracts of 48525 articles, of which 1280 were selected for full-text screening. A total of 196 articles ${ }^{22-216}$ were included in the meta-analysis (online supplemental eFigure 1 ), covering 94 cohorts and reporting 330 separate results. The evidence base was largest for all-cause mortality ( 50 results; 163 415543 person-years, 811616 events), total CVD incidence (37 results; 28884209 person-years, 74757 events) and total cancer incidence ( 31 results; 35500867 person-years, 185870 events). Details of all selected and excluded articles can be found in our OSF repository, and data underlying each of the dose-response estimations can be downloaded at https://shiny.mrc-epid.cam.ac. uk/meta-analyses-physical-activity/.

## Primary dose-response analyses

Most study participants reported non-occupational PA levels below 17.5 mMET-hours/week ( $76 \%$ of person-years), with almost all data below 35 mMET -hours/week ( $94 \%$ of personyears). Figure 1 shows the exposure distribution for the cohorts included in the all-cause mortality analysis.

Inverse, curvilinear dose-response associations between PA and most outcomes were observed, with stronger associations at lower volumes of PA. In most cases, diminishing marginal differences in risk and increasing uncertainty were observed at high PA volumes, particularly beyond 17.5 mMET -hours/ week. Interactive dose-response curves and the exposure distributions are available at https://shiny.mrc-epid.cam.ac.uk/ meta-analyses-physical-activity/.

The association was stronger and more curvilinear for all-cause and CVD mortality than for cancer mortality (figure 2, table 1). Compared with inactive individuals, adults accumulating 8.75 mMET-hours/week had 31\% (95\% CI 27 to 35) and 29\% (95\% CI 23 to 34) lower risk of all-cause and CVD mortality, respectively, whereas the risk difference for total cancer mortality was $15 \%$ ( $95 \%$ CI 11 to 19 ).

A strong curvilinear association was observed for total CVD incidence ( $27 \%$ lower risk ( $95 \%$ CI 21 to 31 ) at 8.75 mMEThours/week). However, the associations were weaker and more linear for the incidence of specific CVD outcomes (coronary heart disease, heart failure and stroke), with the strongest association observed for coronary heart disease ( $21 \%$ lower risk ( $95 \%$ CI 16 to 26 ) at 8.75 mMET -hours/week) (figure 3, table 1).

The association was weaker and more linear for total cancer incidence ( $12 \%$ lower risk ( $95 \%$ CI 8 to 15 ) at 8.75 mMET -hours/ week). For the incidence of site-specific cancers, curvilinear and stronger associations were observed for head and neck, myeloid leukaemia, myeloma, and gastric cardia (from 35\% to $22 \%$ lower risk at 8.75 mMET -hours/week). Weaker and more linear associations were observed for lung, liver, endometrial, colon and breast (from $16 \%$ to $5 \%$ lower risk at 8.75 mMET -hours/ week). Non-significant associations were observed for bladder, oesophageal, prostate and rectal cancer (figure 4, table 1). No eligible studies were available for malignant melanoma.

## Potential population impact

Assuming a causal relationship between non-occupational PA and the examined health outcomes, shifting the distribution of non-occupational PA in the cohorts towards the equivalent recommended level of moderate-to-vigorous aerobic activity ( 8.75 mMET -hours/week) would have averted a substantial fraction of the population disease burden. For example, if all individuals accumulated at least 8.75 mMET -hours/week, then $15.7 \%$ ( $95 \%$ CI 13.2 to 18.2 ), $12.3 \%$ ( $95 \%$ CI 9.4 to 15.2 ) and 7.1\% (95\% CI 5.1 to 9.0 ) of all-cause, CVD-related and cancerrelated deaths, respectively, potentially would have been averted. Additionally, 10.9\% (95\% CI 8.4 to 13.3) and 5.2\% (95\% CI 3.6 to 6.9) of all incident cases of CVD and cancer would have been prevented. Notably, $10.1 \% ~(95 \%$ CI 8.3 to 11.9 ) of all deaths would have been prevented if all adults achieved at least half this PA level (table 1).


Figure 2 Dose-response association between non-occupational physical activity and mortality outcomes. Vertical dashed lines: cubic spline knots (0th, 37.5th and 75th percentiles of person-years); dashed line beyond the upper knot: constrained to be linear. MET, metabolic equivalent of task.

## Systematic review

Table 1 Relative risk of mortality and incidence of cardiovascular diseases and cancers at three physical activity levels in relation to 0 mMET hours/week and respective potential impact fractions

| Outcomes | 4.375 mMET-hours/week |  | 8.75 mMET-hours/week |  | 17.5 mMET-hours/week |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | RR (95\% CI) | PIF (95\% CI) | RR (95\% CI) | PIF (95\% CI) | RR (95\% CI) | PIF (95\% CI) |
| Mortality |  |  |  |  |  |  |
| All-cause mortality | $\begin{aligned} & 0.77 \\ & (0.73 \text { to } 0.80) \end{aligned}$ | $\begin{aligned} & 10.11 \\ & (8.32 \text { to 11.91) } \end{aligned}$ | $\begin{aligned} & 0.69 \\ & (0.65 \text { to } 0.73) \end{aligned}$ | $\begin{aligned} & 15.66 \\ & (13.16 \text { to } 18.15 \text { ) } \end{aligned}$ | $\begin{aligned} & 0.66 \\ & (0.62 \text { to } 0.70) \end{aligned}$ | $\begin{aligned} & 18.75 \\ & \text { (16.09 to } 21.39 \text { ) } \end{aligned}$ |
| Total CVD | $\begin{aligned} & 0.81 \\ & (0.77 \text { to } 0.85) \end{aligned}$ | $\begin{aligned} & 6.02 \\ & (4.42 \text { to } 7.69) \end{aligned}$ | $\begin{aligned} & 0.71 \\ & (0.66 \text { to } 0.77) \end{aligned}$ | $\begin{aligned} & 12.25 \\ & \text { (9.37 to 15.17) } \end{aligned}$ | $\begin{aligned} & 0.65 \\ & (0.60 \text { to } 0.71) \end{aligned}$ | $\begin{aligned} & 17.05 \\ & \text { (13.92 to 20.19) } \end{aligned}$ |
| Total cancer | $\begin{aligned} & 0.90 \\ & (0.88 \text { to } 0.93) \end{aligned}$ | $\begin{aligned} & 3.68 \\ & (2.54 \text { to } 4.86) \end{aligned}$ | $\begin{aligned} & 0.85 \\ & (0.81 \text { to } 0.89) \end{aligned}$ | $\begin{aligned} & 7.05 \\ & \text { (5.1 to 9.00) } \end{aligned}$ | $\begin{aligned} & 0.82 \\ & (0.78 \text { to } 0.86) \end{aligned}$ | $\begin{aligned} & 9.29 \\ & (7.36 \text { to } 11.22) \end{aligned}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total CVD | $\begin{aligned} & 0.83 \\ & (0.79 \text { to } 0.87) \end{aligned}$ | $\begin{aligned} & 5.29 \\ & (3.93 \text { to } 6.70) \end{aligned}$ | $\begin{aligned} & 0.73 \\ & (0.69 \text { to } 0.79) \end{aligned}$ | $\begin{aligned} & 10.86 \\ & \text { (8.43 to 13.31) } \end{aligned}$ | $\begin{aligned} & 0.67 \\ & (0.63 \text { to } 0.72) \end{aligned}$ | $\begin{aligned} & 15.42 \\ & \text { (13.01 to 17.85) } \end{aligned}$ |
| Coronary heart disease | $\begin{aligned} & 0.86 \\ & (0.83 \text { to } 0.90) \end{aligned}$ | $\begin{aligned} & 5.51 \\ & (3.95 \text { to } 7.11) \end{aligned}$ | $\begin{aligned} & 0.79 \\ & (0.74 \text { to } 0.84) \end{aligned}$ | $\begin{aligned} & 10.28 \\ & \text { (7.61 to 12.96) } \end{aligned}$ | $\begin{aligned} & 0.74 \\ & (0.69 \text { to } 0.80) \end{aligned}$ | $\begin{aligned} & 13.58 \\ & (10.51 \text { to } 16.64) \end{aligned}$ |
| Stroke | $\begin{aligned} & 0.86 \\ & (0.83 \text { to } 0.90) \end{aligned}$ | $\begin{aligned} & 5.53 \\ & (3.96 \text { to } 7.15) \end{aligned}$ | $\begin{aligned} & 0.80 \\ & (0.75 \text { to } 0.85) \end{aligned}$ | $\begin{aligned} & 9.77 \\ & (7.31 \text { to } 12.24) \end{aligned}$ | $\begin{aligned} & 0.77 \\ & (0.72 \text { to } 0.82) \end{aligned}$ | $\begin{aligned} & 12.37 \\ & (9.63 \text { to } 15.10) \end{aligned}$ |
| Heart failure | $\begin{aligned} & 0.90 \\ & (0.85 \text { to } 0.96) \end{aligned}$ | $\begin{aligned} & 2.23 \\ & (0.80 \text { to } 3.89) \end{aligned}$ | $\begin{aligned} & 0.84 \\ & (0.75 \text { to } 0.93) \end{aligned}$ | $\begin{aligned} & 4.63 \\ & (1.90 \text { to } 7.66) \end{aligned}$ | $\begin{aligned} & 0.77 \\ & (0.68 \text { to } 0.87) \end{aligned}$ | $\begin{aligned} & 7.86 \\ & (4.31 \text { to } 11.68) \end{aligned}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total cancer | $\begin{aligned} & 0.93 \\ & (0.91 \text { to } 0.95) \end{aligned}$ | $\begin{aligned} & 2.53 \\ & (1.66 \text { to } 3.42) \end{aligned}$ | $\begin{aligned} & 0.88 \\ & (0.85 \text { to } 0.92) \end{aligned}$ | $\begin{aligned} & 5.22 \\ & (3.55 \text { to } 6.90) \end{aligned}$ | $\begin{aligned} & 0.85 \\ & (0.81 \text { to } 0.89) \end{aligned}$ | $\begin{aligned} & 7.80 \\ & (5.65 \text { to } 9.93) \end{aligned}$ |
| Head and neck | $\begin{aligned} & 0.74 \\ & (0.59 \text { to } 0.94) \end{aligned}$ | $\begin{aligned} & 10.59 \\ & (2.10 \text { to } 19.96) \end{aligned}$ | $\begin{aligned} & 0.65 \\ & (0.46 \text { to } 0.91) \end{aligned}$ | $\begin{aligned} & 17.46 \\ & \text { (3.68 to 30.98) } \end{aligned}$ | $\begin{aligned} & 0.63 \\ & (0.42 \text { to } 0.94) \end{aligned}$ | $\begin{aligned} & 19.83 \\ & \text { (1.23 to } 36.55 \text { ) } \end{aligned}$ |
| Myeloid leukaemia | $\begin{aligned} & 0.80 \\ & (0.66 \text { to } 0.97) \end{aligned}$ | $\begin{aligned} & 4.93 \\ & (0.68 \text { to } 9.70) \end{aligned}$ | $\begin{aligned} & 0.75 \\ & (0.60 \text { to } 0.95) \end{aligned}$ | $\begin{aligned} & 7.08 \\ & (1.65 \text { to } 12.94) \end{aligned}$ | $\begin{aligned} & 0.75 \\ & (0.60 \text { to } 0.94) \end{aligned}$ | $\begin{aligned} & 7.57 \\ & (2.23 \text { to } 13.33 \text { ) } \end{aligned}$ |
| Myeloma | $\begin{aligned} & 0.84 \\ & (0.74 \text { to } 0.95) \end{aligned}$ | $\begin{aligned} & 3.34 \\ & (0.90 \text { to } 6.26) \end{aligned}$ | $\begin{aligned} & 0.75 \\ & (0.61 \text { to } 0.92) \end{aligned}$ | $\begin{aligned} & 6.76 \\ & (1.90 \text { to } 12.09) \end{aligned}$ | $\begin{aligned} & 0.72 \\ & (0.57 \text { to } 0.92) \end{aligned}$ | $\begin{aligned} & 8.30 \\ & (1.91 \text { to } 14.99) \end{aligned}$ |
| Gastric cardia | $\begin{aligned} & 0.86 \\ & (0.78 \text { to } 0.95) \end{aligned}$ | $\begin{aligned} & 1.95 \\ & (0.58 \text { to } 3.68) \end{aligned}$ | $\begin{aligned} & 0.78 \\ & (0.66 \text { to } 0.91) \end{aligned}$ | $\begin{aligned} & 4.77 \\ & (1.58 \text { to } 8.57) \end{aligned}$ | $\begin{aligned} & 0.73 \\ & (0.60 \text { to } 0.88) \end{aligned}$ | $\begin{aligned} & 6.77 \\ & (2.55 \text { to 11.63) } \end{aligned}$ |
| Lung | $\begin{aligned} & 0.89 \\ & (0.87 \text { to } 0.92) \end{aligned}$ | $\begin{aligned} & 4.39 \\ & (3.16 \text { to } 5.63) \end{aligned}$ | $\begin{aligned} & 0.84 \\ & (0.81 \text { to } 0.88) \end{aligned}$ | $\begin{aligned} & 7.26 \\ & (5.10 \text { to } 9.40) \end{aligned}$ | $\begin{aligned} & 0.83 \\ & (0.76 \text { to } 0.91) \end{aligned}$ | $\begin{aligned} & 8.54 \\ & (3.04 \text { to 13.98) } \end{aligned}$ |
| Liver | $\begin{aligned} & 0.90 \\ & (0.83 \text { to } 0.98) \end{aligned}$ | $\begin{aligned} & 3.49 \\ & (0.58 \text { to } 6.71) \end{aligned}$ | $\begin{aligned} & 0.84 \\ & (0.73 \text { to } 0.96) \end{aligned}$ | $\begin{aligned} & 6.75 \\ & \text { (1.44 to 12.31) } \end{aligned}$ | $\begin{aligned} & 0.78 \\ & (0.66 \text { to } 0.93) \end{aligned}$ | $\begin{aligned} & 10.27 \\ & \text { (3.26 to 17.31) } \end{aligned}$ |
| Endometrial | $\begin{aligned} & 0.94 \\ & (0.90 \text { to } 0.99) \end{aligned}$ | $\begin{aligned} & 1.10 \\ & (0.26 \text { to } 2.02) \end{aligned}$ | $\begin{aligned} & 0.90 \\ & (0.84 \text { to } 0.97) \end{aligned}$ | $\begin{aligned} & 2.62 \\ & (0.76 \text { to } 4.60) \end{aligned}$ | $\begin{aligned} & 0.87 \\ & (0.80 \text { to } 0.95) \end{aligned}$ | $\begin{aligned} & 4.54 \\ & (1.88 \text { to } 7.28 \text { ) } \end{aligned}$ |
| Colon | $\begin{aligned} & 0.96 \\ & (0.93 \text { to } 0.99) \end{aligned}$ | $\begin{aligned} & 0.70 \\ & (0.11 \text { to } 1.33 \text { ) } \end{aligned}$ | $\begin{aligned} & 0.93 \\ & (0.87 \text { to } 0.99) \end{aligned}$ | $\begin{aligned} & 1.69 \\ & (0.33 \text { to } 3.12) \end{aligned}$ | $\begin{aligned} & 0.90 \\ & (0.84 \text { to } 0.97) \end{aligned}$ | $\begin{aligned} & 2.96 \\ & (0.92 \text { to } 5.05) \end{aligned}$ |
| Breast | $\begin{aligned} & 0.97 \\ & (0.96 \text { to } 0.99) \end{aligned}$ | $\begin{aligned} & 0.69 \\ & (0.32 \text { to } 1.07 \text { ) } \end{aligned}$ | $\begin{aligned} & 0.95 \\ & (0.92 \text { to } 0.97) \end{aligned}$ | $\begin{aligned} & 1.62 \\ & (0.79 \text { to } 2.46 \text { ) } \end{aligned}$ | $\begin{aligned} & 0.92 \\ & (0.88 \text { to } 0.96) \end{aligned}$ | $\begin{aligned} & 3.23 \\ & (1.85 \text { to } 4.63) \end{aligned}$ |
| Bladder | $\begin{aligned} & 0.93 \\ & (0.84 \text { to } 1.02) \end{aligned}$ | $\begin{aligned} & 1.91 \\ & (-0.54 \text { to } 4.52) \end{aligned}$ | $\begin{aligned} & 0.90 \\ & (0.80 \text { to } 1.02) \end{aligned}$ | $\begin{aligned} & 2.98 \\ & (-0.24 \text { to } 6.33) \end{aligned}$ | $\begin{aligned} & 0.90 \\ & (0.81 \text { to } 1.01) \end{aligned}$ | $\begin{aligned} & 3.11 \\ & (0.02 \text { to } 6.35) \end{aligned}$ |
| Rectum | $\begin{aligned} & 0.96 \\ & (0.92 \text { to } 1.01) \end{aligned}$ | $\begin{aligned} & 0.77 \\ & (-0.15 \text { to } 1.75) \end{aligned}$ | $\begin{aligned} & 0.95 \\ & (0.88 \text { to } 1.02) \end{aligned}$ | $\begin{aligned} & 1.43 \\ & (-0.45 \text { to } 3.36) \end{aligned}$ | $\begin{aligned} & 0.96 \\ & (0.88 \text { to } 1.04) \end{aligned}$ | $\begin{aligned} & 0.52 \\ & (-1.74 \text { to } 2.82) \end{aligned}$ |
| Oesophageal | $\begin{aligned} & 0.97 \\ & (0.89 \text { to } 1.05) \end{aligned}$ | $\begin{aligned} & 0.68 \\ & (-0.95 \text { to } 2.68) \end{aligned}$ | $\begin{aligned} & 0.95 \\ & (0.82 \text { to } 1.09) \end{aligned}$ | $\begin{aligned} & 1.38 \\ & (-2.06 \text { to } 5.32) \end{aligned}$ | $\begin{aligned} & 0.94 \\ & (0.79 \text { to } 1.12) \end{aligned}$ | $\begin{aligned} & 1.57 \\ & (-3.05 \text { to } 6.67) \end{aligned}$ |
| Prostate | $\begin{aligned} & 1.00 \\ & (0.99 \text { to } 1.02) \end{aligned}$ | $\begin{aligned} & -0.10 \\ & (-0.48 \text { to } 0.29) \end{aligned}$ | $\begin{aligned} & 1.01 \\ & (0.98 \text { to } 1.04) \end{aligned}$ | $\begin{aligned} & -0.21 \\ & (-1.10 \text { to } 0.71) \end{aligned}$ | $\begin{aligned} & 1.01 \\ & (0.96 \text { to } 1.05) \end{aligned}$ | $\begin{aligned} & -0.10 \\ & (-1.61 \text { to } 1.42) \end{aligned}$ |
| Kidney | $\begin{aligned} & 1.02 \\ & (0.92 \text { to } 1.13 \text { ) } \end{aligned}$ | $\begin{aligned} & -0.65 \\ & (-3.69 \text { to } 2.81) \end{aligned}$ | $\begin{aligned} & 1.03 \\ & (0.89 \text { to } 1.19) \end{aligned}$ | $\begin{aligned} & -1.23 \\ & (-6.39 \text { to } 4.34) \end{aligned}$ | $\begin{aligned} & 1.04 \\ & (0.88 \text { to } 1.24) \end{aligned}$ | $\begin{aligned} & -1.91 \\ & (-9.20 \text { to } 5.63) \end{aligned}$ |

CVD, cardiovascular disease; mMET, marginal metabolic equivalent of task; PII, potential impact fraction; RR, relative risk.

## Subgroup analysis

Pooled estimates from studies that reported results for all-cause, CVD and cancer mortality
The pooled analysis from the 11 studies that reported results for all-cause, CVD and cancer mortality showed weaker associations for all-cause mortality and stronger associations for CVD and cancer mortality (online supplemental eResults 1 ).

## Sex-stratified results

Sex-stratified results were available for all-cause, CVD and cancer mortality and incidence of total CVD, coronary heart disease,
stroke, total cancer, and cancers of the colon and rectum. There was some evidence of stronger associations in women than in men for all-cause and CVD mortality and CVD incidence, but the reverse for cancer mortality and incidence (online supplemental eResults 2).

## Risk of bias

Across the five outcomes with the largest number of separate results (all-cause mortality, and total CVD and cancer mortality and incidence), $83 \%-93 \%$ of the studies used statistical adjustments to control for other morbidities at baseline, often


Figure 3 Dose-response association between non-occupational physical activity and incidence (fatal and non-fatal events combined) of cardiovascular diseases. Vertical dashed lines: cubic spline knots (0th, 37.5 th and 75 th percentiles of person-years); dashed line beyond the upper knot: constrained to be linear. MET, metabolic equivalent of task.


Figure 4 Dose-response association between non-occupational physical activity and incidence (fatal and non-fatal events combined) of cancers. Vertical dashed lines: cubic spline knots (0th, 37.5th and 75th percentiles of person-years); dashed line beyond the upper knot: constrained to be linear. MET, metabolic equivalent of task.
combined with exclusion of adults with more serious pre-existing conditions. Studies that predominantly used statistical adjustments tended to report stronger associations for CVD mortality compared with studies that excluded adults with pre-existing conditions at baseline. Between $54 \%$ and $59 \%$ of the studies did not exclude mortality and disease events occurring within the first few years of follow-up, and those that did tended to report weaker associations for all-cause mortality and CVD mortality and incidence. The median follow-up time was 10 years for each outcome, with no evidence of bias between studies with longer and shorter follow-up time. Data imputation was required for $58 \%-64 \%$ of the studies, but no evidence of bias was found. The most frequently used procedures for exposure harmonisation were measurement unit conversions ( $42 \%-49 \%$ of studies) and the assumption of standard values for the intensity and duration of PA reported ( $39 \%-50 \%$ ), but no evidence of bias was found. In $75 \%$ of the studies, the original exposure assessment did not include occupational PA and no evidence of bias was observed for studies requiring domain separation (online supplemental eResults 3).

## Sensitivity analyses

In studies that did not report the duration or intensity of PA, assuming (where appropriate) shorter session duration ( 0.5 hours instead of 0.75 hours) and lower intensity ( 1 mMET lower for moderate and vigorous PA) did not materially alter the dose-response associations for most outcomes, especially analyses which included the largest number of separate results (online supplemental eResults 4). When shorter duration and lower intensity were used, associations were stronger for CVD outcomes, particularly at lower PA volumes. Placing the restricted cubic spline knots at the 42.5 th and 85 th percentiles resulted in less stable estimations at higher PA volumes, with those specific segments of the dose-response curves being based on less data and with a higher risk of exposure misclassification.

Sensitivity analyses using analytical models that did not include adjustment for adiposity showed stronger associations for allcause and CVD mortality, and the incidence of total CVD, heart failure, and site-specific cancers of the endometrium, kidney, lung and rectum (online supplemental eResults 4). Notably, the association was significant for rectal cancer.

## DISCUSSION

We present comprehensive dose-response meta-analyses of the associations between non-occupational PA and a wide range of mortality and disease outcomes. Our extensive exposure data harmonisation allowed inclusion of a larger evidence base than previous meta-analyses for 17 of 22 health outcomes investigated. For instance, our meta-analysis for all-cause mortality includes over 160 million person-years and 810000 deaths. These are 17 and 7 times larger, respectively, than what were included in the previously largest dose-response analysis to date ( 9.39 million person-years and 117000 deaths). ${ }^{2}$ Our inclusive approach has a number of advantages. First, we were able to estimate dose-response associations for nine site-specific cancers for the first time. Second, inclusion of more data increases confidence in the results beyond previous estimates. Third, it allowed us to include data from a larger number of countries. Fourth, having used consistent methods for several health outcomes allows the best possible comparison of the shape of the doseresponse functions across these outcomes. For example, having one set of dose-response results consistently estimated across
several outcomes is particularly useful for health impact modelling, for example, to quantify the probable impacts of changes to population-level PA.

We showed inverse non-linear dose-response associations for all-cause mortality and a range of CVD and cancer outcomes. This suggests that the greatest potential benefits can be achieved through small increases in non-occupational PA for those with an inactive lifestyle, with incrementally smaller additional benefits up to approximately 17.5 mMET -hours/week. Above this level, the evidence base was weaker. Shifting population levels of activity towards achieving the equivalent to $150 \mathrm{~min} / \mathrm{week}$ of moderate-to-vigorous aerobic PA ( 8.75 mMET -hours/week) potentially would have prevented $16 \%$ of all premature deaths recorded.

Compared with previous studies, we found similar associations for all-cause ${ }^{23}$ and cancer mortality, ${ }^{4}$ and stronger associations and narrower CIs for CVD mortality, ${ }^{5}{ }^{6}$ at the equivalent recommended levels of moderate-to-vigorous aerobic PA. For cancers of the bladder, breast, colon, endometrium, oesophagus, liver and rectum, our results were largely similar to that of a recent pooled analysis. ${ }^{7}$ However, we found stronger associations for cancers of the gastric cardia, head and neck, myeloid leukaemia, and myeloma, whereas the association for kidney cancer was non-significant. Contrasting with Moore et al's ${ }^{8}$ finding of harmful effects of PA on prostate cancer, our results did not show an association. Comparisons should be interpreted with caution as most previous studies have focused solely on leisure-time $\mathrm{PA}^{236-8}$ and meta-analyses by Li et al ${ }^{4}$ and Wahid et $a l^{5}$ included studies that assessed PA in any domain.

Compared with the results from the GBD, ${ }^{9}$ which has assessed total PA rather than non-occupational PA, we found stronger associations for heart disease and stroke at the equivalent minimum recommended moderate-to-vigorous aerobic PA level. Associations reported by the GBD at approximately 130 MET-hours/week for total PA were observed in our study at 17.5 mMET-hours/week for non-occupational PA, a much lower volume even considering that we excluded energy expenditure from the resting metabolic rate and occupational activity. Given the challenges of assessing occupational activity, estimates of total PA from self-report are often implausibly high. ${ }^{217}$ Hence, the importance of PA may have been underestimated by the GBD. This, combined with uncertainties around the health benefits of occupational PA, ${ }^{10218}$ means our results may be more relevant from a public health perspective.

It is surprising that the risk difference for all-cause mortality ( $31 \%$ at the equivalent minimum recommended moderate-tovigorous aerobic PA level) is similar to that for total CVD (29\%) and much larger than for total cancer mortality (15\%). Equally, it is surprising that the association for total CVD incidence is stronger than that for coronary heart disease or stroke. Weaker associations would be expected for more composite outcomes (eg, all-cause mortality and total CVD incidence) than for the outcomes within them for which a significant association has been established. Potential explanations include detection bias for some disease events, misclassification of causes of death (especially for more specific disease outcomes), differential residual confounding, reverse causality by outcome, and different inclusion criteria by disease outcome, such as the inclusion of different disease groups which may have stronger associations with PA. ${ }^{219}$ There may also be study-level confounders, and this is supported by our post-hoc subgroup analysis, which showed that studies reporting all three mortality outcomes found stronger associations for CVD than for all-cause mortality. Taken together, it is probable that the
risk estimates for all-cause mortality are more accurate than for specific disease outcomes.

Our risk of bias and sensitivity analyses showed that the methodological assumptions and decisions made for the pooled analyses did not significantly impact the dose-response associations observed. However, some methodological differences between the original studies seem to alter the magnitude of the pooled associations. Studies that did not exclude people with pre-existing conditions at baseline or mortality or disease events occurring within the first years of follow-up tended to observe stronger associations, as did studies with shorter follow-up, which may in part be indicative of reverse causality. ${ }^{11}{ }^{220}$ For some outcomes, stronger associations were also observed in studies that did not include adjustment for adiposity in their analytical models, which can be interpreted as either being prone to residual confounding or a more inclusive estimation of the total causal effect, if adiposity is considered a mediator between PA and the investigated health outcomes.

A strength of our study was the use of comprehensive exposure data harmonisation methods that enabled the inclusion of a larger evidence base. This also allowed us to study health associations over a wider range of the PA exposure and increased the density of data in the area of the dose-response curves with high non-linearity. Another strength is the use of more sophisticated meta-analytical methods that allow the shape of the dose-response association to vary across the exposure range, rather than linear models of transformed exposure or grouping doses within high versus low PA or multiple exposure intervals. We improved the placement of spline knots compared with our previous work ${ }^{13}$ by considering the distribution of personyears instead of non-weighted associations across the PA range, acknowledging the paucity of data at higher volumes of PA.

Our study also has limitations. There are levels of the PA exposure for which health associations are not reported in many of the original studies and hence there is still substantial uncertainty at those levels in the meta-analyses for some outcomes. Many of the included studies relied on selfreported questionnaires without validation or calibration data that could be used in the exposure harmonisation. In the exposure data harmonisation procedures, it was also sometimes necessary to make assumptions about parameters of PA, such as intensity and duration, where these were not explicitly reported. Nonetheless, our sensitivity analyses demonstrated the robustness of our results to the assumptions made. Measurement error is likely to lead to an underestimation of the true association between PA and the various outcomes, as demonstrated by the stronger associations observed in studies using device-based measures of PA. ${ }^{221}$ Regression dilution bias, particularly in studies with longer follow-up times, might also have affected the associations observed, ${ }^{220}$ which can be mitigated by repeated PA measures over time. Misclassification of some outcomes will have occurred in original studies as ascertainment of outcomes may not be similarly accurate across all outcomes and studies. Residual confounding and reverse causation could remain. To mitigate confounding, the most comprehensively adjusted risk estimates were used in this meta-analysis. However, the level of covariate adjustment and the degree to which these covariates effectively control for confounding were not consistent across all studies. We excluded studies with less than 3 years of follow-up to mitigate reverse causation. ${ }^{220}$ Although the bias from reverse causation diminishes with longer periods of follow-up, changes in PA level over time could be possible. ${ }^{11}{ }^{222}$ Our estimates of population impact are based on the assumptions
that the dose-response relationships are causal and that the prevalence of PA in our cohorts is representative of the wider population. The time lag between searches and publication of our results is longer than typical due to the scale of this review. We did not use validated tools to assess risk of bias or certainty of evidence. Nonetheless, we assessed six critical potential sources of bias for observational studies in PA and health outcomes and quantified their impacts on our results. Aspects included in other tools but not quantified by us, such as methods to measure exposure and outcome and attempt to control for established confounding factors (eg, sex and age), were not materially different across the included studies and hence it was not possible to assess their impact. Our analyses also cover aspects that are important for judging the confidence in the evidence base, such as the dose-response gradient, precision of the effect estimates, risk of bias assessment and subgroup analysis to investigate the effect of studylevel confounders.

Our findings support the current PA recommendations of $150-300 \mathrm{~min} /$ week of moderate aerobic PA (or 75-150 $\mathrm{min} /$ week of vigorous aerobic PA , or an equivalent combination of moderate and vigorous activities), ${ }^{21}$ in that this exposure level generally seems to equate to maximum or near-to-maximal benefits. However, the dose-response associations also demonstrate that appreciable health benefits can be gained from $75 \mathrm{~min} /$ week or less of moderate activity (ie, half the recommended minimum level). Thus, our findings support the recent change in public health messaging to 'doing some PA is better than doing none', and suggest that the emphasis on threshold-based recommendations could be further reduced.

It should be noted that our exposure estimates are derived from a variety of self-reported questionnaires that capture mostly moderate and vigorous activities. These exposure estimates differ from those derived using device-based measures, which also record light-intensity and intermittent activities that are more difficult to recall. ${ }^{221} 223224$ Self-report and device-based measures are therefore complementary but not interchangeable, ${ }^{224}$ an important consideration when formulating public health messages.

Future research should investigate the reasons for the apparent inconsistencies in dose-response associations between composite and individual disease endpoints. Although our risk of bias and sensitivity analyses showed robustness to the approaches we took during data handling and dose harmonisation, future studies could quantify methodological uncertainties (eg, inaccuracies in exposure assessment) and propagate them in the aetiological analyses to provide more realistic uncertainty ranges for the dose-response associations. The evidence base was weaker for very high volumes of activity and further research is required to ascertain the shape of associations more reliably at the higher end of the PA continuum.

## CONCLUSION

We found evidence of dose-dependent associations between increasing non-occupational PA and a wide range of mortality, CVD and cancer outcomes. The strongest associations were observed for all-cause and CVD mortality, with weaker associations for the incidence of cancer, including variation by site. Appreciable population health benefits might be gained from increasing PA levels of people who are inactive to just half the current health recommendations, with further
benefits for all reaching at least the recommended level and smaller additional benefits beyond that.

## What is already known

$\Rightarrow$ Higher levels of physical activity are associated with lower rates of premature death and chronic disease outcomes.
$\Rightarrow$ The shape of the dose-response association has been more difficult to determine and has not been established for a range of chronic diseases.
$\Rightarrow$ Accurate estimation of the dose-response association between physical activity and disease outcomes is needed to assess the disease burden of physical inactivity and the potential impact of changes to population levels of physical activity.

## What are the findings?

$\Rightarrow$ Our findings suggest an appreciably lower risk of mortality, cardiovascular diseases and cancers from the equivalent of $75 \mathrm{~min} /$ week or less of moderate-intensity aerobic physical activity (ie, half the recommended minimum levels).
$\Rightarrow$ Our results include the first dose-response meta-analysis of nine site-specific cancers: bladder, esophageal, gastric cardia, head and neck, kidney, liver, lung, myeloid leukaemia and myeloma.
$\Rightarrow$ One in 10 premature deaths could have been prevented if everyone achieved even half the recommended level of physical activity.

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Paper: Non-occupational physical activity and risk of cardiovascular disease, cancer, and mortality outcomes: a doseresponse meta-analysis of large prospective studies

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## eMethods 1: study inclusion and exclusion criteria

| Include | Exclude |
| :--- | :--- |
| Participants | Cohorts of institutionalised adults, medical patients <br> (i.e., in secondary or tertiary prevention) or high-risk <br> populations (e.g., hypertension, diabetes - except <br> conditions inevitable with ageing, as post-menopause) |
| Exposure  <br> Volume (marginal MET-h/week) of non-occupational <br> physical activity - this includes leisure-time physical <br> activity alone, combined with other non-occupational <br> physical activity domains (e.g., transport and/or <br> domestic activity), or combined with specific types of <br> activity such as walking. Physical activity volume can be <br> either self-reported or measured by devices and must <br> be reported in at least three exposure levels Measures of physical activity from which occupational <br> activity cannot be factored out; individual domains of <br> physical activity which occur outside of work but do not <br> include leisure-time activity (e.g., travel physical <br> activity only); other risk factors either alone or <br> combined with physical activity <br> Comparators  <br> Lower volumes of physical activity (as defined in  <br> 'Interventions')  |  |
| Outcomes |  |

## utcomes

1) All-cause mortality $\quad$ Less than three years of follow-up period
2) Cardiovascular diseases (fatal and non-fatal):
a. Total CVD (IOO-I99)*
b. Stroke (160-166)
c. Heart failure (I50, I11.0, I13.0, I13.2)
d. Coronary heart disease (I20-125)
3) Cancers** (fatal and non-fatal):
a. Total cancer (C00-D49)
b. Breast (C50)
c. Endometrial (C54)
d. Lung (C34)
e. Colon (C18)
f. Esophageal (C15)
g. Liver (C22-C24)
h. Kidney (C64-C65)
. Gastric cardia (C16.0)
j. Myeloid leukemia (C92)
k. Myeloma (C90)
I. Head and neck (C76.0)
m. Rectum (C20)
n. Bladder (C67)
o. Prostate (C61)
p. Malignant melanoma (C43)

Cases ascertained via health, death, cancer, hospital or insurance registers; death certificates; participants and their next-of-kin

## Study design

General population prospective cohort studies
(including case-cohort and nested case-control studies) with sample size larger than 10,000 participants; results must be reported either as hazard ratios, relative risks or odds ratios with confidence intervals

* Diseases coded using the International statistical classification of diseases and related health problems, 10th revision. ${ }^{1}$
** Cancers associated with leisure-time physical activity in Moore et al. ${ }^{2}$
- Type of documents: peer-reviewed articles published in academic journals.
- No limits on language and date of publication.


## eMethods 2: search strings

## Pubmed

((physical activit*[Title/Abstract]) OR (physical inactivity[Title/Abstract]) OR (exercise[Title/Abstract]) OR
(exercises[Title/Abstract]) OR (exercising[Title/Abstract]) OR (recreational activit*[Title/Abstract]) OR (sport[Title/Abstract]) OR (sports[Title/Abstract]) OR (active transport[Title/Abstract]) OR (active transportation[Title/Abstract]) OR (active commut*[Title/Abstract]) OR (active travel*[Title/Abstract]) OR (household activit*[Title/Abstract]) OR (housework[Title/Abstract]) OR (non-exercise activit*[Title/Abstract]) OR (nonexercise activit*[Title/Abstract]) OR (activities of daily living[Title/Abstract]) OR (bicycle[Title/Abstract]) OR (bicycling[Title/Abstract]) OR (bike[Title/Abstract]) OR (biking[Title/Abstract]) OR (walk[Title/Abstract]) OR (walking[Title/Abstract]) OR (run[Title/Abstract]) OR (running[Title/Abstract]) OR (jogging[Title/Abstract]) OR (swim[Title/Abstract]) OR (swimming[Title/Abstract]) OR (resistance training[Title/Abstract]) OR (weight lifting[Title/Abstract]) OR (physical fitness[Title/Abstract]) OR (physical endurance[Title/Abstract]) OR (activity energy expenditure[Title/Abstract]) OR (caloric expenditure[Title/Abstract]) OR (motor activity[Mesh:NoExp]) OR (exercise[Mesh:NoExp]) OR (human physical conditioning[Mesh]) OR (leisure activities[Mesh:NoExp]) OR (recreation[Mesh:NoExp]) OR (dancing[Mesh]) OR (gardening[Mesh]) OR (sports[Mesh]) OR (activities of daily living[Mesh:NoExp]))

AND
((mortality[Title/Abstract]) OR (cardiovascular disease*[Title/Abstract]) OR (acute coronary syndrome[Title/Abstract]) OR (myocardial infarction[Title/Abstract]) OR (myocardial ischemia[Title/Abstract]) OR (heart disease*[Title/Abstract]) OR (coronary disease*[Title/Abstract]) OR (coronary artery disease*[Title/Abstract]) OR (heart failure[Title/Abstract]) OR (cardiac failure[Title/Abstract]) OR (stroke[Title/Abstract]) OR (brain ischemia[Title/Abstract]) OR (cerebrovascular accident*[Title/Abstract]) OR (cerebrovascular disorder*[Title/Abstract]) OR (cerebrovascular disease*[Title/Abstract]) OR (intracranial arterial disease*[Title/Abstract]) OR (ganglia hemorrhage[Title/Abstract]) OR (ganglia haemorrhage[Title/Abstract]) OR (cerebral intraventricular hemorrhage[Title/Abstract]) OR (cerebral intraventricular haemorrhage[Title/Abstract]) OR (hypertensive intracranial hemorrhage[Title/Abstract]) OR (hypertensive intracranial haemorrhage[Title/Abstract]) OR (cerebral haemorrhage[Title/Abstract]) OR (cerebral hemorrhage[Title/Abstract]) OR (cancer[Title/Abstract]) OR (cancers[Title/Abstract]) OR (tumour[Title/Abstract]) OR (tumours[Title/Abstract]) OR (tumor[Title/Abstract]) OR (tumors[Title/Abstract]) OR (neoplasm[Title/Abstract]) OR (neoplasms[Title/Abstract]) OR (mortality[Mesh:NoExp]) OR (cause of death[Mesh]) OR (premature mortality[Mesh]) OR (cardiovascular diseases[Mesh:NoExp]) OR (heart diseases[Mesh:NoExp]) OR (myocardial ischemia[Mesh]) OR (heart failure[Mesh]) OR (cerebrovascular disorders[Mesh:NoExp]) OR (brain ischemia[Mesh]) OR (cerebral small vessel diseases[Mesh]) OR (intracranial arterial diseases[Mesh]) OR (basal ganglia hemorrhage [Mesh]) OR (cerebral intraventricular hemorrhage [Mesh]) OR (hypertensive intracranial hemorrhage [Mesh]) OR (stroke[Mesh]) OR (neoplasms[Mesh]))

AND
((cohort[Title/Abstract]) OR (cohorts[Title/Abstract]) OR (follow-up study[Title/Abstract]) OR (follow-up studies[Title/Abstract]) OR (prospective study[Title/Abstract]) OR (prospective studies[Title/Abstract]) OR (longitudinal study[Title/Abstract]) OR (longitudinal studies[Title/Abstract]) OR (cohort studies[Mesh:NoExp]) OR (follow-up studies[Mesh]) OR (longitudinal studies[Mesh:NoExp]) OR (prospective studies[Mesh]))

## Scopus

(TITLE-ABS-KEY("physical activit*") OR TITLE-ABS-KEY("physical inactivity") OR TITLE-ABS-KEY(exercise) OR TITLE-ABSKEY(exercises) OR TITLE-ABS-KEY(exercising) OR TITLE-ABS-KEY("recreational activit*") OR TITLE-ABS-KEY(sport) OR TITLE-ABSKEY(sports) OR TITLE-ABS-KEY("active transport") OR TITLE-ABS-KEY("active transportation") OR TITLE-ABS-KEY("active commut*") OR TITLE-ABS-KEY("active travel*") OR TITLE-ABS-KEY("household activit*") OR TITLE-ABS-KEY(housework) OR TITLE-ABS-KEY("non-exercise activit*") OR TITLE-ABS-KEY("nonexercise activit*") OR TITLE-ABS-KEY("activities of daily living") OR TITLE-ABS-KEY(bicycle) OR TITLE-ABS-KEY(bicycling) OR TITLE-ABS-KEY(bike) OR TITLE-ABS-KEY(biking) OR TITLE-ABS-KEY(walk) OR TITLE-ABS-KEY(walking) OR TITLE-ABS-KEY(run) OR TITLE-ABS-KEY(running) OR TITLE-ABS-KEY(jogging) OR TITLE-ABS-KEY(swim) OR TITLE-ABS-KEY(swimming) OR TITLE-ABS-KEY("resistance training") OR TITLE-ABS-KEY("weight lifting") OR TITLE-ABSKEY("physical fitness") OR TITLE-ABS-KEY("physical endurance") OR TITLE-ABS-KEY("activity energy expenditure") OR TITLE-ABSKEY("caloric expenditure"))
AND
(TITLE-ABS-KEY(mortality) OR TITLE-ABS-KEY("cardiovascular disease*") OR TITLE-ABS-KEY("acute coronary syndrome") OR TITLE-ABS-KEY("myocardial infarction") OR TITLE-ABS-KEY("myocardial ischemia") OR TITLE-ABS-KEY("heart disease*") OR TITLE-ABSKEY("coronary disease*") OR TITLE-ABS-KEY("coronary artery disease*") OR TITLE-ABS-KEY("heart failure") OR TITLE-ABSKEY("cardiac failure") OR TITLE-ABS-KEY(stroke) OR TITLE-ABS-KEY("brain ischemia") OR TITLE-ABS-KEY("cerebrovascular accident*") OR TITLE-ABS-KEY("cerebrovascular disorder*") OR TITLE-ABS-KEY("cerebrovascular disease*") OR TITLE-ABSKEY("intracranial arterial disease*") OR TITLE-ABS-KEY("ganglia hemorrhage") OR TITLE-ABS-KEY("ganglia haemorrhage") OR TITLE-ABS-KEY("cerebral intraventricular hemorrhage") OR TITLE-ABS-KEY("cerebral intraventricular haemorrhage") OR TITLE-ABS-KEY("hypertensive intracranial hemorrhage") OR TITLE-ABS-KEY("hypertensive intracranial haemorrhage") OR TITLE-ABSKEY("cerebral hemorrhage") OR TITLE-ABS-KEY("cerebral haemorrhage") OR TITLE-ABS-KEY(cancer) OR TITLE-ABS-KEY(cancers) OR TITLE-ABS-KEY(tumour) OR TITLE-ABS-KEY(tumours) OR TITLE-ABS-KEY(tumor) OR TITLE-ABS-KEY(tumors) OR TITLE-ABSKEY(neoplasm) OR TITLE-ABS-KEY(neoplasms))
AND
(TITLE-ABS-KEY(cohort) OR TITLE-ABS-KEY(cohorts) OR TITLE-ABS-KEY("follow-up study") OR TITLE-ABS-KEY("follow-up studies") OR TITLE-ABS-KEY("prospective study") OR TITLE-ABS-KEY("prospective studies") OR TITLE-ABS-KEY("longitudinal study") OR TITLE-ABS-KEY("Iongitudinal studies"))

## Web of Science

(TS=("physical activit*") OR TS=("physical inactivity") OR TS=(exercise) OR TS=(exercises) OR TS=(exercising) OR TS=("recreational activit*") OR TS=(sport) OR TS=(sports) OR TS=("active transport") OR TS=("active transportation") OR TS=("active commut*") OR TS=("active travel*") OR TS=("household activit*") OR TS=(housework) OR TS=("non-exercise activit*") OR TS=("nonexercise activit*") OR TS=("activities of daily living") OR TS=(bicycle) OR TS=(bicycling) OR TS=(bike) OR TS=(biking) OR TS=(walk) OR $T S=($ walking ) OR TS=(run) OR TS=(running) OR TS=(jogging) OR TS=(swim) OR TS=(swimming) OR TS=("resistance training") OR TS=("weight lifting") OR TS=("physical fitness") OR TS=("physical endurance") OR TS=("activity energy expenditure") OR TS=("caloric expenditure"))
AND
(TS=(mortality) OR TS=("cardiovascular disease*") OR TS=("acute coronary syndrome") OR TS=("myocardial infarction") OR TS=("myocardial ischemia") OR TS=("heart disease*") OR TS=("coronary disease*") OR TS=("coronary artery disease*") OR $T S=($ "heart failure") $O R T S=($ "cardiac failure") $O R T S=($ stroke ) OR TS=("brain ischemia") OR TS=("cerebrovascular accident*") OR TS=("cerebrovascular disorder*") OR TS=("cerebrovascular disease*") OR TS=("intracranial arterial disease*") OR TS=("ganglia hemorrhage") OR TS=("ganglia haemorrhage") OR TS=("cerebral intraventricular hemorrhage") OR TS=("cerebral intraventricular haemorrhage") OR TS=("hypertensive intracranial hemorrhage") OR TS=("hypertensive intracranial haemorrhage") OR $T S=$ ("cerebral hemorrhage") OR TS=("cerebral haemorrhage") OR TS=(cancer) OR TS=(cancers) OR TS=(tumour) OR TS=(tumours) OR TS=(tumor) OR TS=(tumors) OR TS=(neoplasm) OR TS=(neoplasms))
AND
(TS=(cohort) OR TS=(cohorts) OR TS=("follow-up study") OR TS=("follow-up studies") OR TS=("prospective study") OR TS=("prospective studies") OR TS=("longitudinal study") OR TS=("longitudinal studies"))
eMethods 3: article selection criteria when multiple reports on the same cohort and outcome were available

The following criteria were used in the indicated hierarchy. That is, if two or more article were found and they balanced each other out in terms of the criteria (i.e., one was better for one criterion, but the other one for a second criterion), this hierarchy was then used to decide which article to select.

1) Lower risk of bias (exposure assessment, outcome ascertainment, exclusion of cases at baseline, exclusion of participants with relevant comorbidities at baseline or inclusion of baseline comorbidities as covariates in the regression model, and exclusion of new cases in the first years of follow-up).
2) Preferred measure of physical activity (e.g., MET-h/day rather than sessions).
3) More physical activity levels.
4) Separate results for men and women.
5) Longer follow-up period.

## eMethods 4: data imputation procedures

## CRITICAL INFORMATION (required to run the meta-analysis)

## Number of individuals in each exposure category (required only when risk estimate presented as relative risk or

 odds ratio):1) Estimated via proportional weighting using the following equation:

$$
\begin{equation*}
\frac{p_{i}}{P} S \tag{1}
\end{equation*}
$$

Where $p_{i}$ is person-years in the $t^{\text {th }}$ exposure category, $P$ is total person-years, and $S$ is total analytical sample size.
2) Or estimated via proportional weighting using the following steps (when person-years in each exposure category was not reported):

$$
\begin{gather*}
w_{i}=\frac{c_{i}}{\left(c_{1} R R_{i}\right)}  \tag{2}\\
s_{1}=\frac{S}{\sum_{i=1}^{n} w_{i}}  \tag{3}\\
s_{i}=w_{i} s_{1} \tag{4}
\end{gather*}
$$

Where $w_{i}$ is the ratio between person-years in the $i^{\text {th }}$ exposure category and in the reference exposure category, $c_{i}$ is cases in the $i^{\text {th }}$ exposure category (subscript 1 refers to the reference level), $R R_{i}$ is minimally adjusted relative risk in the $i^{\text {th }}$ exposure category, $s_{i}$ is number of individuals in the $i^{\text {th }}$ exposure category, and $S$ is total analytical sample size.

Equations 3 and 5 derive from:

$$
\begin{equation*}
R R_{i}=\frac{\frac{c_{i}}{s_{i}}}{\frac{c_{1}}{s_{1}}}=\frac{c_{i} s_{1}}{c_{1} s_{i}} \rightarrow s_{i}=\frac{c_{i} s_{1}}{c_{1} R R_{i}} \rightarrow \frac{s_{i}}{s_{1}}=\frac{c_{i}}{c_{1} R R_{i}} \tag{5}
\end{equation*}
$$

Equation 4 derives from:

$$
\begin{equation*}
S=\sum_{i=1}^{n} s_{i}=\sum_{i=1}^{n} w_{i} s_{1} \tag{6}
\end{equation*}
$$

Once $s_{1}$ is found, it can be used in Equation 5 to estimate number of individuals in all other exposure categories.
3) Or authors contacted.

## Person-years in each exposure category (required only when risk estimate presented as hazard ratio):

1) Estimated via proportional weighting using the following equation:

$$
\begin{equation*}
\frac{n_{i}}{S} P \tag{7}
\end{equation*}
$$

Where $n_{i}$ is number of individuals in the $i^{\text {th }}$ exposure category, $S$ is total analytical sample size, and $P$ is total person-years.
2) Or estimated via proportional weighting (when number of individuals in each exposure category was not reported) using Equations 3 to 5 substituting the number of individuals in the $i^{\text {th }}$ exposure category $\left(s_{i}\right)$ and total analytical sample size $(S)$ by person-years in the $i^{\text {th }}$ exposure category and total person-years, respectively.
3) Or authors contacted.

## Cases in each exposure category:

1) Estimated via proportional weighting using the following steps:

$$
\begin{gather*}
c_{1_{t}}=\frac{R R_{1}}{\sum_{i=1}^{n} R R_{i}} C  \tag{8}\\
r_{1}=\frac{c_{1_{t}}}{n_{1}}  \tag{9}\\
r_{i}=R R_{i} r_{1}  \tag{10}\\
c_{i}=n_{i} r_{i} \frac{C}{\sum_{i=1}^{n}\left(n_{i} r_{i}\right)} \tag{11}
\end{gather*}
$$

Where $c_{i}$ is cases in the $i^{\text {th }}$ exposure category (subscript 1 refers to the reference level; subscript $t$ indicates temporary (non-corrected) number of cases), $R R_{i}$ is risk estimate in the $i^{\text {th }}$ exposure category, $C$ is total number of cases, $r_{i}$ is risk in the $i^{\text {th }}$ exposure category, $n_{i}$ is person-years (or number of individuals) in the $i^{\text {th }}$ exposure category. Equation 11 is also used to estimate the final number of cases in the reference level.
2) Or authors contacted.

## BACKGROUND INFORMATION (obtained or estimated only when needed to impute at least one of the critical information)

## Total analytical sample size:

1) Calculated via summation of the number of individuals in each exposure category.
2) Or reported in the article.
3) Or estimated dividing total person-years by mean follow-up.
4) Or authors contacted.

## Mean follow-up:

1) Reported in the article (mean or median follow-up).
2) Or calculated by dividing total person-years by total analytical sample size.
3) Or reported study follow-up duration (e.g., 1990 to $2010=20$ years), as an approximate surrogate.
4) Or authors contacted.

## Total person-years:

1) Calculated via summation of person-years in each exposure category.
2) Or reported in the article.
3) Or estimated multiplying total analytical sample size by mean follow-up.
4) Or authors contacted.

## Total number of cases:

1) Calculated via summation of cases in each exposure category.
2) Or reported in the article.
3) Or authors contacted.

## eMethods 5: estimating the resting component of energy expenditure to convert MET to mMET

Total physical activity volume can be calculated by multiplying duration by the rate of energy expenditure (intensity). Rate of energy expenditure is often expressed in gross units of metabolic equivalent of task (MET), which includes both a resting ( 1 MET ) and an activity component (the remainder, e.g., 3.5 METs for a 4.5 gross MET activity).

When publications report activity volume in total MET-hours (hours * MET) per week, it is necessary to obtain information on the duration of activities making up this total such that 1 MET can be subtracted for each hour to remove the resting component and give physical activity energy expenditure in marginalised MET (mMET).

In the example below, a study reports total physical activity volume as 9 MET-hours. Knowledge of the duration of activity of two hours is necessary to calculate and remove the resting component giving marginalised MET (mMET).


For studies that did not provide activity duration, a conversion equation from gross to marginal units is required. For the current analyses, we used a regression equation derived from the studies that provided both estimates, weighted for sample size per exposure category:

$$
\begin{equation*}
\text { mMET-hours }=0.89 * \text { MET-hours }-0.52 * \text { MET-hours }^{0.5} \tag{1}
\end{equation*}
$$

The studies/cohorts contributing to this equation were:

| Authors and year | Cohort | Participants |
| :--- | :--- | :--- |
| Leet et al. $^{3}$ | Aerobics Center Longitudinal Study | Men and women aged 20-82 years |
| Chomistek et al. ${ }^{4}$ | Health Professionals Follow-up Study | Men aged 40-75 years |
| Chomistek et al. $^{5 *}$ | Women's Genome Health Study | Women aged 45+ years |
| Wen et al. $^{6}$ | Taiwan Medical Screening Program | Men and women aged 20+ years |
| Mok et al. $^{7}$ | Severance Cohort Study | Men and women aged 30-93 years |
| Hu et al. |  | Nurses' Health Study |

[^0]eMethods 6: potential population impact fraction (PIF) formula

The equation below has been adapted from Equation 7 in Zapata-Diomedi et al, ${ }^{10}$ replacing prevalence for person-years.

$$
\text { PIF }=\frac{\sum_{i=1}^{n} p_{i} R R_{i}-\sum_{i=1}^{n} p_{i} R R_{i}}{\sum_{i=1}^{n} p_{i} R R_{i}}
$$

Where $p_{i}$ is the person-years in the $t^{\text {th }}$ exposure category, $p_{i}^{\prime}$ is the counterfactual, and $R R_{i}$ is the relative risk of the exposed compared to the reference level of exposure.
efigure 1: study screening and selection flowchart


SR: systematic reviews. PA: physical activity.
eResults 1: meta-analysis of the 11 studies that reported all-cause, cardiovascular and cancer mortality risk

| Outcomes | 4.375 mMET-h/week | 8.75 mMET-h/week | 17.5 mMET-h/week |
| :---: | :---: | :---: | :---: |
|  | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Subset of $11{\text { studies }{ }^{6,11-20}}^{\text {a }}$ |  |  |  |
| All-cause mortality | $\begin{gathered} 0.81 \\ (0.74-0.89) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.57-0.78) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.52-0.73) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.77 \\ (0.69-0.85) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.57-0.78) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.52-0.73) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.89 \\ (0.85-0.94) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.79-0.90) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.76-0.86) \end{gathered}$ |
| All studies |  |  |  |
| All-cause mortality | $\begin{gathered} 0.77 \\ (0.73-0.80) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.65-0.73) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.62-0.70) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.81 \\ (0.77-0.85) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.77) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.90 \\ (0.88-0.93) \\ \hline \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.81-0.89) \\ \hline \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.86) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{RR}=$ relative risk; $95 \% \mathrm{Cl}=95 \%$ confidence interval. CVD = cardiovascular disease. Reference group $=0 \mathrm{mMET}$-h/week.
eResults 2: sex-stratified results

|  | 4.375 mMET-h/week |  | 8.75 mMET-h/week |  | 17.5 mMET-h/week |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Men | Women | Men | Women | Men | Women |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Mortality |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.8-0.87) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.71-0.80) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.87 \\ (0.82-0.94) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.74-0.88) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.72-0.89) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.60-0.77) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.68-0.82) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.60-0.77) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.90 \\ (0.87-0.94) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.92-0.98) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.80-0.91) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.83-0.93) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.79-0.09) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.83-0.93) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 0.89 \\ (0.84-0.93) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.76-0.91) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.75-0.88) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.62-0.79) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.62-0.79) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 0.92 \\ (0.85-0.99) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.75-0.93) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.87) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.76-0.97) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.87) \end{gathered}$ |
| Stroke | $\begin{gathered} 0.90 \\ (0.86-0.94) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.97) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.79-0.91) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.66-0.88) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.76-0.89) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.66-0.88) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 0.95 \\ (0.92-0.98) \end{gathered}$ | $\begin{gathered} 0.98 \\ (0.96-0.99) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.97) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.97) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.82-0.96) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.97) \end{gathered}$ |
| Colon | $\begin{gathered} 0.91 \\ (0.86-0.96) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.92-1.02) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.78-0.94) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.84-1.03) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.72-0.91) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.84-1.03) \end{gathered}$ |
| Rectum | $\begin{gathered} 0.92 \\ (0.80-1.07) \\ \hline \end{gathered}$ | $\begin{gathered} 1.09 \\ (0.90-1.33) \\ \hline \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.74-1.1) \\ \hline \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.73-1.76) \\ \hline \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.76-1.11) \\ \hline \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.73-1.76) \\ \hline \end{gathered}$ |

mMET = marginal metabolic equivalent of task; RR = relative risk; $95 \% \mathrm{Cl}=95 \%$ confidence interval. CVD = cardiovascular disease.

Potential impact fraction of physical activity on mortality and incidence of cardiovascular diseases and cancers at three physical activity levels, by sex

|  | 4.375 mMET-h/week |  | 8.75 mMET-h/week |  | 17.5 mMET-h/week |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Men | Women | Men | Women | Men | Women |
| Outcomes | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| Mortality |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 3.74 \\ (2.69-4.83) \end{gathered}$ | $\begin{gathered} 5.43 \\ (4.00-6.94) \end{gathered}$ | $\begin{gathered} 7.39 \\ (5.52-9.31) \end{gathered}$ | $\begin{gathered} 9.82 \\ (7.42-12.29) \end{gathered}$ | $\begin{gathered} 10.69 \\ (8.37-13.03) \end{gathered}$ | $\begin{gathered} 12.30 \\ (9.30-15.35) \end{gathered}$ |
| Total CVD | $\begin{gathered} 3.16 \\ (1.51-4.86) \end{gathered}$ | $\begin{gathered} 6.15 \\ (3.54-8.85) \end{gathered}$ | $\begin{gathered} 7.78 \\ (4.48-11.02) \end{gathered}$ | $\begin{gathered} 12.83 \\ (8.06-17.52) \end{gathered}$ | $\begin{gathered} 11.82 \\ (9.62-14.04) \end{gathered}$ | $\begin{gathered} 15.65 \\ (11.65-19.64) \end{gathered}$ |
| Total cancer | $\begin{gathered} 2.72 \\ (1.57-3.90) \end{gathered}$ | $\begin{gathered} 1.56 \\ (0.67-2.48) \end{gathered}$ | $\begin{gathered} 5.13 \\ (3.11-7.18) \end{gathered}$ | $\begin{gathered} 3.51 \\ (1.68-5.36) \end{gathered}$ | $\begin{gathered} 6.21 \\ (4.20-8.25) \end{gathered}$ | $\begin{gathered} 6.27 \\ (3.94-8.59) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 2.78 \\ (1.54-4.05) \end{gathered}$ | $\begin{gathered} 4.95 \\ (2.45-7.54) \end{gathered}$ | $\begin{gathered} 6.64 \\ (4.17-9.10) \end{gathered}$ | $\begin{gathered} 10.4 \\ (5.90-14.84) \end{gathered}$ | $\begin{gathered} 10.06 \\ (8.23-11.91) \end{gathered}$ | $\begin{gathered} 13.65 \\ (10.48-16.86) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 2.99 \\ (0.38-5.72) \end{gathered}$ | $\begin{gathered} 7.10 \\ (2.81-11.68) \end{gathered}$ | $\begin{gathered} 5.07 \\ (0.74-9.44) \end{gathered}$ | $\begin{gathered} 12.17 \\ (4.98-19.42) \end{gathered}$ | $\begin{gathered} 6.15 \\ (1.21-11.06) \end{gathered}$ | $\begin{gathered} 14.60 \\ (6.11-22.94) \end{gathered}$ |
| Stroke | $\begin{gathered} 3.21 \\ (1.72-4.80) \end{gathered}$ | $\begin{gathered} 4.71 \\ (1.02-8.60) \end{gathered}$ | $\begin{gathered} 6.12 \\ (3.47-8.89) \end{gathered}$ | $\begin{gathered} 8.90 \\ (2.92-14.91) \end{gathered}$ | $\begin{gathered} 7.93 \\ (4.87-11.07) \end{gathered}$ | $\begin{gathered} 12.79 \\ (7.22-18.38) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 1.38 \\ (0.40-2.41) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.28-1.19) \end{gathered}$ | $\begin{gathered} 3.09 \\ (0.94-5.29) \end{gathered}$ | $\begin{gathered} 1.77 \\ (0.72-2.84) \end{gathered}$ | $\begin{gathered} 4.94 \\ (1.63-8.21) \end{gathered}$ | $\begin{gathered} 3.92 \\ (1.81-6.04) \end{gathered}$ |
| Colon | $\begin{gathered} 2.07 \\ (0.78-3.48) \end{gathered}$ | $\begin{gathered} 0.67 \\ (-0.44-1.87) \end{gathered}$ | $\begin{gathered} 4.13 \\ (1.68-6.71) \end{gathered}$ | $\begin{gathered} 1.39 \\ (-0.80-3.68) \end{gathered}$ | $\begin{gathered} 6.42 \\ (3.07-9.85) \end{gathered}$ | $\begin{gathered} 2.25 \\ (-0.55-5.11) \end{gathered}$ |
| Rectum | $\begin{gathered} 1.90 \\ (-1.52-5.71) \\ \hline \end{gathered}$ | $\begin{gathered} -2.64 \\ (-7.02-3.40) \\ \hline \end{gathered}$ | $\begin{gathered} 3.10 \\ (-2.79-9.21) \\ \hline \end{gathered}$ | $\begin{gathered} -4.66 \\ (-10.03-2.64) \\ \hline \end{gathered}$ | $\begin{gathered} 1.43 \\ (-3.83-6.99) \\ \hline \end{gathered}$ | $\begin{gathered} -4.57 \\ (-31.13-20.26) \\ \hline \end{gathered}$ |

mMET = marginal metabolic equivalent of task; PIF = potential impact fraction; 95\% CI=95\% confidence interval. CVD = cardiovascular disease.

## eResults 3: risk of bias assessment

For the risk of bias assessment, we classified the harmonisation methods in two ways. Firstly, we classified studies depending on whether we made assumptions about the occupational component of an aggregated PA exposure (occupational PA not included in exposure; or assumptions about occupational PA made). Secondly, we described the overall method of converting exposure data to mMET-h/week (measurement unit conversion from MET, kcal, or kJ data; calibration using validation studies; using assumptions on $\leq 2$ of intensity, duration, or frequency; or conversion of non-numeric data using assumptions on intensity, duration, and frequency). Note that for all-cause mortality and CVD outcomes one study is missing because 8.75 mMET -h/week was not included in the exposure range reported in the original publication.

## All-cause mortality



Total CVD mortality


## Total cancer mortality



Total CVD incidence (fatal and non-fatal events combined)


## Total cancer incidence (fatal and non-fatal events combined)



|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Mortality |  |  |  |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 0.78 \\ (0.75-0.81) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.65-0.74) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.62-0.71) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.72-0.79) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.63-0.72) \end{gathered}$ | $\begin{gathered} 0.64 \\ (0.60-0.69) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.63-0.76) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.57-0.71) \end{gathered}$ | $\begin{gathered} 0.60 \\ (0.54-0.68) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.83 \\ (0.79-0.87) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.67-0.79) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.73-0.82) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.61-0.74) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.57-0.69) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.68-0.84) \end{gathered}$ | $\begin{gathered} 0.64 \\ (0.54-0.75) \end{gathered}$ | $\begin{gathered} 0.57 \\ (0.47-0.69) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.91 \\ (0.89-0.94) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.82-0.89) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.86) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.86-0.92) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.80-0.88) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.79-0.86) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.81-0.92) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.74-0.87) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.71-0.84) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 0.85 \\ (0.81-0.88) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.70-0.80) \end{gathered}$ | $\begin{gathered} 0.68 \\ (0.63-0.73) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.84) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.65-0.76) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.72-0.84) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.59-0.75) \end{gathered}$ | $\begin{gathered} 0.60 \\ (0.51-0.69) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.69-0.80) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.87) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.68-0.80) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.8-0.89) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ |
| Stroke | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.81) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.81-0.88) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.84) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.72-0.84) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.82-0.91) \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.74-0.85) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.70-0.81) \end{gathered}$ |
| Heart failure | $\begin{gathered} 0.77 \\ (0.63-0.94) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.48-0.91) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.42-0.94) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.86-0.95) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.76-0.91) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.66-0.86) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.79-0.93) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.68-0.86) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.63-0.78) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 0.94 \\ (0.92-0.96) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.87-0.93) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.80-0.89) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.89-0.94) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.84-0.91) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.81-0.89) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.84-0.93) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.78-0.90) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.74-0.88) \end{gathered}$ |
| Head and neck | $\begin{gathered} 0.77 \\ (0.63-0.94) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.48-0.91) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.42-0.94) \end{gathered}$ | $\begin{gathered} 0.72 \\ (0.50-1.03) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.45-1.00) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.40-0.99) \end{gathered}$ | $\begin{gathered} 0.72 \\ (0.59-0.88) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.47-0.84) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.41-0.91) \end{gathered}$ |
| Myeloid leukemia | $\begin{gathered} 0.85 \\ (0.78-0.93) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.67-0.88) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.62-0.89) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.60-0.99) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.58-0.97) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.54-0.97) \end{gathered}$ | - | - | - |
| Myeloma | $\begin{gathered} 0.84 \\ (0.72-0.98) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.62-0.96) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.62-0.94) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.72-0.96) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.60-0.93) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.60-0.97) \end{gathered}$ | - | - | - |
| Gastric cardia | $\begin{gathered} 0.89 \\ (0.82-0.96) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.70-0.92) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.88) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.77-0.96) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.66-0.92) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.90) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.78-1.05) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.66-1.08) \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.57-1.10) \end{gathered}$ |
| Lung | $\begin{gathered} 0.90 \\ (0.88-0.93) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.80-0.89) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.74-0.91) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.85-0.90) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.79-0.87) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.74-0.95) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.78-0.88) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.69-0.84) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.66-0.91) \end{gathered}$ |
| Liver | $\begin{gathered} 0.90 \\ (0.83-0.97) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.72-0.94) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.63-0.89) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.97) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.70-0.95) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.65-0.93) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.80-0.99) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.68-0.98) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.60-0.96) \end{gathered}$ |
| Endometrial | $\begin{gathered} 0.95 \\ (0.92-0.99) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.86-0.97) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.79-0.95) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.98) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.82-0.97) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.77-0.95) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.84-0.95) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.73-0.91) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.62-0.86) \end{gathered}$ |
| Colon | $\begin{gathered} 0.97 \\ (0.94-0.99) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.89-0.99) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.84-0.98) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.91-0.99) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.98) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.83-0.97) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.93-1.01) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.87-1.02) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.84-1.01) \end{gathered}$ |
| Breast | $\begin{gathered} 0.97 \\ (0.96-0.99) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.93-0.97) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.89-0.95) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.94-0.98) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.90-0.97) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.87-0.95) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.94-1.00) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.90-1.00) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.98) \end{gathered}$ |
| Bladder | $\begin{gathered} 0.94 \\ (0.86-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.81-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.81-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.82-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.81-1.01) \\ \hline \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.76-1.06) \\ \hline \end{gathered}$ | - | - | - |

Relative risk of all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels in relation to 0 mMET - $\mathrm{h} /$ week, after assigning alternative knots position ( $0^{\text {th }}, 42.5^{\text {th }}$, and $85^{\text {th }}$ percentile), using alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposity-adjusted models (continuation). $\qquad$

|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Rectum | $\begin{gathered} 0.97 \\ (0.93-1.01) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.89-1.03) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.87-1.05) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.9-1.0) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.87-1.01) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.89-1.04) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.84-0.97) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.78-0.96) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \end{gathered}$ |
| Esophageal | $\begin{gathered} 0.98 \\ (0.91-1.05) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.85-1.08) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.80-1.12) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.85-1.07) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.78-1.11) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.77-1.13) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.78-1.06) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.67-1.11) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.63-1.16) \end{gathered}$ |
| Prostate | $\begin{gathered} 1.00 \\ (0.99-1.02) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.03) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.97-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.99-1.03) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.96-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.04) \end{gathered}$ | $\begin{gathered} 1.02 \\ (0.97-1.07) \end{gathered}$ | $\begin{gathered} 1.02 \\ (0.95-1.10) \end{gathered}$ |
| Kidney | $\begin{gathered} 1.02 \\ (0.94-1.11) \\ \hline \end{gathered}$ | $\begin{gathered} 1.04 \\ (0.91-1.19) \\ \hline \end{gathered}$ | $\begin{gathered} 1.05 \\ (0.88-1.26) \\ \hline \end{gathered}$ | $\begin{gathered} 1.03 \\ (0.90-1.16) \\ \hline \end{gathered}$ | $\begin{gathered} 1.04 \\ (0.88-1.22) \\ \hline \end{gathered}$ | $\begin{gathered} 1.06 \\ (0.84-1.33) \\ \hline \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \\ \hline \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.71-0.96) \\ \hline \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.68-0.93) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{RR}=$ relative risk; $95 \% \mathrm{CI}=95 \%$ confidence interval. CVD = cardiovascular disease.

Potential impact fraction of physical activity on all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels (in mMET-h/wk) after alternative placement of knots ( $0^{\text {th }}, 42.5^{\text {th }}$, and $85^{\text {th }}$ percentile), alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposityadjusted models. $\qquad$
Alt

| Alternative PA intensity and duration assump |  |  |
| :---: | :---: | :---: |
| 4.375 | 8.75 | 17.5 |
| PIF $(95 \% \mathrm{CI})$ | PIF $(95 \% \mathrm{Cl})$ | PIF $(95 \%$ |


| native knots pos |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| $\begin{gathered} 15.66 \\ (13.16-18.15) \end{gathered}$ | $\begin{gathered} 18.75 \\ (16.09-21.39) \end{gathered}$ | $\begin{gathered} 10.73 \\ (8.88-12.62) \end{gathered}$ | $\begin{gathered} 17.08 \\ (14.36-19.77) \end{gathered}$ | $\begin{gathered} 20.05 \\ (17.01-23.04) \end{gathered}$ | $\begin{gathered} 13.98 \\ (10.35-17.65) \end{gathered}$ | $\begin{gathered} 18.49 \\ (14.15-22.8) \end{gathered}$ | $\begin{gathered} 21.99 \\ (17.4-26.5) \end{gathered}$ |
| $\begin{gathered} 12.25 \\ (9.37-15.17) \end{gathered}$ | $\begin{gathered} 17.05 \\ (13.92-20.19) \end{gathered}$ | $\begin{gathered} 8.00 \\ (5.89-10.20) \end{gathered}$ | $\begin{gathered} 15.08 \\ (11.52-18.68) \end{gathered}$ | $\begin{gathered} 18.66 \\ (14.79-22.53) \end{gathered}$ | $\begin{gathered} 7.39 \\ (4.41-10.67) \end{gathered}$ | $\begin{gathered} 13.83 \\ (8.65-19.19) \end{gathered}$ | $\begin{gathered} 18.33 \\ (12.26-24.43) \end{gathered}$ |
| $\begin{gathered} 7.05 \\ (5.10-9.00) \end{gathered}$ | $\begin{gathered} 9.29 \\ (7.36-11.22) \end{gathered}$ | $\begin{gathered} 4.52 \\ (3.13-5.94) \end{gathered}$ | $\begin{gathered} 7.71 \\ (5.68-9.75) \end{gathered}$ | $\begin{gathered} 9.00 \\ (7.20-10.80) \end{gathered}$ | $\begin{gathered} 7.22 \\ (4.07-10.46) \end{gathered}$ | $\begin{gathered} 11.37 \\ (7.09-15.68) \end{gathered}$ | $\begin{gathered} 13.73 \\ (9.38-18.06) \end{gathered}$ |
| $\begin{gathered} 10.86 \\ (8.43-13.31) \end{gathered}$ | $\begin{gathered} 15.42 \\ (13.01-17.85) \end{gathered}$ | $\begin{gathered} 6.84 \\ (5.10-8.63) \end{gathered}$ | $\begin{gathered} 13.16 \\ (10.24-16.1) \end{gathered}$ | $\begin{gathered} 16.94 \\ (14.07-19.82) \end{gathered}$ | $\begin{gathered} 6.43 \\ (4.19-8.88) \end{gathered}$ | $\begin{gathered} 12.4 \\ (8.41-16.54) \end{gathered}$ | $\begin{gathered} 17.18 \\ (12.36-22.06) \end{gathered}$ |
| $\begin{gathered} 10.28 \\ (7.61-12.96) \end{gathered}$ | $\begin{gathered} 13.58 \\ (10.51-16.64) \end{gathered}$ | $\begin{gathered} 7.93 \\ (5.58-10.32) \end{gathered}$ | $\begin{gathered} 12.13 \\ (8.93-15.33) \end{gathered}$ | $\begin{gathered} 14.31 \\ (10.43-18.14) \end{gathered}$ | $\begin{gathered} 6.26 \\ (4.30-8.27) \end{gathered}$ | $\begin{gathered} 11.28 \\ (8.23-14.33) \end{gathered}$ | $\begin{gathered} 14.97 \\ (12.06-17.87) \end{gathered}$ |
| $\begin{gathered} 9.77 \\ (7.31-12.24) \end{gathered}$ | $\begin{gathered} 12.37 \\ (9.63-15.1) \end{gathered}$ | $\begin{gathered} 7.20 \\ (5.33-9.10) \end{gathered}$ | $\begin{gathered} 10.40 \\ (8.12-12.69) \end{gathered}$ | $\begin{gathered} 12.66 \\ (8.46-16.77) \end{gathered}$ | $\begin{gathered} 5.13 \\ (3.29-7.03) \end{gathered}$ | $\begin{gathered} 9.31 \\ (6.51-12.14) \end{gathered}$ | $\begin{gathered} 12.25 \\ (9.45-15.08) \end{gathered}$ |
| $\begin{gathered} 4.63 \\ (1.90-7.66) \end{gathered}$ | $\begin{gathered} 7.86 \\ (4.31-11.68) \end{gathered}$ | $\begin{gathered} 2.36 \\ (1.15-3.74) \end{gathered}$ | $\begin{gathered} 5.00 \\ (2.49-7.75) \end{gathered}$ | $\begin{gathered} 9.43 \\ (4.94-14.10) \end{gathered}$ | $\begin{gathered} 3.34 \\ (1.34-5.78) \end{gathered}$ | $\begin{gathered} 6.25 \\ (3.09-9.90) \end{gathered}$ | $\begin{gathered} 9.21 \\ (5.86-12.84) \end{gathered}$ |
|  |  |  |  |  |  |  |  |
| $\begin{gathered} 5.22 \\ (3.55-6.90) \end{gathered}$ | $\begin{gathered} 7.80 \\ (5.65-9.93) \end{gathered}$ | $\begin{gathered} 3.48 \\ (2.33-4.66) \end{gathered}$ | $\begin{gathered} 6.56 \\ (4.57-8.55) \end{gathered}$ | $\begin{gathered} 8.57 \\ (6.31-10.81) \end{gathered}$ | $\begin{gathered} 5.67 \\ (3.24-8.18) \end{gathered}$ | $\begin{gathered} 9.12 \\ (5.51-12.76) \end{gathered}$ | $\begin{gathered} 11.12 \\ (6.91-15.33) \end{gathered}$ |
| $\begin{gathered} 17.46 \\ (3.68-30.98) \end{gathered}$ | $\begin{gathered} 19.83 \\ (1.23-36.55) \end{gathered}$ | $\begin{gathered} 13.82 \\ (-1.07-28.5) \end{gathered}$ | $\begin{gathered} 18.21 \\ (1.05-34.26) \end{gathered}$ | $\begin{gathered} 23.04 \\ (2.16-41.14) \end{gathered}$ | $\begin{gathered} 11.66 \\ (4.19-19.84) \end{gathered}$ | $\begin{gathered} 18.82 \\ (6.67-30.81) \end{gathered}$ | $\begin{gathered} 20.07 \\ (0.44-37.22) \end{gathered}$ |
| $\begin{gathered} 7.08 \\ (1.65-12.94) \end{gathered}$ | $\begin{gathered} 7.57 \\ (2.23-13.33) \end{gathered}$ | $\begin{gathered} 6.67 \\ (0.40-13.47) \end{gathered}$ | $\begin{gathered} 8.33 \\ (1.91-15.25) \end{gathered}$ | $\begin{gathered} 10.22 \\ (1.38-19.18) \end{gathered}$ | - | - | - |
| $\begin{gathered} 6.76 \\ (1.90-12.09) \end{gathered}$ | $\begin{gathered} 8.30 \\ (1.91-14.99) \end{gathered}$ | $\begin{gathered} 3.71 \\ (0.79-7.23) \\ \hline \end{gathered}$ | $\begin{gathered} 7.79 \\ (1.75-14.37) \end{gathered}$ | $\begin{gathered} 6.57 \\ (-0.43-14.07) \end{gathered}$ | - | - | - |


| Cancer incidence (fatal and non-fatal events combined) |
| :--- |
| $(0.80-3.89)$ |

(continues)

Potential impact fraction of physical activity on all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels (in mMET-h/wk) after assigning alternative knots position ( $0^{\mathrm{th}}, 42.5^{\mathrm{th}}$, and $85^{\text {th }}$ percentile), using alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposity-adjusted models (continuation).

|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| Gastric cardia | $\begin{gathered} 1.95 \\ (0.58-3.68) \end{gathered}$ | $\begin{gathered} 4.77 \\ (1.58-8.57) \end{gathered}$ | $\begin{gathered} 6.77 \\ (2.55-11.63) \end{gathered}$ | $\begin{gathered} 2.45 \\ (0.64-4.78) \end{gathered}$ | $\begin{gathered} 5.40 \\ (1.56-10.00) \end{gathered}$ | $\begin{gathered} 7.29 \\ (2.34-13.03) \end{gathered}$ | $\begin{gathered} 1.13 \\ (-0.42-3.29) \end{gathered}$ | $\begin{gathered} 3.17 \\ (-1.19-8.63) \end{gathered}$ | $\begin{gathered} 5.12 \\ (-1.81-13.09) \end{gathered}$ |
| Lung | $\begin{gathered} 4.39 \\ (3.16-5.63) \end{gathered}$ | $\begin{gathered} 7.26 \\ (5.10-9.4) \end{gathered}$ | $\begin{gathered} 8.54 \\ (3.04-13.98) \end{gathered}$ | $\begin{gathered} 5.88 \\ (4.05-7.37) \end{gathered}$ | $\begin{gathered} 9.56 \\ (6.13-12.49) \end{gathered}$ | $\begin{gathered} 8.44 \\ (-0.66-17.5) \end{gathered}$ | $\begin{gathered} 8.01 \\ (4.69-11.23) \end{gathered}$ | $\begin{gathered} 12.27 \\ (6.66-17.64) \end{gathered}$ | $\begin{gathered} 10.52 \\ (0.77-20.21) \end{gathered}$ |
| Liver | $\begin{gathered} 3.49 \\ (0.58-6.71) \end{gathered}$ | $\begin{gathered} 6.75 \\ (1.44-12.31) \end{gathered}$ | $\begin{gathered} 10.27 \\ (3.26-17.31) \end{gathered}$ | $\begin{gathered} 4.59 \\ (0.90-8.59) \end{gathered}$ | $\begin{gathered} 8.37 \\ (2.11-14.76) \end{gathered}$ | $\begin{gathered} 11.07 \\ (3.45-18.63) \end{gathered}$ | $\begin{gathered} 4.62 \\ (0.24-9.54) \end{gathered}$ | $\begin{gathered} 8.72 \\ (0.79-16.97) \end{gathered}$ | $\begin{gathered} 12.86 \\ (2.32-23.21) \end{gathered}$ |
| Endometrial | $\begin{gathered} 1.10 \\ (0.26-2.02) \end{gathered}$ | $\begin{gathered} 2.62 \\ (0.76-4.60) \end{gathered}$ | $\begin{gathered} 4.54 \\ (1.88-7.28) \end{gathered}$ | $\begin{gathered} 1.50 \\ (0.37-2.73) \end{gathered}$ | $\begin{gathered} 3.66 \\ (1.07-6.38) \end{gathered}$ | $\begin{gathered} 5.91 \\ (2.17-9.72) \end{gathered}$ | $\begin{gathered} 2.23 \\ (0.89-3.77) \end{gathered}$ | $\begin{gathered} 5.66 \\ (2.38-9.23) \end{gathered}$ | $\begin{gathered} 10.82 \\ (4.99-16.76) \end{gathered}$ |
| Colon | $\begin{gathered} 0.70 \\ (0.11-1.33) \end{gathered}$ | $\begin{gathered} 1.69 \\ (0.33-3.12) \end{gathered}$ | $\begin{gathered} 2.96 \\ (0.92-5.05) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.19-1.74) \end{gathered}$ | $\begin{gathered} 2.12 \\ (0.49-3.82) \end{gathered}$ | $\begin{gathered} 3.73 \\ (1.24-6.25) \end{gathered}$ | $\begin{gathered} 0.45 \\ (-0.15-1.11) \end{gathered}$ | $\begin{gathered} 1.19 \\ (-0.32-2.79) \end{gathered}$ | $\begin{gathered} 2.29 \\ (-0.06-4.70) \end{gathered}$ |
| Breast | $\begin{gathered} 0.69 \\ (0.32-1.07) \end{gathered}$ | $\begin{gathered} 1.62 \\ (0.79-2.46) \end{gathered}$ | $\begin{gathered} 3.23 \\ (1.85-4.63) \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.53-1.75) \end{gathered}$ | $\begin{gathered} 2.44 \\ (1.21-3.69) \end{gathered}$ | $\begin{gathered} 4.09 \\ (2.35-5.83) \end{gathered}$ | $\begin{gathered} 0.79 \\ (-0.05-1.67) \end{gathered}$ | $\begin{gathered} 1.78 \\ (0.10-3.50) \end{gathered}$ | $\begin{gathered} 3.68 \\ (1.45-5.94) \end{gathered}$ |
| Bladder | $\begin{gathered} 1.91 \\ (-0.54-4.52) \end{gathered}$ | $\begin{gathered} 2.98 \\ (-0.24-6.33) \end{gathered}$ | $\begin{gathered} 3.11 \\ (0.02-6.35) \end{gathered}$ | $\begin{gathered} 2.72 \\ (-0.64-6.23) \end{gathered}$ | $\begin{gathered} 3.70 \\ (0.16-7.39) \end{gathered}$ | $\begin{gathered} 4.59 \\ (-3.62-12.48) \end{gathered}$ | - | - | - |
| Rectum | $\begin{gathered} 0.77 \\ (-0.15-1.75) \end{gathered}$ | $\begin{gathered} 1.43 \\ (-0.45-3.36) \end{gathered}$ | $\begin{gathered} 0.52 \\ (-1.74-2.82) \end{gathered}$ | $\begin{gathered} 1.30 \\ (-0.09-2.74) \end{gathered}$ | $\begin{gathered} 2.07 \\ (-0.49-4.65) \end{gathered}$ | $\begin{gathered} 0.02 \\ (-2.60-2.67) \end{gathered}$ | $\begin{gathered} 2.07 \\ (0.53-3.73) \end{gathered}$ | $\begin{gathered} 3.74 \\ (0.90-6.66) \end{gathered}$ | $\begin{gathered} 2.69 \\ (-0.19-5.66) \end{gathered}$ |
| Esophageal | $\begin{gathered} 0.68 \\ (-0.95-2.68) \end{gathered}$ | $\begin{gathered} 1.38 \\ (-2.06-5.32) \end{gathered}$ | $\begin{gathered} 1.57 \\ (-3.05-6.67) \end{gathered}$ | $\begin{gathered} 1.02 \\ (-1.34-3.88) \end{gathered}$ | $\begin{gathered} 1.87 \\ (-2.65-6.95) \end{gathered}$ | $\begin{gathered} 1.58 \\ (-3.44-7.13) \end{gathered}$ | $\begin{gathered} 1.86 \\ (-1.08-5.71) \end{gathered}$ | $\begin{gathered} 3.7 \\ (-2.48-10.93) \end{gathered}$ | $\begin{gathered} 3.96 \\ (-4.07-12.86) \end{gathered}$ |
| Prostate | $\begin{gathered} -0.10 \\ (-0.48-0.29) \end{gathered}$ | $\begin{gathered} -0.21 \\ (-1.10-0.71) \end{gathered}$ | $\begin{gathered} -0.10 \\ (-1.61-1.42) \end{gathered}$ | $\begin{gathered} -0.16 \\ (-0.64-0.35) \end{gathered}$ | $\begin{gathered} -0.29 \\ (-1.36-0.81) \end{gathered}$ | $\begin{gathered} -0.11 \\ (-1.75-1.54) \end{gathered}$ | $\begin{gathered} -0.23 \\ (-0.90-0.48) \end{gathered}$ | $\begin{gathered} -0.5 \\ (-2.02-1.08) \end{gathered}$ | $\begin{gathered} -0.65 \\ (-3.10-1.85) \end{gathered}$ |
| Kidney | $\begin{gathered} -0.65 \\ (-3.69-2.81) \\ \hline \end{gathered}$ | $\begin{gathered} -1.23 \\ (-6.39-4.34) \\ \hline \end{gathered}$ | $\begin{gathered} -1.91 \\ (-9.20-5.63) \\ \hline \end{gathered}$ | $\begin{gathered} -0.95 \\ (-5.25-3.85) \end{gathered}$ | $\begin{gathered} -1.78 \\ (-8.56-5.40) \\ \hline \end{gathered}$ | $\begin{gathered} -3.06 \\ (-15.89-9.34) \end{gathered}$ | $\begin{gathered} 5.61 \\ (0.92-10.50) \\ \hline \end{gathered}$ | $\begin{gathered} 9.24 \\ (2.27-16.16) \\ \hline \end{gathered}$ | $\begin{gathered} 11.73 \\ (4.40-18.93) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{PIF}=$ potential impact fraction; $95 \% \mathrm{CI}=95 \%$ confidence interval. $\mathrm{CVD}=$ cardiovascular disease.

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Paper: Non-occupational physical activity and risk of cardiovascular disease, cancer, and mortality outcomes: a doseresponse meta-analysis of large prospective studies

Authors: Leandro Garcia, Matthew Pearce, Ali Abbas, Alexander Mok, Tessa Strain, Sara Ali, Alessio Crippa, Paddy C. Dempsey, Rajna Golubic, Paul Kelly, Yvonne Laird, Eoin McNamara, Samuel Moore, Thiago Herick de Sa, Andrea D. Smith, Katrien Wijndaele, James Woodcock, Søren Brage

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## eMethods 1: study inclusion and exclusion criteria

| Include | Exclude |
| :--- | :--- |
| Participants | Cohorts of institutionalised adults, medical patients <br> (i.e., in secondary or tertiary prevention) or high-risk <br> populations (e.g., hypertension, diabetes - except <br> conditions inevitable with ageing, as post-menopause) |
| Exposure  <br> Volume (marginal MET-h/week) of non-occupational <br> physical activity - this includes leisure-time physical <br> activity alone, combined with other non-occupational <br> physical activity domains (e.g., transport and/or <br> domestic activity), or combined with specific types of <br> activity such as walking. Physical activity volume can be <br> either self-reported or measured by devices and must <br> be reported in at least three exposure levels Measures of physical activity from which occupational <br> activity cannot be factored out; individual domains of <br> physical activity which occur outside of work but do not <br> include leisure-time activity (e.g., travel physical <br> activity only); other risk factors either alone or <br> combined with physical activity <br> Comparators  <br> Lower volumes of physical activity (as defined in  <br> 'Interventions')  |  |
| Outcomes |  |

## utcomes

1) All-cause mortality $\quad$ Less than three years of follow-up period
2) Cardiovascular diseases (fatal and non-fatal):
a. Total CVD (IOO-I99)*
b. Stroke (160-166)
c. Heart failure (I50, I11.0, I13.0, I13.2)
d. Coronary heart disease (I20-125)
3) Cancers** (fatal and non-fatal):
a. Total cancer (C00-D49)
b. Breast (C50)
c. Endometrial (C54)
d. Lung (C34)
e. Colon (C18)
f. Esophageal (C15)
g. Liver (C22-C24)
h. Kidney (C64-C65)
. Gastric cardia (C16.0)
j. Myeloid leukemia (C92)
k. Myeloma (C90)
I. Head and neck (C76.0)
m. Rectum (C20)
n. Bladder (C67)
o. Prostate (C61)
p. Malignant melanoma (C43)

Cases ascertained via health, death, cancer, hospital or insurance registers; death certificates; participants and their next-of-kin

## Study design

General population prospective cohort studies
(including case-cohort and nested case-control studies) with sample size larger than 10,000 participants; results must be reported either as hazard ratios, relative risks or odds ratios with confidence intervals

* Diseases coded using the International statistical classification of diseases and related health problems, 10th revision. ${ }^{1}$
** Cancers associated with leisure-time physical activity in Moore et al. ${ }^{2}$
- Type of documents: peer-reviewed articles published in academic journals.
- No limits on language and date of publication.


## eMethods 2: search strings

## Pubmed

((physical activit*[Title/Abstract]) OR (physical inactivity[Title/Abstract]) OR (exercise[Title/Abstract]) OR
(exercises[Title/Abstract]) OR (exercising[Title/Abstract]) OR (recreational activit*[Title/Abstract]) OR (sport[Title/Abstract]) OR (sports[Title/Abstract]) OR (active transport[Title/Abstract]) OR (active transportation[Title/Abstract]) OR (active commut*[Title/Abstract]) OR (active travel*[Title/Abstract]) OR (household activit*[Title/Abstract]) OR (housework[Title/Abstract]) OR (non-exercise activit*[Title/Abstract]) OR (nonexercise activit*[Title/Abstract]) OR (activities of daily living[Title/Abstract]) OR (bicycle[Title/Abstract]) OR (bicycling[Title/Abstract]) OR (bike[Title/Abstract]) OR (biking[Title/Abstract]) OR (walk[Title/Abstract]) OR (walking[Title/Abstract]) OR (run[Title/Abstract]) OR (running[Title/Abstract]) OR (jogging[Title/Abstract]) OR (swim[Title/Abstract]) OR (swimming[Title/Abstract]) OR (resistance training[Title/Abstract]) OR (weight lifting[Title/Abstract]) OR (physical fitness[Title/Abstract]) OR (physical endurance[Title/Abstract]) OR (activity energy expenditure[Title/Abstract]) OR (caloric expenditure[Title/Abstract]) OR (motor activity[Mesh:NoExp]) OR (exercise[Mesh:NoExp]) OR (human physical conditioning[Mesh]) OR (leisure activities[Mesh:NoExp]) OR (recreation[Mesh:NoExp]) OR (dancing[Mesh]) OR (gardening[Mesh]) OR (sports[Mesh]) OR (activities of daily living[Mesh:NoExp]))

AND
((mortality[Title/Abstract]) OR (cardiovascular disease*[Title/Abstract]) OR (acute coronary syndrome[Title/Abstract]) OR (myocardial infarction[Title/Abstract]) OR (myocardial ischemia[Title/Abstract]) OR (heart disease*[Title/Abstract]) OR (coronary disease*[Title/Abstract]) OR (coronary artery disease*[Title/Abstract]) OR (heart failure[Title/Abstract]) OR (cardiac failure[Title/Abstract]) OR (stroke[Title/Abstract]) OR (brain ischemia[Title/Abstract]) OR (cerebrovascular accident*[Title/Abstract]) OR (cerebrovascular disorder*[Title/Abstract]) OR (cerebrovascular disease*[Title/Abstract]) OR (intracranial arterial disease*[Title/Abstract]) OR (ganglia hemorrhage[Title/Abstract]) OR (ganglia haemorrhage[Title/Abstract]) OR (cerebral intraventricular hemorrhage[Title/Abstract]) OR (cerebral intraventricular haemorrhage[Title/Abstract]) OR (hypertensive intracranial hemorrhage[Title/Abstract]) OR (hypertensive intracranial haemorrhage[Title/Abstract]) OR (cerebral haemorrhage[Title/Abstract]) OR (cerebral hemorrhage[Title/Abstract]) OR (cancer[Title/Abstract]) OR (cancers[Title/Abstract]) OR (tumour[Title/Abstract]) OR (tumours[Title/Abstract]) OR (tumor[Title/Abstract]) OR (tumors[Title/Abstract]) OR (neoplasm[Title/Abstract]) OR (neoplasms[Title/Abstract]) OR (mortality[Mesh:NoExp]) OR (cause of death[Mesh]) OR (premature mortality[Mesh]) OR (cardiovascular diseases[Mesh:NoExp]) OR (heart diseases[Mesh:NoExp]) OR (myocardial ischemia[Mesh]) OR (heart failure[Mesh]) OR (cerebrovascular disorders[Mesh:NoExp]) OR (brain ischemia[Mesh]) OR (cerebral small vessel diseases[Mesh]) OR (intracranial arterial diseases[Mesh]) OR (basal ganglia hemorrhage [Mesh]) OR (cerebral intraventricular hemorrhage [Mesh]) OR (hypertensive intracranial hemorrhage [Mesh]) OR (stroke[Mesh]) OR (neoplasms[Mesh]))

AND
((cohort[Title/Abstract]) OR (cohorts[Title/Abstract]) OR (follow-up study[Title/Abstract]) OR (follow-up studies[Title/Abstract]) OR (prospective study[Title/Abstract]) OR (prospective studies[Title/Abstract]) OR (longitudinal study[Title/Abstract]) OR (longitudinal studies[Title/Abstract]) OR (cohort studies[Mesh:NoExp]) OR (follow-up studies[Mesh]) OR (longitudinal studies[Mesh:NoExp]) OR (prospective studies[Mesh]))

## Scopus

(TITLE-ABS-KEY("physical activit*") OR TITLE-ABS-KEY("physical inactivity") OR TITLE-ABS-KEY(exercise) OR TITLE-ABSKEY(exercises) OR TITLE-ABS-KEY(exercising) OR TITLE-ABS-KEY("recreational activit*") OR TITLE-ABS-KEY(sport) OR TITLE-ABSKEY(sports) OR TITLE-ABS-KEY("active transport") OR TITLE-ABS-KEY("active transportation") OR TITLE-ABS-KEY("active commut*") OR TITLE-ABS-KEY("active travel*") OR TITLE-ABS-KEY("household activit*") OR TITLE-ABS-KEY(housework) OR TITLE-ABS-KEY("non-exercise activit*") OR TITLE-ABS-KEY("nonexercise activit*") OR TITLE-ABS-KEY("activities of daily living") OR TITLE-ABS-KEY(bicycle) OR TITLE-ABS-KEY(bicycling) OR TITLE-ABS-KEY(bike) OR TITLE-ABS-KEY(biking) OR TITLE-ABS-KEY(walk) OR TITLE-ABS-KEY(walking) OR TITLE-ABS-KEY(run) OR TITLE-ABS-KEY(running) OR TITLE-ABS-KEY(jogging) OR TITLE-ABS-KEY(swim) OR TITLE-ABS-KEY(swimming) OR TITLE-ABS-KEY("resistance training") OR TITLE-ABS-KEY("weight lifting") OR TITLE-ABSKEY("physical fitness") OR TITLE-ABS-KEY("physical endurance") OR TITLE-ABS-KEY("activity energy expenditure") OR TITLE-ABSKEY("caloric expenditure"))
AND
(TITLE-ABS-KEY(mortality) OR TITLE-ABS-KEY("cardiovascular disease*") OR TITLE-ABS-KEY("acute coronary syndrome") OR TITLE-ABS-KEY("myocardial infarction") OR TITLE-ABS-KEY("myocardial ischemia") OR TITLE-ABS-KEY("heart disease*") OR TITLE-ABSKEY("coronary disease*") OR TITLE-ABS-KEY("coronary artery disease*") OR TITLE-ABS-KEY("heart failure") OR TITLE-ABSKEY("cardiac failure") OR TITLE-ABS-KEY(stroke) OR TITLE-ABS-KEY("brain ischemia") OR TITLE-ABS-KEY("cerebrovascular accident*") OR TITLE-ABS-KEY("cerebrovascular disorder*") OR TITLE-ABS-KEY("cerebrovascular disease*") OR TITLE-ABSKEY("intracranial arterial disease*") OR TITLE-ABS-KEY("ganglia hemorrhage") OR TITLE-ABS-KEY("ganglia haemorrhage") OR TITLE-ABS-KEY("cerebral intraventricular hemorrhage") OR TITLE-ABS-KEY("cerebral intraventricular haemorrhage") OR TITLE-ABS-KEY("hypertensive intracranial hemorrhage") OR TITLE-ABS-KEY("hypertensive intracranial haemorrhage") OR TITLE-ABSKEY("cerebral hemorrhage") OR TITLE-ABS-KEY("cerebral haemorrhage") OR TITLE-ABS-KEY(cancer) OR TITLE-ABS-KEY(cancers) OR TITLE-ABS-KEY(tumour) OR TITLE-ABS-KEY(tumours) OR TITLE-ABS-KEY(tumor) OR TITLE-ABS-KEY(tumors) OR TITLE-ABSKEY(neoplasm) OR TITLE-ABS-KEY(neoplasms))
AND
(TITLE-ABS-KEY(cohort) OR TITLE-ABS-KEY(cohorts) OR TITLE-ABS-KEY("follow-up study") OR TITLE-ABS-KEY("follow-up studies") OR TITLE-ABS-KEY("prospective study") OR TITLE-ABS-KEY("prospective studies") OR TITLE-ABS-KEY("longitudinal study") OR TITLE-ABS-KEY("Iongitudinal studies"))

## Web of Science

(TS=("physical activit*") OR TS=("physical inactivity") OR TS=(exercise) OR TS=(exercises) OR TS=(exercising) OR TS=("recreational activit*") OR TS=(sport) OR TS=(sports) OR TS=("active transport") OR TS=("active transportation") OR TS=("active commut*") OR TS=("active travel*") OR TS=("household activit*") OR TS=(housework) OR TS=("non-exercise activit*") OR TS=("nonexercise activit*") OR TS=("activities of daily living") OR TS=(bicycle) OR TS=(bicycling) OR TS=(bike) OR TS=(biking) OR TS=(walk) OR $T S=($ walking ) OR TS=(run) OR TS=(running) OR TS=(jogging) OR TS=(swim) OR TS=(swimming) OR TS=("resistance training") OR TS=("weight lifting") OR TS=("physical fitness") OR TS=("physical endurance") OR TS=("activity energy expenditure") OR TS=("caloric expenditure"))
AND
(TS=(mortality) OR TS=("cardiovascular disease*") OR TS=("acute coronary syndrome") OR TS=("myocardial infarction") OR TS=("myocardial ischemia") OR TS=("heart disease*") OR TS=("coronary disease*") OR TS=("coronary artery disease*") OR $T S=($ "heart failure") $O R T S=($ "cardiac failure") $O R T S=($ stroke ) OR TS=("brain ischemia") OR TS=("cerebrovascular accident*") OR TS=("cerebrovascular disorder*") OR TS=("cerebrovascular disease*") OR TS=("intracranial arterial disease*") OR TS=("ganglia hemorrhage") OR TS=("ganglia haemorrhage") OR TS=("cerebral intraventricular hemorrhage") OR TS=("cerebral intraventricular haemorrhage") OR TS=("hypertensive intracranial hemorrhage") OR TS=("hypertensive intracranial haemorrhage") OR $T S=$ ("cerebral hemorrhage") OR TS=("cerebral haemorrhage") OR TS=(cancer) OR TS=(cancers) OR TS=(tumour) OR TS=(tumours) OR TS=(tumor) OR TS=(tumors) OR TS=(neoplasm) OR TS=(neoplasms))
AND
(TS=(cohort) OR TS=(cohorts) OR TS=("follow-up study") OR TS=("follow-up studies") OR TS=("prospective study") OR TS=("prospective studies") OR TS=("longitudinal study") OR TS=("longitudinal studies"))
eMethods 3: article selection criteria when multiple reports on the same cohort and outcome were available

The following criteria were used in the indicated hierarchy. That is, if two or more article were found and they balanced each other out in terms of the criteria (i.e., one was better for one criterion, but the other one for a second criterion), this hierarchy was then used to decide which article to select.

1) Lower risk of bias (exposure assessment, outcome ascertainment, exclusion of cases at baseline, exclusion of participants with relevant comorbidities at baseline or inclusion of baseline comorbidities as covariates in the regression model, and exclusion of new cases in the first years of follow-up).
2) Preferred measure of physical activity (e.g., MET-h/day rather than sessions).
3) More physical activity levels.
4) Separate results for men and women.
5) Longer follow-up period.

## eMethods 4: data imputation procedures

## CRITICAL INFORMATION (required to run the meta-analysis)

## Number of individuals in each exposure category (required only when risk estimate presented as relative risk or

 odds ratio):1) Estimated via proportional weighting using the following equation:

$$
\begin{equation*}
\frac{p_{i}}{P} S \tag{1}
\end{equation*}
$$

Where $p_{i}$ is person-years in the $t^{\text {th }}$ exposure category, $P$ is total person-years, and $S$ is total analytical sample size.
2) Or estimated via proportional weighting using the following steps (when person-years in each exposure category was not reported):

$$
\begin{gather*}
w_{i}=\frac{c_{i}}{\left(c_{1} R R_{i}\right)}  \tag{2}\\
s_{1}=\frac{S}{\sum_{i=1}^{n} w_{i}}  \tag{3}\\
s_{i}=w_{i} s_{1} \tag{4}
\end{gather*}
$$

Where $w_{i}$ is the ratio between person-years in the $i^{\text {th }}$ exposure category and in the reference exposure category, $c_{i}$ is cases in the $i^{\text {th }}$ exposure category (subscript 1 refers to the reference level), $R R_{i}$ is minimally adjusted relative risk in the $i^{\text {th }}$ exposure category, $s_{i}$ is number of individuals in the $i^{\text {th }}$ exposure category, and $S$ is total analytical sample size.

Equations 3 and 5 derive from:

$$
\begin{equation*}
R R_{i}=\frac{\frac{c_{i}}{s_{i}}}{\frac{c_{1}}{s_{1}}}=\frac{c_{i} s_{1}}{c_{1} s_{i}} \rightarrow s_{i}=\frac{c_{i} s_{1}}{c_{1} R R_{i}} \rightarrow \frac{s_{i}}{s_{1}}=\frac{c_{i}}{c_{1} R R_{i}} \tag{5}
\end{equation*}
$$

Equation 4 derives from:

$$
\begin{equation*}
S=\sum_{i=1}^{n} s_{i}=\sum_{i=1}^{n} w_{i} s_{1} \tag{6}
\end{equation*}
$$

Once $s_{1}$ is found, it can be used in Equation 5 to estimate number of individuals in all other exposure categories.
3) Or authors contacted.

## Person-years in each exposure category (required only when risk estimate presented as hazard ratio):

1) Estimated via proportional weighting using the following equation:

$$
\begin{equation*}
\frac{n_{i}}{S} P \tag{7}
\end{equation*}
$$

Where $n_{i}$ is number of individuals in the $i^{\text {th }}$ exposure category, $S$ is total analytical sample size, and $P$ is total person-years.
2) Or estimated via proportional weighting (when number of individuals in each exposure category was not reported) using Equations 3 to 5 substituting the number of individuals in the $i^{\text {th }}$ exposure category $\left(s_{i}\right)$ and total analytical sample size $(S)$ by person-years in the $i^{\text {th }}$ exposure category and total person-years, respectively.
3) Or authors contacted.

## Cases in each exposure category:

1) Estimated via proportional weighting using the following steps:

$$
\begin{gather*}
c_{1_{t}}=\frac{R R_{1}}{\sum_{i=1}^{n} R R_{i}} C  \tag{8}\\
r_{1}=\frac{c_{1_{t}}}{n_{1}}  \tag{9}\\
r_{i}=R R_{i} r_{1}  \tag{10}\\
c_{i}=n_{i} r_{i} \frac{C}{\sum_{i=1}^{n}\left(n_{i} r_{i}\right)} \tag{11}
\end{gather*}
$$

Where $c_{i}$ is cases in the $i^{\text {th }}$ exposure category (subscript 1 refers to the reference level; subscript $t$ indicates temporary (non-corrected) number of cases), $R R_{i}$ is risk estimate in the $i^{\text {th }}$ exposure category, $C$ is total number of cases, $r_{i}$ is risk in the $i^{\text {th }}$ exposure category, $n_{i}$ is person-years (or number of individuals) in the $i^{\text {th }}$ exposure category. Equation 11 is also used to estimate the final number of cases in the reference level.
2) Or authors contacted.

## BACKGROUND INFORMATION (obtained or estimated only when needed to impute at least one of the critical information)

## Total analytical sample size:

1) Calculated via summation of the number of individuals in each exposure category.
2) Or reported in the article.
3) Or estimated dividing total person-years by mean follow-up.
4) Or authors contacted.

## Mean follow-up:

1) Reported in the article (mean or median follow-up).
2) Or calculated by dividing total person-years by total analytical sample size.
3) Or reported study follow-up duration (e.g., 1990 to $2010=20$ years), as an approximate surrogate.
4) Or authors contacted.

## Total person-years:

1) Calculated via summation of person-years in each exposure category.
2) Or reported in the article.
3) Or estimated multiplying total analytical sample size by mean follow-up.
4) Or authors contacted.

## Total number of cases:

1) Calculated via summation of cases in each exposure category.
2) Or reported in the article.
3) Or authors contacted.

## eMethods 5: estimating the resting component of energy expenditure to convert MET to mMET

Total physical activity volume can be calculated by multiplying duration by the rate of energy expenditure (intensity). Rate of energy expenditure is often expressed in gross units of metabolic equivalent of task (MET), which includes both a resting ( 1 MET ) and an activity component (the remainder, e.g., 3.5 METs for a 4.5 gross MET activity).

When publications report activity volume in total MET-hours (hours * MET) per week, it is necessary to obtain information on the duration of activities making up this total such that 1 MET can be subtracted for each hour to remove the resting component and give physical activity energy expenditure in marginalised MET (mMET).

In the example below, a study reports total physical activity volume as 9 MET-hours. Knowledge of the duration of activity of two hours is necessary to calculate and remove the resting component giving marginalised MET (mMET).


For studies that did not provide activity duration, a conversion equation from gross to marginal units is required. For the current analyses, we used a regression equation derived from the studies that provided both estimates, weighted for sample size per exposure category:

$$
\begin{equation*}
\text { mMET-hours }=0.89 * \text { MET-hours }-0.52 * \text { MET-hours }^{0.5} \tag{1}
\end{equation*}
$$

The studies/cohorts contributing to this equation were:

| Authors and year | Cohort | Participants |
| :--- | :--- | :--- |
| Leet et al. $^{3}$ | Aerobics Center Longitudinal Study | Men and women aged 20-82 years |
| Chomistek et al. ${ }^{4}$ | Health Professionals Follow-up Study | Men aged 40-75 years |
| Chomistek et al. $^{5 *}$ | Women's Genome Health Study | Women aged 45+ years |
| Wen et al. $^{6}$ | Taiwan Medical Screening Program | Men and women aged 20+ years |
| Mok et al. $^{7}$ | Severance Cohort Study | Men and women aged 30-93 years |
| Hu et al. |  | Nurses' Health Study |

[^1]eMethods 6: potential population impact fraction (PIF) formula

The equation below has been adapted from Equation 7 in Zapata-Diomedi et al, ${ }^{10}$ replacing prevalence for person-years.

$$
\text { PIF }=\frac{\sum_{i=1}^{n} p_{i} R R_{i}-\sum_{i=1}^{n} p_{i} R R_{i}}{\sum_{i=1}^{n} p_{i} R R_{i}}
$$

Where $p_{i}$ is the person-years in the $t^{\text {th }}$ exposure category, $p_{i}^{\prime}$ is the counterfactual, and $R R_{i}$ is the relative risk of the exposed compared to the reference level of exposure.
efigure 1: study screening and selection flowchart


SR: systematic reviews. PA: physical activity.
eResults 1: meta-analysis of the 11 studies that reported all-cause, cardiovascular and cancer mortality risk

| Outcomes | 4.375 mMET-h/week | 8.75 mMET-h/week | 17.5 mMET-h/week |
| :---: | :---: | :---: | :---: |
|  | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Subset of $11{\text { studies }{ }^{6,11-20}}^{\text {a }}$ |  |  |  |
| All-cause mortality | $\begin{gathered} 0.81 \\ (0.74-0.89) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.57-0.78) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.52-0.73) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.77 \\ (0.69-0.85) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.57-0.78) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.52-0.73) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.89 \\ (0.85-0.94) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.79-0.90) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.76-0.86) \end{gathered}$ |
| All studies |  |  |  |
| All-cause mortality | $\begin{gathered} 0.77 \\ (0.73-0.80) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.65-0.73) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.62-0.70) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.81 \\ (0.77-0.85) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.77) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.90 \\ (0.88-0.93) \\ \hline \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.81-0.89) \\ \hline \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.86) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{RR}=$ relative risk; $95 \% \mathrm{Cl}=95 \%$ confidence interval. CVD = cardiovascular disease. Reference group $=0 \mathrm{mMET}$-h/week.
eResults 2: sex-stratified results

|  | 4.375 mMET-h/week |  | 8.75 mMET-h/week |  | 17.5 mMET-h/week |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Men | Women | Men | Women | Men | Women |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Mortality |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.8-0.87) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.71-0.80) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.87 \\ (0.82-0.94) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.74-0.88) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.72-0.89) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.60-0.77) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.68-0.82) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.60-0.77) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.90 \\ (0.87-0.94) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.92-0.98) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.80-0.91) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.83-0.93) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.79-0.09) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.83-0.93) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 0.89 \\ (0.84-0.93) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.76-0.91) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.75-0.88) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.62-0.79) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.62-0.79) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 0.92 \\ (0.85-0.99) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.75-0.93) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.87) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.76-0.97) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.87) \end{gathered}$ |
| Stroke | $\begin{gathered} 0.90 \\ (0.86-0.94) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.97) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.79-0.91) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.66-0.88) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.76-0.89) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.66-0.88) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 0.95 \\ (0.92-0.98) \end{gathered}$ | $\begin{gathered} 0.98 \\ (0.96-0.99) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.97) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.97) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.82-0.96) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.97) \end{gathered}$ |
| Colon | $\begin{gathered} 0.91 \\ (0.86-0.96) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.92-1.02) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.78-0.94) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.84-1.03) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.72-0.91) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.84-1.03) \end{gathered}$ |
| Rectum | $\begin{gathered} 0.92 \\ (0.80-1.07) \\ \hline \end{gathered}$ | $\begin{gathered} 1.09 \\ (0.90-1.33) \\ \hline \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.74-1.1) \\ \hline \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.73-1.76) \\ \hline \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.76-1.11) \\ \hline \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.73-1.76) \\ \hline \end{gathered}$ |

mMET = marginal metabolic equivalent of task; RR = relative risk; $95 \% \mathrm{Cl}=95 \%$ confidence interval. CVD = cardiovascular disease.

Potential impact fraction of physical activity on mortality and incidence of cardiovascular diseases and cancers at three physical activity levels, by sex

|  | 4.375 mMET-h/week |  | 8.75 mMET-h/week |  | 17.5 mMET-h/week |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Men | Women | Men | Women | Men | Women |
| Outcomes | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| Mortality |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 3.74 \\ (2.69-4.83) \end{gathered}$ | $\begin{gathered} 5.43 \\ (4.00-6.94) \end{gathered}$ | $\begin{gathered} 7.39 \\ (5.52-9.31) \end{gathered}$ | $\begin{gathered} 9.82 \\ (7.42-12.29) \end{gathered}$ | $\begin{gathered} 10.69 \\ (8.37-13.03) \end{gathered}$ | $\begin{gathered} 12.30 \\ (9.30-15.35) \end{gathered}$ |
| Total CVD | $\begin{gathered} 3.16 \\ (1.51-4.86) \end{gathered}$ | $\begin{gathered} 6.15 \\ (3.54-8.85) \end{gathered}$ | $\begin{gathered} 7.78 \\ (4.48-11.02) \end{gathered}$ | $\begin{gathered} 12.83 \\ (8.06-17.52) \end{gathered}$ | $\begin{gathered} 11.82 \\ (9.62-14.04) \end{gathered}$ | $\begin{gathered} 15.65 \\ (11.65-19.64) \end{gathered}$ |
| Total cancer | $\begin{gathered} 2.72 \\ (1.57-3.90) \end{gathered}$ | $\begin{gathered} 1.56 \\ (0.67-2.48) \end{gathered}$ | $\begin{gathered} 5.13 \\ (3.11-7.18) \end{gathered}$ | $\begin{gathered} 3.51 \\ (1.68-5.36) \end{gathered}$ | $\begin{gathered} 6.21 \\ (4.20-8.25) \end{gathered}$ | $\begin{gathered} 6.27 \\ (3.94-8.59) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 2.78 \\ (1.54-4.05) \end{gathered}$ | $\begin{gathered} 4.95 \\ (2.45-7.54) \end{gathered}$ | $\begin{gathered} 6.64 \\ (4.17-9.10) \end{gathered}$ | $\begin{gathered} 10.4 \\ (5.90-14.84) \end{gathered}$ | $\begin{gathered} 10.06 \\ (8.23-11.91) \end{gathered}$ | $\begin{gathered} 13.65 \\ (10.48-16.86) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 2.99 \\ (0.38-5.72) \end{gathered}$ | $\begin{gathered} 7.10 \\ (2.81-11.68) \end{gathered}$ | $\begin{gathered} 5.07 \\ (0.74-9.44) \end{gathered}$ | $\begin{gathered} 12.17 \\ (4.98-19.42) \end{gathered}$ | $\begin{gathered} 6.15 \\ (1.21-11.06) \end{gathered}$ | $\begin{gathered} 14.60 \\ (6.11-22.94) \end{gathered}$ |
| Stroke | $\begin{gathered} 3.21 \\ (1.72-4.80) \end{gathered}$ | $\begin{gathered} 4.71 \\ (1.02-8.60) \end{gathered}$ | $\begin{gathered} 6.12 \\ (3.47-8.89) \end{gathered}$ | $\begin{gathered} 8.90 \\ (2.92-14.91) \end{gathered}$ | $\begin{gathered} 7.93 \\ (4.87-11.07) \end{gathered}$ | $\begin{gathered} 12.79 \\ (7.22-18.38) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 1.38 \\ (0.40-2.41) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.28-1.19) \end{gathered}$ | $\begin{gathered} 3.09 \\ (0.94-5.29) \end{gathered}$ | $\begin{gathered} 1.77 \\ (0.72-2.84) \end{gathered}$ | $\begin{gathered} 4.94 \\ (1.63-8.21) \end{gathered}$ | $\begin{gathered} 3.92 \\ (1.81-6.04) \end{gathered}$ |
| Colon | $\begin{gathered} 2.07 \\ (0.78-3.48) \end{gathered}$ | $\begin{gathered} 0.67 \\ (-0.44-1.87) \end{gathered}$ | $\begin{gathered} 4.13 \\ (1.68-6.71) \end{gathered}$ | $\begin{gathered} 1.39 \\ (-0.80-3.68) \end{gathered}$ | $\begin{gathered} 6.42 \\ (3.07-9.85) \end{gathered}$ | $\begin{gathered} 2.25 \\ (-0.55-5.11) \end{gathered}$ |
| Rectum | $\begin{gathered} 1.90 \\ (-1.52-5.71) \\ \hline \end{gathered}$ | $\begin{gathered} -2.64 \\ (-7.02-3.40) \\ \hline \end{gathered}$ | $\begin{gathered} 3.10 \\ (-2.79-9.21) \\ \hline \end{gathered}$ | $\begin{gathered} -4.66 \\ (-10.03-2.64) \\ \hline \end{gathered}$ | $\begin{gathered} 1.43 \\ (-3.83-6.99) \\ \hline \end{gathered}$ | $\begin{gathered} -4.57 \\ (-31.13-20.26) \\ \hline \end{gathered}$ |

mMET = marginal metabolic equivalent of task; PIF = potential impact fraction; 95\% CI=95\% confidence interval. CVD = cardiovascular disease.

## eResults 3: risk of bias assessment

For the risk of bias assessment, we classified the harmonisation methods in two ways. Firstly, we classified studies depending on whether we made assumptions about the occupational component of an aggregated PA exposure (occupational PA not included in exposure; or assumptions about occupational PA made). Secondly, we described the overall method of converting exposure data to mMET-h/week (measurement unit conversion from MET, kcal, or kJ data; calibration using validation studies; using assumptions on $\leq 2$ of intensity, duration, or frequency; or conversion of non-numeric data using assumptions on intensity, duration, and frequency). Note that for all-cause mortality and CVD outcomes one study is missing because 8.75 mMET -h/week was not included in the exposure range reported in the original publication.

## All-cause mortality



Total CVD mortality


## Total cancer mortality



Total CVD incidence (fatal and non-fatal events combined)


## Total cancer incidence (fatal and non-fatal events combined)



|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Mortality |  |  |  |  |  |  |  |  |  |
| All-cause mortality | $\begin{gathered} 0.78 \\ (0.75-0.81) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.65-0.74) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.62-0.71) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.72-0.79) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.63-0.72) \end{gathered}$ | $\begin{gathered} 0.64 \\ (0.60-0.69) \end{gathered}$ | $\begin{gathered} 0.69 \\ (0.63-0.76) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.57-0.71) \end{gathered}$ | $\begin{gathered} 0.60 \\ (0.54-0.68) \end{gathered}$ |
| Total CVD | $\begin{gathered} 0.83 \\ (0.79-0.87) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.67-0.79) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.73-0.82) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.61-0.74) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.57-0.69) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.68-0.84) \end{gathered}$ | $\begin{gathered} 0.64 \\ (0.54-0.75) \end{gathered}$ | $\begin{gathered} 0.57 \\ (0.47-0.69) \end{gathered}$ |
| Total cancer | $\begin{gathered} 0.91 \\ (0.89-0.94) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.82-0.89) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.86) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.86-0.92) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.80-0.88) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.79-0.86) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.81-0.92) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.74-0.87) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.71-0.84) \end{gathered}$ |
| CVD incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |  |  |  |
| Total CVD | $\begin{gathered} 0.85 \\ (0.81-0.88) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.70-0.80) \end{gathered}$ | $\begin{gathered} 0.68 \\ (0.63-0.73) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.84) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.65-0.76) \end{gathered}$ | $\begin{gathered} 0.65 \\ (0.60-0.71) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.72-0.84) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.59-0.75) \end{gathered}$ | $\begin{gathered} 0.60 \\ (0.51-0.69) \end{gathered}$ |
| Coronary heart disease | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.69-0.80) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.78-0.87) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.68-0.80) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.8-0.89) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.82) \end{gathered}$ | $\begin{gathered} 0.71 \\ (0.66-0.76) \end{gathered}$ |
| Stroke | $\begin{gathered} 0.88 \\ (0.85-0.91) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.76-0.85) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.71-0.81) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.81-0.88) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.76-0.84) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.72-0.84) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.82-0.91) \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.74-0.85) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.70-0.81) \end{gathered}$ |
| Heart failure | $\begin{gathered} 0.77 \\ (0.63-0.94) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.48-0.91) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.42-0.94) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.86-0.95) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.76-0.91) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.66-0.86) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.79-0.93) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.68-0.86) \end{gathered}$ | $\begin{gathered} 0.70 \\ (0.63-0.78) \end{gathered}$ |
| Cancer incidence (fatal and non-fatal events combined) |  |  |  |  |  |  |  |  |  |
| Total cancer | $\begin{gathered} 0.94 \\ (0.92-0.96) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.87-0.93) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.80-0.89) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.89-0.94) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.84-0.91) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.81-0.89) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.84-0.93) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.78-0.90) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.74-0.88) \end{gathered}$ |
| Head and neck | $\begin{gathered} 0.77 \\ (0.63-0.94) \end{gathered}$ | $\begin{gathered} 0.66 \\ (0.48-0.91) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.42-0.94) \end{gathered}$ | $\begin{gathered} 0.72 \\ (0.50-1.03) \end{gathered}$ | $\begin{gathered} 0.67 \\ (0.45-1.00) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.40-0.99) \end{gathered}$ | $\begin{gathered} 0.72 \\ (0.59-0.88) \end{gathered}$ | $\begin{gathered} 0.63 \\ (0.47-0.84) \end{gathered}$ | $\begin{gathered} 0.61 \\ (0.41-0.91) \end{gathered}$ |
| Myeloid leukemia | $\begin{gathered} 0.85 \\ (0.78-0.93) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.67-0.88) \end{gathered}$ | $\begin{gathered} 0.74 \\ (0.62-0.89) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.60-0.99) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.58-0.97) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.54-0.97) \end{gathered}$ | - | - | - |
| Myeloma | $\begin{gathered} 0.84 \\ (0.72-0.98) \end{gathered}$ | $\begin{gathered} 0.77 \\ (0.62-0.96) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.62-0.94) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.72-0.96) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.60-0.93) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.60-0.97) \end{gathered}$ | - | - | - |
| Gastric cardia | $\begin{gathered} 0.89 \\ (0.82-0.96) \end{gathered}$ | $\begin{gathered} 0.80 \\ (0.70-0.92) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.88) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.77-0.96) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.66-0.92) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.60-0.90) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.78-1.05) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.66-1.08) \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.57-1.10) \end{gathered}$ |
| Lung | $\begin{gathered} 0.90 \\ (0.88-0.93) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.80-0.89) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.74-0.91) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.85-0.90) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.79-0.87) \end{gathered}$ | $\begin{gathered} 0.84 \\ (0.74-0.95) \end{gathered}$ | $\begin{gathered} 0.83 \\ (0.78-0.88) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.69-0.84) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.66-0.91) \end{gathered}$ |
| Liver | $\begin{gathered} 0.90 \\ (0.83-0.97) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.72-0.94) \end{gathered}$ | $\begin{gathered} 0.75 \\ (0.63-0.89) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.97) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.70-0.95) \end{gathered}$ | $\begin{gathered} 0.78 \\ (0.65-0.93) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.80-0.99) \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.68-0.98) \end{gathered}$ | $\begin{gathered} 0.76 \\ (0.60-0.96) \end{gathered}$ |
| Endometrial | $\begin{gathered} 0.95 \\ (0.92-0.99) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.86-0.97) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.79-0.95) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.89-0.98) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.82-0.97) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.77-0.95) \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.84-0.95) \end{gathered}$ | $\begin{gathered} 0.81 \\ (0.73-0.91) \end{gathered}$ | $\begin{gathered} 0.73 \\ (0.62-0.86) \end{gathered}$ |
| Colon | $\begin{gathered} 0.97 \\ (0.94-0.99) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.89-0.99) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.84-0.98) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.91-0.99) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.98) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.83-0.97) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.93-1.01) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.87-1.02) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.84-1.01) \end{gathered}$ |
| Breast | $\begin{gathered} 0.97 \\ (0.96-0.99) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.93-0.97) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.89-0.95) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.94-0.98) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.90-0.97) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.87-0.95) \end{gathered}$ | $\begin{gathered} 0.97 \\ (0.94-1.00) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.90-1.00) \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.86-0.98) \end{gathered}$ |
| Bladder | $\begin{gathered} 0.94 \\ (0.86-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.81-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.81-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.92 \\ (0.82-1.02) \\ \hline \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.81-1.01) \\ \hline \end{gathered}$ | $\begin{gathered} 0.89 \\ (0.76-1.06) \\ \hline \end{gathered}$ | - | - | - |

Relative risk of all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels in relation to 0 mMET - $\mathrm{h} /$ week, after assigning alternative knots position ( $0^{\text {th }}, 42.5^{\text {th }}$, and $85^{\text {th }}$ percentile), using alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposity-adjusted models (continuation). $\qquad$

|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) | RR (95\% CI) |
| Rectum | $\begin{gathered} 0.97 \\ (0.93-1.01) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.89-1.03) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.87-1.05) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.9-1.0) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.87-1.01) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.89-1.04) \end{gathered}$ | $\begin{gathered} 0.90 \\ (0.84-0.97) \end{gathered}$ | $\begin{gathered} 0.87 \\ (0.78-0.96) \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \end{gathered}$ |
| Esophageal | $\begin{gathered} 0.98 \\ (0.91-1.05) \end{gathered}$ | $\begin{gathered} 0.96 \\ (0.85-1.08) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.80-1.12) \end{gathered}$ | $\begin{gathered} 0.95 \\ (0.85-1.07) \end{gathered}$ | $\begin{gathered} 0.93 \\ (0.78-1.11) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.77-1.13) \end{gathered}$ | $\begin{gathered} 0.91 \\ (0.78-1.06) \end{gathered}$ | $\begin{gathered} 0.86 \\ (0.67-1.11) \end{gathered}$ | $\begin{gathered} 0.85 \\ (0.63-1.16) \end{gathered}$ |
| Prostate | $\begin{gathered} 1.00 \\ (0.99-1.02) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.03) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.97-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.99-1.03) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.96-1.05) \end{gathered}$ | $\begin{gathered} 1.01 \\ (0.98-1.04) \end{gathered}$ | $\begin{gathered} 1.02 \\ (0.97-1.07) \end{gathered}$ | $\begin{gathered} 1.02 \\ (0.95-1.10) \end{gathered}$ |
| Kidney | $\begin{gathered} 1.02 \\ (0.94-1.11) \\ \hline \end{gathered}$ | $\begin{gathered} 1.04 \\ (0.91-1.19) \\ \hline \end{gathered}$ | $\begin{gathered} 1.05 \\ (0.88-1.26) \\ \hline \end{gathered}$ | $\begin{gathered} 1.03 \\ (0.90-1.16) \\ \hline \end{gathered}$ | $\begin{gathered} 1.04 \\ (0.88-1.22) \\ \hline \end{gathered}$ | $\begin{gathered} 1.06 \\ (0.84-1.33) \\ \hline \end{gathered}$ | $\begin{gathered} 0.88 \\ (0.79-0.98) \\ \hline \end{gathered}$ | $\begin{gathered} 0.82 \\ (0.71-0.96) \\ \hline \end{gathered}$ | $\begin{gathered} 0.79 \\ (0.68-0.93) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{RR}=$ relative risk; $95 \% \mathrm{CI}=95 \%$ confidence interval. CVD = cardiovascular disease.

Potential impact fraction of physical activity on all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels (in mMET-h/wk) after alternative placement of knots ( $0^{\text {th }}, 42.5^{\text {th }}$, and $85^{\text {th }}$ percentile), alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposityadjusted models. $\qquad$
Alt

| Alternative PA intensity and duration assump |  |  |
| :---: | :---: | :---: |
| 4.375 | 8.75 | 17.5 |
| PIF $(95 \% \mathrm{CI})$ | PIF $(95 \% \mathrm{Cl})$ | PIF $(95 \%$ |


| native knots pos |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| $\begin{gathered} 15.66 \\ (13.16-18.15) \end{gathered}$ | $\begin{gathered} 18.75 \\ (16.09-21.39) \end{gathered}$ | $\begin{gathered} 10.73 \\ (8.88-12.62) \end{gathered}$ | $\begin{gathered} 17.08 \\ (14.36-19.77) \end{gathered}$ | $\begin{gathered} 20.05 \\ (17.01-23.04) \end{gathered}$ | $\begin{gathered} 13.98 \\ (10.35-17.65) \end{gathered}$ | $\begin{gathered} 18.49 \\ (14.15-22.8) \end{gathered}$ | $\begin{gathered} 21.99 \\ (17.4-26.5) \end{gathered}$ |
| $\begin{gathered} 12.25 \\ (9.37-15.17) \end{gathered}$ | $\begin{gathered} 17.05 \\ (13.92-20.19) \end{gathered}$ | $\begin{gathered} 8.00 \\ (5.89-10.20) \end{gathered}$ | $\begin{gathered} 15.08 \\ (11.52-18.68) \end{gathered}$ | $\begin{gathered} 18.66 \\ (14.79-22.53) \end{gathered}$ | $\begin{gathered} 7.39 \\ (4.41-10.67) \end{gathered}$ | $\begin{gathered} 13.83 \\ (8.65-19.19) \end{gathered}$ | $\begin{gathered} 18.33 \\ (12.26-24.43) \end{gathered}$ |
| $\begin{gathered} 7.05 \\ (5.10-9.00) \end{gathered}$ | $\begin{gathered} 9.29 \\ (7.36-11.22) \end{gathered}$ | $\begin{gathered} 4.52 \\ (3.13-5.94) \end{gathered}$ | $\begin{gathered} 7.71 \\ (5.68-9.75) \end{gathered}$ | $\begin{gathered} 9.00 \\ (7.20-10.80) \end{gathered}$ | $\begin{gathered} 7.22 \\ (4.07-10.46) \end{gathered}$ | $\begin{gathered} 11.37 \\ (7.09-15.68) \end{gathered}$ | $\begin{gathered} 13.73 \\ (9.38-18.06) \end{gathered}$ |
| $\begin{gathered} 10.86 \\ (8.43-13.31) \end{gathered}$ | $\begin{gathered} 15.42 \\ (13.01-17.85) \end{gathered}$ | $\begin{gathered} 6.84 \\ (5.10-8.63) \end{gathered}$ | $\begin{gathered} 13.16 \\ (10.24-16.1) \end{gathered}$ | $\begin{gathered} 16.94 \\ (14.07-19.82) \end{gathered}$ | $\begin{gathered} 6.43 \\ (4.19-8.88) \end{gathered}$ | $\begin{gathered} 12.4 \\ (8.41-16.54) \end{gathered}$ | $\begin{gathered} 17.18 \\ (12.36-22.06) \end{gathered}$ |
| $\begin{gathered} 10.28 \\ (7.61-12.96) \end{gathered}$ | $\begin{gathered} 13.58 \\ (10.51-16.64) \end{gathered}$ | $\begin{gathered} 7.93 \\ (5.58-10.32) \end{gathered}$ | $\begin{gathered} 12.13 \\ (8.93-15.33) \end{gathered}$ | $\begin{gathered} 14.31 \\ (10.43-18.14) \end{gathered}$ | $\begin{gathered} 6.26 \\ (4.30-8.27) \end{gathered}$ | $\begin{gathered} 11.28 \\ (8.23-14.33) \end{gathered}$ | $\begin{gathered} 14.97 \\ (12.06-17.87) \end{gathered}$ |
| $\begin{gathered} 9.77 \\ (7.31-12.24) \end{gathered}$ | $\begin{gathered} 12.37 \\ (9.63-15.1) \end{gathered}$ | $\begin{gathered} 7.20 \\ (5.33-9.10) \end{gathered}$ | $\begin{gathered} 10.40 \\ (8.12-12.69) \end{gathered}$ | $\begin{gathered} 12.66 \\ (8.46-16.77) \end{gathered}$ | $\begin{gathered} 5.13 \\ (3.29-7.03) \end{gathered}$ | $\begin{gathered} 9.31 \\ (6.51-12.14) \end{gathered}$ | $\begin{gathered} 12.25 \\ (9.45-15.08) \end{gathered}$ |
| $\begin{gathered} 4.63 \\ (1.90-7.66) \end{gathered}$ | $\begin{gathered} 7.86 \\ (4.31-11.68) \end{gathered}$ | $\begin{gathered} 2.36 \\ (1.15-3.74) \end{gathered}$ | $\begin{gathered} 5.00 \\ (2.49-7.75) \end{gathered}$ | $\begin{gathered} 9.43 \\ (4.94-14.10) \end{gathered}$ | $\begin{gathered} 3.34 \\ (1.34-5.78) \end{gathered}$ | $\begin{gathered} 6.25 \\ (3.09-9.90) \end{gathered}$ | $\begin{gathered} 9.21 \\ (5.86-12.84) \end{gathered}$ |
|  |  |  |  |  |  |  |  |
| $\begin{gathered} 5.22 \\ (3.55-6.90) \end{gathered}$ | $\begin{gathered} 7.80 \\ (5.65-9.93) \end{gathered}$ | $\begin{gathered} 3.48 \\ (2.33-4.66) \end{gathered}$ | $\begin{gathered} 6.56 \\ (4.57-8.55) \end{gathered}$ | $\begin{gathered} 8.57 \\ (6.31-10.81) \end{gathered}$ | $\begin{gathered} 5.67 \\ (3.24-8.18) \end{gathered}$ | $\begin{gathered} 9.12 \\ (5.51-12.76) \end{gathered}$ | $\begin{gathered} 11.12 \\ (6.91-15.33) \end{gathered}$ |
| $\begin{gathered} 17.46 \\ (3.68-30.98) \end{gathered}$ | $\begin{gathered} 19.83 \\ (1.23-36.55) \end{gathered}$ | $\begin{gathered} 13.82 \\ (-1.07-28.5) \end{gathered}$ | $\begin{gathered} 18.21 \\ (1.05-34.26) \end{gathered}$ | $\begin{gathered} 23.04 \\ (2.16-41.14) \end{gathered}$ | $\begin{gathered} 11.66 \\ (4.19-19.84) \end{gathered}$ | $\begin{gathered} 18.82 \\ (6.67-30.81) \end{gathered}$ | $\begin{gathered} 20.07 \\ (0.44-37.22) \end{gathered}$ |
| $\begin{gathered} 7.08 \\ (1.65-12.94) \end{gathered}$ | $\begin{gathered} 7.57 \\ (2.23-13.33) \end{gathered}$ | $\begin{gathered} 6.67 \\ (0.40-13.47) \end{gathered}$ | $\begin{gathered} 8.33 \\ (1.91-15.25) \end{gathered}$ | $\begin{gathered} 10.22 \\ (1.38-19.18) \end{gathered}$ | - | - | - |
| $\begin{gathered} 6.76 \\ (1.90-12.09) \end{gathered}$ | $\begin{gathered} 8.30 \\ (1.91-14.99) \end{gathered}$ | $\begin{gathered} 3.71 \\ (0.79-7.23) \\ \hline \end{gathered}$ | $\begin{gathered} 7.79 \\ (1.75-14.37) \end{gathered}$ | $\begin{gathered} 6.57 \\ (-0.43-14.07) \end{gathered}$ | - | - | - |


| Cancer incidence (fatal and non-fatal events combined) |
| :--- |
| $(0.80-3.89)$ |

(continues)

Potential impact fraction of physical activity on all-cause mortality and incidence of cardiovascular diseases and cancers at three physical activity levels (in mMET-h/wk) after assigning alternative knots position ( $0^{\mathrm{th}}, 42.5^{\mathrm{th}}$, and $85^{\text {th }}$ percentile), using alternative assumptions for physical activity intensity ( 1 mMET less to MPA and VPA) and session duration ( 0.5 hour rather than 0.75 ), and including only non-adiposity-adjusted models (continuation).

|  | Alternative knots position |  |  | Alternative PA intensity and duration assumptions |  |  | Non-adiposity-adjusted models only |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 | 4.375 | 8.75 | 17.5 |
| Outcomes | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) | PIF (95\% CI) |
| Gastric cardia | $\begin{gathered} 1.95 \\ (0.58-3.68) \end{gathered}$ | $\begin{gathered} 4.77 \\ (1.58-8.57) \end{gathered}$ | $\begin{gathered} 6.77 \\ (2.55-11.63) \end{gathered}$ | $\begin{gathered} 2.45 \\ (0.64-4.78) \end{gathered}$ | $\begin{gathered} 5.40 \\ (1.56-10.00) \end{gathered}$ | $\begin{gathered} 7.29 \\ (2.34-13.03) \end{gathered}$ | $\begin{gathered} 1.13 \\ (-0.42-3.29) \end{gathered}$ | $\begin{gathered} 3.17 \\ (-1.19-8.63) \end{gathered}$ | $\begin{gathered} 5.12 \\ (-1.81-13.09) \end{gathered}$ |
| Lung | $\begin{gathered} 4.39 \\ (3.16-5.63) \end{gathered}$ | $\begin{gathered} 7.26 \\ (5.10-9.4) \end{gathered}$ | $\begin{gathered} 8.54 \\ (3.04-13.98) \end{gathered}$ | $\begin{gathered} 5.88 \\ (4.05-7.37) \end{gathered}$ | $\begin{gathered} 9.56 \\ (6.13-12.49) \end{gathered}$ | $\begin{gathered} 8.44 \\ (-0.66-17.5) \end{gathered}$ | $\begin{gathered} 8.01 \\ (4.69-11.23) \end{gathered}$ | $\begin{gathered} 12.27 \\ (6.66-17.64) \end{gathered}$ | $\begin{gathered} 10.52 \\ (0.77-20.21) \end{gathered}$ |
| Liver | $\begin{gathered} 3.49 \\ (0.58-6.71) \end{gathered}$ | $\begin{gathered} 6.75 \\ (1.44-12.31) \end{gathered}$ | $\begin{gathered} 10.27 \\ (3.26-17.31) \end{gathered}$ | $\begin{gathered} 4.59 \\ (0.90-8.59) \end{gathered}$ | $\begin{gathered} 8.37 \\ (2.11-14.76) \end{gathered}$ | $\begin{gathered} 11.07 \\ (3.45-18.63) \end{gathered}$ | $\begin{gathered} 4.62 \\ (0.24-9.54) \end{gathered}$ | $\begin{gathered} 8.72 \\ (0.79-16.97) \end{gathered}$ | $\begin{gathered} 12.86 \\ (2.32-23.21) \end{gathered}$ |
| Endometrial | $\begin{gathered} 1.10 \\ (0.26-2.02) \end{gathered}$ | $\begin{gathered} 2.62 \\ (0.76-4.60) \end{gathered}$ | $\begin{gathered} 4.54 \\ (1.88-7.28) \end{gathered}$ | $\begin{gathered} 1.50 \\ (0.37-2.73) \end{gathered}$ | $\begin{gathered} 3.66 \\ (1.07-6.38) \end{gathered}$ | $\begin{gathered} 5.91 \\ (2.17-9.72) \end{gathered}$ | $\begin{gathered} 2.23 \\ (0.89-3.77) \end{gathered}$ | $\begin{gathered} 5.66 \\ (2.38-9.23) \end{gathered}$ | $\begin{gathered} 10.82 \\ (4.99-16.76) \end{gathered}$ |
| Colon | $\begin{gathered} 0.70 \\ (0.11-1.33) \end{gathered}$ | $\begin{gathered} 1.69 \\ (0.33-3.12) \end{gathered}$ | $\begin{gathered} 2.96 \\ (0.92-5.05) \end{gathered}$ | $\begin{gathered} 0.94 \\ (0.19-1.74) \end{gathered}$ | $\begin{gathered} 2.12 \\ (0.49-3.82) \end{gathered}$ | $\begin{gathered} 3.73 \\ (1.24-6.25) \end{gathered}$ | $\begin{gathered} 0.45 \\ (-0.15-1.11) \end{gathered}$ | $\begin{gathered} 1.19 \\ (-0.32-2.79) \end{gathered}$ | $\begin{gathered} 2.29 \\ (-0.06-4.70) \end{gathered}$ |
| Breast | $\begin{gathered} 0.69 \\ (0.32-1.07) \end{gathered}$ | $\begin{gathered} 1.62 \\ (0.79-2.46) \end{gathered}$ | $\begin{gathered} 3.23 \\ (1.85-4.63) \end{gathered}$ | $\begin{gathered} 1.13 \\ (0.53-1.75) \end{gathered}$ | $\begin{gathered} 2.44 \\ (1.21-3.69) \end{gathered}$ | $\begin{gathered} 4.09 \\ (2.35-5.83) \end{gathered}$ | $\begin{gathered} 0.79 \\ (-0.05-1.67) \end{gathered}$ | $\begin{gathered} 1.78 \\ (0.10-3.50) \end{gathered}$ | $\begin{gathered} 3.68 \\ (1.45-5.94) \end{gathered}$ |
| Bladder | $\begin{gathered} 1.91 \\ (-0.54-4.52) \end{gathered}$ | $\begin{gathered} 2.98 \\ (-0.24-6.33) \end{gathered}$ | $\begin{gathered} 3.11 \\ (0.02-6.35) \end{gathered}$ | $\begin{gathered} 2.72 \\ (-0.64-6.23) \end{gathered}$ | $\begin{gathered} 3.70 \\ (0.16-7.39) \end{gathered}$ | $\begin{gathered} 4.59 \\ (-3.62-12.48) \end{gathered}$ | - | - | - |
| Rectum | $\begin{gathered} 0.77 \\ (-0.15-1.75) \end{gathered}$ | $\begin{gathered} 1.43 \\ (-0.45-3.36) \end{gathered}$ | $\begin{gathered} 0.52 \\ (-1.74-2.82) \end{gathered}$ | $\begin{gathered} 1.30 \\ (-0.09-2.74) \end{gathered}$ | $\begin{gathered} 2.07 \\ (-0.49-4.65) \end{gathered}$ | $\begin{gathered} 0.02 \\ (-2.60-2.67) \end{gathered}$ | $\begin{gathered} 2.07 \\ (0.53-3.73) \end{gathered}$ | $\begin{gathered} 3.74 \\ (0.90-6.66) \end{gathered}$ | $\begin{gathered} 2.69 \\ (-0.19-5.66) \end{gathered}$ |
| Esophageal | $\begin{gathered} 0.68 \\ (-0.95-2.68) \end{gathered}$ | $\begin{gathered} 1.38 \\ (-2.06-5.32) \end{gathered}$ | $\begin{gathered} 1.57 \\ (-3.05-6.67) \end{gathered}$ | $\begin{gathered} 1.02 \\ (-1.34-3.88) \end{gathered}$ | $\begin{gathered} 1.87 \\ (-2.65-6.95) \end{gathered}$ | $\begin{gathered} 1.58 \\ (-3.44-7.13) \end{gathered}$ | $\begin{gathered} 1.86 \\ (-1.08-5.71) \end{gathered}$ | $\begin{gathered} 3.7 \\ (-2.48-10.93) \end{gathered}$ | $\begin{gathered} 3.96 \\ (-4.07-12.86) \end{gathered}$ |
| Prostate | $\begin{gathered} -0.10 \\ (-0.48-0.29) \end{gathered}$ | $\begin{gathered} -0.21 \\ (-1.10-0.71) \end{gathered}$ | $\begin{gathered} -0.10 \\ (-1.61-1.42) \end{gathered}$ | $\begin{gathered} -0.16 \\ (-0.64-0.35) \end{gathered}$ | $\begin{gathered} -0.29 \\ (-1.36-0.81) \end{gathered}$ | $\begin{gathered} -0.11 \\ (-1.75-1.54) \end{gathered}$ | $\begin{gathered} -0.23 \\ (-0.90-0.48) \end{gathered}$ | $\begin{gathered} -0.5 \\ (-2.02-1.08) \end{gathered}$ | $\begin{gathered} -0.65 \\ (-3.10-1.85) \end{gathered}$ |
| Kidney | $\begin{gathered} -0.65 \\ (-3.69-2.81) \\ \hline \end{gathered}$ | $\begin{gathered} -1.23 \\ (-6.39-4.34) \\ \hline \end{gathered}$ | $\begin{gathered} -1.91 \\ (-9.20-5.63) \\ \hline \end{gathered}$ | $\begin{gathered} -0.95 \\ (-5.25-3.85) \end{gathered}$ | $\begin{gathered} -1.78 \\ (-8.56-5.40) \\ \hline \end{gathered}$ | $\begin{gathered} -3.06 \\ (-15.89-9.34) \end{gathered}$ | $\begin{gathered} 5.61 \\ (0.92-10.50) \\ \hline \end{gathered}$ | $\begin{gathered} 9.24 \\ (2.27-16.16) \\ \hline \end{gathered}$ | $\begin{gathered} 11.73 \\ (4.40-18.93) \\ \hline \end{gathered}$ |

$\mathrm{mMET}=$ marginal metabolic equivalent of task; $\mathrm{PIF}=$ potential impact fraction; $95 \% \mathrm{CI}=95 \%$ confidence interval. $\mathrm{CVD}=$ cardiovascular disease.

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[^0]:    * Identified by systematic literature review and used in equation derivation but not included in main analyses because full results were available in a parent study.

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