**QUEEN'S
UNIVERSITY
BELFAST**

Physical activity and cancer risk: Findings from the UK Biobank, a large prospective cohort study

Murray, J. M., Coleman, H. G., & Hunter, R. F. (2020). Physical activity and cancer risk: Findings from the UK Biobank, a large prospective cohort study. *Cancer Epidemiology*, 68, [101780].
<https://doi.org/10.1016/j.canep.2020.101780>

Published in:
Cancer Epidemiology

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2020 Elsevier.

This manuscript is distributed under a Creative Commons Attribution-NonCommercial-NoDerivs License

(<https://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits distribution and reproduction for non-commercial purposes, provided the author and source are cited.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Title: Physical activity and cancer risk: Findings from the UK Biobank, a large prospective cohort study

Running title: Physical activity and cancer risk

Jennifer M Murray, Helen G Coleman, Ruth F Hunter

Jennifer M Murray, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK

Helen G Coleman, Centre for Public Health and Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, Northern Ireland, UK

Ruth F Hunter, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK

Corresponding authors: Ruth Hunter, Centre for Public Health, Queen's University Belfast, Royal

Victoria Hospital, Grosvenor Road, Belfast, BT12 6BJ; Tel: 02890978944; E-mail:

Ruth.Hunter@qub.ac.uk;

Jennifer Murray, Centre for Public Health, Queen's University Belfast, Royal Victoria Hospital,

Grosvenor Road, Belfast, BT12 6BJ; Tel: 02890978955; E-mail: Jennifer.Murray@qub.ac.uk

Article DOI: 10.1016/j.canep.2020.101780

Link: <https://doi.org/10.1016/j.canep.2020.101780>

© 2020. This manuscript version is made available under the CC-BY-NC-ND 4.0 license

<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Highlights

- Moderate physical activity levels were associated with lower risk of oropharyngeal and lung cancers
- High physical activity levels were associated with lung, breast, hepatobiliary and colon cancers
- Sensitivity analyses showed associations with lower oesophageal and higher prostate cancer incidence
- Results varied by deprivation, smoking, or combined body fat and physical activity
- Promoting high levels of physical activity may be required for cancer prevention

ABSTRACT

Objectives: This study aimed to investigate the association between physical activity and site-specific cancer incidence.

Methods: UK Biobank is a prospective population-based cohort study. 364,899 adults (51.6% females, mean age 56.0 years) were included. The exposure variable was physical activity level derived from the International Physical Activity Questionnaire-Short Form (IPAQ-SF). Participants were categorised at 'high' ($\geq 1,500$ MET-minutes/week), 'moderate' (≥ 600 MET-minutes/week) or 'low' levels of activity following standardised IPAQ-SF scoring guidance. Primary outcome measures included incident cancers at 20 sites. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) showing relationships between physical activity and cancer.

Results: 21,816 incident cancers were identified. Significant associations were identified between high physical activity levels and lower risk of lung (HR 0.81, 95% CI: 0.70, 0.94), breast (female only) (HR 0.85, 95% CI: 0.77, 0.94), hepatobiliary tract (HR 0.72, 95% CI: 0.53, 0.97), and colon (HR 0.86, 95% CI: 0.74, 0.99) cancers compared to low physical activity levels. Moderate levels of physical activity were associated with significantly lower risk of oropharyngeal (HR 0.71, 95% CI: 0.55, 0.93), and lung cancer (HR 0.86, 95% CI: 0.74, 0.99) compared to low physical activity levels. Sensitivity analyses showed associations of higher physical activity with lower oesophageal and higher prostate cancer incidence.

Conclusions: Regular physical activity is significantly associated with reduced risk for lung, breast, hepatobiliary tract, colon and oropharyngeal cancers. Our findings highlight the importance of physical activity promotion, particularly high levels of physical activity, in cancer prevention.

Keywords: Physical activity; Cancer; Cohort; UK Biobank.

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality globally, responsible for one in eight deaths worldwide [1]. New cancer cases are set to increase by almost 70% by 2030 [1]. Furthermore, the global economic cost of cancer is projected to reach US\$458 billion [2]. However, 30-50% of cancers could be prevented through healthy lifestyles, and tackling modifiable risk factors provides an economically viable option of controlling cancer [3]. Thus, it is of major public health importance to establish an evidence-base of potential modifiable risk factors that are associated with cancer risk, such as physical inactivity, for informing cancer prevention policies.

There is convincing evidence that physical activity behaviour is related to the risk of developing certain types of cancer, including endometrial, colorectal and postmenopausal breast cancers [3–7]. However, according to a 2018 report of the American Institute for Cancer Research, there is inconclusive evidence for other cancers (or limited-suggestive evidence for oesophagus, lung, liver and premenopausal breast cancers [3]). Together these cancers (other than endometrial, colorectal and postmenopausal breast cancers) constitute around 70% of new incident cancers worldwide [8]. The 2018 U.S. Physical Activity Guidelines also conducted a comprehensive literature review and concluded that there was strong evidence linking the highest (versus lowest) physical activity levels with lower risk of bladder, breast, colon, endometrial, oesophageal adenocarcinoma, renal, and gastric cancers [9]. However, the committee concluded there was limited or low-grade evidence for lung, hematologic, head and neck, ovary, pancreas, rectal, brain or thyroid cancers [9]. The committee also found insufficient evidence to make conclusions about other cancers (e.g. liver, gallbladder, small intestine, soft tissue or melanoma) [9].

Whilst many prospective studies exist investigating the association between cancer risk and physical activity, relatively small sample sizes and case numbers may have masked an underlying significant association for some cancer sites [3,10]. A meta-analysis by Moore et al, which investigated the relationship between leisure-time physical activity and cancer incidence for 26 types of cancer,

overcame this issue by pooling results from 12 prospective cohort studies (1.44 million participants in total) and found evidence linking physical activity to a range of cancer types including oesophageal adenocarcinoma, gallbladder, liver and lung [10]. However, they investigated leisure-time physical activity only. Other relevant observational studies and systematic reviews have tended to focus on a subset of cancers [7,11–16] or on specific domains of physical activity (e.g. leisure-time physical activity, active commuting) [15,17,18]. To investigate the potential role of physical activity to inform the efforts of initiatives like the Cancer Prevention and Control Research Network (CPCRN) [19] in developing cancer prevention policy, it is important to increase understanding of the association between physical activity and cancer risk, and to provide a broad overview for a range of cancer sites.

Several UK Biobank papers have already been published examining the association of physical activity with the risk of developing certain cancers [20] including oesophago-gastric and colorectal cancers [7,21]. We sought to provide a broader overview by primarily investigating physical activity behaviour, derived from time spent in walking, moderate- and vigorous-activities from the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [22,23], in relation to cancer risk at a number of sites (including sites for which there is already strong evidence for showing an association with physical activity, e.g. endometrial, colorectal and breast cancers) but also to other cancers within the most common incident cancer sites affecting the UK population (e.g. prostate, lung and bowel cancers [24]) in a large prospective cohort-based study. We also investigated whether associations varied by gender, age, socio-economic status (deprivation), smoking and excess body weight.

METHODS

Study design

UK Biobank is a prospective population-based cohort study.

Patient and public involvement

Between 2006 and 2010, UK Biobank recruited 502,619 adults (5.5% response rate) aged 40-69 years from the general population [25,26]. Approximately 9.2 million invitations were mailed to potential participants who were registered with the National Health Service (NHS) and living within a 25-mile radius of one of 22 assessment centres across England, Scotland and Wales. All participants provided informed consent.

We excluded participants if: (1) they had been diagnosed with malignant cancer (excluding non-melanoma skin cancer) prior to baseline (n=26,867); (2) they provided incomplete physical activity data for the IPAQ-SF (n=110,740); (3) they requested to be removed from the UK Biobank dataset as per General Data Protection Regulation (GDPR) (n=113). This resulted in 364,899 participants being included in the present analysis.

No participants informed the design, formation of the research questions or conduct of the current study.

Physical activity measurement

The exposure variable was self-report physical activity level derived from the well-validated IPAQ-SF [23]. Participants reported the frequency (days/week) and duration (minutes/day) of walking, moderate- and vigorous-intensity physical activity in the past seven days. For walking, participants were asked to include walking they do at work, travelling to and from work, and for sport or leisure. For moderate- and vigorous-intensity activity, participants were asked to consider physical activity undertaken for work, leisure, travel and around the house. Durations of <10 minutes/day were recoded to 0 and durations of >180 minutes were truncated at 180. A composite physical activity score (MET minutes/week) was computed as the summation of the frequency and duration of physical activity in walking, moderate-intensity and vigorous-intensity activity, weighted by the energy expended for each type of activity according to the IPAQ scoring manual (i.e. x3.3 for walking, x4.0 for moderate-intensity activity, x8.0 for vigorous-intensity activity) [23].

Participants were classified as 'low' (not meeting criteria for the 'moderate' or 'high' categories), 'moderate' (at least 20 minutes of vigorous-intensity physical activity on three or more days/week; at least 30 minutes of moderate-intensity physical activity or walking on five or more days/week; five or more days/week spent in any combination of walking, moderate- or vigorous-intensity physical activity achieving at least 600 MET minutes/week) or 'high' (at least three days/week of vigorous-intensity physical activity achieving at least 1,500 MET minutes/week; at least seven days/week spent in any combination of walking, moderate- or vigorous-intensity physical activity achieving at least 3,000 MET minutes/week) activity levels. All data processing followed the standardised IPAQ-SF scoring guidance [23].

Assessment of covariates

Height (m), weight (kg), waist and hip circumference (cm) were measured by staff at the UK Biobank study centre. BMI was calculated from weight and height measurements (kg/m^2). Waist circumference measurements were taken from the umbilicus level and regarded as a measure of central obesity, using official cut-off values established by the International Diabetes Federation (>94cm in men and >80cm in women) [27]. Age, sex and postcodes were acquired from a central registry for all participants and updated by the participant. Participants also self-reported their ethnicity, education, lifestyle behaviours (smoking status, alcohol consumption, dietary intake, and sunscreen/UV protection use) and medical history using electronic questionnaires. Townsend deprivation scores were derived from postcodes [28].

Missing data were below 1% for all covariates apart from fruit and vegetable consumption (1.2%), age at menarche (1.2%), age at menopause (1.6%), family history of cancer (1.5%) and hysterectomy status (5.3%).

Cancer ascertainment

The main outcomes were region- and site-specific cancers diagnosed by 31 March 2016 for England/Wales, 31 October 2015 for Scotland. Incident cancers were identified through national cancer registries (Health and Social Care Information Centre and the NHS Central Register) and coded according to the International Classification of Diseases, 9th and 10th revisions (ICD-9 [29] and ICD-10 [30]) as shown in Table 1.

Statistical analyses

Descriptive statistics for all covariates are presented according to participants' IPAQ categories. Categorical variables are presented as participant numbers and percentages. Means and standard deviations (SDs) are presented for continuous variables. Follow-up time in days from baseline was used as the timescale and end of follow-up occurred at: (1) cancer diagnosis date; (2) date of emigration; (3) date of death; or (4) end of follow-up (31 March 2016 for England/Wales, 31 October 2015 for Scotland), whichever came first.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) showing the relationship between IPAQ categories of physical activity and cancer. The 'low' physical activity category was the referent (HR=1.00). Tests for trend were assessed by including physical activity categories as a continuous variable. Wald tests were also conducted examining the overall significance of the categorised physical activity variable ($p < 0.05$ provided evidence for a significant association). We also examined the impact of removing prevalent cancers by repeating the analyses confined to cancers diagnosed at least two years following baseline.

All analyses were adjusted for age and sex in the baseline model. Additional covariates were added in the second adjusted model and included ethnicity, deprivation index, education, fruit and vegetable intake, BMI, height, smoking status and alcohol intake. Cancer site-specific covariates were included in the third adjusted model for each type of cancer (details included in the footnotes of Tables 3-6). These included use of sun/UV protection, HRT use, oral contraceptive use, number of live births, age

at menarche, age at menopause, hysterectomy status, diabetes at baseline, aspirin use, red meat intake, processed meat intake. For analyses including gender-specific covariates (e.g. colorectal cancer, colon cancer, and rectum cancer), separate models were run for males and females and HRs were combined using inverse variance meta-analysis and a fixed-effects model [31–33]. We did not adjust for total dietary energy intake due to the large amount of missing data (for 55% of participants). Further analyses were conducted to investigate the role of anthropometric factors by running all models with and without adjustment for central obesity. Models including incident breast cancer, prostate cancer and lung cancer were run with and without adjustment for self-report family history. The oesophageal cancer model was also run with and without adjustment for self-reported gastro-oesophageal reflux (GORD). It has been argued that change-in-estimate criteria may not be appropriate to assess confounding in survival models due to non-collapsibility of effect estimates [34,35]. Therefore, we also assessed confounding by central obesity, family history and GORD using a modified change-in-estimate criterion [36]. Where applying the modified change-in-estimate criterion resulted in a model adjusted for a different set of confounders, we have reported the effect estimates separately and indicated this in the footnotes of table 3. However, there were no major changes to the results and all subgroup analyses and sensitivity analyses were subsequently applied to the final models indicated in Table 3.

We repeated the analyses examining all incident cancers diagnosed post-baseline and the analyses examining the impact of removing prevalent cancers, using restricted cubic splines to facilitate detailed description of the dose-response curves [37,38]. Using splines, HRs and 95% CIs were estimated for specific MET hours/week values and used to describe the shape of the overall dose-response curves for each site. The reference value was set to 0 MET hours/week. Splines used five knots specified at the locations recommended by Harrell (2015; at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles) [39]. Wald tests were used to evaluate the statistical significance of the overall association ($p < 0.05$ provided evidence for a significant association). Non-linearity of the dose-response curves

was examined visually and using likelihood ratio tests ($p < 0.05$ provided evidence for a non-linear association; Supplementary file 1).

Sensitivity analyses were conducted by repeating the main analysis by type and intensity of physical activity according to the IPAQ-SF (i.e. walking, moderate- and vigorous-intensity physical activity). Sensitivity analyses were conducted using alternative categories defined using IPAQ-measured MET-hours/week (i.e. <10 , $10- <20$, $20- <40$, $40- <60$, ≥ 60 MET-hours/week). We assessed robustness to unmeasured or uncontrolled confounding and robustness to selection bias by calculating E-values representing the magnitude of uncontrolled confounding or selection bias that would be required to reduce the observed HR estimates to the null [40,41]. Sensitivity analyses were carried out to examine the impact on the results if imputing missing exposure data ($n=110,740$). Missing data were imputed using multiple imputation by chained equations (MICE) with 10 imputations and 10 iterations using the 'mi estimate' command in Stata [42–44]. Rubin's rules were used to obtain final estimates from the estimates derived in the 10 imputed data sets [45]. The results of all sensitivity analyses are presented in Supplementary file 2.

Subgroup analyses were conducted by selected baseline characteristics including sex, age, deprivation index, smoking status and BMI (with reference to obese/non-obese thresholds defined in a previous UK Biobank study [46]). Further analyses were conducted by creating four categories based on body fat percentage (low/optimal versus high) and physical activity levels (high/moderate versus low) defined according to the IPAQ-SF. Body fat percentage cut-points were derived from previously established thresholds [47]. Subgroup analyses were conducted by menopausal status for female-specific cancers. Interactions were tested using the Wald test for homogeneity and declared significant if $p < 0.01$ [10].

The proportional hazards assumption was tested for each model using formal tests of Schoenfeld residuals, and by visual inspection of scaled Schoenfeld residual plots [48] and log-log plots (parallel curves indicated that there was no evidence for violation of the proportional hazards assumption).

Whilst the Schoenfeld residual tests indicated that some of our models may not have been in line with the proportional hazards assumption, visual inspection of log-log plots and Schoenfeld residual plots showed no serious violations. Therefore, we proceeded with the analyses as planned.

To quantify the potential degree of regression dilution bias, we followed procedures used in a previous UK Biobank study by Strain and colleagues, using data from two sub-samples who undertook repeat IPAQ-SF assessments at a median of 4.4 years (n=20,346) and 8.7 years (n=43,190) post-baseline [49]. We also created a subsample of participants who undertook the first assessment <3 years post-baseline with a minimum follow-up of 2 years (n=2,297). We standardised the [natural log of the continuous variable total MET-hours/week+1] at each follow-up to the baseline scale (subtracting the baseline mean and dividing by the baseline standard deviation). Coefficients from linear regressions of follow-up variables on the baseline variable (transformed and standardised as above) were estimated to indicate the degree of stability in the measured exposure variable over time. All analyses were conducted using Stata 13 [50].

RESULTS

Participant characteristics are shown in Table 2. Among the 364,899 participants, 51.6% were women and the mean age was 56.0 years. During a mean follow-up of 6.9 years (SD 1.3, median 7.1, interquartile range 6.4-7.7), 21,816 incident cancers were identified. Only 17.3% of participants reported low physical activity levels. Compared to participants in the moderate (41.6%) and high (41.1%) categories, participants with low physical activity levels were more likely to be current smokers, to have an obese BMI or high waist-hip ratio, to have diabetes diagnosed at baseline, to report never or rarely using sun protection at baseline, or to have a poorer diet (less fruit and vegetable consumption, higher red and processed meat consumption).

Association of cancer risk and physical activity

Table 3 shows the association between physical activity and site-specific cancer risk. The corresponding E-values for confounding (E_c) and selection bias (E_s) are presented in Supplementary file 2, Table 2.3. High levels of physical activity were associated with significantly lower risk of lung (HR 0.81, 95% CI: 0.70, 0.94; $E_c=1.79$, $E_s=1.47$), breast (HR 0.85, 95% CI: 0.77, 0.94; $E_c=1.62$, $E_s=1.38$), hepatobiliary tract (HR 0.72, 95% CI: 0.53, 0.97; $E_c=2.13$, $E_s=1.64$), and colon (HR 0.86, 95% CI: 0.74, 0.99; $E_c=1.60$, $E_s=1.37$) cancers when compared with low levels. Moderate levels of physical activity were associated with significantly lower risk of oropharyngeal (HR 0.71, 95% CI: 0.55, 0.93; $E_c=2.15$, $E_s=1.65$), and lung (HR 0.86, 95% CI: 0.74, 0.99; $E_c=1.60$, $E_s=1.37$) cancers compared to low levels. Wald tests examining the overall significance of the categorised physical activity variable showed associations for oropharyngeal ($p=0.04$), lung ($p=0.02$), and breast ($p=0.003$) cancers.

Sensitivity analyses showed, after excluding cancers diagnosed within the first 2 years following baseline, the only associations which remained significant were those between high physical activity levels and lower risk of lung (HR 0.85, 95% CI: 0.72, 0.999), and breast (HR 0.89, 95% CI: 0.79, 0.997) cancers when compared to low levels (Table 4). This suggests that the results of our main analyses could be affected by reverse causation bias. An alternative explanation is that the results for some sites became non-significant due to the drop in number of cancer cases resulting from excluding cancers diagnosed over the 2-year period (e.g. all sites drop $\geq 20\%$ of cases). Wald tests examining the overall significance of the categorised physical activity variable showed associations for breast ($p=0.04$), and oesophagus ($p=0.03$) cancers.

Using restricted cubic splines, likelihood ratio tests showed evidence for non-linearity of the dose-response curves for lung ($p=0.01$), and prostate ($p=0.02$) cancers (Supplementary File 1). Inspection of graphs showed that the dose-response relationships appeared to be curvilinear for these cancer sites. Wald tests examining the overall significance of the dose-response relationships showed associations for lung ($p=0.002$), and breast ($p=0.01$) cancers (Table 5). After excluding cancers diagnosed within the first 2 years following baseline, likelihood ratio tests showed evidence for non-linearity of the dose-

response curves for prostate ($p=0.04$) cancers (Supplementary File 1). Wald tests examining the overall significance of the dose-response relationships showed associations for breast cancers ($p=0.01$; Table 6).

Sensitivity analyses using alternative physical activity categories defined using IPAQ-measured MET-hours/week showed a similar pattern of results. In addition, there was a significantly lower risk of oesophagus (HR 0.71, 95% CI: 0.51, 0.97) cancers for participants who undertook 20-<40 MET-hours/week of physical activity compared to <10 MET-hours/week. Conversely, there was a significantly higher risk of prostate cancer for participants who undertook 40-<60 MET-hours/week of physical activity compared to <10 MET-hours/week (HR 1.13, 95% CI: 1.01, 1.25). Wald tests examining the overall significance of the categorised physical activity variable showed associations for lung ($p=0.002$), breast ($p=0.01$), colon (males; $p=0.04$), and rectum (males; $p=0.047$) cancers (Supplementary File 2, Table 2.1). After imputing missing data, only the associations between high levels of physical activity and lower risk of lung, and breast cancers remained significant, although associations were marginally significant for hepatobiliary tract, and colon cancers (Supplementary File 2, Table 2.4).

Tests for effect modification indicated that HR estimates for stomach cancer differed according to socio-economic status ($p=0.004$). HR estimates for rectum cancer (females) differed according to smoking status ($p<0.001$). HR estimates differed according to the combined body fat percentage and physical activity level for some cancer sites: lung ($p=0.01$), hepatobiliary tract ($p=0.009$), rectum (females) ($p<0.001$), and haematological malignancies ($p=0.003$). All other tests of effect modification were non-significant. Subgroup analyses are presented in Supplementary File 3, Tables 3.1-3.7.

The coefficients from the regression of standardised total MET-hrs/week at follow-up on the standardised baseline variable were 0.60 (SE 0.018) for those who undertook the first assessment <3 years post-baseline, 0.57 (SE 0.006) for the entire sub-sample at first follow-up (median 4.4 years

post-baseline), and 0.46 (SE 0.004) for the entire sub-sample at second follow-up (median 8.7 years post-baseline).

DISCUSSION

Our study shows that high levels of physical activity were inversely related to incident lung, breast, hepatobiliary tract, and colon cancers. Moderate physical activity levels were inversely related to lung, and oropharyngeal cancer incidence. When examining incident cases diagnosed at least two years after baseline, all associations were attenuated except for breast or lung cancer incidence. We also used restricted cubic splines to examine the shape of the dose-response curves for each cancer site, which suggested that the associations for lung and prostate cancers were curvilinear. There were also significant associations between dose-response curves and incident lung and breast cancers. Subgroup analyses indicated that for some cancer sites, associations differed according to socio-economic status, smoking status, and combined body fat percentage and physical activity level.

Strengths and limitations

Our study improves upon previous research by providing a broader overview of cancer risk. The UK Biobank study is representative of the UK population in terms of age, sex, ethnicity and deprivation for the targeted age group but is not representative in terms of obesity prevalence and comorbidities, potentially indicating a healthy volunteer selection bias [17,51,52]. This may limit the generalisability of our findings. However, the findings of recently published studies suggest that risk factor associations estimated from UK Biobank data are generalizable to England and Scotland [52,53]. Our models were also adjusted for a wide range of socio-demographic, health and behavioural variables, including BMI, which is hypothesized to be on the causal pathway between screen time and cancer incidence. Some have argued that this may lead to over-adjustment and therefore underestimation of the strength of the tested associations [54].

Our analysis relies on self-report physical activity data, which was measured using a well-validated questionnaire, but may be subject to response and recall bias [18]. Whilst the IPAQ-SF only measures activity lasting at least ten minutes, the most recent version of the UK Chief Medical Officers' Physical Activity Guidelines have removed the requirement for at least ten minutes of physical activity [55]. Furthermore, whilst the IPAQ-SF captures walking, moderate- and vigorous- physical activity across several domains (leisure-time, domestic and gardening, work-related, transport-related), it does not capture all possible forms of physical activity (e.g. light-intensity physical activity) [23] and previous research has shown the IPAQ-SF to be a weak measure of total physical activity when compared to objective measures [56]. Other systematic reviews and observational studies have tended to focus on examining the association of specific domains of physical activity (e.g. leisure-time physical activity, active commuting) with cancer incidence [15,17,18], and our estimates of 'total physical activity' may be greater by comparison. We were unable to examine the association between cancer incidence and accelerometer data as follow-up was too short (mean follow-up time 1.2 years). We estimated the extent of potential regression dilution bias (i.e. the bias which causes associations with baseline measurements of a risk factor to underestimate the true strength of associations with long-term average levels of the risk factor [57]) and found the magnitude of regression dilution over 3-9 years post-baseline to be fairly stable. Previous research has also demonstrated regression dilution bias which is reflected in the reduced ability of self-report measures (e.g. the IPAQ) to detect significant trends with some risk factors when compared to objective measures [58,59]. However, a study by Celis-Morales and colleagues showed similar overall patterns of physical activity and risk factor trends for both measurement approaches (e.g. IPAQ and accelerometer), and the authors suggested that such bias could potentially be overcome by studying larger cohorts (e.g. UK Biobank) [58].

The nature of the observational study means we cannot attribute causal interpretations to our results due to potential residual confounding. For example, in relation to our lung cancer findings, previous studies examining associations between physical activity and cancer incidence have highlighted the potential for residual confounding by smoking reflecting an inability to completely adjust for smoking

habits of current and former smokers [10,60]. However, we examined effect modification for all sites and found no evidence that effect estimates differed according to smoking status for lung cancer. Sensitivity analyses assessing robustness to unmeasured or uncontrolled confounding and selection bias suggested that fairly weak unobserved confounding or selection bias (relative risk<2) could potentially explain away the observed associations for lung, breast, and colon cancers [40,41]. However, it has been noted that E-value interpretation is dependent on context, particularly on the measured covariates for which adjustment has already been made [40]. Whilst we note that some of our models for specific cancer sites may have been impacted by unmeasured confounding (e.g. hepatitis disease for hepatobiliary cancers [61]), our models were adjusted for a very comprehensive set of covariates. During peer-review, our approach was critiqued for not applying causal inference methodologies. It is our opinion that further biological understanding of the associations shown is required to draw such conclusions. However, we accept that collider bias is possible due to potential bi-directional relationships between physical activity, the covariates included in our models, and cancer risk. This would affect the precision of the risk estimates shown.

Most significant associations were attenuated when excluding cancers diagnosed within the first two years of follow-up, suggesting that our results could have been affected by reverse causation bias. This accords with the findings of a recent study showing that results estimated from UK Biobank data are potentially affected by reverse causality [49]. However, this could also have been driven by the decrease in cases resulting from excluding cancers diagnosed over the 2-year period. Some sites had a small number of cases (e.g. stomach, thyroid), which limits our ability to make clear conclusions about the association of physical activity with cancer risk for these sites.

Relation of findings to previous research

Previous research has provided mixed findings regarding the relationship between physical activity and the risk of developing some of these cancers [4,62–66]. Mechanistically, higher levels of physical activity may reduce lung cancer risk via increased respiratory ventilation, reducing the concentration

of carcinogenic agents and duration of agent-air particle interaction time in the lungs [67]. For oropharyngeal cancers, circulating levels of insulin and growth factors, which are lowered through increased physical activity, may pass the blood-brain barrier and contribute to meningioma development [66]. Physical activity may also influence head and neck cancer risk through its effects on immune function [64] and on the content and composition of saliva via continuous contact with the oral cavity, pharynx and larynx [64]. For hepatobiliary cancers, potential mechanisms include beneficial effects on whole body weight and insulin sensitivity, reduced chronic inflammation, reduced liver fat stores (i.e. steatohepatitis), and the reduction of biliary stasis brought about by increased gallbladder motility [68–70]. Our findings are in accordance with previous research showing an inverse relationship between physical activity level and incident breast [10,13,15,71,72] and colon [7,10,72–74] cancers. Our findings are also supported by previous UK Biobank studies examining the association of physical activity, including studies using Mendelian Randomisation methods or accelerometer-derived physical activity levels, with breast or colon cancer incidence [7,75,76].

Whilst not significant in the main analysis, sensitivity analyses suggested that there may be an association between higher levels of physical activity (20-<40 MET-hours/week versus <10 MET-hours/week) and lower incidence of oesophagus cancers. A recently published UK Biobank study also showed a significant association between moderate physical activity levels and lower oesophageal adenocarcinoma incidence [21]. Reduced adiposity is one likely mechanism through which increased physical activity may lead to lower incidence rates of these cancers [21,77]. Paradoxically, our results also suggest that there may be an association between higher levels of physical activity (40-<60 MET-hours/week versus <10 MET-hours/week) and higher incidence of prostate cancer. Moore and colleagues also found a positive association between physical activity and prostate cancer risk in their pooled analysis of 12 cohort studies [10]. They propose that this may be due to a screening bias, whereby physically active men are more likely to elect to receive prostate-specific antigen screening, leading to a cancer diagnosis. By contrast, in their Mendelian-randomization study, Kazmi and colleagues find evidence for an inverse association between physical activity (measured as 'average

accelerations' but not other measures of physical activity) and overall prostate cancer risk [78]. When replicated using UK Biobank participants' accelerometer data, they found a consistent inverse direction of association of average acceleration with overall prostate cancer risk but with a non-significant p-value ($p=0.07$), noting that power was low for the UK Biobank analysis [78].

In contrast to the current literature, we found no association between physical activity level and rectum [10,16,79] or uterus [10,16,80,81] cancers. Moore and colleagues [10] found significant associations between higher physical activity levels and decreased risk of both rectum (HR 0.87, 95% CI: 0.80, 0.95), and endometrial (HR 0.79, 95% CI: 0.68, 0.92) cancers. However, our results are in line with the study conducted by Morris et al. which found no association between physical activity levels and rectal cancer risk for UK Biobank participants [7]. There were significant interactions for combined body fat percentage and physical activity level categories, socio-economic status, and smoking status for some cancer sites. Previous research has also supported the importance of physical activity and body fat percentage in contributing to disease morbidity and mortality [82] and that socio-economic status may be an important determinant of physical activity across the life course [83]. For UK Biobank participants, previous studies have shown there may be an association between smoking status and obesity [84].

Implications for clinicians and policymakers

Our findings suggest that, high levels of physical activity in particular are significantly associated with reduced cancer risk at several sites. High levels of physical activity equate to at least three days/week of vigorous-intensity physical activity achieving 1,500 MET-minutes, or at least seven days/week spent in any combination of walking, moderate- or vigorous-intensity physical activity achieving 3,000 MET-minutes. The current UK Physical Activity Guidelines [55] recommend at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity (or combined equivalent) physical activity/week for health benefits which equates to the 'moderate' level of physical activity in our study. However, the recent US physical activity guidance [85] recommends the need for 150-300

minutes of moderate-intensity physical activity/week (during leisure-time) for cancer prevention and suggests that additional risk reduction can be achieved for some site-specific cancers by increasing to over 300 minutes. Our results, examining the association of a self-report measure of total physical activity with cancer incidence, provide further supporting evidence that higher levels of physical activity may be required for cancer prevention.

Population rates of physical inactivity are high, with 39% of adults in the UK not meeting minimum recommendations [86]. Our evidence supports promoting a higher level of physical activity for cancer prevention (as opposed to general public health benefits for which moderate levels of physical activity are usually recommended) and therefore represents a major challenge for policymakers and practitioners involved in the promotion of physical activity.

Implications for future research

Whilst the UK Biobank has collected data on objectively-measured physical activity and sedentary behaviour from a subsample of participants (n=98,720) using wrist-worn triaxial accelerometers, we were unable to make use of this data due to the short follow-up time (2013-2015) [87], which does not allow reverse causation to be ruled out [88,89]. Future research can generate a better understanding of the magnitude of the underlying associations between physical activity and cancer risk, particularly by intensity of activity, by evaluating the risk of developing these cancers in relation to accelerometer-derived physical activity.

CONCLUSION

Our results support that high or moderate levels of physical activity were associated with lower cancer risk at five of the 20 cancer sites examined (oropharyngeal, lung, breast, hepatobiliary tract, and colon cancers). Restricted cubic splines were used to examine the shape of the dose-response curves for each cancer site, and suggested that the associations for lung and prostate cancers were curvilinear. When excluding cancers diagnosed within the first two years of follow-up, all associations were

attenuated except for lung, and breast cancer incidence. Subgroup analyses indicated that associations varied depending on socio-economic status, smoking status or the combined body fat percentage and physical activity level category for some sites. These findings support the promotion of physical activity in cancer prevention, particularly high levels of physical activity.

SUPPLEMENTARY FILES

Supplementary file 1: Restricted cubic splines analyses.

Supplementary file 2: Sensitivity analyses.

Supplementary file 3: Subgroup analyses.

Ethics approval and consent to participate: UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

Consent for publication: Not applicable.

Data sharing: Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Conflict of interest: The authors declare they have no competing interests.

Funding: The UK Biobank was supported by the Wellcome Trust; Medical Research Council; Department of Health; Scottish government; and Northwest Regional Development Agency. It has also had funding from the Welsh Assembly government; and British Heart Foundation. The research was designed, conducted, analysed, and interpreted by the authors entirely independently of the funding sources. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

466 **Authors' Contributions:** RFH and HGC had the initial idea for the study. JMM, HGC and RFH
467 contributed to the design of the study, advised on all statistical aspects, and interpreted the data.
468 JMM performed the statistical analysis. JMM and RFH drafted the manuscript. JMM, HGC and RFH
469 reviewed the manuscript and approved the final version to be published. JMM, HGC and RFH had full
470 access to all of the data in the study and take responsibility for the integrity of the data and the
471 accuracy of the data analysis. RFH is the guarantor.

472 **Acknowledgements:** This research was conducted using the UK Biobank resource. We thank the
473 participants of the UK Biobank. The authors would like to thank Dr. Christopher R. Cardwell (Queen's
474 University Belfast) for providing on-going advice on conducting and interpreting statistical analyses.

475 **Table 1. Coding of cancer outcomes according to the International Classification of Diseases 9th**
 476 **and 10th revisions**

Cancer site	ICD-10 codes	ICD-9 codes
All cancers (excluding non-melanoma skin cancer)	C00-C97 excluding C44	140-209 excluding 173
Melanoma	C43	172
Oropharyngeal	C00-C14	140-149
Lung	C33-C34	162
Breast (female only)	C50	174
Uterus	C54	182
Ovary	C56	183
Prostate	C61	185
Oesophagus	C15	150
Stomach	C16	151
Hepatobiliary tract	C22-C24	155-156
Pancreatic	C25	157
Kidney	C64-C65	189.0-189.1
Bladder	C66-C67	188, 189.2
Colorectal	C18-C21	153-154
Colon	C18	153
Rectum	C19-C20	1540-1541
Brain tumours	C71	191
Thyroid	C73	193
Haematological malignancies	C81-C96	200-208
Non-Hodgkin's lymphoma	C82-C85	200, 202

477

478 **Table 2. Baseline characteristics by IPAQ physical activity category. Values are numbers and**
 479 **percentages unless otherwise stated.**

	Physical activity categories							
	Total		Low		Moderate		High	
	No./mean	%/SD	No./mean	%/SD	No./mean	%/SD	No./mean	%/SD
Total participants	364,899	100%	63,221	17.3%	151,605	41.6%	150,073	41.1%
IPAQ physical activity (mean/SD)								
Minutes of walking	314.4	326.4	61.3	62.3	222.6	159.4	513.8	395.6
Minutes of moderate-intensity physical activity	233.4	303.2	20.5	37.8	112.8	112.4	445.1	362.8
Minutes of vigorous-intensity physical activity	85.7	146.8	4.8	15.8	29.0	40.5	177.1	190.5
Age at baseline (mean/SD)	56.0	8.1	55.4	7.9	56.2	8.1	56.1	8.3
Height (m) (mean/SD)	1.69	0.09	1.69	0.09	1.69	0.09	1.69	0.09
Sex								
Female	188,263	51.6%	31,669	50.1%	82,382	54.3%	74,212	49.5%
Male	176,636	48.4%	31,552	49.9%	69,223	45.7%	75,861	50.6%
Ethnicity								
White	345,610	95.0%	59,219	93.9%	143,952	95.2%	142,439	95.2%
Black	5,394	1.5%	1,072	1.7%	2,071	1.4%	2,251	1.5%
South Asian	6,479	1.8%	1,498	2.4%	2,609	1.7%	2,372	1.6%
Chinese	1,143	0.3%	224	0.4%	479	0.3%	440	0.3%
Mixed background or others	5,203	1.4%	1,028	1.6%	2,074	1.4%	2,101	1.4%
Townsend deprivation quintile								
1 (Least deprived)	75,836	20.8%	13,375	21.2%	32,047	21.2%	30,414	20.3%
2	74,472	20.4%	12,837	20.3%	31,050	20.5%	30,585	20.4%
3	73,585	20.2%	12,599	20.0%	30,481	20.1%	30,505	20.4%
4	72,698	20.0%	12,339	19.6%	30,113	19.9%	30,246	20.2%
5 (Most deprived)	67,847	18.6%	11,974	19.0%	27,727	18.3%	28,146	18.8%
Education								
University degree	131,367	36.2%	22,961	36.5%	58,986	39.1%	49,420	33.2%
A-levels/HNC/HND/NVQ	67,142	18.5%	11,683	18.6%	27,671	18.4%	27,788	18.7%
GCSE/O-level/CSE	96,088	26.5%	16,712	26.6%	38,353	25.4%	41,023	27.5%
Other	18,354	5.1%	3,031	4.8%	7,495	5.0%	7,828	5.3%
None	49,718	13.7%	8,462	13.5%	18,328	12.2%	22,928	15.4%
Smoking status^a								
Never	200,571	55.1%	34,091	54.1%	84,763	56.0%	81,717	54.6%
Former light smoker	94,181	25.9%	14,949	23.7%	38,963	25.8%	40,269	26.9%
Former heavy smoker	32,301	8.9%	6,262	9.9%	12,914	8.5%	13,125	8.8%
Current light smoker	21,278	5.9%	4,032	6.4%	8,557	5.7%	8,689	5.8%
Current heavy smoker	15,666	4.3%	3,698	5.9%	6,067	4.0%	5,901	3.9%
Alcohol intake								
Never	13,999	3.8%	2,940	4.7%	5,633	3.7%	5,426	3.6%
Former drinker	12,130	3.3%	2,490	3.9%	4,686	3.1%	4,954	3.3%
Current drinker: <once/week	77,880	21.4%	14,920	23.6%	31,867	21.0%	31,093	20.7%
Current drinker: ≥once/week	260,716	71.5%	42,835	67.8%	109,362	72.2%	108,519	72.4%
Dietary intake (mean/SD)								
Fruits and vegetables (portion/day)	4.8	3.1	4.0	2.6	4.6	2.8	5.2	3.4
Red meat (portion/week)	2.1	1.4	2.2	1.4	2.1	1.4	2.1	1.5
Processed meat (portion/week)	1.5	1.4	1.6	1.4	1.5	1.4	1.4	1.4
Body Mass Index (Kg/m²) (mean/SD)	27.3	4.7	28.5	5.4	27.2	4.6	26.8	4.3
Body Mass Index (Kg/m²)								

	<18.5	1,808	0.5%	268	0.4%	790	0.5%	750	0.5%
	18.5-<25	121,478	33.4%	16,224	25.9%	50,421	33.4%	54,833	36.7%
	25-<30	156,156	43.0%	25,760	41.1%	65,187	43.2%	65,209	43.6%
	30+	83,947	23.1%	20,494	32.7%	34,673	23.0%	28,780	19.2%
Body fat percentage (mean/SD)		30.8	8.4	32.6	8.6	31.4	8.3	29.6	8.3
Waist:hip ratio^b									
Waist:hip ratio (mean/SD)		0.87	0.09	0.89	0.09	0.87	0.09	0.87	0.09
Below IDF guideline		162,712	44.7%	21,318	33.9%	65,428	43.3%	75,966	50.7%
Above IDF guideline		201,214	55.3%	41,627	66.1%	85,830	56.7%	73,757	49.3%
Health status									
Diabetes ^c		17,741	4.9%	4,439	7.1%	7,319	4.8%	5,983	4.0%
Gastro-oesophageal reflux ^d		16,859	4.6%	3,502	5.6%	6,976	4.6%	6,381	4.3%
Family history^e									
Prostate cancer		29,339	8.2%	5,086	8.2%	12,224	8.2%	12,029	8.1%
Breast cancer		38,642	10.8%	6,736	10.8%	16,128	10.8%	15,778	10.7%
Lung cancer		44,995	12.5%	7,751	12.5%	18,399	12.3%	18,845	12.8%
Bowel cancer		40,660	11.3%	7,104	11.4%	16,736	11.2%	16,820	11.4%
Use of sun/UV protection									
Never/rarely/sometimes		157,513	43.2%	29,328	46.5%	64,275	42.4%	63,910	42.6%
Most of the time/always		205,137	56.3%	33,123	52.5%	86,464	57.1%	85,550	57.1%
Do not go out in sunshine		1,826	0.5%	628	1.0%	712	0.5%	486	0.3%
Aspirin use									
Regularly uses aspirin ^f		49,364	13.7%	9,547	15.3%	20,666	13.8%	19,151	12.9%
HRT use^g									
Ever used HRT		68,342	36.4%	11,306	35.9%	29,636	36.1%	27,400	37.0%
Oral contraceptive use^g									
Ever taken oral contraceptive pill		155,518	82.8%	26,616	84.3%	67,928	82.6%	60,974	82.3%
Number of live births (0, 1, 2, 3+ live births)^g(mean/SD)		1.78	1.19	1.75	1.20	1.76	1.18	1.82	1.20
Age at menarche (mean/SD)^g		13.0	1.6	12.9	1.6	13.0	1.6	13.0	1.6
Age at menopause (mean/SD)^g		49.8	5.0	49.7	5.1	49.9	4.9	49.8	5.1
Menopausal status^g									
Had menopause		110,013	58.5%	17,459	55.2%	48,607	59.1%	43,947	59.3%
Not had menopause		50,150	26.7%	8,834	27.9%	21,767	26.5%	19,549	26.4%
Unsure		27,886	14.8%	5,326	16.8%	11,911	14.5%	10,649	14.4%
Hysterectomy status^g									
Had hysterectomy		12,328	7.3%	1,959	7.0%	5,151	7.0%	5,218	7.8%
Not had hysterectomy/unsure		156,729	92.7%	26,092	93.0%	69,004	93.1%	61,633	92.2%

HRT: hormone-replacement therapy; IDF: International Diabetes Federation; MVPA: moderate-vigorous intensity physical activity; UV: ultraviolet.

^aDefined in terms of pack-years: light (<20 pack-years), heavy (≥20 pack-years).

^bBased on IDF criteria (waist circumference >94cm in men; >80cm in women).

^cDiagnosed by doctor.

^dSelf-reported.

^eBased on self-reported illnesses of father, mother and siblings.

^fRegular use defined as most days of the week for the last 4 weeks.

^gFemale participants only.

489 **Table 3. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity categories and cancer**
 490 **incidence.**

		Physical activity categories~				Wald test	Total MET hrs/week	p-value
		Low	Moderate	High	p-trend			
Person-years		432,176	1,033,729	1,021,349				
Skin, melanoma	Cases	199	533	510			1,242	
	HR (95% CI)*	1.00	1.08 (0.92, 1.27)	1.06 (0.90, 1.24)	0.66**	p=0.66	0.9999 (0.999, 1.001)	0.86**
	HR (95% CI)†	1.00	1.06 (0.90, 1.25)	1.04 (0.88, 1.23)	0.72	p=0.79	1.0002 (0.999, 1.001)	0.77
	HR (95% CI) ^a	1.00	1.05 (0.89, 1.24)	1.03 (0.88, 1.22)	0.80	p=0.84	1.0002 (0.999, 1.002)	0.74
Oropharyngeal	Cases	90	148	168			406	
	HR (95% CI)*	1.00	0.70 (0.54, 0.91)	0.82 (0.63, 1.05)	0.33	p=0.03	0.999 (0.997, 1.001)	0.28
	HR (95% CI)†	1.00	0.71 (0.55, 0.93)	0.79 (0.61, 1.03)	0.21	p=0.04	0.998 (0.996, 1.0002)	0.08
	HR (95% CI)	1.00	0.71 (0.55, 0.93)	0.79 (0.61, 1.03)	0.21	p=0.04	0.998 (0.996, 1.0002)	0.08
Lung	Cases	284	550	513			1,347	
	HR (95% CI)*	1.00	0.72 (0.63, 0.83)	0.69 (0.69, 0.79)	<0.001	p<0.001	0.999 (0.998, 1.0002)	0.09**
	HR (95% CI)† ⁱ	1.00	0.86 (0.74, 0.99)	0.81 (0.70, 0.94)	0.009**	p=0.02	0.999 (0.997, 0.9999)	0.03
	HR (95% CI) ^h	1.00	0.86 (0.74, 0.99)	0.81 (0.70, 0.94)	0.007	p=0.02	0.999 (0.997, 0.9998)	0.03
Breast (female only)	Cases	623	1,560	1,251			3,434	
	HR (95% CI)*	1.00	0.92 (0.84, 0.998)	0.82 (0.75, 0.89)	<0.001	p<0.001	0.998 (0.997, 0.999)	<0.001
	HR (95% CI)†	1.00	0.93 (0.85, 1.01)	0.85 (0.77, 0.93)	<0.001**	p<0.001	0.999 (0.998, 0.999)	0.001**
	HR (95% CI) ^{b, i}	1.00	0.94 (0.86, 1.03)	0.85 (0.77, 0.94)	0.001	p=0.003	0.999 (0.998, 0.999)	0.001**
Uterus	HR (95% CI) ^{b, h}	1.00	0.94 (0.86, 1.03)	0.85 (0.77, 0.94)	0.001	p=0.003	0.999 (0.998, 0.9995)	0.003
	Cases	112	254	197			563	
	HR (95% CI)*	1.00	0.80 (0.65, 0.99)	0.67 (0.54, 0.84)	<0.001	p=0.002	0.997 (0.995, 0.999)	0.004
	HR (95% CI)†	1.00	0.98 (0.79, 1.22)	0.92 (0.73, 1.16)	0.43	p=0.71	0.999 (0.997, 1.001)	0.47
Ovary	HR (95% CI) ^c	1.00	0.98 (0.78, 1.23)	0.94 (0.74, 1.19)	0.58	p=0.85	0.9997 (0.997, 1.002)	0.76**
	Cases	65	170	169			404	
	HR (95% CI)*	1.00	0.94 (0.71, 1.24)	1.03 (0.78, 1.37)	0.62	p=0.65	1.002 (0.999, 1.004)	0.14
	HR (95% CI)†	1.00	0.97 (0.73, 1.30)	1.08 (0.81, 1.45)	0.46	p=0.62	1.002 (0.9996, 1.004)	0.10

Prostate	HR (95% CI)	1.00	0.97 (0.73, 1.30)	1.08 (0.81, 1.45)	0.46	p=0.62	1.002 (0.9996, 1.004)	0.10
	Cases	734	1,877	1,981			4,592	
	HR (95% CI)*	1.00	1.06 (0.97, 1.15)	1.06 (0.98, 1.15)	0.22	p=0.34	1.0001 (0.9995, 1.001)	0.73
	HR (95% CI)†, i	1.00	1.02 (0.94, 1.11)	1.03 (0.95, 1.13)	0.45	p=0.75	1.0001 (0.9995, 1.001)	0.66
Oesophagus	HR (95% CI)h	1.00	1.02 (0.94, 1.12)	1.04 (0.95, 1.13)	0.44**	p=0.73	1.0001 (0.9995, 1.001)	0.72**
	Cases	74	140	166			380	
	HR (95% CI)*	1.00	0.77 (0.58, 1.01)	0.88 (0.67, 1.15)	0.67	p=0.15	1.001 (0.999, 1.003)	0.38
	HR (95% CI)†, i	1.00	0.86 (0.64, 1.14)	1.04 (0.78, 1.37)	0.50	p=0.23	1.001 (0.999, 1.003)	0.33
Stomach	HR (95% CI)f	1.00	0.86 (0.65, 1.14)	1.05 (0.79, 1.39)	0.43	p=0.20	1.001 (0.999, 1.003)	0.28
	Cases	53	108	104			265	
	HR (95% CI)*	1.00	0.81 (0.59, 1.12)	0.79 (0.57, 1.09)	0.19	p=0.32	1.0001 (0.998, 1.003)	0.93
	HR (95% CI)†	1.00	0.88 (0.63, 1.23)	0.82 (0.59, 1.15)	0.27	p=0.52	0.9995 (0.997, 1.002)	0.72
Hepatobiliary tract	HR (95% CI)	1.00	0.88 (0.63, 1.23)	0.82 (0.59, 1.15)	0.27	p=0.52	0.9995 (0.997, 1.002)	0.72
	Cases	72	137	116			325	
	HR (95% CI)*	1.00	0.73 (0.55, 0.96)	0.62 (0.47, 0.83)	0.002**	p=0.006	0.998 (0.995, 1.001)	0.15**
	HR (95% CI)†	1.00	0.84 (0.63, 1.12)	0.72 (0.53, 0.97)	0.03**	p=0.10	0.998 (0.996, 1.001)	0.22**
Pancreatic	HR (95% CI)	1.00	0.84 (0.63, 1.12)	0.72 (0.53, 0.97)	0.03**	p=0.10	0.998 (0.996, 1.001)	0.22**
	Cases	90	187	183			460	
	HR (95% CI)*	1.00	0.80 (0.62, 1.02)	0.81 (0.63, 1.04)	0.17	p=0.16	0.9998 (0.998, 1.002)	0.88
	HR (95% CI)†	1.00	0.89 (0.69, 1.14)	0.92 (0.71, 1.20)	0.69	p=0.65	1.001 (0.998, 1.003)	0.62
Kidney	HR (95% CI)d	1.00	0.89 (0.69, 1.15)	0.94 (0.72, 1.22)	0.77	p=0.69	1.001 (0.999, 1.003)	0.54
	Cases	106	248	208			562	
	HR (95% CI)*	1.00	0.91 (0.73, 1.13)	0.77 (0.61, 0.96)	0.01	p=0.048	0.999 (0.997, 1.001)	0.46
	HR (95% CI)†	1.00	1.06 (0.84, 1.33)	0.92 (0.72, 1.17)	0.34	p=0.34	1.0001 (0.998, 1.002)	0.95
Bladder	HR (95% CI)	1.00	1.06 (0.84, 1.33)	0.92 (0.72, 1.17)	0.34	p=0.34	1.0001 (0.998, 1.002)	0.95
	Cases	82	205	210			497	
	HR (95% CI)*	1.00	0.99 (0.77, 1.28)	0.97 (0.75, 1.25)	0.79	p=0.96	1.0001 (0.998, 1.002)	0.93
	HR (95% CI)†	1.00	1.07 (0.82, 1.38)	1.07 (0.83, 1.39)	0.65**	p=0.86	1.0003 (0.998, 1.002)	0.78**
	HR (95% CI)	1.00	1.07 (0.82, 1.38)	1.07 (0.83, 1.39)	0.65**	p=0.86	1.0003 (0.998, 1.002)	0.78**

Colorectal	Cases	423	996	961			2,380	
	HR (95% CI)*	1.00	0.92 (0.82, 1.03)	0.89 (0.79, 0.99)	0.04**	p=0.11	0.999 (0.998, 1.0001)	0.08**
	HR (95% CI)†	1.00	0.95 (0.85, 1.06)	0.93 (0.83, 1.05)	0.27	p=0.49	0.999 (0.999, 1.0004)	0.29**
	HR (95% CI) ^{e, g, i}	1.00	0.95 (0.85, 1.07)	0.95 (0.84, 1.06)	0.41	p=0.50 (females); p=0.83 (males)	1.000 (0.999, 1.001)	0.41
	HR (95% CI) ^{e, f(males), g}	1.00	0.96 (0.85, 1.07)	0.95 (0.85, 1.07)	0.48	p=0.50 (females); p=0.85 (males)	1.000 (0.999, 1.001)	0.41
Colon	Cases	285	649	580			1,514	
	HR (95% CI)*	1.00	0.87 (0.76, 0.99)	0.78 (0.68, 0.90)	<0.001**	p=0.002	0.998 (0.997, 0.999)	0.001**
	HR (95% CI)†	1.00	0.90 (0.79, 1.04)	0.83 (0.72, 0.96)	0.01**	p=0.04	0.998 (0.997, 0.9996)	0.009**
	HR (95% CI) ^{e, g, i}	1.00	0.92 (0.80, 1.06)	0.85 (0.74, 0.99)	0.03	p=0.56 (females); p=0.12 (males)	0.999 (0.997, 1.000)	0.02**
	HR (95% CI) ^{e, f(males), g}	1.00	0.92 (0.80, 1.06)	0.86 (0.74, 0.99)	0.04	p=0.56 (females); p=0.15 (males)	0.999 (0.997, 1.000)	0.02**
Rectum	Cases	130	324	358			812	
	HR (95% CI)*	1.00	1.02 (0.84, 1.24)	1.11 (0.91, 1.35)	0.20	p=0.40	1.001 (0.999, 1.002)	0.29**
	HR (95% CI)†	1.00	1.04 (0.85, 1.28)	1.15 (0.94, 1.41)	0.13	p=0.29	1.001 (0.9996, 1.003)	0.16
	HR (95% CI) ^{e, g, i}	1.00	1.02 (0.83, 1.25)	1.14 (0.93, 1.40)	0.13	p=0.69 (females); p=0.08 (males)	1.001 (1.000, 1.003)	0.18
	HR (95% CI) ^{e, f(males), g}	1.00	1.02 (0.83, 1.26)	1.15 (0.93, 1.41)	0.11	p=0.69 (females); p=0.06 (males)	1.001 (1.000, 1.003)	0.15
Brain tumours	Cases	63	141	137			341	
	HR (95% CI)*	1.00	0.93 (0.69, 1.25)	0.89 (0.66, 1.19)	0.44	p=0.74	0.999 (0.996, 1.001)	0.35
	HR (95% CI)†	1.00	0.90 (0.67, 1.21)	0.87 (0.64, 1.18)	0.40	p=0.66	0.998 (0.996, 1.001)	0.24
	HR (95% CI)	1.00	0.90 (0.67, 1.21)	0.87 (0.64, 1.18)	0.40	p=0.66	0.998 (0.996, 1.001)	0.24
Thyroid	Cases	33	72	74			179	
	HR (95% CI)*	1.00	0.90 (0.59, 1.35)	0.97 (0.64, 1.46)	0.99	p=0.83	0.9996 (0.996, 1.003)	0.80
	HR (95% CI)†	1.00	0.89 (0.59, 1.35)	0.997 (0.65, 1.52)	0.85	p=0.75	1.0002 (0.997, 1.004)	0.91
	HR (95% CI)	1.00	0.89 (0.59, 1.35)	0.997 (0.65, 1.52)	0.85	p=0.75	1.0002 (0.997, 1.004)	0.91

Haematological malignancies	Cases	316	742	719			1,777	
	HR (95% CI)*	1.00	0.93 (0.81, 1.05)	0.90 (0.79, 1.02)	0.12	p=0.27	0.9998 (0.999, 1.001)	0.72
	HR (95% CI)†	1.00	0.94 (0.82, 1.07)	0.93 (0.81, 1.06)	0.32	p=0.53	1.0001 (0.999, 1.001)	0.83
	HR (95% CI)	1.00	0.94 (0.82, 1.07)	0.93 (0.81, 1.06)	0.32	p=0.53	1.0001 (0.999, 1.001)	0.83
Non-Hodgkin's lymphoma	Cases	152	350	356			858	
	HR (95% CI)*	1.00	0.89 (0.74, 1.07)	0.91 (0.76, 1.10)	0.48	p=0.47	0.9996 (0.998, 1.001)	0.63
	HR (95% CI)†	1.00	0.92 (0.76, 1.11)	0.96 (0.79, 1.17)	0.88	p=0.66	1.0001 (0.999, 1.002)	0.90
	HR (95% CI)	1.00	0.92 (0.76, 1.11)	0.96 (0.79, 1.17)	0.88	p=0.66	1.0001 (0.999, 1.002)	0.90

*Models adjusted for age and sex (total observations=364,899).

†Models adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).

^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).

^gResults for males and females combined using meta-analysis as covariates are different.

^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

ⁱFinal model indicated by the modified change-in-estimate criterion.

~Number of cases are based on final models.

**Schoenfeld test indicated potential violation of the proportional hazards assumption (p<0.05).

Table 4. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity categories and cancer incidence (excluding cancers diagnosed within the first 2 years following baseline).

		Physical activity categories			p-trend	Wald test
		Low	Moderate	High		
Skin, melanoma	Cases	160	395	375		
	HR (95% CI) ^a	1.00	0.97 (0.81, 1.17)	0.96 (0.79, 1.16)	0.64	p=0.90
Oropharyngeal	Cases	63	120	129		
	HR (95% CI)	1.00	0.84 (0.62, 1.15)	0.89 (0.65, 1.21)	0.60**	p=0.56
Lung	Cases	222	444	412		
	HR (95% CI) ^h	1.00	0.90 (0.76, 1.05)	0.85 (0.72, 0.999)	0.06**	p=0.14
Breast (female only)	Cases	451	1,164	925		
	HR (95% CI) ^{b, h}	1.00	0.98 (0.88, 1.10)	0.89 (0.79, 0.997)	0.02**	p=0.04
Uterus	Cases	84	191	151		
	HR (95% CI) ^c	1.00	0.97 (0.75, 1.26)	0.95 (0.72, 1.25)	0.70	p=0.93
Ovary	Cases	50	128	116		
	HR (95% CI)	1.00	0.95 (0.69, 1.33)	0.96 (0.68, 1.35)	0.85	p=0.96
Prostate	Cases	540	1,449	1,501		
	HR (95% CI) ^h	1.00	1.09 (0.98, 1.20)	1.08 (0.98, 1.19)	0.23**	p=0.24
Oesophagus	Cases	59	100	135		
	HR (95% CI) ^f	1.00	0.78 (0.56, 1.07)	1.09 (0.80, 1.50)	0.24**	p=0.03
Stomach	Cases	36	86	81		
	HR (95% CI)	1.00	1.03 (0.69, 1.52)	0.94 (0.63, 1.41)	0.70	p=0.87
Hepatobiliary tract	Cases	53	113	90		
	HR (95% CI)	1.00	0.96 (0.69, 1.34)	0.77 (0.54, 1.09)	0.10**	p=0.21
Pancreatic	Cases	73	155	148		
	HR (95% CI) ^d	1.00	0.93 (0.70, 1.23)	0.95 (0.71, 1.26)	0.78	p=0.87
Kidney	Cases	87	194	162		
	HR (95% CI)	1.00	1.02 (0.79, 1.31)	0.87 (0.67, 1.14)	0.23	p=0.34
Bladder	Cases	59	155	149		
	HR (95% CI)	1.00	1.16 (0.86, 1.57)	1.11 (0.81, 1.51)	0.68**	p=0.63
Colorectal	Cases	319	733	714		
	HR (95% CI) ^{e, f(males), g}	1.00	0.94 (0.82, 1.07)	0.95 (0.83, 1.08)	0.54	p=0.59 (females); p=0.53 (males)
Colon	Cases	213	477	437		
	HR (95% CI) ^{e, f(males), g}	1.00	0.91 (0.78, 1.08)	0.88 (0.74, 1.04)	0.13	p=0.83 (females); p=0.27 (males)
Rectum	Cases	99	236	264		
	HR (95% CI) ^{e, f(males), g}	1.00	0.98 (0.77, 1.24)	1.12 (0.88, 1.41)	0.22	p=0.84 (females); p=0.11 (males)
Brain tumours	Cases	48	107	106		
	HR (95% CI)	1.00	0.89 (0.63, 1.26)	0.87 (0.62, 1.24)	0.50	p=0.74
Thyroid	Cases	22	55	51		

	HR (95% CI)	1.00	1.03 (0.62, 1.69)	1.02 (0.61, 1.71)	0.95	p=0.99
Haematological malignancies	Cases	254	559	544		
	HR (95% CI)	1.00	0.88 (0.76, 1.02)	0.88 (0.75, 1.02)	0.15	p=0.19
Non-Hodgkin's lymphoma	Cases	115	266	272		
	HR (95% CI)	1.00	0.92 (0.74, 1.15)	0.98 (0.78, 1.22)	0.99	p=0.73

All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).

^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).

^gResults for males and females combined using meta-analysis as covariates are different.

^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

**Schoenfeld test indicated potential violation of the proportional hazards assumption (p<0.05).

543 **Table 5. Non-linear associations between IPAQ-measured physical activity and cancer.**

		Cases	Total physical activity (MET hours/week), HR (95% CI)						Wald test
			0 MET hours/week (ref)	5 th percentile (2.75 MET hours/week)	27.5 th percentile (15.25 MET hours/week)	50 th percentile (29.9 MET hours/week)	72.5 th percentile (55.1 MET hours/week)	95 th percentile (135.1 MET hours/week)	
Skin, melanoma	Baseline model	1,265	1.00	1.00 (0.95, 1.06)	1.03 (0.79, 1.33)	1.09 (0.87, 1.38)	1.12 (0.90, 1.39)	1.02 (0.79, 1.31)	p=0.61**
	Final model ^a	1,242	1.00	0.99 (0.94, 1.06)	0.98 (0.75, 1.28)	1.02 (0.80, 1.30)	1.05 (0.84, 1.32)	1.02 (0.79, 1.33)	p=0.91
Oropharyngeal	Baseline model	416	1.00	0.90 (0.82, 0.99)	0.62 (0.41, 0.94)	0.62 (0.43, 0.89)	0.72 (0.52, 1.00)	0.64 (0.43, 0.95)	p=0.08
	Final model	406	1.00	0.92 (0.84, 1.01)	0.68 (0.45, 1.03)	0.67 (0.46, 0.96)	0.73 (0.52, 1.03)	0.61 (0.40, 0.92)	p=0.11
Lung	Baseline model	1,442	1.00	0.89 (0.84, 0.93)	0.56 (0.45, 0.69)	0.50 (0.41, 0.60)	0.49 (0.41, 0.59)	0.57 (0.47, 0.70)	p<0.001**
	Final model ^h	1,347	1.00	0.95 (0.91, 1.01)	0.79 (0.63, 0.99)	0.72 (0.59, 0.88)	0.69 (0.57, 0.83)	0.71 (0.57, 0.88)	p=0.002**
Breast (female only)	Baseline model	4,171	1.00	0.98 (0.95, 1.01)	0.90 (0.79, 1.03)	0.88 (0.78, 0.99)	0.80 (0.71, 0.90)	0.76 (0.66, 0.87)	p<0.001
	Final model ^{b, h}	3,821	1.00	0.98 (0.95, 1.02)	0.92 (0.79, 1.07)	0.91 (0.79, 1.05)	0.85 (0.74, 0.96)	0.80 (0.68, 0.94)	p=0.01**
Uterus	Baseline model	624	1.00	0.97 (0.90, 1.04)	0.83 (0.59, 1.16)	0.69 (0.51, 0.93)	0.65 (0.49, 0.87)	0.61 (0.43, 0.88)	p=0.005
	Final model ^c	564	1.00	1.03 (0.95, 1.12)	1.12 (0.78, 1.62)	1.00 (0.72, 1.39)	1.00 (0.73, 1.36)	1.04 (0.71, 1.54)	p=0.86
Ovary	Baseline model	414	1.00	0.92 (0.83, 1.01)	0.67 (0.43, 1.05)	0.72 (0.48, 1.06)	0.81 (0.57, 1.17)	0.93 (0.61, 1.42)	p=0.20
	Final model	404	1.00	0.93 (0.84, 1.03)	0.73 (0.46, 1.15)	0.77 (0.51, 1.15)	0.86 (0.59, 1.26)	1.00 (0.65, 1.55)	p=0.28
Prostate	Baseline model	4,802	1.00	1.02 (0.98, 1.05)	1.09 (0.96, 1.25)	1.20 (1.06, 1.35)	1.15 (1.03, 1.28)	1.08 (0.95, 1.23)	p=0.005
	Final model ^h	4,592	1.00	1.00 (0.97, 1.04)	1.03 (0.90, 1.19)	1.12 (0.99, 1.27)	1.08 (0.96, 1.22)	1.04 (0.91, 1.19)	p=0.09**
Oesophagus	Baseline model	396	1.00	0.93 (0.84, 1.02)	0.68 (0.44, 1.05)	0.59 (0.40, 0.87)	0.65 (0.46, 0.93)	0.84 (0.57, 1.25)	p=0.04
	Final model ^f	380	1.00	0.97 (0.87, 1.07)	0.83 (0.53, 1.29)	0.74 (0.50, 1.10)	0.85 (0.59, 1.22)	1.03 (0.68, 1.57)	p=0.31
Stomach	Baseline model	275	1.00	0.86 (0.76, 0.97)	0.50 (0.30, 0.84)	0.55 (0.35, 0.86)	0.62 (0.42, 0.94)	0.64 (0.40, 1.03)	p=0.11
	Final model	265	1.00	0.90 (0.79, 1.01)	0.61 (0.36, 1.02)	0.65 (0.41, 1.04)	0.75 (0.49, 1.14)	0.69 (0.42, 1.14)	p=0.36
Hepatobiliary tract	Baseline model	333	1.00	0.91 (0.82, 1.01)	0.64 (0.41, 1.01)	0.57 (0.38, 0.86)	0.55 (0.38, 0.79)	0.58 (0.37, 0.89)	p=0.03**
	Final model	325	1.00	0.97 (0.88, 1.08)	0.87 (0.55, 1.38)	0.77 (0.51, 1.17)	0.71 (0.48, 1.04)	0.73 (0.46, 1.15)	p=0.37**
Pancreatic	Baseline model	474	1.00	0.97 (0.89, 1.06)	0.83 (0.55, 1.23)	0.66 (0.46, 0.94)	0.69 (0.50, 0.96)	0.85 (0.58, 1.24)	p=0.07
	Final model ^d	460	1.00	1.00 (0.91, 1.10)	0.96 (0.64, 1.44)	0.79 (0.55, 1.14)	0.85 (0.61, 1.20)	1.05 (0.71, 1.56)	p=0.32
Kidney	Baseline model	584	1.00	0.95 (0.87, 1.03)	0.78 (0.54, 1.12)	0.82 (0.60, 1.13)	0.75 (0.56, 1.00)	0.74 (0.52, 1.05)	p=0.26
	Final model	562	1.00	0.99 (0.91, 1.08)	0.98 (0.68, 1.42)	1.04 (0.75, 1.45)	0.96 (0.71, 1.31)	0.96 (0.67, 1.38)	p=0.80
Bladder	Baseline model	514	1.00	1.06 (0.96, 1.16)	1.26 (0.83, 1.91)	1.08 (0.74, 1.57)	1.10 (0.78, 1.56)	1.20 (0.80, 1.78)	p=0.67

Colorectal	Final model	497	1.00	1.09 (0.99, 1.20)	1.44 (0.94, 2.20)	1.28 (0.87, 1.89)	1.30 (0.90, 1.86)	1.37 (0.91, 2.06)	p=0.51**
	Baseline model	2,519	1.00	0.98 (0.94, 1.02)	0.92 (0.77, 1.09)	0.88 (0.75, 1.04)	0.85 (0.73, 0.98)	0.84 (0.71, 1.00)	p=0.14**
	Final model ^a , f(males), g	2,379	1.00	0.99 (0.95, 1.03)	0.96 (0.79, 1.16)	0.94 (0.80, 1.12)	0.92 (0.79, 1.08)	0.92 (0.77, 1.11)	p=0.58 (females); p=0.99 (males)
Colon	Baseline model	1,608	1.00	0.99 (0.94, 1.04)	0.91 (0.73, 1.13)	0.78 (0.65, 0.95)	0.74 (0.62, 0.88)	0.73 (0.59, 0.91)	p<0.001**
	Final model ^a , f(males), g	1,513	1.00	1.00 (0.95, 1.05)	0.98 (0.78, 1.23)	0.86 (0.70, 1.06)	0.82 (0.68, 0.99)	0.82 (0.65, 1.02)	p=0.46 (females); p=0.10 (males)
Rectum	Baseline model	854	1.00	0.98 (0.91, 1.05)	0.94 (0.68, 1.29)	1.14 (0.85, 1.51)	1.12 (0.86, 1.46)	1.06 (0.78, 1.43)	p=0.18**
	Final model ^a , f(males), g	812	1.00	0.99 (0.92, 1.06)	0.95 (0.68, 1.34)	1.16 (0.86, 1.56)	1.16 (0.88, 1.54)	1.13 (0.82, 1.56)	p=0.96 (females); p=0.06 (males)
Brain tumours	Baseline model	356	1.00	1.01 (0.91, 1.13)	1.06 (0.66, 1.70)	1.00 (0.65, 1.53)	0.97 (0.65, 1.44)	0.90 (0.56, 1.44)	p=0.91
	Final model	341	1.00	1.01 (0.90, 1.12)	1.02 (0.62, 1.66)	0.97 (0.62, 1.51)	0.94 (0.62, 1.42)	0.83 (0.51, 1.36)	p=0.84
Thyroid	Baseline model	183	1.00	1.01 (0.87, 1.18)	1.04 (0.53, 2.03)	0.99 (0.54, 1.81)	1.06 (0.60, 1.87)	0.97 (0.49, 1.90)	p=0.96
	Final model	179	1.00	1.01 (0.87, 1.18)	1.04 (0.53, 2.07)	1.00 (0.54, 1.85)	1.09 (0.61, 1.93)	1.06 (0.53, 2.11)	p=0.97
Haematological malignancies	Baseline model	1,830	1.00	0.96 (0.92, 1.01)	0.83 (0.68, 1.03)	0.83 (0.69, 1.00)	0.83 (0.70, 0.99)	0.85 (0.70, 1.04)	p=0.34
	Final model	1,777	1.00	0.96 (0.92, 1.01)	0.85 (0.68, 1.05)	0.86 (0.71, 1.04)	0.86 (0.72, 1.03)	0.89 (0.73, 1.10)	p=0.48
Non-Hodgkin's lymphoma	Baseline model	882	1.00	0.95 (0.89, 1.02)	0.80 (0.59, 1.07)	0.77 (0.59, 1.01)	0.83 (0.65, 1.05)	0.82 (0.62, 1.09)	p=0.39
	Final model	858	1.00	0.96 (0.90, 1.03)	0.83 (0.61, 1.14)	0.81 (0.62, 1.07)	0.88 (0.68, 1.13)	0.90 (0.67, 1.21)	p=0.59

Baseline models were adjusted for age and sex. All final models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

553 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
554 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
555 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
556 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
557 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
558 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
559 ^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).
560 ^gResults for males and females combined using meta-analysis as covariates are different.
561 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).
562 ^{**}Schoenfeld test indicated potential violation of the proportional hazards assumption (p<0.05).

563 **Table 6. Non-linear associations between IPAQ-measured physical activity and cancer (excluding cancers diagnosed within the first 2 years following**
 564 **baseline).**

		Total physical activity (MET hours/week), HR (95% CI)							
	Cases	0 MET hours/week (ref)	5 th percentile (2.75 MET hours/week)	27.5 th percentile (15.25 MET hours/week)	50 th percentile (29.9 MET hours/week)	72.5 th percentile (55.1 MET hours/week)	95 th percentile (135.1 MET hours/week)	Wald test	
Skin, melanoma	Baseline model	946	1.00	0.99 (0.92, 1.06)	0.96 (0.71, 1.29)	1.04 (0.79, 1.35)	1.05 (0.82, 1.35)	0.94 (0.70, 1.25)	p=0.70**
	Final model ^a	930	1.00	0.97 (0.91, 1.04)	0.90 (0.66, 1.22)	0.96 (0.73, 1.26)	0.99 (0.77, 1.28)	0.94 (0.69, 1.26)	p=0.88
Oropharyngeal	Baseline model	322	1.00	0.93 (0.84, 1.04)	0.72 (0.45, 1.17)	0.72 (0.47, 1.09)	0.85 (0.57, 1.25)	0.75 (0.47, 1.19)	p=0.34
	Final model	312	1.00	0.96 (0.86, 1.07)	0.80 (0.49, 1.31)	0.78 (0.51, 1.21)	0.88 (0.59, 1.31)	0.72 (0.45, 1.17)	p=0.46
Lung	Baseline model	1,155	1.00	0.89 (0.85, 0.95)	0.58 (0.46, 0.75)	0.53 (0.43, 0.66)	0.53 (0.43, 0.64)	0.59 (0.47, 0.75)	p<0.001**
	Final model ^h	1,078	1.00	0.97 (0.91, 1.02)	0.85 (0.66, 1.09)	0.79 (0.63, 0.99)	0.76 (0.61, 0.93)	0.73 (0.57, 0.94)	p=0.06**
Breast (female only)	Baseline model	3,081	1.00	0.98 (0.95, 1.02)	0.93 (0.79, 1.09)	0.94 (0.81, 1.08)	0.82 (0.72, 0.94)	0.78 (0.66, 0.91)	p<0.001**
	Final model ^{b, h}	2,828	1.00	0.98 (0.95, 1.02)	0.94 (0.78, 1.12)	0.97 (0.83, 1.14)	0.86 (0.74, 1.00)	0.81 (0.67, 0.97)	p=0.007**
Uterus	Baseline model	468	1.00	0.95 (0.87, 1.04)	0.78 (0.52, 1.16)	0.72 (0.51, 1.03)	0.69 (0.50, 0.96)	0.60 (0.40, 0.91)	p=0.10
	Final model ^c	427	1.00	1.00 (0.91, 1.10)	1.02 (0.67, 1.56)	1.03 (0.70, 1.51)	1.05 (0.73, 1.50)	1.01 (0.64, 1.58)	p=0.998
Ovary	Baseline model	299	1.00	0.94 (0.83, 1.05)	0.72 (0.43, 1.21)	0.64 (0.40, 1.02)	0.75 (0.49, 1.14)	0.93 (0.57, 1.52)	p=0.22
	Final model	294	1.00	0.96 (0.85, 1.08)	0.80 (0.47, 1.37)	0.69 (0.43, 1.12)	0.81 (0.52, 1.25)	1.02 (0.62, 1.70)	p=0.28
Prostate	Baseline model	3,662	1.00	1.03 (1.00, 1.07)	1.19 (1.02, 1.39)	1.29 (1.12, 1.48)	1.22 (1.07, 1.39)	1.17 (1.01, 1.36)	p=0.004**
	Final model ^h	3,490	1.00	1.03 (0.99, 1.06)	1.14 (0.97, 1.34)	1.21 (1.05, 1.41)	1.17 (1.02, 1.34)	1.13 (0.96, 1.32)	p=0.07**
Oesophagus	Baseline model	308	1.00	0.91 (0.81, 1.02)	0.63 (0.38, 1.02)	0.53 (0.34, 0.82)	0.64 (0.43, 0.95)	0.87 (0.56, 1.36)	p=0.02
	Final model ^f	294	1.00	0.95 (0.84, 1.06)	0.75 (0.45, 1.25)	0.67 (0.43, 1.06)	0.85 (0.56, 1.28)	1.12 (0.70, 1.77)	p=0.07**
Stomach	Baseline model	212	1.00	0.86 (0.75, 0.99)	0.52 (0.28, 0.95)	0.66 (0.39, 1.12)	0.71 (0.44, 1.14)	0.71 (0.41, 1.23)	p=0.25
	Final model	203	1.00	0.89 (0.78, 1.03)	0.62 (0.33, 1.14)	0.77 (0.45, 1.33)	0.83 (0.50, 1.36)	0.76 (0.43, 1.35)	p=0.59
Hepatobiliary tract	Baseline model	264	1.00	0.92 (0.82, 1.04)	0.69 (0.41, 1.14)	0.64 (0.41, 1.00)	0.59 (0.39, 0.90)	0.54 (0.32, 0.90)	p=0.11
	Final model	256	1.00	1.00 (0.89, 1.13)	0.98 (0.58, 1.66)	0.90 (0.56, 1.45)	0.80 (0.51, 1.25)	0.70 (0.41, 1.19)	p=0.44**
Pancreatic	Baseline model	388	1.00	0.97 (0.88, 1.07)	0.84 (0.54, 1.30)	0.69 (0.47, 1.03)	0.71 (0.50, 1.03)	0.86 (0.56, 1.30)	p=0.24
	Final model ^d	376	1.00	1.01 (0.91, 1.12)	1.01 (0.65, 1.59)	0.86 (0.57, 1.30)	0.90 (0.62, 1.31)	1.07 (0.69, 1.66)	p=0.67
Kidney	Baseline model	461	1.00	0.92 (0.84, 1.00)	0.69 (0.46, 1.03)	0.78 (0.55, 1.11)	0.70 (0.50, 0.97)	0.63 (0.43, 0.93)	p=0.11
	Final model	443	1.00	0.96 (0.88, 1.05)	0.86 (0.57, 1.29)	0.99 (0.69, 1.43)	0.89 (0.63, 1.25)	0.79 (0.53, 1.19)	p=0.48

Bladder	Baseline model	376	1.00	1.09 (0.98, 1.22)	1.43 (0.88, 2.33)	1.12 (0.72, 1.75)	1.14 (0.76, 1.72)	1.24 (0.77, 1.99)	p=0.38
	Final model	363	1.00	1.14 (1.02, 1.28)	1.80 (1.09, 2.97)	1.47 (0.93, 2.33)	1.46 (0.95, 2.25)	1.54 (0.94, 2.51)	p=0.20**
Colorectal	Baseline model	1,877	1.00	0.96 (0.92, 1.01)	0.83 (0.68, 1.02)	0.84 (0.70, 1.01)	0.82 (0.70, 0.98)	0.80 (0.66, 0.98)	p=0.23**
	Final model ^a , f(males), g	1,765	1.00	0.97 (0.92, 1.02)	0.87 (0.70, 1.07)	0.90 (0.75, 1.09)	0.89 (0.74, 1.06)	0.87 (0.71, 1.08)	p=0.51 (females); p=0.85 (males) p=0.02**
Colon	Baseline model	1,204	1.00	0.96 (0.91, 1.02)	0.83 (0.65, 1.07)	0.76 (0.61, 0.95)	0.73 (0.59, 0.89)	0.74 (0.58, 0.94)	p=0.82 (females); p=0.34 (males) p=0.18**
	Final model ^a , f(males), g	1,126	1.00	0.97 (0.92, 1.03)	0.88 (0.68, 1.15)	0.84 (0.66, 1.06)	0.80 (0.64, 1.00)	0.82 (0.63, 1.06)	p=0.78 (females); p=0.15 (males) p=0.70
Rectum	Baseline model	632	1.00	0.95 (0.88, 1.03)	0.83 (0.58, 1.21)	1.06 (0.77, 1.47)	1.07 (0.79, 1.45)	0.96 (0.68, 1.36)	p=0.54
	Final model ^a , f(males), g	599	1.00	0.96 (0.88, 1.05)	0.86 (0.59, 1.27)	1.09 (0.77, 1.54)	1.12 (0.82, 1.55)	1.03 (0.71, 1.49)	p=0.90
Brain tumours	Baseline model	272	1.00	1.07 (0.95, 1.22)	1.35 (0.77, 2.37)	1.18 (0.71, 1.97)	1.16 (0.72, 1.86)	1.07 (0.61, 1.87)	p=0.93
	Final model	261	1.00	1.05 (0.93, 1.20)	1.24 (0.70, 2.19)	1.07 (0.64, 1.79)	1.04 (0.64, 1.68)	0.88 (0.49, 1.57)	p=0.22**
Thyroid	Baseline model	130	1.00	1.02 (0.85, 1.22)	1.07 (0.48, 2.37)	0.93 (0.45, 1.91)	1.05 (0.54, 2.04)	0.97 (0.43, 2.15)	p=0.29
	Final model	128	1.00	1.03 (0.86, 1.23)	1.11 (0.50, 2.48)	0.97 (0.47, 2.01)	1.07 (0.54, 2.12)	1.03 (0.45, 2.32)	p=0.67
Haematological malignancies	Baseline model	1,392	1.00	0.95 (0.90, 1.00)	0.79 (0.63, 1.01)	0.82 (0.66, 1.01)	0.80 (0.66, 0.97)	0.81 (0.64, 1.01)	p=0.84
	Final model	1,357	1.00	0.95 (0.90, 1.01)	0.80 (0.63, 1.02)	0.84 (0.68, 1.04)	0.82 (0.67, 1.00)	0.83 (0.66, 1.05)	
Non-Hodgkin's lymphoma	Baseline model	668	1.00	0.95 (0.88, 1.03)	0.79 (0.56, 1.12)	0.81 (0.59, 1.09)	0.84 (0.63, 1.11)	0.80 (0.57, 1.11)	
	Final model	653	1.00	0.96 (0.89, 1.04)	0.83 (0.58, 1.18)	0.85 (0.62, 1.16)	0.89 (0.67, 1.19)	0.88 (0.62, 1.23)	

Baseline models were adjusted for age and sex. All final models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

571 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
572 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
573 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
574 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
575 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
576 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
577 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
578 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
579 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
580 ^fFinal model also adjusted for waist-hip ratio (>94 cm in men, >80 cm in women).
581 ^gResults for males and females combined using meta-analysis as covariates are different.
582 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).
583 ^{**}Schoenfeld test indicated potential violation of the proportional hazards assumption ($p < 0.05$).

REFERENCES

- [1] International Agency for Research on Cancer, Cancer Today, 2016.
<http://gco.iarc.fr/today/home>.
- [2] D.E. Bloom, E.T. Cafiero, E. Jané-Llopis, S. Abrahams-Gessel, L.R. Bloom, S. Fathima, A.B. Feigl, T. Gaziano, M. Mowafi, A. Pandya, K. Prettnner, L. Rosenberg, B. Seligman, A.Z. Stein, C. Weinstein, The global economic burden of noncommunicable diseases: a report by the World Economic Forum and Harvard School of Public Health., 2011.
- [3] World Cancer Research Fund/American Institute for Cancer Research, Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project Expert Report 2018, 2018. dietandcancerreport.org.
- [4] J. Clague, L. Bernstein, Physical activity and cancer., Curr. Oncol. Rep. 14 (2012) 550–558.
<https://doi.org/10.1007/s11912-012-0265-5>.
- [5] Cancer Research UK, Physical activity facts and evidence, Phys. Act. Cancer. (2016).
http://www.cancerresearchuk.org/about-cancer/causes-of-cancer/physical-activity-and-cancer/physical-activity-facts-and-evidence#activity_facts3 (accessed February 5, 2018).
- [6] National Institutes of Health. National Cancer Institute, Physical Activity and Cancer, (2017).
<https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/physical-activity-fact-sheet> (accessed February 5, 2018).
- [7] J.S. Morris, K.E. Bradbury, A.J. Cross, M.J. Gunter, N. Murphy, Physical activity, sedentary behaviour and colorectal cancer risk in the UK Biobank, Br. J. Cancer. (2018).
<https://doi.org/10.1038/bjc.2017.496>.
- [8] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: Sources, methods and major patterns in

- 607 GLOBOCAN 2012, *Int. J. Cancer*. 136 (2015) E359–E386. <https://doi.org/10.1002/ijc.29210>.
- 608 [9] Department of Health and Human Services, 2018 Physical Activity Guidelines Advisory
609 Committee Scientific Report, 2018. <https://health.gov/paguidelines/second-edition/report/>.
- 610 [10] S.C. Moore, I.-M. Lee, E. Weiderpass, P.T. Campbell, J.N. Sampson, C.M. Kitahara, S.K. Keadle,
611 H. Arem, A. Berrington de Gonzalez, P. Hartge, H.-O. Adami, C.K. Blair, K.B. Borch, E. Boyd,
612 D.P. Check, A. Fournier, N.D. Freedman, M. Gunter, M. Johansson, K.-T. Khaw, M.S. Linet, N.
613 Orsini, Y. Park, E. Riboli, K. Robien, C. Schairer, H. Sesso, M. Spriggs, R. Van Dusen, A. Wolk,
614 C.E. Matthews, A. V. Patel, Association of leisure-time physical activity with risk of 26 types of
615 cancer in 1.44 million adults, *JAMA Intern. Med.* 176 (2016) 816.
616 <https://doi.org/10.1001/jamainternmed.2016.1548>.
- 617 [11] Y. Je, J.Y. Jeon, E.L. Giovannucci, J.A. Meyerhardt, Association between physical activity and
618 mortality in colorectal cancer: a meta-analysis of prospective cohort studies, *Int. J. Cancer*.
619 133 (2013) 1905–1913. <https://doi.org/10.1002/ijc.28208>.
- 620 [12] M. Keimling, G. Behrens, D. Schmid, C. Jochem, M.F. Leitzmann, The association between
621 physical activity and bladder cancer: systematic review and meta-analysis, *Br. J. Cancer*. 110
622 (2014) 1862–1870. <https://doi.org/10.1038/bjc.2014.77>.
- 623 [13] P.D. Loprinzi, B.J. Cardinal, E. Smit, K.M. Winters-Stone, Physical activity and breast cancer
624 risk, *J. Exerc. Sci. Fit.* 10 (2012) 1–7. <https://doi.org/10.1016/j.jesf.2012.04.004>.
- 625 [14] D. Schmid, M.F. Leitzmann, Association between physical activity and mortality among breast
626 cancer and colorectal cancer survivors: a systematic review and meta-analysis, *Ann. Oncol.* 25
627 (2014) 1293–1311. <https://doi.org/10.1093/annonc/mdu012>.
- 628 [15] J.S. Hildebrand, S.M. Gapstur, P.T. Campbell, M.M. Gaudet, A. V. Patel, Recreational physical
629 activity and leisure-time sitting in relation to postmenopausal breast cancer risk, *Cancer*

- 630 Epidemiol. Biomarkers Prev. 22 (2013) 1906–1912. <https://doi.org/10.1158/1055-9965.EPI->
 631 13-0407.
- 632 [16] D. Schmid, G. Behrens, M. Keimling, C. Jochem, C. Ricci, M. Leitzmann, A systematic review
 633 and meta-analysis of physical activity and endometrial cancer risk, *Eur. J. Epidemiol.* 30 (2015)
 634 397–412. <https://doi.org/10.1007/s10654-015-0017-6>.
- 635 [17] C.A. Celis-Morales, D.M. Lyall, P. Welsh, J. Anderson, L. Steell, Y. Guo, R. Maldonado, D.F.
 636 Mackay, J.P. Pell, N. Sattar, J.M.R. Gill, Association between active commuting and incident
 637 cardiovascular disease, cancer, and mortality: prospective cohort study., *BMJ.* 357 (2017)
 638 j1456. <https://doi.org/10.1136/bmj.j1456>.
- 639 [18] S.A. Prince, K.B. Adamo, M.E. Hamel, J. Hardt, S. Connor Gorber, M. Tremblay, A comparison
 640 of direct versus self-report measures for assessing physical activity in adults: a systematic
 641 review., *Int. J. Behav. Nutr. Phys. Act.* 5 (2008) 56. <https://doi.org/10.1186/1479-5868-5-56>.
- 642 [19] A. White, S.A. Sabatino, C. Vinson, D. Chambers, M.C. White, The Cancer Prevention and
 643 Control Research Network (CPCRN): advancing public health and implementation science,
 644 *Prev. Med. (Baltim).* (2019) 105824. <https://doi.org/10.1016/J.YPMED.2019.105824>.
- 645 [20] P.C. Elwood, A. Whitmarsh, J. Gallacher, A. Bayer, R. Adams, L. Heslop, J. Pickering, G.
 646 Morgan, J. Galante, S. Dolwani, M. Longley, Z.E. Roberts, Healthy living and cancer: evidence
 647 from UK Biobank., *Ecancermedicalscience.* 12 (2018) 792.
 648 <https://doi.org/10.3332/ecancer.2018.792>.
- 649 [21] A.T. Kunzmann, K.P. Mallon, R.F. Hunter, C.R. Cardwell, Ú.C. McMenamin, A.D. Spence, H.G.
 650 Coleman, Physical activity, sedentary behaviour and risk of oesophago-gastric cancer: a
 651 prospective cohort study within UK Biobank., *United Eur. Gastroenterol. J.* 6 (2018) 1144–
 652 1154. <https://doi.org/10.1177/2050640618783558>.

- 653 [22] C.L. Craig, A.L. Marshall, M. Sjöström, A.E. Bauman, M.L. Booth, B.E. Ainsworth, M. Pratt, U.
 654 Ekelund, A. Yngve, J.F. Sallis, P. Oja, International Physical Activity Questionnaire: 12-country
 655 reliability and validity, *Med. Sci. Sport. Exerc.* 35 (2003) 1381–1395.
 656 <https://doi.org/10.1249/01.MSS.0000078924.61453.FB>.
- 657 [23] IPAQ Research Committee, Guidelines for data processing and analysis of the International
 658 Physical Activity Questionnaire (IPAQ)-short and long forms, (2005).
 659 [https://www.researchgate.net/publication/267932370_Guidelines_for_data_processing_and](https://www.researchgate.net/publication/267932370_Guidelines_for_data_processing_and_analysis_of_the_International_Physical_Activity_Questionnaire_IPAQ2005_URL_httpwwwIP)
 660 [_analysis_of_the_International_Physical_Activity_Questionnaire_IPAQ2005_URL_httpwwwIP](https://www.researchgate.net/publication/267932370_Guidelines_for_data_processing_and_analysis_of_the_International_Physical_Activity_Questionnaire_IPAQ2005_URL_httpwwwIP)
 661 [AQkise](https://www.researchgate.net/publication/267932370_Guidelines_for_data_processing_and_analysis_of_the_International_Physical_Activity_Questionnaire_IPAQ2005_URL_httpwwwIP) (accessed February 1, 2018).
- 662 [24] Cancer Research UK, Cancer incidence for common cancers, *Cancer Incid. Stat.* (2015).
 663 [http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-](http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared)
 664 [cancers-compared](http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared) (accessed February 5, 2018).
- 665 [25] N. Allen, C. Sudlow, P. Downey, T. Peakman, J. Danesh, P. Elliott, J. Gallacher, J. Green, P.
 666 Matthews, J. Pell, T. Sprosen, R. Collins, UK Biobank: current status and what it means for
 667 epidemiology, *Heal. Policy Technol.* 1 (2012) 123–126.
 668 <https://doi.org/10.1016/j.hlpt.2012.07.003>.
- 669 [26] C. Sudlow, J. Gallacher, N. Allen, V. Beral, P. Burton, J. Danesh, P. Downey, P. Elliott, J. Green,
 670 M. Landray, B. Liu, P. Matthews, G. Ong, J. Pell, A. Silman, A. Young, T. Sprosen, T. Peakman,
 671 R. Collins, UK Biobank: an open access resource for identifying the causes of a wide range of
 672 complex diseases of middle and old age, *PLOS Med.* 12 (2015) e1001779.
 673 <https://doi.org/10.1371/journal.pmed.1001779>.
- 674 [27] K.G.M. Alberti, P. Zimmet, J. Shaw, IDF Epidemiology Task Force Consensus Group, The
 675 metabolic syndrome—a new worldwide definition, *Lancet.* 366 (2005) 1059–1062.
 676 [https://doi.org/10.1016/S0140-6736\(05\)67402-8](https://doi.org/10.1016/S0140-6736(05)67402-8).

- 677 [28] P. Townsend, Deprivation, *J. Soc. Policy.* 16 (1987) 125.
 678 <https://doi.org/10.1017/S0047279400020341>.
- 679 [29] Complete ICD-9 Manual, (n.d.).
 680 ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD-9/ucod.txt (accessed July 20,
 681 2018).
- 682 [30] World Health Organization, International Statistical Classification of Diseases and Related
 683 Health Problems 10th Revision, (2016).
 684 <https://www.who.int/classifications/icd/icdonlineversions/en/>.
- 685 [31] J.P. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions version
 686 5.1.0 [updated March 2011], Cochrane Collab. (2011). <http://handbook.cochrane.org/>.
- 687 [32] R. DerSimonian, N. Laird, Meta-analysis in clinical trials., *Control. Clin. Trials.* 7 (1986) 177–
 688 188. [https://doi.org/10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2).
- 689 [33] T.A. Stukel, E. Demidenko, J. Dykes, M.R. Karagas, Two-stage methods for the analysis of
 690 pooled data, *Stat. Med.* 20 (2001) 2115–2130. <https://doi.org/10.1002/sim.852>.
- 691 [34] J. De Neve, T.A. Gerds, On the interpretation of the hazard ratio in Cox regression,
 692 *Biometrical J.* (2019) 1–9. <https://doi.org/10.1002/bimj.201800255>.
- 693 [35] T. Martinussen, S. Vansteelandt, On collapsibility and confounding bias in Cox and Aalen
 694 regression models, *Lifetime Data Anal.* 19 (2013) 279–296. [https://doi.org/10.1007/s10985-](https://doi.org/10.1007/s10985-013-9242-z)
 695 013-9242-z.
- 696 [36] S. Greenland, R. Daniel, N. Pearce, Outcome modelling strategies in epidemiology: traditional
 697 methods and basic alternatives, *Int. J. Epidemiol.* 45 (2016) 565–575.
 698 <https://doi.org/10.1093/ije/dyw040>.
- 699 [37] F.E. Harrell Jr, K.L. Lee, B.G. Pollock, Regression models in clinical studies: determining

- relationships between predictors and response, *J. Natl. Cancer Inst.* 80 (1988) 1198–1202.
<https://doi.org/10.1093/jnci/80.15.1198>.
- [38] L. Desquilbet, F. Mariotti, Dose-response analyses using restricted cubic spline functions in public health research, *Stat. Med.* 29 (2010) 1037–1057. <https://doi.org/10.1002/sim.3841>.
- [39] F.E. Harrell Jr, *Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*, Second Edi, Springer, Cham, 2015.
<https://doi.org/10.1007/978-3-319-19425-7>.
- [40] T.J. Van Der Weele, P. Ding, Sensitivity analysis in observational research: introducing the E-Value, *Ann. Intern. Med.* 167 (2017) 268–274. <https://doi.org/10.7326/M16-2607>.
- [41] L.H. Smith, T.J. Vanderweele, Bounding bias due to selection, *Epidemiology*. 30 (2019) 509–516. <https://doi.org/10.1097/EDE.0000000000001032>.
- [42] I.R. White, P. Royston, A.M. Wood, Multiple imputation using chained equations: Issues and guidance for practice, *Stat. Med.* 30 (2011) 377–399.
- [43] M.R. Baneshi, A.R. Talei, Multiple imputation in survival models: applied on breast cancer data., *Iran. Red Crescent Med. J.* 13 (2011) 544–9.
- [44] E.A. Stuart, M. Azur, C. Frangakis, P. Leaf, Multiple imputation with large data sets: a case study of the children’s mental health initiative, *Am. J. Epidemiol.* 169 (2009).
<https://jhu.pure.elsevier.com/en/publications/multiple-imputation-with-large-data-sets-a-case-study-of-the-chil-4> (accessed May 18, 2020).
- [45] D.B. Rubin, *Multiple imputation for nonresponse in surveys*, J. Wiley & Sons, New York, 1987.
- [46] U.E. Ntuk, J.M.R. Gill, D.F. Mackay, N. Sattar, J.P. Pell, Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK Biobank participants, *Diabetes Care*. 37 (2014) 2500–2507. <https://doi.org/10.2337/dc13-2966>.

- 723 [47] D. Gallagher, S.B. Heymsfield, M. Heo, S.A. Jebb, P.R. Murgatroyd, Y. Sakamoto, Healthy
724 percentage body fat ranges: an approach for developing guidelines based on body mass
725 index, *Am. J. Clin. Nutr.* 72 (2000) 694–701. <https://doi.org/10.1093/ajcn/72.3.694>.
- 726 [48] D. Schoenfeld, Partial residuals for the proportional hazards regression model, *Biometrika*. 69
727 (1982) 239–241. <https://doi.org/10.1093/biomet/69.1.239>.
- 728 [49] T. Strain, K. Wijndaele, S.J. Sharp, P.C. Dempsey, N. Wareham, S. Brage, Impact of follow-up
729 time and analytical approaches to account for reverse causality on the association between
730 physical activity and health outcomes in UK Biobank, *Int. J. Epidemiol.* 49 (2019) 162–172.
731 <https://doi.org/10.1093/ije/dyz212>.
- 732 [50] StataCorp, Stata Statistical Software: Release 13. College Station, TX: StataCorp LP., (2013).
- 733 [51] A. Fry, T. Littlejohns, C. Sudlow, N. Doherty, N. Allen, OP41 The representativeness of the UK
734 Biobank cohort on a range of sociodemographic, physical, lifestyle and health-related
735 characteristics, *J. Epidemiol. Community Health*. 70 (2016) A26. [https://doi.org/10.1136/jech-](https://doi.org/10.1136/jech-2016-208064.41)
736 [2016-208064.41](https://doi.org/10.1136/jech-2016-208064.41).
- 737 [52] G.D. Batty, C.R. Gale, M. Kivimäki, I.J. Deary, S. Bell, Comparison of risk factor associations in
738 UK Biobank against representative, general population based studies with conventional
739 response rates: prospective cohort study and individual participant meta-analysis., *BMJ*. 368
740 (2020) m131. <https://doi.org/10.1136/bmj.m131>.
- 741 [53] G.D. Batty, C. Gale, M. Kivimäki, I. Deary, S. Bell, Generalisability of results from UK Biobank:
742 comparison with a pooling of 18 cohort studies, *MedRxiv*. (2019) 19004705.
743 <https://doi.org/10.1101/19004705>.
- 744 [54] C.A. Celis-Morales, D.M. Lyall, L. Steell, S.R. Gray, S. Iliodromiti, J. Anderson, D.F. Mackay, P.
745 Welsh, T. Yates, J.P. Pell, N. Sattar, J.M.R. Gill, Associations of discretionary screen time with

- 746 mortality, cardiovascular disease and cancer are attenuated by strength, fitness and physical
747 activity: findings from the UK Biobank study, *BMC Med.* 16 (2018) 77.
- 748 [55] Department of Health and Social Care, Physical activity guidelines: UK Chief Medical Officers'
749 report, 2019. [https://www.gov.uk/government/publications/physical-activity-guidelines-uk-](https://www.gov.uk/government/publications/physical-activity-guidelines-uk-chief-medical-officers-report)
750 [chief-medical-officers-report](https://www.gov.uk/government/publications/physical-activity-guidelines-uk-chief-medical-officers-report).
- 751 [56] P.H. Lee, D.J. Macfarlane, T.H. Lam, S.M. Stewart, Validity of the international physical activity
752 questionnaire short form (IPAQ-SF): a systematic review, *Int. J. Behav. Nutr. Phys. Act.* 8
753 (2011) 115. <https://doi.org/10.1186/1479-5868-8-115>.
- 754 [57] Fibrinogen Studies Collaboration, A. Wood, I. White, S. Thompson, S. Lewington, J. Danesh,
755 Regression dilution methods for meta-analysis: assessing long-term variability in plasma
756 fibrinogen among 27,247 adults in 15 prospective studies, *Int. J. Epi.* 35 (2006) 1570–1578.
757 <https://doi.org/10.1093/ije/dyl233>.
- 758 [58] C.A. Celis-Morales, F. Perez-Bravo, L. Ibañez, C. Salas, M.E.S. Bailey, J.M.R. Gill, Objective vs.
759 self-reported physical activity and sedentary time: effects of measurement method on
760 relationships with risk biomarkers, *PLoS One.* 7 (2012).
761 <https://doi.org/10.1371/journal.pone.0036345>.
- 762 [59] C. Frost, S.G. Thompson, Correcting for regression dilution bias: comparison of methods for a
763 single predictor variable, *J. R. Stat. Soc. Ser. A.* 163 (2000) 173–189.
764 <https://doi.org/10.1111/1467-985X.00164>.
- 765 [60] C.E. Matthews, S.C. Moore, H. Arem, M.B. Cook, B. Trabert, N. Håkansson, S.C. Larsson, A.
766 Wolk, S.M. Gapstur, B.M. Lynch, R.L. Milne, N.D. Freedman, W.-Y. Huang, A. Berrington de
767 Gonzalez, C.M. Kitahara, M.S. Linet, E.J. Shiroma, S. Sandin, A. V. Patel, I.-M. Lee, Amount and
768 intensity of leisure-time physical activity and lower cancer risk, *J. Clin. Oncol.* (2019)
769 JCO.19.02407. <https://doi.org/10.1200/jco.19.02407>.

- 770 [61] S.E. Baumeister, M.F. Leitzmann, J. Linseisen, S. Schlesinger, Physical activity and the risk of
 771 liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis,
 772 J. Natl. Cancer Inst. 111 (2019). <https://doi.org/10.1093/jnci/djz111>.
- 773 [62] I.M. Lee, H.D. Sesso, R.S. Paffenbarger, Physical activity and risk of lung cancer., Int. J.
 774 Epidemiol. 28 (1999) 620–625. <https://doi.org/10.1093/ije/28.4.620>.
- 775 [63] H. Bak, J. Christensen, B.L. Thomsen, A. Tjønneland, K. Overvad, S. Loft, O. Raaschou-Nielsen,
 776 Physical activity and risk for lung cancer in a Danish cohort, Int. J. Cancer. 116 (2005) 439–
 777 444. <https://doi.org/10.1002/ijc.21085>.
- 778 [64] M.F. Leitzmann, C. Koebnick, N.D. Freedman, Y. Park, R. Ballard-Barbash, A.R. Hollenbeck, A.
 779 Schatzkin, C.C. Abnet, Physical activity and head and neck cancer risk., Cancer Causes Control.
 780 19 (2008) 1391–1399. <https://doi.org/10.1007/s10552-008-9211-0>.
- 781 [65] C.-L. Lin, W.-T. Lee, C.-Y. Ou, J.-R. Hsiao, C.-C. Huang, J.-S. Huang, T.-Y. Wong, K.-C. Chen, S.-T.
 782 Tsai, S.-Y. Fang, T.-T. Huang, J.-L. Wu, Y.-H. Wu, W.-T. Hsueh, C.-J. Yen, Y.-H. Lai, H.-C. Liao, S.-
 783 Y. Wu, M.-W. Yang, F.-C. Lin, J.-Y. Chang, Y.-H. Wang, Y.-L. Weng, H.-C. Yang, Y.-S. Chen, J.S.
 784 Chang, Regular recreational physical activity and risk of head and neck cancer, BMC Cancer.
 785 17 (2017) 286. <https://doi.org/10.1186/s12885-017-3223-7>.
- 786 [66] T. Niedermaier, G. Behrens, D. Schmid, I. Schlecht, B. Fischer, M.F. Leitzmann, Body mass
 787 index, physical activity, and risk of adult meningioma and glioma: a meta-analysis.,
 788 Neurology. 85 (2015) 1342–1350. <https://doi.org/10.1212/WNL.0000000000002020>.
- 789 [67] K.S. Courneya, C.M. Friedenreich, Physical Activity and Cancer, Springer, 2011.
- 790 [68] R.J. Shephard, Physical activity and the biliary tract in health and disease., Sport. Med. 45
 791 (2015) 1295–1309. <https://doi.org/10.1007/s40279-015-0346-3>.
- 792 [69] G. Behrens, C.E. Matthews, S.C. Moore, N.D. Freedman, K.A. McGlynn, J.E. Everhart, A.R.

- 793 Hollenbeck, M.F. Leitzmann, The association between frequency of vigorous physical activity
794 and hepatobiliary cancers in the NIH-AARP Diet and Health Study., *Eur. J. Epidemiol.* 28
795 (2013) 55–66. <https://doi.org/10.1007/s10654-013-9767-1>.
- 796 [70] S.E. Baumeister, S. Schlesinger, K. Aleksandrova, C. Jochem, M. Jenab, M.J. Gunter, K.
797 Overvad, A. Tjønneland, M.C. Boutron-Ruault, F. Carbonnel, A. Fournier, T. Kühn, R. Kaaks, T.
798 Pischon, H. Boeing, A. Trichopoulou, C. Bamia, C. La Vecchia, G. Masala, S. Panico, F. Fasanelli,
799 R. Tumino, S. Grioni, B. Bueno de Mesquita, R. Vermeulen, A.M. May, K.B. Borch, S.O.
800 Oyeyemi, E. Ardanaz, M. Rodríguez-Barranco, M. Dolores Chirlaque López, M. Felez-Nobrega,
801 E. Sonestedt, B. Ohlsson, O. Hemmingsson, M. Werner, A. Perez-Cornago, P. Ferrari, M.
802 Stepien, H. Freisling, K.K. Tsilidis, H. Ward, E. Riboli, E. Weiderpass, M.F. Leitzmann,
803 Association between physical activity and risk of hepatobiliary cancers: a multinational cohort
804 study, *J. Hepatol.* 70 (2019) 885–892. <https://doi.org/10.1016/j.jhep.2018.12.014>.
- 805 [71] V. Lope, M. Martín, A. Castelló, S. Casla, A. Ruiz, J.M. Baena-Cañada, A.M. Casas, L. Calvo, B.
806 Bermejo, M. Muñoz, M. Ramos, A. de Juan-Ferré, C. Jara, A. Antón, M.Á. Jimeno, A. Lluch, S.
807 Antolín, J.Á. García-Sáenz, P. Estévez, E. Arriola-Arellano, J. Gavilá, B. Pérez-Gómez, E.
808 Carrasco, M. Pollán, the S.B.C.G. GEICAM, Physical activity and breast cancer risk by
809 pathological subtype, *Gynecol. Oncol.* 144 (2017) 577–585.
810 <https://doi.org/10.1016/j.ygyno.2016.12.014>.
- 811 [72] H.H. Kyu, V.F. Bachman, L.T. Alexander, J.E. Mumford, A. Afshin, K. Estep, J.L. Veerman, K.
812 Delwiche, M.L. Iannarone, M.L. Moyer, K. Cercy, T. Vos, C.J.L. Murray, M.H. Forouzanfar,
813 Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and
814 ischemic stroke events: systematic review and dose-response meta-analysis for the Global
815 Burden of Disease Study 2013., *BMJ.* 354 (2016) i3857. <https://doi.org/10.1136/bmj.i3857>.
- 816 [73] C. Friedenreich, T. Norat, K. Steindorf, M.-C. Boutron-Ruault, T. Pischon, M. Mazuir, F. Clavel-

- 817 Chapelon, J. Linseisen, H. Boeing, M. Bergman, N.F. Johnsen, A. Tjønneland, K. Overvad, M.
 818 Mendez, J.R. Quiros, C. Martinez, M. Dorronsoro, C. Navarro, A.B. Gurrea, S. Bingham, K.-T.
 819 Khaw, N. Allen, T. Key, A. Trichopoulou, D. Trichopoulos, N. Orfanou, V. Krogh, D. Palli, R.
 820 Tumino, S. Panico, P. Vineis, H.B. Bueno-de-Mesquita, P.H.M. Peeters, E. Monninkhof, G.
 821 Berglund, J. Manjer, P. Ferrari, N. Slimani, R. Kaaks, E. Riboli, Physical activity and risk of colon
 822 and rectal cancers: the European Prospective Investigation into Cancer and Nutrition, *Cancer*
 823 *Epidemiol. Biomarkers Prev.* 15 (2006) 2398–2407. [https://doi.org/10.1158/1055-9965.EPI-](https://doi.org/10.1158/1055-9965.EPI-06-0595)
 824 06-0595.
- 825 [74] K.Y. Wolin, Y. Yan, G.A. Colditz, I.-M. Lee, Physical activity and colon cancer prevention: a
 826 meta-analysis, *Br. J. Cancer.* 100 (2009) 611–616. <https://doi.org/10.1038/sj.bjc.6604917>.
- 827 [75] N. Papadimitriou, N. Dimou, K.K. Tsilidis, B. Banbury, R.M. Martin, S.J. Lewis, N. Kazmi, T.M.
 828 Robinson, D. Albanes, K. Aleksandrova, S.I. Berndt, D. Timothy Bishop, H. Brenner, D.D.
 829 Buchanan, B. Bueno-de-Mesquita, P.T. Campbell, S. Castellví-Bel, A.T. Chan, J. Chang-Claude,
 830 M. Ellingjord-Dale, J.C. Figueiredo, S.J. Gallinger, G.G. Giles, E. Giovannucci, S.B. Gruber, A.
 831 Gsur, J. Hampe, H. Hampel, S. Harlid, T.A. Harrison, M. Hoffmeister, J.L. Hopper, L. Hsu, J.
 832 María Huerta, J.R. Huyghe, M.A. Jenkins, T.O. Keku, T. Kühn, C. La Vecchia, L. Le Marchand,
 833 C.I. Li, L. Li, A. Lindblom, N.M. Lindor, B. Lynch, S.D. Markowitz, G. Masala, A.M. May, R.
 834 Milne, E. Monninkhof, L. Moreno, V. Moreno, P.A. Newcomb, K. Offit, V. Perduca, P.D.P.
 835 Pharoah, E.A. Platz, J.D. Potter, G. Rennert, E. Riboli, M.J. Sánchez, S.L. Schmit, R.E. Schoen, G.
 836 Severi, S. Sieri, M.L. Slattery, M. Song, C.M. Tangen, S.N. Thibodeau, R.C. Travis, A.
 837 Trichopoulou, C.M. Ulrich, F.J.B. van Duijnhoven, B. Van Guelpen, P. Vodicka, E. White, A.
 838 Wolk, M.O. Woods, A.H. Wu, U. Peters, M.J. Gunter, N. Murphy, Physical activity and risks of
 839 breast and colorectal cancer: a Mendelian randomisation analysis, *Nat. Commun.* 11 (2020)
 840 1–10. <https://doi.org/10.1038/s41467-020-14389-8>.
- 841 [76] W. Guo, G.K. Fensom, G.K. Reeves, T.J. Key, Physical activity and breast cancer risk: results

- 842 from the UK Biobank prospective cohort, *Br. J. Cancer*. 122 (2020) 726–732.
 843 <https://doi.org/10.1038/s41416-019-0700-6>.
- 844 [77] G. Behrens, C. Jochem, M. Keimling, C. Ricci, D. Schmid, M.F. Leitzmann, The association
 845 between physical activity and gastroesophageal cancer: systematic review and meta-analysis,
 846 *Eur. J. Epidemiol.* 29 (2014) 151–170. <https://doi.org/10.1007/s10654-014-9895-2>.
- 847 [78] N. Kazmi, P. Haycock, K. Tsilidis, B.M. Lynch, T. Truong, P. PRACTICAL Consortium, CRUK,
 848 BPC3, CAPS, R.M. Martin, S.J. Lewis, Appraising causal relationships of dietary, nutritional and
 849 physical-activity exposures with overall and aggressive prostate cancer: two-sample
 850 Mendelian-randomization study based on 79 148 prostate-cancer cases and 61 106 controls.,
 851 *Int. J. Epidemiol.* (2019). <https://doi.org/10.1093/ije/dyz235>.
- 852 [79] M.L. Slattery, S. Edwards, K. Curtin, K. Ma, R. Edwards, R. Holubkov, D. Schaffer, Physical
 853 activity and colorectal cancer, *Am. J. Epidemiol.* 158 (2003) 214–224.
 854 <https://doi.org/10.1093/aje/kwg134>.
- 855 [80] C.E. Matthews, W.H. Xu, W. Zheng, Y.T. Gao, Z.X. Ruan, J.R. Cheng, Y.B. Xiang, X.O. Shu,
 856 Physical Activity and risk of endometrial cancer: a report from the Shanghai Endometrial
 857 Cancer Study, *Cancer Epidemiol. Biomarkers Prev.* 14 (2005) 779–785.
 858 <https://doi.org/10.1158/1055-9965.EPI-04-0665>.
- 859 [81] K.B. Borch, E. Weiderpass, T. Braaten, M. Jareid, O.A. Gavrilyuk, I. Licaj, Physical activity and
 860 risk of endometrial cancer in the Norwegian Women and Cancer (NOWAC) study, *Int. J.*
 861 *Cancer*. 140 (2017) 1809–1818. <https://doi.org/10.1002/ijc.30610>.
- 862 [82] V. Hainer, H. Toplak, V. Stich, Fat or fit: what is more important?, *Diabetes Care*. 32 Suppl 2
 863 (2009) S392–S397. <https://doi.org/10.2337/dc09-S346>.
- 864 [83] G. O'Donoghue, A. Kennedy, A. Puggina, K. Aleksovska, C. Buck, C. Burns, G. Cardon, A. Carlin,

- 865 D. Ciarapica, M. Colotto, G. Condello, T. Coppinger, C. Cortis, S. D’Haese, M. De Craemer, A. Di
 866 Blasio, S. Hansen, L. Iacoviello, J. Issartel, P. Izzicupo, L. Jaeschke, M. Kanning, F. Ling, A.
 867 Luzak, G. Napolitano, J.A. Nazare, C. Perchoux, C. Pesce, T. Pischon, A. Polito, A. Sannella, H.
 868 Schulz, C. Simon, R. Sohun, A. Steinbrecher, W. Schlicht, C. MacDonncha, L. Capranica, S.
 869 Boccia, Socio-economic determinants of physical activity across the life course: a
 870 “DEterminants of Diet and Physical Activity” (DEDIPAC) umbrella literature review, PLoS One.
 871 13 (2018). <https://doi.org/10.1371/journal.pone.0190737>.
- 872 [84] S. Dare, D.F. Mackay, J.P. Pell, Relationship between smoking and obesity: a cross-sectional
 873 study of 499,504 middle-aged adults in the UK general population, PLoS One. 10 (2015).
 874 <https://doi.org/10.1371/journal.pone.0123579>.
- 875 [85] U.S. Department of Health and Human Services, Physical Activity Guidelines for Americans,
 876 2nd edition., Washington DC, 2018. [https://health.gov/paguidelines/second-](https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf)
 877 [edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf](https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf).
- 878 [86] British Heart Foundation, Physical inactivity across the Four Nations, Phys. Inact. Sedentary
 879 Behav. Rep. 2017. (2017). [https://www.bhf.org.uk/publications/statistics/physical-inactivity-](https://www.bhf.org.uk/publications/statistics/physical-inactivity-report-2017)
 880 [report-2017](https://www.bhf.org.uk/publications/statistics/physical-inactivity-report-2017) (accessed September 14, 2017).
- 881 [87] A. Doherty, D. Jackson, N. Hammerla, T. Plötz, P. Olivier, M.H. Granat, T. White, V.T. van Hees,
 882 M.I. Trenell, C.G. Owen, S.J. Preece, R. Gillions, S. Sheard, T. Peakman, S. Brage, N.J.
 883 Wareham, Large scale population assessment of physical activity using wrist worn
 884 accelerometers: The UK Biobank Study, PLoS One. 12 (2017) e0169649.
 885 <https://doi.org/10.1371/journal.pone.0169649>.
- 886 [88] A.J. Fox, P.O. Goldblatt, A.M. Adelstein, Selection and mortality differentials., J. Epidemiol.
 887 Community Health. 36 (1982) 69–79. <https://doi.org/10.1136/jech.36.2.69>.
- 888 [89] J. Barker, K. Smith Byrne, A. Doherty, C. Foster, K. Rahimi, R. Ramakrishnan, M. Woodward, T.

889 Dwyer, Physical activity of UK adults with chronic disease: cross-sectional analysis of
890 accelerometer-measured physical activity in 96 706 UK Biobank participants, *Int. J. Epidemiol.*
891 (2019). <https://doi.org/10.1093/ije/dyy294>.

892

Supplementary file 1: Restricted cubic splines analyses.

Spline graphs and tests for non-linear trend

Graphs show non-linear associations between total MET-hours/week and cancer risk in **final adjusted models**. Likelihood ratio tests for non-linear associations are shown for: (1) models adjusted for sex and age; (2) final adjusted models.

Skin, melanoma

899

900 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.71$, $p=0.4380$

901 LR test (final adjusted model): $\text{Chi}^2(3)=0.89$, $p=0.8282$

902 **Oropharyngeal**

903

904 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=7.12$, $p=0.0680$ 905 LR test (final adjusted model): $\text{Chi}^2(3)=4.59$, $p=0.2042$ 906 **Lung**

907

908 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=56.98$, $p=0.0000$ 909 LR test (final adjusted model): $\text{Chi}^2(3)=11.76$, $p=0.0083$

910 **Breast (female only)**

911

912 LR test (model adjusted for age and sex): $\text{Chi}^2(2)=9.45$, $p=0.0089$

913 LR test (final adjusted model): $\text{Chi}^2(3)=4.30$, $p=0.2304$

914 **Uterus**

915

916 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.66$, $p=0.1293$

917 LR test (final adjusted model): $\text{Chi}^2(3)=1.20$, $p=0.7526$

918 **Ovary**

919

920 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.76$, $p=0.2883$ 921 LR test (final adjusted model): $\text{Chi}^2(2)=2.49$, $p=0.2874$ 922 **Prostate**

923

924 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=14.59$, $p=0.0022$ 925 LR test (final adjusted model): $\text{Chi}^2(2)=7.80$, $p=0.0203$

926 **Oesophagus**

927

928 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=8.99$, $p=0.0294$ 929 LR test (final adjusted model): $\text{Chi}^2(3)=3.59$, $p=0.3092$ 930 **Stomach**

931

932 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=7.25$, $p=0.0643$ 933 LR test (final adjusted model): $\text{Chi}^2(3)=4.15$, $p=0.2455$

934 **Hepatobiliary tract**

935

936 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=7.93$, $p=0.0474$

937 LR test (final adjusted model): $\text{Chi}^2(3)=2.72$, $p=0.4362$

938 **Pancreatic**

939

940 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=8.65$, $p=0.0344$

941 LR test (final adjusted model): $\text{Chi}^2(3)=4.35$, $p=0.2257$

942 **Kidney**

943

944 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.67$, $p=0.1980$

945 LR test (final adjusted model): $\text{Chi}^2(3)=1.61$, $p=0.6573$

946 **Bladder**

947

948 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.35$, $p=0.5028$

949 LR test (final adjusted model): $\text{Chi}^2(3)=3.29$, $p=0.3489$

950 **Colorectal**951 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.82$, $p=0.2819$ 952 **Colon**953 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=9.45$, $p=0.0238$ 954 **Rectum**955 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.08$, $p=0.1662$

956

957 **Colorectal (females)**

958

959 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.33$, $p=0.5077$ 960 LR test (final adjusted model): $\text{Chi}^2(3)=1.47$, $p=0.6887$

961 **Colorectal (males)**

962

963 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.80$, $p=0.4235$

964 LR test (final adjusted model): $\text{Chi}^2(3)=0.21$, $p=0.9755$

965 **Colon (females)**

966

967 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.24$, $p=0.7433$

968 LR test (final adjusted model): $\text{Chi}^2(3)=0.84$, $p=0.8394$

969 **Colon (males)**

970

971 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=11.15$, $p=0.0109$

972 LR test (final adjusted model): $\text{Chi}^2(3)=4.97$, $p=0.1742$

973 **Rectum (females)**

974

975 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.89$, $p=0.5953$

976 LR test (final adjusted model): $\text{Chi}^2(3)=0.51$, $p=0.9167$

977 **Rectum (males)**

978

979 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.97$, $p=0.2651$ 980 LR test (final adjusted model): $\text{Chi}^2(3)=5.86$, $p=0.1188$ 981 **Brain tumors**

982

983 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=0.13$, $p=0.9882$ 984 LR test (final adjusted model): $\text{Chi}^2(3)=0.05$, $p=0.9969$

985 **Thyroid**

986

987 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=0.61$, $p=0.8941$

988 LR test (final adjusted model): $\text{Chi}^2(3)=0.52$, $p=0.9136$

989 **Haematological malignancies**

990

991 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.23$, $p=0.2380$

992 LR test (final adjusted model): $\text{Chi}^2(3)=3.38$, $p=0.3362$

993 **Non-Hodgkin's lymphoma**

994

995 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.78$, $p=0.2861$

996 LR test (final adjusted model): $\text{Chi}^2(3)=2.78$, $p=0.4271$

997 **Skin, melanoma (with removal of prevelant cancers)**

998

999 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.98$, $p=0.5773$

1000 LR test (final adjusted model): $\text{Chi}^2(3)=1.17$, $p=0.7593$

1001 **Oropharyngeal (with removal of prevelant cancers)**

1002

1003 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.41$, $p=0.2207$

1004 LR test (final adjusted model): $\text{Chi}^2(3)=2.66$, $p=0.4467$

1005 **Lung (with removal of prevelant cancers)**

1006

1007 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=35.37$, $p=0.0000$

1008 LR test (final adjusted model): $\text{Chi}^2(3)=3.99$, $p=0.2622$

1009 **Breast (female only; with removal of prevalent cancers)**

1010

1011 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=11.16$, $p=0.0109$

1012 LR test (final adjusted model): $\text{Chi}^2(3)=7.18$, $p=0.0663$

1013 **Uterus (with removal of prevalent cancers)**

1014

1015 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.99$, $p=0.5752$

1016 LR test (final adjusted model): $\text{Chi}^2(3)=0.13$, $p=0.9882$

1017 **Ovary (with removal of prevalent cancers)**

1018

1019 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.86$, $p=0.1822$

1020 LR test (final adjusted model): $\text{Chi}^2(3)=3.97$, $p=0.2643$

1021 **Prostate (with removal of prevalent cancers)**

1022

1023 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=15.01$, $p=0.0018$

1024 LR test (final adjusted model): $\text{Chi}^2(3)=8.49$, $p=0.0369$

1025 **Oesophagus (with removal of prevalent cancers)**

1026

1027 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=10.20$, $p=0.0170$

1028 LR test (final adjusted model): $\text{Chi}^2(3)=5.40$, $p=0.1448$

1029 **Stomach (with removal of prevalent cancers)**

1030

1031 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.87$, $p=0.1816$

1032 LR test (final adjusted model): $\text{Chi}^2(3)=2.80$, $p=0.4243$

1033 **Hepatobiliary tract (with removal of prevalent cancers)**

1034

1035 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.17$, $p=0.3662$

1036 LR test (final adjusted model): $\text{Chi}^2(3)=0.52$, $p=0.9141$

1037 **Pancreatic (with removal of prevalent cancers)**

1038

1039 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.41$, $p=0.1442$

1040 LR test (final adjusted model): $\text{Chi}^2(3)=2.19$, $p=0.5346$

1041 **Kidney (with removal of prevelant cancers)**

1042

1043 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.94$, $p=0.1144$

1044 LR test (final adjusted model): $\text{Chi}^2(3)=3.05$, $p=0.3842$

1045 **Bladder (with removal of prevelant cancers)**

1046

1047 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.17$, $p=0.2433$

1048 LR test (final adjusted model): $\text{Chi}^2(3)=6.20$, $p=0.1022$

1049

1050 **Colorectal (with removal of prevalent cancers)**1051 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=3.88$, $p=0.2742$ 1052 **Colon (with removal of prevalent cancers)**1053 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=7.19$, $p=0.0660$ 1054 **Rectum (with removal of prevalent cancers)**1055 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.83$, $p=0.1200$

1056

1057 **Colorectal (females; with removal of prevalent cancers)**

1058

1059 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.75$, $p=0.4323$ 1060 LR test (final adjusted model): $\text{Chi}^2(3)=2.11$, $p=0.5499$

1061 **Colorectal (males; with removal of prevalent cancers)**

1062

1063 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.27$, $p=0.2340$

1064 LR test (final adjusted model): $\text{Chi}^2(3)=1.28$, $p=0.7342$

1065 **Colon (females; with removal of prevalent cancers)**

1066

1067 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.22$, $p=0.7494$

1068 LR test (final adjusted model): $\text{Chi}^2(3)=1.05$, $p=0.7888$

1069 **Colon (males; with removal of prevalent cancers)**

1070

1071 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=9.40$, $p=0.0244$

1072 LR test (final adjusted model): $\text{Chi}^2(3)=3.73$, $p=0.2923$

1073 **Rectum (females; with removal of prevalent cancers)**

1074

1075 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=2.97$, $p=0.3963$

1076 LR test (final adjusted model): $\text{Chi}^2(3)=1.35$, $p=0.7169$

1077 **Rectum (males; with removal of prevalent cancers)**

1078

1079 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=4.13$, $p=0.2477$

1080 LR test (final adjusted model): $\text{Chi}^2(3)=4.80$, $p=0.1871$

1081 **Brain tumors (with removal of prevalent cancers)**

1082

1083 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.52$, $p=0.6768$

1084 LR test (final adjusted model): $\text{Chi}^2(3)=1.10$, $p=0.7780$

1085 **Thyroid (with removal of prevalent cancers)**

1086

1087 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.07$, $p=0.7832$

1088 LR test (final adjusted model): $\text{Chi}^2(3)=0.88$, $p=0.8309$

1089 **Haematological malignancies (with removal of prevalent cancers)**

1090

1091 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=5.32$, $p=0.1495$

1092 LR test (final adjusted model): $\text{Chi}^2(3)=4.87$, $p=0.1818$

1093 **Non-Hodgkin's lymphoma (with removal of prevalent cancers)**

1094

1095 LR test (model adjusted for age and sex): $\text{Chi}^2(3)=1.90$, $p=0.5944$

1096 LR test (final adjusted model): $\text{Chi}^2(3)=1.40$, $p=0.7049$

1097

1098 **Supplementary file 2: Sensitivity analyses.**

1099 **Table 2.1. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence with**
 1100 **categories defined by MET-hours/week.**

		Physical activity categories					p-trend	Wald test
		<10	10-<20	20-<40	40-<60	≥60		
Person-years		453,032	438,769	629,225	352,724	613,503		
Skin, melanoma	Cases	217	214	325	186	323		
	HR (95% CI)*	1.00	1.003 (0.83, 1.21)	1.06 (0.89, 1.26)	1.07 (0.88, 1.30)	1.05 (0.88, 1.24)	0.50**	p=0.93
	HR (95% CI)†	1.00	0.99 (0.82, 1.20)	1.03 (0.86, 1.22)	1.04 (0.86, 1.28)	1.06 (0.89, 1.26)	0.43	p=0.95
	HR (95% CI) ^a	1.00	0.99 (0.82, 1.19)	1.02 (0.85, 1.21)	1.03 (0.85, 1.26)	1.05 (0.88, 1.26)	0.45	p=0.96
Oropharyngeal	Cases	93	63	101	52	107		
	HR (95% CI)*	1.00	0.71 (0.52, 0.98)	0.80 (0.60, 1.06)	0.73 (0.52, 1.03)	0.83 (0.63, 1.10)	0.36	p=0.22
	HR (95% CI)†	1.00	0.73 (0.53, 1.01)	0.80 (0.60, 1.07)	0.75 (0.53, 1.05)	0.77 (0.58, 1.02)	0.14	p=0.27
	HR (95% CI)	1.00	0.73 (0.53, 1.01)	0.80 (0.60, 1.07)	0.75 (0.53, 1.05)	0.77 (0.58, 1.02)	0.14	p=0.27
Lung	Cases	337	252	303	202	348		
	HR (95% CI)*	1.00	0.74 (0.62, 0.87)	0.61 (0.52, 0.71)	0.71 (0.59, 0.84)	0.67 (0.58, 0.78)	<0.001	p<0.001
	HR (95% CI)†	1.00	0.84 (0.71, 0.99)	0.72 (0.61, 0.85)	0.81 (0.68, 0.97)	0.72 (0.61, 0.84)	<0.001	p<0.001
	HR (95% CI) ^h	1.00	0.88 (0.74, 1.04)	0.76 (0.64, 0.89)	0.85 (0.71, 1.02)	0.74 (0.63, 0.87)	<0.001**	p=0.002
Breast (female only)	Cases	816	788	1,125	557	885		
	HR (95% CI)*	1.00	0.94 (0.85, 1.03)	0.94 (0.86, 1.03)	0.83 (0.75, 0.93)	0.80 (0.73, 0.88)	<0.001	p<0.001
	HR (95% CI)†	1.00	0.94 (0.85, 1.04)	0.96 (0.88, 1.06)	0.86 (0.77, 0.96)	0.84 (0.76, 0.93)	<0.001**	p=0.002
	HR (95% CI) ^{b, h}	1.00	0.95 (0.85, 1.06)	0.97 (0.88, 1.08)	0.87 (0.77, 0.98)	0.85 (0.76, 0.95)	0.001	p=0.01
Uterus	Cases	139	119	159	76	131		
	HR (95% CI)*	1.00	0.82 (0.64, 1.05)	0.77 (0.61, 0.97)	0.66 (0.50, 0.87)	0.68 (0.53, 0.86)	0.001	p=0.009
	HR (95% CI)†	1.00	0.97 (0.75, 1.24)	0.96 (0.76, 1.22)	0.89 (0.66, 1.18)	0.92 (0.72, 1.19)	0.45	p=0.94
	HR (95% CI) ^c	1.00	0.96 (0.74, 1.25)	0.97 (0.76, 1.24)	0.88 (0.65, 1.19)	0.98 (0.75, 1.26)	0.75**	p=0.95
Ovary	Cases	73	70	100	57	114		
	HR (95% CI)*	1.00	0.92 (0.66, 1.27)	0.92 (0.68, 1.24)	0.93 (0.66, 1.31)	1.11 (0.83, 1.49)	0.38	p=0.61

Prostate	HR (95% CI)†	1.00	0.96 (0.69, 1.34)	0.93 (0.68, 1.27)	0.96 (0.67, 1.37)	1.15 (0.85, 1.56)	0.31	p=0.61
	HR (95% CI)	1.00	0.96 (0.69, 1.34)	0.93 (0.68, 1.27)	0.96 (0.67, 1.37)	1.15 (0.85, 1.56)	0.31	p=0.61
	Cases	791	792	1,231	741	1,247		
	HR (95% CI)*	1.00	1.04 (0.94, 1.15)	1.12 (1.02, 1.23)	1.17 (1.06, 1.29)	1.04 (0.95, 1.13)	0.24	p=0.008
	HR (95% CI)†	1.00	1.02 (0.92, 1.13)	1.08 (0.98, 1.18)	1.13 (1.02, 1.25)	1.02 (0.93, 1.12)	0.39	p=0.10
	HR (95% CI) ^h	1.00	1.02 (0.92, 1.13)	1.07 (0.98, 1.18)	1.13 (1.01, 1.25)	1.02 (0.93, 1.12)	0.47**	p=0.12
Oesophagus	Cases	86	67	76	55	112		
	HR (95% CI)*	1.00	0.79 (0.57, 1.09)	0.62 (0.46, 0.84)	0.78 (0.56, 1.09)	0.86 (0.65, 1.14)	0.49	p=0.045
	HR (95% CI)†	1.00	0.84 (0.61, 1.17)	0.70 (0.51, 0.97)	0.89 (0.63, 1.27)	0.96 (0.72, 1.29)	0.92	p=0.20
	HR (95% CI) ^f	1.00	0.84 (0.61, 1.17)	0.71 (0.51, 0.97)	0.90 (0.64, 1.28)	0.98 (0.73, 1.31)	0.83	p=0.19
Stomach	Cases	62	39	54	43	77		
	HR (95% CI)*	1.00	0.63 (0.42, 0.94)	0.60 (0.42, 0.87)	0.83 (0.56, 1.22)	0.80 (0.58, 1.13)	0.68	p=0.051
	HR (95% CI)†	1.00	0.68 (0.45, 1.03)	0.66 (0.45, 0.96)	0.89 (0.60, 1.34)	0.84 (0.59, 1.19)	0.78	p=0.17
	HR (95% CI)	1.00	0.96 (0.69, 1.34)	0.93 (0.68, 1.27)	0.96 (0.67, 1.37)	1.15 (0.85, 1.56)	0.31	p=0.61
Hepatobiliary tract	Cases	81	51	78	45	78		
	HR (95% CI)*	1.00	0.63 (0.44, 0.89)	0.67 (0.49, 0.91)	0.67 (0.47, 0.97)	0.64 (0.47, 0.87)	0.02**	p=0.02
	HR (95% CI)†	1.00	0.71 (0.50, 1.02)	0.78 (0.57, 1.07)	0.74 (0.50, 1.08)	0.71 (0.51, 0.98)	0.08**	p=0.22
	HR (95% CI)	1.00	0.71 (0.50, 1.02)	0.78 (0.57, 1.07)	0.74 (0.50, 1.08)	0.71 (0.51, 0.98)	0.08**	p=0.22
Pancreatic	Cases	98	88	100	55	133		
	HR (95% CI)*	1.00	0.89 (0.67, 1.19)	0.70 (0.53, 0.93)	0.68 (0.49, 0.94)	0.90 (0.69, 1.17)	0.31**	p=0.047
	HR (95% CI)†	1.00	0.96 (0.72, 1.29)	0.76 (0.57, 1.02)	0.78 (0.56, 1.10)	1.02 (0.78, 1.34)	0.95	p=0.14
	HR (95% CI) ^d	1.00	0.97 (0.72, 1.30)	0.77 (0.58, 1.03)	0.80 (0.57, 1.11)	1.04 (0.79, 1.37)	0.95	p=0.14
Kidney	Cases	117	104	140	80	143		
	HR (95% CI)*	1.00	0.90 (0.69, 1.18)	0.84 (0.66, 1.08)	0.84 (0.63, 1.12)	0.82 (0.64, 1.05)	0.12	p=0.55
	HR (95% CI)†	1.00	0.99 (0.76, 1.30)	0.98 (0.76, 1.26)	0.94 (0.70, 1.26)	0.96 (0.75, 1.24)	0.70	p=0.99
	HR (95% CI)	1.00	0.99 (0.76, 1.30)	0.98 (0.76, 1.26)	0.94 (0.70, 1.26)	0.96 (0.75, 1.24)	0.70	p=0.99
Bladder	Cases	83	93	127	67	144		
	HR (95% CI)*	1.00	1.12 (0.84, 1.51)	1.06 (0.80, 1.40)	0.96 (0.70, 1.33)	1.11 (0.85, 1.46)	0.73	p=0.82
	HR (95% CI)†	1.00	1.16 (0.85, 1.57)	1.16 (0.87, 1.54)	1.04 (0.75, 1.45)	1.18 (0.89, 1.56)	0.44**	p=0.74

Colorectal	HR (95% CI)	1.00	1.16 (0.85, 1.57)	1.16 (0.87, 1.54)	1.04 (0.75, 1.45)	1.18 (0.89, 1.56)	0.44**	p=0.74
	Cases	482	452	626	344	615		
	HR (95% CI)*	1.00	0.95 (0.83, 1.08)	0.91 (0.81, 1.02)	0.88 (0.76, 1.01)	0.86 (0.77, 0.97)	0.01**	p=0.14
	HR (95% CI)†	1.00	0.97 (0.85, 1.11)	0.95 (0.84, 1.07)	0.93 (0.80, 1.07)	0.91 (0.80, 1.03)	0.10**	p=0.61
	HR (95% CI) ^{e, f(males), g}	1.00	0.98 (0.86, 1.12)	0.96 (0.85, 1.09)	0.94 (0.82, 1.09)	0.93 (0.82, 1.05)	0.20	p=0.48 (females); p=0.97 (males)
Colon	Cases	328	314	390	203	373		
	HR (95% CI)*	1.00	0.96 (0.82, 1.12)	0.83 (0.71, 0.96)	0.75 (0.63, 0.90)	0.76 (0.66, 0.89)	<0.001**	p<0.001
	HR (95% CI)†	1.00	0.996 (0.85, 1.17)	0.88 (0.75, 1.02)	0.81 (0.68, 0.97)	0.81 (0.69, 0.95)	0.001**	p=0.02
	HR (95% CI) ^{e, f(males), g}	1.00	1.02 (0.87, 1.20)	0.89 (0.76, 1.04)	0.84 (0.70, 1.004)	0.84 (0.72, 0.98)	0.004**	p=0.36 (females); p=0.04 (males)
Rectum	Cases	144	126	229	131	224		
	HR (95% CI)*	1.00	0.90 (0.71, 1.14)	1.13 (0.92, 1.40)	1.14 (0.90, 1.44)	1.07 (0.87, 1.32)	0.21	p=0.22
	HR (95% CI)†	1.00	0.91 (0.72, 1.17)	1.16 (0.93, 1.44)	1.17 (0.92, 1.50)	1.12 (0.90, 1.39)	0.11	p=0.18
	HR (95% CI) ^{e, f(males), g}	1.00	0.90 (0.70, 1.15)	1.16 (0.93, 1.44)	1.17 (0.91, 1.49)	1.12 (0.90, 1.40)	0.09	p=0.92 (females); p=0.047 (males)
Brain tumours	Cases	65	65	90	48	88		
	HR (95% CI)*	1.00	1.02 (0.73, 1.44)	0.98 (0.71, 1.35)	0.92 (0.63, 1.34)	0.93 (0.67, 1.28)	0.52	p=0.97
	HR (95% CI)†	1.00	0.99 (0.70, 1.41)	0.96 (0.69, 1.33)	0.92 (0.62, 1.34)	0.89 (0.64, 1.24)	0.41	p=0.95
	HR (95% CI)	1.00	0.99 (0.70, 1.41)	0.96 (0.69, 1.33)	0.92 (0.62, 1.34)	0.89 (0.64, 1.24)	0.41	p=0.95
Thyroid	Cases	33	35	45	25	45		
	HR (95% CI)*	1.00	1.07 (0.66, 1.71)	0.96 (0.61, 1.50)	0.95 (0.57, 1.60)	1.004 (0.64, 1.58)	0.88	p=0.99
	HR (95% CI)†	1.00	1.04 (0.64, 1.68)	0.96 (0.61, 1.51)	0.95 (0.56, 1.62)	1.06 (0.67, 1.67)	0.92	p=0.99
	HR (95% CI)	1.00	1.04 (0.64, 1.68)	0.96 (0.61, 1.51)	0.95 (0.56, 1.62)	1.06 (0.67, 1.67)	0.92	p=0.99
Haematological malignancies	Cases	345	310	445	259	471		
	HR (95% CI)*	1.00	0.90 (0.77, 1.05)	0.90 (0.78, 1.03)	0.91 (0.78, 1.07)	0.92 (0.80, 1.05)	0.37	p=0.61
	HR (95% CI)†	1.00	0.91 (0.78, 1.07)	0.91 (0.79, 1.06)	0.93 (0.78, 1.09)	0.95 (0.82, 1.10)	0.71	p=0.75

	HR (95% CI)	1.00	0.91 (0.78, 1.07)	0.91 (0.79, 1.06)	0.93 (0.78, 1.09)	0.95 (0.82, 1.10)	0.71	p=0.75
Non-Hodgkin's lymphoma	Cases	171	141	209	130	231		
	HR (95% CI)*	1.00	0.83 (0.66, 1.03)	0.85 (0.69, 1.04)	0.92 (0.74, 1.16)	0.91 (0.75, 1.11)	0.75	p=0.45
	HR (95% CI)†	1.00	0.87 (0.69, 1.09)	0.89 (0.72, 1.09)	0.95 (0.75, 1.20)	0.98 (0.80, 1.21)	0.77	p=0.65
	HR (95% CI)	1.00	0.87 (0.69, 1.09)	0.89 (0.72, 1.09)	0.95 (0.75, 1.20)	0.98 (0.80, 1.21)	0.77	p=0.65

1101 *Models adjusted for age and sex.

1102 †Models adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

1106 ‡Final adjusted models.

1107 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

1109 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1112 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1115 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

1116 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).

1118 ^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).

1119 ^gResults for males and females combined using meta-analysis.

1120 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

1121 **Schoenfeld test indicated potential violation of the proportional hazards assumption (p<0.05).

1122 **Table 2.2. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence for**
 1123 **subgroups defined by IPAQ domain of physical activity.**

		Walking			Moderate			Vigorous		
		Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	382	573	287	771	297	174	862	22	358
	HR (95% CI) ^a	1.00	1.03 (0.91, 1.18)	1.05 (0.90, 1.22)	1.00	0.99 (0.86, 1.13)	1.09 (0.92, 1.29)	1.00	0.76 (0.50, 1.16)	0.98 (0.86, 1.11)
Oropharyngeal	Cases	144	179	83	256	95	55	278	9	119
	HR (95% CI)	1.00	0.86 (0.69, 1.07)	0.77 (0.58, 1.01)	1.00	0.87 (0.69, 1.10)	0.98 (0.73, 1.31)	1.00	0.997 (0.51, 1.94)	1.02 (0.82, 1.27)
Lung	Cases	476	577	294	801	358	188	1,023	30	294
	HR (95% CI) ^h	1.00	0.82 (0.73, 0.93)	0.77 (0.67, 0.90)	1.00	1.02 (0.90, 1.16)	0.97 (0.82, 1.13)	1.00	1.20 (0.83, 1.72)	0.82 (0.72, 0.93)
Breast (female only)	Cases	1,087	1,647	700	2,242	758	434	2,517	66	851
	HR (95% CI) ^{b, h}	1.00	0.99 (0.92, 1.07)	0.88 (0.80, 0.97)	1.00	0.92 (0.85, 0.999)	0.93 (0.84, 1.03)	1.00	0.90 (0.71, 1.15)	0.93 (0.86, 1.005)
Uterus	Cases	184	261	118	374	126	63	426	12	125
	HR (95% CI) ^c	1.00	1.01 (0.84, 1.23)	1.03 (0.82, 1.31)	1.00	0.96 (0.78, 1.17)	0.89 (0.68, 1.16)	1.00	1.10 (0.62, 1.96)	0.93 (0.76, 1.14)
Ovary	Cases	127	176	101	243	96	65	291	8	105
	HR (95% CI)	1.00	0.88 (0.70, 1.11)	1.02 (0.78, 1.33)	1.00	1.03 (0.82, 1.31)	1.20 (0.91, 1.58)	1.00	1.004 (0.50, 2.03)	1.01 (0.81, 1.27)
Prostate	Cases	1,414	2,105	1,073	2,769	1,222	601	3,055	87	1,450
	HR (95% CI) ^h	1.00	1.03 (0.96, 1.10)	1.02 (0.94, 1.11)	1.00	1.01 (0.95, 1.09)	0.98 (0.89, 1.07)	1.00	0.84 (0.68, 1.04)	1.04 (0.98, 1.11)
Oesophagus	Cases	122	164	94	220	100	60	262	4	114
	HR (95% CI) ^f	1.00	0.98 (0.77, 1.23)	1.10 (0.84, 1.45)	1.00	1.10 (0.87, 1.40)	1.28 (0.96, 1.72)	1.00	0.54 (0.20, 1.45)	1.16 (0.93, 1.45)
Stomach	Cases	89	115	61	164	65	36	188	5	72
	HR (95% CI)	1.00	0.90 (0.68, 1.18)	0.89 (0.64, 1.24)	1.00	0.92 (0.69, 1.23)	0.95 (0.66, 1.36)	1.00	0.88 (0.36, 2.14)	0.94 (0.71, 1.23)
Hepatobiliary tract	Cases	118	138	69	204	84	37	241	7	77
	HR (95% CI)	1.00	0.83 (0.64, 1.06)	0.80 (0.59, 1.08)	1.00	0.99 (0.77, 1.28)	0.82 (0.58, 1.17)	1.00	0.97 (0.46, 2.07)	0.82 (0.63, 1.06)
Pancreatic	Cases	157	192	111	289	109	62	324	9	127
	HR (95% CI) ^d	1.00	0.86 (0.70, 1.07)	1.01 (0.79, 1.30)	1.00	0.94 (0.75, 1.17)	1.01 (0.76, 1.33)	1.00	0.99 (0.51, 1.92)	1.07 (0.87, 1.32)
Kidney	Cases	200	246	116	368	125	69	410	9	143

	HR (95% CI)	1.00	0.91 (0.75, 1.10)	0.86 (0.68, 1.09)	1.00	0.85 (0.69, 1.04)	0.92 (0.71, 1.19)	1.00	0.73 (0.38, 1.42)	0.91 (0.75, 1.10)
Bladder	Cases	138	239	120	285	136	76	353	9	135
	HR (95% CI)	1.00	1.22 (0.99, 1.50)	1.16 (0.90, 1.49)	1.00	1.11 (0.91, 1.37)	1.16 (0.90, 1.50)	1.00	0.89 (0.46, 1.74)	0.96 (0.78, 1.17)
Colorectal	Cases	748	1,102	530	1,483	609	288	1,673	45	662
	HR (95% CI) ^{e, f(males), g}	1.00	1.02 (0.92, 1.11)	0.97 (0.87, 1.09)	1.00	1.01 (0.92, 1.11)	0.89 (0.79, 1.02)	1.00	0.90 (0.67, 1.21)	0.99 (0.90, 1.08)
Colon	Cases	491	713	310	976	358	180	1,091	25	398
	HR (95% CI) ^{e, f(males), g}	1.00	0.999 (0.89, 1.12)	0.87 (0.75, 1.000)	1.00	0.90 (0.80, 1.02)	0.85 (0.72, 0.998)	1.00	0.77 (0.52, 1.14)	0.93 (0.83, 1.04)
Rectum	Cases	241	368	203	473	240	99	544	19	249
	HR (95% CI) ^{e, f(males), g}	1.00	1.07 (0.91, 1.26)	1.18 (0.97, 1.42)	1.00	1.24 (1.06, 1.45)	0.98 (0.79, 1.22)	1.00	1.15 (0.73, 1.81)	1.11 (0.95, 1.29)
Brain tumours	Cases	99	161	81	217	83	41	240	12	89
	HR (95% CI)	1.00	1.11 (0.86, 1.43)	1.10 (0.82, 1.49)	1.00	0.92 (0.71, 1.19)	0.86 (0.61, 1.21)	1.00	1.51 (0.84, 2.69)	0.86 (0.67, 1.11)
Thyroid	Cases	58	80	41	107	51	21	130	0	49
	HR (95% CI)	1.00	0.95 (0.68, 1.34)	1.03 (0.68, 1.55)	1.00	1.26 (0.90, 1.77)	0.98 (0.61, 1.57)	1.00	-	0.96 (0.69, 1.35)
Haematological malignancies	Cases	564	811	402	1,094	449	234	1,239	39	499
	HR (95% CI)	1.00	0.98 (0.88, 1.09)	0.96 (0.84, 1.09)	1.00	0.997 (0.89, 1.11)	0.96 (0.84, 1.11)	1.00	1.01 (0.74, 1.40)	0.98 (0.89, 1.09)
Non-Hodgkin's lymphoma	Cases	152	350	356	525	210	123	592	16	250
	HR (95% CI)	1.00	0.96 (0.82, 1.13)	0.99 (0.82, 1.19)	1.00	0.98 (0.83, 1.15)	1.06 (0.87, 1.29)	1.00	0.89 (0.54, 1.46)	1.05 (0.90, 1.22)

1124 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-
1125 level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light
1126 smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol
1127 intake (never, former, current [<once/week], current [≥once/week]).

1128 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in
1129 sunshine).

1130 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1131 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
1132 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1133 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1134 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
1135 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1136 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

1137 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
1138 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
1139 ^fModel also adjusted for waist-hip ratio (>94cm in men, >80cm in women).
1140 ^gResults for males and females combined using meta-analysis as covariates are different.
1141 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).
1142 - Not estimated as there were too few incident thyroid cancers.

1143 Table 2.3. Sensitivity analyses assessing robustness to bias (E-values for confounding and selection bias).

Site	E-values for confounding/selection bias			
	Physical activity categories		Continuous variable	Interpretation
	Moderate	High	Total MET hrs/week	
Skin, melanoma	E-value for HR=1.283 E-value for LL=1.000 E-value for selection=1.186	E-value for HR=1.225 E-value for LL=1.000 E-value for selection=1.150	E-value for HR=1.015 E-value for LL=1.000 E-value for selection=1.011	
Oropharyngeal	E-value for HR=2.145 E-value for UL=1.354 E-value for selection=1.647	E-value for HR=1.831 E-value for UL=1.000 E-value for selection=1.493	E-value for HR=1.048 E-value for UL=1.000 E-value for selection=1.033	The observed HR for the moderate vs. low categories of 0.71 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 2.145-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.354 could explain away the upper confidence limit (0.93), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.647.
Lung	E-value for HR=1.603 E-value for UL=1.097 E-value for selection=1.372	E-value for HR=1.786 E-value for UL=1.342 E-value for selection=1.469	E-value for HR=1.038 E-value for UL=1.013 E-value for selection=1.027	The observed HR for the moderate vs. low categories of 0.86 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.603-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.097 could explain away the upper confidence limit (0.99), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.372. The observed HR for the high vs. low categories of 0.81 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.786-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.342 could explain away the upper confidence limit (0.94), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.469.

				The observed HR for the <u>continuous exposure variable total MET hrs/week</u> of 0.999 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.038-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.013 could explain away the upper confidence limit (0.9998), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.027.
Breast (female only)	E-value for HR=1.323 E-value for UL=1.000 E-value for selection=1.211	E-value for HR=1.618 E-value for UL=1.315 E-value for selection=1.380	E-value for HR=1.038 E-value for UL=1.022 E-value for selection=1.027	<p>The observed HR for the <u>high vs. low categories</u> of 0.85 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.618-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.315 could explain away the upper confidence limit (0.94), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.380.</p> <p>The observed HR for the <u>continuous exposure variable total MET hrs/week</u> of 0.999 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.038-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.022 could explain away the upper confidence limit (0.9995), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.027.</p>
Uterus	E-value for HR=1.168 E-value for UL=1.000 E-value for selection=1.114	E-value for HR=1.332 E-value for UL=1.000 E-value for selection=1.216	E-value for HR=1.019 E-value for UL=1.000 E-value for selection=1.013	
Ovary	E-value for HR=1.197 E-value for UL=1.000 E-value for selection=1.132	E-value for HR=1.376 E-value for LL=1.000 E-value for selection=1.242	E-value for HR=1.045 E-value for LL=1.000 E-value for selection=1.032	
Prostate	E-value for HR=1.178 E-value for LL=1.000 E-value for selection=1.120	E-value for HR=1.226 E-value for LL=1.000 E-value for selection=1.151	E-value for HR=1.011 E-value for LL=1.000 E-value for selection=1.008	
Oesophagus	E-value for HR=1.603 E-value for UL=1.000 E-value for selection=1.372	E-value for HR=1.287 E-value for LL=1.000 E-value for selection=1.189	E-value for HR=1.035 E-value for LL=1.000 E-value for selection=1.025	

Stomach	E-value for HR=1.533 E-value for UL=1.000 E-value for selection=1.333	E-value for HR=1.732 E-value for UL=1.000 E-value for selection=1.441	E-value for HR=1.022 E-value for UL=1.000 E-value for selection=1.016	
Hepatobiliary tract	E-value for HR=1.668 E-value for UL=1.000 E-value for selection=1.407	E-value for HR=2.133 E-value for UL=1.205 E-value for selection=1.641	E-value for HR=1.042 E-value for UL=1.000 E-value for selection=1.029	The observed HR for the high vs. low categories of 0.72 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 2.133-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.205 could explain away the upper confidence limit (0.97), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.641.
Pancreatic	E-value for HR=1.480 E-value for UL=1.000 E-value for selection=1.303	E-value for HR=1.329 E-value for UL=1.000 E-value for selection=1.214	E-value for HR=1.026 E-value for LL=1.000 E-value for selection=1.018	
Kidney	E-value for HR=1.309 E-value for LL=1.000 E-value for selection=1.202	E-value for HR=1.392 E-value for UL=1.000 E-value for selection=1.252	E-value for HR=1.008 E-value for LL=1.000 E-value for selection=1.005	
Bladder	E-value for HR=1.331 E-value for LL=1.000 E-value for selection=1.216	E-value for HR=1.348 E-value for LL=1.000 E-value for selection=1.226	E-value for HR=1.017 E-value for LL=1.000 E-value for selection=1.012	
Colorectal	E-value for HR=1.265 E-value for UL=1.000 E-value for selection=1.175	E-value for HR=1.277 E-value for UL=1.000 E-value for selection=1.182	E-value for HR=1.000 E-value for selection=1.000	
Colon	E-value for HR=1.384 E-value for UL=1.000 E-value for selection=1.247	E-value for HR=1.601 E-value for UL=1.091 E-value for selection=1.371	E-value for HR=1.033 E-value for UL=1.000 E-value for selection=1.023	The observed HR for the high vs. low categories of 0.86 could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a HR of 1.601-fold each, above and beyond the measured confounders, but weaker confounding could not do so. An unmeasured confounder associated with the exposure and the outcome by a HR of 1.091 could explain away the upper confidence limit (0.99), but weaker confounding could not. The magnitude of selection bias that would be required to shift the HR to null=1.371.
Rectum	E-value for HR=1.176 E-value for LL=1.000 E-value for selection=1.119	E-value for HR=1.555 E-value for LL=1.000 E-value for selection=1.345	E-value for HR=1.033 E-value for LL=1.000 E-value for selection=1.023	
Brain tumours	E-value for HR=1.469 E-value for UL=1.000 E-value for selection=1.297	E-value for HR=1.566 E-value for UL=1.000 E-value for selection=1.351	E-value for HR=1.041 E-value for UL=1.000 E-value for selection=1.029	
Thyroid	E-value for HR=1.505 E-value for UL=1.000	E-value for HR=1.060 E-value for UL=1.000	E-value for HR=1.015 E-value for LL=1.000	

	E-value for selection=1.317	E-value for selection=1.041	E-value for selection=1.010	
Haematological malignancies	E-value for HR=1.332 E-value for UL=1.000 E-value for selection=1.216	E-value for HR=1.372 E-value for UL=1.000 E-value for selection=1.240	E-value for HR=1.011 E-value for LL=1.000 E-value for selection=1.008	
Non-Hodgkin's lymphoma	E-value for HR=1.399 E-value for UL=1.000 E-value for selection=1.256	E-value for HR=1.243 E-value for UL=1.000 E-value for selection=1.161	E-value for HR=1.010 E-value for LL=1.000 E-value for selection=1.007	

1144 HR: hazard ratio; LL=lower limit; UL=upper limit.

Table 2.4. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence with imputation of missing exposure data using multiple imputation by chained equations*.

		Physical activity categories			p-trend
		Low	Moderate	High	
Skin, melanoma	HR (95% CI) ^a	1.00	1.04 (0.87, 1.23)	1.03 (0.87, 1.21)	0.84
Oropharyngeal	HR (95% CI)	1.00	0.78 (0.60, 1.01)	0.87 (0.68, 1.11)	0.49
Lung	HR (95% CI) ^h	1.00	0.88 (0.76, 1.02)	0.85 (0.74, 0.97)	0.02
Breast (female only)	HR (95% CI) ^{b, h}	1.00	0.95 (0.86, 1.05)	0.88 (0.79, 0.97)	0.007
Uterus	HR (95% CI) ^c	1.00	0.95 (0.76, 1.18)	0.89 (0.69, 1.14)	0.35
Ovary	HR (95% CI)	1.00	0.95 (0.72, 1.26)	1.01 (0.76, 1.35)	0.79
Prostate	HR (95% CI) ^h	1.00	1.005 (0.93, 1.09)	1.01 (0.93, 1.10)	0.79
Oesophagus	HR (95% CI) ^f	1.00	0.92 (0.70, 1.20)	1.04 (0.81, 1.34)	0.55
Stomach	HR (95% CI)	1.00	0.93 (0.67, 1.29)	0.89 (0.65, 1.22)	0.50
Hepatobiliary tract	HR (95% CI)	1.00	0.87 (0.66, 1.15)	0.76 (0.58, 1.01)	0.051
Pancreatic	HR (95% CI) ^d	1.00	0.90 (0.69, 1.17)	0.93 (0.71, 1.21)	0.69
Kidney	HR (95% CI)	1.00	1.03 (0.84, 1.27)	0.92 (0.74, 1.14)	0.31
Bladder	HR (95% CI)	1.00	1.04 (0.82, 1.32)	1.01 (0.79, 1.30)	0.99
Colorectal	HR (95% CI) ^{e, f(males), g}	1.00	0.95 (0.86, 1.06)	0.96 (0.86, 1.07)	0.51
Colon	HR (95% CI) ^{e, f(males), g}	1.00	0.93 (0.82, 1.06)	0.88 (0.78, 1.004)	0.06
Rectum	HR (95% CI) ^{e, f(males), g}	1.00	0.999 (0.83, 1.20)	1.12 (0.92, 1.36)	0.18
Brain tumours	HR (95% CI)	1.00	0.93 (0.69, 1.25)	0.90 (0.66, 1.24)	0.53
Thyroid	HR (95% CI)	1.00	1.02 (0.69, 1.51)	1.08 (0.73, 1.59)	0.67
Haematological malignancies	HR (95% CI)	1.00	0.95 (0.83, 1.08)	0.93 (0.81, 1.06)	0.28
Non-Hodgkin's lymphoma	HR (95% CI)	1.00	0.93 (0.78, 1.12)	0.94 (0.78, 1.13)	0.61

All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]). Total observations=475,639

^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

1167 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin
1168 use (regular use/non-regular use or no use), HRT use (ever used/never used), red meat intake
1169 (portion/week), processed meat intake (portion/week).

1170 ^fModel also adjusted for waist-hip ratio (>94cm in men, >80cm in women).

1171 ^gResults for males and females combined using meta-analysis as covariates are different.

1172 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family
1173 history).

1174 *The following variables were included in the imputation model: IPAQ physical activity category,
1175 IPAQ total MET-hours/week, ethnicity, deprivation index, education, smoking status, alcohol intake,
1176 BMI, sun/UV protection use, diabetes at baseline, aspirin use, fruit/vegetable intake, red meat
1177 intake, processed meat intake, family history of cancer.

1178 **Supplementary file 3: Subgroup analyses.**

1179 **Table 3.1. Results of Cox proportional hazards analyses investigating the association between**
 1180 **IPAQ-measured physical activity and cancer incidence for subgroups defined by participant sex.**

		Females			Males		
		Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	93	245	242	106	288	268
	HR (95% CI) ^a	1.00	0.94 (0.74, 1.19)	1.04 (0.81, 1.32)	1.00	1.16 (0.93, 1.46)	1.04 (0.82, 1.30)
Oropharyngeal	Cases	30	49	54	60	99	114
	HR (95% CI)	1.00	0.62 (0.39, 0.98)	0.76 (0.48, 1.21)	1.00	0.76 (0.55, 1.06)	0.80 (0.58, 1.11)
Lung	Cases	128	258	216	156	292	297
	HR (95% CI) ^h	1.00	0.80 (0.65, 0.99)	0.75 (0.60, 0.94)	1.00	0.90 (0.74, 1.10)	0.85 (0.70, 1.04)
Breast (female only)	Cases	623	1,560	1,251	-	-	-
	HR (95% CI) ^{b, h}	1.00	0.94 (0.86, 1.03)	0.85 (0.77, 0.94)	-	-	-
Uterus	Cases	112	254	197	-	-	-
	HR (95% CI) ^c	1.00	0.98 (0.78, 1.23)	0.94 (0.74, 1.19)	-	-	-
Ovary	Cases	65	170	169	-	-	-
	HR (95% CI)	1.00	0.97 (0.73, 1.30)	1.08 (0.81, 1.45)	-	-	-
Prostate	Cases	-	-	-	734	1,877	1,981
	HR (95% CI) ^h	-	-	-	1.00	1.02 (0.94, 1.12)	1.04 (0.95, 1.13)
Oesophagus	Cases	16	41	36	58	99	130
	HR (95% CI) ^f	1.00	0.92 (0.52, 1.65)	0.91 (0.50, 1.66)	1.00	0.83 (0.60, 1.16)	1.10 (0.80, 1.51)
Stomach	Cases	16	36	27	37	72	77
	HR (95% CI)	1.00	0.85 (0.47, 1.54)	0.70 (0.37, 1.32)	1.00	0.90 (0.60, 1.34)	0.88 (0.59, 1.32)
Hepatobiliary tract	Cases	24	52	53	48	85	63
	HR (95% CI)	1.00	0.87 (0.53, 1.42)	1.01 (0.61, 1.66)	1.00	0.85 (0.59, 1.21)	0.59 (0.40, 0.87)
Pancreatic	Cases	41	79	79	49	108	104
	HR (95% CI) ^d	1.00	0.76 (0.52, 1.12)	0.88 (0.60, 1.30)	1.00	1.01 (0.72, 1.42)	0.98 (0.69, 1.38)
Kidney	Cases	39	86	51	67	162	157
	HR (95% CI)	1.00	0.93 (0.64, 1.37)	0.66 (0.43, 1.02)	1.00	1.12 (0.84, 1.50)	1.06 (0.79, 1.41)
Bladder	Cases	18	42	45	64	163	165
	HR (95% CI)	1.00	0.91 (0.52, 1.59)	1.08 (0.61, 1.89)	1.00	1.10 (0.82, 1.48)	1.06 (0.79, 1.42)
Colorectal	Cases	168	431	361	255	565	600
	HR (95% CI) ^{e, f(males)}	1.00	0.95 (0.79, 1.13)	0.90 (0.74, 1.08)	1.00	0.96 (0.83, 1.12)	0.99 (0.85, 1.15)
Colon	Cases	116	307	250	169	342	330
	HR (95% CI) ^{e, f(males)}	1.00	0.98 (0.79, 1.21)	0.90 (0.72, 1.13)	1.00	0.88 (0.73, 1.06)	0.83 (0.68, 1.002)
Rectum	Cases	47	108	96	83	216	262
	HR (95% CI) ^{e, f(males)}	1.00	0.86 (0.61, 1.22)	0.87 (0.61, 1.24)	1.00	1.12 (0.87, 1.45)	1.32 (1.02, 1.69)
Brain tumours	Cases	19	45	53	44	96	84
	HR (95% CI)	1.00	0.86 (0.50, 1.47)	1.15 (0.67, 1.96)	1.00	0.93 (0.65, 1.33)	0.74 (0.51, 1.08)
Thyroid	Cases	20	55	54	13	17	20
	HR (95% CI)	1.00	1.12 (0.67, 1.88)	1.30 (0.77, 2.19)	1.00	0.53 (0.26, 1.10)	0.55 (0.27, 1.13)
Haematological malignancies	Cases	139	320	258	177	422	461

Non-Hodgkin's lymphoma	HR (95% CI)	1.00	0.84 (0.69, 1.03)	0.76 (0.61, 0.94)	1.00	1.01 (0.85, 1.21)	1.06 (0.89, 1.27)
	Cases	68	156	143	84	194	213
	HR (95% CI)	1.00	0.84 (0.63, 1.12)	0.86 (0.64, 1.16)	1.00	0.98 (0.76, 1.28)	1.04 (0.81, 1.35)

1181 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles),
1182 education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and
1183 vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never,
1184 former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker
1185 [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current
1186 [<once/week], current [≥once/week]).

1187 ^aAdditional site-specific covariates in the final model include use of sun/UV protection
1188 (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

1189 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral
1190 contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at
1191 menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at
1192 menopause (45-55 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure),
1193 hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1194 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral
1195 contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at
1196 menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at
1197 menopause (45-55 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure),
1198 hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1199 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).

1200 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin
1201 use (regular use/non-regular use or no use), HRT use (ever used/never used), red meat intake
1202 (portion/week), processed meat intake (portion/week).

1203 ^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).

1204 ^gResults for males and females combined using meta-analysis.

1205 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family
1206 history).

1207 - Indicates not possible to estimate (e.g. incidence of sex-specific cancers).

1208 **Table 3.2. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence for**
 1209 **subgroups defined by participant age.**

		<50 years			50-55 years			55-60 years			60-65 years			≥65 years		
		Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	30	75	92	31	70	63	44	89	85	55	177	145	39	122	125
	HR (95% CI) ^a	1.00	1.05 (0.69, 1.61)	1.24 (0.82, 1.90)	1.00	1.06 (0.69, 1.63)	1.01 (0.65, 1.56)	1.00	0.94 (0.65, 1.36)	1.07 (0.74, 1.55)	1.00	1.18 (0.87, 1.60)	1.01 (0.74, 1.39)	1.00	0.97 (0.68, 1.40)	0.94 (0.65, 1.36)
Oropharyngeal	Cases	16	18	21	13	26	34	27	32	34	19	35	41	15	37	38
	HR (95% CI)	1.00	0.48 (0.24, 0.94)	0.49 (0.25, 0.96)	1.00	1.04 (0.53, 2.03)	1.25 (0.65, 2.39)	1.00	0.57 (0.34, 0.96)	0.65 (0.39, 1.09)	1.00	0.69 (0.40, 1.22)	0.79 (0.46, 1.38)	1.00	0.97 (0.53, 1.77)	1.03 (0.56, 1.89)
Lung	Cases	10	24	17	27	34	42	50	95	72	87	174	183	110	223	199
	HR (95% CI) ^h	1.00	1.14 (0.54, 2.40)	0.71 (0.32, 1.57)	1.00	0.72 (0.43, 1.20)	0.84 (0.51, 1.37)	1.00	0.996 (0.70, 1.41)	0.78 (0.54, 1.13)	1.00	0.90 (0.70, 1.17)	0.99 (0.76, 1.28)	1.00	0.77 (0.61, 0.97)	0.69 (0.54, 0.87)
Breast (female only)	Cases	157	386	281	99	211	175	139	299	228	161	401	351	67	263	216
	HR (95% CI) ^{b, h}	1.00	1.01 (0.84, 1.22)	0.82 (0.67, 0.999)	1.00	0.94 (0.74, 1.20)	0.91 (0.71, 1.17)	1.00	0.90 (0.73, 1.10)	0.83 (0.67, 1.03)	1.00	0.82 (0.68, 0.98)	0.80 (0.66, 0.97)	1.00	1.19 (0.91, 1.56)	1.02 (0.77, 1.35)
Uterus	Cases	10	23	20	26	44	17	35	61	40	29	75	75	12	51	45
	HR (95% CI) ^c	1.00	1.06 (0.50, 2.26)	1.06 (0.48, 2.34)	1.00	0.83 (0.50, 1.36)	0.42 (0.22, 0.79)	1.00	0.85 (0.56, 1.30)	0.76 (0.47, 1.21)	1.00	1.03 (0.67, 1.59)	1.27 (0.81, 1.97)	1.00	1.54 (0.81, 2.93)	1.53 (0.79, 2.96)
Ovary	Cases	12	31	23	12	23	17	14	27	35	15	48	45	12	41	49
	HR (95% CI)	1.00	1.14 (0.58, 2.24)	0.998 (0.49, 2.04)	1.00	0.83 (0.41, 1.69)	0.74 (0.34, 1.58)	1.00	0.82 (0.43, 1.57)	1.29 (0.68, 2.42)	1.00	1.06 (0.59, 1.90)	1.09 (0.60, 1.98)	1.00	1.03 (0.54, 1.97)	1.27 (0.67, 2.41)
Prostate	Cases	29	47	55	61	133	123	132	309	291	280	723	757	232	665	755
	HR (95% CI) ^h	1.00	0.83 (0.51, 1.32)	0.84 (0.53, 1.34)	1.00	1.12 (0.83, 1.52)	0.97 (0.71, 1.33)	1.00	1.14 (0.93, 1.40)	1.09 (0.88, 1.34)	1.00	1.04 (0.90, 1.19)	1.07 (0.93, 1.24)	1.00	0.95 (0.82, 1.11)	0.99 (0.86, 1.16)
Oesophagus	Cases	5	4	7	4	10	13	20	27	32	19	38	55	26	61	59
	HR (95% CI) ^f	1.00	0.37 (0.10, 1.39)	0.54 (0.16, 1.77)	1.00	1.55 (0.48, 4.97)	2.04 (0.65, 6.42)	1.00	0.80 (0.44, 1.43)	1.04 (0.59, 1.85)	1.00	0.86 (0.49, 1.50)	1.28 (0.75, 2.18)	1.00	0.88 (0.55, 1.40)	0.88 (0.55, 1.40)
Stomach	Cases	8	11	8	5	7	11	7	17	7	13	32	37	20	41	41
	HR (95% CI)	1.00	0.74 (0.30, 1.86)	0.49 (0.18, 1.33)	1.00	0.74 (0.23, 2.36)	1.10 (0.37, 3.26)	1.00	1.32 (0.54, 3.23)	0.61 (0.21, 1.78)	1.00	1.01 (0.53, 1.93)	1.13 (0.59, 2.16)	1.00	0.75 (0.44, 1.29)	0.72 (0.41, 1.24)
Hepatobiliary tract	Cases	7	4	4	8	14	16	14	29	15	25	39	38	18	51	53
	HR (95% CI)	1.00	0.27 (0.08, 0.93)	0.22 (0.06, 0.80)	1.00	0.96 (0.40, 2.30)	1.11 (0.46, 2.66)	1.00	1.003 (0.53, 1.91)	0.59 (0.28, 1.23)	1.00	0.65 (0.39, 1.07)	0.64 (0.38, 1.08)	1.00	1.19 (0.69, 2.05)	0.997 (0.57, 1.75)

Pancreatic	Cases	6	7	10	12	18	12	17	30	38	27	60	61	28	72	62
	HR (95% CI) ^d	1.00	0.66 (0.22, 1.98)	0.95 (0.33, 2.71)	1.00	0.86 (0.41, 1.80)	0.63 (0.27, 1.43)	1.00	0.92 (0.50, 1.68)	1.38 (0.76, 2.48)	1.00	0.89 (0.56, 1.40)	0.95 (0.60, 1.52)	1.00	0.92 (0.59, 1.44)	0.82 (0.52, 1.30)
Kidney	Cases	13	18	13	12	18	18	22	42	37	29	83	70	30	87	70
	HR (95% CI)	1.00	0.73 (0.35, 1.50)	0.45 (0.20, 0.99)	1.00	0.88 (0.42, 1.83)	1.01 (0.48, 2.13)	1.00	1.05 (0.62, 1.77)	1.06 (0.61, 1.82)	1.00	1.22 (0.80, 1.87)	1.07 (0.69, 1.67)	1.00	1.10 (0.72, 1.67)	0.89 (0.57, 1.38)
Bladder	Cases	2	7	6	11	12	11	13	29	33	28	68	67	28	89	93
	HR (95% CI)	1.00	1.70 (0.35, 8.26)	1.17 (0.23, 5.93)	1.00	0.61 (0.27, 1.40)	0.51 (0.22, 1.21)	1.00	1.13 (0.58, 2.17)	1.37 (0.71, 2.63)	1.00	1.09 (0.70, 1.69)	1.07 (0.68, 1.68)	1.00	1.12 (0.73, 1.72)	1.13 (0.73, 1.74)
Colorectal	Cases	30	80	77	56	112	109	95	172	152	127	310	308	115	322	315
	HR (95% CI) ^e , f(males), g	1.00	1.18 (0.77, 1.80)	1.10 (0.71, 1.70)	1.00	0.99 (0.72, 1.37)	1.02 (0.73, 1.42)	1.00	0.87 (0.68, 1.12)	0.84 (0.65, 1.10)	1.00	0.94 (0.76, 1.15)	0.97 (0.79, 1.20)	1.00	0.96 (0.78, 1.20)	0.94 (0.75, 1.17)
Colon	Cases	21	49	50	33	70	51	58	107	93	89	203	191	84	220	195
	HR (95% CI) ^e , f(males), g	1.00	1.02 (0.60, 1.73)	1.04 (0.62, 1.77)	1.00	1.04 (0.68, 1.57)	0.78 (0.50, 1.23)	1.00	0.89 (0.65, 1.23)	0.85 (0.61, 1.19)	1.00	0.87 (0.68, 1.12)	0.86 (0.67, 1.12)	1.00	0.91 (0.71, 1.18)	0.82 (0.63, 1.07)
Rectum	Cases	9	26	30	22	39	53	34	59	58	37	100	105	28	100	112
	HR (95% CI) ^e , f(males), g	1.00	1.29 (0.60, 2.77)	1.42 (0.66, 3.05)	1.00	0.89 (0.52, 1.52)	1.31 (0.78, 2.21)	1.00	0.83 (0.54, 1.27)	0.89 (0.58, 1.38)	1.00	1.05 (0.72, 1.53)	1.14 (0.78, 1.67)	1.00	1.21 (0.79, 1.84)	1.28 (0.83, 1.95)
Brain tumours	Cases	8	19	14	4	16	15	13	32	26	22	34	41	16	40	41
	HR (95% CI)	1.00	1.05 (0.46, 2.42)	0.74 (0.31, 1.79)	1.00	2.18 (0.72, 6.57)	2.17 (0.71, 6.67)	1.00	1.16 (0.60, 2.21)	1.04 (0.53, 2.05)	1.00	0.61 (0.35, 1.05)	0.77 (0.45, 1.30)	1.00	0.76 (0.42, 1.36)	0.70 (0.39, 1.26)
Thyroid	Cases	11	15	12	5	8	15	6	14	15	5	26	19	6	9	13
	HR (95% CI)	1.00	0.66 (0.30, 1.45)	0.55 (0.24, 1.28)	1.00	0.73 (0.24, 2.25)	1.44 (0.51, 4.08)	1.00	1.10 (0.42, 2.88)	1.43 (0.54, 3.75)	1.00	1.89 (0.72, 4.95)	1.52 (0.56, 4.13)	1.00	0.40 (0.14, 1.15)	0.59 (0.22, 1.60)
Haematological malignancies	Cases	32	58	68	39	57	87	57	120	106	102	259	229	86	248	229
	HR (95% CI)	1.00	0.81 (0.53, 1.26)	0.86 (0.56, 1.32)	1.00	0.72 (0.48, 1.09)	1.10 (0.75, 1.62)	1.00	1.01 (0.73, 1.39)	0.98 (0.70, 1.36)	1.00	0.97 (0.77, 1.22)	0.88 (0.69, 1.11)	1.00	0.98 (0.76, 1.25)	0.91 (0.71, 1.17)
Non-Hodgkin's lymphoma	Cases	14	22	34	20	28	38	26	57	64	46	125	102	46	118	118
	HR (95% CI)	1.00	0.67 (0.34, 1.31)	0.89 (0.47, 1.68)	1.00	0.70 (0.39, 1.25)	0.96 (0.55, 1.67)	1.00	1.05 (0.65, 1.67)	1.29 (0.81, 2.06)	1.00	1.03 (0.73, 1.45)	0.87 (0.61, 1.25)	1.00	0.88 (0.62, 1.24)	0.89 (0.63, 1.27)

1210 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

1211

1212

1213

1214 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

1215

1216 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1217 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1218 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1219 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1220 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1221 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1222 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
1223 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
1224 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
1225 ^fFinal model also adjusted for waist-hip ratio (>94 cm in men, >80 cm in women).
1226 ^gResults for males and females combined using meta-analysis.
1227 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

1228 **Table 3.3. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence for**
 1229 **subgroups defined by deprivation quintile.**

		1 (least deprived)			2			3			4			5 (most deprived)		
		Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	47	145	129	47	121	133	39	101	111	33	103	78	33	63	59
	HR (95% CI) ^a	1.00	1.23 (0.89, 1.72)	1.16 (0.82, 1.62)	1.00	1.03 (0.73, 1.45)	1.17 (0.83, 1.64)	1.00	0.995 (0.69, 1.44)	1.14 (0.79, 1.66)	1.00	1.17 (0.79, 1.74)	0.89 (0.59, 1.35)	1.00	0.76 (0.50, 1.17)	0.70 (0.45, 1.09)
Oropharyngeal	Cases	13	19	26	15	31	32	24	35	27	16	29	35	22	34	48
	HR (95% CI)	1.00	0.67 (0.33, 1.37)	0.96 (0.48, 1.90)	1.00	0.87 (0.47, 1.62)	0.92 (0.49, 1.71)	1.00	0.62 (0.37, 1.05)	0.47 (0.27, 0.82)	1.00	0.79 (0.43, 1.47)	0.95 (0.52, 1.75)	1.00	0.70 (0.41, 1.21)	0.92 (0.55, 1.54)
Lung	Cases	41	90	71	50	102	77	36	97	83	55	113	108	102	148	174
	HR (95% CI) ^h	1.00	0.90 (0.62, 1.31)	0.75 (0.50, 1.11)	1.00	0.90 (0.64, 1.26)	0.70 (0.49, 1.01)	1.00	1.09 (0.74, 1.60)	0.91 (0.61, 1.36)	1.00	0.87 (0.63, 1.21)	0.82 (0.59, 1.14)	1.00	0.72 (0.55, 0.92)	0.83 (0.65, 1.07)
Breast (female only)	Cases	141	348	271	135	312	291	140	307	238	115	340	260	92	253	191
	HR (95% CI) ^{b, h}	1.00	0.95 (0.78, 1.15)	0.83 (0.67, 1.02)	1.00	0.88 (0.72, 1.08)	0.93 (0.76, 1.15)	1.00	0.81 (0.66, 0.99)	0.71 (0.57, 0.88)	1.00	1.10 (0.89, 1.36)	0.94 (0.75, 1.18)	1.00	1.01 (0.79, 1.29)	0.90 (0.69, 1.16)
Uterus	Cases	20	41	37	23	51	44	24	52	37	24	63	40	21	47	39
	HR (95% CI) ^c	1.00	0.87 (0.50, 1.50)	0.91 (0.52, 1.61)	1.00	0.98 (0.59, 1.61)	1.08 (0.64, 1.82)	1.00	0.94 (0.57, 1.54)	0.80 (0.47, 1.38)	1.00	1.13 (0.70, 1.82)	0.87 (0.52, 1.47)	1.00	0.96 (0.57, 1.62)	1.07 (0.62, 1.85)
Ovary	Cases	8	26	33	11	39	37	17	41	36	15	35	30	14	29	33
	HR (95% CI)	1.00	1.14 (0.51, 2.54)	1.55 (0.71, 3.41)	1.00	1.37 (0.70, 2.68)	1.43 (0.72, 2.83)	1.00	0.97 (0.55, 1.73)	1.01 (0.56, 1.83)	1.00	0.85 (0.46, 1.57)	0.81 (0.43, 1.52)	1.00	0.74 (0.39, 1.41)	0.94 (0.49, 1.78)
Prostate	Cases	174	457	463	172	392	469	154	407	412	130	346	351	104	275	286
	HR (95% CI) ^h	1.00	1.08 (0.91, 1.29)	1.11 (0.93, 1.32)	1.00	0.87 (0.73, 1.04)	0.98 (0.82, 1.17)	1.00	1.06 (0.88, 1.27)	0.999 (0.83, 1.21)	1.00	1.02 (0.83, 1.25)	0.98 (0.80, 1.20)	1.00	1.17 (0.93, 1.47)	1.17 (0.93, 1.47)
Oesophagus	Cases	17	23	30	14	23	35	13	35	35	13	20	35	17	39	31
	HR (95% CI) ^f	1.00	0.59 (0.31, 1.11)	0.81 (0.44, 1.49)	1.00	0.72 (0.37, 1.41)	1.07 (0.56, 2.02)	1.00	1.12 (0.59, 2.12)	1.14 (0.60, 2.19)	1.00	0.73 (0.36, 1.47)	1.31 (0.68, 2.51)	1.00	1.17 (0.66, 2.09)	1.02 (0.56, 1.87)
Stomach	Cases	6	15	24	8	11	27	6	23	20	15	36	19	18	23	14
	HR (95% CI)	1.00	0.95 (0.37, 2.47)	1.49 (0.60, 3.71)	1.00	0.60 (0.24, 1.49)	1.50 (0.67, 3.37)	1.00	1.52 (0.61, 3.77)	1.30 (0.51, 3.28)	1.00	1.06 (0.58, 1.96)	0.53 (0.27, 1.06)	1.00	0.61 (0.33, 1.15)	0.37 (0.18, 0.76)
Hepatobiliary tract	Cases	11	13	26	11	28	16	20	32	29	11	37	20	19	27	25
	HR (95% CI)	1.00	0.53 (0.23, 1.19)	1.10 (0.53, 2.29)	1.00	1.10 (0.54, 2.23)	0.66 (0.30, 1.46)	1.00	0.65 (0.37, 1.14)	0.59 (0.33, 1.06)	1.00	1.41 (0.71, 2.78)	0.74 (0.35, 1.57)	1.00	0.77 (0.42, 1.39)	0.71 (0.38, 1.31)
Pancreatic	Cases	19	35	31	17	44	38	21	37	46	13	36	32	20	35	36
	HR (95% CI) ^d	1.00	0.74	0.68	1.00	1.10	1.07	1.00	0.76	0.97	1.00	1.23	1.16	1.00	0.79	0.87

			(0.42, 1.29)	(0.38, 1.23)		(0.62, 1.94)	(0.59, 1.92)		(0.44, 1.31)	(0.57, 1.64)		(0.65, 2.33)	(0.60, 2.25)		(0.45, 1.38)	(0.50, 1.53)
Kidney	Cases	21	63	43	16	45	53	23	70	44	27	26	35	19	44	33
	HR (95% CI)	1.00	1.33 (0.81, 2.19)	0.97 (0.57, 1.65)	1.00	1.24 (0.70, 2.21)	1.57 (0.88, 2.78)	1.00	1.30 (0.81, 2.09)	0.84 (0.50, 1.42)	1.00	0.44 (0.25, 0.75)	0.57 (0.34, 0.97)	1.00	1.22 (0.71, 2.11)	0.94 (0.53, 1.68)
Bladder	Cases	19	42	48	19	37	47	23	43	43	10	46	36	11	37	36
	HR (95% CI)	1.00	0.91 (0.53, 1.57)	1.03 (0.60, 1.78)	1.00	0.78 (0.45, 1.36)	0.94 (0.54, 1.62)	1.00	0.79 (0.47, 1.31)	0.76 (0.45, 1.28)	1.00	1.92 (0.96, 3.82)	1.49 (0.73, 3.04)	1.00	1.59 (0.81, 3.14)	1.52 (0.77, 3.03)
Colorectal	Cases	93	214	227	97	209	219	85	204	169	71	184	196	77	185	150
	HR (95% CI) ^e f(males), g	1.00	0.95 (0.74, 1.21)	1.08 (0.85, 1.39)	1.00	0.88 (0.69, 1.12)	0.96 (0.75, 1.23)	1.00	0.97 (0.75, 1.26)	0.83 (0.64, 1.08)	1.00	1.01 (0.77, 1.34)	1.08 (0.82, 1.43)	1.00	0.996 (0.76, 1.31)	0.82 (0.62, 1.09)
Colon	Cases	62	129	140	75	133	132	50	143	96	50	125	124	48	119	88
	HR (95% CI) ^e f(males), g	1.00	0.87 (0.64, 1.19)	1.03 (0.76, 1.40)	1.00	0.73 (0.55, 0.97)	0.77 (0.57, 1.03)	1.00	1.17 (0.84, 1.62)	0.81 (0.57, 1.15)	1.00	0.95 (0.69, 1.33)	0.95 (0.68, 1.32)	1.00	1.02 (0.72, 1.43)	0.77 (0.54, 1.11)
Rectum	Cases	30	86	85	22	75	80	34	56	70	19	53	63	25	54	60
	HR (95% CI) ^e f(males), g	1.00	1.15 (0.76, 1.75)	1.19 (0.78, 1.83)	1.00	1.38 (0.86, 2.23)	1.50 (0.93, 2.42)	1.00	0.66 (0.43, 1.02)	0.84 (0.55, 1.28)	1.00	1.07 (0.62, 1.85)	1.24 (0.72, 2.15)	1.00	0.93 (0.58, 1.50)	1.03 (0.64, 1.67)
Brain tumours	Cases	7	27	24	18	39	22	11	28	30	15	29	30	12	18	31
	HR (95% CI)	1.00	1.56 (0.68, 3.60)	1.50 (0.64, 3.54)	1.00	0.90 (0.51, 1.58)	0.52 (0.27, 0.98)	1.00	1.04 (0.51, 2.09)	1.07 (0.53, 2.17)	1.00	0.75 (0.40, 1.40)	0.73 (0.39, 1.39)	1.00	0.58 (0.28, 1.22)	0.99 (0.50, 1.95)
Thyroid	Cases	8	20	13	8	18	13	3	11	13	9	10	21	5	13	14
	HR (95% CI)	1.00	1.07 (0.46, 2.44)	0.78 (0.32, 1.93)	1.00	0.86 (0.37, 2.00)	0.69 (0.28, 1.69)	1.00	1.49 (0.41, 5.42)	1.87 (0.52, 6.75)	1.00	0.50 (0.20, 1.23)	1.16 (0.52, 2.60)	1.00	0.94 (0.33, 2.67)	1.02 (0.36, 2.88)
Haematological malignancies	Cases	69	173	168	75	139	144	63	162	138	43	150	137	66	118	132
	HR (95% CI)	1.00	0.98 (0.74, 1.29)	0.98 (0.73, 1.30)	1.00	0.73 (0.55, 0.96)	0.78 (0.58, 1.03)	1.00	1.04 (0.77, 1.39)	0.89 (0.66, 1.21)	1.00	1.37 (0.97, 1.93)	1.25 (0.88, 1.77)	1.00	0.75 (0.55, 1.02)	0.85 (0.63, 1.15)
Non-Hodgkin's lymphoma	Cases	38	77	87	42	64	63	25	77	64	20	69	80	27	63	62
	HR (95% CI)	1.00	0.78 (0.52, 1.15)	0.89 (0.60, 1.32)	1.00	0.59 (0.40, 0.87)	0.60 (0.40, 0.89)	1.00	1.25 (0.80, 1.98)	1.09 (0.68, 1.75)	1.00	1.37 (0.83, 2.26)	1.59 (0.97, 2.62)	1.00	1.001 (0.63, 1.58)	0.995 (0.63, 1.58)

1230 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

1234 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

1236 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1239 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1240 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
1241 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1242 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
1243 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
1244 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
1245 ^fFinal model also adjusted for waist-hip ratio (>94cm in men, >80cm in women).
1246 ^gResults for males and females combined using meta-analysis.
1247 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

1248 **Table 3.4. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence for**
 1249 **subgroups defined by smoking status.**

		Never			Former light smoker			Former heavy smoker			Current light smoker			Current heavy smoker		
		Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	119	301	293	51	157	146	16	48	43	6	11	21	7	16	7
	HR (95% CI) ^a	1.00	0.96 (0.77, 1.19)	0.97 (0.78, 1.21)	1.00	1.15 (0.84, 1.58)	1.06 (0.77, 1.47)	1.00	1.49 (0.84, 2.64)	1.38 (0.77, 2.48)	1.00	0.78 (0.29, 2.12)	1.66 (0.66, 4.19)	1.00	1.31 (0.54, 3.21)	0.60 (0.21, 1.73)
Oropharyngeal	Cases	29	55	54	20	33	58	15	25	21	7	10	13	19	25	22
	HR (95% CI)	1.00	0.76 (0.48, 1.20)	0.75 (0.47, 1.20)	1.00	0.64 (0.36, 1.11)	1.09 (0.65, 1.83)	1.00	0.76 (0.40, 1.46)	0.61 (0.31, 1.21)	1.00	0.62 (0.23, 1.63)	0.73 (0.29, 1.88)	1.00	0.77 (0.42, 1.40)	0.66 (0.35, 1.22)
Lung	Cases	38	90	70	26	84	101	101	172	149	35	49	54	84	155	139
	HR (95% CI) ^h	1.00	0.83 (0.57, 1.22)	0.67 (0.45, 1.01)	1.00	1.15 (0.74, 1.79)	1.33 (0.86, 2.07)	1.00	0.72 (0.56, 0.92)	0.63 (0.48, 0.81)	1.00	0.57 (0.37, 0.89)	0.62 (0.40, 0.95)	1.00	1.08 (0.83, 1.42)	1.003 (0.76, 1.32)
Breast (female only)	Cases	353	909	716	159	413	356	45	91	86	32	86	64	34	61	29
	HR (95% CI) ^{b, h}	1.00	0.94 (0.83, 1.07)	0.86 (0.75, 0.98)	1.00	0.93 (0.77, 1.11)	0.86 (0.71, 1.04)	1.00	0.81 (0.56, 1.16)	0.89 (0.61, 1.29)	1.00	1.11 (0.74, 1.68)	0.96 (0.62, 1.48)	1.00	1.02 (0.67, 1.56)	0.62 (0.37, 1.03)
Uterus	Cases	76	165	122	24	63	51	7	16	17	4	3	6	1	7	1
	HR (95% CI) ^c	1.00	0.93 (0.71, 1.23)	0.87 (0.64, 1.17)	1.00	1.04 (0.65, 1.68)	0.98 (0.59, 1.61)	1.00	1.21 (0.49, 3.01)	1.76 (0.70, 4.42)	1.00	0.29 (0.06, 1.35)	0.63 (0.16, 2.45)	1.00	3.69 (0.42, 32.52)	0.98 (0.06, 16.65)
Ovary	Cases	39	98	97	12	46	42	8	12	18	3	6	8	3	8	4
	HR (95% CI)	1.00	0.91 (0.63, 1.32)	1.03 (0.70, 1.51)	1.00	1.39 (0.74, 2.64)	1.40 (0.73, 2.68)	1.00	0.59 (0.24, 1.47)	0.94 (0.40, 2.22)	1.00	0.83 (0.21, 3.38)	1.25 (0.32, 4.87)	1.00	1.45 (0.38, 5.53)	0.85 (0.18, 3.90)
Prostate	Cases	328	923	969	217	583	610	106	224	237	38	81	102	45	66	63
	HR (95% CI) ^h	1.00	1.09 (0.96, 1.24)	1.11 (0.98, 1.27)	1.00	0.996 (0.85, 1.17)	0.96 (0.82, 1.13)	1.00	0.95 (0.75, 1.20)	0.97 (0.77, 1.23)	1.00	0.91 (0.62, 1.35)	1.09 (0.75, 1.60)	1.00	0.95 (0.65, 1.40)	0.90 (0.61, 1.33)
Oesophagus	Cases	24	42	46	19	41	55	16	31	36	3	11	15	12	15	14
	HR (95% CI) ^f	1.00	0.73 (0.44, 1.22)	0.83 (0.50, 1.37)	1.00	0.90 (0.52, 1.56)	1.23 (0.72, 2.10)	1.00	0.91 (0.49, 1.67)	1.11 (0.61, 2.03)	1.00	1.72 (0.47, 6.20)	2.70 (0.77, 9.47)	1.00	0.71 (0.33, 1.54)	0.67 (0.31, 1.48)
Stomach	Cases	22	39	36	15	30	27	9	20	23	2	8	10	5	11	8
	HR (95% CI)	1.00	0.63 (0.37, 1.07)	0.56 (0.32, 0.96)	1.00	0.85 (0.45, 1.58)	0.76 (0.40, 1.45)	1.00	1.09 (0.49, 2.41)	1.15 (0.52, 2.55)	1.00	1.92 (0.40, 9.12)	2.65 (0.57, 12.25)	1.00	1.39 (0.48, 4.03)	1.06 (0.34, 3.31)
Hepatobiliary tract	Cases	39	42	49	10	51	31	13	24	22	3	6	7	7	14	7
	HR (95% CI)	1.00	0.43 (0.28, 0.67)	0.51 (0.33, 0.79)	1.00	2.04 (1.03, 4.04)	1.19 (0.57, 2.45)	1.00	0.93 (0.47, 1.84)	0.87 (0.43, 1.75)	1.00	0.94 (0.23, 3.84)	1.03 (0.26, 4.15)	1.00	1.44 (0.58, 3.61)	0.75 (0.26, 2.18)

Pancreatic	Cases	43	83	82	20	46	39	9	29	28	4	10	14	14	19	20
	HR (95% CI) ^d	1.00	0.76 (0.52, 1.10)	0.83 (0.57, 1.22)	1.00	0.90 (0.53, 1.52)	0.77 (0.44, 1.34)	1.00	1.46 (0.69, 3.11)	1.44 (0.67, 3.09)	1.00	1.15 (0.36, 3.72)	1.63 (0.52, 5.04)	1.00	0.82 (0.41, 1.65)	0.97 (0.48, 1.94)
Kidney	Cases	44	120	79	28	70	66	22	28	38	6	11	13	6	19	12
	HR (95% CI)	1.00	1.14 (0.80, 1.62)	0.79 (0.54, 1.15)	1.00	1.01 (0.65, 1.57)	0.96 (0.61, 1.51)	1.00	0.68 (0.39, 1.20)	0.93 (0.54, 1.61)	1.00	0.97 (0.35, 2.69)	1.17 (0.43, 3.18)	1.00	2.02 (0.80, 5.10)	1.42 (0.53, 3.84)
Bladder	Cases	25	50	72	17	63	61	19	56	39	6	14	17	15	22	21
	HR (95% CI)	1.00	0.74 (0.46, 1.20)	1.05 (0.66, 1.68)	1.00	1.34 (0.78, 2.30)	1.22 (0.70, 2.10)	1.00	1.33 (0.79, 2.26)	0.93 (0.53, 1.62)	1.00	1.16 (0.44, 3.06)	1.59 (0.61, 4.12)	1.00	0.92 (0.48, 1.79)	0.86 (0.44, 1.68)
Colorectal	Cases	192	488	438	101	284	291	75	129	150	25	55	41	30	40	41
	HR (95% CI) ^e , f(males), g	1.00	0.99 (0.84, 1.17)	0.94 (0.79, 1.12)	1.00	1.04 (0.83, 1.31)	1.05 (0.84, 1.33)	1.00	0.80 (0.60, 1.07)	0.96 (0.72, 1.28)	1.00	0.91 (0.56, 1.49)	0.61 (0.36, 1.06)	1.00	0.73 (0.45, 1.19)	0.82 (0.49, 1.37)
Colon	Cases	130	325	288	69	192	162	50	78	84	16	38	26	20	16	20
	HR (95% CI) ^e , f(males), g	1.00	0.97 (0.79, 1.19)	0.92 (0.75, 1.14)	1.00	1.04 (0.78, 1.34)	0.87 (0.65, 1.16)	1.00	0.75 (0.52, 1.07)	0.82 (0.57, 1.18)	1.00	0.96 (0.52, 1.76)	0.55 (0.27, 1.12)	1.00	0.44 (0.23, 0.86)	0.60 (0.32, 1.14)
Rectum	Cases	58	153	139	30	88	124	25	50	63	9	14	15	8	19	17
	HR (95% CI) ^e , f(males), g	1.00	1.05 (0.77, 1.42)	0.98 (0.71, 1.34)	1.00	1.08 (0.71, 1.64)	1.45 (0.96, 2.19)	1.00	0.88 (0.54, 1.44)	1.14 (0.70, 1.86)	1.00	0.71 (0.30, 1.66)	0.72 (0.30, 1.72)	1.00	1.21 (0.50, 2.90)	2.52 (0.84, 7.60)
Brain tumours	Cases	25	73	72	12	45	49	13	9	8	5	9	4	8	5	4
	HR (95% CI)	1.00	1.10 (0.69, 1.73)	1.10 (0.69, 1.75)	1.00	1.43 (0.75, 2.71)	1.55 (0.82, 2.94)	1.00	0.33 (0.14, 0.79)	0.30 (0.12, 0.74)	1.00	0.80 (0.27, 2.42)	0.32 (0.09, 1.24)	1.00	0.40 (0.13, 1.25)	0.29 (0.09, 0.99)
Thyroid	Cases	18	45	38	6	16	25	6	6	4	2	4	4	1	1	3
	HR (95% CI)	1.00	0.99 (0.57, 1.72)	0.93 (0.52, 1.65)	1.00	1.06 (0.41, 2.74)	1.75 (0.70, 4.36)	1.00	0.43 (0.14, 1.36)	0.30 (0.08, 1.11)	1.00	0.81 (0.15, 4.49)	0.90 (0.16, 5.05)	1.00	0.66 (0.04, 11.52)	2.73 (0.25, 29.90)
Haematological malignancies	Cases	149	360	376	79	213	183	43	91	97	17	40	29	28	38	34
	HR (95% CI)	1.00	0.91 (0.75, 1.10)	0.99 (0.81, 1.20)	1.00	0.999 (0.77, 1.30)	0.84 (0.64, 1.10)	1.00	0.97 (0.67, 1.40)	1.05 (0.73, 1.51)	1.00	1.04 (0.59, 1.84)	0.74 (0.40, 1.36)	1.00	0.79 (0.48, 1.30)	0.73 (0.44, 1.22)
Non-Hodgkin's lymphoma	Cases	72	177	200	37	96	81	19	35	47	8	23	11	16	19	17
	HR (95% CI)	1.00	0.92 (0.70, 1.21)	1.09 (0.83, 1.44)	1.00	0.96 (0.66, 1.41)	0.80 (0.54, 1.18)	1.00	0.84 (0.48, 1.47)	1.15 (0.66, 1.98)	1.00	1.35 (0.60, 3.04)	0.67 (0.26, 1.69)	1.00	0.71 (0.36, 1.38)	0.66 (0.33, 1.32)

1250 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-
1251 level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light
1252 smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol
1253 intake (never, former, current [<once/week], current [≥once/week]).
1254 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in
1255 sunshine).

1256 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1257 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1258 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1259 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1260 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1261 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1262 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
1263 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
1264 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
1265 ^fFinal model also adjusted for waist-hip ratio (>94 cm in men, >80 cm in women).
1266 ^gResults for males and females combined using meta-analysis.
1267 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).

1268 **Table 3.5. Results of Cox proportional hazards analyses investigating the association between**
 1269 **IPAQ-measured physical activity and cancer incidence for subgroups defined by participant BMI.**

		Non-obese			Obese		
		Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	136	416	421	63	117	89
	HR (95% CI) ^a	1.00	1.05 (0.87, 1.28)	1.05 (0.86, 1.28)	1.00	1.06 (0.78, 1.44)	0.98 (0.71, 1.37)
Oropharyngeal	Cases	56	107	137	34	41	31
	HR (95% CI)	1.00	0.73 (0.53, 1.01)	0.86 (0.63, 1.18)	1.00	0.73 (0.46, 1.15)	0.65 (0.40, 1.07)
Lung	Cases	191	406	405	93	144	108
	HR (95% CI) ^h	1.00	0.83 (0.70, 0.98)	0.79 (0.66, 0.94)	1.00	0.94 (0.73, 1.23)	0.85 (0.64, 1.12)
Breast (female only)	Cases	426	1,190	1,021	197	370	230
	HR (95% CI) ^{b, h}	1.00	0.91 (0.82, 1.02)	0.84 (0.75, 0.94)	1.00	0.999 (0.84, 1.19)	0.87 (0.71, 1.05)
Uterus	Cases	52	159	113	60	95	84
	HR (95% CI) ^c	1.00	0.96 (0.70, 1.31)	0.75 (0.54, 1.05)	1.00	0.95 (0.68, 1.31)	1.25 (0.89, 1.76)
Ovary	Cases	45	120	136	20	50	33
	HR (95% CI)	1.00	0.84 (0.59, 1.18)	0.98 (0.70, 1.38)	1.00	1.37 (0.81, 2.31)	1.30 (0.74, 2.29)
Prostate	Cases	502	1,453	1,620	232	424	361
	HR (95% CI) ^h	1.00	1.03 (0.93, 1.14)	1.06 (0.96, 1.17)	1.00	1.02 (0.87, 1.20)	0.95 (0.81, 1.13)
Oesophagus	Cases	44	99	112	30	41	54
	HR (95% CI) ^f	1.00	0.84 (0.59, 1.20)	0.94 (0.66, 1.34)	1.00	0.89 (0.55, 1.43)	1.38 (0.87, 2.18)
Stomach	Cases	27	78	86	26	30	18
	HR (95% CI)	1.00	1.03 (0.66, 1.60)	1.04 (0.67, 1.60)	1.00	0.72 (0.42, 1.23)	0.50 (0.27, 0.93)
Hepatobiliary tract	Cases	41	75	78	31	62	38
	HR (95% CI)	1.00	0.64 (0.44, 0.94)	0.63 (0.43, 0.93)	1.00	1.20 (0.77, 1.85)	0.83 (0.51, 1.34)
Pancreatic	Cases	51	136	131	39	51	52
	HR (95% CI) ^d	1.00	0.94 (0.68, 1.31)	0.91 (0.66, 1.26)	1.00	0.80 (0.53, 1.23)	1.04 (0.68, 1.60)
Kidney	Cases	53	164	138	53	84	70
	HR (95% CI)	1.00	1.12 (0.82, 1.53)	0.91 (0.66, 1.26)	1.00	0.97 (0.68, 1.37)	0.96 (0.67, 1.39)
Bladder	Cases	47	137	160	35	68	50
	HR (95% CI)	1.00	1.05 (0.75, 1.46)	1.13 (0.81, 1.57)	1.00	1.13 (0.75, 1.70)	0.94 (0.61, 1.47)
Colorectal	Cases	283	720	750	140	276	211
	HR (95% CI) ^{e, f(males), g}	1.00	0.89 (0.77, 1.02)	0.91 (0.79, 1.05)	1.00	1.13 (0.92, 1.39)	1.03 (0.83, 1.29)
Colon	Cases	183	459	445	102	190	135
	HR (95% CI) ^{e, f(males), g}	1.00	0.86 (0.72, 1.02)	0.83 (0.70, 0.99)	1.00	1.06 (0.83, 1.35)	0.90 (0.69, 1.17)
Rectum	Cases	95	239	284	35	85	74
	HR (95% CI) ^{e, f(males), g}	1.00	0.90 (0.71, 1.14)	1.04 (0.82, 1.32)	1.00	1.41 (0.95, 2.10)	1.44 (0.96, 2.17)
Brain tumours	Cases	42	107	108	21	34	29
	HR (95% CI)	1.00	0.87 (0.60, 1.24)	0.84 (0.58, 1.20)	1.00	0.97 (0.56, 1.68)	0.96 (0.54, 1.69)
Thyroid	Cases	20	52	55	13	20	19
	HR (95% CI)	1.00	0.89 (0.53, 1.50)	0.97 (0.57, 1.62)	1.00	0.86 (0.43, 1.74)	1.07 (0.52, 2.21)
Haematological malignancies	Cases	209	563	560	107	179	159
	HR (95% CI)	1.00	0.93 (0.79, 1.09)	0.90 (0.77, 1.06)	1.00	0.94 (0.74, 1.20)	0.99 (0.77, 1.27)

1296 **Table 3.6. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and cancer incidence for**
 1297 **subgroups defined by body fat percentage and physical activity level.**

		High/moderate PA and low/optimal BFP			Low PA and low/optimal BFP			High/moderate PA and high BFP			Low PA and high BFP		
		Physical activity categories			Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Skin, melanoma	Cases	-	130	147	67	122	131	-	113	92	129	163	135
	HR (95% CI) ^a	1.00	0.94 (0.74, 1.19)	-	1.00	1.23 (0.83, 1.82)	1.04 (0.71, 1.55)	1.00	0.89 (0.67, 1.17)	-	1.00	1.09 (0.82, 1.43)	0.98 (0.73, 1.30)
Oropharyngeal	Cases	-	25	28	26	35	52	-	23	23	64	62	62
	HR (95% CI)	1.00	0.90 (0.52, 1.56)	-	1.00	0.67 (0.39, 1.17)	0.73 (0.44, 1.23)	1.00	0.78 (0.43, 1.39)	-	1.00	0.76 (0.52, 1.12)	0.83 (0.56, 1.22)
Lung	Cases	-	120	121	74	88	109	-	132	90	198	202	181
	HR (95% CI) ^h	1.00	1.05 (0.81, 1.35)	-	1.00	0.80 (0.56, 1.14)	0.72 (0.51, 1.02)	1.00	1.09 (0.83, 1.43)	-	1.00	0.98 (0.77, 1.23)	0.95 (0.75, 1.20)
Breast (female only)	Cases	-	680	635	229	27	19	-	803	554	387	33	23
	HR (95% CI) ^{b, h}	1.00	1.12 (1.002, 1.25)	-	1.00	0.86 (0.43, 1.69)	0.63 (0.30, 1.29)	1.00	1.07 (0.96, 1.20)	-	1.00	1.22 (0.65, 2.27)	0.93 (0.48, 1.82)
Uterus	Cases	-	81	78	21	2	3	-	160	109	89	8	6
	HR (95% CI) ^c	1.00	1.06 (0.77, 1.45)	-	1.00	0.32 (0.05, 2.33)	0.53 (0.09, 3.21)	1.00	1.02 (0.80, 1.31)	-	1.00	1.14 (0.34, 3.82)	0.95 (0.27, 3.40)
Ovary	Cases	-	65	93	24	4	3	-	96	71	37	4	2
	HR (95% CI)	1.00	0.76 (0.55, 1.04)	-	1.00	0.44 (0.10, 1.96)	0.34 (0.07, 1.71)	1.00	0.99 (0.73, 1.35)	-	1.00	0.66 (0.15, 2.95)	0.37 (0.06, 2.23)
Prostate	Cases	-	-	-	229	777	970	-	-	-	489	1065	987
	HR (95% CI) ^h	-	-	-	1.00	1.04 (0.90, 1.21)	1.06 (0.91, 1.22)	-	-	-	1.00	1.01 (0.91, 1.13)	1.02 (0.91, 1.14)
Oesophagus	Cases	-	21	25	16	27	35	-	19	9	56	68	91
	HR (95% CI) ^f	1.00	0.84 (0.47, 1.51)	-	1.00	0.98 (0.47, 2.05)	1.01 (0.49, 2.08)	1.00	1.62 (0.73, 3.60)	-	1.00	0.81 (0.55, 1.18)	1.21 (0.84, 1.74)
Stomach	Cases	-	20	18	10	13	38	-	16	7	43	56	41
	HR (95% CI)	1.00	1.19 (0.63, 2.25)	-	1.00	0.72 (0.28, 1.82)	1.57 (0.69, 3.60)	1.00	1.51 (0.62, 3.68)	-	1.00	0.90 (0.58, 1.39)	0.67 (0.42, 1.07)
Hepatobiliary tract	Cases	-	20	21	17	15	22	-	29	32	52	70	39
	HR (95% CI)	1.00	1.02 (0.55, 1.89)	-	1.00	0.39 (0.19, 0.81)	0.42 (0.21, 0.83)	1.00	0.68 (0.41, 1.12)	-	1.00	1.05 (0.70, 1.56)	0.61 (0.39, 0.97)
Pancreatic	Cases	-	33	38	20	33	49	-	39	35	69	76	57
	HR (95% CI) ^d	1.00	0.88	-	1.00	0.91	1.15	1.00	0.82	-	1.00	1.13	0.95

			(0.55, 1.41)			(0.48, 1.72)	(0.63, 2.12)	(0.52, 1.30)			(0.76, 1.68)	(0.62, 1.45)	
Kidney	Cases	-	30	21	28	59	60	-	53	29	74	104	95
	HR (95% CI)	1.00	1.52 (0.87, 2.67)	-	1.00	1.16 (0.68, 1.99)	0.92 (0.53, 1.57)	1.00	1.27 (0.80, 2.00)	-	1.00	1.12 (0.80, 1.56)	1.12 (0.79, 1.58)
Bladder	Cases	-	15	26	25	50	68	-	25	19	55	113	92
	HR (95% CI)	1.00	0.61 (0.32, 1.16)	-	1.00	0.72 (0.43, 1.20)	0.76 (0.46, 1.24)	1.00	1.01 (0.56, 1.85)	-	1.00	1.43 (0.995, 2.04)	1.26 (0.86, 1.82)
Colorectal	Cases	-	182	206	132	184	246	-	229	142	283	391	352
	HR (95% CI) ^{e, f(males), g}	1.00	0.93 (0.76, 1.14)	-	1.00	0.78 (0.60, 1.03)	0.87 (0.67, 1.13)	1.00	1.17 (0.95, 1.45)	-	1.00	1.05 (0.88, 1.26)	1.03 (0.86, 1.23)
Colon	Cases	-	132	139	85	108	126	-	161	99	196	242	207
	HR (95% CI) ^{e, f(males), g}	1.00	1.003 (0.79, 1.28)	-	1.00	0.71 (0.50, 1.001)	0.68 (0.48, 0.95)	1.00	1.18 (0.92, 1.52)	-	1.00	0.96 (0.78, 1.20)	0.89 (0.71, 1.12)
Rectum	Cases	-	42	55	44	71	115	-	60	40	83	147	141
	HR (95% CI) ^{e, f(males), g}	1.00	0.81 (0.54, 1.21)	-	1.00	0.82 (0.52, 1.29)	1.16 (0.76, 1.77)	1.00	1.07 (0.72, 1.61)	-	1.00	1.27 (0.93, 1.74)	1.34 (0.97, 1.83)
Brain tumours	Cases	-	15	31	15	50	37	-	30	21	47	46	45
	HR (95% CI)	1.00	0.51 (0.27, 0.94)	-	1.00	1.33 (0.72, 2.48)	0.75 (0.39, 1.43)	1.00	1.06 (0.61, 1.87)	-	1.00	0.73 (0.46, 1.14)	0.76 (0.48, 1.21)
Thyroid	Cases	-	20	26	12	11	9	-	31	19	20	9	20
	HR (95% CI)	1.00	0.77 (0.43, 1.39)	-	1.00	0.86 (0.31, 2.39)	0.58 (0.20, 1.70)	1.00	1.17 (0.66, 2.07)	-	1.00	0.61 (0.24, 1.54)	1.44 (0.65, 3.20)
Haematological malignancies	Cases	-	158	131	122	178	209	-	153	114	189	247	255
	HR (95% CI)	1.00	1.27 (1.01, 1.60)	-	1.00	0.88 (0.66, 1.16)	0.82 (0.62, 1.08)	1.00	1.01 (0.79, 1.29)	-	1.00	1.07 (0.86, 1.33)	1.20 (0.97, 1.50)
Non-Hodgkin's lymphoma	Cases	-	78	72	63	75	97	-	72	67	86	121	118
	HR (95% CI)	1.00	1.12 (0.81, 1.54)	-	1.00	0.71 (0.47, 1.05)	0.72 (0.49, 1.05)	1.00	0.81 (0.58, 1.13)	-	1.00	1.16 (0.84, 1.60)	1.24 (0.90, 1.72)

1298 BFP: Body fat percentage; PA: Physical activity.

1299 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol intake (never, former, current [<once/week], current [≥once/week]).

1303 ^aAdditional site-specific covariates in the final model include use of sun/UV protection (Never/rarely/sometimes; most of the time/always; do not go out in sunshine).

1304

1305 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1306 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1307 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1308 ^cAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
1309 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥ 15 years]), age at menopause (45-55
1310 years, <40 years, 40-45 years, ≥ 55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).
1311 ^dAdditional site-specific covariates in the final model include diabetes at baseline (yes/no).
1312 ^eAdditional site-specific covariates in the final model include diabetes at baseline (yes/no), aspirin use (regular use/non-regular use or no use), HRT use
1313 (ever used/never used), red meat intake (portion/week), processed meat intake (portion/week).
1314 ^fFinal model also adjusted for waist-hip ratio (>94 cm in men, >80 cm in women).
1315 ^gResults for males and females combined using meta-analysis.
1316 ^hFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).
1317 Indicates not possible to estimate (e.g. no observations in category).

1318 **Table 3.7. Results of Cox proportional hazards analyses investigating the association between IPAQ-measured physical activity and female-specific**
 1319 **cancer incidence for subgroups defined by participant menopausal status**

1320

		Not had menopause			Had menopause			Unsure		
		Physical activity categories			Physical activity categories			Physical activity categories		
		Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Breast (female only)	Cases	171	432	306	405	1,054	872	47	74	73
	HR (95% CI) ^{a, c}	1.00	1.02 (0.85, 1.21)	0.81 (0.67, 0.98)	1.00	0.93 (0.83, 1.05)	0.87 (0.77, 0.99)	1.00	0.72 (0.50, 1.04)	0.86 (0.59, 1.25)
Uterus	Cases	22	40	28	81	198	165	9	16	4
	HR (95% CI) ^b	1.00	0.82 (0.48, 1.39)	0.68 (0.38, 1.21)	1.00	1.02 (0.79, 1.33)	1.06 (0.80, 1.39)	1.00	1.10 (0.47, 2.57)	0.33 (0.10, 1.12)
Ovary	Cases	12	30	27	45	117	126	8	23	16
	HR (95% CI)	1.00	1.09 (0.56, 2.15)	1.19 (0.59, 2.39)	1.00	0.91 (0.64, 1.28)	1.08 (0.76, 1.53)	1.00	1.20 (0.53, 2.71)	0.91 (0.38, 2.18)

1321 All models were adjusted for age, sex, ethnicity (white/other), deprivation index (quintiles), education (University degree, A-levels/HNC/HND/NVQ, GCSE/O-
 1322 level/CSE, OTHER, None), fruit and vegetable intake (<5 portions/day, ≥5 portions/day), BMI (kg/m²), height (m), smoking status (never, former light
 1323 smoker [<20 pack-years], former heavy smoker [≥20 pack-years], current light smoker [<20 pack-years], current heavy smoker [≥20 pack-years]) and alcohol
 1324 intake (never, former, current [<once/week], current [≥once/week]).

1325 ^aAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
 1326 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
 1327 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1328 ^bAdditional site-specific covariates in the final model include HRT use (ever used/never used), oral contraceptive use (ever used/never used), number of live
 1329 births (0, 1, 2, 3+ live births), age at menarche (early menarche [<12 years], menarche at 12-14 years, late menarche [≥15 years]), age at menopause (45-55
 1330 years, <40 years, 40-45 years, ≥55 years, not had menopause/unsure), hysterectomy status (had hysterectomy, not had hysterectomy/unsure).

1331 ^cFinal model also adjusted for family history of cancer (mother/father/sibling had cancer, no family history).