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TITLE

Amount and intensity of daily total physical activity, step count, and risk of incident cancer in the UK Biobank

AUTHORS

Alaina H. Shreves, M.S.[1-3]; Scott R. Small, D.Phil.[1,2,4]; Rosemary Walmsley, D.Phil.[1,2]; Shing Chan, Ph.D.[1,2]; Pedro F. Saint-Maurice, Ph.D.[3,6]; Steven C. Moore, Ph.D.[3]; Keren Papier, Ph.D.[5]; Kezia Gaitskell, D.Phil.[5]; Ruth C. Travis, D.Phil.[5]; Charles E. Matthews, Ph.D.[3]; Aiden Doherty, Ph.D.[1,2]

AFFILIATIONS

[1] Nuffield Department of Population Health, University of Oxford, UK.

[2] Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, UK.

[3] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

[4] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK.

[5] Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK.

[6] Champalimaud Foundation, Lisbon, Portugal.

RUNNING TITLE: Physical Activity, Step Count, and Cancer Risk in the UK Biobank

Corresponding Author: Alaina Shreves, M.S.

ADDRESS: Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, Maryland 20850

EMAIL: alaina.shreves@nih.gov

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PREPRINT AND PRESENTATIONS

The work is entirely original and is not being considered elsewhere. An abstract with preliminary results was presented at the UK Public Health Science 2023 meeting and was shared in *The Lancet* (https://doi.org/10.1016/S0140-6736(23)02147-5). Preliminary findings were presented at the Oxford Centre for Early Cancer Detection Annual Symposium (2023, Oxford, England), the Cancer Research UK Data-driven Cancer Research Conference (2024, Manchester, England), the Digital Health Horizons Conference (2024, Oxford, England), the American College of Sports Medicine Annual Meeting (2024, Boston, Massachusetts), and the International Conference on Ambulatory Monitoring of Physical Activity and Movement (2024, Rennes, France). A preprint was shared on medRxiv (https://www.medrxiv.org/content/10.1101/2023.12.04.23299386v1) on 4 December 2023.

ABSTRACT

OBJECTIVES: To investigate associations between daily physical activity, activity intensity, and step counts with incident cancer risk.

METHODS: Prospective analysis of UK Biobank participants who wore wrist-based accelerometers for 7-days, followed for cancer incidence (mean follow-up 5.8 years, standard deviation 1.3). Time-series machine learning models derived total physical activity, sedentary behaviour (SB), light-intensity activity (LIPA), moderate-vigorous-intensity activity (MVPA), and step counts. The outcome was a composite of 13 cancers previously associated with low physical activity in questionnaire-based studies. Cox proportional hazard models estimated hazard ratios (HR) and 95% confidence intervals [CI], adjusted for demographic, health, and lifestyle factors. We also explored associations of LIPA, MVPA, and SB with cancer risk.

RESULTS: Among 85,394 participants (median age 63 [interquartile range 56-68]), 2,633 were diagnosed with cancer during follow-up. Compared to individuals in the lowest quintile of total physical activity (<21.6 milligravity units), those in the highest (34.3+) had a 26% lower cancer risk (HR=0.74, [0.65-0.84]). After mutual adjustment, LIPA (HR=0.94, [0.90-0.98]) and MVPA (HR=0.87, [0.79-0.94]) were associated with lower risk, but SB was not. Similar associations were observed for substituting 1-hour/day of SB with LIPA or MVPA. Daily step counts were inversely associated with cancer, with the dose-response beginning to plateau at around 9,000 steps/day (HR=0.89, [0.83-0.96] 7,000 vs. 5,000 steps; HR=0.84, [0.76-0.93] 9,000 vs. 5,000 steps). There was no significant association between stepping intensity (peak 30-minute cadence) and cancer after adjusting for step count.

CONCLUSION: Total physical activity, LIPA, MVPA, and step counts were inversely associated with incident cancer.

SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Studies using self-reported questionnaires have found that physical activity is inversely associated with the risk of several cancers.
- Studies using accelerometer-measured physical activity have focused mainly on associations with vigorous physical activity, with few investigating associations between lower-intensity activities and sedentary behaviour with cancer risk.

WHAT THIS STUDY ADDS

- Using data from a prospective cohort, we found that light and moderate-to-vigorous-intensity physical activity was inversely associated with incident cancer risk, while sedentary behaviour was not uniquely associated with cancer risk.
- Higher daily step counts were associated with a lower cancer risk, with the dose-response curve beginning to plateau at around 9,000 steps/day (HR=0.89, [95% confidence interval 0.83-0.96] 7,000 vs. 5,000 steps; HR=0.84, [0.76-0.93] 9,000 vs. 5,000 steps).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- These findings suggest that physical activity and stepping at light or moderate-vigorous intensities may lower the risk of certain cancers, which could inform future activity guidelines, but further studies are necessary to understand associations with site-specific cancer risks.

INTRODUCTION

Epidemiological data suggest that over half of all new cancers in high-income countries could be avoided by modifying lifestyle factors, including addressing physical inactivity [1,2]. Physical activity (PA) has been inversely associated with the risk of various cancers, including bladder, breast, colon, endometrial, oesophageal adenocarcinoma, renal, and gastric cancer [3–5]. However, an understanding of the associations between different types and intensities of PA and cancer remains incomplete.

Many studies rely on self-reported questionnaires, which primarily focus on moderate-vigorous-intensity physical activity (MVPA) during leisure time [6,7]. Additionally, most individuals spend the majority of their waking day in sedentary behaviour (SB) or engaging in light-intensity physical activity (LIPA), such as casual walking, household chores, and shopping [8–10]. Therefore, there is a growing interest in understanding whether light or moderate-intensity activities may also be associated with a lower cancer risk.

Wearable accelerometers measure total daily activity, including SB, LIPA, and MVPA, across home, work, transportation, and leisure [11]. These devices often track steps, an indicator of daily ambulatory activity that is accessible to most individuals [12]. Consequently, global PA guideline committees have highlighted the need for more prospective studies using accelerometers to describe the dose-response relationships between PA and incident cancer [3–5,13,14].

We used data from a large prospective cohort to describe relationships between daily PA, activity intensity, and step counts with incident cancer risk using a composite outcome of 13 cancer sites previously associated with low PA in studies of self-reported leisure-time activity [6].

METHODS

STUDY POPULATION

The UK Biobank is a prospective cohort study that enrolled 502,536 adults in England, Scotland, and Wales between 2006-2010 [15,16]. At baseline, participants completed a touchscreen questionnaire, provided anthropometric and biological data, and consented for linkage to medical records [15,16]. Between 2013-2015, 106,053 participants with valid email addresses were invited to join an accelerometer sub-study [10]. Participants received an Axivity AX3 wrist-worn accelerometer by mail and were instructed to wear it on their non-dominant wrist for 7 days [10].

ACCELEROMETER DATA PROCESSING

Accelerometer data from 103,712 participants was processed using methods recommended for use in the UK Biobank ("accelerometer", v7.1.0) [11]. The mean daily vector magnitude, expressed in milligravity (m*g*) units, was averaged across days to derive total PA, reflecting the intensity and duration of activity over 24 hours [16]. This wrist accelerometer metric has been externally validated against the doubly labelled water method, a gold standard for measuring energy expenditure [11,17].

Proportions of daily time in sleep, SB, LIPA, and MVPA were calculated using random forest and hidden Markov model machine-learning methods [10]. These models were trained using wearable cameras and time-use diaries recorded in free-living conditions [10]. These methods classify free-living sleep, SB, LIPA, and MVPA with a mean accuracy of 88% (95% confidence intervals [CI] 87-89) and Cohen's kappa 0.80 [0.79-0.82] compared to a labelled dataset using wearable cameras and time-use diaries [10].

Stepping was derived using a hybrid self-supervised learning model trained on ground truth free-living stepping data ("stepcount", v3.1.1), which had a 12.5% mean average percent error (inferred steps vs. camera-counted steps) [18]. Step counts were reported as the median number of steps over valid days. Cadence metrics serve as a proxy for ambulatory intensity [19]. Across days with at least 30 minutes of walking, peak 30-minute cadence was calculated by averaging the 30 highest one-minute daily cadences, representing peak activity levels, although these minutes may not be consecutive [18,20].

Missing time due to non-wear was imputed by averaging the behaviour in the corresponding times across valid days [10]. Processing details are in eTables 1-2.

OUTCOME ASCERTAINMENT

The outcome was the first diagnosis of a composite of 13 cancer sites previously associated with low PA (bladder, breast, colon, endometrial, oesophageal adenocarcinoma, gastric cardia, head and neck, kidney, liver, lung, myeloid leukaemia, myeloma, and rectal) [6]. Cancers were identified through the National Health Service (NHS) Digital for England and Wales, and the NHS Central Register for Scotland (eTable 3) [21]. Death data were obtained from national registries.

ANALYTIC SAMPLE

We excluded participants with device calibration or reading errors (>1% values +/-8*g*), inadequate wear time (<72 hours), unreasonably high average acceleration (>100 m*g*), and missing steps data. We also excluded individuals with prevalent cancer before accelerometer wear (except non-melanoma skin cancer), missing healthcare linkages, or missing covariate data. The final sample included 85,394 participants (eFigure 1).

STATISTICAL ANALYSES

Cox proportional hazard regression models estimated Hazard Ratios (HRs) with 95% CI overall and separately among males and females. Attained age was the time scale. Individuals were followed until a cancer diagnosis, censoring, death, or the end of cancer registry follow-up (31 December 2020 for England, 31 December 2016 for Wales, and 30 November 2021 for Scotland), whichever occurred first.

TOTAL PA

We fitted models for quintiles of total PA and incident cancer. Nonlinear associations were analysed using restricted cubic spline regression, with the 10th percentile as the reference and knots at the 5th, 50th, and 95th percentiles, as recommended [22]. Likelihood ratio tests compared linear models with those including spline terms.

SEDENTARY TIME AND ACTIVITY INTENSITY

We also investigated associations for behaviours of the waking day (SB, LIPA, and MVPA) with incident cancer. First, linear models (1-factor models) estimated if +1 hour/day of SB, LIPA, or MVPA were associated with cancer risk. Second, partition models estimated the risk associated with each behaviour (e.g., MVPA) while holding the other behaviour time during the waking day constant (e.g., SB and LIPA). Third, isotemporal substitution models that adjust for waking time, as proposed by Mekary [23], estimated cancer risk associated with substituting 1-hour/day in one behaviour (e.g., SB) for 1-hour/day in another (e.g., MVPA) while holding the third behaviour constant (e.g., LIPA).

Recognizing the potential for bias from substitution effects from sleep (i.e., non-waking time) in our substitution models that only considered waking day behaviours, we applied a compositional approach by Chastin [24] to assess associations between the relative distribution of

daily activities and cancer risk. Further details on these methods are presented in the Supplementary Methods.

STEP COUNT AND STEPPING INTENSITY

Next, we estimated how stepping may be associated with cancer risk using models for quintiles of step counts and restricted cubic spline regression. Additionally, we estimated the associations for stepping intensity (peak 30-minute cadence) and cancer risk, both before and after adjusting for step count.

COVARIATES

Multivariable models were adjusted for sex, self-identified ethnicity, smoking status, alcohol consumption, education, area-based deprivation (Townsend Deprivation Index [TDI]), self-rated health, fresh fruit and vegetable consumption, and red and processed meat consumption. Female-specific models were further adjusted for oral contraception ever use, hormone replacement therapy ever use, and parity. Participants provided covariate data at the baseline assessment (eTable 1).

We used Schoenfeld residuals to assess the proportional hazards assumption and found no violations for the exposures.

SENSITIVITY ANALYSES

We performed sensitivity analyses to understand how individual cancer sites contributed to our composite outcome by fitting models for each of the 13 PA-related cancers. To assess confounding and reverse causality, we estimated whether a 1-SD increase in total PA and step counts was associated with incident cancer. We also fit a model for all malignant incident cancer sites (except for nonmelanoma skin cancer). Since lung cancer accounted for a significant

proportion of total cancer cases and to account for the potential for residual confounding due to smoking, we fit a model for the composite outcome excluding lung cancer and conducted stratified analyses by smoking status. Additional models were stratified by age, sex, disability (blue badge), history of diabetes, cardiovascular disease (CVD), and body mass index (BMI). We explored reverse causality by excluding data from the first two and four years of follow-up. E-values estimated the minimum association level an unmeasured confounder would need with both the exposure and the outcome to explain the observed associations [25,26].

Statistical analyses were performed from May 2023 to September 2024 using R (v4.2.2; R Foundation for Statistical Computing). Two-sided *P*-values of <0.05 were considered statistically significant.

We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (STROBE; eTable 4) [27] and the CHecklist for statistical Assessment of Medical Papers (CHAMP) [28].

PATIENT AND PUBLIC INVOLVEMENT

No members of the public or patients were involved in the planning, design, data collection, analysis, or interpretation of this study.

EQUITY, DIVERSITY, INCLUSION STATEMENT

The author group is gender-balanced and consists of junior, mid-career, and senior researchers. Our study sample represented UK Biobank participants with valid accelerometer data, and we addressed generalizability in the discussion.

RESULTS

Among 85,394 participants, the median age at accelerometer assessment was 63 years [interquartile range (IQR)=56-68]. Most participants were female (56%), identified as White (97%), and were in the least deprived TDI quintile (eTable 5). Compared to the full cohort, accelerometer study participants had higher socioeconomic status, greater educational attainment, lower BMI, and better self-rated health (eTable 6). The median daily PA was 27.3 m*g* [IQR=22.7-32.7] and the median daily step count was 9,076 [IQR=6,844-11,687].

Throughout a mean follow-up of 5.8 years [SD=1.3], 2,633 individuals were diagnosed with a cancer of interest over 497,824 person-years (eTable 7). The most prevalent cancers considered among males were colon (n=203), lung (n=145), and rectal (n=119) and among females were breast (n=984), colon (n=173), endometrial (n=151), and lung (n=146).

TOTAL PA

We first assessed associations between total PA and incident cancer. Total daily PA was inversely associated with incident cancer (eTable 8, Figure 1, eFigure 2). Compared to individuals in the lowest quintile (<21.6 m*g*), individuals in the second quintile (21.6-25.4 m*g*) had an 18% lower risk (HR=0.82, [0.73-0.92]). Those in the highest quintile (34.3+ m*g*) had a 26% lower risk (HR=0.74, [0.65-0.84]). Males and females in the upper four quintiles had a lower risk than the lowest quintile (eTable 9, Figure 1). The dose-response relationship was linear for males (*P*-value for non-linearity=0.28), but not for females (*P*-value=0.003) (eTable 10). In models for all incident cancers (excluding nonmelanoma skin cancer), total PA was associated with a lower cancer risk. Compared to individuals in the first quintile of total PA (<21.6 m*g*), those in the second quintile (21.6-25.4 m*g*) had an 11% lower risk (HR=0.89 [0.82–0.96]), and those in the highest quintile (34.3+ m*g*) had an 18% lower risk (HR=0.82 [0.75–0.89]) (eTable 11). The associations for all cancers were similar to those for the PA-related cancers.

We observed significant associations for six cancer sites and suggestive associations (10% risk) for three additional sites (eFigure 3). Site-specific associations were similar after BMI adjustment, except for endometrial cancer (eFigure 3), which attenuated toward the null (HR=0.78, [0.64-0.94] to HR=0.87, [0.72-1.06]). For the composite cancer outcome, estimates were largely consistent after excluding lung cancer and stratifying by age, sex, disability, diabetes, CVD, and smoking (eTable 12, Figure 2). After BMI adjustment, the HR attenuated by 2% (HR=0.87, [0.83-0.91] to HR=0.89, [0.85-0.93]), and associations were similar across BMI subgroups (eTable 13). The estimates attenuated after removing the first two and four years of follow-up. The E-values suggested that substantial unmeasured confounding would be needed to explain the observed associations.

SEDENTARY TIME AND ACTIVITY INTENSITY

Individually, SB, LIPA, and MVPA was associated with cancer risk (Table 1). In partition models that mutually adjust for time in the other waking day behaviours, a +1-hour/day of LIPA (HR=0.94, [0.90-0.98]; *P*-trend<0.001) and MVPA (HR=0.87, [0.79-0.94]; *P*-trend=0.002) were significantly associated with lower cancer risk, while SB (HR=1.00, [0.97-1.04]*; P*-trend=*0.14*) was not (Table 1, eTable 14). Next, we fit isotemporal substitution models, which are interpreted as the risk associated with reallocating am equal amount of time from one behaviour (e.g., SB) to another (e.g., MVPA) while holding other behaviours of the waking day (e.g., LIPA) constant.

Substituting 1- hour/day of SB with LIPA was associated with a lower risk (HR=0.93, [0.91-0.96]),

Table 1. Associations of daily time spent doing sedentary behaviour, light-intensity physical activity, and moderate-vigorous-intensity physical activity with risk of physical-activity-related cancer in UK Biobank participants.

	Sedentary behaviour	Light-intensity physical activity	Moderate-vigorous-intensity physical activity
Model	HR per 1-hour/day (95% CI)	HR per 1-hour/day (95% CI)	HR per 1-hour/day (95% CI)
Overall			
1-factor model[a]	1.06 (1.04 to 1.08)	0.93 (0.91 to 0.96)	0.85 (0.79 to 0.92)
Partition model[b]	1.00 (0.97 to 1.04)	0.94 (0.90 to 0.98)	0.87 (0.79 to 0.94)
Male			
1-factor model[a]	1.06 (1.02 to 1.10)	0.93 (0.89 to 0.98)	0.80 (0.71 to 0.90)
Partition model[b]	0.99 (0.94 to 1.05)	0.94 (0.88 to 1.00)	0.80 (0.70 to 0.92)
Female			
1-factor model[a]	1.06 (1.04 to 1.09)	0.93 (0.90 to 0.96)	0.90 (0.81 to 1.00)
Partition model[b]	1.02 (0.97 to 1.07)	0.95 (0.90 to 1.00)	0.93 (0.83 to 1.04)

Hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression models. Estimates represent the risk for incident physical-activity-related cancer associated with time spent in sedentary behaviour, light-intensity physical activity behaviours (LIPA), and moderate-vigorous-intensity physical (MVPA) during the waking day. The composite outcome of physical-activity-related cancer included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). Models used age as the underlying time variable. Models were adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable consumption, and red and processed meat consumption. The overall model was adjusted for sex. Female models were further adjusted for oral contraception, ever use of hormone replacement therapy, and parity. The overall model was based on 2,633 events in 85,394 participants. The male model was based on 882 events in 37,472 participants, and the female model was based on 1,751 events in 47,922 participants. [a]Associations represent risk from separate models for each type of behaviour, adjusted only for covariates. [b]Associations represent a single risk estimate that accounts for sedentary time, light and moderate-vigorous activity, and covariates.

as was substituting SB with MVPA (HR=0.86, [0.80-0.93]) (Figure 3).

Among males, substituting SB with MVPA (HR=0.81, [0.72-0.91]) or with LIPA (HR=0.94, [0.90-0.99]) was inversely associated with cancer risk. Males also had a lower cancer risk when substituting LIPA with MVPA (HR=0.86, [0.75-0.98]). For females, substituting SB with LIPA was inversely associated with cancer risk (HR=0.93, [0.90-0.96]), but no significant

associations were observed for substituting SB with MVPA (HR=0.91, [0.82-1.01]) or for substituting LIPA with MVPA (HR=0.98, [0.88-1.09]).

Findings from the compositional models were broadly consistent with these estimates (eTable 15, eFigures 4-6). Substituting SB with LIPA or MVPA was associated with a lower risk, while substituting LIPA with MVPA was not.

Table 2. Adjusted hazard ratios for median daily step count and physical-activity-related cancer risk in UK Biobank participants by sex.

	Overall	Male	Female
Total	N=83,688	N=36,722	N=46,963
Cases	2,569	853	1,715
Median daily step count	HR (95% CI)	HR (95% CI)	HR (95% CI)
3,000	1.19 (1.04 to 1.37)	1.37 (1.10 to 1.70)	1.10 (0.92 to 1.32)
5,000 (REF, ~10th percentile)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
7,000	0.89 (0.83 to 0.96)	0.82 (0.73 to 0.93)	0.93 (0.85 to 1.02)
9,000	0.84 (0.76 to 0.93)	0.74 (0.62 to 0.87)	0.89 (0.78 to 1.01)
11,000	0.82 (0.73 to 0.91)	0.71 (0.59 to 0.85)	0.87 (0.76 to 1.00)
13,000	0.80 (0.71 to 0.90)	0.72 (0.59 to 0.88)	0.84 (0.72 to 0.97)
16,000 (~95th percentile)	0.75 (0.64 to 0.87)	0.69 (0.53 to 0.90)	0.77 (0.64 to 0.94)
P-value for trend[a]	<0.001	<0.001	0.002
P-value for non-linearity[b]	0.12	0.02	0.35

Estimated hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression models with restricted cubic spline functions. Observations were trimmed at the 1% and 99% of the distribution, and 3 knots were placed at the 5th, 50th, and 95th percentile for the exposures. The ~10th percentile was set as the referent group (5,000 steps). The composite outcome of physical-activity-related cancers included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). Models used attained age as the underlying time variable and were adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable consumption, and red and processed meat consumption. The overall model was adjusted for sex. The female model was further adjusted for the use of oral contraception, use of hormone replacement therapy, and parity. [a]A significant *P*-value for trend indicates that there is a trend in the association. [b]A non-significant P-value for departure from linearity indicates there is no evidence to suggest that the data deviates from a linear association.

STEP COUNT AND STEPPING INTENSITY

Daily step counts were inversely associated with cancer risk (Table 2, eFigure 2, eFigure 7). Compared to individuals who took 5,000 steps (reference), those taking 7,000 had an 11%

lower risk (HR=0.89, [0.83-0.96]), those taking 9,000 steps had a 16% lower cancer risk (HR=0.84, [0.76-0.93]) and those taking 13,000 had a 20% lower risk (HR=0.80, [0.71-0.90]). The dose-response relationship was non-linear for males (*P* for non-linearity=0.02), but linear for

females (*P*=0.35). We found significant inverse associations for step intensity (peak 30-minute

Table 3. Adjusted hazard ratios for stepping intensity (peak 30-minute cadence) and physical-activity-related cancer risk in UK Biobank participants before and after adjusting for daily step count.

	Overall	Male	Female
Total	N=83,746	N=36,759	N=46,973
Cases	2,574	857	1,717
Peak 30-minute cadence (steps/minute)	HR (95% CI)	HR (95% CI)	HR (95% CI)
60	1.12 (1.00 to 1.26)	1.25 (1.04 to 1.49)	1.04 (0.90 to 1.21)
70 (REF, ~10th percentile)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
80	0.89 (0.82 to 0.97)	0.85 (0.74 to 0.99)	0.92 (0.82 to 1.02)
90	0.85 (0.76 to 0.95)	0.76 (0.63 to 0.92)	0.90 (0.78 to 1.04)
100	0.81 (0.72 to 0.91)	0.69 (0.57 to 0.84)	0.87 (0.75 to 1.01)
110	0.78 (0.68 to 0.89)	0.71 (0.56 to 0.90)	0.81 (0.69 to 0.95)
120 (~95th percentile)	0.77 (0.62 to 0.95)	0.79 (0.54 to 1.16)	0.76 (0.59 to 0.98)
P-value for trend[a]	<0.001	<0.001	0.008
P-value for non-linearity[b]	0.35	0.11	0.2
Peak 30-minute cadence (steps/minute) + median daily step count	HR (95% CI)	HR (95% CI)	HR (95% CI)
60	1.09 (0.97 to 1.22)	1.20 (1.00 to 1.45)	1.02 (0.87 to 1.19)
70 (REF, ~10th percentile)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
80	0.92 (0.84 to 1.01)	0.89 (0.76 to 1.04)	0.94 (0.84 to 1.06)
90	0.92 (0.81 to 1.04)	0.84 (0.67 to 1.04)	0.96 (0.82 to 1.12)
100	0.91 (0.79 to 1.06)	0.80 (0.62 to 1.03)	0.96 (0.80 to 1.15)
110	0.92 (0.76 to 1.10)	0.86 (0.62 to 1.18)	0.92 (0.74 to 1.15)
120 (~95th percentile)	0.94 (0.72 to 1.21)	0.98 (0.62 to 1.56)	0.90 (0.65 to 1.23)
P-value for trend[a]	0.21	0.08	0.58
P-value for non-linearity[b]	0.30	0.11	0.20

Estimated hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression models with restricted cubic spline functions. Observations were trimmed at the 1% and 99% of the distribution, and 3 knots were placed at the 5th, 50th, and 95th percentile for the exposures. The ~10th percentile was set as the referent group in the main analytic sample (70 steps per minute). The composite outcome of physical-activity-related cancers included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). Models used attained age as the underlying time variable and were adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable consumption, and red and processed meat consumption. The overall model was adjusted for sex. The female model was further adjusted for the use of oral contraception, use of hormone replacement therapy, and parity. [a]A significant *P*-value for trend indicates that there is a trend in the association. [b]A non-significant P-value for departure from linearity indicates there is no evidence to suggest that the data deviates from a linear association.

cadence) and incident cancer risk before adjusting for daily steps (Table 3). However, the associations were no longer statistically significant after adjustment for step counts. In our sensitivity analyses, the associations remained after excluding lung cancer from the composite cancer outcome and stratifying by demographic, health, and lifestyle factors (eTable 12, eFigure 8). After adjusting for BMI, the HR attenuated by 2% (HR=0.90 [0.87–0.94] to HR=0.92, [0.88-0.96]). Stratified models showed some differences across BMI groups (eTable 12, eTable 16, eFigure 8), with the HRs for a 1-SD increase in step count closer to the null in the lowest BMI group (≤24.9 kg/m², HR=0.93, [0.87–1.00]) and the highest group (≥30 kg/m², HR=0.96 [0.88–1.04]) (eTable 12).

DISCUSSION

In this prospective study, higher total PA, measured by accelerometers, was inversely associated with the risk of a composite outcome of all incident malignant cancers and a composite outcome of 13 cancers previously associated with low PA. In models fitted for PA-related cancers, individuals in the highest PA quintile (34.3+ m*g*) had a 26% lower cancer risk compared to the lowest (<21.6 m*g*). The estimates remained after adjusting for demographic, health, and lifestyle factors. Daily LIPA and MVPA were inversely associated with cancer, as were step counts, though stepping intensity (peak 30-minute cadence) was not after adjusting for daily step count. These findings suggest that PA and stepping at light or moderate-vigorous intensities may be inversely associated with incident cancer.

These results are consistent with prior questionnaire-based studies from the UK Biobank, which demonstrated inverse associations between self-reported PA and cancer [29,30]. Our analysis utilised data from accelerometer measurements and found similar inverse associations,

consistent with previous research conducted among older women [31] and for breast cancer [32,33].

While many previous studies have focused on vigorous PA, we expand the current evidence by analysing associations for lower-intensity activities. For instance, one study found that 12 minutes of weekly vigorous PA was associated with a 17% lower cancer risk, while another found that 3.7 minutes of daily vigorous PA was associated with a 28% lower risk [34,35]. We observed inverse linear dose-response associations for LIPA and MVPA with cancer after adjusting for other daily behaviours, whereas SB was not uniquely associated with cancer. These findings align with previous studies that suggest any level of activity, regardless of intensity, may lower the risk of chronic diseases, including cancer [29,36,37]. This is distinct from findings in CVD research, where intensity may play a more pivotal role in determining health benefits [10,36].

Similarly, we found that daily step volume may be more important for cancer risk than stepping intensity (peak 30-minute cadence). Although earlier UK Biobank research identified inverse associations for peak cadence [38], we found null results for stepping intensity after adjusting for step counts. These differences may be attributed to variations in inclusion criteria, statistical methods, adjustment factors, or the algorithms used to predict steps, highlighting the need for further studies on stepping intensity and cancer risk.

Daily walking, an indicator of total PA, is often promoted in community and clinical messaging due to its trackability and accessibility [39]. We found that higher daily step counts were inversely associated with cancer risk. Compared to taking 5,000 steps per day, the risk was 11% lower for those taking 7,000 steps and 16% lower for those taking 9,000 steps per day. Beyond this level, further reductions in risk were modest for males and females. We chose 5,000 steps as the reference group due to its strong internal validity (10th percentile) and because this

threshold was previously used to classify a 'sedentary lifestyle' [12,40]. Walking one mile equates to about 2,000 steps for most adults [41], suggesting that inactive individuals may lower their cancer risk by walking an additional two miles daily, roughly equivalent to 40 minutes at three miles per hour.

Additionally, we observed some sex-specific differences. Total PA had a linear association with cancer risk in females, while step counts had a linear association in males. Males also had a lower cancer risk for substituting LIPA with MVPA. The sex differences in the strength of association in the composite cancer outcome might stem from variations in the strength of association for sex-specific cancers and differences in the putative biological mechanisms for these cancers. For example, total PA had a weak association with breast cancer, which was the most common cancer among females. In contrast, PA showed stronger associations with colon and lung cancers, the most common cancers in males in our analysis. These differences may explain the varying estimates for risk of the composite cancer outcome between the sexes. A previous pooled analysis of leisure-time PA found a linear dose-response for breast, colon, endometrial cancers, and oesophageal adenocarcinoma, but no linear dose-response for kidney, gastric, liver cancers, or myeloma [7]. This highlights the importance of conducting future site-specific cancer analyses to understand these relationships.

Several hypothesised mechanisms have been proposed to explain the inverse associations between PA and cancer risk, including hormonal changes, insulin levels, inflammation, immune function, and oxidative stress [37]. Long-term interventions to lower SB have shown changes in body size, waist circumference, body fat percentage, fasting glucose and insulin levels, glycated haemoglobin, high-density lipoprotein cholesterol, systolic blood pressure, and vascular function [42].

Since BMI may act as a confounder or a mediator, we conducted subgroup analyses and additional models adjusting for BMI. After BMI adjustment, associations were similar for most cancer types, except for endometrial cancer, which weakened. For the composite cancer outcome, the HRs for a 1-SD change in total PA and step count showed minimal differences (Total PA: HR=0.87, [0.83-0.91] to HR=0.89, [0.85-1-0.93]; Step count: HR=0.90 [0.87–0.94] to HR=0.92, [0.88-0.96]). Total PA estimates were consistent across BMI subgroups, but the association with step count varied by BMI, with HRs attenuating in the lowest and highest BMI groups. This suggests BMI may modify the step count–cancer risk association. However, BMI was measured several years before the accelerometer data, which could introduce imprecision over time [43].

Our study has several strengths. First, we used accelerometer data from a large cohort, minimising biases common in questionnaire-based studies [44,45]. We used validated machine-learning methods trained on free-living data to explore associations with various PA intensities and stepping. This builds upon existing literature that has mainly focused on moderate-vigorous leisure-time activities. Lastly, we conducted extensive sensitivity analyses to test the robustness of our findings.

LIMITATIONS

This study has some limitations. First, the UK Biobank includes primarily mid-life individuals, limiting our ability to study cancers that develop in younger or older populations. Additionally, the relative incidence of cancer types contributing to the composite outcome may differ in wider population. Second, we could not assess associations for less common cancer sites, requiring future studies with more cases. As an observational study, we cannot rule out unmeasured confounding. However, excluding follow-up years resulted in minor changes to our estimates. Third, the accelerometer data captured one seven-day period during middle age, and

behaviour may change over time, potentially underestimating risk [46]. However, one seven-day period of accelerometer wear has shown stability over six months to several years (correlations from 0.54-0.82) [47–49]. Next, our models for activity intensities estimated the theoretical associations of substituting time between behaviours, but we did not observe actual replacements. Finally, these findings may not apply to all populations, as most UK Biobank participants were White and healthier than the general UK population [50]. Participants who wore accelerometers had higher socioeconomic status, education, lower BMI, and better self-rated health. However, the findings are likely to be broadly applicable [51].

IMPLICATIONS

This study adds to the growing body of literature on PA and cancer risk, suggesting that total PA, activities of light and moderate-vigorous intensities, and step counts may be inversely associated with cancer. Our results support the notion that encouraging incorporating lower- and higher-intensity activities into daily routines, particularly during middle age, and promoting walking as a fundamental component of public health initiatives may effectively lower the risk of certain cancers. Future longitudinal studies on specific cancer types will be necessary to understand potential underlying mechanisms and inform public health recommendations.

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The funders did not play a role in the design of the study, the data collection, the data analysis, the interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

COMPETING INTERESTS

Shreves, Moore, Gaitskell, Travis, and Matthews declare no competing interests.

Small was an employee of Novo Nordisk at the time of submission.

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Doherty, Walmsley, and Chan have released accelerometer analysis software under an academic use license that has resulted in commercial entities paying license fees for their use.

DATA AVAILABILITY

This research was conducted utilising the UK Biobank Resource under Application Number 59070. Data are accessible through the UK Biobank following an application process and approval from the UK Biobank Research Ethics Committee.

ETHICS STATEMENTS

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APROVAL

UK Biobank participants provided written informed consent. The UK Biobank received ethical approval by the National Information Governance Board for Health and Social Care and the NHS North West Multicentre Research Ethics Committee (06/MRE08/65).

AUTHOR CONTRIBUTIONS

Guarantor: Shreves

Concept and design: Shreves, Travis, Matthews, and Doherty.

Acquisition, analysis, or interpretation of data: Shreves, Small, Walmsley, Saint-Maurice, Papier, Gaitskell, Travis, Matthews, and Doherty.

Drafting of the manuscript: Shreves, Travis, Matthews, and Doherty.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shreves.

Obtained funding: Shreves, Travis, Matthews, and Doherty.

Administrative, technical, or material support: Shreves, Chan, Walmsley, and Doherty.

Supervision: Doherty, Matthews, and Travis.

FIGURE LEGENDS

Figure 1. Association of mean total physical activity (milligravity units) by quintiles and physical-activity-related cancer risk in UK Biobank participants. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression models for quintiles of the mean total physical activity. The CIs were estimated with the floated absolute risk. The composite outcome of physical-activity-related cancer included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). Models used attained age as the underlying time variable and were adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable consumption, and red and processed meat consumption. The overall model was adjusted for sex. The female models were further adjusted for the use of oral contraception, use of hormone replacement therapy, and parity. The shading on the lower axis represents sample clustering in the main analytic sample. HRs are above, and the number of events is below each data point. The overall model was based on 2,633 events in 85,394 participants. The male model was based on 882 events in 37,472 participants, and the female model was based on 1,751 events in 47,922 participants.

Figure 2. Association of mean total physical activity (milligravity units) and physical-activity-related cancer risk in UK Biobank participants, main models and sensitivity analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox proportional hazard models. All models used age as the underlying time variable. The composite outcome of physical-activity-related cancer included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). The standard deviation (SD) of the mean total physical activity in the main analytical sample was 8.3 milligravity units (m*g*). For males, the SD

was 8.6 m*g*. For females, the SD was 8.0 m*g*. The dashed line is at the HR for the multivariable-adjusted model in the main analytic sample. Model 1: Unadjusted. Model 2: Adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable consumption, and red and processed meat consumption. The overall model was adjusted for sex. Female models were further adjusted for oral contraception, ever use of hormone replacement therapy, and parity. The model without lung cancer as an outcome excluded lung cancer from the composite outcome. Model 2 stratified by smoking status was adjusted for all variables in Model 2, but not smoking status. CVD = cardiovascular disease, BMI = body mass index, FU = follow-up. The likelihood ratio test comparing the fit between models with and without interaction terms found: For sex, the *P*-value was 0.0003 for total PA and for smoking status, the *P*-value was 0.02.

Figure 3. Isotemporal substitution model for associations of time in sedentary behaviour, light intensity physical activity, and moderate-vigorous-intensity physical activity with risk of physical-activity-related cancer risk in UK Biobank participants. Hazard ratios (HR) and 95% confidence intervals (CI) for incident physical-activity-related cancer associated with substituting time from one behaviour to another are presented. Models are isotemporal substitution models that account for time that consider time in (SB), light-intensity physical activity (LIPA), moderate-vigorous-intensity physical activity (MVPA), and wear time within the waking day. Models estimate the HR when replacing 1-hour/day of one behaviour with 1-hour/day of another, keeping total waking time constant. The composite outcome of physical-activity-related cancers included 13 site-specific cancers (oesophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukaemia, myeloma, colon, head and neck, rectal, bladder, and breast). Models used attained age as the underlying time variable and were adjusted for ethnicity, smoking status, alcohol consumption, deprivation, education, self-rated health, fruit and vegetable

consumption, and red and processed meat consumption. The overall model was adjusted for sex. Female models were further adjusted for ever use of oral contraception, ever use of hormone replacement therapy, and parity. The overall model was based on 2,633 events in 85,394 participants. The female model was based on 1,751 events in 47,922 participants, and the male model was based on 882 events in 37,472 participants.

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