Associations of physical activity with breast cancer risk: Findings from the UK Biobank prospective cohort study

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Number of words: 2824
Number of Tables: 3

Abstract

Purpose: Although physical activity (PA) has been consistently associated with breast cancer, existing evidence is limited to self-reported physical activity which is prone to dilution bias. Therefore, this aims to examine the associations of device-measured PA domains with breast cancer risk and whether it differ by menopausal status.

Methods: Prospective cohort study. Data from 48,286 women from the UK Biobank cohort was analyzed. A wrist triaxial accelerometer was used to collect physical activity data for light, moderate, vigorous, moderate to vigorous (MVPA) and total PA. Cox proportional models were performed to examine the association between PA domains, menopausal status and breast cancer risk.

Results: 836 breast cancer cases were diagnosed during a median of 5.4 years (Interquartile range: 4.7-5.9). For total PA, those in the most active quartile had a 26% lower risk of breast cancer (HR: 0.74 [95% CI: 0.61; 0.91]) compared to those least active. Similar results were observed for light PA (HR: 0.79 [95% CI: 0.64; 0.96]), and MVPA (HR: 0.78 [95% CI: 0.64; 0.96]). However, moderate PA (HR: 0.73 [95% CI: 0.44; 0.1.19]) and vigorous PA (HR: 0.77 [95% CI: 0.56; 1.05]) was borderline significant. No evidence of interaction between PA domains and menopause status was found ($p>0.100$).

Conclusion: High levels of PA are associated with a lower risk of breast cancer with similar magnitude of associations observed across different intensity domains.

Keywords: breast cancer, physical activity; accelerometer

Introduction

Breast cancer has been the most common cancer diagnosis among women living in the UK, with 55,176 cases diagnosed and 11,399 deaths between 2015-2017 (1). Previous epidemiological studies have identified an inverse association between physical activity (PA) and the risk of breast cancer diagnosis (2-5). The International Agency for Research on Cancer (IARC), as part of the World Health Organization (WHO) estimated a possible 20% to 40% decreased risk of breast cancer in the most physically active women (6). A recent meta-analysis of 38 prospective cohort studies conducted between 1994-2017 found an overall relative risk of 0.87 (95% CI 0.84; 0.90) for those women in the most physically active category compared with those in the least active category (7).

The association between PA and breast cancer risk has previously been reported to be stronger in postmenopausal than premenopausal women (2-5, 8). However, attempts to identify differences in the association between subgroups of women in large-scale prospective studies may be limited by the use of questionnaires, which are prone to measurement error (9). While much of the current research has focused on self-reported PA, emerging evidence suggests that the magnitude of association between device-based PA and health outcomes such as all-cause mortality could be up to two times large than those estimated from questionnaires. However, evidence for device-based PA and other health outcomes such as cancer is limited (8, 10). A recent study has reported a lower risk of breast cancer associated with total acceleration derived from accelerometers as a proxy of total PA (8, 11). However, this study did not investigate any potential dose-response association of total and different intensity domains with the risk of breast cancer (8). This information could help tailor future PA recommendations for breast cancer prevention.

We hypothesize that PA is associated with a lower risk of breast cancer in a dose-response manner and that these associations may differ by menopausal status. Therefore, this study

aimed to investigate the associations of different PA intensity domains with the risk of breast cancer and whether such associations differ by menopausal status in the UK Biobank, a large prospective cohort study.

Methods

Participants

The UK Biobank longitudinal cohort began in between 2006-2010, when more than 500,000 adults were enrolled following postal invitations, which was sent out to approximately 9.2 million adults from the National Health Service (NHS) registry (12). Participants aged 37-73 years attended one of 22 assessment centers across Scotland, Wales, and England. Data was collected at these assessment centers via touchscreen questionnaires, physical measurements, and biological samples (13). Subsets of the cohort have since been included in ongoing enhanced data collection, including online questionnaires and repeated baseline samples, while all participants are continually followed up for assessment of health conditions using linkage to national electronic health-related datasets (14). In this study, we included 48,286 women from the UK Biobank study with available data for device-based PA.

Procedures

Outcomes

Breast cancer incidence (fatal and non-fatal were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Detailed information about the linkage procedures can be found at http://content.digital.nhs.uk/services. We defined incident cancer as fatal or non-fatal events. Breast cancer was defined using the 10th revision of the International Classification of Diseases (ICD-10). An ICD-10 code C50 on hospital admissions, cancer registries or death certificates denoted an incidence of breast

cancer. Date of hospital admission or deaths due to breast cancers were ascertained until 31 March 2017 for Scotland and Wales and until 01 June 2020 for England. Participants were censored at the date of breast cancer hospitalization or death or end of follow-up, whichever occurred earlier.

Menopausal status was self-reported at baseline assessment visit. Women were defined as being pre-menopausal or post-menopausal based on whether they reported that their periods had stopped; for this study, women who reported an unknown menopausal status who were under the age of 45 who had not undergone a bilateral oophorectomy were categorized as premenopausal and women at the age of 53 or over and/or had both ovaries removed were categorized as postmenopausal, as described elsewhere (8).

Device-measured Physical Activity

AxivityAX3 wrist-worn triaxial accelerometers were used to measure PA from 103,686 UK Biobank participants between 2013 and 2015. The dominant wrist of each individual was used over a period of 7 days at 100 Hz and combined into 5-s epochs for analysis (15). After performing a data quality check 7161 participants with insufficient wear time (<72-h wear), missing data, or poor device calibration were excluded, leaving 96,525 participants with valid device-measured PA data. Of these 54,374 (56.3%) were women). The median wear time was 6.91 days with less than 20% of participants wore <6 days. More details about data collection and processing can be found elsewhere (15). Minutes per week (min/week) spent on light (LPA), moderate (MPA), and vigorous (VPA) PA were determined as the time spent between >30 milligravities (mg) and 125 mg, >125 mg and 400 mg, and >400 mg, respectively, extrapolated from fraction of time spent over the total wear time (16, 17). This assumes the time spent in various PA was similar in measured and unmeasured period. Total

PA was estimated as the sum of time spent on LPA, MPA and VPA and expressed as total minutes per week.

Covariates

We assessed self-reported information on age, ethnicity (white, mixed, Asian or British Asian, Black or Black British, Chinese, or another ethnic group) and sociodemographic status at baseline. Socioeconomic status was defined using the postcode of residence of each participant and using the assigned Townsend score for that area (18). Ethnicity was categorized into. Smoking status (never, former, or current smokers), alcohol intake frequency, number of hours spent were all collected using a self-reported lifestyle questionnaire. Height and body weight were measured by trained nurses when participants visited baseline assessment centers. BMI was calculated as (weight in kg / height in m^2) and classified, as per WHO criteria, into: underweight <18.5, normal weight ≥18.5–24.9, overweight ≥25.0–29.9, and obese ≥30.0 kg m^2 (19). Hormonal factors (age at menarche, use of hormone replacement therapy (HRT), and oral contraceptive use (never, previous, and current)) were collected from the self-completed baseline assessment questionnaire. Total time spent on sedentary behaviors was derived from total discretionary time spent driving, in front of a computer and watching television. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Ethics Approval

All participants provided written informed consent before enrolment in UK Biobank, which was conducted in accordance with the Declaration of Helsinki. The UK Biobank study, and the sharing of anonymized data with the research community, was approved from the Northwest Multi-center Research Ethics Committee (REC reference: 12/NW/03820)

Statistical Analysis

Descriptive statistics of participants' characteristics were presented as means with standard deviation (SD) for continuous variables and as numbers (proportions) for categorical variables. Cox-proportional hazard models were used to examine the association of device-measured PA and breast cancer risk. Quartiles were derived for device-measured PA domains, including total, light, moderate, vigorous, MVPA and total PA expressed as minutes per week for which HR and 95% CI were calculated using the lowest category of time spent on PA as the reference.

Participants with missing data for covariates or the exposure or outcome were excluded from the analyses (Supplementary Figure 1). From participants with valid accelerometer data, we excluded 2,227 reported having breast cancer at baseline, 7,778 provided incomplete data for one or more covariates (Supplementary Figure 1). Analyses were adjusted incrementally: Model 1 included age, ethnicity and area defined deprivation index; Model 2 additionally included smoking status, alcohol intake frequency and sedentary behavior; Model 3 additionally adjusted for BMI; and 'Model 4' additionally included menopausal status, age at menarche, contraceptive use, number of live births, and any use of HRT.

To investigate if the association between PA domain and risk of breast cancer differs by menopausal status, a multiplicative interaction term between PA and menopausal status was added to Model 3.

All analyses were performed among participants free of breast cancer at the baseline assessment. In addition, to reduce the effect of reverse causation, a 2-year landmark analysis was conducted to exclude any participants that had events in the first two years of follow-up. Schoenfeld residuals test indicated that there was no evidence of a violation of the proportional hazards assumption. All analyses were performed using R Statistical Software, version 3.6.2, with the package survival.

Results

Of the 48,286 participants included in the study 836 cases of breast cancer were ascertained over a median follow-up period of 5.4 years (interquartile range: 4.7-5.9) after excluding 2 years of landmark period.

The characteristics of the participants by quartiles of PA are presented in Table 1. Briefly, women in the highest PA category were slightly younger and less deprived, had a lower prevalence of obesity, menopause and multimorbidity but a higher alcohol consumption (Table 1). As only a subsample of the UK Biobank cohort took part in the device-based PA measurement, the characteristics of participants with and without accelerometer data are presented in supplementary Table 1. Compared to people with device-measured PA those without accelerometer data had a similar age (56.5 v 55.3 years) but were more deprived (34.0% v 28.7%), had a higher prevalence of obesity (4.1% v 5.9%), were more likely to be current smoker (5.8% v 9.7%), and had a higher prevalence of multimorbidity (25.1% v 34.7%).

Table 2 shows the associations of device-based PA domains and the risk of breast cancer. In model 1 (minimally adjusted) there was evidence of an inverse trend for all PA domains and risk of breast cancer. For light PA, those in the most active quartile (>2419 min/week) had a 33% (95% CI: 0.63; 0.94) lower risk of breast cancer compared to the least active quartile (<1854 min/week). A bigger magnitude of associations was observed for moderate (HR: 0.65 [95% CI: 0.45; 1.05]) and vigorous PA (HR: 0.70 [95% CI: 0.52; 0.94]). Those in the highest quartile for total PA (>3031 min/week) had a 29% (95% CI: 0.59; 0.87) compared to those least active. Similar results were found for MVPA (Table 2). When analyses were further adjusted for lifestyle factors (Model 2) and BMI (Model 3) the magnitude of associations were slightly attenuated but remained significant for all intensity domains (Table 2). Additional adjustment for specific-risk factors for breast cancer did not change the associations for light, MVPA and total PA. However the association of moderate and vigorous PA become borderline

significant, maintaining similar hazard estimates but wider confidence intervals (Table 2). When total PA was expressed in average acceleration units (milligravity), similar associations to those reported for total PA expressed in minutes per week were observed (Table 2). There was no evidence of a significant interaction between PA domains and menopausal status on risk of breast cancer as presented in Supplementary Table 2. Therefore, a similar trend for pre- and post-menopausal women towards a lower risk of breast cancer by increasing light PA (HR_{pre}: 0.87 [95% CI: 0.76; 0.99 and HR_{post}:0.90 [95% CI: 0.83; 0.98]) and total PA (HR_{pre}: 0.86 [95% CI: 0.75; 0.97 and HR_{post}:0.92 [95% CI: 0.84; 0.99]) was found. However, the trend was not significant for moderate, vigorous and MVPA (Supplementary Table 2).

Discussion

In this prospective cohort study, higher levels of device-measured PA were inversely associated with a lower risk of breast cancer after being adjusted for key confounding factors, including sociodemographic and lifestyle factors and adiposity. Similar associations were observed across different intensity domains, which agree with current PA recommendations that all PA matters. There was no evidence that the association between PA and breast cancer risk differs by menopausal status. These findings highlight the potential role of PA in breast cancer prevention for pre- and post-menopausal women.

With most of the existing evidence derived from self-reported PA studies, there is a lack of evidence from studies using device-measured PA (8). Although our findings agree with existing evidence from self-reported PA (26, 27), the magnitude of associations was larger in our study than in previous studies based on questionnaires (20, 21). Our findings are also in agreement with accelerometer-based studies (8). A prospective study of 174,160 UK biobank participants reported an inverse linear trend between overall accelerometer acceleration as a

proxy of total PA and breast cancer risk. However, there was no stratification by PA intensity domains (8). Guo et al., reported that 5 miligravity units increment on overall acceleration was associated with a 18% and 21% lower risk of breast cancer in pre- and post-menopausal women independent of major confounding factors, including adiposity (8). The magnitude of association reported by Guo et al was in the same direction that the ones observed in our study were pre- and post-menopausal women in the highest category for total PA levels had a 39% and 25% lower risk of breast cancer (8). Although the associations reported by Guo et al. were significant, using acceleration units does not allow for disentangling the contribution of different intensity domains to the prevention of breast cancer risk. This is particularly important as PA recommendations could be tailored to PA intensity that are most beneficial for breast cancer prevention. As reported in our study, light PA is inversely associated with a lower risk of breast cancer among pre- and post-menopausal women. This is important as this intensity domain represents the largest proportion of time spent on PA among adults. increasing light PA may be more feasible than increasing moderate and vigorous PA, especially among inactive individuals. Although moderate, vigorous and MVPA showed a similar trend to those observed for total and light PA, the lack of association could be related to a lack of power due to the distribution of these PA intensities. For moderate PA, only two cases of breast cancer were diagnosed out of 116 participants classified in this category PA (<150 min/week).

Although our study is observational and therefore cannot establish causality, recent evidence from a Mendelian Randomization study supports a causal link between physical activity and breast cancer risk (22). The study reported that 1-SD increment in overall acceleration (equivalent to 8.1 milli-gravities) was associated with a 49% lower risk of breast cancer. If we translate milligravities into PA intensities, then 8.1 milligravities would equal 50 minutes per week of moderate PA or approximately 8 minutes of vigorous PA per week (22, 23). Several

biological mechanisms make the inverse association between PA and breast cancer risk plausible (24). Higher PA has been associated with lower concentrations of insulin and insulin-like growth factor, which promote a higher proliferation in breast tissue and has also been associated with the development of breast cancer (24-26). Estradiol, estrone and sex hormone binding globulin are risk factors for breast cancer which have been inversely associated with PA levels (26). High levels of PA have been also linked to an improved immune response with increasing surveillance and high removal of cancerous cells (27). Systemic inflammation and PA are other hypotheses behind the link between breast cancer and PA. Higher levels of PA have been linked to a reduction in the concentration of pro-inflammatory factors, including C-reactive protein, interleukin 6, and tumor necrosis factor-alpha, which play a key role in the development of cancer (26, 28).

Strengths and limitations

The strengths of this study are the large sample size of the UK Biobank cohort, which allowed for enough power to assess associations between breast cancer and intensity-specific PA, the prospective study design, and the availability of a large number of exposures and covariates. However, this study is not exempt from limitations. The UK Biobank population is not representative of the UK population. Participants who volunteered for the UK Biobank study were more likely to be from less deprived areas, younger, and have a lower BMI; they were also more likely to be alcohol drinkers and have a lower prevalence of multimorbidity. However, the breast cancer rates within the UK Biobank were mostly comparable to the UK population average, with a higher-than-average breast cancer rate only in those aged 45-49 in the cohort (12, 29). Although our study is one of the largest studies conducted on breast cancer using device-based PA measures, it still lacks longer follow-up to allow for more statistical power when looking at stratified analysis by breast cancer risk factors. It must also be noted

that details such as grade, stage and the hormone receptor status of breast cancer tumors were not available in the UK Biobank; therefore, we were not able to include in this analysis. The analysis adjusted for adiposity to provide a conservative estimates but it should be noted that adiposity could be a mediator.

Perspective

The findings from this prospective cohort study indicate that device-measured PA is inversely associated with breast cancer in all women. Our results confirmed the significance of people adhering to the current aerobic PA recommendations and highlighted the public health message that every step counts.

Funding

UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation. All authors had final responsibility for submission for publication. SPS was funded by the Chilean Government PhD scholarship program. No other funding has been received for conducting this study.

Conflict of interest

None to declare.

Acknowledgements: We are grateful to UK Biobank participants. This research has been conducted using the UK Biobank resource under application number 7155 and we express our gratitude to the participants and those involved in building the resource. The results of the present study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation and do not constitute endorsement by American College of Sports Medicine.

Authors' contributions: Study conception and design: S.P-S, F.H, J.P.P and C.C-M. Data analysis: S.P-S, CT, F.H and C.C-M. Interpretation of results: all authors. First draft: S.P-S, C.T and C.C-M. Review, editing and approval of final manuscript: all authors.

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Table 1. Baseline characteristics of participants by categories of total physical activity.

	Categories of Total Physical Activity (min/week)			
	Lowest	**Low-Middle**	**Middle-High**	**Highest**
n	12317 (25.51)	12021 (24.9)	11924 (24.69)	12024 (24.90)
Age Mean (years)	56.42 (7.706075)	55.52 (7.73)	55.03 (7.70)	54.39 (7.70)
Townsend deprivation index (%)				
Lower deprivation	4197 (34.07)	4392 (36.54)	4537 (38.05)	4573 (38.03)
Middle deprivation	4199 (34.09)	4221 (35.11)	4130 (34.64)	4150 (34.51)
Higher deprivation	3921 (31.83)	3408 (28.35)	3257 (27.31)	3301 (27.45)
Ethnicity (%)				
White	11937 (96.91)	11660 (97)	11525 (96.65)	11546 (96.02)
Mixed	143 (1.16)	149 (1.24)	162 (1.36)	172 (1.43)
South Asian	87 (0.71)	83 (0.69)	110 (0.92)	101 (0.84)
Black	119 (0.97)	96 (0.8)	100 (0.84)	151 (1.26)
Chinese	31 (0.25)	33 (0.27)	27 (0.23)	54 (0.45)
Height (m)	1.63 (0.06)	1.63 (0.06)	1.63 (0.06)	1.63 (0.06)
Waist (cm)	86.81 (13.18)	82.92 (11.53)	81.38 (10.78)	79.32 (10.31)
Body fat % (%)	38.12 (6.77)	35.82 (6.49)	34.65 (6.54)	32.94 (6.62)
Body Mass Index (kg/m^2)	28.01 (5.59)	26.33 (4.66)	25.69 (4.31)	24.88 (4.04)
BMI (kg/m^2)				
Underweight	4067 (33.21)	5345 (44.72)	5957 (50.44)	6925 (58.38)

Normal	4518 (36.89)	4439 (37.14)	4180 (35.39)	3689 (31.1)
Overweight	2283 (18.64)	1508 (12.62)	1232 (10.43)	955 (8.05)
Obese	930 (7.59)	492 (4.12)	342 (2.9)	240 (2.02)
Morbid Obese	450 (3.67)	167 (1.4)	100 (0.85)	52 (0.44)
Device-measured physical activity				
Light PA (min/week)	1,642.28 (242.85)	2,020.98 (169.96)	2,268.78 (195.87)	2,631.85 (299.81)
Moderate PA (min/week)	292.88 (130.09)	430.31 (143.16)	538.08 (166.24)	730.70 (240.22)
Vigorous PA (min/week)	14.00 (24.27)	23.45 (30.69)	32.48 (38.56)	46.25 (49.71)
MVPA (min/week)	306.88 (141.55)	453.77 (157.44)	570.56 (184.32)	776.95 (265.33)
Smoking (%)				
Never	7353 (59.7)	7459 (62.05)	7330 (61.47)	7503 (62.4)
Previous	4026 (32.69)	3909 (32.52)	3968 (33.28)	3895 (32.39)
Current	938 (7.62)	653 (5.43)	626 (5.25)	626 (5.21)
Alcohol intake (%)				
Daily or almost daily	2032 (16.51)	2278 (18.96)	2351 (19.72)	2383 (19.83)
3-4 times a week	2581 (20.96)	2869 (23.88)	3045 (25.54)	3064 (25.5)
Once or twice a week	3133 (25.45)	3201 (26.64)	3097 (25.98)	2935 (24.43)
1-3 times a month	1785 (14.5)	1543 (12.84)	1464 (12.28)	1441 (11.99)
Special occasions only	1855 (15.07)	1386 (11.54)	1280 (10.74)	1413 (11.76)
Never	925 (7.51)	738 (6.14)	684 (5.74)	780 (6.49)
No answer				
Age at menarche (years)	13.22 (2.72)	13.33 (2.72)	13.34 (2.72)	13.41 (2.71)
Number live births	1.67 (1.18)	1.70 (1.15)	1.73 (1.14)	1.78 (1.14)
Menopausal Status (%)				
Premenopausal	2853 (23.16)	3190 (26.54)	3423 (28.71)	3761 (31.28)
Postmenopausal	7346 (59.64)	7068 (58.8)	6818 (57.18)	6705 (55.76)
Unknown menopausal status	2118 (17.2)	1763 (14.67)	1683 (14.11)	1558 (12.96)
Contraceptive (%)				

No	1925 (15.63)	1782 (14.82)	1574 (13.2)	1764 (14.67)
Yes	10374 (84.23)	10226 (85.07)	10337 (86.69)	10237 (85.14)
Missing	18 (0.14)	13 (0.11)	13 (0.11)	23 (0.19)
Hormonal replacement (%)				
No	7346 (59.64)	7625 (63.43)	7777 (65.22)	8255 (68.65)
Yes	4942 (40.12)	4375 (36.39)	4128 (34.62)	3751 (31.2)
Missing	29 (0.24)	21 (0.17)	19 (0.16)	18 (0.15)
Multimorbidity (%)				
No illness	4274 (34.7)	5117 (42.57)	5288 (44.35)	5652 (47.01)
1 illness	4076 (33.09)	3928 (32.68)	3923 (32.9)	3883 (32.29)
2+ illness	3967 (32.21)	2976 (24.76)	2713 (22.75)	2489 (20.7)

Data is presented as mean and standard deviation for continuous variables and frequency and percent for categorical variables.

Table 2. Association between device-measured physical activity domains and breast cancer risk.

			Model 1		**Model 2**		**Model 3**		**Model 4**	
Exposure	**Total n**	**Events**	**HR 95% CI**	**P value**	**HR 95% CI**	**P value**	**HR 95% CI**	**P value**	**HR 95% CI**	**P value**
Light PA (min/week)										
<1854	12,361	235	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
1854-2126	11,905	221	0.96 (0.80; 1.16)	0.740	0.96 (0.80; 1.16)	0.740	0.97 (0.81; 1.17)	0.821	0.97 (0.81; 1.17)	0.821
2127-2419	12,241	203	0.86 (00.71; 1.03)	0.117	0.85 (0.71; 1.03)	0.112	0.87 (0.71; 1.05)	0.152	0.87 (0.71; 1.05)	0.152
>2419	11,779	177	0.77 (0.63; 0.94)	0.011	0.77 (0.63; 0.94)	0.011	0.79 (0.64; 0.96)	0.020	0.79 (0.64; 0.96)	0.020
HR for trend	48,286	836	0.91 (0.86; 0.97)	0.006	0.92 (0.86; 0.97)	0.005	0.92 (0.87; 0.98)	0.010	0.92 (0.87; 0.98)	0.010
Moderate PA (min/week)										
<150	1,623	31	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
150-300	8,072	161	1.04 (0.70; 1.52)	0.840	1.04 (0.70; 1.52)	0.840	1.05 (0.71; 1.55)	0.785	1.07 (0.72; 1.57)	0.722
301-900	35,729	608	0.88 (0.61; 1.26)	0.502	0.88 (0.61; 1.27)	0.506	0.91 (0.63; 1.31)	0.623	0.95 (0.66; 1.38)	0.806
>900	2,857	36	0.65 (0.45; 1.05)	0.084	0.65 (0.40; 1.05)	0.084	0.68 (0.41; 1.11)	0.127	0.73 (0.44; 1.19)	0.211
HR for trend	48,286	836	0.86 (0.77; 0.96)	0.012	0.86 (0.77; 0.97)	0.013	0.87 (0.78; 0.98)	0.032	0.90 (0.80; 1.01)	0.089
Vigorous PA (min/week)										
None	8,141	168	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
1-35	28,068	473	0.81 (0.67; 0.96)	0.019	0.80 (0.67; 0.96)	0.018	0.82 (0.68; 0.97)	0.029	0.83 (0.70; 1.00)	0.055
36-75	8,133	137	0.80 (0.64; 100)	0.058	0.80 (0.64; 1.00)	0.058	0.82 (0.65; 1.03)	0.100	0.86 (0.68; 1.08)	0.212
>75	3,944	58	0.70 (0.52; 0.94)	0.021	0.70 (0.52; 0.95)	0.022	0.72 (0.53; 0.98)	0.040	0.77 (0.56; 1.05)	0.099
HR for trend	48,286	836	0.90 (0.82; 0.98)	0.019	0.90 (0.82; 0.98)	0.020	0.91 (0.83; 0.99)	0.043	0.93 (0.84; 1.01)	0.122
MVPA (min/week)										
<343	12,541	251	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
343-490	12,038	196	0.80 (0.67; 0.97)	0.026	0.80 (0.67; 0.97)	0.025	0.81 (0.67; 0.98)	0.035	0.83 (0.68; 1.00)	0.059
491-672	11,739	211	0.89 (0.74; 1.07)	0.239	0.89 (0.74; 1.07)	0.242	0.91 (0.75; 1.09)	0.327	0.94 (0.77; 1.13)	0.534
>672	11,968	178	0.73 (0.60; 0.89)	0.002	0.74 (0.61; 0.89)	0.002	0.76 (0.62; 0.92)	0.006	0.78 (0.64; 0.96)	0.022
HR for trend	48,286	836	0.92 (0.86; 0.97)	0.008	0.92 (0.86; 0.97)	0.008	0.92 (0.87; 0.98)	0.022	0.94 (0.88; 1.00)	0.047
Total PA (min/week)										
<2275	12,317	243	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2275-2646	12,021	214	0.89 (0.74; 1.07)	0.252	0.89 (0.74; 1.07)	0.252	0.90 (0.75; 1.09)	0.304	0.91 (0.75; 1.10)	0.345
2647-3031	11,924	206	0086 (0.72; 1.04)	0.141	0.86 (0.71; 1.04)	0.133	0.87 (0.72; 1.06)	0.184	0.89 (0.73; 1.07)	0.237
>3031	12,024	173	0.71 (0.59; 0.87)	0.001	0.71 (0.59; 0.87)	0.001	0.73 (0.59; 0.89)	0.002	0.74 (0.61; 0.91)	0.004
HR for trend	48,286	836	0.90 (0.85; 0.96)	0.001	0.90 (0.85; 0.96)	0.001	0.91 (0.85; 0.96)	0.003	0.92 (0.85; 0.97)	0.006
Overall acceleration average (milligravity)										
<23	12,087	248	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
23-28	12,077	199	0.79 (0.66; 0.96)	0.017	0.79 (0.65; 0.95)	0.016	0.80 (0.66; 0.96)	0.021	0.81 (0.67; 0.98)	0.031
29-33	12,065	210	0.84 (0.70; 1.01)	0.067	0.84 (0.69; 1.01)	0.065	0.85 (0.70; 1.02)	0.095	0.87 (0.72; 1.05)	0.159
>33	12,057	179	0.71 (0.58; 0.86)	0.001	0.71 (0.58; 0.86)	0.001	0.72 (0.59; 0.88)	0.002	0.75 (0.61; 0.92)	0.007

HR for trend	48,286	836	0.90 (0.85; 0.96)	0.002	0.90 (0.85; 0.96)	0.002	0.91 (0.85; 0.97)	0.005	0.92 (0.86; 0.98)	0.018

Data presented as hazard ratios and their 95% CI. The PA exposures were presented as minutes per day spent in different intensity PA. The reference group was defined as the lowest category of PA for each intensity domain. The HR for trend represents the hazard equivalent to a 1-category increment on PA. Analyses were adjusted for: Model 1 age, deprivation and ethnicity; Model 2 was adjusted for model 1 plus alcohol intake, smoking and sedentary time; Model 3 was additionally adjusted for BMI; Model 4 was additionally adjusted for menopausal status, age at menarche, hormonal replacement, contraceptive use and the number of live births.

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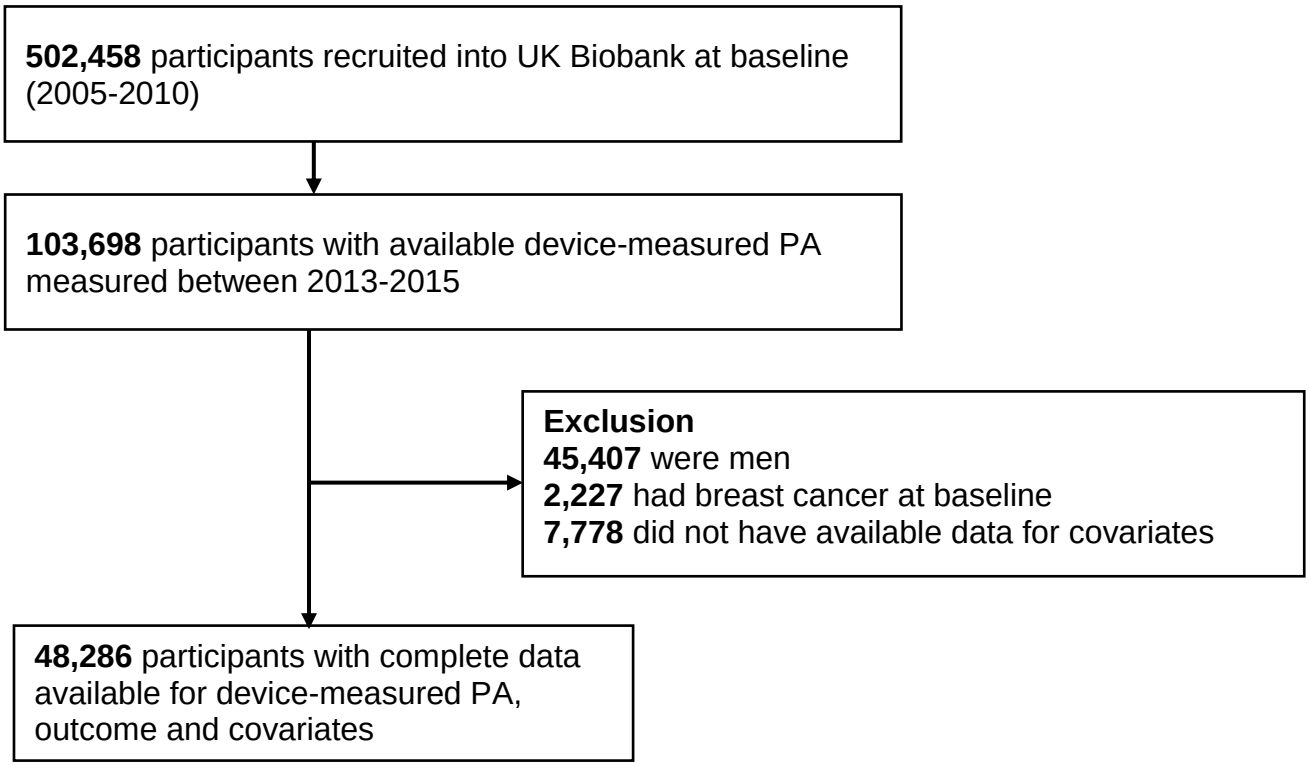

Supplementary Figure 1. Flowchart of participants

Supplementary Table 1: Baseline characteristics of participants included in the study, those with device-measured PA but not included and participants without device-measured PA.

	Participants included in the study	Participants with device-measured PA but not included in the study	Participants without device-measured PA and not included in the study
n	48,286	10,005	215,100
Age Mean (years)	55.35 (7.74)	56.57 (7.62)	56.56 (8.06)
Townsend deprivation index (%)			
Lower deprivation	17699 (36.65)	3498 (35.2)	69711 (32.45)
Middle deprivation	16700 (34.59)	3406 (34.28)	72027 (33.53)
Higher deprivation	13887 (28.76)	3033 (30.52)	73103 (34.03)
Ethnicity (%)			
White	46668 (96.65)	9521 (96.87)	201254 (94.04)
Mixed	626 (1.3)	115 (1.17)	3709 (1.73)
South Asian	381 (0.79)	88 (0.9)	4119 (1.92)
Black	466 (0.97)	76 (0.77)	4112 (1.92)
Chinese	145 (0.3)	29 (0.3)	816 (0.38)
Waist (cm)	82.63 (11.84)	83.60 (12.10)	85.26 (12.69)
Body fat % (%)	35.40 (6.87)	35.88 (6.82)	36.90 (6.89)
Body Mass Index (kg/m^2)	26.24 (4.83)	26.51 (5.01)	27.31 (5.26)
BMI (kg/m^2)			
Underweight	22294 (46.57)	4361 (44.56)	79008 (37.23)
Normal	16826 (35.15)	3472 (35.48)	79593 (37.5)
Overweight	5978 (12.49)	1320 (13.49)	35431 (16.69)

Obese	2004 (4.19)	434 (4.43)	12516 (5.9)
Morbid Obese	769 (1.61)	200 (2.04)	5678 (2.68)
Smoking (%)			
Never	29645 (61.39)	5698 (57.09)	126713 (59.03)
Previous	15798 (32.72)	3496 (35.03)	66162 (30.82)
Current	2843 (5.89)	662 (6.63)	20861 (9.72)
Missing	0 (0.0)	124 (1.24)	939 (0.44)
Alcohol intake (%)			
Daily or almost daily	9044 (18.74)	1978 (19.83)	32845 (15.32)
3-4 times a week	11559 (23.95)	2363 (23.69)	41975 (19.58)
Once or twice a week	12366 (25.62)	2447 (24.53)	55361 (25.82)
1-3 times a month	6233 (12.91)	1208 (12.11)	28064 (13.09)
Special occasions only	5934 (12.3)	1268 (12.71)	33952 (15.83)
Never	3127 (6.48)	712 (7.14)	22215 (10.36)
No answer			
Multimorbidity (%)			
No illness	20331 (42.11)	2033 (20.32)	70815 (32.92)
1 illness	15810 (32.74)	3592 (35.9)	69464 (32.29)
2+ illness	12145 (25.15)	4380 (43.78)	74821 (34.78)

Data is presented as mean and standard deviation for continuous variables and frequency and percent for categorical variables.

Supplementary Table 2. Association between device-measured physical activity domains and breast cancer risk by menopausal status.

	Pre-menopausal				Post-menopausal				
Exposure	**Total n**	**Events**	**HR 95% CI**	**P value**	**Total n**	**Events**	**HR 95% CI**	**P value**	**P Interaction**
Light PA (min/week)									
<1854	3,529	67	1.00 (Ref.)		6,834	139	1.00 (Ref.)		0.074
1854-2126	3,302	42	0.67 (0.46; 0.99)	0.050	6,846	142	1.02 (0.80; 1.29)	0.864	
2127-2419	3,329	50	0.80 (0.55; 1.15)	0.239	7,153	119	0.81 (0.63; 1.04)	0.113	
>2419	3,067	36	0.61 (0.40; 0.92)	0.020	7,104	112	0.77 (0.60; 0.99)	0.050	
HR for trend	13,227	195	0.87 (0.76; 0.99)	0.039	27,937	512	0.90 (0.83; 0.98)	0.016	
Moderate PA (min/week)									
<150	116	2	1.00 (Ref.)		1,189	22	1.00 (Ref.)		0.656
150-300	1,225	22	1.02 (0.24; 4.38)	0.969	5,455	111	1.11 (0.70; 1.76)	0.644	
301-900	10,711	159	0.83 (0.20; 3.38)	0.801	19,948	362	1.01 (0.65; 1.58)	0.931	
>900	1,174	12	0.57 (0.12; 2.57)	0.465	1,342	17	0.73 (0.38; 1.39)	0.344	
HR for trend	13,226	195	0.78 (0.58; 1.05)	0.114	27,934	512	0.92 (0.79; 1.07)	0.302	
Vigorous PA (min/week)									
None	1,088	23	1.00 (Ref.)		5,716	119	1.00 (Ref.)		0.611
1-35	7,141	98	0.64 (0.40; 1.01)	0.058	16,623	300	0.87 (0.70; 1.08)	0.237	
36-75	3,087	49	0.72 (0.43; 1.20)	0.212	4,020	68	0.83 (0.61; 1.13)	0.326	
>75	1,911	25	0.59 (0.33; 1.05)	0.073	1,578	25	0.80 (0.51; 1.24)	0.326	
HR for trend	13,227	195	0.91 (0.76; 1.08)	0.307	27,937	512	0.92 (0.81; 1.04)	0.188	
MVPA (min/week)									
<343	1,852	33	1.00 (Ref.)		8,539	174	1.00 (Ref.)		0.578
343-490	3,001	41	0.75 (0.47; 1.19)	0.234	7,152	122	0.84 (0.67; 1.07)	0.164	
491-672	3,773	65	0.93 (0.61; 1.43)	0.763	6,347	120	0.96 (0.75; 1.21)	0.742	
>672	4,601	56	0.65 (0.41; 1.01)	0.057	5,899	96	0.83 (0.64; 1.07)	0.167	
HR for trend	13,227	195	0.89 (0.78; 1.02)	0.123	27,937	512	0.95 (0.88; 1.03)	0.291	
Total PA (min/week)									
<2275	2,853	54	1.00 (Ref.)		7,346	149	1.00 (Ref.)		0.198
2275-2646	3,190	47	0.77 (0.52; 1.14)	0.205	7,068	135	0.94 (0.74; 1.20)	0.660	
2647-3031	3,423	49	0.75 (0.50; 1.11)	0.154	6,818	128	0.93 (0.73; 1.19)	0.596	
>3031	3,761	45	0.61 (0.40; 0.91)	0.018	6,705	100	0.75 (0.57; 0.97)	0.031	
HR for trend	13,227	195	0.86 (0.75; 0.97)	0.022	27,937	512	0.92 (0.84; 0.99)	0.042	
Overall acceleration average (milligravity)									
<23	2,149	42	1.00 (Ref.)		7,832	165	1.00 (Ref.)		0.285
23-28	2,923	43	0.73 (0.48; 1.13)	0.168	7,288	122	0.79 (0.062; 1.00)	0.057	
29-33	3,575	49	0.68 (0.4; 1.03)	0.075	6,799	136	0.96 (0.76; 1.21)	0.772	
>33	4,580	61	0.64 (0.43; 0.97)	0.037	6,018	89	0.72 (0.55; 0.94)	0.016	

HR for trend	13,227	195	0.87 (0.76; 1.00)	0.051	27,937	512	0.92 (0.85; 1.00)	0.077	

Data presented as hazard ratios and their 95% CI. The PA exposures were presented as minutes per week spent in different intensity PA. The reference group was defined as the lowest category of PA for each intensity domain. The HR for trend represents the hazard equivalent to 1-category increment on PA. Analyses were adjusted for age, deprivation, ethnicity, alcohol intake, smoking, sedentary time, BMI, age at menarche, hormonal replacement, contraceptive use and the number of live births. P for interaction was tested by adding a multiplicative interaction between PA and menopausal status.