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Physical Activity and Risk of Endometrial Adenocarcinoma in the Nurses' Health Study

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Abstract

Studies suggest greater physical activity may reduce endometrial cancer risk. However, the role of the timing, duration, and intensity of activity is unclear. We therefore examined recent and past recreational activities in relation to incident endometrial adenocarcinoma, and compared the importance of total and moderate- or vigorous-intensity activities, as well as walking. We analyzed data from 71,570 women in the Nurses' Health Study, a prospective cohort that assessed activity in 1986, with updates every 2–4 years. Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). During follow-up from 1986–2008 (1.2 million person-years), 777 invasive endometrial adenocarcinoma cases were documented. In multivariable models, compared with <3 MET-hrs/wk (<1 hr/wk walking), women engaged in moderate (9–<18 MET-hrs/wk: RR=0.61, 95% CI: 0.48–0.78) or high (≥27 MET-hrs/wk: RR=0.73, 95% CI: 0.58–0.92) amounts of recent total recreational activity were at reduced risk (*P*-trend=0.001). Past total activity was unassociated with risk. Greater recent moderate- or vigorous-intensity activity was associated with reduced risk (≥4 vs 0 hrs/wk: RR=0.65, 95% CI: 0.47–0.88, *P*-trend=0.002). Among women who did not perform any vigorous activity, recent walking was associated with reduced risk (≥3 vs <0.5 hrs/wk: RR=0.65, 95% CI:

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0.45–0.93, *P*-trend=0.01), and faster walking pace was independently associated with risk reduction. After additional adjustment for body mass index, all associations were statistically non-significant. Greater recent physical activity may reduce endometrial adenocarcinoma risk, including activity of moderate duration and intensity such as walking. This relation is largely mediated or confounded by body mass index.

Keywords

physical activity; exercise; endometrial cancer; endometrial adenocarcinoma; prospective study

Endometrial cancer is the most common gynecologic malignancy and the fourth most common incident cancer among US women.[1] Obesity has been estimated to account for approximately 40% of endometrial cancer incidence, supporting the critical role of energy balance in its etiology.[2, 3] Exercise helps regulate energy balance and reduce obesity.[4] Prospective studies have shown an inverse association between activity and endometrial cancer risk,[5–10] with estimated risk reductions of 20–40% comparing active with inactive women.[11–13]

Most studies, however, have utilized 1 baseline measure of activity, precluding the evaluation of whether recent, past, or long-term activities are most relevant for risk reduction. Moreover, given that physical activity is a complex behavior that may vary throughout time, a single assessment may be more vulnerable to measurement error. Few studies have compared activities of different intensities or examined specifically the role of walking, the most common form of exercise among middle-aged and older women,[14] although evidence supports its health benefits for heart disease, diabetes, and other cancers.[15–18] Data are also inconsistent regarding the duration of activity necessary to reduce risk and whether this relation varies by other factors related to endometrial cancer, such as body mass index (BMI, calculated as weight in kg/height in m^2) or postmenopausal hormone therapy (HT).[11, 13] Moreover, few studies have addressed the influence of BMI on the relation between activity and risk in a systematic manner.[5, 6, 19] To the extent that anthropometric characteristics may guide exercise behavior, body mass index, an established risk factor for endometrial cancer,[2, 3, 13] may act as a confounder. But body mass index may also mediate this relation (i.e., be in the causal chain), as physical activity helps prevent obesity, which can in turn reduce endometrial cancer risk.[4, 13]

We therefore examined recreational physical activity in relation to risk of endometrial adenocarcinoma in the Nurses' Health Study (NHS) prospective cohort. We used detailed assessments of physical activity updated every 2–4 years over 22 years of follow-up to quantify the importance of recent, past, and long-term average activities. We also examined separately the potential benefits of total and moderate- or vigorous-intensity activities, as well as walking and walking pace. As the role of BMI in the relationship between activity and risk is unclear, we distinguished between models adjusting and not adjusting for BMI and additionally assessed effect modification by BMI.

MATERIAL AND METHODS

Study population

The NHS prospective cohort was established in 1976, when 121,700 female registered nurses residing in 11 US states and aged 30–55 years provided detailed information on individual characteristics and behaviors in mailed questionnaires administered at baseline. Biennially thereafter, participants received follow-up questionnaires to update information on lifestyle factors, including endometrial cancer risk factors, and new disease diagnoses.

The response rate in the initial invitation cycle was 71%, and response rates of approximately 90% have been achieved in each follow-up cycle. Deaths were identified by next-of-kin reports, the US Postal Service, or through the National Death Index. The human research committees at Brigham and Women's Hospital, Boston, MA, USA approved this study.

At the start of follow-up in 1986, when detailed physical activity was first assessed, we excluded nurses who had died or reported previous cancers except non-melanoma skin cancer (*N*=10,174), reported a hysterectomy or surgical menopause (*N*=31,666), or were missing all activity data during follow-up (*N*=8,290). At each subsequent follow-up cycle, we censored deaths or cancer diagnoses, as well as women reporting hysterectomy or surgical menopause. The final study population comprised 71,570 eligible participants with 1,235,880 person-years of follow-up.

Assessment of physical activity

Detailed information on recreational physical activity during the past year was assessed by questionnaire in 1986. Participants reported their average weekly time spent on any of 8 activities: walking or hiking, jogging, running, bicycling, lap swimming, playing tennis, calisthenics/aerobics/aerobic dance/rowing machine, and playing squash or racquetball. Participants also reported their usual walking pace and the number of flights of stairs climbed daily. These questions were repeated, with minor changes, every 2–4 years (1988, 1992, 1994, 1996, 1998, 2000, and 2004). Starting in 1992, information was collected on other lower intensity (e.g., yoga, stretching, toning) and vigorous (e.g., lawn mowing) activities. Starting in 1990, participants were asked whether their health limited them in performing typical activities (e.g., walking 1 block, moderate activities, and vigorous activities). Physical activity data were carried forward when activity was not included on the biennial questionnaires (e.g., 1988 data used in the 1990–1992 follow-up). However, activity data were not carried forward when women failed to answer physical activity questions (e.g., 1992 data were not carried forward if a woman was missing 1994 data).

To incorporate activity frequency, duration, and intensity, we calculated total metabolic equivalent (MET) hours of activity per week (MET-hrs/wk).[20, 21] During each questionnaire cycle, participants with unreasonably high levels of activity (125+ MET-hrs/wk, or approximately 6 hours per day of average recreational walking) were assigned missing activity values. In analyses of moderate- or vigorous-intensity activities, we defined *a priori* only brisk or very brisk walking, jogging, or running as moderate or vigorous activity. Because of the variable intensity with which activities such as swimming and biking may be performed, excluding these activities may reduce potential misclassification of moderate or vigorous activity.[18] In analyses of walking and walking pace, however, we were interested specifically in whether walking was beneficial even if women did not perform any vigorous activities. We thus used a more general definition of vigorous activities, which included any activities that were *potentially* vigorous (6 METS or greater: jogging, running, bicycling, swimming, tennis, calisthenics/aerobics, racquet sports, and other vigorous activity) in analyses of walking.[22] We categorized total recreational activity into multiples of 3 as 3 METs represents 1 hour of average walking.[20] Moderate or vigorous activity was categorized by hours per week for increased comparability to existing physical activity guidelines.[22] For adequate statistical power to examine high levels of activity, we selected category cut points that resulted in an approximately even distribution of cases in higher activity categories.

The reproducibility and validity of these questions have been described previously.[23] In a similar population of NHS II participants (*N*=151), the correlation over a 1-year period between activity reported by questionnaire and that assessed by past-week recalls was 0.79,

and the correlation between moderate or vigorous activity reported by questionnaire and that assessed by activity diaries was 0.62.

Assessment of covariates

Age was calculated from birth date to questionnaire return date. Age at menarche, height, and age at first birth were asked in 1976. Weight at age 18 years was assessed in 1980. Information on oral contraceptives (OCs) was collected until 1982 and parity biennially until 1984. Family history of endometrial cancer was collected once in 1996 and colorectal cancer in 1982 and every 4 years since 1988. Waist and hip measurements were collected in 1986, 1996, and 2000. Employment status was collected every 4 years from 1988. Alcohol, caffeine, and energy intakes were assessed with a semiquantitative food frequency questionnaire[24] every 4 years from 1986. Total time spent sitting was reported in 1992. Smoking, current weight, menopausal status, HT, age at menopause, and diagnosis of diabetes were assessed biennially.

Ascertainment of endometrial adenocarcinoma cases

Information on endometrial cancer was collected from questionnaires at each follow-up cycle. To confirm cancer diagnoses, study physicians masked to exposure status reviewed medical records after obtaining permission from participants. Data was collected on histological type, presence of invasion and stage, as well as grade. In the present analysis, we included cases of invasive endometrial adenocarcinoma (ICD-O histology code 8380/3) because of potential heterogeneity by histological subtype. Cases were defined by the 1988 International Federation of Gynecology and Obstetrics (FIGO) criteria as stage IA to IVB diagnosed from 1986 to May 2008 and confirmed by medical records (99% of reported cases confirmed). Women diagnosed with non-epithelial tumors (N=129), types of epithelial tumors other than adenocarcinoma (e.g., squamous cell) (N=127), or non-invasive tumors (endometrial intraepithelial neoplasia, atypical hyperplasia, or adenocarcinoma *in situ*) (N=288) were censored during follow-up. For confirmed cases, the distribution of tumor stage was 87% stage I, 4% stage II, 2% stage III, and 7.0% stage IV; the distribution of tumor grade was 49% well differentiated, 37% moderately differentiated, and 14% poorly differentiated.

Statistical analyses

Participants contributed person-time from the date of return of the 1986 questionnaire until the earliest of the following dates: confirmed endometrial adenocarcinoma, other cancer diagnosis (including endometrial tumors that did not meet the case definition), hysterectomy or surgical menopause, death, or June 1, 2008. To quantify the relation between activity and endometrial adenocarcinoma risk, we used Cox proportional hazards models, stratified jointly by age in months and calendar time at the beginning of each follow-up cycle, to estimate adjusted hazard ratios [relative risks (RRs)] and their corresponding 95% confidence intervals (CIs). We tested the proportional hazards assumption by including interaction terms between activity and calendar time or age and using likelihood ratio tests comparing nested models with and without interaction terms. The proportional hazards assumption was met in all analyses.

To reduce confounding and avoid potential overfitting, we included in our multivariable models only covariates that were *a priori* established risk factors for endometrial cancer risk, and were also associated with risk in the present analysis. For potential risk factors with less consistent evidence in previous studies, we checked whether their inclusion in the models changed estimates by ≥10%. Primary multivariable models adjusted for various endometrial cancer risk factors, including age at menarche; past OC use; parity and ages at first and last birth; menopausal status, age at menopause; HT use, duration, and type; BMI at

age 18; recent pack-years of smoking; family history of endometrial or colorectal cancer; and alcohol and caffeine intakes. Adiposity may be a confounder of the association between activity and risk (i.e., overweight or obese individuals may be less likely to be active and have increased risk of endometrial cancer). However, biological evidence suggests that adiposity may also mediate the association (i.e., activity leads to reduced adiposity, which in turn results in reduced risk[2, 3, 13]). Thus, we did not include BMI, waist/hip ratio, or diabetes in our primary multivariable models as including these may attenuate the true association with physical activity. In separate analyses, we included these variables to assess the extent to which they influenced the relations as potential mediators or confounders.

To assess the importance of timing, we quantified recreational activity in 3 ways: 1) baseline, assessed from activity in 1986, reflecting past exposure, 2) simple update, assessed from the most recent questionnaire cycle (prior to diagnosis, for cases), reflecting recent exposure, and 3) cumulative average, calculated by averaging MET-hrs/wk or hrs/wk from all available questionnaires up to the start of each follow-up cycle, reflecting long-term average exposure. We tested for trend across activity categories by including midpoints of categories modeled continuously. Preliminary evidence suggested a potential U-shaped relation; we evaluated departures from linearity using likelihood ratio tests comparing nested models that included midpoints of activity categories modeled continuously vs. activity categories modeled as indicator variables.

We evaluated whether associations differed by categories of BMI (18.5–<25, ≥25 kg/m^2), weight change since age 18 years (<10, ≥10 kg), or HT (ever, never) using likelihood ratio tests comparing nested models with and without interaction terms between activity and these variables. *P*-values were 2-tailed and $P<0.05$ was considered significant. All statistical analyses used SAS, version 9.2, software (SAS Institute Inc, Cary, NC).

RESULTS

During 22 years of follow-up (1,235,880 person-years), we documented 777 cases of invasive endometrial adenocarcinoma. The mean age of participants at baseline was 52 years. More active women were more likely to have used OCs in the past and to currently use HT, less likely to currently smoke, less likely to have diabetes, had higher alcohol and energy intakes but lower caffeine intake, and spent less time sitting (Table 1). As expected, these women also had lower recent BMI and gained less weight since age 18 years.

Baseline total recreational activity was not associated with endometrial adenocarcinoma risk (≥27 vs <3 MET-hrs/wk: multivariable RR=0.86, 95% CI: 0.66–1.11, *P*-trend=0.15) (Table 2). Although greater cumulative average activity appeared beneficial (≥27 vs <3 MET-hrs/wk: multivariable RR=0.77, 95% CI: 0.59–1.01), the trend was non-significant (*P*-trend=0.09). However, the simple update assessment, reflecting recent activity, was inversely associated with risk. The age-adjusted RRs across categories (<3, 3 to <9, 9 to <18, 18 to <27, ≥27 MET-hrs/wk) were 1.00, 0.95, 0.63, 0.73, 0.76, respectively (*P*-trend=0.004). Associations were slightly stronger after multivariable adjustment, with HT and smoking accounting primarily for the difference. The multivariable-adjusted RRs across categories (<3, 3 to <9, 9 to <18, 18 to <27, ≥27 MET-hrs/wk) were 1.00, 0.94, 0.61, 0.71, 0.73, respectively. Although there was evidence of a non-linear relation with simple update total activity (*P*=0.007), we found a significant dose-response relation (*P*-trend=0.001). Because body weight, waist/hip ratio, and diabetes may act as mediators or confounders, we adjusted for each in separate models. RRs for the simple update assessment were slightly attenuated after additional adjustment for waist/hip ratio or diabetes, but the inverse association remained (data not shown). After additionally adjusting for BMI, however, RRs were attenuated substantially. Multivariable RRs across categories (<3, 3 to <9, 9 to <18, 18

to <27, ≥27 MET-hrs/wk) were 1.00, 1.08, 0.77, 0.92, 1.01, respectively and the test for trend was statistically non-significant (*P*-trend=0.64). Results were unchanged after additional adjustment for energy and coffee intakes, or total time spent sitting.

Estimates from multivariable models were consistent across categories of BMI (*P*-interaction=0.88), weight change since age 18 years (*P*-interaction=0.85), or HT (*P*-interaction=0.68), and remained essentially unchanged after restricting analyses to postmenopausal women (*N*=600 cases). We examined changes in activity between 1986 and the most recent assessment. Compared with consistently less active women (<9 MET-hrs/wk at both periods), those who decreased their activity from ≥9 to <9 MET-hrs/wk had similar risk (multivariable RR=1.02, 95% CI: 0.78–1.33, *P*=0.88), while those consistently active (≥9 MET-hrs/wk at both periods: RR=0.79, 95% CI: 0.63–0.98, *P*=0.03) and those who increased their activity (<9 to ≥9 MET-hrs/wk: RR=0.63, 95% CI: 0.47–0.83, *P*=0.001) were at reduced risk.

For baseline moderate or vigorous recreational activity, >0 to <2 hours per week was associated with reduced endometrial adenocarcinoma risk (multivariable RR=0.65, 95% CI: 0.51–0.84); however, greater amounts were not associated and, like total activity, the trend was non-significant (*P*-trend=0.65) (Table 3). Inverse associations with cumulative average and simple update moderate or vigorous activities were strengthened after multivariable adjustment, with easy walking, HT, and smoking accounting primarily for the difference. Multivariable RRs across categories (0, >0 to <2, 2 to <4, ≥4 hrs/wk) were 1.00, 0.86, 0.68, 0.65, respectively, for simple update; and 1.00, 0.82, 0.64, 0.82, respectively, for cumulative average. Dose-response relations were significant for both assessments (*P*-trend=0.002 for simple update; and *P*-trend=0.03 for cumulative average). Results were unchanged after excluding women who reported limitations in performing moderate and vigorous activities (including 45 cases). Like total activity, after additional adjustment for BMI, RRs were attenuated and tests for trend became statistically non-significant (*P*-trend=0.70 for simple update; and *P*-trend=0.60 for cumulative average).

To evaluate the importance of walking, and to reduce confounding by other activities, we examined the simple update assessment of walking among women who reported no vigorous activities (44% of participants). Recent walking was inversely associated with risk (≥3 vs <0.5 hrs/wk: multivariable RR=0.65, 95% CI: 0.45–0.93, *P*-trend=0.01) (Table 4). Independent of hours spent walking, faster walking pace was associated with reduced risk. Compared with women who reported an easy usual pace (<3.2 km/hr), multivariable RRs were 0.64 (95% CI: 0.49–0.86) for a normal pace (3.2–4.8 km/hr) and 0.66 (95% CI: 0.46–0.96) for a brisk or very brisk pace (>4.8 km/hr). Results were unchanged after excluding women who reported limitations in walking (including 27 cases). After additional adjustment for BMI, associations were statistically non-significant for both recent walking (*P*-trend=0.52) and usual walking pace (normal vs. easy: RR=0.91, 95% CI: 0.67–1.22; brisk/very brisk vs. easy: RR=1.11, 95% CI: 0.75–1.64).

In sensitivity analyses, we examined associations for all endometrial adenocarcinomas (288 non-invasive and 777 invasive) and observed similar results [e.g., simple update total activity: multivariable RRs across categories (<3, 3 to <9, 9 to <18, 18 to <27, ≥27 MET-hrs/wk) were 1.00, 0.94, 0.73, 0.70, 0.71, respectively (*P*-trend<0.001)].

DISCUSSION

In this large prospective cohort analysis with 22 years of follow-up, greater amounts of recent total and moderate- or vigorous-intensity recreational activities, including that of moderate duration, was associated with reduced risk of endometrial adenocarcinoma after

adjustment for age, HT, smoking, and other potential confounders. Walking, a common and moderate-intensity activity amenable to older populations was also associated with reduced risk. In addition, faster walking pace was associated with reduced risk. Reinforcing the importance of recent activity, women who were less active at baseline but increased their activity levels during follow-up had reduced risk compared with women who decreased their activity or remained inactive. The relation with total activity did not differ by BMI, HT, or weight change since age 18 years. After additional adjustment for recent BMI, all associations became statistically non-significant, suggesting that the relation between activity and risk is largely mediated or confounded by adiposity.

Many prospective studies,[5–10] but not all,[19, 25–29] and 2 systematic reviews[11, 12] have linked greater activity with reduced risk of endometrial cancer. Our observations are consistent with these findings and help clarify various details. Previous studies have used baseline or recalled measures of activity,[5–10, 19, 25–29] making it difficult to address the role of recent activity. Baseline activity was not associated with risk in our analyses, as in 2 other studies followed for more than 15 years,[27, 29] suggesting that activity at baseline may be less relevant for predicting risk over time. In our study, the first with updated assessments of activity throughout follow-up, we observed that recent activity was most strongly associated with risk. Previous studies with shorter follow-up (<9 years) found no relation;[19, 25, 26, 28] however, statistical power was likely limited in these studies as they included fewer than 270 cases, with the exception of the study by Friedenreich et al.[25] Although we cannot exclude the possibility that undiagnosed disease may have affected recent activity levels and influenced our findings, we observed similar protective associations for recent activity after repeating the analyses using a 2-year lag (e.g., 1986 activity for 1988–1990 follow-up), suggesting that the magnitude of this bias was likely minimal. Moreover, most endometrial cancers are diagnosed early at the first sign of vaginal bleeding (88% in stage I or II),[30] further reducing this bias and supporting the validity of our findings.

Among studies examining intensity, 2 reported associations specifically with vigorous-intensity activity[6, 28] while, similar to our results, others reported associations with activities of any intensity.[5, 13] Unlike our findings, Conroy et al. reported no relation with walking, although their analysis included only 264 cases.[28] In some studies, risk was reported to decrease with increasing amounts of activity;[5, 6, 8, 9] whereas in the present study, and in others, moderate amounts conferred similar or greater benefits as the highest amounts.[8, 28] Few studies have examined whether associations vary by risk factors. As in the present analysis, most studies have observed consistent associations by HT.[5, 6, 25] In some studies, stronger associations were observed among overweight compared with lean women,[5, 6] while in others, the present analysis included, there was no difference by BMI.[25, 28] These discrepancies may be due in part to differences between studies in activity assessment (e.g., questionnaires, job codes), or amount of variation in activity levels throughout follow-up. In addition, many studies presented only results adjusted for body mass index.[8, 9, 25, 27, 28] We cannot preclude the possibility of confounding by body mass index; however, activity also reduces obesity, which predicts subsequent endometrial cancer risk.[2, 3, 13] Thus, physical activity may reduce risk through its effect on adiposity, and adjustment for body mass index may result in an underestimation of the true benefit of physical activity.

Strong biological evidence suggests that obesity and exposure to estrogen unopposed by progesterone, the best established risk factors for endometrial cancer,[3] may mediate the association between activity and risk. According to the “unopposed estrogen hypothesis”, exposure of the endometrium to estrogen without sufficient progesterone stimulates endometrial cell proliferation and increases risk.[3, 31] Exercise may reduce serum estradiol levels by facilitating weight maintenance and reducing adiposity.[3, 4, 32–36] In adipose tissue, androgens are converted to estrogens by aromatase,[37] a process that acts as the primary

source of bioavailable estrogens in postmenopausal women.[3, 4, 13] Thus, improved weight maintenance may result in lower circulating estrogen levels.[2, 4] In addition, reduced adiposity may also improve insulin sensitivity and reduce hyperinsulinemia.[38] These conditions have been associated with lower levels of sex hormone-binding globulin (SHBG), which binds free estradiol.[3] In pre- and postmenopausal women, reduced SHBG has been associated with increased risk of subsequent endometrial cancer.[2, 39, 40] Epidemiologic studies have consistently shown obesity as a strong predictor of endometrial cancer regardless of menopausal status,[2, 3] with many emphasizing the importance of more recent, rather than baseline, body mass index.[8, 41–44]

Based on these potential mechanisms, it is unsurprising that we, along with Patel et al.[5] and Gierach et al.[6], observed attenuated associations after additional adjustment for BMI. It is important to note, however, that residual confounding by BMI may have accounted in part or entirely for the observed associations. Accordingly, we presented estimates both adjusted and unadjusted for BMI; however, this approach was unable to quantify the extent to which the association with physical activity was mediated or confounded by adiposity. BMI is a complex trait that is correlated over time and may change from a confounder to a mediator depending on the temporal order of events (i.e., time-dependent confounding).[45] Given these methodological complexities, standard assumptions for mediation analyses that estimate the proportion of an association explained by intermediate variables are likely violated.[46–49] NHS researchers are currently exploring the use of novel methods to adjust for time-dependent confounding, and evaluating the validity of these approaches in large prospective studies for lifestyle factors such as physical activity is an area of ongoing research.[50]

The large study population, followed prospectively for 22 years, as well as updated assessments of activity and many covariates provided the opportunity to clarify the temporal relation between activity and endometrial adenocarcinoma. However, activity was assessed based on self-report and measurement errors may have attenuated associations. Repeated assessments helped reduce measurement error and accounted for changes in activity over time. In addition, in the NHS these activity data have been associated with reduced risk of breast[18, 21] and colorectal[51] cancers, cholecystectomy,[52] coronary heart disease,[17] and type 2 diabetes.[53] Our questionnaire primarily assessed recreational activity, preventing us from addressing household or occupational activity, although our results were unchanged after adjustment for employment status (e.g., homemaker, retired, full-time, part-time). We observed consistent associations by major risk factors, supporting the generalizability of our findings. However, our study population comprised predominantly white registered nurses. Because the incidence of endometrial adenocarcinomas may differ among African American and Asian women,[54] our findings may not be generalizable to other ethnicities. The homogeneity of our population, however, reduced confounding and increased the internal validity of our analyses.

In summary, we confirmed the association between greater physical activity and reduced endometrial adenocarcinoma risk. Moreover, our findings support the importance of recent activity of moderate duration and intensity for risk reduction in women of all body sizes and postmenopausal hormone therapy status. We observed risk reductions of 30–40% among women who either walked at least 3 hours/week or performed moderate or vigorous activity at least 2 hours/week. These results should be interpreted with caution, however, as the associations were statistically non-significant after additional adjustment for BMI, suggesting that the observed associations between physical activity and risk is largely mediated or confounded by adiposity.

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Abbreviations used

BMI	body mass index
CI	confidence interval
HT	postmenopausal hormone therapy
MET	metabolic equivalent
OC	oral contraceptive
PY	person-years of follow-up
RR	relative risk
SD	standard deviation

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Novelty and impact

Greater physical activity may reduce endometrial cancer risk, but the importance remains unclear of the timing, duration, and intensity of activity. In this large population followed prospectively for 22 years, repeated assessments of activity provided the opportunity to clarify this relation. Recent recreational activity of moderate duration and intensity, such as walking ≥3 hours/week, was associated with 30–40% reduced risk in multivariable adjusted models. After additional adjustment for body mass index, associations were statistically non-significant.

Table 1

Age and age-standardized characteristics of 71,570 women in the Nurses' Health Study during follow-up from 1986 to 2008[a,b]

	Total recreational activity (MET-hours/week)[c]		
Characteristic	**< 3**	**9 to < 18**	**≥ 27**
Person-years	222,656	210,570	206,208
Baseline age[d] (years)	52.2 (7.3)	51.7 (7.1)	51.5 (7.0)
Age at menarche (years)	12.5 (1.4)	12.6 (1.4)	12.6 (1.4)
Past oral contraceptive use	44.5%	47.6%	49.4%
Nulliparous	5.3%	5.2%	5.8%
Parity[e] (number of children)	3.2 (1.6)	3.1 (1.5)	3.1 (1.4)
Age at first birth (years)	25.4 (3.5)	25.3 (3.3)	25.1 (3.3)
Age at last birth (years)	31.6 (4.7)	31.3 (4.5)	30.9 (4.4)
Postmenopausal	80.0%	80.0%	80.4%
Age at menopause (years)	50.1 (4.6)	50.4 (4.5)	50.5 (4.6)
Postmenopausal hormone therapy[f]			
Never	43.3%	38.7%	36.8%
Past	25.7%	27.4%	28.7%
Current	21.8%	27.6%	28.9%
Smoking status			
Never	40.8%	44.5%	43.2%
Past	39.4%	43.0%	45.6%
Current	19.6%	12.3%	10.9%
BMI at age 18 (kg/m^2)	21.6 (3.3)	21.3 (2.8)	21.2 (2.7)
Recent BMI (kg/m^2)	27.6 (6.2)	25.9 (4.8)	24.9 (4.3)
Weight gain since age 18 (kg)	16.0 (14.7)	12.3 (11.8)	9.8 (11.1)
Waist/hip ratio	0.84 (0.12)	0.82 (0.11)	0.81 (0.11)
Family history of endometrial cancer	3.1%	3.1%	2.9%
Family history of colorectal cancer	16.9%	16.6%	16.9%
Diabetes	7.1%	3.9%	2.9%
Alcohol intake (g/d)	5.2 (10.6)	5.8 (9.9)	6.8 (10.5)
Caffeine intake (mg/d)	245.4 (217.8)	224.6 (198.5)	218.6 (197.2)
Energy intake (kcal/d)	1671.5 (542.3)	1740.3 (526.3)	1792.7 (545.0)
Total sitting in 1992 (hrs/wk)	37.2 (23.8)	36.0 (21.7)	34.5 (21.3)
Total activity (MET-hrs/wk)	1.3 (0.9)	13.1 (2.7)	47.3 (19.4)

Abbreviations: BMI, body mass index; MET-hrs/wk, metabolic equivalent hours of activity per week; SD, standard deviation

[a] Values are means(SD) or percentages, and standardized to the age distribution of the study population during follow-up from 1986 to 2008

[b] Values may not add to 100% because of missing data

[c] Lowest, middle, and highest categories of total activity are presented

[d] Value not age-adjusted

[e] Among parous women

[f] Among postmenopausal women

Table 2

Relative risk and 95% CI of endometrial adenocarcinoma by total physical activity, Nurses' Health Study, 1986–2008

	Total recreational activity in MET-hours/week, RR (95% CI)					
	< 3	3 to < 9	9 to < 18	18 to < 27	≥ 27	*P* trend[c]
Baseline (1986)						
Cases (PY)	176 (258057)	165 (252,330)	122 (181,103)	59 (100,911)	87 (139,255)	
Age-adjusted	1.00 (ref)	0.96 (0.77–1.18)	0.99 (0.79–1.25)	0.85 (0.63–1.14)	0.91 (0.70–1.18)	0.35
Multivariable[a]	1.00 (ref)	0.93 (0.75–1.16)	0.95 (0.75–1.20)	0.80 (0.59–1.08)	0.86 (0.66–1.11)	0.15
Multivariable + BMI[b]	1.00 (ref)	1.03 (0.83–1.28)	1.09 (0.86–1.38)	0.96 (0.71–1.30)	1.06 (0.81–1.38)	0.83
Simple update						
Cases (PY)	183 (222656)	183 (240,370)	108 (210,570)	78 (129,703)	131 (206,208)	
Age-adjusted	1.00 (ref)	0.95 (0.77–1.16)	0.63 (0.49–0.80)	0.73 (0.56–0.96)	0.76 (0.61–0.96)	0.004
Multivariable[a]	1.00 (ref)	0.94 (0.76–1.16)	0.61 (0.48–0.78)	0.71 (0.54–0.93)	0.73 (0.58–0.92)	0.001
Multivariable + BMI[b]	1.00 (ref)	1.08 (0.88–1.33)	0.77 (0.60–0.98)	0.92 (0.70–1.21)	1.01 (0.80–1.29)	0.64
Cumulative average						
Cases (PY)	112 (152,164)	181 (268,222)	176 (264,877)	98 (148,550)	116 (175,695)	
Age-adjusted	1.00 (ref)	0.84 (0.66–1.07)	0.79 (0.62–1.01)	0.78 (0.59–1.03)	0.81 (0.62–1.05)	0.17
Multivariable[a]	1.00 (ref)	0.83 (0.65–1.06)	0.77 (0.60–0.98)	0.76 (0.57–1.00)	0.77 (0.59–1.01)	0.09
Multivariable + BMI[b]	1.00 (ref)	0.95 (0.74–1.21)	0.96 (0.75–1.24)	1.00 (0.75–1.32)	1.10 (0.84–1.45)	0.32

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent; OC, oral contraceptive; HT, post menopausal hormone therapy; PY, person-years of follow-up; RR, relative risk

[a] Adjusted for age at menarche (7–12, >12–13, >13–18, missing yrs), OC use (never, < 1, 1–<3, 3–<6, ≥6, missing yrs), parity and age at first birth (nulliparous, 1–2 children <25 yrs, 1–2 children 25–29 yrs, 1–2 children ≥30 years, 3–4 children <25 yrs, 3–4 children 25–29 yrs, 3–4 children ≥30 years, ≥5 children <25 yrs, ≥5 children ≥25 yrs, missing), age at last birth (nulliparous, <25, 25–29, 30–34, 35–39, ≥40, missing yrs), menopausal status (pre-, post-, dubious or missing), age at menopause (continuous), HT (never, past, current <5 yrs, current ≥5 yrs, missing), HT type (never, E only, E+P, other, missing), BMI at age 18 (<19, 19–<21, 21–<23, ≥23, missing kg/m^2), pack-years of smoking (0, 0–<20, 20–<40, ≥40, missing), family history of endometrial cancer (yes, no), family history of colorectal cancer (yes, no), alcohol intake (none, <5, 5–<15, ≥15, missing g/day), caffeine intake (quartiles, missing)

[b] Recent BMI (continuous)

[c] *P* values are 2-sided

Table 3

Relative risk and 95% CI of endometrial adenocarcinoma by moderate or vigorous activity, Nurses' Health Study, 1986–2008

	Moderate- or vigorous-intensity activity[c] in hours/week, RR (95% CI)				
	0	**> 0 to < 2**	**2 to < 4**	**≥ 4**	***P* trend[d]**
Baseline (1986)					
Cases (PY)	423 (599,974)	84 (181,479)	51 (73,106)	56 (81,193)	
Age-adjusted	1.00 (ref)	0.70 (0.55–0.88)	1.03 (0.77–1.38)	0.98 (0.74–1.30)	0.88
Multivariable[a]	1.00 (ref)	0.65 (0.51–0.84)	0.93 (0.68–1.28)	0.89 (0.66–1.20)	0.65
Multivariable + BMI[b]	1.00 (ref)	0.77 (0.60–1.00)	1.14 (0.83–1.57)	1.11 (0.81–1.50)	0.28
Simple update					
Cases (PY)	513 (694,125)	85 (145,651)	42 (82,191)	49 (97,574)	
Age-adjusted	1.00 (ref)	0.93 (0.74–1.17)	0.77 (0.56–1.06)	0.74 (0.55–0.99)	0.01
Multivariable[a]	1.00 (ref)	0.86 (0.67–1.10)	0.68 (0.49–0.95)	0.65 (0.47–0.88)	0.002
Multivariable + BMI[b]	1.00 (ref)	1.15 (0.89–1.48)	0.96 (0.68–1.36)	0.96 (0.69–1.32)	0.70
Cumulative average					
Cases (PY)	348 (465,678)	237 (368,072)	57 (111,820)	47 (73,971)	
Age-adjusted	1.00 (ref)	0.85 (0.71–1.01)	0.67 (0.51–0.90)	0.90 (0.66–1.22)	0.06
Multivariable[a]	1.00 (ref)	0.82 (0.69–0.98)	0.64 (0.48–0.86)	0.82 (0.60–1.13)	0.03
Multivariable + BMI[b]	1.00 (ref)	1.01 (0.84–1.20)	0.89 (0.66–1.19)	1.20 (0.87–1.66)	0.60

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent; OC, oral contraceptive; HT, postmenopausal hormone therapy; PY, person-years of follow-up; RR, relative risk

[a] Adjusted for age at menarche (7–12, >12–13, >13–18, missing yrs), OC use (never, < 1, 1–<3, 3–<6, ≥6, missing yrs), parity and age at first birth (nulliparous, 1–2 children <25 yrs, 1–2 children 25–29 yrs, 1–2 children ≥30 years, 3–4 children <25 yrs, 3–4 children 25–29 yrs, 3–4 children ≥30 years, ≥5 children <25 yrs, ≥5 children ≥25 yrs, missing), age at last birth (nulliparous, <25, 25–29, 30–34, 35–39, ≥40, missing yrs), menopausal status (pre-, post-, dubious or missing), age at menopause (continuous), HT (never, past, current <5 yrs, current ≥5 yrs, missing), HT type (never, E only, E+P, other, missing), BMI at age 18 (<19, 19–<21, 21–<23, ≥23, missing kg/m^2), pack-years of smoking (0, 0–<20, 20–<40, ≥40, missing), family history of endometrial cancer (yes, no), family history of colorectal cancer (yes, no), alcohol intake (none, <5, 5–<15, ≥15, missing g/day), caffeine intake (quartiles, missing), easy walking (<0.5, 0.5–<2, 2–<3, ≥3 hrs/wk)

[b] Recent BMI (continuous)

[c] Defined as only brisk walking, jogging, or running;

[d] *P* values are 2-sided

Table 4

Relative risk and 95% CI of endometrial adenocarcinoma by recent walking and walking pace among women who did not perform vigorous activities, Nurses' Health Study, 1986–2008

		RR (95% CI)		
	Cases (PY)	**Age-adjusted**	**Multivariable[a]**	**Multivariable + BMI[b]**
Walking, hours/week				
< 0.5	122 (150,017)	1.00 (ref)	1.00 (ref)	1.00 (ref)
0.5 to < 2	116 (156,849)	0.93 (0.72–1.21)	0.92 (0.71–1.20)	1.09 (0.83–1.43)
2 to < 3	46 (73,775)	0.75 (0.53–1.06)	0.73 (0.51–1.03)	0.96 (0.67–1.37)
≥ 3	42 (75,163)	0.67 (0.47–0.96)	0.65 (0.45–0.93)	0.91 (0.63–1.32)
P trend[c]		0.02	0.01	0.52
Usual walking pace[d,e]				
Easy	93 (87,516)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Normal	156 (237,502)	0.62 (0.47–0.81)	0.64 (0.49–0.86)	0.91 (0.67–1.22)
Brisk or very brisk	67 (115,882)	0.59 (0.42–0.82)	0.66 (0.46–0.96)	1.11 (0.75–1.64)

Abbreviations: BMI, body mass index; CI, confidence interval; MET, metabolic equivalent; OC, oral contraceptive; HT, postmenopausal hormone therapy; PY, person-years of follow-up; RR, relative risk

[a] Adjusted for age at menarche (7–12, >12–13, >13–18, missing yrs), OC use (never, < 1, 1–<3, 3–<6, ≥6, missing yrs), parity and age at first birth (nulliparous, 1–2 children <25 yrs, 1–2 children 25–29 yrs, 1–2 children ≥30 years, 3–4 children <25 yrs, 3–4 children 25–29 yrs, 3–4 children ≥30 years, ≥5 children <25 yrs, ≥5 children ≥25 yrs, missing), age at last birth (nulliparous, <25, 25–29, 30–34, 35–39, ≥40, missing yrs), menopausal status (pre-, post-, dubious or missing), age at menopause (continuous), HT (never, past, current <5 yrs, current ≥5 yrs, missing), HT type (never, E only, E+P, other, missing), BMI at age 18 (<19, 19–<21, 21–<23, ≥23, missing kg/m^2), pack-years of smoking (0, 0–<20, 20–<40, ≥40, missing), family history of endometrial cancer (yes, no), family history of colorectal cancer (yes, no), alcohol intake (none, <5, 5–<15, ≥15, missing g/day), caffeine intake (quartiles, missing)

[b] Recent BMI (continuous)

[c] *P* values are 2-sided

[d] Easy, <3.2 km/hr; normal, 3.2–4.8 km/hr; brisk or very brisk, >4.8 km/hr

[e] Additionally adjusted for walking (<0.5, 0.5–<2, 2–<3, ≥3 hrs/wk)