Quantifying the Effect of Physical Activity on Endometrial Cancer Risk

Sarah J. Kitson[1], Olivia Aurangzeb[1], Jawaria Parvaiz[1], Artitaya Lophatananon[2], Kenneth R. Muir[2], and Emma J. Crosbie[1,3]

ABSTRACT

Endometrial cancer incidence is rising, with 435,000 global cases in 2019. An effective, low-cost primary prevention strategy is required to reduce disease burden. Obesity, insulin resistance, and inflammation contribute to endometrial carcinogenesis and physical activity targets these pathways. This study sought to quantify the amount of physical activity required to impact upon endometrial cancer risk. Physical activity data from 222,031 female participants with an intact uterus in the UK Biobank study were analyzed using a multivariable Cox proportional hazards model. A systematic review of the literature was performed, searching CENTRAL, Embase, and MEDLINE databases up to April 19, 2021. Studies including participants with and without endometrial cancer investigating the effect of physical activity measured in MET-hours/week (MET-h/week) on disease risk were included. Two reviewers independently selected studies, extracted data, and evaluated the risk of bias. Within the UK Biobank, each 1 MET-h/week increase in total physical activity was associated with a 0.2% [95% confidence interval (CI), 0.1–0.4; $P = 0.020$] reduction in endometrial cancer risk, equating to a 10.4% reduction if performing 50 MET-h/week or 7 hours of jogging per week. Eleven cohort and 12 case–control studies were identified in the systematic review, including 821,599 participants. One study reported a non-significant effect of 1 MET-h/week increases in physical activity on endometrial cancer risk (OR, 1.00; 95% CI, 0.99–1.00). Eight studies found significant reductions in disease risk of 15%–53%, but only in the most physically active individuals. Physical activity reduces endometrial cancer risk, but the effect size appears small. Regular vigorous activity should be encouraged to maximize the health benefit observed.

Prevention Relevance: Effective, low-cost primary prevention strategies are urgently needed to tackle the rapid global increase in endometrial cancer. We sought to quantify the effect of physical activity on endometrial cancer risk, noting a linear inverse relationship influenced by body mass index. The most beneficial type and amount of activity remain unclear.

Introduction

Endometrial cancer accounts for 3% of all new cancer cases diagnosed in the United Kingdom and 3.5% of all new cancer cases in the United States (1, 2). A woman's lifetime risk of endometrial cancer is currently estimated to be 3.1% (3), although for some women their individual risk is substantially greater than this. Risk factors include increasing age, obesity, insulin resistance, and lifetime estrogen exposure (4). As a consequence of the increasing prevalence of these risk factors within the population, endometrial cancer case numbers are rising, with a doubling in diagnoses in the United Kingdom over the last 30 years and a 0.5% increase in age-adjusted rates year-on-year in the United States (1, 2). The increase in disease incidence is not purely limited to high sociodemographic index nations, however, with rising case numbers observed in nearly all global regions (5). While early presentation with postmenopausal bleeding means that the majority of cases are diagnosed at an early stage and are potentially curable with surgery, endometrial cancer deaths are also rising and are projected to become the sixth most common cause of death in women in the United Kingdom by 2035 (6). Treatment for endometrial cancer is also not without its risks, particularly in an increasingly elderly and obese population with multiple comorbid conditions, and in younger women where surgery will result in loss of fertility.

Strategies aimed at reducing the risk of endometrial cancer are, therefore, urgently required not only to negate the physical and psychologic impact of an endometrial cancer diagnosis and its treatment, but also to reduce the costs of this disease to National Health Services. For primary disease prevention to be

[1]Gynaecological Oncology Research Group, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary's Hospital, Manchester, United Kingdom. [2]Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom. [3]Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom.

Corresponding Author: Sarah J. Kitson, Division of Cancer Sciences, University of Manchester, 5th Floor – Research, St Mary's Hospital, Manchester M13 9WL, United Kingdom. Phone: 4401-6127-66388; E-mail. sarah.kitson@manchester.ac.uk

Cancer Prev Res 2022;15:605–22

doi: 10.1158/1940-6207.CAPR-22-0129

©2022 American Association for Cancer Research

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

effective at a population level, it should not only be effective, but also inexpensive, accessible, and associated with minimal side effects. Physical activity, by reducing adiposity, improving insulin sensitivity, decreasing serum estradiol levels, and modulating the immune response, could fulfill these criteria (7–9). Epidemiologic evidence suggests that active individuals could have a 16%–25% lower risk of developing endometrial cancer compared with more sedentary women (10–13). Previously conducted meta-analyses have, however, frequently only compared the most with the least physically active, with limited attempts to establish a dose–response relationship. Indeed, any such relationship may even be lost once adiposity is adjusted for (12). The close association between endometrial cancer and obesity may provide some explanation for the significant heterogeneity in effect size observed between studies, which could be compounded by the simultaneous analysis of cohort and case–control studies, with the latter at risk of recall bias. As a result, umbrella reviews of the literature have concluded, on the basis of their stringent methodologic criteria, that there is only "probable" evidence of an association between physical activity and endometrial cancer prevention (14, 15). Before physical activity can be incorporated into any future endometrial cancer prevention strategies, the optimal duration and intensity of exercise for cancer risk reduction needs to be determined (12), in their meta-analysis in 2020, concluded that there was likely to be a linear relationship between increasing physical activity and a reduction in endometrial cancer risk, but were unable to comment on whether moderate and vigorous activity was more beneficial due to a small sample size. The authors based their analysis on data from only eight prospective cohort studies that had contributed to the NCI Cohort Consortium, all of which were conducted in the United States, Europe, and Australia. By considering only leisure time activity, they also failed to consider other domains of physical activity that can contribute significantly to an individual's total daily physical activity levels, including transportation and occupational activity. Subsequent data from the UK Biobank, a large prospective cohort study of over half a million UK adults, was also suggestive of a linear inverse relationship between total physical activity levels and endometrial cancer risk (16). The authors here, however, failed to include almost half of the potential incident endometrial cancer cases within the dataset in their analysis by excluding individuals with a history of any malignancy and those with incomplete physical activity data. They also did not consider a number of potential confounding variables including waist circumference and diabetes status and did not adequately control for women who had undergone a hysterectomy and were, therefore, no longer at risk of endometrial cancer.

This study, therefore, aims to quantify the amount of total physical activity needed to significantly impact upon endometrial cancer risk using data from the UK Biobank study, adjusted for all potential confounding risk factors in the at-risk population. In addition, it seeks to compare these results with previously published data identified through a systematic review of the literature. As a secondary objective, it aims to identify the types and domains of activity associated with the greatest reduction in endometrial cancer risk and the age at which such activity is most beneficial.

Materials and Methods

UK Biobank study

The UK Biobank is a major national and international health resource, created to improve the prevention, diagnosis, and treatment of serious and life-threatening illnesses, including cancer (17). The female cohort consists of 273,384 individuals ages between 39 and 71 years, after exclusion of withdrawals from the study. Health, demographic, and anthropometric data were collected using standardized questions posed through computer terminals and by trained nurses and were supplemented with the donation of biological samples, including blood, saliva, and urine. Cancer diagnoses were ascertained through linkage to national cancer registries in England, Scotland, and Wales. Deaths were ascertained through linkage to death registries. Complete follow-up was available through to March 31, 2016 for England and Wales and October 31, 2015 for Scotland. Full details can be found at https://www.ukbiobank.ac.uk.

The study was approved by the North West Multi-Centre Research Ethics Committee (16/NW/0274), Patient Information Advisory Group (England and Wales) and the Community Health Index Advisory Group (Scotland). All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

All cancers were recorded within the UK Biobank using either the International Classification of Diseases 9 or 10 or self-reported data. Identification of endometrial cancer cases was performed using all three of these sources. Within the database, each participant had nine follow-up timepoint records for ICD10, 11 follow-up timepoint records for ICD9, and nine follow-up points for self-reported cancer status. Cases were characterized as incident or prevalent using the age when they attended the UK Biobank centre and the age at diagnosis of endometrial cancer. Cases were regarded as incident if the age of cancer diagnosis was greater than the age at which they first attended the centre and prevalent if the reverse were true. If there was a discrepancy between the self-reported age of cancer diagnosis and that recorded by the cancer registry, the age documented by the cancer registry was used. Only incident endometrial cancer cases occurring at least 2 years after recruitment into the UK Biobank study were considered for this analysis, to minimize the risk of reverse causality. Female participants were defined as controls if they had no record of endometrial cancer and had not previously undergone a hysterectomy. Data were censored at date of endometrial cancer diagnosis, hysterectomy, death, or last data collection.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Individuals self-reported their physical activity levels by answering adapted questions from the validated short International Physical Activity Questionnaire (IPAQ), which covers the frequency and duration of walking, moderate, and vigorous activity. Responses were considered to be greater than zero if activity was performed for at least 10 minutes and limited to 180 minutes per day, as it was deemed unlikely that individuals would be undertaking physical activity for longer than this in any one 24-hour period. Time spent undertaking activities of differing intensity was weighted by the energy expended for each of these categories using the IPAQ data processing rules and expressed in MET-hours per week (MET-h/week; ref. 18). A MET-h is a ratio of an individual's working metabolic rate compared with a standard resting rate of 1 kcal/kg/hour (defined as quiet sitting for 1 hour). The Compendium of Physical activities provides a list of specific physical activity types and their MET values (19). Walking was considered to have a MET value of 3.3, moderate activity a MET value of 4.0, and vigorous activity a MET value of 8.0. The effect of each category of variable intensity physical activity on endometrial cancer risk was considered as a continuous variable expressed in MET-h/week. Total physical activity represented the summation of each individual category of physical activity intensity and was also considered as a continuous variable.

Systematic review

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (20).

Data sources and searches

A comprehensive literature search was conducted using CENTRAL, Ovid Embase, and Ovid MEDLINE databases. The databases were searched from date of inception to April 19, 2021. Search terms were "endometrial cancer" and physical activity" with associated Medical Subject Headings. The full search strategy for each database can be found in Supplementary Data S1. In addition, gray literature including conference proceedings, internal gynecologic oncology journals, clinical trial databases, and reference lists of included studies were hand searched for eligible publications.

Study selection

Studies investigating the effect of physical activity on endometrial cancer risk as either a primary or secondary outcome were eligible for inclusion. While all domains of physical activity were considered, including recreational and occupational activity, sufficient information must have been collected during the study about the type and duration of physical activity performed to allow MET-h/week to be calculated. No limits were placed on the age or body mass index (BMI) of study participants. All study designs were included to ensure a comprehensive analysis of the literature. Studies were required to include a reference population who did not develop endometrial cancer for comparison. Searches were restricted to English language publications.

Data extraction

Titles and abstracts were collated into Microsoft Excel 2016. Duplicate publications were removed using Endnote 20. All titles and abstracts were screened independently by two reviewers (O. Aurangzeb and J. Parvaiz). Conflicts were resolved by agreement with a third reviewer (S.J. Kitson). Those studies identified as meeting the inclusion criteria underwent full text review and data extraction by two independent reviewers (O. Aurangzeb and J. Parvaiz).

Baseline data extracted included study design, selection criteria, number of participants and endometrial cancer cases, setting, follow-up, demographic data, domain of exercise studied, and risk estimates, such as ORs and HRs with corresponding 95% confidence intervals (CI) and the adjustment variables in multivariable analyses. Study authors were contacted for additional information where this was not provided in the original publication.

A risk of bias (RoB) assessment was undertaken independently by two reviewers (O. Aurangzeb and J. Parvaiz), based on the ROBINS-1 tool (ref. 21; Supplementary Data S1), with discrepancies resolved through discussion with a third reviewer (S.J. Kitson). The RoB assessment included the risk of confounding, selection, information, deviation from intended intervention, missing data, detection, and reporting bias.

Statistical analysis

Continuous and categorical variables in the UK Biobank dataset were compared using a Mann–Whitney U and χ^2 test, respectively. Multiple imputations were performed to deal with missing data in the UK Biobank dataset, which was assessed to be missing at random. The proportion of missing data for each variable is reported in **Table 1**. A Cox proportional hazards model was used to determine the association between total physical activity and endometrial cancer risk, using time from baseline assessment as the underlying time variable. HRs and corresponding 95% CIs were calculated after checking the proportional hazards assumption graphically with log-log plots and by examining Schoenfeld residuals. A multivariable model was generated, adjusting for potential confounders of endometrial cancer risk including age (logarithmic), BMI, waist circumference, age at menarche (squared), age at last birth (squared), age at menopause (<55 years or ≥55 years), hormone replacement therapy (HRT) use (current, never/prior), oral contraceptive pill use (never/use for <5 years, use for ≥5 years), tamoxifen use (current, never/prior), type 2 diabetes mellitus (yes, no), and smoking (never, current/prior). Data on family history of endometrial cancer were, unfortunately, not collected from the UK Biobank cohort. A family history of bowel cancer in at least one first-degree relative has been shown to be associated with a statistically significant increase in the risk of endometrial cancer because of shared genetic (Lynch syndrome) and lifestyle factors (22). A family history of bowel cancer (none, one, or more first-degree relatives diagnosed) was, therefore, also included in the multivariable model. The impact of transformation of predictor variables and restricted cubic splines on model fit was assessed using the mvrs program

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 1. Demographic and baseline characteristic data for endometrial cancer cases and controls in the UK Biobank cohort, including proportion of missing data. Results given as median (IQR) or *n* (%).

Characteristic	Endometrial cancer cases (*n* = 902)	Controls (*n* = 221,129)
Age at recruitment, years	61 (55–65)	56 (49–62)
Duration of follow-up, years	4.1 (2.6–5.7)	7.2 (6.4–7.7)
BMI, kg/m^2		
<25.0	204 (22.6)	92,048 (41.6)
25.0–29.9	300 (33.3)	79,448 (35.9)
30.0–34.9	190 (21.1)	32,373 (14.6)
35.0–39.9	106 (11.8)	11,092 (5.0)
≥40.0	94 (10.4)	4,983 (2.3)
Missing	8 (0.9)	1,185 (0.5)
Ethnicity		
White	848 (94.0)	20,7755 (94.0)
Black or Black British	8 (0.9)	3,651 (1.7)
Mixed	4 (0.4)	1,591 (0.7)
Indian	14 (1.6)	2,514 (1.1)
Pakistani	2 (0.2)	634 (0.3)
Bangladeshi	0 (0.0)	62 (0.03)
Chinese	4 (0.4)	879 (0.4)
Other Asian	3 (0.3)	724 (0.3)
Other ethnic background	14 (1.6)	2,192 (1.0)
Missing	5 (0.6)	1,127 (0.5)
Family history of colorectal cancer		
Yes	117 (13.0)	23,037 (10.4)
No	785 (87.0)	198,092 (89.6)
Smoking		
Never	586 (65.0)	132,288 (59.8)
Current/previous	310 (34.4)	87,599 (39.6)
Missing	6 (0.7)	1,242 (0.6)
Waist circumference, cm	90 (81–101)	82 (75–91)
Missing	4 (0.4)	904 (0.4)
Age at menarche, years		
<12	233 (25.8)	40,685 (18.4)
≥12	605 (67.1)	160,601 (72.6)
Missing	64 (7.1)	19,843 (9.0)
Age at menopause, years		
Premenopausal at study entry	146 (16.2)	72,740 (32.9)
<55	568 (63.0)	126,502 (57.2)
≥55	188 (20.8)	21,887 (9.9)
Age at last birth, years	27 (18–31)	29 (23–33)
Missing	6 (0.7)	1,345 (0.6)
HRT use		
Never/prior use	790 (87.6)	198,695 (89.9)
Current use	62 (6.9)	12,303 (5.6)
Missing	50 (5.5)	10,131 (4.6)
Oral contraceptive pill use		
<5 years or never use	465 (51.6)	79,849 (36.1)
≥5 years	354 (39.3)	121,244 (54.8)
Missing	83 (9.2)	20,036 (9.1)
Tamoxifen use		
Current	15 (1.7)	1,320 (0.6)
Never/prior use	887 (98.3)	219,809 (99.4)
Type 2 diabetes		
Yes	73 (8.1)	5,587 (2.5)
No	825 (91.5)	214,517 (97.0)
Missing	4 (0.4)	1,025 (0.5)
Walking MET-h/week	8.3 (4.4–23.1)	11.6 (5.5–23.1)
Missing	211 (23.4)	48,782 (22.1)
Moderate activity MET-h/week	7.0 (1.3–18.7)	8.0 (2.0–20.0)
Missing	211 (23.4)	48,782 (22.1)
Vigorous MET-h/week	2.0 (0.0–10.7)	2.7 (0.0–12.0)
Missing	211 (23.4)	48,782 (22.1)

(Continued on the following column)

Table 1. Demographic and baseline characteristic data for endometrial cancer cases and controls in the UK Biobank cohort, including proportion of missing data. Results given as median (IQR) or *n* (%). (Cont'd)

in Stata. Sensitivity analyses were undertaken to examine the effect of excluding self-reported endometrial cancer cases and of imputing missing data.

All analyses were performed using STATA version 14 (23). A P value <0.05 was considered statistically significant.

Public and patient involvement

The research question was developed in collaboration with clinicians, patients, and the general public as part of a James Lind Alliance Priority Setting Partnership, in which the development of a personalized risk score to reflect an individual's risk of endometrial cancer and the identification of prevention strategies were identified as the most important unanswered research question (24).

Data availability

The data analyzed in this study were obtained from the UK Biobank under application number 5791. The dataset is available to researchers through an open application at https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access.

Results

UK Biobank

In total, 902 cases and 221,129 controls were eligible for analysis. No incident ICD9-coded endometrial cancer cases were identified. Eight cases were based on a self-reported diagnosis of endometrial cancer which could not be verified in the linked cancer registry data. In total, 5,817 and 479 women in the control group died and/or underwent a hysterectomy during follow-up, respectively. The baseline characteristics of cases and controls within the UK Biobank are described in **Table 1**. As anticipated, cases were older at the time of recruitment into the study, had a higher BMI, were more likely to have type 2 diabetes, and too have longer periods of endogenous estrogen exposure ($P < 0.0001$). Women who did not develop endometrial cancer during follow-up were significantly more physically active at study recruitment than those subsequently diagnosed with the disease [median MET-h/week 28.7 (interquartile range, IQR, 13.3–55.8) vs. 23.4 (10.6–49.8), $P < 0.0001$]. A linear dose–response relationship between increasing physical activity levels and endometrial cancer risk was observed. A 1 MET-h/week increase in physical activity

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

was associated with a 0.4% (95% CI, 0.2–0.6; $P < 0.0005$) reduction in endometrial cancer risk, after adjusting for age alone. In a multivariable analysis taking baseline BMI into account, the effect size was reduced, with each 1 MET-h/week increase in total physical activity associated with a 0.2% (95% CI, 0.01–0.4; $P = 0.020$) reduction in endometrial cancer risk. This effect equated to a 10.4% (95% CI, 1.7–18.3; $P = 0.020$) decrease in endometrial cancer risk for each additional 50 MET-h/week of physical activity or 7 hours of jogging (assuming jogging is equivalent to 7.0 MET-h; ref. 19). Walking and moderate intensity physical activity were associated with statistically significant decreases in endometrial cancer risk, with each 1 MET-h/week increase associated with a decrease in endometrial cancer risk of 0.5% (95% CI, 0.1–0.9; $P = 0.027$) and 0.4% (95% CI, 0.1–0.8; $P = 0.042$), respectively. Increasing levels of vigorous activity were associated with a smaller, nonsignificant, reduction in endometrial cancer risk (HR, 0.998; 95% CI, 0.994–1.003; $P = 0.427$).

Sensitivity analysis showed no effect of excluding self-reported endometrial cancer cases (HR, 0.998; 95% CI, 0.996–0.999; $P = 0.023$). While the effect size was unchanged when only unimputed data were considered, the result was no longer statistically significant (HR, 0.998; 95% CI, 0.996–1.001; $P = 0.161$).

Systematic review

Study selection and characteristics

Database and hand searching initially identified 3,954 articles, of which 3,871 were excluded because of duplicate publications ($n = 409$) or irrelevance ($n = 3,462$). Of the 83 full-text articles reviewed, 23 met the eligibility criteria for this review and were included, including 12 case–control studies and 11 cohort studies (**Fig. 1**; refs. 25–47). A detailed summary of the characteristics of the included studies is shown in **Table 2**.

A total of 821,599 participants were included in this review, including 10,445 endometrial cancer cases, with the age of participants ranging from 18 to >84 years. The included studies were conducted in a wide range of geographical locations, including United States, Canada, Mexico, United Kingdom, Norway, Sweden, Poland, The Netherlands, Europe, and China. Cohort studies frequently recruited women from the general population, with the exception of those studies focusing on health professionals (28, 30) and teachers (29). Robsahm and colleagues (44) conducted a study of world-class professional Norwegian athletes and compared their incidence of cancer with that of the general population. Data were collected by self-administered questionnaire in 14 studies and by interview in the remaining nine. None of the studies measured physical activity objectively, instead relying on patient recall. The studies considered a range of domains of physical activity including recreational, occupational, household activity, and physical activity for transportation, either singularly or in combination as "total physical activity." While the majority of studies asked participants to report the number of hours of each activity performed in a specific time period Colbert and colleagues (27), and Friberg and colleagues (31) also collected data on sleep duration to allow the calculation of total MET-h of activity in a 24-hour period. As a result, the median and total reported MET-h/week varied dramatically between studies, with the most active individuals in the study by Friberg and colleagues (31) undertaking more than 46 MET-h/day. Reported physical activity levels were also influenced by whether studies considered all intensities of physical activity undertaken or solely reported on moderate and vigorous activity (25, 29, 34, 37, 40). Endometrial cancer risk estimates were based on long-term physical activity levels in seven studies (25, 29, 30, 33, 36, 39, 41), with the others considering short-term snapshots of activity only. With the exception of the study by Plagens-Rotman and colleagues (43), all studies provided adjusted estimates of endometrial cancer risk. The majority of studies adjusted for many of the most important endometrial cancer risk factors, including age, BMI, parity, age at menarche and menopause, oral contraceptive pill, and HRT use and family history of endometrial and/or colorectal cancer. Fourteen studies also reported estimates of endometrial cancer risk without BMI adjustment (25–28, 30–35, 38, 42, 44, 47).

Primary outcome

A summary of the results of the 23 included studies is provided in **Table 3**. Only one study published data on the effect of 1 MET-h/week on endometrial cancer risk, finding a nonsignificant OR of 1.00 (95% CI, 0.99–1.00; ref. 33). The authors of the remaining 22 studies were contacted for this information but either did not reply ($n = 10$) or were unfortunately unable to access the original study data for reanalysis ($n = 12$). For this reason, alongside the significant variability in study design, a meta-analysis could not be performed.

Of the 11 cohort studies appraised, five found a statistically significant reduction in endometrial cancer risk with increasing physical activity, with risk estimates ranging from 0.54 to 0.85 (26, 28, 29, 34, 46). These risk estimates were based on performing 10.5 hours of total physical activity or 5 hours of moderate and vigorous activity each week compared with individuals performing less than 30 minutes of total physical activity each day or no moderate or vigorous activity. While the risk estimates were reduced in each of these studies following BMI adjustment, the range remained the same, although only three studies demonstrated statistically significant effects of physical activity on endometrial cancer risk in multivariable analyses (25, 30, 42). Five of the 12 case–control studies also found statistically significant reductions in endometrial cancer risk with increasing physical activity levels in both age-adjusted and multivariable analyses (25, 35, 36, 39, 45). BMI-unadjusted ORs ranged from 0.46 to 0.65, when comparing those in the most active with those in the least active groups, with slightly higher ORs observed following BMI adjustment (0.47–0.71). The greatest reduction in endometrial cancer risk was seen in the study by (45), where ≥38 MET-h/week or 5 hours of vigorous physical activity each week was associated with a 53% (95% CI, 14–74) reduction in endometrial cancer risk

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

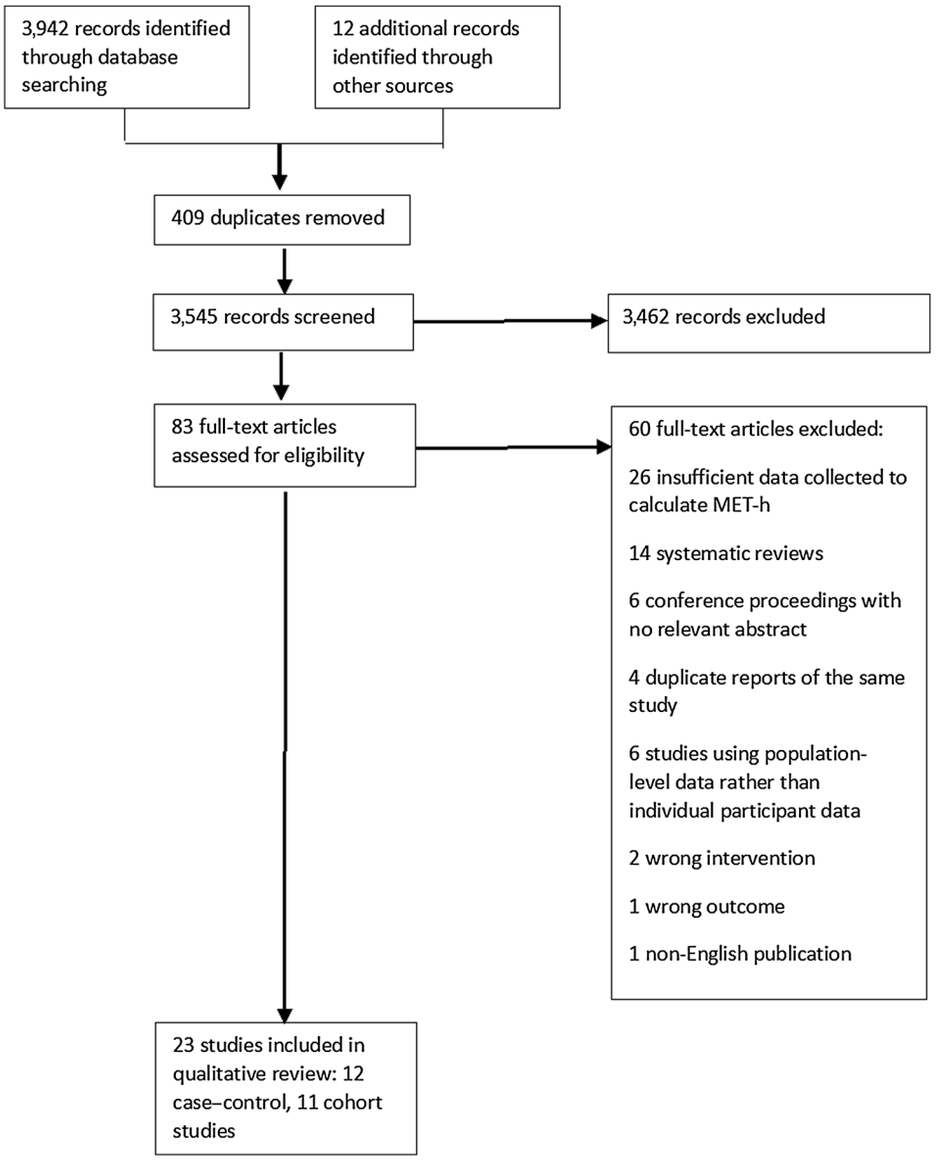


Figure 1.
Flow diagram of study selection. Of the 3,954 records identified through a systematic search of the literature, 83 full-text articles were assessed for eligibility, of which 23 were included in the qualitative analysis.

compared with women undertaking ≤29 MET-h/week or 3.5 hours of vigorous activity each week, after adjusting for age, anovulatory index, smoking, menopausal status, hypertension, diabetes, and BMI. The remaining studies found no statistically significant effect of increasing physical activity levels on endometrial cancer risk, with the exception of the study by Modesitt and colleagues (40), which failed to report the effect of physical activity on endometrial cancer risk, despite collecting the relevant data.

Secondary outcome

No studies reported the effect of different types of physical activity on the risk of endometrial cancer in continuous MET-h/week. Eighteen of the 23 included studies undertook at least one analysis to determine whether the domain or intensity of physical activity performed impacted upon endometrial cancer risk (25, 27–39, 41, 42, 46, 47). Four of the 10 studies that assessed vigorous or moderate and vigorous activity together found a statistically significant reduction in endometrial cancer risk for the most active compared with the least active group (25, 29, 34, 36). Endometrial cancer risk reductions ranged from 23% to 36% in those undertaking between 3 and 8 hours of vigorous activity per week compared with women who never or rarely undertook physical activity of this intensity. Two studies noted a decrease in endometrial cancer risk in association with increasing levels of light physical activity only, with up to a 40% reduction in endometrial cancer risk for women undertaking more than 3.7 hours of walking each week compared with those performing no physical activity (33, 38).

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 2. Characteristics of included studies.

Study	Study period	Study design	Study population	Number of participants	Age of participants (years)	Physical activity questionnaire	Method of administering questionnaire	Follow-up duration
Arem *et al.* 2011	2004–2008	Case–control study	Residents of Connecticut, USA	1,329 (667 EC cases)	35–79	Kriska's modifiable activity questionnaire, reliable and validated	In-person interview	n/a
Barberio *et al.* 2018	2000–2016	Cohort study	Residents of Alberta, Canada	15,368 women (90 EC cases)	35–69	Past year total physical activity questionnaire (PYTPAQ), reliable and validated	Self-administered	Mean 6.6 years cases, 11.1 years controls
Colbert *et al.* 2003	1987–1998	Cohort study	Participants in Breast Cancer Detection Demonstration Project (BCDDP), USA	23,374 (253 EC cases)	Unknown, mean age 60–62 years	Nonvalidated questionnaire, reliability not checked	Self-administered	Average 8.2 years
Conroy *et al.* 2009	1992–2007	Cohort study	Health professionals enrolled into Women's Health Study, USA	19,917 (264 EC cases)	45+	Nonvalidated questionnaire, reliability not checked	Self-administered	Mean 8.8 years
Dieli-Conwright *et al.* 2013	1995–2007	Cohort study	Public school teachers/ administrators enrolled into California Teachers Study, USA	93,888 (976 EC cases)	20+	Nonvalidated questionnaire, reliability confirmed	Self-administered	Median 12.1 years
Du *et al.* 2014	1986–2008	Cohort study	Registered nurses enrolled in Nurses' Health Study, USA	71,570 (777 EC cases)	30–55	Nonvalidated questionnaire, reliability confirmed	Self-administered	1,235,880 person-years
Friberg *et al.* 2006	1997–2005	Cohort study	Residents of Uppsala and Västmanland counties, Sweden	33,723 (199 EC cases)	50–83	Nonvalidated questionnaire, reliability confirmed	Self-administered	Mean 7.25 years
Friedenreich *et al.* 2007	1992–2004	Cohort study	General adult population of 10 European countries enrolled into EPIC study	253,023 (689 EC cases)	35–70	Modified version of Baecke questionnaire, reliability confirmed, not validated	Self-administered	Mean 6.6 years
Friedenreich *et al.* 2010	2002–2006	Case–control study	Residents of Alberta, Canada	1,574 (542 EC cases)	30–79	Nonvalidated questionnaire, reliability confirmed	In-person interview	n/a
Gierach *et al.* 2009	1995–2003	Cohort study	Members of the American Association of Retired Persons who participated in NIH-AARP Diet and Health Study, USA	109,621 (1,052 EC cases)	50–71	Nonvalidated questionnaire, reliability not checked	Self-administered	Mean 3.8 years cases, 7.0 years for controls
Goodman *et al.* 1997	1985–1993	Case–control study	Residents of Oahu, Hawaii of Japanese, Caucasian, Native Hawaian, Filipino and Chinese ethnicity	843 (332 EC cases)	18–84	Nonvalidated questionnaire, reliability not checked	In-person interview	n/a
John *et al.* 2010	1996–1999	Case–control study	Non-hispanic white, Hispanic and African American residents of San Francisco bay area, USA	970 (500 EC cases)	35–79	Nonvalidated questionnaire, reliability not checked	In-person interview	n/a

(Continued on the following page)

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 2. Characteristics of included studies. (Cont'd)

Study	Study period	Study design	Study population	Number of participants	Age of participants (years)	Physical activity questionnaire	Method of administering questionnaire	Follow-up duration
Kwon *et al.* 2012	2009	Case–control study	Participants in Behavioral Risk Factor Surveillance System (BFRSS), USA	144,012 (1,080 EC cases)	40–79	Nonvalidated questionnaire, reliability not checked	Computer-assisted telephone interviews	n/a
Littman *et al.* 2001	1985–1991	Case–control study	Residents of King, Pierce and Snohomish counties, Washington, USA	1,933 (822 EC cases)	45–74	Modified version of Minnesota Leisure Time Physical Activity questionnaire, validated	In-person interviews	n/a
Matthews *et al.* 2005	1997–2001	Case–control study	Residents of Shanghai, China	1,678 (832 EC cases)	30–69	Nonvalidated questionnaire, reliability confirmed	In-person interview	n/a
Modesitt *et al.* 2012	2007–2009	Case–control study	Overweight and obese postmenopausal women due for hysterectomy for EC or benign indications, USA	38 (22 EC cases)	Mean age 58.3	Modified version of Aerobics Center Longitudinal Study Physical Activity questionnaire, reliability not checked and validity in determining MET-h/week unknown	Self-administered	n/a
Olson *et al.* 1997	1986–1991	Case–control study	Residents of New York state, USA	863 (232 EC cases)	40–85	Nonvalidated questionnaire, reliability not checked	In-person interview	n/a
Patel *et al.* 2008	1992–2003	Cohort study	Participants in Cancer Prevention II study Nutrition Cohort, USA	42,672 (466 EC cases)	50–74	Nonvalidated questionnaire, reliability not checked	Self-administered	Not reported
Plagens-Rotman *et al.* 2020	2011–2013	Case–control study	Patients at the Gynaecological and Obstetric Hospital of the Medical University of Poznan, Poland	751 (68 EC cases)	21–84	Nonvalidated questionnaire, reliability not checked	Self-administered	n/a
Robsahm *et al.* 2010	1953–2007	Cohort study	Norwegian world class athletes	1,424 (3 EC cases)	18+	Nonvalidated questionnaire, reliability not checked	Self-administered	Not reported
Salazar-Martinez *et al.* 2000	1995–1997	Case–control study	Patients attending Castelazo Ayala Hospital, Mexico	753 (85 EC cases)	<40→71	Nonvalidated questionnaire, reliability not checked	Self-administered	n/a
Schouten *et al.* 2004	1986–1995	Cohort study	Participants in The Netherlands Cohort Study on Diet and Cancer, Netherlands	1,739 (226 EC cases)	55–69	Nonvalidated questionnaire, reliability not checked	Self-administered	Average 9.3 years
Shu *et al.* 1993	1988–1990	Case–control study	Residents of the Shanghai metropolitan area, China	536 (268 EC cases)	18–74	Nonvalidated questionnaire, reliability not checked	In-person interview	n/a

Abbreviation: EC, endometrial cancer.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 3. Summary of results of included studies.

Study	Domains/types of physical activity studied	Comparison	Age-adjusted relative effect ratio (95% CI)	Age-adjusted P_{trend}	Adjusted variables	Adjusted relative effect ratio (95% CI)	Multivariate adjusted P_{trend}
Barberio *et al.* 2018	Employment, transportation-related, household and recreational activities of all intensities	≤113.7 vs. ≥201.2 MET-h/week	HR = 0.54 (0.30–0.98)	<0.01	Age, ethnicity, marriage status, highest level of education, area of residence, smoking, alcohol use, mean energy intake, self-reported BMI, cardiovascular and respiratory history, family history, menopausal status. Exclusion of cancers within 2 years of baseline assessment	HR = 0.71 (0.36–1.40)	0.13
Colbert *et al.* 2003	All types and intensities of physical activity including sleep. Entire 24-hour period considered.	Low (Q1) vs. high Median MET-h/week 8.0 vs. 56.0	RR = 0.8 (0.5–1.1)	0.24	Age, parity, education	RR = 0.8 (0.5–1.1)	0.24
Conroy *et al.* 2009	Walking, jogging, running, bicycling, use of stationary machines, aerobic exercise, aerobic dance, use of exercise machines, tennis/squash or racquetball, lap swimming, yoga/stretching/toning	Total energy expenditure ≥20.4 vs.<2.7 MET-h/week	RR = 1.42 (1.01–1.98)	0.02	Age, BMI, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, menopausal status	RR = 1.15 (0.79–1.67)	0.39
Dieli-Conwright *et al.* 2013	Longterm moderate and strenuous recreational activity	≤0.5 vs. ≥5.5 hours/week/year	Not reported	Not reported	Age, race, BMI	RR = 0.85 (0.68–1.06)	0.03
Du *et al.* 2014	Cumulative average walking, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic dance/rowing machine, squash/racquetball	<3 vs. ≥27 MET-h/week	RR = 0.81 (0.62–1.05)	0.17	Age at menarche, OCP use, parity and age at first birth, age at last birth, menopausal status, age at menopause, HT use, HT type, BMI at age 18, pack-years of smoking, family history of endometrial cancer, family history of colorectal cancer, alcohol intake, caffeine intake, recent BMI	RR = 1.10 (0.84–1.45)	0.32
Friberg *et al.* 2006	Occupational, household, leisure time activity, walking/biking, watching TV/sitting, sleep. Entire 24-hour period considered.	<38.9 vs. ≥45.9 MET-h/day	RR = 0.74 (0.50–1.09)	0.14	Age, parity, diabetes, total fruit and vegetable intake, education, BMI	RR = 0.79 (0.53–1.17)	0.27
Friedenreich *et al.* 2007	Occupational, recreational, household activity	Household <25.12 vs. ≥85.10 MET-h/week Recreational <12.01 vs. ≥41.26 MET-h/week	Household HR = 0.91 (0.69–1.19) Recreational HR = 0.92 (0.74–1.15)	0.62 0.38	Age, centre, BMI, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of OCP, ever use of HT, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, energy intake	Household HR = 0.93 (0.70–1.22) Recreational HR = 0.94 (0.75–1.18)	0.73 0.47
Gierach *et al.* 2009	Vigorous activity at work or home in past 12 months	Never/rarely vs. 5+ times/week	RR = 0.60 (0.49–0.73)	<0.0001	Age, race, smoking status, parity, OCP use, age at menopause, HT use, BMI	RR = 0.77 (0.63–0.95)	0.02

(Continued on the following page)

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 3. Summary of results of included studies. (Cont'd)

Study	Domains/types of physical activity studied	Comparison	Age-adjusted relative effect ratio (95% CI)	Age-adjusted P_{trend}	Adjusted variables	Adjusted relative effect ratio (95% CI)	Multivariate adjusted P_{trend}
Patel *et al.* 2008	Recreational, non-recreational activity (baseline)	Recreational <7 vs. ≥31.5 MET-h/week Nonrecreational <5.0 vs. ≥18.5 MET-h/week	Recreational RR = 0.65 (0.42–1.00) Nonrecreational RR = 0.78 (0.60–1.01)	 ns ns	Age, age at menarche, age at menopause, duration OCP use, parity, smoking, total caloric intake, diabetes, postmenopausal HT use, BMI	Recreational RR = 0.79 (0.52–1.22) Non-recreational RR = 0.83 (0.64–1.07)	0.18 0.13
Robsahm *et al.* 2010	Physical activity of any intensity	Athletes that developed EC vs. general Norwegian population	SIR = 0.79 (0.16–2.30)	n/a	Age	SIR = 0.79 (0.16–2.30)	n/a
Schouten *et al.* 2004	Transportation to work, household, recreational activity	<30 minutes/day vs. ≥90 minutes/day	Not reported	Not reported	Age, BMI, age at menarche, OCP use, age at menopause, parity, smoking status	RR = 0.54 (0.34–0.85)	0.002
Arem *et al.* 2011	Moderate and vigorous sport/recreational activity (2–5 years before interview)	0 vs. 7.5 MET-h/week	OR = 0.46 (0.36–0.60)	<0.001	Age, BMI, race, number of live births, menopausal status, OCP use, hypertension, smoking status	OR = 0.66 (0.50–0.87)	0.002
Friedenreich *et al.* 2010	Occupational, recreational, household activity (lifetime)	Per MET-h/week/year	OR = 1.00 (0.99–1.00)	ns	Age	OR = 1.00 (0.99–1.00)	ns
Goodman *et al.* 1997	Recreational and nonrecreational activity	Recreational 0 vs. 3339 lifetime hours since age 15 Nonrecreational 0 vs. 20089 lifetime hours since age 15	Recreational OR = 0.9 (not given) Nonrecreational OR = 0.8 (not given)	0.50 0.27	BMI	Recreational OR = 0.9 (not given) Nonrecreational OR = 0.7 (not given)	0.34 0.08
John *et al.* 2010	Lifetime transportation to work, occupational, household, recreational activity of any intensity	<43.2 vs. ≥91.9 MET-h/week	Not reported	Not reported	Age, ethnicity, education, family history of endometrial cancer, age at menarche, parity, duration OCP use, duration HT use, menopausal status, BMI, height	OR = 0.61 (0.43–0.87)	0.01
Kwon *et al.* 2012	Nonoccupational moderate and vigorous activity	Non cancer vs. endometrial cancer Means of weekly moderate intensity physical activity equivalents (MIE, minutes per week)	Not reported	Not reported	Age, ethnicity, education, annual household income	Age 40–64 91 (90–93) vs. 80 (66–97) Age 65–79 61 (58–63) vs. 59 (48–74)	ns
Littman *et al.* 2001	Nonoccupational activity, including transportation to work, of all intensities	Low vs. high (no exercise vs. Q5)	OR = 0.65 (0.46–0.92)	0.23	Age, county, unopposed estrogen use and duration, income, BMI	OR = 0.78 (0.55–1.11)	0.38

(Continued on the following page)

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Table 3. Summary of results of included studies. (Cont'd)

Study	Domains/types of physical activity studied	Comparison	Age-adjusted relative effect ratio (95% CI)	Age-adjusted P_{trend}	Adjusted variables	Adjusted relative effect ratio (95% CI)	Multivariate adjusted P_{trend}
Matthews *et al.* 2005	Total adult occupational, walking/cycling for transportation, household activity	<3.64 vs. >8.81 MET-h/day	Not reported	Not reported	Age, age at menarche, menopausal status and age, parity, OCP use, current smoking, ever drinking, family history of cancer, education, height, BMI	OR = 0.71 (0.52–0.96)	<0.01
Modesitt *et al.* 2012	Sleep, watching TV, moderate and vigorous physical activity	Activity data not reported					
Olson *et al.* 1997	Walking, occupational, vigorous recreational activity (10 years ago)	Vigorous activity None vs. ≥100 hours/year	Not reported	Not reported	Age, education, BMI, diabetes, smoking, parity, age at menarche, menopausal status, use of unopposed estrogen	OR = 0.72 (0.43–1.19)	0.10
Plagens-Rotman *et al.* 2020	Work-related physical activity	<10 hours vs. >30 hours per week	Not reported	Not reported	None	OR = 1.65 (0.72–3.79)	ns
Salazar-Martinez *et al.* 2000	Not stated	≤29 vs. ≥38 MET-h/week	Not reported	Not reported	Age, anovulatory index, smoking, menopausal status, hypertension, diabetes, BMI	OR = 0.47 (0.26–0.86)	0.01
Shu *et al.* 1993	Occupational, recreational activity of all intensities	Occupational Inactive (Q1) vs. Active (Q4) Nonoccupational age ≥60 Inactive (Q1) vs. Active (Q4)	Occupational RR = 0.8 (0.5–1.4) Nonoccupational RR = 0.6 (0.3–1.4)	 ns ns	Age, parity, BMI, caloric intake	Occupational RR = 0.9 (0.6–1.6) Non-occupational RR = 0.5 (0.2–1.3)	ns ns

Abbreviations: CI, confidence interval; HR, hazard ratio; HT, hormone therapy; ns, not significant; OCP, oral contraceptive pill; OR, odds ratio; RR, risk ratio; SIR, standardized incidence ratio.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Two studies found a statistically significant reduction in endometrial cancer risk in women undertaking regular recreational activity, with risk reductions of 36%–46% for women performing at least 90 minutes of recreational activity each day or 16.9 MET-h/week compared with those performing minimal recreational activity (33, 46). Matthews and colleagues (39) found a statistically significant decrease in endometrial cancer risk in women walking daily for transportation for more than 1 hour (OR, 0.64; 95% CI, 0.47–0.87; $P_{trend} < 0.01$) and in those performing more than 3 hours of household chores each day (OR, 0.62; 95% CI, 0.46–0.85, $P_{trend} < 0.01$). No other statistically significant relationships between domain or intensity of physical activity and endometrial cancer risk were noted in the remaining studies.

Eleven studies investigated the effect of either long-term physical activity or physical activity levels at different points in a woman's lifetime on endometrial cancer risk (27, 29, 30, 33–36, 39, 41, 42, 47). The findings were inconsistent, with three studies finding increased benefit with sustained high physical activity levels (12, 36, 42) and the others noting no demonstrable difference (27, 29, 30, 33–35, 41, 47).

Risk of bias in included studies

The RoB summary and assessment for each individual study is shown in **Fig. 2**. Overall, the 11 cohort studies were considered at moderate RoB while the 12 case–control studies were considered at high RoB, predominately due to the risk of recall bias in a number of studies.

Of the included studies, 18 were considered to be at low risk of selection bias as participants were selected from the general population and physical activity levels were assessed after participant recruitment (25–36, 38, 42, 43, 45–47). Robsahm and colleagues (44) assessed cancer risk in Norwegian world-class athletes, thereby placing this study at high risk of selection bias. Modesitt and colleagues (40) restricted their inclusion criteria to obese women and compared their physical activity levels with women undergoing a hysterectomy for benign indications and whose activity levels may have been affected by their underlying pathology. The study by Matthews and colleagues (12) was deemed to be at unclear risk of selection bias as there was a 12% lower response rate from controls than cases, which may have impacted upon the results observed. A further study was also assessed to be at unclear risk of selection bias due to the identification of controls from lists of driving license holders, who may have been less physically active than women without a driving license and who relied on walking or bicycling for transportation (41).

Eleven studies were deemed at unclear risk of performance bias as they did not report whether study personnel were blinded to endometrial cancer diagnosis at the time of participant interview (25, 33, 35–39, 41, 43, 45, 47). This was because of the potential risk of recall bias and influence in interviews of lifestyle factors on cancer diagnosis.

Only one study was considered at high risk of detection bias as endometrial cancer diagnoses were based on patient report only (43). All other studies were considered at low risk due to endometrial cancer case ascertainment through cancer registries and histologic confirmation.

None of the included studies published their protocols prospectively. Seven studies were considered to be at unclear or high risk of reporting bias as they failed to report all data collected (26, 38, 40, 42, 43, 45, 46).

Three studies were considered at low risk of information bias as data were collected using questionnaires whose reliability had been checked through comparison with other well-described questionnaires or within the same individuals over time and had been validated against objective measurements of physical activity using accelerometers (25, 26, 38). Four further studies were also considered at low risk of information bias as the questionnaires used had been shown to be reliable although their validity had not been assessed (29–31, 33). This decision was taken based on the relatively modest correlation between all subjective assessments of physical activity tested and accelerometer-measured activity levels. Nine studies were deemed to be at unclear risk of information bias as the questionnaires used did not appear to have been assessed for reliability and had not been validated (26–31, 34–37, 40–42, 46). While there is a risk of recall error in case–control studies, which, by their nature, require participants to retrospectively recall information while being aware of their outcome status, such studies were not considered at increased risk of information bias if a broad range of data on potential endometrial cancer risk factors were collected at the time of interview and/or the study authors utilized techniques to minimize the possibility of systemic overreporting or underreporting of physical activity levels. Seven studies in total were assessed to be at high risk of information bias (32, 39, 40, 43–45, 47). Three studies used nonvalidated questionnaires whose reliability had not been assessed and did not attempt to mitigate the risk of biased recall of physical activity levels (43, 45, 47). The study by Modesitt and colleagues (40) utilized a questionnaire designed to quantify fitness levels and which has not been assessed for use in determining physical activity levels. The questionnaire used by Friedenreich and colleagues (32) had previously been shown to satisfactorily rank participants in terms of their activity levels, but information about duration and frequency of some activity types was lacking with a risk of measurement error in other domains. Matthews and colleagues (39) reported occupational activity based on job title only and (44) used next-of-kin in 416 instances to quantify physical activity levels as the subjects themselves were deceased.

All but one study was considered at low risk of confounding bias as they had adjusted for at least one variable in their analysis (43).

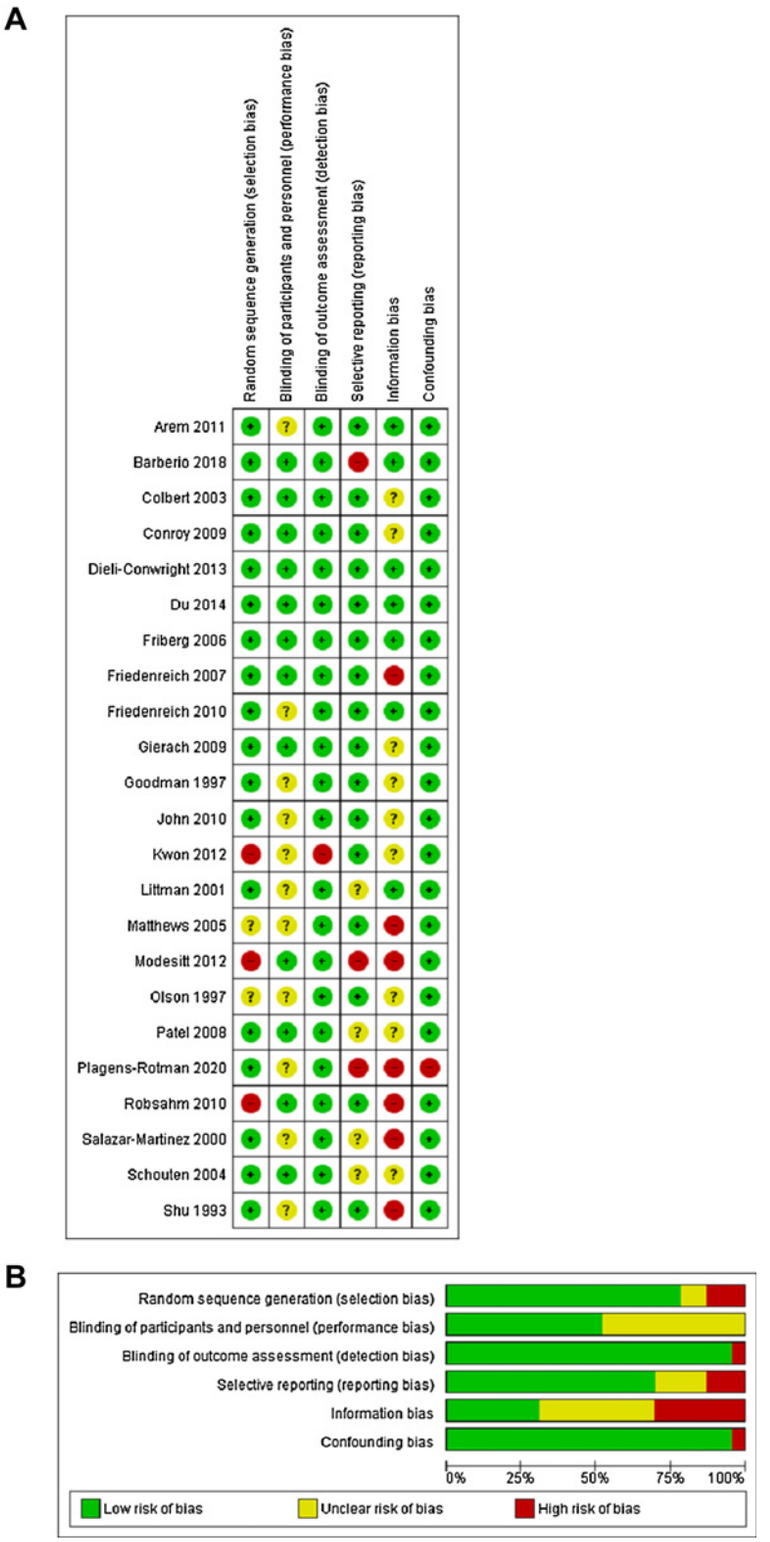
Discussion

In this study, we assessed the impact of physical activity levels on endometrial cancer risk in a primary analysis of participants of the UK Biobank and through a systematic review of the

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Figure 2.

RoB summary per individual study (**A**) and per domain (**B**). **A,** Cohort studies were considered to be at moderate risk of bias overall while case–control studies were generally considered at high risk of bias due to the potential for recall bias. **B,** At least one study was considered to be at high RoB in all of the domains considered, with the exception of performance bias.



Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

literature. Data from the UK Biobank revealed a statistically significant reduction in endometrial cancer risk with each 1 MET-h/week increase in total physical activity. Only one previously published study, by Friedenreich and colleagues (33), was identified through the systematic review to have reported on the impact of a 1 MET-h/week increase in physical activity on endometrial cancer risk, finding no significant effect of increasing lifetime physical activity. Ten of the cohort and case–control studies reviewed found a statistically significant reduction in endometrial cancer risk but only in the group of most active individuals, who were undertaking regular vigorous physical activity for at least 5 hours each week, equating to approximately 40 MET-h/week. While only eight of these studies retained statistically significant results following BMI adjustment, suggesting some obscuring of the true impact of physical activity on endometrial cancer prevention, the overall range of effect size remained unchanged. Vigorous and sustained physical activity over an individual's lifetime may be associated with a greater reduction in endometrial risk, although study findings were inconsistent. These results suggest that large amounts of physical activity may be needed for an individual's endometrial cancer risk to be reduced significantly. Currently, there is limited evidence on which to base firm recommendations about the type and amount of physical activity associated with the greatest reduction in endometrial cancer risk. More robust studies aimed at quantifying the impact of physical activity in MET-h/week on endometrial cancer risk are required to standardize findings and allow for interstudy comparisons.

The World Health Organization (WHO) and U.S. Physical Activity Guidelines Advisory committee recently concluded that there was moderate to high-certainty evidence that high physical activity levels were associated with a reduction in endometrial cancer risk, based on their appraisal of a number of systematic reviews and meta-analyses that have been conducted on the topic to date (48, 49). The largest of these meta-analyses found that compared with individuals who undertook "low" levels of physical activity, those that participated in "high" levels had a 20% lower risk of endometrial cancer [Relative Risk (RR), 0.80; 95% CI, 0.75–0.85; ref. 10]. This meta-analysis was conducted, however, by pooling the results of 33 studies that had variably defined "high" and "low" physical activity levels and incorporated different types and intensities of physical activity. There also appeared to be a disparity between the level of cancer risk reduction observed between cohort and case–control studies, with only a 16% reduction found in the more methodologically robust cohort studies. Neither the WHO nor the U.S. Physical Activity Guidelines Advisory committee were able to comment on the nature of any dose–response relationship between physical activity and endometrial cancer risk or advise on the optimal type and intensity of activity to be undertaken, which this study aimed to address. Keum and colleagues (50) had previously suggested that a 3 MET-h/week increase in leisure-time activity could be associated with a nonsignificant 2% (95% CI, 0–5) reduction in endometrial cancer risk based on their review of three cohort and three case–control studies, which are also included in this review (25, 28, 32, 33, 39, 42). The authors found moderate heterogeneity between studies, a likely reflection of differences in study design and approach to calculation of physical activity levels, and had used modeled risk estimates based on limited reported data, with the inherent inaccuracies associated with this statistical approach (51). Matthews and colleagues (12) also attempted to address the question of the dose–response relationship between increasing physical activity levels and endometrial cancer risk and found, as in this study, that the association was approximately linear. Unlike in this study, however, they noted, that the relationship was no longer statistically significant after BMI was taken into account (HR, 1.02; 95% CI, 0.91–1.14). This may reflect the fact that total physical activity levels were considered in the current study compared with only leisure-time activity in the earlier meta-analysis.

The current study, as well as providing an up to date review of the literature on the effect of physical activity on endometrial cancer risk, also presents novel data from the UK Biobank, a large biomedical resource containing detailed demographic and anthropometric information on over 250,000 women with linkage to the National Cancer Registry. Multiple imputations were utilized to deal with the modest amount of missing physical activity data and sensitivity analyses performed to determine the impact of this on the results observed. Appropriate statistical analysis techniques, including cubic spline analysis, were also employed to investigate the dose–response relationship between physical activity and endometrial cancer risk. While the physical activity levels studied here were self-reported, they were determined using a widely utilized questionnaire, validated against objectively measured physical activity levels as determined by an accelerometer (52, 53). Although the correlation between self-reported and accelerometer measured physical activity levels is relatively modest with all surveys in current use, self-reported data do allow the accurate ranking of individuals within a population and hence the determination of a dose–response relationship, which was the focus of this study. Thus, while the use of self-reported physical activity levels may have underestimated effects on disease risk, these data were used in preference to those based on accelerator-measured physical activity as accelerometers were worn by only 80,000 participants in the UK Biobank study and had shorter follow-up duration. The UK Biobank, like many cohort studies, has been shown to include a preferentially healthy population, of lower BMI and with fewer comorbidities than the general population (54). The disease–exposure relationships observed in this analysis are in keeping with those previously published in the literature and along with the heterogeneity in physical activity levels observed within the cohort means that the findings reported here are generalizable to other populations.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

The systematic review was conducted in accordance with the gold-standard methodology proposed by The Cochrane Collaboration and included a wide and systematic search of the literature to identify eligible studies, including hand searching of the grey literature and no limitations on publication or study type, with the exception of language. The RoB in the review process was minimized by having two authors independently screening titles, abstracts, and full texts, with consensus reached in the presence of a third assessor in the case of disagreements. In addition, two authors worked independently to extract the data and to assess the RoB of included studies.

A limitation of this study is the fact that it was not possible to complete a dose–response assessment of the effect of physical activity on endometrial cancer risk across more of the studies identified in the systematic review. Despite making contact, many study authors were unable to access the primary data due to the length of time since completion of their studies. The significant differences between studies in the methodology employed to calculate MET-h/week of physical activity, including the types of physical activity assessed and whether this incorporated all activity within a 24-hour period including sleep, would anyway have meant that any meta-analysis would have had to combine smaller numbers of similarly conducted studies only. It was also not possible to assess the most beneficial type or intensity of physical activity or the age at which it has maximal impact on endometrial cancer risk for the same reasons. No randomized controlled trials have been performed to investigate the effect of physical activity on endometrial cancer risk and are unlikely to ever be undertaken given that in excess of 35,000 high-risk women would potentially need to be recruited and followed up for 5 years for any benefit to be observed according to calculations performed using similar data for breast cancer prevention (55). Any conclusions about the effect of physical activity on endometrial cancer risk will, therefore, continue to be based on observational data only. While this review included 23 studies and over 10,000 endometrial cancer cases, there were concerns about the moderate to high RoB in included studies and inconsistency in reported results, which reduces the level of certainty around the evidence.

This study, like previous meta-analyses, has considered the impact of physical activity on endometrial cancer risk in isolation, without taking into account its important preventive effect on weight gain and the development of obesity and the potential value it may add to a dietary intervention as part of a weight loss strategy. This has not been possible as the majority of included primary studies have collected data on physical activity and BMI at study entry only, which has usually been in mid-life, and have not documented long-term changes in physical activity and BMI levels. When this has been explored within the NIH-AARP Diet and Health study using mediation analysis, it appears that the majority (56%–63%) of the benefit from increased physical activity in preventing endometrial cancer is mediated through a reduction in the risk of obesity (56). Encouragingly, the authors of that study were also able to demonstrate that previously inactive individuals gained a substantial benefit from increasing their physical activity levels in mid-life, suggesting that it is never too late to take up physical activity. This study did, however, rely on retrospectively recalled physical activity and BMI data and included only 1,468 endometrial cancer cases, resulting in wide CIs.

Any future studies of physical activity and endometrial cancer risk need to take the effect of physical activity on BMI into account and should, ideally, be prospectively conducted using standardized methodology to allow for pooling of results and a meaningful meta-analysis. They should incorporate objective measurement of physical activity levels using accelerometers to reduce the risk of information bias. Categorization of data should be avoided, wherever possible, to maximize information gathering. Studies should focus on the effects of different types of physical activity on endometrial cancer risk and the age at which such activity has maximal beneficial effect. Until more evidence is available, women of all ages should continue to be encouraged to undertake 150 minutes of moderate to vigorous physical activity each week for its broader health benefits in line with WHO recommendations (49).

Conclusions

There is a paucity of high-quality evidence to determine the dose–response relationship between physical activity and endometrial cancer risk. The available data indicate a weak inverse linear relationship, with frequent prolonged periods of physical activity associated with greatest endometrial cancer risk reduction. Regular vigorous physical activity is encouraged to maximize the health benefit observed, in line with WHO recommendations.

Authors' Disclosures

S.J. Kitson reports grants from Wellbeing of Women and other support from NIHR during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

S.J. Kitson: Conceptualization, resources, formal analysis, supervision, investigation, methodology, writing–original draft, writing–review and editing. **O. Aurangzeb:** Data curation, formal analysis, methodology, writing–original draft, writing–review and editing. **J. Parvaiz:** Data curation, formal analysis, methodology, writing–review and editing. **A. Lophatananon:** Data curation, formal analysis, methodology, writing–review and editing. **K.R. Muir:** Data curation, formal analysis, supervision, writing–review and editing. **E.J. Crosbie:** Conceptualization, supervision, methodology, writing–review and editing.

Acknowledgments

We would like to express our appreciation to UK Biobank participants and staff for providing the research community with this valuable source of data. This work used data from the application number 5791.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

S.J. Kitson is a NIHR Academic Clinical Lecturer and the recipient of a Wellbeing of Women Postdoctoral Research Fellowship (PRF101). E.J. Crosbie is supported by a National Institute for Health Research (NIHR) Advanced Fellowship (NIHR300650) and the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007). A. Lophatananon and K.R. Muir are supported by the European Union's funded Project iHELP under grant agreement 101017441.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note

Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

Received March 16, 2022; revised May 3, 2022; accepted June 9, 2022; published first June 13, 2022.

References

1. Cancer Research UK. Uterine cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer#heading-Zero.
2. NCI SEER. Cancer stat facts: uterine cancer. Bethesda, MD. Available from: https://seer.cancer.gov/statfacts/html/corp.html.
3. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet 2022;399:1412–28.
4. Kitson SJ, Evans DG, Crosbie EJ. Identifying high-risk women for endometrial cancer prevention strategies: proposal of an endometrial cancer risk prediction model. Cancer Prev Res 2017;10:1–13.
5. Gu B, Shang X, Yan M, Li X, Wang W, Wang Q, et al. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990–2019. Gynecol Oncol 2021;161:573–80.
6. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. Br J Cancer 2016;115:1147–55.
7. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer 2008;8:205–11.
8. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19:3119–30.
9. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Mol Oncol 2021;15:790–800.
10. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol 2015;30:397–412.
11. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomarkers Prev 2007;16:639–48.
12. Matthews CE, Moore SC, Arem H, Cook MB, Trabert B, Hakansson N, et al. Amount and intensity of leisure-time physical activity and lower cancer risk. J Clin Oncol 2020;38:686–97.
13. McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical activity in cancer prevention and survival: a systematic review. Med Sci Sports Exerc 2019;51:1252–61.
14. Rezende LFM, Sa TH, Markozannes G, Rey-Lopez JP, Lee IM, Tsilidis KK, et al. Physical activity and cancer: an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. Br J Sports Med 2018;52:826–33.
15. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. Int J Cancer 2019;145:1719–30.
16. Murray JM, Coleman HG, Hunter RF. Physical activity and cancer risk: findings from the UK Biobank, a large prospective cohort study. Cancer Epidemiol 2020;68:101780.
17. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
18. IPAQ Research Committee. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ) – short and long forms. Available from: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/ipaq_analysis.pdf.
19. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. The compendium of physical activities tracking guide. Healthy Lifestyles Research Center, College of Nursing & Health Innovation, Arizona State University. Available from: https://sites.google.com/site/compendiumofphysicalactivities/.
20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
21. Sterne JAC, Hernán MA, McAleenan A, Reeves BC, Higgins PT. Chapter 25: Assessing risk of bias in a non-randomized study. Cochrane Handbook for Systematic Reviews of Interventions version 6.2; 2021.
22. Lucenteforte E, Talamini R, Montella M, Dal Maso L, Pelucchi C, Franceschi S, et al. Family history of cancer and the risk of endometrial cancer. Eur J Cancer Prev 2009;18:95–9.
23. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.
24. Wan YL, Beverley-Stevenson R, Carlisle D, Clarke S, Edmondson RJ, Glover S, et al. Working together to shape the endometrial cancer research agenda: the top ten unanswered research questions. Gynecol Oncol 2016;143:287–93.
25. Arem H, Irwin ML, Zhou Y, Lu L, Risch H, Yu H. Physical activity and endometrial cancer in a population-based case-control study. Cancer Causes Control 2011;22:219–26.
26. Barberio AM, Friedenreich CM, Lynch BM, Campbell KL, Arora P, Brenner DR. Physical activity and cancer incidence in Alberta's tomorrow project: results from a prospective cohort of 26,538 participants. Cancer Epidemiol Biomarkers Prev 2018;27:945–54.
27. Colbert LH, Lacey JV Jr, Schairer C, Albert P, Schatzkin A, Albanes D. Physical activity and risk of endometrial cancer in a prospective cohort study (United States). Cancer Causes Control 2003;14:559–67.
28. Conroy MB, Sattelmair JR, Cook NR, Manson JE, Buring JE, Lee IM. Physical activity, adiposity, and risk of endometrial cancer. Cancer Causes Control 2009;20:1107–15.
29. Dieli-Conwright CM, Ma H, Lacey JV Jr, Henderson KD, Neuhausen S, Horn-Ross PL, et al. Long-term and baseline recreational physical activity and risk of endometrial cancer: the California Teachers Study. Br J Cancer 2013;109:761–8.
30. Du M, Kraft P, Eliassen AH, Giovannucci E, Hankinson SE, De Vivo I. Physical activity and risk of endometrial adenocarcinoma in the Nurses' Health Study. Int J Cancer 2014;134:2707–16.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

31. Friberg E, Mantzoros CS, Wolk A. Physical activity and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:2136–40.
32. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, et al. Physical activity and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Int J Cancer 2007;121:347–55.
33. Friedenreich CM, Cook LS, Magliocco AM, Duggan MA, Courneya KS. Case-control study of lifetime total physical activity and endometrial cancer risk. Cancer Causes Control 2010;21:1105–16.
34. Gierach GL, Chang SC, Brinton LA, Lacey JV Jr, Hollenbeck AR, Schatzkin A, et al. Physical activity, sedentary behavior, and endometrial cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer 2009;124:2139–47.
35. Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, et al. Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res 1997;57:5077–85.
36. John EM, Koo J, Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev 2010;19:1276–83.
37. Kwon S, Hou N, Wang M. Comparison of physical activity levels between cancer survivors and non-cancer participants in the 2009 BRFSS. J Cancer Surviv 2012;6:54–62.
38. Littman AJ, Voigt LF, Beresford SA, Weiss NS. Recreational physical activity and endometrial cancer risk. Am J Epidemiol 2001;154:924–33.
39. Matthews CE, Xu WH, Zheng W, Gao YT, Ruan ZX, Cheng JR, et al. Physical activity and risk of endometrial cancer: a report from the Shanghai endometrial cancer study. Cancer Epidemiol Biomarkers Prev 2005;14:779–85.
40. Modesitt SC, Geffel DL, Via J, A LW. Morbidly obese women with and without endometrial cancer: are there differences in measured physical fitness, body composition, or hormones? Gynecol Oncol 2012;124:431–6.
41. Olson SH, Vena JE, Dorn JP, Marshall JR, Zielezny M, Laughlin R, et al. Exercise, occupational activity, and risk of endometrial cancer. Ann Epidemiol 1997;7:46–53.
42. Patel AV, Feigelson HS, Talbot JT, McCullough ML, Rodriguez C, Patel RC, et al. The role of body weight in the relationship between physical activity and endometrial cancer: results from a large cohort of US women. Int J Cancer 2008;123:1877–82.
43. Plagens-Rotman K, Piskorz-Szymendera M, PIĘTA B. Lifestyle with particular emphasis on physical activity and genital carcinomas in women. Eur J Gynaecol Oncol 2020;41:233–9.
44. Robsahm TE, Hestvik UE, Veierod MB, Fagerlie A, Nystad W, Engebretsen L, et al. Cancer risk in Norwegian world class athletes. Cancer Causes Control 2010;21:1711–9.
45. Salazar-Martinez E, Lazcano-Ponce EC, Lira-Lira GG, Escudero-De los Rios P, Salmeron-Castro J, Larrea F, et al. Case-control study of diabetes, obesity, physical activity and risk of endometrial cancer among Mexican women. Cancer Causes Control 2000;11:707–11.
46. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. J Natl Cancer Inst 2004;96:1635–8.
47. Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA. Physical activity and risk of endometrial cancer. Epidemiology 1993;4:342–9.
48. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services; 2018. p. F4–18.
49. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–62.
50. Keum N, Ju W, Lee DH, Ding EL, Hsieh CC, Goodman JE, et al. Leisure-time physical activity and endometrial cancer risk: dose-response meta-analysis of epidemiological studies. Int J Cancer 2014;135:682–94.
51. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–9.
52. Guo W, Key TJ, Reeves GK. Accelerometer compared with questionnaire measures of physical activity in relation to body size and composition: a large cross-sectional analysis of UK Biobank. BMJ Open 2019;9:e024206.
53. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.
54. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 2017;186:1026–34.
55. Ballard-Barbash R, Hunsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, et al. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. J Natl Cancer Inst 2009;101:630–43.
56. Saint-Maurice PF, Sampson JN, Michels KA, Moore SC, Loftfield E, McClain K, et al. Physical activity from adolescence through midlife and associations with body mass index and endometrial cancer risk. JNCI Cancer Spectr 2021;5:pkab065.

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024

Downloaded from http://aacrjournals.org/cancerpreventionresearch/article-pdf/15/9/605/3199216/605.pdf by guest on 08 December 2024