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META-ANALYSIS

# A systematic review and meta-analysis of physical activity and endometrial cancer risk

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**Abstract** Physical activity is related to decreased endometrial cancer risk. However, a comprehensive investigation of activity domains, intensities, time periods in life, and potential interaction with body mass index is unavailable. We performed a meta-analysis of physical activity and endometrial cancer studies published through October 2014. We identified 33 eligible studies comprising 19,558 endometrial cancer cases. High versus low physical activity was related to reduced endometrial cancer risk [relative risk (RR) = 0.80; 95 % confidence interval (CI) 0.75–0.85]. The corresponding RRs for recreational activity, occupational activity, household activity, and walking were 0.84 (95 % CI 0.78–0.91), 0.81 (95 % CI 0.75–0.87), 0.70 (95 % CI 0.47–1.02), and 0.82 (95 % CI 0.69–0.97), respectively ($P_{difference} = 0.88$). Walking/biking for transportation, walking for recreation, and walking without specification revealed summary RRs of 0.70 (95 % CI 0.58–0.85), 0.94 (95 % CI 0.76–1.17), and 0.88 (95 % CI 0.52–1.50), respectively ($P_{difference} = 0.13$). Inverse associations were noted for light (RR 0.65; 95 % CI 0.49–0.86), moderate to vigorous (RR 0.83; 95 % CI 0.71–0.96), and vigorous activity (RR 0.80; 95 % CI 0.72–0.90; $P_{difference} = 0.35$). A statistically significant inverse relation was found for postmenopausal (RR 0.81; 95 % CI 0.67–0.97), but not premenopausal women (RR 0.74; 95 % CI 0.49–1.13; $P_{difference} = 0.78$). Physical activity performed during childhood/adolescence, young adulthood/midlife, and older age yielded RRs of 0.94 (95 % CI 0.82–1.08), 0.77 (95 % CI 0.58–1.01), and 0.69 (95 % CI 0.37–1.28), respectively ($P_{difference} = 0.51$). An inverse relation was evident in overweight/obese (RR 0.69; 95 % CI 0.52–0.91), but not normal weight women (RR 0.97; 95 % CI 0.84–1.13; $P_{difference} = 0.07$). In conclusion, recreational physical activity, occupational physical activity, and walking/biking for transportation are related to decreased endometrial cancer risk. Inverse associations are evident for physical activity of light, moderate to vigorous, and vigorous intensities. The inverse relation with physical activity is limited to women who are overweight or obese.

**Keywords** Physical activity · Endometrial cancer · Meta-analysis

## Introduction

Worldwide, endometrial cancer is the fifth most common cancer in women [1] and it represents one of the most frequent gynecologic malignancies [1]. In 2014, endometrial cancer is projected to develop in about 52,630 women in the United States (US) and an estimated 8590 US women will die from this cancer [2]. Each year, approximately 7406 new cases occur in the UK and 88,068 new cases occur in the European Union [3]. The most important risk factors for endometrial cancer are postmenopausal unopposed estrogen therapy, obesity, and nulliparity [4, 5]. In contrast, physical activity represents an important modifiable preventive factor for endometrial cancer [6]. Plausible biologic mechanisms linking increased physical activity to decreased endometrial

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cancer risk include decreased levels of sex steroids, insulin resistance, and chronic inflammation [7]. Physical activity may be directly involved in these biologic pathways or indirectly by reducing obesity.

Four publications have summarized the available epidemiologic evidence regarding physical activity in relation to risk of endometrial cancer [8–11]. Concertedly, findings from those studies suggest that physical activity is associated with reduced risk of developing endometrial cancer [8–11]. However, those investigations did not provide summary risk estimates for specific activity domains, such as household activity and walking, which greatly contribute to women's total daily activity [12–14]. For example, it is not known whether walking for transportation better characterizes the aspect of physical activity that is relevant for protection against endometrial cancer than strenuous exercise performed during recreation. Because the hormonal milieu changes throughout the life course, it also remains to be evaluated whether the apparent protective effect of physical activity on endometrial cancer risk depends on specific time periods in life. Moreover, obesity is an important risk factor for endometrial cancer [15, 16] and is inversely associated with physical activity [17], but whether adiposity modifies the relation of physical activity to endometrial cancer or represents an intermediate factor linking physical activity to endometrial cancer remains unclear.

We conducted a comprehensive systematic review and meta-analysis with a specific focus on evaluating physical activity across various domains and intensities, age levels, and body mass index (BMI) groups.

## Materials and methods

### Literature search and inclusion criteria

In preparing the present meta-analysis, we followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [18]. We conducted a comprehensive literature search in 28 databases (e.g., EMBASE, Medline, Cochrane database of Systematic Reviews, Database of Abstracts of Reviews of Effects, SciSearch, Social SciSearch, PSYNDEX, PsycINFO) up to October 2014. The following search terms were used: physical activity, motor activity, exercise, walking, sports, athletes, endurance training, physical fitness, sedentary (lifestyle), sedentariness, physical inactivity, sitting, motor inactivity, recreation. The search included the following terms for cancer: (endometrium; endometrial; endometrioid; uterus; uterine) cancer(s), carcinoma (s), adenocarcinoma(s), neoplasm (s), tumor (s), tumour (s), or sarcoma(s). In addition, we screened references lists from retrieved original articles to identify further potentially eligible studies. We imposed a restriction to articles on human studies and those published in English. The inclusion criteria were as follows: (1) the study was a cohort study, case–control study, or case–cohort study; (2) the study investigated the association between physical activity and endometrial cancer incidence; (3) the relative risk (RR), odds ratio (OR), or standardized incidence ratio (SIR) and corresponding 95 % confidence interval (CI) was provided or could be calculated; (4) age as a risk factor was taken into account. If studies were found to overlap, we included the study that provided the most comprehensive data.

### Data extraction and study quality assessment

From each article, two authors (D.S. and M.F.L.) independently extracted the following information: name of the first author, year of publication, country where the study was performed, total number of individuals and cases, method of physical activity assessment, RRs, ORs, or SIRs with corresponding 95 % CIs comparing the highest with the lowest level of physical activity, and confounding factors that were adjusted for in the analysis. If a study provided unadjusted and adjusted effect measures, the most completely adjusted effect measure that also adjusted for age was used.

Quality assessment was conducted using the Newcastle-Ottawa-Scale (NOS), a validated scale that awards a maximum of nine points to each cohort study (four for quality of selection, two for comparability, and three for quality of outcome and adequacy of follow-up) or case–control study (four for quality of selection, two for comparability, and three for quality of exposure) [19]. We considered studies with a NOS score of $\geq 6$ as high quality studies and those with a NOS score of $<6$ as low quality studies.

### Statistical analysis

*Main analysis*

In the main analysis, we pooled the risk estimates comparing the highest versus the lowest categories of physical activity in relation to endometrial cancer, with the exception of one study that compared the highest versus the second lowest physical activity category [20]. Most studies provided data on recent physical activity. Thus, we prioritized risk estimates for recent physical activity in the main analysis. If data from more than one physical activity domain were available, we prioritized risk estimates in the following order: total physical activity, recreational activity, occupational activity. If physical activity was expressed using more than one metric (i.e., MET-hours per week, hours per week, times per week), we used MET-hours per week because it represents the most comprehensive physical activity measure, combining activity intensity, duration, and frequency [21].

Risk estimates were interpreted as relative risk estimates ($RR_i$) and were log-transformed to $\log(RR_i)$. Standard errors of the log-transformed relative risks $\log(RR_i)$ were defined as $si = d_i/1.96$, where $d_i$ represented the maximum of [log(upper 95 % CI bound of $RR_i$)-$\log(RR_i)$] and [($\log(RR_i)$-log(lower 95 % CI bound of $RR_i$)]. To meta-analyze those log-values, we employed random effects models to allow for study heterogeneity [22].

The Q-statistic was used to test for between-study heterogeneity and the $I^2$-statistic was used to quantify the proportion of the total variation due to heterogeneity [22]. Potential publication bias was assessed by visual inspection of a funnel plot and by using Egger's regression test [23] and Begg's rank correlation test [24].

To investigate the robustness of our main analysis, we performed a sensitivity analysis in which we excluded one study at a time from the initial meta-analysis to assess whether a particular study may have influenced the summary risk estimate.

### *Stratified analyses*

In stratified analyses, we investigated high versus low levels of physical activity of different domains in relation to endometrial cancer using a random-effects model. Specifically, we considered recreational activity, occupational activity, household activity, and walking (walking/biking for transportation, walking for recreation, and walking without specification). One study [25] investigated walking for transportation and three studies [26–28] examined walking/biking for transportation. We assigned studies to the category walking/biking for transportation that defined walking as walking for transportation [25], walking/bicycling to school or work [26], number of years walked or biked to work most days [27], or walking/bicycling (mainly for transportation) [28]. One study provided two separate risk estimates for walking for transportation and biking for transportation, of which we included the risk estimate for walking for transportation in our meta-analysis [25]. The category walking for recreation included three studies [29–31] that examined walking/hiking and one study [32] that investigated walking/biking during recreation. Three studies reported risk estimates for walking [33], walking for exercise, pleasure, or transportation [34], and walking/biking to work, shopping, and/or walking the dog [32], which were defined as unspecified walking in the present meta-analysis.

Moreover, we explored different intensities of physical activity (light, moderate to vigorous, and vigorous) in relation to risk of endometrial cancer. We further investigated whether the association between physical activity and endometrial cancer varied across different time periods in life (childhood/adolescence, young adulthood/midlife, older age). To evaluate whether BMI modifies the physical activity and endometrial cancer relation, we summarized physical activity risk estimates for women with a BMI $< 25$ kg/m$^2$ and those with a BMI $\geq 25$ kg/m$^2$. Using random-effects meta-regression, we further summarized studies that adjusted for adiposity and those that did not adjust for adiposity to investigate whether the physical activity and endometrial cancer relation is mediated by regulation of body weight. In addition, we assessed potential heterogeneity of the physical activity and endometrial cancer relation according to geographic location, number of participants, number of cases, study quality, and adjustments for parity, oral contraceptive use, and hormonal replacement therapy.

We calculated the $P$ for difference across strata using meta-regression comparing the model including the stratification variable as explanatory variable with the null model not including any explanatory variables.

### *Dose–response meta-analysis*

Because studies used different measures of physical activity, we conducted an additional analysis that was restricted to studies that used MET-hours per week as physical activity measure. To account for variability in the range of MET-hour levels in the individual studies, we further performed analyses summarizing studies that provided RRs for approximately 3–8, 9–20, and >20 MET-hours as compared with <3 MET-hours of physical activity per week.

Finally, we performed a non-linear dose–response meta-analysis of recreational physical activity expressed in MET-hours per week in relation to endometrial cancer using second degree fractional polynomials [35]. We excluded two studies [28, 36] from the dose–response meta-analysis because in those studies, MET-hours calculations were based on the combination of all activities and inactivities, including time spent sitting and sleeping.

All statistical analyses were conducted using the R-packages 'metafor' [37] and 'mvmeta' [38]. The analyses were two tailed and a $P < 0.05$ was considered statistically significant.

## Results

### Literature search and description of the studies

Supplementary Figure 1 shows details of the literature search strategy and study selection. A total of 2636 publications were retrieved from the electronic literature search databases and one article was identified by manual search. After removal of 889 duplicate articles identified in different databases, 1748 remained for evaluation. After screening titles and abstracts, 1703 articles were excluded that were not original articles related to physical activity and endometrial cancer incidence. A total of 45 articles remained for full review, of which twelve were excluded because they provided information from overlapping studies [10, 39], combined different exposures or different outcomes [40–44], compared different stages of endometrial cancer with each other [45], did not adjust for age [46], or lacked appropriate data to calculate risk estimates [47, 48]. One study was excluded that used individuals with prevalent cancer as controls [49]. The remaining 33 articles met the pre-specified inclusion criteria and were included in our meta-analysis [20, 25–34, 36, 50–70].

Descriptive data from studies included in the present meta-analysis are shown in Table 1. We included 18 cohort studies, one case–cohort study, and 14 case–control studies, yielding a total number of 2,219,151 participants and 19,558 endometrial cancer cases. Physical activity was assessed by self-administered questionnaire in 16 studies, by interview in ten studies, and in four studies physical activity assessment was based on job titles. In three studies, total or recreational physical activity was assessed by interviews or self-administered questionnaires and occupational physical activity was assessed by job titles. The number of adjustment factors in the models ranged from one to 18. Twenty studies showed a quality score equal to or greater than six points and thirteen studies had a quality score of less than six points (Table 1).

### Main analysis

As shown in Fig. 1, the highest compared with the lowest physical activity category revealed a summary RR of endometrial cancer of 0.80 (95 % CI 0.75–0.85). No evidence for heterogeneity between studies was observed ($I^2 = 6.5$ %, $P_{heterogeneity} = 0.38$). Further, no publication bias was indicated by the funnel plot, Egger's regression test ($P = 0.06$), or Begg's rank correlation test ($P = 0.25$). In sensitivity analyses, omission of one study at a time did not materially alter the results.

To investigate whether variability in the underlying physical activity measure may have influenced our results, we meta-analyzed nine studies that provided physical activity measures expressed as MET-hours per week. We obtained a RR of 0.80 (95 % CI 0.70–0.92) comparing the highest versus lowest level of overall physical activity (recreational physical activity only: RR 0.85; 95 % CI 0.74–0.97; total physical activity only: RR 0.68; 95 % CI 0.50–0.93). We further summarized studies that used relatively uniform categories of MET-hours per week of recreational physical activity and obtained RRs of 0.94 (95 % CI 0.74–1.20), 0.79 (95 % CI 0.64–0.98), and 0.87 (95 % CI 0.71–1.06) for approximately 3–8, 9–20, and greater than 20 MET-hours as compared with less than 3 MET-hours of physical activity per week (Supplementary Figure 2). Within the range of 0 to approximately 40 MET-hours per week of recreational physical activity, we observed a non-linear inverse dose–response relation for recreational physical activity with endometrial cancer risk ($P_{non-linearity} < 0.05$), which indicated a 5 % reduced risk in endometrial cancer for those engaging in 12 MET-hours per week of recreational physical activity compared to those not engaging in regular recreational physical activity (RR 0.95; 95 % CI 0.91–0.99).

### Stratified analyses

Investigating the association between physical activity and endometrial cancer risk by study design showed a RR of 0.84 (95 % CI 0.78–0.91) for cohort studies and a RR of 0.72 (95 % CI 0.64–0.80) for case–control studies ($P_{difference} = 0.03$, Fig. 1). Our analyses of physical activity domain included 22 studies of recreational activity, 19 studies of occupational activity, and seven studies of household activity. Comparisons of high versus low levels of recreational activity, occupational activity, and household activity resulted in summary RRs of 0.84 (95 % CI 0.78–0.91), 0.81 (95 % CI 0.75–0.87), and 0.70 (95 % CI 0.47–1.02), respectively (Fig. 2). Ten studies explored the relation between walking or walking in combination with hiking or biking and endometrial cancer risk. One study [32] provided two risk estimates: one for walking/biking for transportation and one for walking/biking during recreation. When we considered the risk estimate for walking/biking for transportation from that study [32], the summary RR for all ten studies was 0.82 (95 % CI 0.69–0.97; Fig. 2). Inclusion of the risk estimate for walking/biking during recreation from that study [32] did not materially change the summary RR (RR 0.85; 95 % CI 0.73–0.99). The overall *P* value for difference according to activity domain was 0.88 (Fig. 2).

Restricting the analysis of walking to studies that explored walking/biking for transportation, a summary RR of 0.70 (95 % CI 0.58–0.85) was obtained. Walking for recreation (RR 0.94; 95 % CI 0.76–1.17) and walking without specification (RR 0.88; 95 % CI 0.52–1.50) were unrelated to risk of endometrial cancer. The *P* value for difference according to the different categories of walking was 0.13.

Two studies provided information on light intensity activity, eight studies reported on moderate to vigorous intensity activity, and eight studies considered vigorous

**Table 1** Characteristics of the 33 included studies of physical activity and endometrial cancer

| References, geographic location | Number of individuals | Number of cases | Method of physical activity assessment | RR, OR, or SIR [95 % CI], high versus low category (main analysis) | Variables stratified or adjusted for in the model (main analysis) | NOS points |
|---|---|---|---|---|---|---|
| Prospective cohort studies | | | | | | |
| Moradi et al., 1998 [50], Sweden | 989,270 | 5287 | Job titles from census data | 0.76 [0.67, 0.85], very high/high versus sedentary of most recent (year 1970) occupational physical activity | Age, place of residence, calendar year of follow-up, socio-economic status | 5 |
| Terry et al., 1999 [51], Sweden | 9925 | 112 | Self-administered questionnaire | 0.10 [0.04, 0.60], hard versus none of total physical activity | Age, weight, parity | 6 |
| Colbert at al., 2003 [36], USA | 23,369 | 253 | Self-administered questionnaire | 0.80 [0.50, 1.10], 56 versus 8 MET-hour per day of total vigorous and moderate physical activity | Age, parity, education | 5 |
| Folsom et al., 2003 [52], USA | 23,335 | 411 | Self-administered questionnaire | 1.05 [0.84, 1.33], high versus low recreational physical activity | Age | 6 |
| Furberg & Thune, 2003 [53], Norway | 24,460 | 130 | Self-administered questionnaire | 0.79 [0.43, 1.45], highest versus lowest recreational physical activity at baseline | Age, geographic region, height, BMI, recreational or occupational activity, smoking, parity | 6 |
| Friberg et al., 2006 [28], Sweden | 33,723 | 199 | Self-administered questionnaire | 0.79 [0.53, 1.17], ≥45.9 MET-hour per day versus <38.9 MET-hour per day of total physical activity | Age, parity, history of diabetes, education, and total fruit and vegetable intake, BMI | 5 |
| Friedenreich et al., 2007 [54], ten Western European countries | 253,023 | 671 | Self-administered questionnaire | 0.88 [0.61, 1.27], active versus inactive (total physical activity) | Stratified by age and center, adjusted for BMI, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, oral contraceptives, hormone replacement therapy use, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, energy intake | 6 |
| Patel et al., 2008 [20], USA | 42,672 | 466 | Self-administered questionnaire | 0.79 [0.52, 1.22], 31.5+ MET-hour per week versus 0 to <7 MET-hour per week of baseline recreational physical activity | Age, age at menarche, age at menopause, duration of oral contraceptive use, parity, smoking, total caloric intake, personal history of diabetes, postmenopausal hormone replacement therapy use, BMI | 7 |
| Epstein et al., 2009 [55], Sweden | 17,822 | 166 | Self-administered questionnaire | 0.50 [0.30, 1.10] strenuous exercise versus no exercise | Age, education, marital status, hormone use, family history of gynecological cancer | 7 |
| Conroy et al., 2009 [29], USA | 32,642 | 264 | Self-administered questionnaire | 0.87 [0.60, 1.27], ≥20.4 versus <2.7 MET-hour per week of total physical activity | Age, BMI, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy and menopausal status | 7 |
| Gierach et al., 2009 [27], USA | 109,621 | 1045 | Self-administered questionnaire | 0.77 [0.63, 0.95], 5+ times per week versus never/rarely of vigorous physical activity during typical month in the past 12 years | Age, race, smoking status, parity, ever use of oral contraceptives, age at menopause, ever use of hormone therapy, BMI | 6 |
| Robsahm et al., 2010 [56], Norway | 3428 | 3 | Athletes | 0.79 [0.16, 2.30], athletes versus general Norwegian population | Age, birth cohort | 4 |
| Dieli-Conwright et al., 2013 [57], USA | 93,888 | 976 | Self-administered questionnaire | 0.84 [0.69, 1.02], ≥5.5 versus ≤0.5 h per week per year of recent moderate and strenuous recreational physical activity | Age as time metric and stratified by age. Adjustment for race, BMI | 5 |
| Du et al., 2014 [30], USA | 71,570 | 683 | Self-administered questionnaire | 1.01 [0.80, 1.29], ≥27 versus <3 MET-hours per week of total recreational physical activity | Age at menarche, oral contraceptive use, parity and age at first birth, age at last birth, menopausal status, age at menopause, hormone therapy, hormone therapy 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 | 7 |

**Table 1** continued

| References, geographic location | Number of individuals | Number of cases | Method of physical activity assessment | RR, OR, or SIR [95 % CI], high versus low category (main analysis) | Variables stratified or adjusted for in the model (main analysis) | NOS points |
|---|---|---|---|---|---|---|
| Land et al., 2014 [58], USA | 13,208 | 74 | Self-administered questionnaire | 0.63 [0.39–1.03] moderate/heavy versus inactive/light physical activity | Age, race/ethnicity, smoking, alcohol, treatment group, menopausal status, prior estrogen use, age at menarche, number of past pregnancies, family cancer history, diabetes, BMI | 6 |
| Retrospective cohort studies | | | | | | |
| Pukkala et al., 1993 [59], Finland | 1499 | 8 | Teachers of physical education | 1.33 [0.58, 2.62], physical education teachers versus total finish female population | Age, time period | 4 |
| Weiderpass et al., 2001 [60], Finland | 413,877 | 2833 | Job titles | 0.90 [0.80, 1.10] high versus no perceived physical work load | Age, social class, calendar year, parity, age at first birth by occupation, turnover rate | 4 |
| Soll-Johanning & Bach, 2004 [61], Denmark | 17,233 | 2 | Self-administered questionnaire | 0.78 [0.09, 2.83], mail carriers versus Copenhagen population | Age, calendar period | 5 |
| Case–cohort study | | | | | | |
| Schouten et al., 2004 [32], The Netherlands | 1739 | 226 | Self-administered questionnaire | 0.97 [0.49, 1.91], ≥2 h per week versus none of sports/exercise | Age, BMI, age at menarche, use of oral contraceptives, age at menopause, parity, cigarette smoking | 5 |
| Case control studies | | | | | | |
| Levi et al., 1993 [33], Switzerland and Italy | 844 | 272 | Interview | 0.53 [0.25, 1.11] highest versus lowest levels of sports and recreational physical activity | Age, study center, education, parity, menopausal status, oral contraceptive use, estrogen replacement treatment, BMI, calorie intake | 6 |
| Shu et al., 1993 [62], China | 178 | 80 | Interview (self-reported overall physical activity) and job titles (occupational physical activity) | 0.83 [0.14, 5.00] very active versus very inactive (overall physical activity) | Age, parity, BMI, caloric intake | 5 |
| Sturgeon et al., 1993 [31], USA | 695 | 398 | Interview | 0.83 [0.50, 1.43], active versus inactive during recreation | Age, study area, education, parity, years of use of oral contraceptives, years of use of menopausal estrogens, cigarette smoking, BMI, non-recreational activity | 6 |
| Hirose et al., 1996 [63], Japan | 26,825 | 145 | Self-administered questionnaire | 0.60 [0.38, 0.93], ≥3–4 times/week versus none of physical activity (exercise for health) | Age and first visit year | 6 |
| Kalandidi et al., 1996 [64], Greece | 443 | 145 | Interview | 0.41 [0.18, 0.91], manual versus nonmanual occupation | Age, schooling, age at menopause, age at menarche, live births, miscarriages, induced abortions, oral contraceptive use, menopausal estrogens, smoking, alcohol intake, coffee intake, height, BMI, energy intake | 5 |
| Olson et al., 1997 [34], USA | 859 | 232 | Interview | 0.67 [0.42, 1.09], ≥100 versus <100 h per year spent in exercising enough to sweat (2 years ago) | Age, age at menarche, parity, BMI, menopausal status, use of unopposed estrogens, diabetes, smoking, education | 7 |
| Moradi et al., 2000 [65], Sweden | 3689 | 677 | Self-administered questionnaire (recreational physical activity), job titles from census data (occupational physical activity) | 0.77 [0.59, 1.00], >2 h versus never of recent recreational physical activity | Age, parity, age at last birth, BMI 1 year prior to data collection, use of oral contraceptives, use of hormones replacement therapy, smoking, age at menopause | 7 |
| Salazar-Martinez et al., 2000 [66], Mexico | 753 | 85 | Interview | 0.47 [0.26, 0.86], ≥38 versus ≤29 MET-hours per week of total physical activity | Age, anovulatory index[a], smoking, menopausal status, hypertension, diabetes, BMI | 5 |
| Littman et al., 2001 [67], USA | 1933 | 822 | Interview | 0.78 [0.55, 1.11], highest level of total estimated energy expenditure for recreational physical activity versus no exercise | Age, county, unopposed estrogen use, duration, income, BMI | 8 |

**Table 1** continued

| References, geographic location | Number of individuals | Number of cases | Method of physical activity assessment | RR, OR, or SIR [95 % CI], high versus low category (main analysis) | Variables stratified or adjusted for in the model (main analysis) | NOS points |
|---|---|---|---|---|---|---|
| Matthews et al., 2005 [25], China | 1679 | 832 | Interview (recreational physical activity) and job titles (occupational physical activity) | 0.76 [0.50, 1.13], of 2.7–11.3 versus none MET-hour per day per year of recreational physical activity in adults | Age, age at menarche, menopausal status and age, number of pregnancies, oral contraceptive use, current smoking, ever drinking, family history of cancer, education, height, BMI | 6 |
| Tavani et al., 2009 [68], Italy | 1132 | 380 | Interview | 0.97 [0.64, 1.49], >7 versus <2 h per week of sports or exercise at ages 50–59 | Age, center, period of interview, education, BMI, total energy intake, history of diabetes, age at menarche and menopause, menopausal status, parity, oral contraceptive use, hormones replacement therapy use | 6 |
| Friedenreich et al., 2010 [69], Canada | 1574 | 542 | Interview | 0.88 [0.61, 1.26], >131.2 versus 0 to ≤59.7 MET-hour per week per year of total physical activity from menopause to reference date | Age, BMI, waist circumference, age at menarche, hypertension, number of pregnancies of ≥20 weeks gestation, occupational activity, household activity, recreational activity | 6 |
| John et al., 2010 [26], USA | 915 | 472 | Interview | 0.64 [0.45, 0.91], ≥91.9 versus <43.2 MET-hours/week of total physical activity during 10 years prior to reference age | Age, race/ethnicity, education, family history of endometrial cancer, age at menarche, full-term pregnancies, duration of oral contraceptive use, duration of hormone therapy use, menopausal status, BMI, height | 8 |
| Arem et al., 2011 [70], USA | 1329 | 667 | Interview | 0.66 [0.50, 0.87], 7.5+ versus 0 MET-hour per week of moderate and vigorous physical activity | Age, BMI, race, number of live births, menopausal status, oral contraceptive use, hypertension, smoking status | 5 |

*RR* relative risk, *OR* odds ratio, *SIR* standardized incidence rate, *CI* confidence interval, *PA* physical activity, *NOS* Newcastle-Ottawa scale, *MET* metabolic equivalent task, *BMI* body mass index

[a] anovulatory index = no. of pregnancies × 9 + no. of breastfeeding children × 6 + years of oral contraceptive use

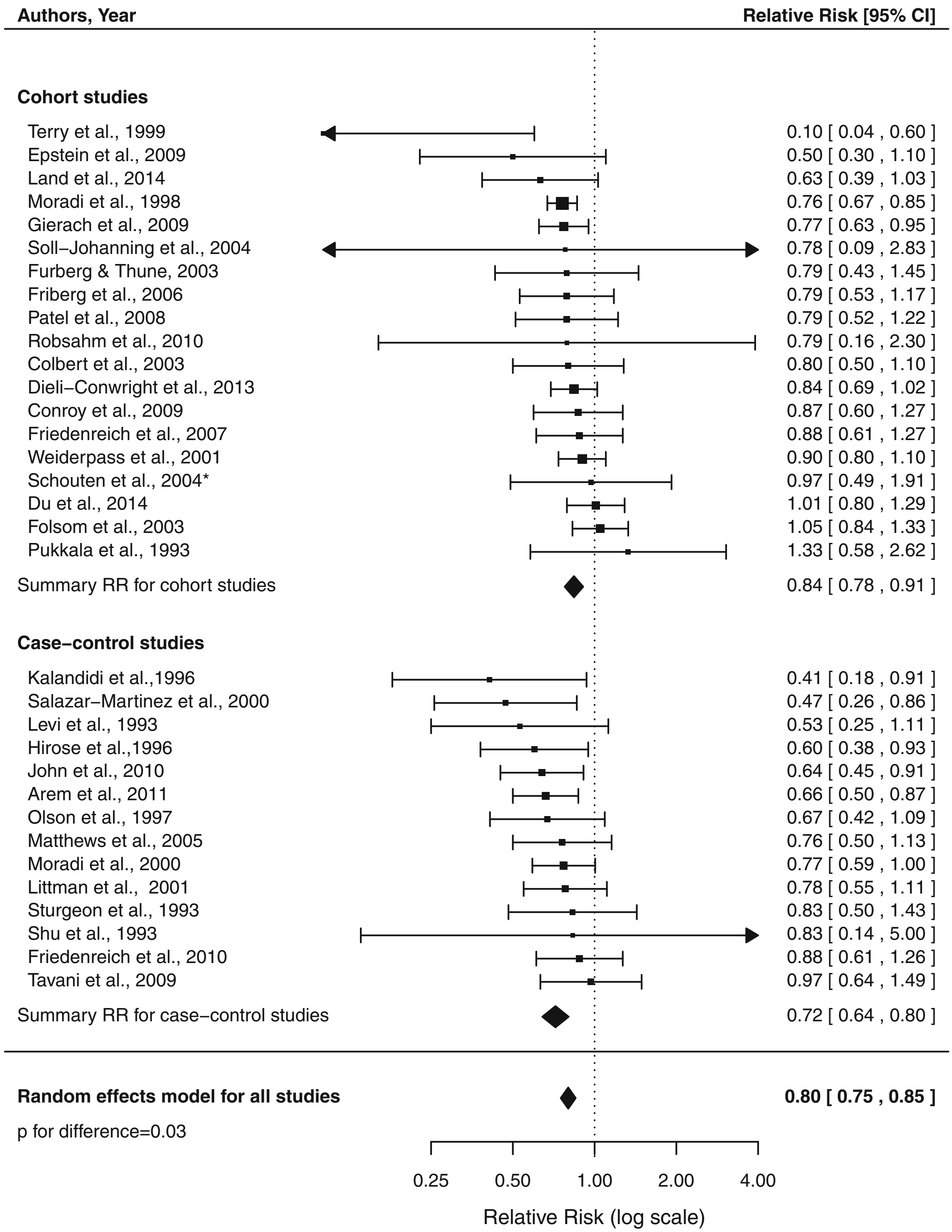


**Fig. 1** Forest plot corresponding to the random effects meta-analysis summarizing the relation of physical activity and risk of endometrial cancer across case–control studies and cohort studies; *case–cohort study; *RR* relative risk; *CI* confidence interval

intensity activity. As shown in Fig. 3, the pooled risk estimates for the associations between high versus low levels of light intensity, moderate to vigorous intensity, and vigorous intensity activity were 0.65 (95 % CI 0.49–0.86), 0.83 (95 % CI 0.71–0.96), and 0.80 (95 % CI 0.72–0.90), respectively ($P_{difference} = 0.35$).

We next examined whether the association between physical activity and endometrial cancer differed across time

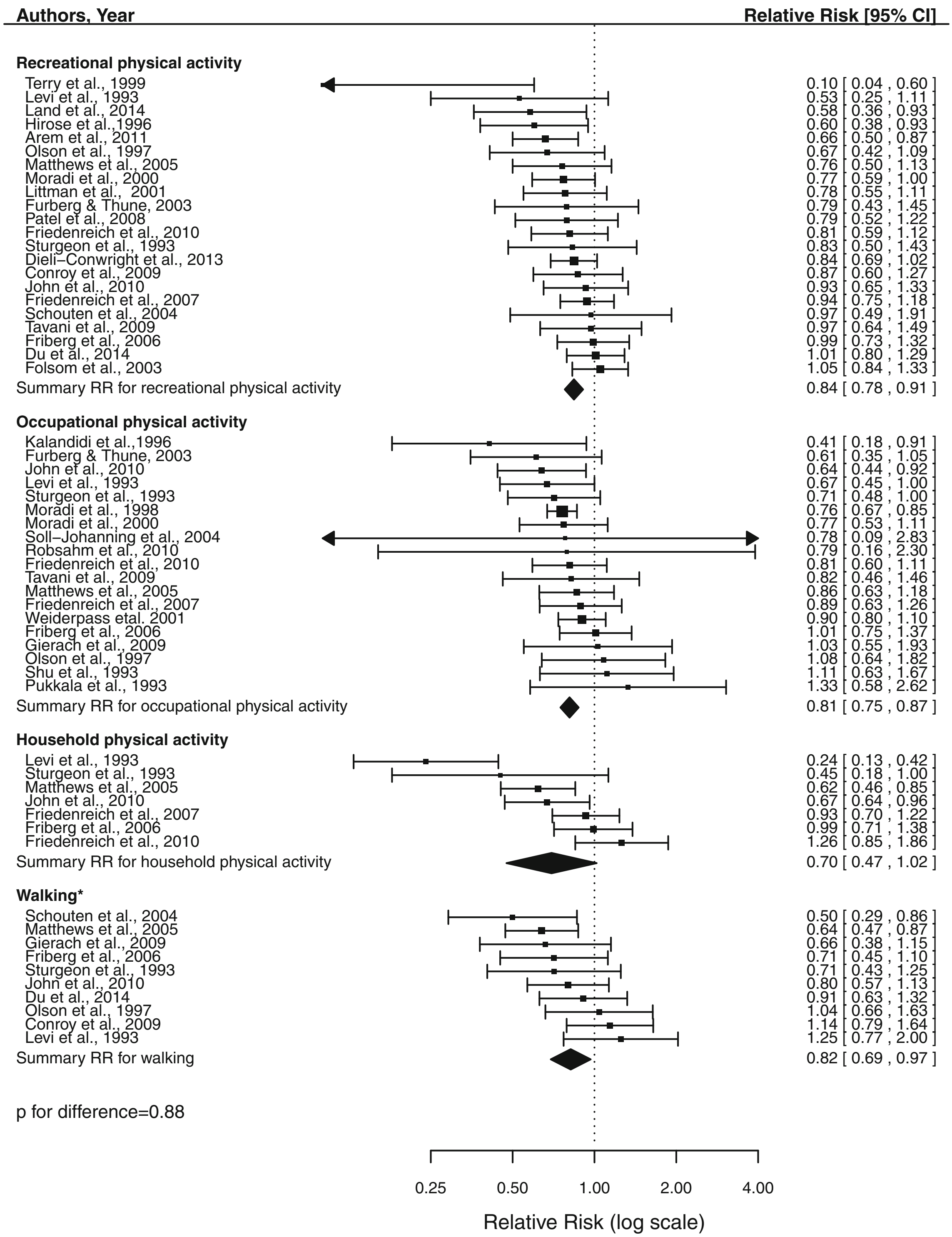


**Fig. 2** Forest plot corresponding to the random effects meta-analysis summarizing the relation of physical activity and risk of endometrial cancer across different activity domains; *Summary effect estimate based on studies related to walking, including walking/biking for transportation, walking for recreation, and unspecified walking; *RR* relative risk; *CI* confidence interval

periods in life. Random effect models yielded summary RRs of 0.94 (95 % CI 0.82–1.08), 0.77 (95 % CI 0.58–1.01), and 0.69 (95 % CI 0.37–1.28) for high versus low physical activity performed during childhood/adolescence, young adulthood/midlife, and older age, respectively ($P_{difference} = 0.51$, Table 2).

We noted a statistically significant inverse relation between physical activity and endometrial cancer in

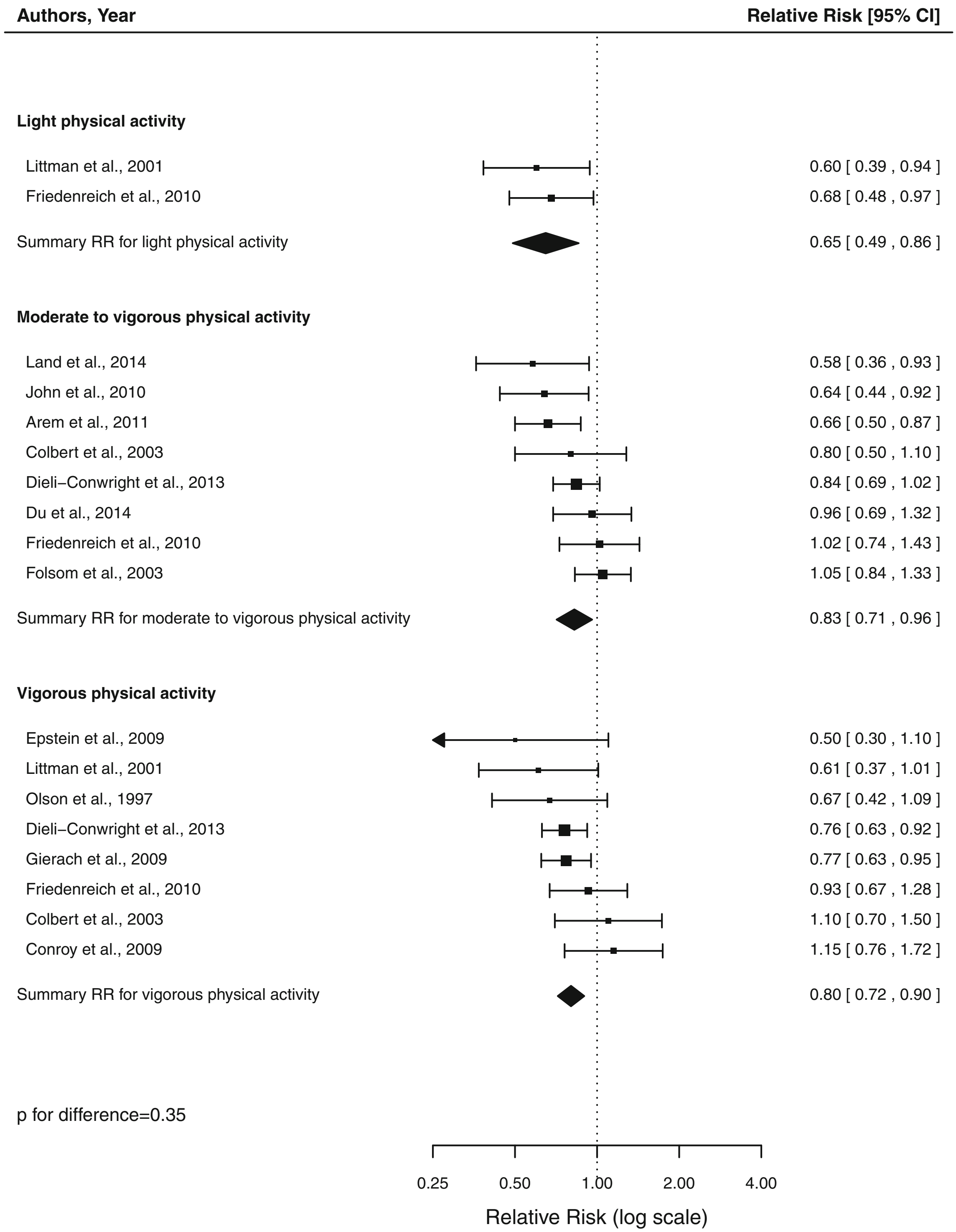


**Fig. 3** Forest plot corresponding to the random effects meta-analysis summarizing the relation of physical activity and risk of endometrial cancer across different activity intensities; *RR* relative risk; *CI* confidence interval

postmenopausal women (RR 0.81; 95 % CI 0.67–0.97), whereas the relation was statistically non-significant in premenopausal women (RR 0.74; 95 % CI 0.49–1.13), although the difference according to menopausal status was not statistically significant ($P_{difference} = 0.78$).

Seven studies provided risk estimates of physical activity in relation to endometrial cancer risk according to standard BMI categories. High versus low physical activity was unrelated to endometrial cancer in women with a BMI $< 25$ kg/m$^2$ (RR 0.97; 95 % CI 0.84–1.13), whereas it

**Table 2** Summary risk estimates from random effects models of physical activity in relation to endometrial cancer, stratified by selected potential effect modifying factors

| Stratification criterion | Number of included RRs | RR (95 % CI) (high vs. low physical activity) | $I^2$ (%) | $P_{difference}$* |
|---|---|---|---|---|
| Geographic location | | | | |
| North America | 16 | 0.81 [0.74, 0.89] | 19 | |
| Europe | 13 | 0.80 [0.73, 0.87] | 0 | |
| Asia | 3 | 0.69 [0.51, 0.93] | 0 | |
| South America | 1 | 0.47 [0.26, 0.86] | – | 0.26 |
| Number of study participants | | | | |
| <3500 | 15 | 0.73 [0.65, 0.83] | 0 | |
| ≥3500 | 18 | 0.82 [0.76, 0.89] | 10 | 0.13 |
| Number of cases | | | | |
| <300 | 17 | 0.70 [0.61, 0.81] | 0 | |
| ≥300 | 16 | 0.82 [0.77, 0.88] | 15 | 0.06 |
| Study quality score | | | | |
| NOS < 6 | 13 | 0.78 [0.72, 0.85] | 0 | |
| NOS ≥ 6 | 20 | 0.81 [0.74, 0.89] | 13 | 0.60 |
| Adjustment for adiposity | | | | |
| Adjusted for adiposity | 24 | 0.79 [0.73, 0.85] | 0 | |
| Not adjusted for adiposity | 9 | 0.83 [0.72, 0.97] | 35 | 0.39 |
| Adjustment for parity | | | | |
| Adjusted for parity | 24 | 0.79 [0.73, 0.86] | 2 | |
| Not adjusted for parity | 9 | 0.82 [0.71, 0.94] | 30 | 0.63 |
| Adjustment for OC use | | | | |
| Adjusted for OC use | 14 | 0.77 [0.70, 0.86] | 13 | |
| Not adjusted for OC use | 19 | 0.82 [0.75, 0.89] | 7 | 0.46 |
| Adjustment for HRT | | | | |
| Adjusted for HRT | 14 | 0.80 [0.72, 0.88] | 0 | |
| Not adjusted for HRT | 19 | 0.80 [0.73, 0.88] | 16 | 0.85 |
| Time period in life[a] | | | | |
| Childhood/adolescence (birth to 19 years) | 7 | 0.94 [0.82, 1.08] | 26 | |
| Young adulthood/midlife (19 to 49 years)[b] | 7 | 0.77 [0.58, 1.01] | 65 | |
| Older age (50 years or older) | 6 | 0.69 [0.37, 1.28] | 84 | 0.51 |
| Menopausal status[a] | | | | |
| Premenopausal | 4 | 0.74 [0.49, 1.13] | 0 | |
| Postmenopausal | 7 | 0.81 [0.67, 0.97] | 41 | 0.78 |

*RR* relative risk, *CI* confidence interval, *NOS* Newcastle-Ottawa scale, *OC* oral contraceptive, *HRT* hormone replacement therapy

* The $P_{difference}$ values were calculated using meta-regression comparing the model including the stratification variable as explanatory variable with the null model without any explanatory variables

[a] The number of RRs does not equal the total number of RRs because only studies that provided RRs according to this factor were considered

[b] One study was included that assessed physical activity during 18–30 years of age

was inversely associated with endometrial cancer in women with a BMI $\geq$ 25 kg/m$^2$ (RR 0.69; 95 % CI 0.52–0.91; $P_{difference} = 0.07$) (Fig. 4). To explore whether adiposity mediates the association between physical activity and endometrial cancer risk, we compared studies that adjusted for adiposity with studies that did not adjust for adiposity. We observed no difference in summary risk estimates according to adjustment for adiposity ($P_{difference} = 0.39$).

Other potential effect modifying factors had no impact on the association between physical activity and

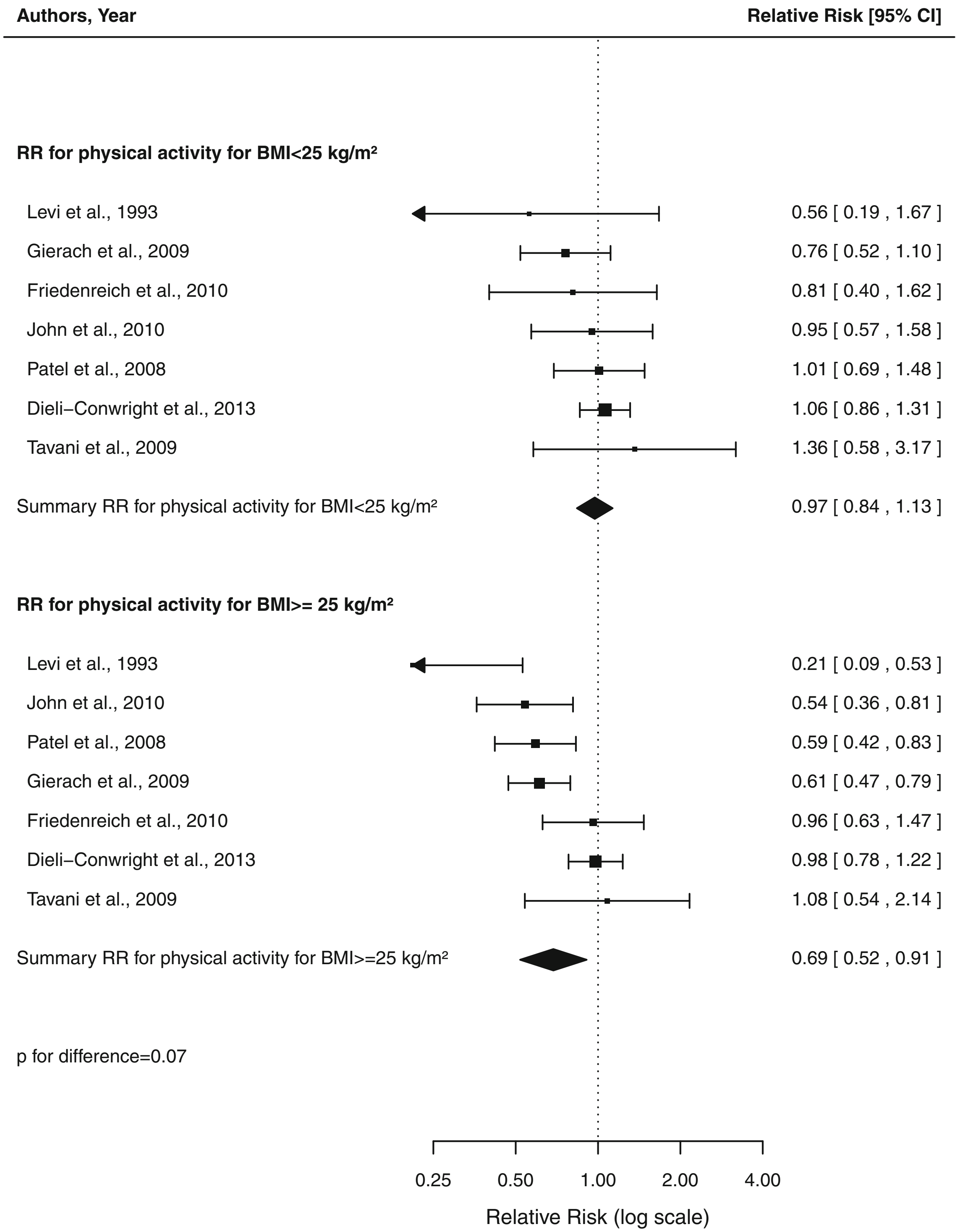


**Fig. 4** Summary risk estimates from random effects models of physical activity in relation to endometrial cancer, stratified by BMI; *BMI* body mass index, *RR* relative risk; *CI* confidence interval

endometrial cancer, including geographic location, number of study participants, number of cases, study quality, and adjustments for parity, oral contraceptive use, or hormone replacement therapy (all $P_{difference} > 0.05$, Table 2).

## Discussion

The present meta-analysis revealed a 20 % reduction in risk of endometrial cancer with high versus low levels of physical activity. The apparent beneficial effect of physical activity on endometrial cancer was statistically significant for recreational activity, occupational activity, and walking/biking for transportation. It was also statistically significant for different physical activity intensities, including activities of light, moderate to vigorous, and vigorous intensities. Taken together, these findings suggest that a broad range of physical activity participation protects against endometrial cancer.

A notable finding of our meta-analysis is that even physical activity of light to moderate intensity, such as walking/biking for transportation, showed an apparent beneficial effect on endometrial cancer risk. By comparison, walking during recreation and walking without further specification was unrelated to endometrial cancer. Walking represents an important physical activity domain as it comprises light physical activity, which contributes to a substantial amount of women's total daily activity [12–14]. It can be easily implemented in the daily routines and requires no specific facilities. One reason for the difference in associations between walking for transportation, walking for recreation, and unspecified walking is potential imprecision in measuring recreational or unspecified walking, whereas participants may be able to more accurately recall walking for transportation specifically. Moreover, three out of four studies on walking for transportation combined walking and biking, the latter of which may consist of more intense or more regular physical activity, leading to a more pronounced inverse association. In contrast, three out of four studies on recreational walking combined walking and hiking, the latter of which may comprise irregular activity and include interruptions in physical activity and breaks. Because overall walking may consist of walking for transportation, recreational walking, and short bouts of walking in the household or at the workplace, future studies should be designed to gather more precise information about the specific walking domain to uncover potential beneficial effects of walking on endometrial cancer risk.

We observed inverse relations between of physical activity and endometrial cancer risk in both pre- and postmenopausal women, although the association did not reach statistical significance in premenopausal women. Physical activity may reduce endometrial cancer risk by decreasing estrogens after menopause directly or indirectly through reducing peripheral adipose tissue [71, 72]. In postmenopausal women, excess estrogen is the main determinant of endometrial cancer because ovarian production of both estrogen and progesterone ceases and estrogens are mainly produced by conversion from androgens in the adipose tissue [73, 74].

In premenopausal women, obesity is associated with conditions that are related to increased endometrial cancer risk, including chronic anovulation, reduced luteal phase progesterone levels, irregular menstrual periods, early menarche, and delayed menopause [8].

We noted a statistically significant inverse association between physical activity and endometrial cancer in overweight/obese women, whereas the relation was null in normal weight women. One likely explanation for a more beneficial effect of physical activity in overweight/obese than normal weight women is that physical activity counterbalances unfavorable effects of obesity on endometrial cancer risk, such as elevated estradiol levels [75] and lower SHBG concentrations [76, 77]. Likewise, physical activity has been shown to improve insulin sensitivity [78, 79], alter the insulin-like growth factor (IGF) axis [80] reduce pro-inflammatory mediators [81, 82], and increase anti-inflammatory mediators [7], conditions that show greater imbalance in overweight and obese individuals than in normal weight persons [83–86] and impact endometrial tumor development [7]. Another possibility is greater residual confounding by BMI in the overweight/obese group than the normal weight group.

It appears worth mentioning that the most studies included in the meta-analysis herein used BMI as a measure of adiposity, which is an imperfect measure of adiposity because it also accounts for lean body mass. Future studies should consider using measures that differentiate between fat mass and lean mass, such as dual energy x-ray absorptiometry (DEXA) or magnetic resonance imaging (MRI) to better clarify whether obesity modifies the physical activity and endometrial cancer relation.

A major strength of our study is that it represents the most comprehensive meta-analysis of physical activity in relation to endometrial cancer risk to date. Our large sample size provided substantial statistical power and permitted extensive sub-analyses, including stratification and meta-regression to explore potential effect modifying factors. Particular attention was paid to examining whether physical activity protects against endometrial cancer across multiple activity domains, intensities, and time periods in life. Moreover, we employed a study quality score that evaluated potential selection bias, misclassification, and confounding. Reassuringly, we observed no variation in risk estimates between high and low quality studies. We also conducted a broad set of sensitivity analyses to confirm the robustness of our results.

One possible shortcoming of our meta-analysis is that we were unable to differentiate between endometrial tumor subtypes because such data were unavailable in the underlying studies. However, one study observed no difference in the relations of physical activity when restricting the endometrial cancer case definition to participants with type I endometrial carcinomas [57]. A further potential limitation is that a determination of the precise nature of the association between physical activity and endometrial cancer may have been hampered by the heterogeneous measures of physical activity and associated misclassification of the exposure across studies. However, we conducted an additional analysis by summarizing data comparing high versus low categories of MET-hours of physical activity; results were similar to our main findings. Our analysis relating increasing MET-hours of physical activity to endometrial cancer risk yielded no clear pattern but the summary risk estimates from that analysis were based on only four studies.

Four previous studies summarized the relations of physical activity to endometrial cancer and observed 18–30 % reductions in endometrial cancer risk with high versus low physical activity levels [8–11]. Our meta-analysis differs from those previous studies [8–11] in a number of important aspects. First, our analysis included 10,022 additional cases compared with the most recent meta-analysis [9]. Second, our study is the first meta-analysis to examine walking in relation to endometrial cancer risk. Third, we provided summary risk estimates for physical activity intensity in relation to endometrial cancer. Fourth, we meta-analyzed the relation of physical activity to endometrial cancer risk across different time periods in life. Finally, we quantified the relation between physical activity and endometrial cancer according to level of BMI.

In summary, our meta-analysis shows a 20 % decrease in risk of endometrial cancer with high versus low levels of physical activity. Reductions in endometrial cancer risk were observed for a broad range of activity domains, including recreational physical activity, occupational physical activity, and walking/biking for transportation, and for different intensities, including light, moderate to vigorous, and vigorous activities. Particular protection from endometrial cancer through physical activity participation was found for women who are overweight or obese, who carry an elevated risk for developing endometrial cancer. Future epidemiologic studies should include physical activity assessments designed to discern which specific durations and frequencies of physical activity are most relevant for protection against endometrial cancer.

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**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr/Default.aspx. Accessed 12 Apr 2014.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;. doi:10.3322/caac.21208.
3. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22(Suppl 6):vi35–9. doi:10.1093/annonc/mdr374.
4. Yang HP, Wentzensen N, Trabert B, Gierach GL, Felix AS, Gunter MJ, et al. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP diet and health study. Am J Epidemiol. 2013;177(2):142–51. doi:10.1093/aje/kws200.
5. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31(20):2607–18. doi:10.1200/JCO.2012.48.2596.
6. Cust AE. Physical activity and gynecologic cancer prevention. Recent Results Cancer Res. 2011;186:159–85. doi:10.1007/978-3-642-04231-7_7.
7. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008;8(3):205–11. doi:10.1038/nrc2325.
8. Cust AE, Armstrong BK, Friedenreich CM, Slimani N, Bauman A. Physical activity and endometrial cancer risk: a review of the current evidence, biologic mechanisms and the quality of physical activity assessment methods. Cancer Causes Control. 2007;18(3):243–58. doi:10.1007/s10552-006-0094-7.
9. 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. 2013;. doi:10.1002/ijc.28687.
10. Moore SC, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. Br J Cancer. 2010;103(7):933–8. doi:10.1038/sj.bjc.6605902.
11. Voskuil DW, Monninkhof EM, Elias SG, Vlems FA, van Leeuwen FE. Task force physical activity and cancer. physical activity and endometrial cancer risk, a systematic review of current evidence. Cancer Epidemiol Biomark Prev. 2007;16(4):639–48. doi:10.1158/1055-9965.EPI-06-0742.
12. Martin KR, Koster A, Murphy RA, Van Domelen DR, Hung MY, Brychta RJ, et al. Changes in daily activity patterns with age in U.S. men and women: national health and nutrition examination survey 2003–04 and 2005–06. J Am Geriatr Soc. 2014;62(7):1263–71. doi:10.1111/jgs.12893.
13. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012;380(9838):247–57. doi:10.1016/S0140-6736(12)60646-1.
14. Tudor-Locke C, Johnson WD, Katzmarzyk PT. Frequently reported activities by intensity for U.S. adults: the American time use survey. Am J Prev Med. 2010;39(4):e13–20. doi:10.1016/j.amepre.2010.05.017.
15. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009;114(1):121–7. doi:10.1016/j.ygyno.2009.03.039.
16. Zhang Y, Liu H, Yang S, Zhang J, Qian L, Chen X. Overweight, obesity and endometrial cancer risk: results from a systematic review and meta-analysis. Int J Biol Markers. 2014;29(1):21–9. doi:10.5301/jbm.5000047.
17. Ismail I, Keating SE, Baker MK, Johnson NA. A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. Obes Rev. 2012;13(1):68–91. doi:10.1111/j.1467-789X.2011.00931.x.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the

PRISMA statement. BMJ. 2009;339:b2535. doi:10.1136/bmj.b2535.
19. Wells SB OCD, Peterson J et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 28 Oct 2013.
20. 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(8):1877–82. doi:10.1002/ijc.23716.
21. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. 2011 Compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575–81. doi:10.1249/MSS.0b013e31821ece12.
22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58. doi:10.1002/sim.1186.
23. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629–34.
24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4): 1088–101.
25. 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 Biomark Prev. 2005;14(4):779–85. doi:10.1158/1055-9965.EPI-04-0665.
26. John EM, Koo J, Horn-Ross PL. Lifetime physical activity and risk of endometrial cancer. Cancer Epidemiol Biomark Prev. 2010;19(5):1276–83. doi:10.1158/1055-9965.EPI-09-1316.
27. 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(9):2139–47. doi:10.1002/ijc.24059.
28. Friberg E, Mantzoros CS, Wolk A. Physical activity and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomark Prev. 2006;15(11):2136–40. doi:10.1158/1055-9965.EPI-06-0465.
29. 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(7):1107–15. doi:10.1007/s10552-009-9313-3.
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(11):2707–16. doi:10.1002/ijc.28599.
31. Sturgeon SR, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, et al. Past and present physical activity and endometrial cancer risk. Br J Cancer. 1993;68(3):584–9.
32. 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(21):1635–8. doi:10.1093/jnci/djh291.
33. Levi F, La Vecchia C, Negri E, Franceschi S. Selected physical activities and the risk of endometrial cancer. Br J Cancer. 1993;67(4):846–51.
34. 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(1):46–53.
35. Rota M, Bellocco R, Scotti L, Tramacere I, Jenab M, Corrao G, et al. Random-effects meta-regression models for studying non-linear dose-response relationship, with an application to alcohol and esophageal squamous cell carcinoma. Stat Med. 2010; 29(26):2679–87. doi:10.1002/sim.4041.
36. 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(6):559–67.
37. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1–48.
38. Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat Med. 2012;31(29):3821–39. doi:10.1002/Sim.5471.
39. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands cohort study. Int J Gynecol Cancer. 2006;16(Suppl 2):492. doi:10.1111/j.1525-1438.2006.00676.x.
40. Inoue-Choi M, Robien K, Mariani A, Cerhan JR, Anderson KE. Sugar-sweetened beverage intake and the risk of type I and type II endometrial cancer among postmenopausal women. Cancer Epidemiol Biomark Prev. 2013;22(12):2384–94. doi:10.1158/1055-9965.EPI-13-0636.
41. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomark Prev. 2007;16(2):276–80. doi:10.1158/1055-9965.EPI-06-0751.
42. Schnohr P, Gronbaek M, Petersen L, Hein HO, Sorensen TI. Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women. Scand J Public Health. 2005;33(4):244–9. doi:10.1080/14034940510005752.
43. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer. 2010;126(2):490–9. doi:10.1002/ijc.24718.
44. Thomson CA, McCullough ML, Wertheim BC, Chlebowski RT, Martinez ME, Stefanick ML, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. Cancer Prev Res (Phila). 2014;7(1):42–53. doi:10.1158/1940-6207.CAPR-13-0258.
45. Bittoni MA, Fisher JL, Fowler JM, Maxwell GL, Paskett ED. Assessment of the effects of severe obesity and lifestyle risk factors on stage of endometrial cancer. Cancer Epidemiol Biomark Prev. 2013;22(1):76–81. doi:10.1158/1055-9965.EPI-12-0843.
46. Lucenteforte E, Bosetti C, Talamini R, Montella M, Zucchetto A, Pelucchi C, et al. Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. Br J Cancer. 2007;97(7):995–8. doi:10.1038/sj.bjc.6603933.
47. 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(22):5077–85.
48. Zheng W, Shu XO, McLaughlin JK, Chow WH, Gao YT, Blot WJ. Occupational physical activity and the incidence of cancer of the breast, corpus uteri, and ovary in Shanghai. Cancer. 1993;71(11):3620–4.
49. Dosemeci M, Hayes RB, Vetter R, Hoover RN, Tucker M, Engin K, et al. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. Cancer Causes Control. 1993;4(4):313–21.
50. Moradi T, Nyren O, Bergstrom R, Gridley G, Linet M, Wolk A, et al. Risk for endometrial cancer in relation to occupational physical activity: a nationwide cohort study in Sweden. Int J Cancer. 1998;76(5):665–70.
51. Terry P, Baron JA, Weiderpass E, Yuen J, Lichtenstein P, Nyren O. Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. Int J Cancer. 1999;82(1):38–42.
52. Folsom AR, Demissie Z, Harnack L. Iowa women's health S. Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. Nutr Cancer. 2003;46(2):119–24. doi:10.1207/S15327914NC4602_03.

53. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer. 2003;104(6):669–76. doi:10.1002/ijc.10974.
54. 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(2):347–55. doi:10.1002/ijc.22676.
55. Epstein E, Lindqvist PG, Geppert B, Olsson H. A population-based cohort study on sun habits and endometrial cancer. Br J Cancer. 2009;101(3):537–40. doi:10.1038/sj.bjc.6605149.
56. 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(10):1711–9. doi:10.1007/s10552-010-9600-z.
57. 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(3):761–8. doi:10.1038/bjc.2013.61.
58. Land SR, Liu Q, Wickerham DL, Costantino JP, Ganz PA. Cigarette smoking, physical activity, and alcohol consumption as predictors of cancer incidence among women at high risk of breast cancer in the NSABP P-1 trial. Cancer Epidemiol Biomark Prev. 2014;23(5):823–32. doi:10.1158/1055-9965.EPI-13-1105-T.
59. Pukkala E, Poskiparta M, Apter D, Vihko V. Life-long physical activity and cancer risk among Finnish female teachers. Eur J Cancer Prev. 1993;2(5):369–76.
60. Weiderpass E, Pukkala E, Vasama-Neuvonen K, Kauppinen T, Vainio H, Paakkulainen H, et al. Occupational exposures and cancers of the endometrium and cervix uteri in Finland. Am J Ind Med. 2001;39(6):572–80.
61. Soll-Johanning H, Bach E. Occupational exposure to air pollution and cancer risk among Danish urban mail carriers. Int Arch Occup Environ Health. 2004;77(5):351–6. doi:10.1007/s00420-004-0510-9.
62. Shu XO, Hatch MC, Zheng W, Gao YT, Brinton LA. Physical activity and risk of endometrial cancer. Epidemiology. 1993;4(4):342–9.
63. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. Jpn J Cancer Res. 1996;87(9):1001–9.
64. Kalandidi A, Tzonou A, Lipworth L, Gamatsi I, Filippa D, Trichopoulos D. A case–control study of endometrial cancer in relation to reproductive, somatometric, and life-style variables. Oncology. 1996;53(5):354–9.
65. Moradi T, Weiderpass E, Signorello LB, Persson I, Nyren O, Adami HO. Physical activity and postmenopausal endometrial cancer risk (Sweden). Cancer Causes Control. 2000;11(9):829–37.
66. 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(8):707–11.
67. Littman AJ, Voigt LF, Beresford SA, Weiss NS. Recreational physical activity and endometrial cancer risk. Am J Epidemiol. 2001;154(10):924–33.
68. Tavani A, Bravi F, Dal Maso L, Zucchetto A, Bosetti C, Pelucchi C, et al. Physical activity and risk of endometrial cancer: an Italian case–control study. Eur J Cancer Prev. 2009;18(4):303–6. doi:10.1097/CEJ.0b013e32831bc3c4.
69. 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(7):1105–16. doi:10.1007/s10552-010-9538-1.
70. 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(2):219–26. doi:10.1007/s10552-010-9689-0.
71. Rinaldi S, Kaaks R, Friedenreich CM, Key TJ, Travis R, Biessy C, et al. Physical activity, sex steroid, and growth factor concentrations in pre- and post-menopausal women: a cross-sectional study within the EPIC cohort. Cancer Causes Control. 2014;25(1):111–24. doi:10.1007/s10552-013-0314-x.
72. McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (Silver Spring). 2006;14(9):1662–77. doi:10.1038/oby.2006.191.
73. Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. Proc Nutr Soc. 2001;60(1):81–9.
74. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomark Prev. 2002;11(12):1531–43.
75. Freeman EW, Sammel MD, Lin H, Gracia CR. Obesity and reproductive hormone levels in the transition to menopause. Menopause. 2010;17(4):718–26. doi:10.1097/gme.0b013e3181cec85d.
76. Cunningham SK, Loughlin T, Culliton M, McKenna TJ. The relationship between sex steroids and sex-hormone-binding globulin in plasma in physiological and pathological conditions. Ann Clin Biochem. 1985;22(Pt 5):489–97.
77. Kopelman PG, Pilkington TR, White N, Jeffcoate SL. Abnormal sex steroid secretion and binding in massively obese women. Clin Endocrinol (Oxf). 1980;12(4):363–9.
78. Mann S, Beedie C, Balducci S, Zanuso S, Allgrove J, Bertiato F, et al. Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence. Diabetes Metab Res Rev. 2014;30(4):257–68. doi:10.1002/dmrr.2488.
79. Dwyer T, Ponsonby AL, Ukoumunne OC, Pezic A, Venn A, Dunstan D, et al. Association of change in daily step count over five years with insulin sensitivity and adiposity: population based cohort study. BMJ. 2011;342:c7249. doi:10.1136/bmj.c7249.
80. Gatti R, De Palo EF, Antonelli G, Spinella P. IGF-I/IGFBP system: metabolism outline and physical exercise. J Endocrinol Invest. 2012;35(7):699–707. doi:10.3275/8456.
81. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol. 2005;78(4):819–35. doi:10.1189/jlb.0505247.
82. Hamer M, Sabia S, Batty GD, Shipley MJ, Tabak AG, Singh-Manoux A, et al. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. Circulation. 2012;126(8):928–33. doi:10.1161/CIRCULATIONAHA.112.103879.
83. Simpson KA, Singh MA. Effects of exercise on adiponectin: a systematic review. Obesity (Silver Spring). 2008;16(2):241–56. doi:10.1038/oby.2007.53.
84. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15(4):6184–223. doi:10.3390/ijms15046184.
85. Kreitschmann-Andermahr I, Suarez P, Jennings R, Evers N, Brabant G. GH/IGF-I regulation in obesity–mechanisms and practical consequences in children and adults. Horm Res Paediatr. 2010;73(3):153–60. doi:10.1159/000284355.
86. Sims EA, Danforth E Jr, Horton ES, Bray GA, Glennon JA, Salans LB. Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res. 1973;29:457–96.