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The association between domain-specific sedentary behavior and endometrial cancer: A systematic review and meta-analysis

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Study Importance Questions

What is already known about this subject?

1. High levels of sedentary behavior have detrimental effects on health.
2. Previous studies reported inconsistent association between sedentary behavior and endometrial cancer.
3. There is supporting evidence for the differences in health effects of different domains of sedentary behavior.
4. Potential interplay between lifestyle factors, such as obesity, physical activity and sedentary behavior may modify the association between sedentary behaviour and health outcomes.

What are the new findings?

1. 55% increased risk of endometrial cancer was observed among individuals with higher levels of total sedentary behavior.
2. The results added to the existing evidence by showing a possible domain-specific effect, particularly for occupational domain, and a borderline significant association within leisure-time domain.
3. Subgroup-analyses suggested greater effect size in studies adjusting for physical activity; yet adjustment for obesity indices may lead to a less pronounced risk estimate.

How might your results change the direction of research or the focus of clinical practice?

In this review, we quantitatively assess the associations of domain-specific and total sedentary behavior with risk of endometrial cancer, with additional attention paid to potential differences in adjustment strategy for BMI and physical activity. Our findings highlight the importance of evaluating the interactive effects of sedentary behavior and other lifestyle factors (physical activity, obesity) while analyzing the association between sedentary behavior and endometrial cancer.

Abstract

Methods A Systematic review with meta-analysis was conducted by searching PubMed, Embase and MEDLINE databases up to 31 March 2021, supplemented by grey literature searches. The eligibility criteria was observational human studies evaluating the association between sedentary behavior and endometrial cancer.

Results Sixteen studies were included in the systematic review. Fourteen studies involving 882686 participants were included in the meta-analysis. The pooled RRs for high versus low level of sedentary behavior was 1.22 (95% CI 1.09-1.37, I^2=13.4%, n=10) for occupational domain, 1.34 (95% CI 0.98-1.83, I^2=53.7%, n=6) for leisure-time domain, and 1.55 (95% CI 1.27-1.89, I^2=0%, n=2) for total sedentary behavior. Greater pooled RRs were observed among studies with adjustment for physical activity and without adjustment for BMI.

Conclusions Higher levels of sedentary behavior, total and occupational sedentary behavior in particular, increases the risk of endometrial cancer. Future studies are needed to investigate the interactive effects of physical activity, adiposity and sedentary time on endometrial cancer.

Introduction *(Manuscript word count: 4400)*

According to the updated global cancer burden estimates from *Global Cancer Statistics 2020*,[1] endometrial cancer ranks the sixth most common cancer in women worldwide, and the most common gynecologic cancer in several developed regions, including the North America, Eastern and Northern Europe. A worrying trend is that, since the late 1990s, the incidence of endometrial cancer has rapidly increased in several developing countries during urbanization, including some Asian countries (Japan, Singapore, China, the Philippines), and South Africa.[2] It is suggested that this phenomenon may be explained, at least partly, by changing environmental and lifestyle risk factors in these regions, such as the epidemic of obesity, lack of physical activity, and long-time sitting. Although obesity is a known risk factor for endometrial cancer, the association between sedentary behavior and endometrial cancer remains largely unclear. Sedentary behavior includes sitting, reclining or lying behavior characterized by low energy expenditure.[3] During the past decades, technological innovation has influenced how people work and spend leisure-time, and has led to inevitably prolonged sitting time, particularly for desk-based office work and screen-based recreation. According to *the World Health Organization (WHO) Guidelines on Physical Activity and Sedentary behavior (2020)*, long sedentary time is associated with various deleterious health outcomes, including all-cause mortality, cardiovascular diseases, obesity, and more recently total cancer morbidity.[3]

Two previous meta-analyses investigating the association between sedentary behavior and multiple cancer risk,[4 5] both published in 2014, reported a 28% to 36% increased risk of endometrial cancer among individuals with higher levels of sedentary behavior by summarizing three and eight studies, respectively. During years after, a number of studies have further been conducted. Recently, two prospective studies,[6 7]

involving 951 cases among 28692 participants, have reported a insignificant association between leisure-time sedentariness and a significant association between occupational sedentary behavior and endometrial cancer risk. Given inconsistent results reported, an up-to-date review of current evidence is in urge need to clarify the association between sedentary behavior and endometrial cancer risk.

No distinction in domains of sedentary behavior is a likely source of the discrepancy in previous findings. The *WHO Guidelines 2020* has operationalized the definition of sedentary behavior to further include self-reported sitting that can be assessed in various domains (including leisure-time and occupational domain) and total sedentary behavior. Meanwhile, the association with adverse health outcomes may differ in certain domains of sedentary behavior.[3] It is increasingly recognized that confounding factors may vary greatly across domains of sedentary behavior, and contribute to varied associations with health-related outcomes.[8] For example, while occupational sedentary behavior is related to education and socioeconomic variables, leisure-time sedentary behavior is likely linked to lifestyle factors such as diet and obesity.[9] Moreover, these two domains are often inversely correlated to physical activity. However, current evidence has been derived mostly from studies that have broadly categorized sedentary behavior according to the level of sitting time involved.[5] [10] Domain-specific analyses, taking account of variability in study characteristics, may help to further clarify the investigated association and to refine the prevention strategy of endometrial cancer.

Besides, the complex interplay within lifestyle factors, including obesity, physical activity and sedentary behavior, needs to be taken into consideration in analysis. Obesity is a known risk factor for endometrial cancer, with a clear dose-response relationship (the higher the body mass index, the greater the risk), detailed documented

by the International Agency for Research on Cancer (IARC) working group.[11] Given that prolonged sitting is likely to be related with high BMI, obesity thus may be a potential mediator linking sedentary behavior to cancer incidence. Under this circumstance, studies adjusting for BMI as a confounding factor may attenuate the true effects of sedentary behavior when evaluating its impacts on endometrial cancer. A few studies have probably recognized this issue and provided results without and with additional adjustment for BMI.[12 13 14 15] In addition, although less evidence presented, similar concerns have been raised with regard to physical activity, which has potential protective effect on cancer risk.

In this systematic review and meta-analysis, we aimed to quantitatively assess the associations of domain-specific (occupational and leisure-time) and total sedentary behavior with risk of endometrial cancer, with additional attention paid to potential difference of the findings related to different adjustment strategy for BMI and physical activity.

Methods

We performed this systematic review and meta-analysis in accordance with the 2020 guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] and guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as well.[17] Reported items in this systematic review and meta-analysis strictly followed the checklist of PRISMA 2020 and MOOSE (Table S1, S2). The full review protocol was registered with International prospective register of systematic reviews (PROSPERO) under the registration number CRD 42021246283.

Search strategy and selection criteria

We conducted a comprehensive literature search of the electronic databases, including

Embase, MEDLINE and PubMed. The search was updated on 31 March 2021, and publication language was limited to English. The search combined MeSH heading with text search using varied terms related to "sedentary behavior" and "endometrial cancer". Detailed search terms and strategy used are listed in the Supplemental Text. Terms associated with physical inactivity and physical activity were also searched since some sedentary behavior studies were conducted in the name of physical activity. In addition, we screened and manually checked references lists from selected articles and relevant reviews to identify other potentially eligible studies.

The inclusion criteria for the studies included in the systematic review listed as follows: (1) observational human study that published in English; (2) evaluated the association between sedentary behavior (total sitting time, leisure-time sedentariness including sitting, television or screen viewing, and occupational sedentary behavior) and incidence of endometrial cancer. Apart from all criteria for systematic review, the studies further included in the meta-analysis should also meet the following criteria: report a relative risk (RR), odds ratio (OR), hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) for highest versus lowest level of sedentary behavior, or provide sufficient data to calculate them.

Studies were excluded if they were published as conference abstracts or papers, letters and short surveys. We also excluded studies for physical activity that used terms "sedentary" or "sitting" to represent the lowest or reference level of physical activity categories.

Data extraction and quality assessment

Two authors (Lei Yuan and JingYi Ni) independently performed the literature search and reviewed potential studies in compliance with the selection criteria. The

disagreements were resolved through discussion. The authors were contacted by e-mail for full text or additional information when needed. Extracted information from each study included: (a) name of the first author and publication year; (b) study design; (c) study area; (d) enrollment period for cohort study, or study period for case-control study; (e) age at baseline; (f) follow-up length for cohort study; (g) study population; (h) sample size; (i) case number; (j) sedentary behavior type and its assessment; (k) diagnostic criteria of EC, and if available, its specific cancer classification; (l) results and if possible, reported risk estimates and their 95% CI; (m) adjusted covariates, if possible, particular attention to adjustment for body mass index (BMI), and physical activity.

In the main analysis, we prioritized risk estimates that were adjusted for physical activity, and unadjusted for BMI in studies with a separate step of BMI adjustment, or other adiposity-related factors when available, due to potential intermediate role of obesity. If study populations overlapped between included studies, we selected the article that contained the most comprehensive data.[18 19]

Quality assessment of the studies included in the meta-analysis was assessed based on the validated Newcastle-Ottawa Scale (NOS) for observational studies,[20] where each study was evaluated based on three categories: participant selection (four items, one star for each item); comparability of study groups (one item, up to two stars); exposure or outcome assessment (three items, one star for each item). Thus, a study can be awarded up to a maximum of nine stars.[20] We used the comparability category of the NOS to judge whether the crucial confounders had been adjusted, that is, the study can be awarded one star for adjusting for age, two stars for also controlling for physical activity. The quality of the study was classified as poor ($\leq$ 4 stars), fair (4-6 stars), and good ($\geq$ 7 stars). We also extracted confounders adjusted by each study, and evaluated

whether the study had adequate adjustment for potential confounders, that is, adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity.[21]

Statistical analysis

Given underlying methodological heterogeneity across studies including study design, participants' characteristics, and adjusted confounders, random effects models were applied to summarize domain-specific (occupational and leisure-time), and total RRs and their 95% CIs for the highest level versus the lowest level of sedentary behavior, regardless of whether statistically significant heterogeneity was found. The natural logarithms of the study-specific RR and corresponding standard errors were calculated using the inverse variance approach. Employing random effects models, the RR of each study was weighted using random effects weights and was further combined to obtain an overall estimate. When studies reported subgroup-specific results such as estimates of different calendar periods, we fitted a fixed effects model to combine the separate results to obtain the overall estimates for the main analysis.[19] For studies not using the lowest category as the reference category of sedentary behavior,[6 7 13 22 23] we used the method by Hamling to recalculate the estimates through changing the lowest category as the reference category.[24] We used I^2 statistics to test for heterogeneity between included studies. I^2 values of more than 25%, 50%, 75% were deemed to indicate low, moderate and high level of significant heterogeneity, separately. Potential publication bias was assessed by inspection of funnel plots, and further evaluated using Egger's regression test as well as Begg's correlation test. Asymmetry in the funnel plots or *p*

value < 0.1 indicated publication bias.

Subgroup analyses were performed according to study design (cohort study, case-control study), study area (Asia, Europe and North America), sample size (≥ 5000, and < 5000), number of cases (≥ 500, and < 500), study quality (good, fair, poor), and adjustment for potential confounding factors (adequate, not adequate). In addition, sedentary behavior, obesity and physical activity are lifestyle factors that are complexly associated and interacted. As obesity potentially mediate the association between sedentary behavior and endometrial cancer risk, in which case the adjustment for BMI would over adjust the association, we conducted subgroup analyses stratified by whether BMI was adjusted.[21] Similarly, we also conducted subgroup analyses by whether adjusting for physical activity.

Associations with total sedentary behavior were reported in only two studies. Therefore, we also included all studies in the analysis to assess the effects of overall sedentary behavior. If a study reported results at a specific domain, we extracted the results as the nearest estimate for overall sedentariness. If a study reported results at multiple domains, we used fixed effects models to combine the separate results to obtain the overall estimates as the total level. Random-effects meta-regression analyses were then conducted to explore whether the estimates differed by main characteristics of the included study. The analyses were unavailable for domain-specific sedentary behavior analysis due to limited number of studies (n ≤ 10). The Tau-squared was used to evaluate between-study variance of each covariate.

We also performed sensitivity analyses to test the robustness of the results in the main analysis. We firstly conducted analyses by omitting one study at each time to recalculate the pooled results to ensure the stability of the results. Secondly, we fitted the trim-and-fill analysis to inspect the impact of publication bias correction on the

pooled outcomes. The statistical analyses were performed using Stata 12.0 software (Stata Corp, College Station, TX, USA). A two-tailed p value < 0.05 was deemed statistically significant.

Patient and Public Involvement

It's not applicable to our research since the data collected in this study is secondary data without any personal information and not transferable.

Results

Studies retrieved and characteristics

Our initial search identified 749 records. After screening and selection (Figure 1), sixteen studies were included in the systematic review of sedentary behavior and risk of endometrial cancer. The main characteristics of the included studies are shown in Table 1. Of these sixteen studies, six were from Europe,[6 13 18 19 23 25] five from Asia,[7 12 26 27 28] and five from North America.[14 15 22 29 30] Detailed data and characteristics of study participants, diagnostic criteria of the outcome, and the assessment of sedentary behavior is provided in Table S3, S4.

The meta-analysis included fourteen studies after excluding two studies, in which one failed to provide 95% CI for risk estimates[27] and the other one was based on less comprehensive data among overlapped study participants.[18] In total, 882686 participants from seven cohort studies and seven case-control studies were involved. In the meta-analysis, two studies (71680 participants, Table 1) investigated the association between total sedentary behavior and risk of endometrial cancer, ten studies (515163 participants) investigated the association with the assessment of occupational sedentary behavior and six studies (458178 participants) with the assessment of leisure-time sedentariness. Three studies (91984 participants) have adjusted for physical activity.

Nine studies (321757 participants) have adjusted for BMI in the multivariate model, and three studies (146746 participants) took a separate step for additional BMI adjustment. Based on the Newcastle-Ottawa quality assessment scale, seven studies were evaluated as having fair quality, and seven as having good quality. Detailed information on the NOS quality assessment of meta-analysed studies is provided in Table S5, S6. Details of confounders adjusted by each study are presented in Table S7.

Occupational sedentary behavior

Twelve studies have investigated impacts of sedentary behavior during work on endometrial cancer, and five of them reported significant association between occupational sedentary behavior and increased risk of endometrial cancer,[7 18 19 25 27] the rest did not observe similar significant effect.[12 13 22 23 26 28 29] Among these studies, the meta-analysis for occupational domain included ten eligible studies, involving 515163 participants and 5855 cases. The summary RR for high versus low occupational sedentary level was 1.22 (95% CI 1.09-1.37, I^2=13.4%, $P_{heterogeneity}$=0.32) (Figure 2). Consistent with the inspection of the funnel plot, the results of Begg's test (P=0.72) and Egger's test (P=0.59) suggested no publication bias (Figure 5).

The adverse effects of occupational sedentary behavior on endometrial cancer incidence persisted in nearly all subgroup analyses stratified by study design, study area, number of participants and cases, study quality, adjustment for confounders including BMI, and physical activity (Figure 2). The association between occupational sedentary behavior and endometrial cancer was stronger among studies that were cohort study ($RR_{summary}$=1.30, 95% CI 1.05-1.62, I^2=37.2%, $P_{heterogeneity}$=0.19), studies conducted in European areas ($RR_{summary}$=1.28, 95% CI 1.14-1.43, I^2=0.0%, $P_{heterogeneity}$=0.41), studies with large number of participants (≥ 5000; $RR_{summary}$=1.30, 95% CI 1.05-1.62,

I^2=37.2%, $P_{heterogeneity}$=0.19) or cases (≥ 500; $RR_{summary}$=1.25, 95% CI 1.10-1.42, I^2=16.7%, $P_{heterogeneity}$=0.31), and studies with good quality ($RR_{summary}$=1.25, 95% CI 1.01-1.56, I^2=35.4%, $P_{heterogeneity}$=0.19). There was moderate heterogeneity in the studies with adequate adjustment and with physical activity adjustment (adequate adjustment for confounders: I^2=50.3%, $P_{heterogeneity}$=0.13; adjustment for physical activity: I^2=57.0%, $P_{heterogeneity}$=0.10). Compared with studies without adequate adjustment or physical activity adjustment, the associations observed in these two groups were slightly attenuated, showing greater estimates and wider confidence intervals. There was only one study adjusting for BMI separately,[13] and no significant risk estimates were exhibited before and after adjustment (before adjustment: RR=1.03, 95% CI 0.76-1.39; after adjustment: RR=0.99, 95% CI 0.73-1.34).

The sensitivity analyses suggested that the association between occupational sedentary behavior and endometrial cancer risk did not change when recalculating the pooled estimates by omitting one study at a time (Table S8). After excluding the most influential research, the summarized RR ranged from 1.19 (95% CI 1.04-1.37) when excluding the study conducted by Moradi et al. to 1.27 (95% CI 1.15-1.40) when excluding the study by Matthews et al.[19 28]

Leisure-time sedentary behavior

Six prospective cohort studies (458178 participants, 2396 cases) have assessed the relation with endometrial cancer and time spent sitting outside of work, including watching television (TV), videos or computer, reading, and other sedentary activity. Three of these studies found significant associations between leisure-time sedentary behavior and risk of endometrial cancer,[13 14 15] and the rest indicated non-significant associations.[6 7 23] The pooled RR for high versus low level of leisure-time sedentary

behavior was 1.34 (95% CI 0.98-1.83, I^2=53.7%, P =0.06), with moderate and non-significant heterogeneity (Figure 3). However, these results seemed to be driven by a large study (253171 participants, 872 cases) that reported inconsistent results with other studies (RR=0.57, 95% CI 0.31-1.03).[6] After excluding this study, no potential heterogeneity remained in the analysis, and the summarized association between leisure-time sedentary behavior and endometrial cancer turned out to be significant ($RR_{summary}$=1.53, 95% CI 1.24-1.87, I^2=0.0%, $P_{heterogeneity}$=0.82). No evidence of publication bias was revealed according to visual inspection of the funnel plot, Begg's test (P=0.85), or Egger's test (P=0.78) (Figure 5).

In subgroup analyses, the significance of the associations across the stratified groups also appeared to be driven by the study reported by Hunter et al. Significant positive associations were observed among studies in north America ($RR_{summary}$=1.48, 95% CI 1.15-1.90, I^2=0.0%, $P_{heterogeneity}$=0.53), studies with good quality ($RR_{summary}$=1.53, 95% CI 1.24-1.87, I^2=0.0%, $P_{heterogeneity}$=0.82), studies with small number of cases ($RR_{summary}$=1.49, 95% CI 1.18-1.87, I^2=0.0%, $P_{heterogeneity}$=0.72), studies without adjustment for BMI ($RR_{summary}$=1.55, 95% CI 1.24-1.93, I^2=0.0%, $P_{heterogeneity}$=0.62) and studies adjusted for physical activity ($RR_{summary}$=1.62, 95% CI 1.14-2.30, I^2=0.0%, $P_{heterogeneity}$=0.61). In three studies with additional adjustment for BMI, despite a decreased effect size, the association remained significant after adjusting for BMI (before adjustment: $RR_{summary}$=1.55, 95% CI 1.24-1.93, I^2=0.0%, $P_{heterogeneity}$=0.62, versus, after adjustment: $RR_{summary}$=1.27, 95% CI 1.04-1.55, I^2=0.0%, $P_{heterogeneity}$=0.44)

In sensitivity analyses, after excluding the most influential research, the summary RRs ranged from 1.24 (95% CI 0.86-1.79) when excluding the study conducted by Friberg et al. to 1.53 (95% CI 1.24-1.87) after excluding the study by Hunter et al.

(Table S8).[6 13]

Total sedentary behavior

Two studies from the US, one large cohort study,[15] and one case-control study,[30] including 71680 participants and 1317 cases in total, have investigated the effect of total sedentary behavior (evaluated as total time spent sitting during a 24-hour day) on endometrial cancer risk, and both proved significantly adverse effect. The pooled RR for high versus low analysis of total sedentary behavior and endometrial cancer risk was 1.55 (95% CI 1.27-1.89, I^2=0.0%, $P_{heterogeneity}$=0.91) (Figure 4). After combing all included studies as evaluating overall sedentary behavior, the pooled RR for high versus low analysis was 1.28 (95% CI 1.14-1.43, I^2=34.8%, $P_{heterogeneity}$=0.10) (Figure 4). No evidence of publication bias was indicated through visual inspection of the funnel plot (Figure 5), which was supported by Begg's test (P=0.38), and Egger's test (P=0.29).

The meta-regression analyses showed that all pre-specified study characteristics explained little of the heterogeneity for overall sedentary behavior (Table S9). There was weak evidence that associations were stronger for cohort study, study conducted in North America, study with large sample size (n ≥ 5000), good quality and adequate adjustment of confounding factors as well as adjustment for physical activity (Figure 4).

Discussion

In this systematic review and comprehensive meta-analysis, 55% increased risk of endometrial cancer was observed among individuals with higher levels of total sedentary behavior, 22% among those with occupational sedentary behavior, and 34% with borderline significancy among those with leisure-time sedentary behavior. The overall increased risk disregarding specific domains was 28%. The pooled associations were consistent within subgroups stratified according to study design, sample size, and adjustment strategy for physical activity and BMI.

The present results added to the existing evidence by showing a possible domain-specific association between sedentary behavior and endometrial cancer, particularly for total and occupational domain. Subgroup analyses were generally supportive of the overall estimates. Our results are partially in line with two previous meta-analyses that focused on effect of sedentary behavior on all-site cancers.[4 5] Including eight studies, Schmid et al.[4] reported a 36% increased risk of endometrial cancer among participants with higher levels of overall sedentary behavior. However, this research did not find a significant association for occupational domain, which could be attributed to the limited number of studies included (n=4) and their heterogeneous quality. Including three prospective studies, Shen et al.[5] reported a 66% increased risk of endometrial cancer for the defined sedentary behavior that was assessed by total sitting and TV viewing time. With limited number of studies included, this research did not discuss on potential heterogeneity of the studies. Our research found that the positive associations between sedentariness and endometrial cancer were more pronounced in studies with high quality, prospective design and large sample size. These studies were more prone to reveal the true association between sedentary behavior and endometrial cancer by reducing possibility of misclassification and selection, recall, and confounding bias.

While we found a significant increased risk of endometrial cancer related to higher levels of occupational sedentary behavior, the results related to leisure-time sedentary behavior was borderline significant. Possible explanations for domain-specific differences may be attributed to changes of sedentary behavior over time, susceptible population, and exposure window across the life span.[8] Compared with leisure-time sedentary behavior, occupational sedentary behavior is more frequently and closely associated with stable biological accumulation of early-onset and long-term exposure of prolonged, uninterrupted sitting.[31] Moreover, leisure-time sedentary behavior interacts in a complex way with other lifestyle factors, such as diet, physical activity, and obesity in association with health outcomes.[9] Failure to account for these factors in research is likely to yield biased results. Besides, the domain-specific differences may be explained, at least partly, by the small number as well as heterogeneity of studies within leisure-time domain, in which the pooled estimates were dominated by a large-sampled study with contrasting findings.[6] Further longitudinal studies incorporating the measures of different domains are needed to better clarify the domain-specific association and the difference across domains.

Subgroup-analyses suggested greater effect size in studies with adjustment for physical activity. Emerging evidence has shown that the sedentary behavior is distinct from lack of physical activity because of its unique postural and intervenable health hazards effects that cannot be offset by physical activity.[32] Without proper adjustment for physical activity, the real correlation between sedentary behavior and endometrial cancer could be attenuated due to the role of physical activity in reducing cancer risk by healthy body weight maintenance and obesity prevention.[8 33] However, most included studies in the analysis did not adjust for physical activity. Our findings highlight the importance of considering the interactive effects of sedentary behavior

and other lifestyle factors may have on endometrial cancer in future studies. Novel analytical method, such as marginal structural models with time-varying exposure assessment, may be particularly important in evaluating the interactive effects of sedentary behavior, physical activity and obesity in association with endometrial cancer, as well as identifying critical exposure windows.[36 37 38]

It is widely hypothesized that sedentary behavior may increase the risk of cancers due to low energy expenditure and by inducing obesity, a well-understood risk factor for endometrial cancer.[39] Under this circumstance, adjusting for obesity indices (mostly BMI) may lead to overadjustment of the association and produce a less pronounced risk estimate. Realizing this issue, three studies included in the meta-analysis have reported respective results with and without adjustment for BMI.[13 14 15] The pooled estimates of these studies showed that the association between sedentary behavior and endometrial cancer attenuated but remained significant after adjusting for BMI, suggesting that other mechanisms distinct from obesity-related pathways likely exist.

The biological mechanisms by which sedentary behavior increases endometrial cancer risk remains unclear. Several pathways related to metabolic abnormalities and insulin sensitivity, chronic systemic inflammation, and endogenous sex hormones are suggested as the main hypothesis linking physical activity, sedentary behavior and obesity to cancer incidence.[33 34 39] Besides, long-time sitting posture might also contribute through its adverse effect on mitochondrial and endothelial function.[33] Given the complex mechanisms, further analysis may help better understand the potential mechanisms through rating evidence separately among different study population, particularly in non-obese and obese, pre-menopausal and post-menopausal women, population with different intensity of physical activity, and for different histological subtypes.[36]

Strengths of this systematic review and meta-analysis include strictly following the uniform criteria for study selection, quality evaluation and reporting. Also, our meta-analysis included substantial numbers of participants and cancer cases, ensuring sufficient statistical power to yield precise associations. Furthermore, our meta-analysis revealed some novel insights not previously investigated, such as varied effects of sedentary behavior on endometrial cancer across different domains. This is also the first study taking the complex interaction between obesity, physical activity, and sedentary behavior into account in the association. Additional merits include the robustness of the pooled associations in multiple subgroups and sensitivity analyses within different sedentary behavior domains.

There are some limitations in our review at the level of the meta-analysis and at the level of included studies that need to be noticed. At the review level, we observed evidence of heterogeneity between subgroups especially within leisure-time domain. However, this seems to be mainly driven by one large-sampled study with contradicting conclusion. After excluding the study, no more indication of heterogeneity was shown. Also, the pooled associations showed little evidence of heterogeneity across different domains of sedentary behavior and endometrial cancer. Secondly, small numbers of studies included in our meta-analysis could lower the statistical power and limit the ability to examine the existence of small study effects and excess significance bias. Thirdly, it should be emphasized that there could be wide interindividual variation in level of sedentary behavior, with all studies assessing self-reported levels of sedentariness based on questionnaires, interviews, or job titles, and neither of these studies applied repeated measures or corrected for measurement errors. Lastly, definitions of high versus low levels of sedentary behavior varied greatly in the included studies. For example, the highest level of sedentary behavior in some studies may vary

from more than 3 to 8 hours/day,[6 30] which may decrease the comparability among studies. There is therefore an urgent need for the combination of self-report assessment, objective quantitative monitors in further prospective cohort studies, to study these associations and improve understanding of benefits brought by reductions in sedentary time.

Conclusion

Higher levels of total and occupational sedentary behavior increase the risk of endometrial cancer. The association between leisure-time sedentary behavior and endometrial cancer is borderline significant. The interactive effects of physical activity, obesity and sedentary behavior on endometrial cancer warrant further investigation. Future longitudinal studies employing objective physical activity monitors may help to clarify the quantitative association between total and domain-specific sedentary behavior and endometrial cancer.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests None declared.

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Authors' contributions The literature reviews were conducted by LY and JN. LY and ZL drafted the manuscript based on discussion involving all the authors, and contributed to the integrity of the data and statistical analysis. ZL and XW contributed to study concept and design, and critical revision of the manuscript and administrative support. WL, and QY supervised the study, critically reviewed the draft and approved the final version before submission.

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Table 1. Study characteristics of the included studies in systematic review.

Publication	Study design	Study area	Enrolment / Study period	Age at baseline (years)	Follow-up period	Number of participants (controls)/cases	Sedentary behavior	Results	NOS study quality
Dosemeci et al. (1993)[26]	Case-control study	Turkey	1979-1984	——	——	275/31	Occupational sedentary	OR (sedentary > 6 hr/d) = 0.50 (0.10, 4.40)	Fair (6)
Shu et al. (1993)[12]	Case-control study	China	1988-1990	18-74	——	536/268	Occupational sedentary	OR = 1.20 (0.70, 2.00)	Fair (5)
Zheng et al. (1993)[27]*	Cross-sectional study	China	1980-1984	≥ 30	——	452/452	Occupational sedentary	SIR (long sitting time) = 110	——
Olson et al. (1997)[22]	Case-control study	US	1986-1991	40-85	——	631/232	Occupational sedentary	OR = 0.93 (0.55, 1.56)	Good (7)
Moradi et al. (1998)[18]*	Cohort study	Sweden	1960 1970 1960 and 1970	16-95	1971-1989	Sub-cohort A (1960): 704904/4462 Sub-cohort B (1970): 982270/5287 Sub-cohort C (1960 and 1970): 253336/1949	Occupational sedentary	RR (1960) = 1.13 (0.99, 1.29) RR (1970) = 1.32 (1.17, 1.50) RR (1960 and 1970) = 1.30 (1.03, 1.65)	——
Moradi et al. (2000)[19]	Case-control study	Sweden	1994-1995	50-74	——	3368/709	Occupational sedentary	OR (1960) = 1.30 (0.80, 2.20) OR (1970) = 1.20 (0.80, 1.90) OR (1980) = 1.40 (1.00, 1.90) OR (1990) = 1.30 (0.90, 1.90)	Good (7)
Weiderpass et al. (2001)[25]	Cohort study	Finland	1970	25-64	1971-1995	413877/2833	Occupational sedentary	RR (high level of sedentary work) = 1.30 (1.10, 1.50)	Fair (5)
Furberg et al. (2003)[23]	Cohort study	Norway	1974-1981	20-49	1981-1996	24460/130	Leisure-time sedentary Occupational sedentary	RR (Grade1-sedentary activity) = 1.27 (0.69, 2.32) RR (Grade1-sedentary work) = 1.64 (0.95, 2.84)	Good (9)
Matthews et al. (2005)[28]	Case-control study	China	1997-2001	30-69	——	846/832	Occupational sedentary	OR (Sitting Q4) = 0.93 (0.67, 1.30)	Fair (5)

Table 1. Study characteristics of the included studies in systematic review (Continued).

Publication	Study design	Study area	Enrolment / Study period	Age at baseline (years)	Follow-up period	Number of participants (controls)/cases	Sedentary behavior	Results	NOS study quality
Friberg et al. (2006)[13]	Cohort study	Sweden	1997	50-83	1997-2005	33723/199	Occupational sedentary Leisure-time sedentary	RR (work/occupation activity, low, mostly sitting down and sitting down more than half of the time) = 1.03 (0.76, 1.39); Additional adjustment for BMI: RR = 0.99 (0.73, 1.34) RR (watching TV/sitting, high, ≥5hr/d) = 1.80 (1.14, 2.83); Additional adjustment for BMI: RR = 1.66 (1.05, 2.61)	Good (8)
Patel et al. (2008)[14]	Cohort study	US	1992	50-74	1997-2003	42672/466	Leisure-time sedentary	RR (sitting ≥6 hr/day) = 1.40 (1.03, 1.89); Additional adjustment for BMI: RR = 1.18 (0.87, 1.59)	Good (7)
Gierach et al. (2009)[15]	Cohort study	US	1995-1996	50-71	1995-2003	70351/650	Leisure-time sedentary Total sedentary	RR (≥ 7 hr) = 1.66 (1.20, 2.88); Additional adjustment for BMI: RR = 1.21 (0.87, 1.67) RR (≥ 7 hr) = 1.56 (1.22, 1.99); Additional adjustment for BMI: RR = 1.26 (0.99, 1.62)	Good (7)
Friedenreich et al. (2010)[29]	Case-control study	Canada	2002-2006	30-79	——	1032/542	Occupational sedentary	OR (Lifetime occupational sedentary activity, > 16.94 hr/wk/yr) = 1.28 (0.89, 1.83)	Fair (6)
Arem et al. (2011)[30]	Case-control study	US	2004-2008	cases: 61.1; controls: 62.1	——	662/667	Total sedentary	OR (≥ 8 hr/d) =1.52 (1.07, 2.16)	Fair (5)
Hunter et al. (2020)[6]	Cohort study	UK	2006-2010	40-69	7.6 (1.4) years	253171/872	Leisure-time sedentary	HR (daily TV viewing time, > 5h) = 0.59 (0.40, 0.88) HR (daily computer use time, > 3h) = 0.82 (0.55, 1.22) HR (daily total screen time, > 8h) = 0.57 (0.31, 1.03)	Fair (6)
Miyata et al. (2020)[7]	Cohort study	Japan	1988-1990	40-79	14.8 years	33801/79	Leisure-time sedentary Occupational sedentary	HR (TV viewing, ≥ 4hr/d) = 2.10 (0.57, 7.71) HR (Occupational activity, mainly sitting) = 2.17 (1.04, 4.56)	Good (8)

*Not included in the meta-analysis and NOS study quality assessment; Table values are mean (SD) for continuous variables.

Figure legends

Figure 1. PRISMA 2020 flow diagram of literature search and selection.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 2. Pooled association between occupational sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

Figure 3. Pooled association between leisure-time sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

Figure 4. Pooled association between total sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

Figure 5. Funnel plot of overall sedentary behavior and endometrial cancer.

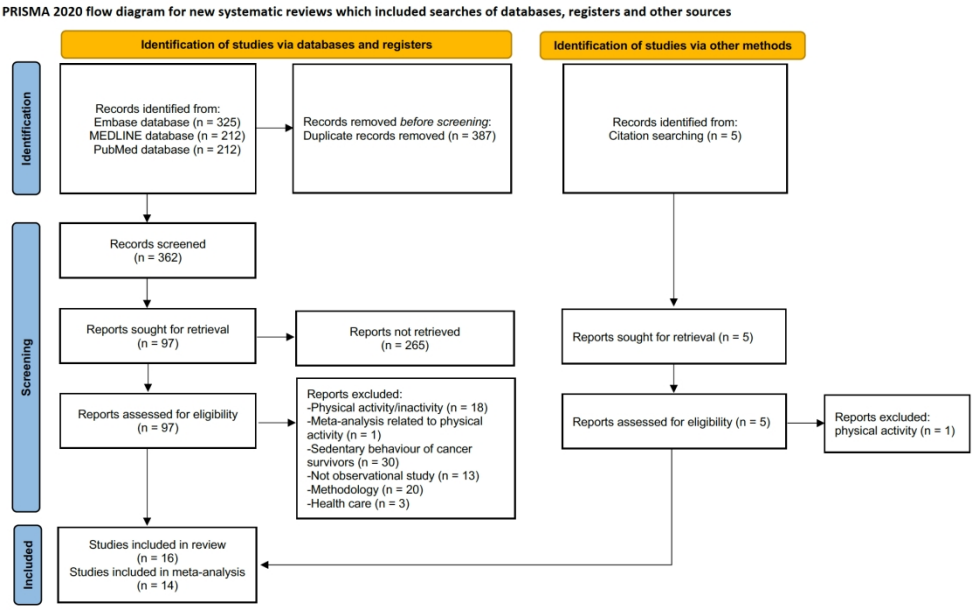

Figure 1. PRISMA 2020 flow diagram of literature search and selection. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

368x232mm (144 x 144 DPI)

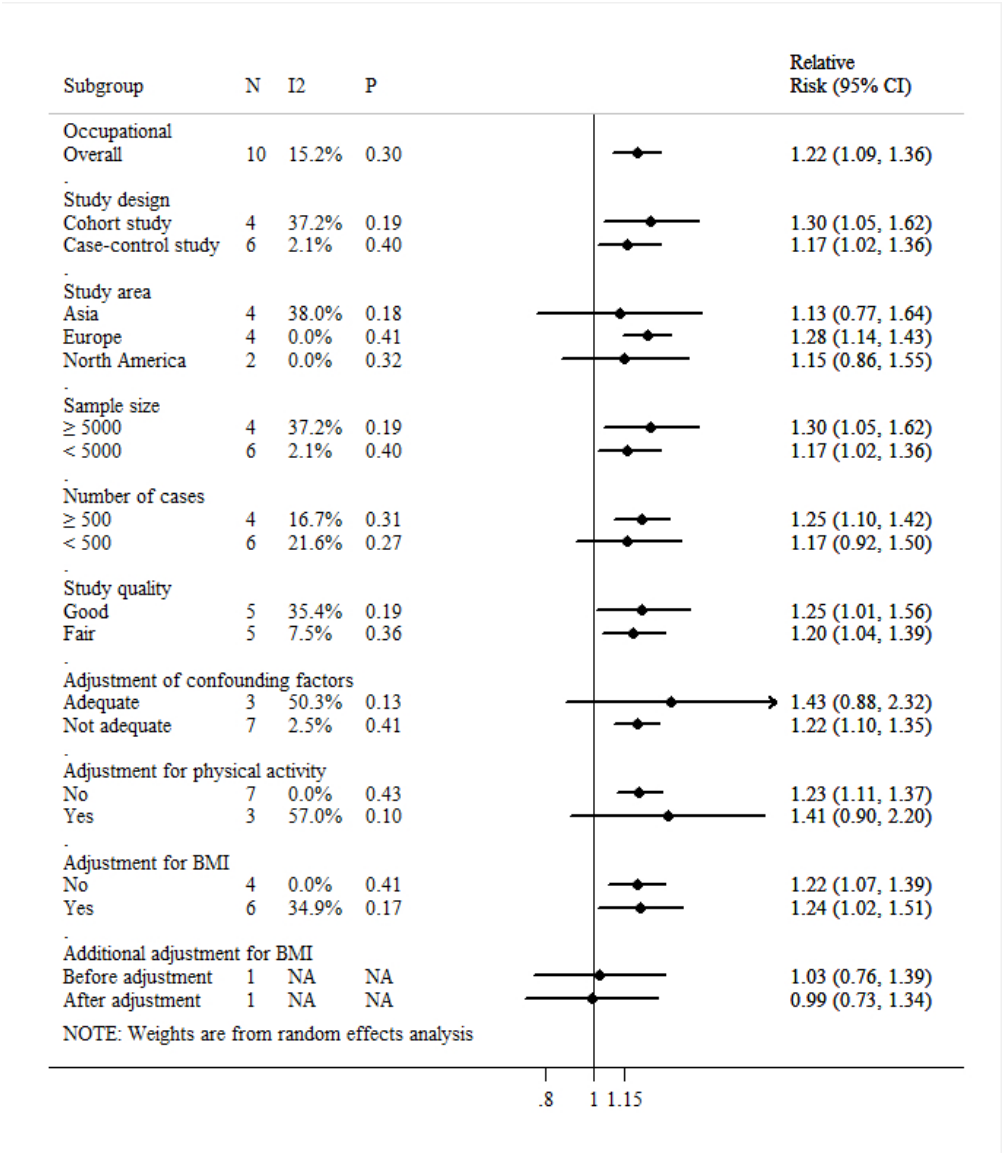

Figure 2. Pooled association between occupational sedentary behavior and endometrial cancer.
Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

241x277mm (72 x 72 DPI)

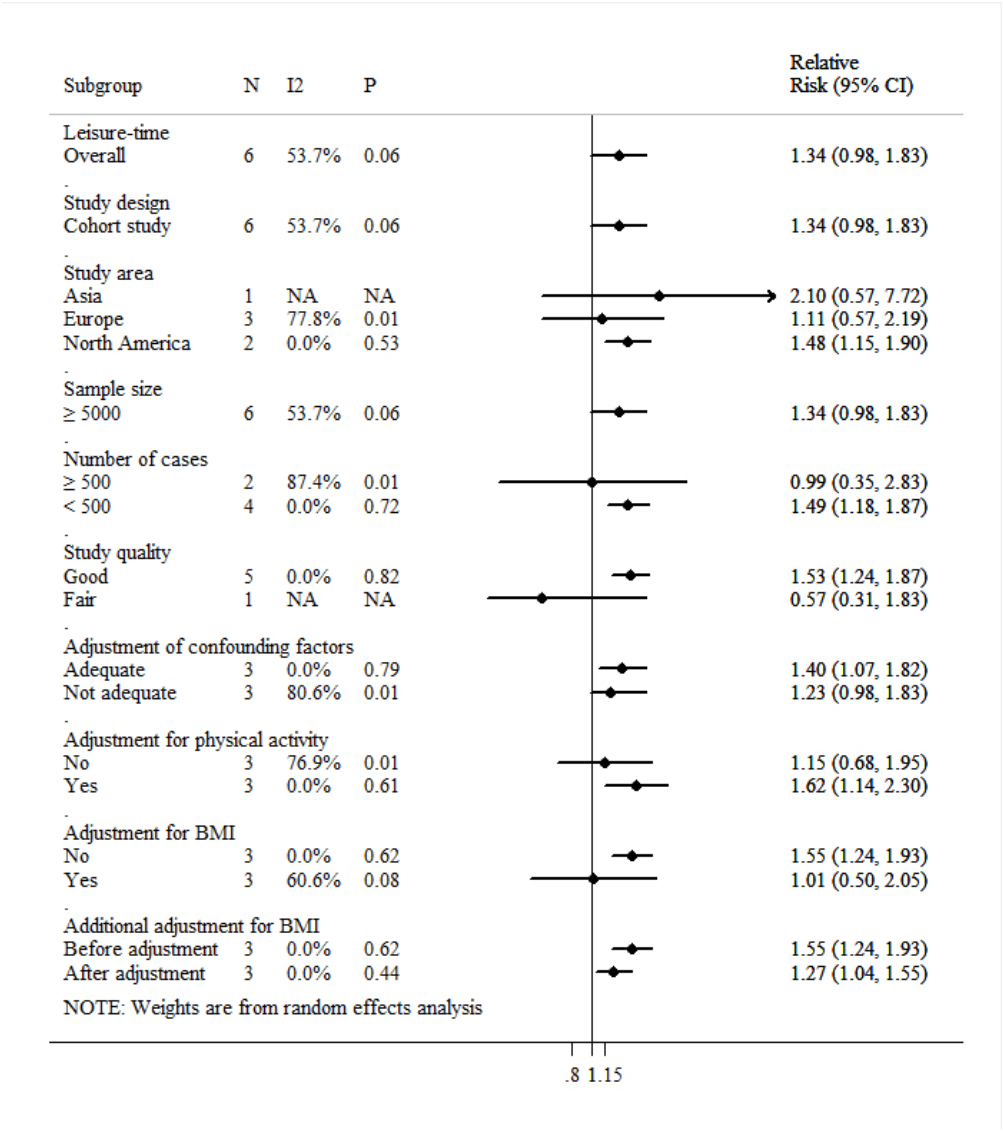

Figure 3. Pooled association between leisure-time sedentary behavior and endometrial cancer.
Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

246x277mm (72 x 72 DPI)

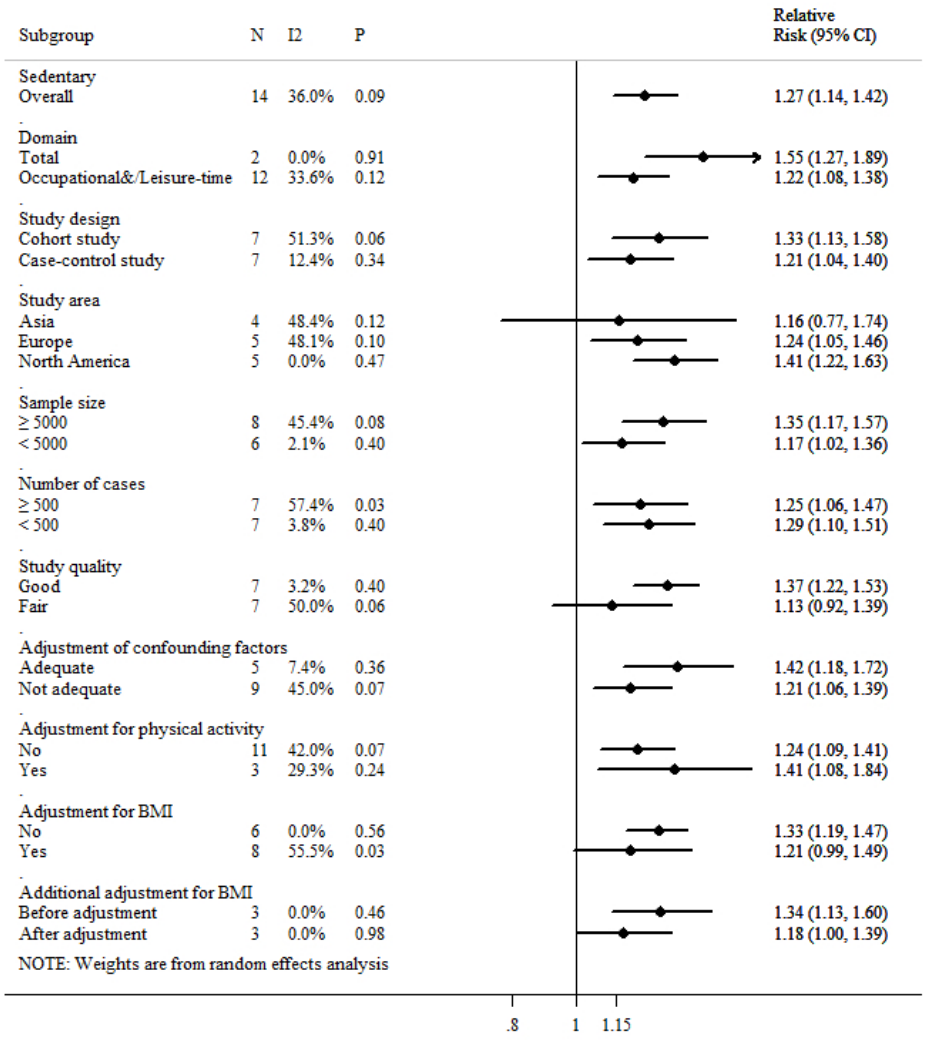

Figure 4. Pooled association between total sedentary behavior and endometrial cancer.
Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

247x277mm (72 x 72 DPI)

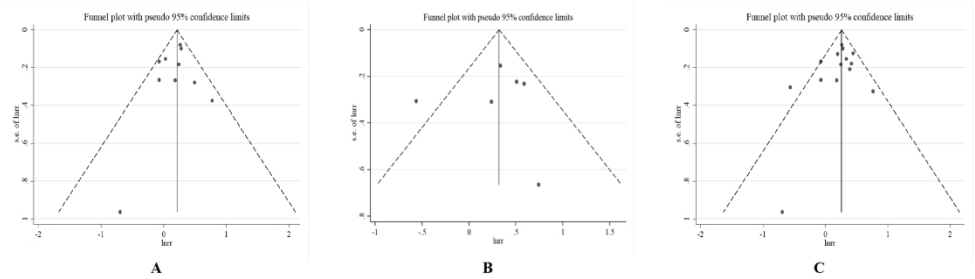

Figure 5. Funnel plot of overall sedentary behavior and endometrial cancer.

450x156mm (144 x 144 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6, Figure 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6-7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7-9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9-10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9-11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	9-11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	9-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9-11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9-11

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	11
Study characteristics	17	Cite each included study and present its characteristics.	11, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	11-15, Table 1, Supplemental material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	11-15, Figure 2-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	11-15, Figure 2-4, Supplemental material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11-15, Supplemental material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11-15, Figure 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11-15, Supplemental material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	16
	23b	Discuss any limitations of the evidence included in the review.	19-20
	23c	Discuss any limitations of the review processes used.	19-20
	23d	Discuss implications of the results for practice, policy, and future research.	16-20
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	21

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	21
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	21

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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MOOSE reporting checklist for meta-analyses of observational studies.

Reporting section and item		Reported on page
Reporting of background		
1	Problem definition	4-5
2	Hypothesis statement	5-6
3	Description of study outcome(s)	6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy		
1	Qualifications of searchers (eg, librarians and investigators)	7-8
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4	Databases and registries searched	6-7
5	Search software used, name and version, including special features used (eg, explosion)	6-7
6	Use of hand searching (eg, reference lists of obtained articles)	6-7
7	List of citations located and those excluded, including justification	Figure 1
8	Method of addressing articles published in languages other than in English	7
9	Method of handing abstracts and unpublished studies	7
10	Description of any contact with authors	8
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4	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	10, Supplemental material
5	Assessment of study quality, including binding of quality assessors; stratification or regression on possible predictors of study results	10, Supplemental material
6	Assessment of heterogeneity	9
7	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analyses) in sufficient detail to be replicated	9
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Supplementary Materials

The association between domain-specific sedentary behavior and endometrial cancer: A systematic review and meta-analysis

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Supplemental Text. Search terms and strategy

Table S3. Detailed data underlying the meta-analysis.

Table S4. Characteristics of participants and assessment of sedentary behaviour and outcome.

Table S5. Newcastle-Ottawa quality assessment scale for cohort study

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Table S7. Detailed information on adjusted confounders of studies included in systematic review

Table S8. Influence analysis of sedentary behaviour and endometrial cancer (given named study is omitted).

Table S9. Results of meta-regression analyses on individual study characteristics for studies included in the meta-analysis of the association between sedentary behaviour and the risk of endometrial cancer.

Search terms and strategy

Search strategy in Embase/MEDLINE

('sedentary behavior':ab,ti OR 'physical inactivity':ab,ti OR 'sedentary lifestyle':ab,ti OR 'sedentary behaviour':ab,ti OR sedentary:ab,ti OR 'sitting time':ab,ti OR 'screen time':ab,ti OR 'television viewing':ab,ti OR 'physical activity':ab,ti) AND ('endometrial cancer':ab,ti OR endometrium:ab,ti OR 'uterus cancer':ab,ti OR 'uterine cancer':ab,ti OR 'corpus uteri cancer':ab,ti)

Search strategy in PubMed

((sedentary behavior[MeSH] OR physical inactivity[Title/Abstract] OR sedentary lifestyle[Title/Abstract] OR sedentary behaviour[Title/Abstract] OR sedentary[Title/Abstract] OR sitting time[Title/Abstract] OR screen time[Title/Abstract] OR television viewing[Title/Abstract] OR physical activity[Title/Abstract]) AND (endometrial cancer[MeSH] OR endometrium[Title/Abstract] OR uterus cancer[Title/Abstract] OR uterine cancer[Title/Abstract] OR corpus uteri cancer[Title/Abstract]

Table S3. Detailed data underlying the meta-analysis.

Table S3-1. Detailed data for overall sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Domain	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI
Gierach	2009	Total	Cohort study	North America	≥ 5000	≥ 500	1.56 (1.22, 1.99)	Not adequate	Good	No	No
Arem	2011	Total	Case-control study	North America	≥ 5000	≥ 500	1.52 (1.07, 2.16)	Adequate	Fair	No	Yes
Dosemeci	1993	Occupational&/Leisure-time	Case-control study	Asia	< 5000	< 500	0.50 (0.10, 4.40)	Not adequate	Fair	No	No
Shu	1993	Occupational&/Leisure-time	Case-control study	Asia	< 5000	< 500	1.20 (0.70, 2.00)	Not adequate	Fair	No	yes
Olson	1997	Occupational&/Leisure-time	Case-control study	North America	< 5000	< 500	0.93 (0.55, 1.56)	Adequate	Good	No	Yes
Moradi	2000	Occupational&/Leisure-time	Case-control study	Europe	< 5000	≥ 500	1.32 (1.08, 1.60)	Not adequate	Good	No	Yes
Weiderpass	2001	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	≥ 500	1.30 (1.10, 1.50)	Not adequate	Fair	No	No
Furberg	2003	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	< 500	1.48 (0.97, 2.20)	Adequate	Good	Yes	Yes
Matthews	2005	Occupational&/Leisure-time	Case-control study	Asia	< 5000	≥ 500	0.93 (0.67, 1.30)	Not adequate	Fair	No	Yes
Friedenreich	2010	Occupational&/Leisure-time	Case-control study	North America	< 5000	≥ 500	1.28 (0.89, 1.83)	Not adequate	Fair	No	Yes
Miyata	2020	Occupational&/Leisure-time	Cohort study	Asia	≥ 5000	< 500	2.15 (1.13, 4.09)	Adequate	Good	Yes	Yes
Friberg	2006	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	< 500	1.22 (0.95, 1.57)	Not adequate	Good	Yes	No
Patel	2008	Occupational&/Leisure-time	Cohort study	North America	≥ 5000	< 500	1.40 (1.03, 1.89)	Adequate	Good	No	No
Hunter	2020	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	≥ 500	0.57 (0.31, 1.03)	Not adequate	Fair	No	Yes

Table S3-2. Detailed data for occupational sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI	Additional adjustment for BMI
Dosemeci	1993	Case-control study	Asia	< 5000	< 500	0.50 (0.10, 4.40)	Not adequate	Fair	No	No	
Shu	1993	Case-control study	Asia	< 5000	< 500	1.20 (0.70, 2.00)	Not adequate	Fair	No	Yes	
Olson	1997	Case-control study	North America	< 5000	< 500	0.93 (0.55, 1.56)	Adequate	Good	No	Yes	
Moradi	2000	Case-control study	Europe	< 5000	≥ 500	1.32 (1.08, 1.60)	Not adequate	Good	No	Yes	
Weiderpass	2001	Cohort study	Europe	≥ 5000	≥ 500	1.30 (1.10, 1.50)	Not adequate	Fair	No	No	
Furberg	2003	Cohort study	Europe	≥ 5000	< 500	1.64 (0.95, 2.84)	Adequate	Good	Yes	Yes	
Matthews	2005	Case-control study	Asia	< 5000	≥ 500	0.93 (0.67, 1.30)	Not adequate	Fair	No	Yes	
Friberg	2006	Cohort study	Europe	≥ 5000	< 500	1.03 (0.76, 1.39)	Not adequate	Good	Yes	No	0.99 (0.73, 1.34)
Friedenreich	2010	Case-control study	North America	< 5000	≥ 500	1.28 (0.89, 1.83)	Not adequate	Fair	No	Yes	
Miyata	2020	Cohort study	Asia	≥ 5000	< 500	2.17 (1.04, 4.56)	Adequate	Good	Yes	Yes	

Table 3-3. Detailed data for leisure-time sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI	Additional adjustment for BMI
Furberg	2003	Cohort study	Europe	≥ 5000	< 500	1.27 (0.69, 2.32)	Adequate	Good	Yes	Yes	
Friberg	2006	Cohort study	Europe	≥ 5000	< 500	1.80 (1.14, 2.83)	Not adequate	Good	Yes	No	1.66 (1.05, 2.61)
Patel	2008	Cohort study	North America	≥ 5000	< 500	1.40 (1.03, 1.89)	Adequate	Good	No	No	1.18 (0.87, 1.59)
Gierach	2009	Cohort study	North America	≥ 5000	≥ 500	1.66 (1.20, 2.88)	Not adequate	Good	No	No	1.21 (0.87, 1.67)
Hunter	2020	Cohort study	Europe	≥ 5000	≥ 500	0.57 (0.31, 1.03)	Not adequate	Fair	No	Yes	
Miyata	2020	Cohort study	Asia	≥ 5000	< 500	2.10 (0.57, 7.71)	Adequate	Good	Yes	Yes	

Table S4. Study characteristics of the included studies in systematic review.

Publication	Participants' characteristics	Outcome		Sedentary behavior	Definition and assessment of sedentary behavior
		Diagnostic criteria	Specific cancer classification		
Dosemeci 1993	Hospital-based study population.	——	——	Occupational sedentary	Occupational Classification (SOC) code system: the sitting-time scale was defined as low activity (sedentary, i.e., sitting more than six hours a day); moderate activity (mod, i.e., sitting two to six hours a day); and high activity (active, i.e., sitting less than two hours a day)
Shu 1993	Cases were identified through the population-based Shanghai Cancer Registry; female controls were individually matched to the cases on age through Shanghai Resident Registry.	Histopathologically confirmed	Adenocarcinomas (76.2%), adenosquamous cancers (6.3%), other type (13.4%), and unspecified (4.1%).	Occupational sedentary	Interview using standardized coding scheme: sitting time index assessing the amount of time in a sitting posture on the job. Job with long sitting-times were defined as those with more than 80% of working hours spent sitting; moderate sitting-time jobs as 20-80% of working hours of time spent sitting; short sitting-time jobs as less than 20% of time spent sitting
Zheng 1993*	Employment information for incident patients with cancer aged 30 years or older whose disease was diagnosed during the period 1980-1984 among the residents of urban Shanghai was compared with occupational data from the 1982 census for the same population.	ICD-9, code 182	——	Occupational sedentary	Same as Shu et al.1993
Olson 1997	Incident cases of primary endometrial cancer were identified from the major hosptials in western New York State. Controls without prior hysterectomy were selected from the community by age.	Histologically confirmed	Adenomatous carcinoma	Occupational sedentary	Three measures were used for occupational activity: an index of cumulative activity; the number of years in occupations with medium, heavy, or very heavy activity; and the activity level of the most recent job. An estimate of physical activity associated with employment was obtained from a detailed occupational history covering

					all jobs held for 6 months or longer. Occupations for job title and industry were coded according to the U.S. Department of Commerce Alphabetical Index of Occupations for the 1980 Census, and the U.S. Department of Lahor's Estimates of Worker Trait Requirements were used to classify the activity level of each job as sedentary, light, medium, heavy, or very heavy based on job title and industry.
Moradi 1998*	Swedish Cancer Environment Registry III (the national Swedish Cancer Register for 1971-1989 linked with the national population censuses from 1960 and 1970)	ICD-7, code 172 and were histologically verified	——	Occupational sedentary	Occupations coding scheme; classified each occupation according to the estimated physical demands of the job, as very high, high, moderate, light and sedentary activity. Assessments were done independently by 3 Swedish specialists in occupational medicine with long experience in job classification.
Moradi 2000	Postmenopausal women with an intact uterus and no previous breast or endometrial cancer diagnosis; Cases were women with an incident, primary, histopathologically confirmed endometrial cancer identified through the six regional cancer registries in Sweden; Control women were randomly selected from the continuously updated population register including all residents of Sweden.	Histopathologically confirmed	——	Occupational sedentary	Occupations coding scheme; classified each occupation according to the estimated physical demands of the job, as very high, high, moderate, light and sedentary activity. Assessments were done independently by 3 Swedish specialists in occupational medicine with long experience in job classification.

Weiderpass 2001	Population Census of Finland 1970 excluded women in the two highest social classes.	ICD-9, code 182	——	Occupational sedentary	A national job-exposure matrix (FINJEM) calculated the product of level and probability of an exposure, and subdivided into three categories: zero (reference category); low (roughly below median among job titles with exposure probability > 0); and medium/high (called for simplicity `high'; defined as equal or above the median among job titles with exposure probability > 0)
Furberg 2003	Alive women with complete data and no diagnosis of any malignant disease 1 year after participation in Norwegian National Health Screening Service's program.	Incident, primary, histopathologically confirmed carcinoma of the endometrium	127 adenocarcinomas (1 serious papillary adenocarcinoma = type II-carcinoma), and 3 unspecified carcinomas	Recreational sedentary	Recreational activity: Grade1, Reading, watching television or other sedentary activity; Grade2, Walking, bicycling or other activity for at least 4 hr per week; Grade3, Recreational athletics, heavy gardening or similar activities at least 4 hr per week; and Grade 4, Regular (several times a week) training or participation in athletic competitions
				Occupational sedentary	Occupational activity: Grade1, mostly sedentary work; Grade2, A lot of walking; Grade3, A lot of walking and lifting; and Grade4, Heavy manual work. The same team of trained nurses conducted interviews with the participants at the screening center in both surveys to confirm the information given
Matthews 2005	Incident cases aged 30-69 who were permanent residents were identified from the Shanghai Cancer Registry; Controls, frequency matched to cases by age (±5 years), were randomly selected from permanent female residents using the Shanghai Resident Registry. Women who had a hysterectomy were not eligible.	The diagnosis of each case was confirmed by medical chart review and a review of the available pathology slides by senior study pathologists	——	Occupational sedentary	Occupations were classified into high, medium, or low levels of estimated sitting time and activity level using job codes based on self-reported jobs held for at least 3 years

Friberg 2006	Cohort members from mammography screening program, women diagnosed with cancer (other than nonmelanoma skin cancer) and those having had a hysterectomy before returning the follow-up questionnaire, and with missing information on physical activity were excluded.	The Swedish Cancer Register and the Regional Cancer Register	——	Occupational sedentary	Duration of specific activities was asked and assigned mean metabolic equivalent (MET) values [multiples of MET (kcal kg-1h -1)] based on specific activities within corresponding categories in a physical activity compendium. Occupational activity: low: mostly sitting (1.3 MET/h), and sitting down more than half the time (1.8 MET/h); high: mostly standing (2.2 MET/h), doing lifts (2.6 MET/h), a lot of lifts (3.0 MET/h), and heavy labor (3.9 MET/h)
				Recreational sedentary	For leisure time inactivity, there were five predefined categories for time spent per day watching TV/sitting (inactive leisure time, <1 hour daily to >6 hours daily, 1.2 MET/h)
Patel 2008	Postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the US, excluded women who reported prevalent cancer (except nonmelanoma skin cancer) or not being postmenopausal or who had a hysterectomy or unknown hysterectomy status at baseline.	Self-report on follow-up questionnaire and subsequently verified from medical records or linkage with state cancer registries, and the National Death Index	Endometrial carcinomas	Recreational sedentary	Based on the question "During the past year, on an average day, (not counting time spent at your job) how many hours per day did you spend sitting (watching TV, reading, etc.)?" Responses included "none, less than 3, 3–5, 6–8, more than 8hr/day." Sedentary behavior at baseline was categorized as 0–<3, 3–5, ⩾6 or missing hr/day
Gierach 2009	Female members of the AARP (the American Association of Retired Persons) and resided in US states.	State cancer registries, and histology was defined using ICD for Oncology codes, 3rd edition	Adenocarcinomas (95.0%)	Recreational sedentary	Information on physical inactivity was based on two questions. Participants were asked about time spent watching TV or videos during a typical 24-hour period over the past 12 months. Time spent watching TV or videos was categorized as none, <1 hour, 1–2, 3–4, 5–6,7–8, and ≥ 9 hours

				Total sedentary	In a separate question, participants were also asked to indicate the number of hours spent sitting during a typical 24-hour period over the past 12 months: <3,3–4, 5–6, 7–8, and ⩾ 9 hours. Both measures of inactivity were collapsed as <3, 3–4, 5–6,and ⩾ 7 hours per day
Friedenreich 2010	Cases were Alberta residents, English-speaking, able to complete interview and questionnaire, and did not have another previous cancer except nonmelanoma skin cancer. Controls were identified using random-digit dialing and frequency matched to cases on age (±5 years).	Incident, histologically confirmed invasive cases of endometrial cancer were identified directly from the Alberta Cancer Registry	——	Occupational sedentary	Lifetime occupational sedentary activity was estimated using a validated questionnaire. The patterns of physical activity were recorded by the interviewer including the age started, age ended, number of months per year, weeks per month, days per week and hours per day that each activity was performed so that the frequency and duration of these activities is determined.
Arem 2011	English-speaking, Connecticut residents diagnosed with primary endometrial cancer. Population-based controls were identified using random-digit dialing (RDD) and were frequency matched on age.	——	——	Total sedentary	Time seated watching multimedia or sitting at work was calculated as hours per week from self-report in the two to five years before interview
Hunter 2020	Participants of UK Biobank cohort without been diagnosed with malignant cancer (excluding non-melanoma skin cancer), and have completed self-report sreen time assessment.	Uterus cancer identified from national cancer registries (ICD-10: C54; ICD-9: 182)	——	Recreational sedentary	Television (TV) viewing time: "In a typical DAY, how many hours do you spend watching TV?"
					Daily recreational computer use time: "In a typical DAY, how many hours do you spend using the computer? (Do not include using a computer at work)."
					Daily total recreational screen time: self-reported time spent watching TV, and time spent using the computer outside of work

Miyata 2020	Japanese inhabitants participated in municipal health screening examinations with completed questionnaires and no history of cancer or uterine surgery at enrolment.	Cancer registries or local major hospital records coded according to the ICD-10: C54	——	Recreational sedentary	Television (TV) viewing (< 1, 1 to < 2, 2 to < 3, 3 to < 4, ⩾ 4hr/day)
				Occupational sedentary	Occupational activity was classified according to the position during work (mainly sitting, mainly standing, moving)

Note: Table values are mean (SD) for continuous variables; ICD, International Classification of Disease; * studies not included in the meta-analysis.

Table S5. Newcastle-Ottawa quality assessment scale for cohort study.

Source	Selection				Comparability	Outcome			Total Stars
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	
Hunter 2020	1	1	-	1	1	1	1	-	6
Miyata 2020	1	1	-	1	2	1	1	1	8
Gierach 2009	1	1	-	1	1	1	1	1	7
Patel 2008	1	1	-	1	1	1	1	1	7
Friberg 2006	1	1	-	1	2	1	1	1	8
Furberg 2003	1	1	1	1	2	1	1	1	9
Weiderpass 2001	1	1	1	-	-	1	1	-	5

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. For comparability in our analysis, a study can be awarded one star for controlling for age; Two stars for also controlling for physical activity.

Table S6. Newcastle-Ottawa quality assessment scale for case-control study.

Source	Selection				Comparability	Exposure			Total Stars
	Is the Case Definition Adequate?	Representatives of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate	
Arem 2011	1	1	1	-	1	-	1	-	5
Friedenreich 2010	1	1	1	1	1	-	1	-	6
Matthews 2005	1	1	1	-	1	-	1	-	5
Moradi 2000	1	1	1	1	1	1	1	-	7
Olson 1997	1	1	1	1	1	-	1	1	7
Shu 1993	1	1	1	-	1	-	1	-	5
Dosemeci 1993	-	1	-	1	1	1	1	1	6

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. For comparability in our analysis, a study can be awarded one star for controlling for age; Two stars for also controlling for physical activity.

Table S7. Adjusted confounders of the included studies in systematic review.

Publication		Number of confounders	Adjusted confounders	How to deal with obesity/BMI (particular attention to potential intermediator BMI)
Author	Year			
Dosemeci	1993	3	Age, smoking and socioeconomic status (based on income and education levels)	——
Shu	1993	4	Age, number of pregnancies, BMI, caloric intake	Adjusted in the multivariate model
Zheng*	1993	——	Age-specific and sex specific person-years estimated in each occupation category	——
Olson	1997	9	Age, education, BMI, diabetes, smoking, parity, age at menarche, menopausal status, and use of unopposed estrogen.	Adjusted in the multivariate model
Moradi*	1998	4	Age at follow-up, place of residence, calender year of follow-up, and socio-economic status	——
Moradi	2000	8	Age, parity, age at last birth, BMI 1 year prior to data collection, use of oral contraceptives, use of hormone replacement therapy, smoking, and age at menopause	Adjusted in the multivariate model
Weiderpass	2001	3	Mean number of children, mean age at first birth, and turnover rate	——
Furberg	2003	9	age, geographical region, height, BMI, recreational or occupational activity and smoking at baseline and parity. Also considered blood pressure and serum glucose	Adjusted in the multivariate model
Matthews	2005	12	Age, age at menarche, menopausal status and age, number of pregnancies, oral contraceptive use, current smoking, ever drinking, family history of cancer, education, height, and BMI	Adjusted in the multivariate model
Friberg	2006	9	Age in months, parity, history of diabetes, total fruit and vegetable, education, and work/occupation, walking/bicycling, household work, leisure time activity, and leisure time inactivity (watching TV/sitting) simultaneously	Additionally adjusted for BMI
Patel	2008	9	Age, age at menarche, age at menopause, duration of oral contraceptive use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal hormone therapy use	Additionally adjusted for BMI
Gierach	2009	7	Age, race, smoking status, parity, ever use of oral contraceptives, age at menopause, hormone therapy formulation	Additionally adjusted for BMI
Friedenreich	2010	6	Age, BMI, waist circumference, age at menarche, hypertension, and number of pregnancies of $\geqslant$ 20 weeks gestation	Adjusted in the multivariate model

Arem	2011	8	Age, BMI, race, number of live births, menopausal status, oral contraceptive use, hypertension, and smoking status	Adjusted in the multivariate model
Hunter	2020	15	Age, sex, ethnicity, deprivation index, education, fruit and vegetable intake, BMI, smoking status, and alcohol intake, hormone therapy use, oral contraceptive use, number of live births, age at menarche, age at menopause, hysterectomy status	Adjusted in the multivariate model
Miyata[7]	2020	13	Age, BMI, weight change since age 20, history of diabetes, history of hypertension, age at menarche, menstrual presence, parity, smoking status, alcohol consumption, occupational activity, hours of physical exercise, walking, and television viewing	Adjusted in the multivariate model

Note: BMI, body mass index. * studies not included in the meta-analysis.

Table S8. Influence analysis of sedentary behaviour and endometrial cancer (given named study is omitted).

Occupational domain		Leisure-time domain	
Study omitted	Estimate (95% CI)	Study omitted	Estimate (95% CI)
Dosemeci 1993	1.23 (1.10, 1.38)	Furberg 2003	1.35 (0.93-1.95)
Shu 1993	1.22 (1.08, 1.38)	Friberg 2006	1.24 (0.86-1.79)
Olson 1997	1.24 (1.11, 1.39)	Patel 2008	1.31 (0.85-2.03)
Moradi 2000	1.19 (1.04, 1.37)	Gierach 2009	1.26 (0.86-1.86)
Weiderpass 2001	1.19 (1.03, 1.38)	Hunter 2020	1.53 (1.24-1.87)
Furberg 2003	1.21 (1.08, 1.36)	Miyata 2020	1.30 (0.93-1.82)
Matthews 2005	1.27 (1.15, 1.40)	Combined	1.34 (0.98-1.83)
Friberg 2006	1.26 (1.12, 1.41)		
Friedenreich 2010	1.21 (1.06, 1.38)		
Miyata 2020	1.22 (1.11, 1.35)		
Combined	1.22 (1.09, 1.37)		

Table S9. Results of meta-regression analyses on individual study characteristics for studies included in the meta-analysis of the association between sedentary behaviour and the risk of endometrial cancer.

Covariates	N	RR	95% CI		I^2	Tau^2	Ratio of RR	95% CI		*P*
Model with no covariates	14	1.28	1.14	1.43	34.8%	0.0000	-	-	-	-
Domain*										
Total	2	1.55	1.27	1.89	29.3%	0.0004	1.00	Reference		
Occupational	10	1.22	1.09	1.37			0.80	0.60	1.07	0.12
Leisure-time	6	1.34	0.98	1.83			0.89	0.62	1.28	0.51
Study design										
Cohort study	7	1.33	1.13	1.58	36.8%	0.0027	1.00	Reference		
Case-control study	7	1.22	1.05	1.41			0.91	0.72	1.17	0.44
Study area										
Asia	4	1.20	0.78	1.83	36.0%	0.0000	1.00	Reference		
Europe	5	1.24	1.05	1.46			1.14	0.78	1.68	0.47
North America	5	1.41	1.22	1.63			1.26	0.84	1.91	0.24
Sample size										
< 5000	6	1.19	1.03	1.37	32.7%	0.0028	1.00	Reference		
≥ 5000	8	1.35	1.17	1.57			1.15	0.90	1.47	0.24
Number of cases										
< 500	7	1.30	1.12	1.51	39.8%	0.0036	1.00	Reference		
≥ 500	7	1.25	1.06	1.47			0.99	0.75	1.29	0.91
Study quality				1.47						
Fair	7	1.14	0.93	1.41	33.4%	0.0049	1.00	Reference		
Good	7	1.37	1.22	1.53			1.14	0.90	1.46	0.25
Adjustment of confounding factors										
Not adequate	9	1.22	1.07	1.40	35.4%	0.0014	1.00	Reference		
Adequate	5	1.42	1.18	1.72			1.13	0.85	1.50	0.36
Adjustment for physical activity										
No	11	1.25	1.10	1.42	39.1%	0.0094	1.00	Reference		
Yes	3	1.41	1.08	1.84			1.10	0.78	1.55	0.55
Adjustment for BMI										
No	5	1.34	1.20	1.49	37.0%	0.0029	1.00	Reference		
Yes	9	1.21	1.01	1.46			0.92	0.72	1.17	0.46

Meta-regression models are fitted assuming random effects that allow for between-study variability. I-squared (%) representing variation due to heterogeneity; Tau-squared representing estimate of between-study variance.

*Number of studies exceeds in total as some research presented risk estimates separately for total sedentary, occupational, leisure-time domain.

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The association between domain-specific sedentary behavior and endometrial cancer: A systematic review and meta-analysis

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Abstract

Objective Sedentary behavior is associated with increased cancer risk. We aim to assess the associations of domain-specific and total sedentary behavior with risk of endometrial cancer, with additional attention paid to potential differences in adjustment strategy for obesity and physical activity.

Design A systematic review and meta-analysis was conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE).

Data sources PubMed, Embase and MEDLINE databases were searched up to 28th February 2023, supplemented by grey literature searches.

Eligibility criteria for selecting studies Observational human studies evaluating the association between sedentary behavior and endometrial cancer.

Data extraction and synthesis Two reviewers extracted data and conducted the quality assessment based on Newcastle-Ottawa Scale (NOS) independently. We used a random-effects model with inverse variance approach to pool the estimates. The extent of heterogeneity was quantified with the I^2 statistics.

Results Sixteen studies were included in the systematic review. Fourteen studies involving 882,686 participants were included in the meta-analysis. The pooled RRs for high versus low level of overall sedentary behavior was 1.28 [95% confidence interval (CI): 1.14-1.43; I^2=34.8%]. The increased risk regarding specific domains was 1.22 (95% CI: 1.09-1.37; I^2=13.4%, n=10) for occupational domain, 1.34 (95% CI: 0.98-1.83; I^2=53.7%, n=6) for leisure-time domain, and 1.55 (95% CI: 1.27-1.89; I^2=0.0%, n=2) for total sedentary behavior. Larger pooled RRs were observed among studies with adjustment for physical activity and studies without adjustment for body mass index.

Conclusions Higher levels of sedentary behavior, total and occupational sedentary behavior in particular, increase the risk of endometrial cancer. Future studies are needed to verify domain-specific associations based on objective quantification of sedentary behavior, as well as the interaction of physical activity, adiposity and sedentary time on endometrial cancer.

Strength and limitation

1. The present systematic review and meta-analysis was conducted following the registered proposal, PRISMA and Moose guidelines, and NOS to report results and evaluate study quality, respectively.
2. Previous studies reported inconsistent associations between sedentary behavior and endometrial cancer.
3. Little is known regarding the association between specific domains of sedentary behaviour and endometrial cancer, as well as the potential role of obesity and physical activity in the association.
4. The results would add to the existing evidence by showing a possible domain-specific effect of sedentary behavior on endometrial cancer.
5. The review highlighted the importance of evaluating the interaction of sedentary behavior with other lifestyle factors when analyzing the association between sedentary behavior and endometrial cancer.

Introduction

According to the updated global cancer burden estimates from *Global Cancer Statistics 2020*[1], endometrial cancer ranks the sixth most common cancer in women worldwide, and the most common gynecologic cancer in several developed regions, including the North America, Eastern and Northern Europe. A worrying trend is that, since the late 1990s, the incidence of endometrial cancer has rapidly increased in several developing countries during urbanization, including some Asian countries (Japan, Singapore, China, the Philippines), and South Africa[2]. It is suggested that this phenomenon may be explained, at least partly, by changing environmental and lifestyle risk factors in these regions, such as the epidemic of obesity, lack of physical activity, and long-time sitting[3-4]. Although obesity is a known risk factor for endometrial cancer, the association between sedentary behavior and endometrial cancer remains largely unclear. Sedentary behavior includes sitting, reclining or lying behavior characterized by low energy expenditure[5]. During the past decades, technological innovation has influenced how people work and spend leisure-time, and has led to inevitably prolonged sitting time, particularly for desk-based office work and screen-based recreation. According to *the World Health Organization (WHO) Guidelines on Physical Activity and Sedentary behavior (2020)*, long sedentary time is associated with various deleterious health outcomes, including all-cause mortality, cardiovascular diseases, obesity, and more recently total cancer morbidity[5].

Three previous meta-analyses investigating the association between sedentary behavior and several types of cancers[6-8], reported a 28% to 36% increased risk of endometrial cancer among individuals with higher levels of sedentary behavior by summarizing three to eleven individual studies. However, some evidence on sedentary behavior and endometrial cancer has not yet been included in existing review and meta-

analyses, the level of evidence for cancer-specific incidence remains unclear[9-10]. Given inconsistent results reported, an up-to-date review of current evidence is in urge need to clarify the association between sedentary behavior and endometrial cancer risk.

No distinction in domains of sedentary behavior is a likely source of the discrepancy in previous findings. The *WHO Guidelines 2020* has operationalized the definition of sedentary behavior to further include self-reported sitting that can be assessed in various domains (including leisure-time and occupational domain) and total sedentary behavior.[5] Meanwhile, the association with adverse health outcomes may differ in certain domains of sedentary behavior[11]. It is increasingly recognized that confounding factors may vary greatly across domains of sedentary behavior, and contribute to varied associations with health-related outcomes[12]. For example, while occupational sedentary behavior is related to education and socioeconomic variables, leisure-time sedentary behavior is likely linked to lifestyle factors such as diet and obesity[13]. Moreover, these two domains are often inversely correlated to physical activity. However, current evidence has been derived mostly from studies that have broadly categorized sedentary behavior according to the level of sitting time involved[7, 14]. Domain-specific analyses, taking account of variability in study characteristics, may help to further clarify the investigated association and to refine the prevention strategy of endometrial cancer.

Besides, the complex interplay within lifestyle factors, including obesity, physical activity and sedentary behavior, needs to be taken into consideration within the context. Obesity is a known risk factor for endometrial cancer, with a clear dose-response relationship (the higher the body mass index, the greater the risk), detailed documented by the International Agency for Research on Cancer (IARC) working group[15]. Given that prolonged sitting is likely to be related with high BMI, obesity thus may be a

potential mediator linking sedentary behavior to cancer incidence. Under this circumstance, studies adjusting for BMI as a confounding factor may attenuate the true effects of sedentary behavior when evaluating its impacts on endometrial cancer. A few studies have probably recognized this issue and provided results without and with additional adjustment for BMI[16-19]. In addition, although less evidence presented, similar concerns have been raised with regard to physical activity, which has potential protective effect on cancer risk[4, 20-21].

In this systematic review and meta-analysis, the primary aim was to analyze comprehensively the existing studies of the associations between domain-specific (occupational and leisure-time) and total sedentary behavior and endometrial cancer risk, with additional attention paid to potential difference of the findings related to different adjustment strategy for BMI and physical activity.

Methods

We performed this systematic review and meta-analysis in accordance with the 2020 guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] and guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as well[23]. Reported items in this systematic review and meta-analysis strictly followed the checklist of PRISMA 2020 and MOOSE (Table S1, S2). The full review protocol was registered with International prospective register of systematic reviews (PROSPERO) under the registration number CRD 42021246283.

Search strategy and selection criteria

We conducted a comprehensive literature search of the electronic databases, including Embase, MEDLINE and PubMed. The search was updated on 28 February 2023, and publication language was limited to English. The search combined MeSH heading with

text search using varied terms related to "sedentary behavior" and "endometrial cancer". Detailed search terms and strategy used are listed in the Supplemental Text. Terms associated with physical activity and physical inactivity (insufficient or low levels of physical activity) were also searched since some sedentary behavior studies were conducted in the name of physical activity. In addition, we screened and manually checked reference lists from selected articles and relevant reviews to identify other potentially eligible studies.

The inclusion criteria for the studies included in the systematic review are listed as follows: (1) observational human study that published in English; (2) evaluated the association between sedentary behavior (total sitting time, leisure-time sedentariness including sitting, television or screen viewing, and occupational sedentary behavior) and incidence of endometrial cancer. Apart from all criteria for systematic review, the studies further included in the meta-analysis should also meet the following criteria: report a relative risk (RR), odds ratio (OR), hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) for highest versus lowest level of sedentary behavior, or provide sufficient data to calculate them.

Studies were excluded if they were published as conference abstracts or papers, letters and short surveys. We also excluded studies for physical activity that used terms "sedentary" or "sitting" to represent the lowest or reference level of physical activity categories.

Data extraction and quality assessment

Two authors (Lei Yuan and JingYi Ni) independently performed the literature search and reviewed potential studies in compliance with the selection criteria. The disagreements were resolved through discussion. The authors were contacted by e-mail

for full text or additional information when needed. Extracted information from each study included: (a) name of the first author and publication year; (b) study design; (c) study area; (d) enrollment period for cohort study, or study period for case-control study; (e) age at baseline; (f) follow-up length for cohort study; (g) study population; (h) sample size; (i) case number; (j) sedentary behavior type and its assessment; (k) diagnostic criteria of EC, and if available, its specific cancer classification; (l) results and if possible, reported risk estimates and their 95% CI; (m) adjusted covariates, if possible, particular attention to adjustment for body mass index (BMI), and physical activity.

In the main analysis, we prioritized risk estimates that were adjusted for physical activity, and unadjusted for BMI in studies with a separate step of BMI adjustment, or other adiposity-related factors when available, due to potential intermediate role of obesity. If study populations overlapped between included studies, we selected the article that contained the most comprehensive data[24-25].

Quality assessment of the studies included in the meta-analysis was assessed based on the validated Newcastle-Ottawa Scale (NOS) for observational studies[26-27], where each study was evaluated based on three categories: participant selection (four items, one star for each item); comparability of study groups (one item, up to two stars); exposure or outcome assessment (three items, one star for each item). Thus, a study can be awarded up to a maximum of nine stars[27]. We used the comparability category of the NOS to determine whether the crucial confounders had been adjusted, that is, the study can be awarded one star for adjusting for age, two stars for also controlling for physical activity. The quality of the study was classified as poor ($\leq$ 4 stars), fair (4-6 stars), and good ($\geq$ 7 stars). We also extracted confounders adjusted by each study, and evaluated whether the study had adequate adjustment for potential confounders, that is,

adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity[28].

Statistical analysis

Given underlying methodological heterogeneity across studies including study design, participants' characteristics, and adjusted confounders, random effects models were applied to summarize domain-specific (occupational and leisure-time), and total RRs and their 95% CIs for the highest level versus the lowest level of sedentary behavior, regardless of whether statistically significant heterogeneity was found. The highest and lowest values were defined by individual studies with different underlying definitions and different measurements of sedentary behavior. Detailed definition and assessment of sedentary behavior in individual study were summarized in Table S3. The natural logarithms of the study-specific RR and corresponding standard errors were calculated using the inverse variance approach[29]. Employing random effects models, the RR of each study was weighted using random effects weights and was further combined to obtain an overall estimate. When studies reported subgroup-specific results such as estimates of different calendar periods, we fitted a fixed effects model to combine the separate results to obtain the overall estimates for the main analysis[25]. For studies not using the lowest category as the reference category of sedentary behavior[9-10, 17, 30-31], we used the method by Hamling to recalculate the estimates through changing the lowest category as the reference category[32]. We used the I^2 statistics to test for heterogeneity between included studies. I^2 values of more than 25%, 50%, 75% were deemed to indicate low, moderate and high level of statistically significant heterogeneity,

separately. Potential publication bias was assessed by inspection of funnel plots, and further evaluated using Egger's regression test as well as Begg's correlation test. Asymmetry in the funnel plots or p value < 0.1 indicated publication bias.

Subgroup analyses were performed according to study design (cohort study, case-control study), study area (Asia, Europe and North America), sample size (≥ 5,000, and < 5,000), number of cases (≥ 500, and < 500), study quality (good, fair, poor), and adjustment for potential confounding factors (adequate, not adequate). In addition, sedentary behavior, obesity and physical activity are lifestyle factors that are complexly associated and interacted. As obesity potentially mediates the association between sedentary behavior and endometrial cancer risk, in which case the adjustment for BMI would over adjust the association, we conducted subgroup analyses stratified by whether BMI was adjusted[28]. Similarly, we also conducted subgroup analyses by whether adjusting for physical activity.

Associations with total sedentary behavior were reported in only two studies. Therefore, we also included all studies in the analysis to assess the effects of overall sedentary behavior. If a study reported results at a specific domain, we extracted the results as the nearest estimate for overall sedentariness. If a study reported results at multiple domains, we used fixed effects models to combine the separate results to obtain the overall estimates as the total level. Random-effects meta-regression analyses were then conducted to explore whether the estimates differed by main characteristics of the included study. The analyses were unavailable for domain-specific sedentary behavior analysis due to limited number of studies (n ≤ 10). The Tau-squared was used to evaluate between-study variance of each covariate.

We also performed sensitivity analyses to test the robustness of the results in the main analysis. We firstly conducted analyses by omitting one study at each time to

recalculate the pooled results to ensure the stability of the results. Secondly, we fitted the trim-and-fill analysis to inspect the impact of publication bias correction on the pooled outcomes. The statistical analyses were performed using Stata 12.0 software (Stata Corp, College Station, TX, USA). A two-tailed p value < 0.05 was deemed statistically significant.

Patient and Public Involvement

This issue is not applicable to our research since the data collected in this study is secondary data without any personal information and not transferable.

Results

Studies retrieved and characteristics

Our initial search identified 749 records. After screening and selection (Figure 1), sixteen studies were included in the systematic review of sedentary behavior and risk of endometrial cancer. The main characteristics of the included studies are shown in Table 1. Of these sixteen studies, six were from Europe[9, 17, 24-25, 31, 33], five from Asia[10, 16, 34-36] and five from North America[18-19, 30, 37-38]. All included studies assessed self-reported sedentary levels based on questionnaires, interviews, or occupations (Table S4). Detailed data and characteristics of study participants, diagnostic criteria of the outcome, and the assessment of sedentary behavior are provided in Table S3, S4.

Table 1. Study characteristics of the included studies in systematic review.

Publication	Study design	Study area	Enrolment / Study period	Age at baseline (years)	Subject (controls/cases)	Sedentary behavior	Results	NOS study quality
Dosemeci et al. (1993)[34]	Case-control study	Turkey	1979-1984	——	275/31	Occupational sedentary	OR (sedentary > 6 hr/d) = 0.50 (0.10, 4.40)	Fair (6)
Shu et al. (1993)[16]	Case-control study	China	1988-1990	18-74	536/268	Occupational sedentary	OR = 1.20 (0.70, 2.00)	Fair (5)
Zheng et al. (1993)[35]*	Cross-sectional study	China	1980-1984	≥ 30	452/452	Occupational sedentary	SIR (long sitting time) = 110	——
Olson et al. (1997)[30]	Case-control study	US	1986-1991	40-85	631/232	Occupational sedentary	OR = 0.93 (0.55, 1.56)	Good (7)
Moradi et al. (1998)[24]*	Cohort study	Sweden	1960 1970 1960 and 1970	16-95	Sub-cohort A (1960): 704904/4462 Sub-cohort B (1970): 982270/5287 Sub-cohort C (1960 and 1970): 253336/1949	Occupational sedentary	RR (1960) = 1.13 (0.99, 1.29) RR (1970) = 1.32 (1.17, 1.50) RR (1960 and 1970) = 1.30 (1.03, 1.65)	——
Moradi et al. (2000)[25]	Case-control study	Sweden	1994-1995	50-74	3368/709	Occupational sedentary	OR (1960) = 1.30 (0.80, 2.20) OR (1970) = 1.20 (0.80, 1.90) OR (1980) = 1.40 (1.00, 1.90) OR (1990) = 1.30 (0.90, 1.90)	Good (7)
Weiderpass et al. (2001)[33]	Cohort study	Finland	1970	25-64	413877/2833	Occupational sedentary	RR (high level of sedentary work) = 1.30 (1.10, 1.50)	Fair (5)
Furberg et al. (2003)[31]	Cohort study	Norway	1974-1981	20-49	24460/130	Leisure-time sedentary Occupational sedentary	RR (Grade1-sedentary activity) = 1.27 (0.69, 2.32) RR (Grade1-sedentary work) = 1.64 (0.95, 2.84)	Good (9)
Matthews et al. (2005)[36]	Case-control study	China	1997-2001	30-69	846/832	Occupational sedentary	OR (Sitting Q4) = 0.93 (0.67, 1.30)	Fair (5)

Table 1. Study characteristics of the included studies in systematic review (Continued).

Publication	Study design	Study area	Enrolment / Study period	Age at baseline (years)	Subject (controls)/cases	Sedentary behavior	Results	NOS study quality
Friberg et al. (2006)[17]	Cohort study	Sweden	1997	50-83	33723/199	Occupational sedentary Leisure-time sedentary	RR (work/occupation activity, low, mostly sitting down and sitting down more than half of the time) = 1.03 (0.76, 1.39); Additional adjustment for BMI: RR = 0.99 (0.73, 1.34) RR (watching TV/sitting, high, ≥5hr/d) = 1.80 (1.14, 2.83); Additional adjustment for BMI: RR = 1.66 (1.05, 2.61)	Good (8)
Patel et al. (2008)[18]	Cohort study	US	1992	50-74	42672/466	Leisure-time sedentary	RR (sitting ≥6 hr/day) = 1.40 (1.03, 1.89); Additional adjustment for BMI: RR = 1.18 (0.87, 1.59)	Good (7)
Gierach et al. (2009)[19]	Cohort study	US	1995-1996	50-71	70351/650	Leisure-time sedentary Total sedentary	RR (≥ 7 hr) = 1.66 (1.20, 2.88); Additional adjustment for BMI: RR = 1.21 (0.87, 1.67) RR (≥ 7 hr) = 1.56 (1.22, 1.99); Additional adjustment for BMI: RR = 1.26 (0.99, 1.62)	Good (7)
Friedenreich et al. (2010)[37]	Case-control study	Canada	2002-2006	30-79	1032/542	Occupational sedentary	OR (Lifetime occupational sedentary activity, > 16.94 hr/wk/yr) = 1.28 (0.89, 1.83)	Fair (6)
Arem et al. (2011)[30]	Case-control study	US	2004-2008	cases: 61.1; controls: 62.1	662/667	Total sedentary	OR (≥ 8 hr/d) =1.52 (1.07, 2.16)	Fair (5)
Hunter et al. (2020)[9]	Cohort study	UK	2006-2010	40-69	253171/872	Leisure-time sedentary	HR (daily TV viewing time, > 5h) = 0.59 (0.40, 0.88) HR (daily computer use time, > 3h) = 0.82 (0.55, 1.22) HR (daily total screen time, > 8h) = 0.57 (0.31, 1.03)	Fair (6)
Miyata et al. (2021)[10]	Cohort study	Japan	1988-1990	40-79	33801/79	Leisure-time sedentary Occupational sedentary	HR (TV viewing, ≥ 4hr/d) = 2.10 (0.57, 7.71) HR (Occupational activity, mainly sitting) = 2.17 (1.04, 4.56)	Good (8)

*Not included in the meta-analysis and NOS study quality assessment; Table values are mean (SD) for continuous variables.

The meta-analysis included fourteen studies after excluding two studies, in which one failed to provide 95% CI for risk estimates[35] and the other one was based on less comprehensive data among overlapped study participants[24]. In total, 882,686 participants from seven cohort studies and seven case-control studies were involved. In the meta-analysis, two studies (71,680 participants, Table 1) investigated the association between total sedentary behavior and risk of endometrial cancer, ten studies (515,163 participants) investigated the association with the assessment of occupational sedentary behavior and six studies (458,178 participants) with the assessment of leisure-time sedentariness. Three studies (91,984 participants) have adjusted for physical activity. Nine studies (321,757 participants) have adjusted for BMI in the multivariate model, and three studies (146,746 participants) took a separate step for additional BMI adjustment. Based on the Newcastle-Ottawa quality assessment scale[27], seven studies were evaluated as having fair quality, and seven as having good quality. Detailed information on the NOS quality assessment of meta-analysed studies is provided in Table S5, S6. Details of confounders adjusted by each study are presented in Table S7.

Occupational sedentary behavior

Twelve studies have investigated impacts of sedentary behavior during work on endometrial cancer, and five of them reported statistically significant association between occupational sedentary behavior and increased risk of endometrial cancer[10, 24-25, 33, 35]. However, seven studies did not observe a similar significant effect[16-17, 30-31, 34, 36-37]. Among these studies, the meta-analysis for occupational domain included ten eligible studies, involving 515,163 participants and 5,855 cases. The summary RR for high versus low occupational sedentary level was 1.22 (95% CI: 1.09-1.37, p<0.01;

I^2=13.4%, $p_{Heterogeneity}$=0.30) (Figure 2). Consistent with the inspection of the funnel plot, the results of Begg's test (p=0.72) and Egger's test (p=0.59) suggested no publication bias (Figure 3A).

The adverse effects of occupational sedentary behavior on endometrial cancer incidence persisted in nearly all subgroup analyses stratified by study design, study area, number of participants and cases, study quality, adjustment for confounders including BMI, and physical activity (Figure 2). The association between occupational sedentary behavior and endometrial cancer was stronger among studies that were cohort study ($RR_{Summary}$=1.30, 95% CI: 1.05-1.62, p=0.02; I^2=37.2%, $p_{Heterogeneity}$=0.19), studies conducted in European areas ($RR_{Summary}$=1.28, 95% CI: 1.14-1.43, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.41), studies with large number of participants (≥ 5000; $RR_{Summary}$=1.30, 95% CI: 1.05-1.62, p=0.02; I^2=37.2%, $p_{Heterogeneity}$=0.19) or cases (≥ 500; $RR_{Summary}$=1.25, 95% CI: 1.10-1.42, p<0.01; I^2=16.7%, $p_{Heterogeneity}$=0.31), and studies with good quality ($RR_{Summary}$=1.25, 95% CI: 1.01-1.56, p=0.04; I^2=35.4%, $p_{Heterogeneity}$= 0.19). There was moderate heterogeneity in the studies with adequate adjustment and with physical activity adjustment (adequate adjustment for confounders: I^2=50.3%, $p_{Heterogeneity}$=0.13; adjustment for physical activity: I^2=57.0%, $p_{Heterogeneity}$=0.10). Compared with studies without adequate adjustment or physical activity adjustment, the associations observed in these two groups were slightly attenuated, showing greater estimates and wider confidence intervals. There was only one study adjusting for BMI separately[17], and no statistically significant risk estimates were exhibited before and after adjustment (before adjustment: RR=1.03, 95% CI: 0.76-1.39; after adjustment: RR=0.99, 95% CI: 0.73-1.34).

The sensitivity analyses suggested that the association between occupational sedentary behavior and endometrial cancer risk did not change when recalculating the

pooled estimates by omitting one study at a time (Table S8). After excluding the most influential research, the summarized RR ranged from 1.19 (95% CI: 1.04-1.37) when excluding the study conducted by Moradi et al. to 1.27 (95% CI: 1.15-1.40) when excluding the study by Matthews et al.[25, 36].

Leisure-time sedentary behavior

Six prospective cohort studies (458,178 participants, 2,396 cases) have assessed the relationship between endometrial cancer and time spent sitting outside of work, including watching television (TV), videos or computer, reading, and other sedentary activities. Three of these studies found statistically significant associations between leisure-time sedentary behavior and risk of endometrial cancer[17-19], and the rest indicated non-statistically significant associations[9-10, 31]. The pooled RR for high versus low level of leisure-time sedentary behavior was 1.34 (95% CI: 0.98-1.83, p=0.07; I^2=53.7%, $p_{Heterogeneity}$=0.06), with moderate and non-statistically significant heterogeneity (Figure 4). However, these results seemed to be driven by a large study (253,171 participants, 872 cases) that reported inconsistent results with other studies (RR=0.57, 95% CI: 0.31-1.03)[9]. After excluding this study, no potential heterogeneity remained in the analysis, and the summarized association between leisure-time sedentary behavior and endometrial cancer turned out to be statistically significant ($RR_{Summary}$=1.53, 95% CI: 1.24-1.87, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.82). No evidence of publication bias was revealed according to visual inspection of the funnel plot, Begg's test (p=0.85), or Egger's test (p=0.78) (Figure 3B).

In subgroup analyses, the significance of the associations across the stratified groups also appeared to be driven by the study reported by Hunter et al. Statistically significant positive associations were observed among studies in North America

(RR$_{Summary}$=1.48, 95% CI: 1.15-1.90, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.53), studies with good quality (RR$_{Summary}$=1.53, 95% CI: 1.24-1.87, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.82), studies with small number of cases (RR$_{Summary}$=1.49, 95% CI: 1.18-1.87, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.72), studies without adjustment for BMI (RR$_{Summary}$=1.55, 95% CI: 1.24-1.93, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.62) and studies adjusted for physical activity (RR$_{Summary}$=1.62, 95% CI: 1.14-2.30, p=0.01; I^2=0.0%, $p_{Heterogeneity}$=0.61). In three studies with additional adjustment for BMI, despite a decreased effect size, the association remained significant after adjusting for BMI (before adjustment: RR$_{Summary}$=1.55, 95% CI: 1.24-1.93, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.62, versus, after adjustment: RR$_{Summary}$=1.27, 95% CI: 1.04-1.55, p=0.02; I^2=0.0%, $p_{Heterogeneity}$=0.44)

In sensitivity analyses, after excluding the most influential research, the summary RRs ranged from 1.24 (95% CI: 0.86-1.79) when excluding the study conducted by Friberg et al. to 1.53 (95% CI: 1.24-1.87) after excluding the study by Hunter et al.[9, 17] (Table S8).

Total sedentary behavior

Two studies from the US, one large cohort study[19], and one case-control study[38], including 71,680 participants and 1,317 cases in total, have investigated the effect of total sedentary behavior (evaluated as total time spent sitting during a 24-hour day) on endometrial cancer risk, and both proved significantly adverse effect. The pooled RR for high versus low analysis of total sedentary behavior and endometrial cancer risk was 1.55 (95% CI: 1.27-1.89, p<0.01; I^2=0.0%, $p_{Heterogeneity}$=0.91) (Figure 5). After combining all included studies as evaluating overall sedentary behavior, the pooled RR for high versus low analysis was 1.28 (95% CI: 1.14-1.43, p<0.01; I^2=34.8%, $p_{Heterogeneity}$=0.10) (Figure 5). No evidence of publication bias was indicated through

visual inspection of the funnel plot (Figure 3C), which was supported by Begg's test (p=0.38), and Egger's test (p=0.29).

The meta-regression analyses showed that all pre-specified study characteristics explained little of the heterogeneity for overall sedentary behavior (Table S9). There was weak evidence that associations were stronger for cohort studies, studies conducted in North America, studies with large sample size (n ≥ 5,000), good quality and adequate adjustment of confounding factors as well as adjustment for physical activity (Figure 5).

Discussion

In this systematic review and comprehensive meta-analysis, 55% increased risk of endometrial cancer was observed among individuals with higher levels of total sedentary behavior (RR=1.55, 95% CI: 1.27-1.89), 22% among those with occupational sedentary behavior (RR=1.22, 95% CI: 1.09-1.37), and 34% with borderline significancy among those with leisure-time sedentary behavior (RR=1.34, 95% CI: 0.98-1.83). The overall increased risk disregarding specific domains was 27% (RR=1.28, 95% CI: 1.14-1.43). The pooled associations were consistent within subgroups stratified according to study design, sample size, and adjustment strategy for physical activity and BMI.

The present results added to the existing evidence by showing a possible domain-specific association between sedentary behavior and endometrial cancer, particularly for total and occupational domain. Subgroup analyses were generally supportive of the overall estimates. Our results are partially in line with three previous meta-analyses that focused on effect of sedentary behavior on all-site cancers[6-8]. Including eight studies, Schmid et al.[6] reported a 36% increased risk of endometrial cancer among participants with higher levels of overall sedentary behavior. However, this research did not find a statistically significant association for occupational domain, which could be attributed to the limited number of studies included (n=4) and their heterogeneous quality. Including three prospective studies, Shen et al.[7] reported a 66% increased risk of endometrial cancer for the defined sedentary behavior that was assessed by total sitting and TV viewing time. With limited number of studies included, this research did not discuss on potential heterogeneity of the studies. The most recent meta-analysis was an umbrella review based on eleven case-control and cohort studies, their results showed that higher overall sedentary behavior was associated with a 29% higher risk of

endometrial cancer[8]. Moreover, differences in geographic region and study design were found to have larger impacts on the results. However, caution is needed when interpreting their findings, as the investigated outcomes were more than one specific site, and the authors called into attention the importance of adjusting for obesity in the context, which could be misleading given its mediating role. Our research found that the positive associations between sedentariness and endometrial cancer were more pronounced in studies with high quality, prospective design and large sample size. These studies were more prone to reveal the true association between sedentary behavior and endometrial cancer by reducing possibility of misclassification and selection, recall, and confounding bias.

While we found a statistically significant increased risk of endometrial cancer related to higher levels of occupational sedentary behavior, the results related to leisure-time sedentary behavior was borderline significant. Possible explanations for domain-specific differences may be attributed to changes of sedentary behavior over time, susceptible population, and exposure window across the life span[12]. Compared with leisure-time sedentary behavior, occupational sedentary behavior is more frequently and closely associated with stable biological accumulation of early-onset and long-term exposure of prolonged, uninterrupted sitting[39]. Moreover, leisure-time sedentary behavior interacts in a complex way with other lifestyle factors, such as diet, physical activity, and obesity in association with health outcomes[13]. Failure to account for these factors in research is likely to yield biased results. Besides, the domain-specific differences may be explained, at least partly, by the small number as well as heterogeneity of studies within leisure-time domain, in which the pooled estimates were dominated by a study with a large sample size showing contrasting findings[9]. Further longitudinal studies incorporating the measures of different domains are needed to

better clarify the domain-specific association and the difference across domains.

Subgroup-analyses suggested greater effect size in studies with adjustment for physical activity. Emerging evidence has shown that the sedentary behavior is distinct from lack of physical activity because of its unique postural and intervenable health hazards effects that cannot be offset by physical activity[40]. Without proper adjustment for physical activity, the real correlation between sedentary behavior and endometrial cancer could be attenuated due to the role of physical activity in reducing cancer risk by healthy body weight maintenance and obesity prevention[12, 41]. However, most included studies in the analysis did not adjust for physical activity. Our findings highlight the importance of considering the interactive effects of sedentary behavior and other lifestyle factors may have on endometrial cancer in future studies. Novel analytical methods, such as marginal structural models with time-varying exposure assessment, may be particularly important in evaluating the interactive effects of sedentary behavior, physical activity and obesity in association with endometrial cancer, as well as identifying critical exposure windows[42, 43, 44].

It is widely hypothesized that sedentary behavior may increase the risk of cancers due to low energy expenditure and by inducing obesity, a well-understood risk factor for endometrial cancer[45]. Under this circumstance, adjusting for obesity indices (mostly BMI) may lead to overadjustment of the association and produce a less pronounced risk estimate. Realizing this issue, three studies included in the meta-analysis have reported respective results with and without adjustment for BMI[17-19]. The pooled estimates of these studies showed that the association between sedentary behavior and endometrial cancer attenuated but remained statistically significant after adjusting for BMI, suggesting that other mechanisms distinct from obesity-related pathways likely exist.

The biological mechanisms by which sedentary behavior increases endometrial

cancer risk remains unclear. Several pathways related to metabolic abnormalities and insulin sensitivity, chronic systemic inflammation, and endogenous sex hormones are suggested as the main hypothesis linking physical activity, sedentary behavior and obesity to cancer incidence[41, 45-46]. Besides, long-time sitting posture might also contribute through its adverse effect on mitochondrial and endothelial function[41]. Given the complex mechanisms, further analysis may help better understand the potential mechanisms through rating evidence separately among different study populations, particularly in non-obese and obese, pre-menopausal and post-menopausal women, populations with different intensity of physical activity, and for different histological subtypes[42].

Strengths of this systematic review and meta-analysis include strictly following the uniform criteria for study selection, quality evaluation and reporting. Also, our meta-analysis included substantial numbers of participants and cancer cases, ensuring sufficient statistical power to yield precise associations. Furthermore, our meta-analysis revealed some novel insights not previously investigated, such as varied effects of sedentary behavior on endometrial cancer across different domains. This is also the first study taking the complex interaction between obesity, physical activity, and sedentary behavior into account in the association. Additional merits include the robustness of the pooled associations in multiple subgroups and sensitivity analyses within different sedentary behavior domains.

There are some limitations in our review at the level of the meta-analysis and at the level of included studies that need to be noticed. At the review level, we observed evidence of heterogeneity between subgroups especially within leisure-time domain. However, this seems to be mainly driven by one large-sampled study with contradicting conclusion. After excluding the study, no more indication of heterogeneity was shown.

Also, the pooled associations showed little evidence of heterogeneity across different domains of sedentary behavior and endometrial cancer. Secondly, the small number of studies included in our meta-analysis could lower the statistical power and limit the ability to examine the existence of small study effects and excess significance bias. For total domain of sedentary behavior, only two studies estimated the association with endometrial cancer. In such case, the reliability of the pooling may be influenced, and the results should be interpreted with caution[47]. Thirdly, it should be emphasized that there could be wide interindividual variation in level of sedentary behavior, with all studies assessing self-reported levels of sedentariness based on questionnaires, interviews, or job titles, and neither of these studies applied repeated measures or corrected for measurement errors. Most included studies compared high versus low level of sedentary behavior and thus, the effect estimate may be inflated compared to a linear analysis. Moreover, definitions of high versus low levels of sedentary behavior varied greatly in the included studies. For example, the highest level of sedentary behavior in some studies may vary from more than 3 to 8 hours/day[9, 38], which may decrease the comparability among studies. There is therefore an urgent need for the combination of self-report assessment, objective quantitative monitors in further prospective cohort studies, to study these associations and improve understanding of benefits brought by reductions in sedentary time. Caution is warranted in interpreting our findings, as despite the association between sedentary behavior and increased endometrial cancer risk, the relatively low cancer incidence means that higher relative risks observed may only lead to slight increases in absolute risk.

Conclusion

Despite the little evidence on domain-specific effect of sedentary behavior on

endometrial cancer, we found, in general, higher levels of total and occupational sedentary behavior increase the risk of endometrial cancer. The association between leisure-time sedentary behavior and endometrial cancer is borderline significant. The pooling may be influenced by limited studies and variations in assessment of sedentary behavior and should be interpreted with caution. Future longitudinal studies employing objective physical activity monitors may help to clarify the quantitative association between total and domain-specific sedentary behavior and endometrial cancer. The interactive effects of physical activity, obesity and sedentary behavior on endometrial cancer warrant further investigation as well.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests None declared.

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Authors' contributions The literature reviews were conducted by LY and JN. LY and ZL drafted the manuscript based on discussion involving all the authors, and contributed to the integrity of the data and statistical analysis. ZL and XW contributed to study concept and design, and critical revision of the manuscript and administrative support. WL, and QY supervised the study, critically reviewed the draft and approved the final version before submission.

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Figure legends

Figure 1. PRISMA 2020 flow diagram of literature search and selection.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 2. Pooled association between occupational sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

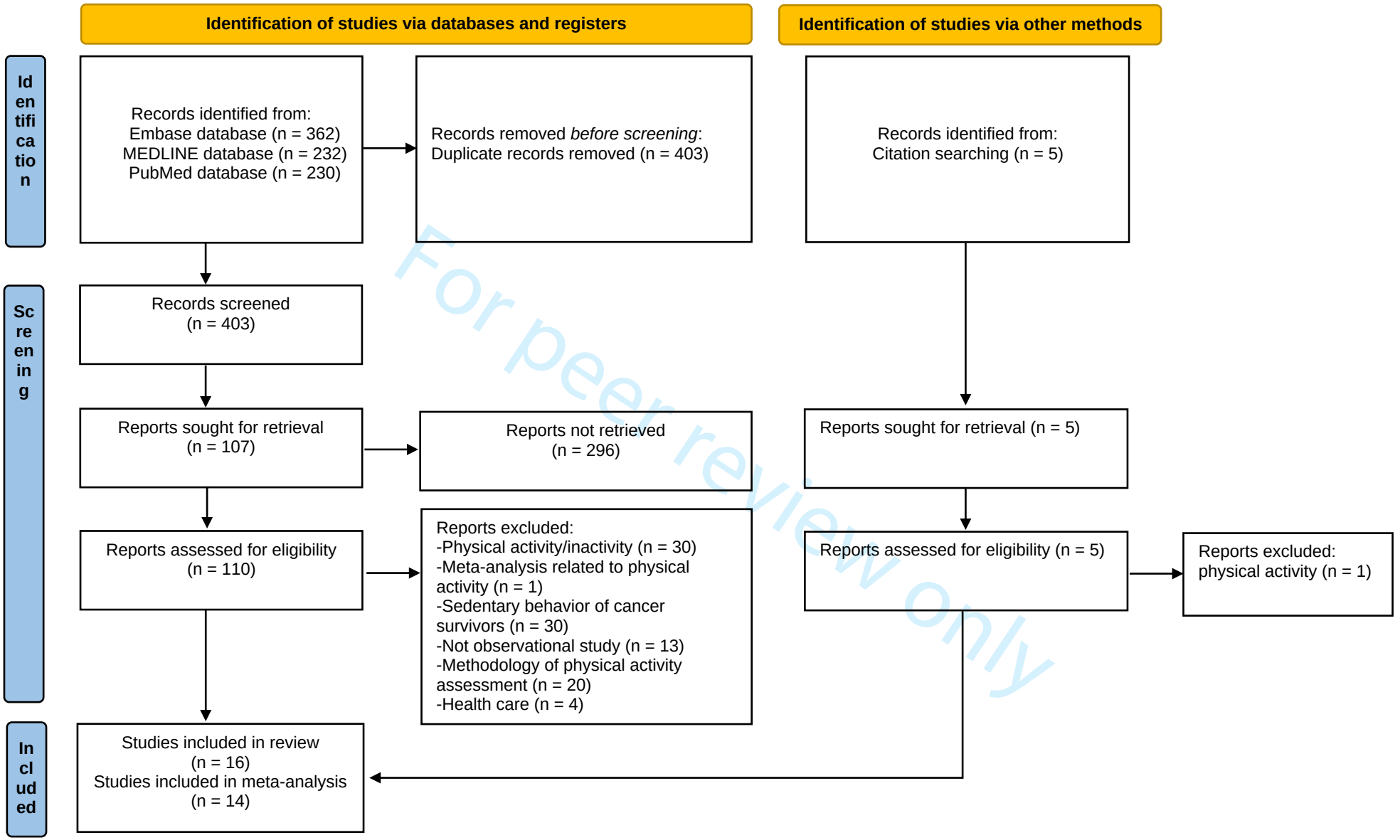
Figure 3. Pooled association between leisure-time sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

Figure 4. Pooled association between total sedentary behavior and endometrial cancer.

Note: I^2 for heterogeneity between studies; *P* value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

Figure 5. Funnel plot of overall sedentary behavior and endometrial cancer.



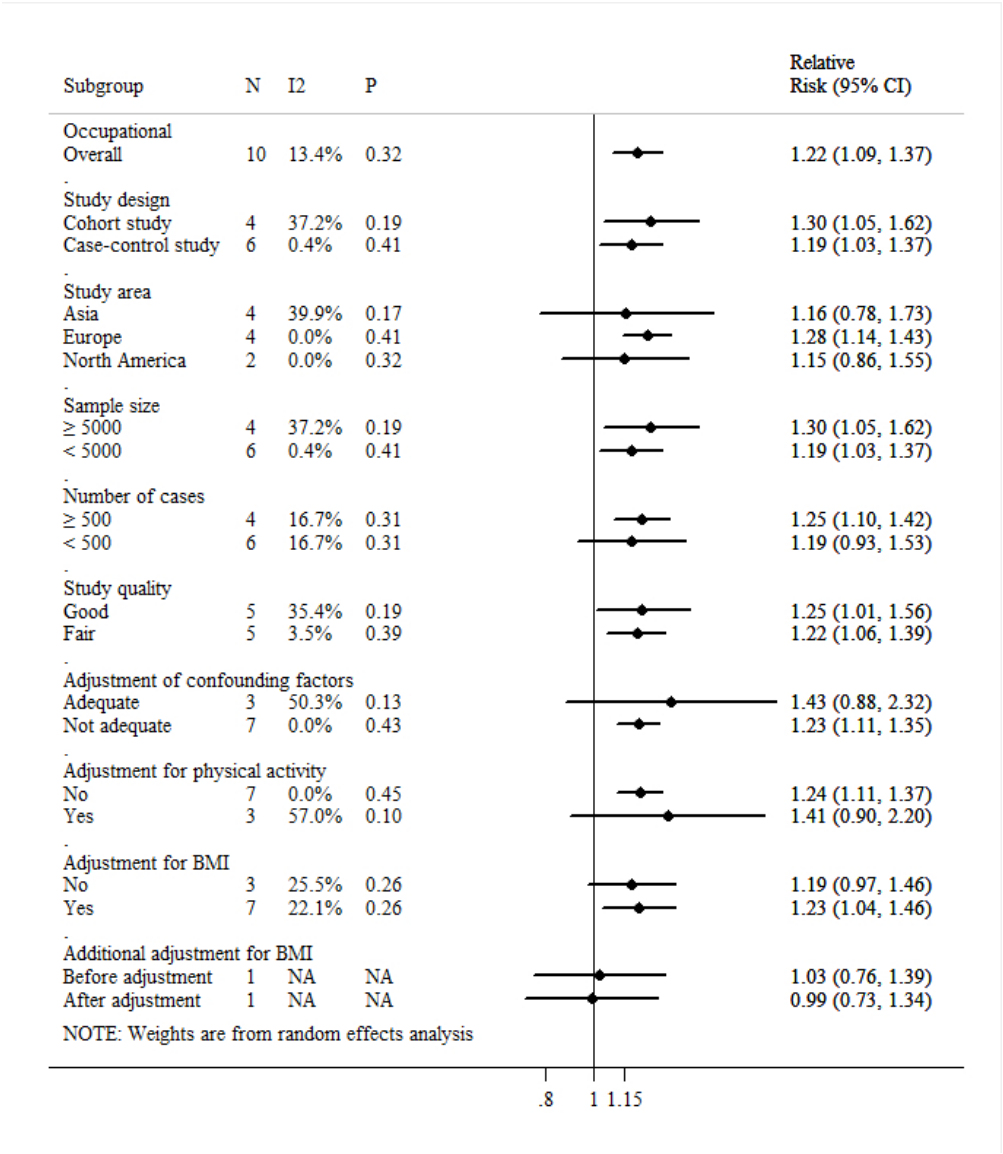


Figure 2. Pooled association between occupational sedentary behavior and endometrial cancer. Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

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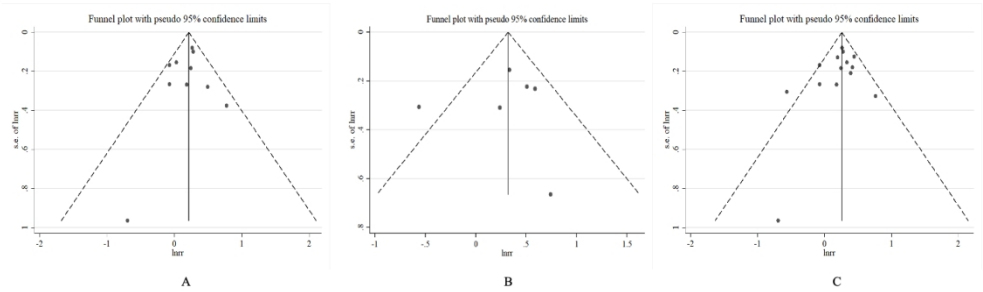

Figure 3. Funnel plot of overall sedentary behavior and endometrial cancer.

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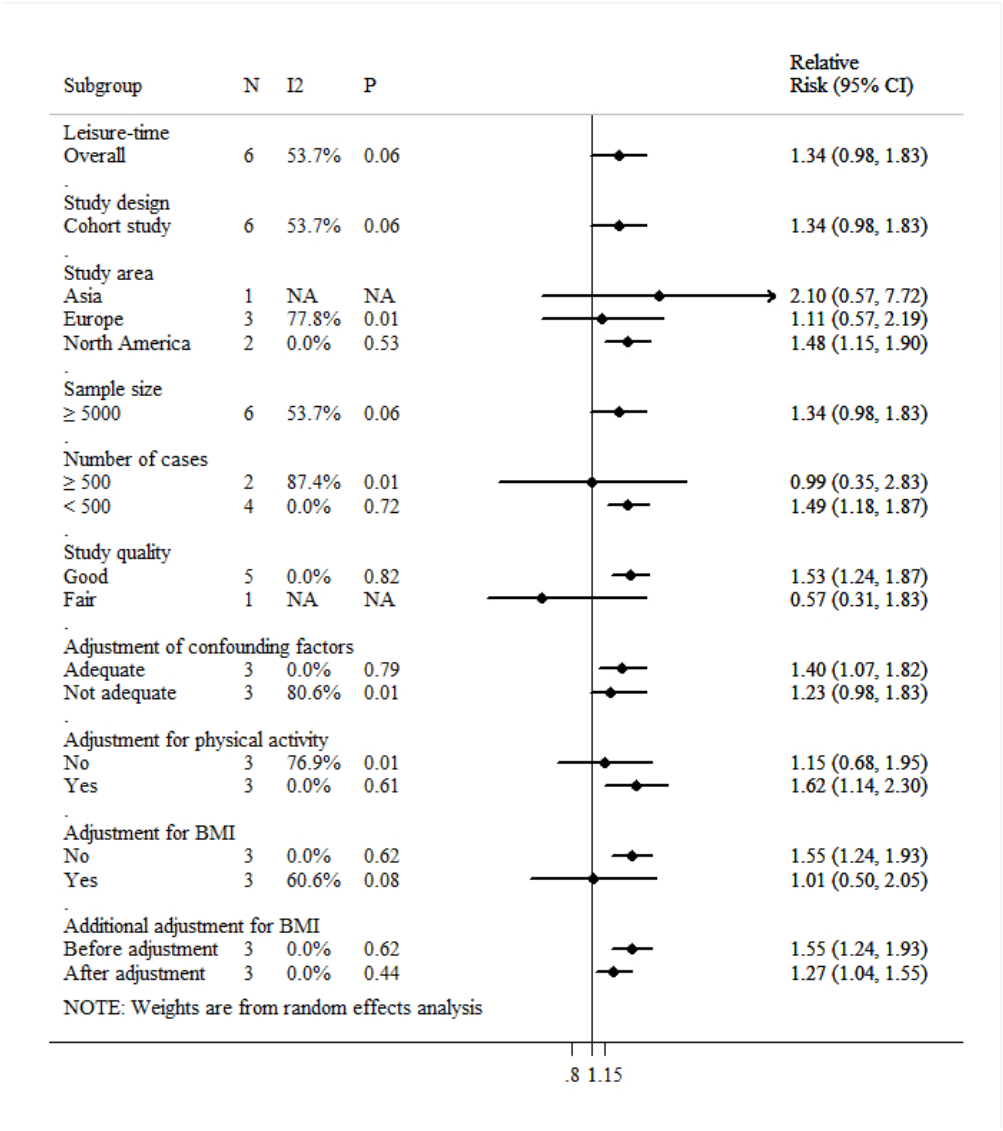

Figure 4. Pooled association between leisure-time sedentary behavior and endometrial cancer. Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

246x277mm (72 x 72 DPI)

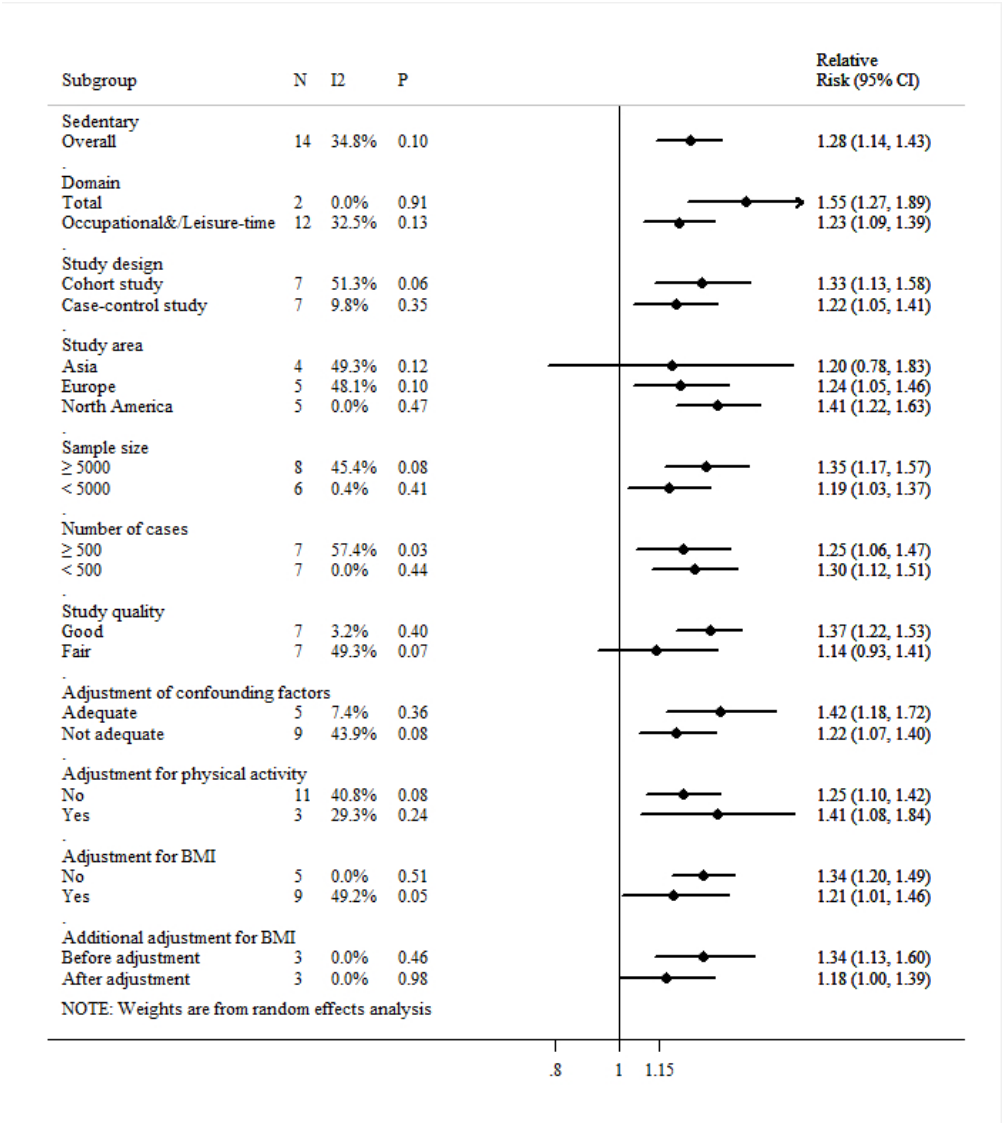

Figure 5. Pooled association between total sedentary behavior and endometrial cancer. Note: I2 for heterogeneity between studies; P value for heterogeneity in subgroups; NA: not applicable. Adequate adjustment denotes adjustment for at least five of seven confounders: age; diabetes, blood glucose; hypertension, blood pressure; age at menarche, menopausal status and age, parity; smoking; oral use of contraceptives, use of hormone replacement therapy; and physical activity. Adjustment for BMI denotes adjustment for BMI in the multivariate model.

247x277mm (72 x 72 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	7, Figure 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	7-8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9-11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9-10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9-10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10-11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9-10

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	12, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	12
Study characteristics	17	Cite each included study and present its characteristics.	12, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2,4-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	12-19, Table 1, Supplemental material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12-19, Figure 2,4-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	12-19, Figure 2,4-5, Supplemental material
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12-19, Supplemental material
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	12-19, Figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	12-19, Supplemental material
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	20
	23b	Discuss any limitations of the evidence included in the review.	20-22
	23c	Discuss any limitations of the review processes used.	22-24
	23d	Discuss implications of the results for practice, policy, and future research.	22-24
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	26
Competing interests	26	Declare any competing interests of review authors.	26
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	26

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

MOOSE reporting checklist for meta-analyses of observational studies.

Reporting section and item		Reported on page
Reporting of background		
1	Problem definition	5-6
2	Hypothesis statement	6-7
3	Description of study outcome(s)	7
4	Type of exposure or intervention used	7
5	Type of study designs used	7
6	Study population	7
Reporting of search strategy		
1	Qualifications of searchers (eg, librarians and investigators)	7-8
2	Search strategy, including time period included in the synthesis and keywords	7-8, Supplementary Text
3	Effort to include all available studies, including contact with authors	8
4	Databases and registries searched	7
5	Search software used, name and version, including special features used (eg, explosion)	7
6	Use of hand searching (eg, reference lists of obtained articles)	7-8
7	List of citations located and those excluded, including justification	Figure 1
8	Method of addressing articles published in languages other than in English	8
9	Method of handing abstracts and unpublished studies	8
10	Description of any contact with authors	8-9
Reporting of methods		
1	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	8-9
2	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	8-9
3	Documentation of how data were classified and coded (eg, multiple raters, binding, and interrater reliability)	9-12, Supplemental material
4	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9-10, Supplemental material
5	Assessment of study quality, including binding of quality assessors; stratification or regression on possible predictors of study results	9-10, Supplemental material
6	Assessment of heterogeneity	10
7	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analyses) in sufficient detail to be replicated	10-12
8	Provision of appropriate tables and graphics	Figure 1, Supplemental material

Reporting of results		
1	Graphic summarizing individual study estimates and overall estimate	Figure 2, 4-5
2	Table giving descriptive information for each study included	Table 1, Supplemental material
3	Results of sensitivity testing (eg, subgroup analysis)	16-19, Supplemental material
4	Indication of statistical uncertainty of findings	16-19, Supplemental material
Reporting of discussion		
1	Quantitative assessment of bias (eg, publication bias)	20-22, Figure 3
2	Justification for exclusion (eg, exclusion for non-English-language citations)	20-24
3	Assessment of quality of included studies	20-22, Supplemental material
Reporting of conclusion		
1	Consideration of alternative explanations for observed results	24-25
2	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	24-25
3	Guideline for future research	24-25
4	Disclosure of funding source	26

Supplementary Materials

Supplemental Text. Search terms and strategy

Table S3. Characteristics of participants and assessment of sedentary behaviour and outcome.

Table S4. Detailed data underlying the meta-analysis.

Table S5. Newcastle-Ottawa quality assessment scale for cohort study

Table S6. Newcastle-Ottawa quality assessment scale for case-control study

Table S7. Detailed information on adjusted confounders of studies included in systematic review

Table S8. Influence analysis of sedentary behaviour and endometrial cancer (given named study is omitted).

Table S9. Results of meta-regression analyses on individual study characteristics for studies included in the meta-analysis of the association between sedentary behaviour and the risk of endometrial cancer.

Search terms and strategy

Search strategy in Embase/MEDLINE

('sedentary behavior':ab,ti OR 'physical inactivity':ab,ti OR 'sedentary lifestyle':ab,ti OR 'sedentary behaviour':ab,ti OR sedentary:ab,ti OR 'sitting time':ab,ti OR 'screen time':ab,ti OR 'television viewing':ab,ti OR 'physical activity':ab,ti) AND ('endometrial cancer':ab,ti OR endometrium:ab,ti OR 'uterus cancer':ab,ti OR 'uterine cancer':ab,ti OR 'corpus uteri cancer':ab,ti)

Search strategy in PubMed

((sedentary behavior[MeSH] OR physical inactivity[Title/Abstract] OR sedentary lifestyle[Title/Abstract] OR sedentary behaviour[Title/Abstract] OR sedentary[Title/Abstract] OR sitting time[Title/Abstract] OR screen time[Title/Abstract] OR television viewing[Title/Abstract] OR physical activity[Title/Abstract]) AND (endometrial cancer[MeSH] OR endometrium[Title/Abstract] OR uterus cancer[Title/Abstract] OR uterine cancer[Title/Abstract] OR corpus uteri cancer[Title/Abstract]))

Table S3. Study characteristics of the included studies in systematic review.

Publication	Participants' characteristics	Follow-up period	Outcome		Sedentary behavior	Definition and assessment of sedentary behavior
			Diagnostic criteria	Specific cancer classification		
Dosemeci 1993	Hospital-based study population.	——	——	——	Occupational sedentary	Occupational Classification (SOC) code system: the sitting-time scale was defined as low activity (sedentary, i.e., sitting more than six hours a day); moderate activity (mod, i.e., sitting two to six hours a day); and high activity (active, i.e., sitting less than two hours a day)
Shu 1993	Cases were identified through the population-based Shanghai Cancer Registry; female controls were individually matched to the cases on age through Shanghai Resident Registry.	——	Histopathologically confirmed	Adenocarcinomas (76.2%), adenosquamous cancers (6.3%), other type (13.4%), and unspecified (4.1%).	Occupational sedentary	Interview using standardized coding scheme: sitting time index assessing the amount of time in a sitting posture on the job. Job with long sitting-times were defined as those with more than 80% of working hours spent sitting; moderate sitting-time jobs as 20-80% of working hours of time spent sitting; short sitting-time jobs as less than 20% of time spent sitting
Zheng 1993*	Employment information for incident patients with cancer aged 30 years or older whose disease was diagnosed during the period 1980-1984 among the residents of urban Shanghai was compared with occupational data from the 1982 census for the same population.	——	ICD-9, code 182	——	Occupational sedentary	Same as Shu et al.1993

Olson 1997	Incident cases of primary endometrial cancer were identified from the major hosptials in western New York State. Controls without prior hysterectomy were selected from the community by age.	——	Histologically confirmed	Adenomatous carcinoma	Occupational sedentary	Three measures were used for occupational activity ： an index of cumulative activity; the number of years in occupations with medium, heavy, or very heavy activity; and the activity level of the most recent job. An estimate of physical activity associated with employment was obtained from a detailed occupational history covering all jobs held for 6 months or longer. Occupations for job title and industry were coded according to the U.S. Department of Commerce Alphabetical Index of Occupations for the 1980 Census, and the U.S. Department of Lahor's Estimates of Worker Trait Requirements were used to classify the activity level of each job as sedentary, light, medium, heavy, or very heavy based on job title and industry.
Moradi 1998*	Swedish Cancer Environment Registry III (the national Swedish Cancer Register for 1971-1989 linked with the national population censuses from 1960 and 1970)	1971-1989	ICD-7, code 172 and were histologically verified	——	Occupational sedentary	Occupations coding scheme; classified each occupation according to the estimated physical demands of the job, as very high, high, moderate, light and sedentary activity. Assessments were done independently by 3 Swedish specialists in occupational medicine with long experience in job classification.

Moradi 2000	Postmenopausal women with an intact uterus and no previous breast or endometrial cancer diagnosis; Cases were women with an incident, primary, histopathologically confirmed endometrial cancer identified through the six regional cancer registries in Sweden; Control women were randomly selected from the continuously updated population register including all residents of Sweden.	——	Histopathologically confirmed	——	Occupational sedentary	Occupations coding scheme; classified each occupation according to the estimated physical demands of the job, as very high, high, moderate, light and sedentary activity. Assessments were done independently by 3 Swedish specialists in occupational medicine with long experience in job classification.
Weiderpass 2001	Population Census of Finland 1970 excluded women in the two highest social classes.	1971-1995	ICD-9, code 182	——	Occupational sedentary	A national job-exposure matrix (FINJEM) calculated the product of level and probability of an exposure, and subdivided into three categories: zero (reference category); low (roughly below median among job titles with exposure probability > 0); and medium/high (called for simplicity `high'; defined as equal or above the median among job titles with exposure probability > 0)
Furberg 2003	Alive women with complete data and no diagnosis of any malignant disease 1 year after participation in Norwegian National Health Screening Service's program.	1981-1996	Incident, primary, histopathologically confirmed carcinoma of the endometrium	127 adenocarcinomas (1 serious papillary adenocarcinoma = type II-carcinoma),	Recreational sedentary	Recreational activity: Grade1, Reading, watching television or other sedentary activity; Grade2, Walking, bicycling or other activity for at least 4 hr per week; Grade3, Recreational athletics, heavy gardening or similar activities at least 4 hr per week; and Grade 4, Regular (several times a week) training or participation in athletic competitions

				and 3 unspecified carcinomas	Occupational sedentary	Occupational activity: Grade1, mostly sedentary work; Grade2, A lot of walking; Grade3, A lot of walking and lifting; and Grade4, Heavy manual work. The same team of trained nurses conducted interviews with the participants at the screening center in both surveys to confirm the information given
Matthews 2005	Incident cases aged 30-69 who were permanent residents were identified from the Shanghai Cancer Registry; Controls, frequency matched to cases by age (±5 years), were randomly selected from permanent female residents using the Shanghai Resident Registry. Women who had a hysterectomy were not eligible.	____	The diagnosis of each case was confirmed by medical chart review and a review of the available pathology slides by senior study pathologists	____	Occupational sedentary	Occupations were classified into high, medium, or low levels of estimated sitting time and activity level using job codes based on self-reported jobs held for at least 3 years
Friberg 2006	Cohort members from mammography screening program, women diagnosed with cancer (other than nonmelanoma skin cancer) and those having had a hysterectomy before returning the follow-up questionnaire, and with missing information on physical activity were excluded.	1997-2005	The Swedish Cancer Register and the Regional Cancer Register	____	Occupational sedentary	Duration of specific activities was asked and assigned mean metabolic equivalent (MET) values [multiples of MET (kcal kg-1h -1)] based on specific activities within corresponding categories in a physical activity compendium. Occupational activity: low: mostly sitting (1.3 MET/h), and sitting down more than half the time (1.8 MET/h); high: mostly standing (2.2 MET/h), doing lifts (2.6 MET/h), a lot of lifts (3.0 MET/h), and heavy labor (3.9 MET/h)
					Recreational sedentary	For leisure time inactivity, there were five predefined categories for time spent per day watching TV/sitting (inactive leisure time, <1 hour daily to >6 hours

						daily, 1.2 MET/h)
Patel 2008	Postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the US, excluded women who reported prevalent cancer (except nonmelanoma skin cancer) or not being postmenopausal or who had a hysterectomy or unknown hysterectomy status at baseline.	1997-2003	Self-report on follow-up questionnaire and subsequently verified from medical records or linkage with state cancer registries, and the National Death Index	Endometrial carcinomas	Recreational sedentary	Based on the question "During the past year, on an average day, (not counting time spent at your job) how many hours per day did you spend sitting (watching TV, reading, etc.)?" Responses included "none, less than 3, 3–5, 6–8, more than 8hr/day." Sedentary behavior at baseline was categorized as 0–<3, 3–5, ⩾6 or missing hr/day
Gierach 2009	Female members of the AARP (the American Association of Retired Persons) and resided in US states.	1995-2003	State cancer registries, and histology was defined using ICD for Oncology codes, 3rd edition	Adenocarcinomas (95.0%)	Recreational sedentary	Information on physical inactivity was based on two questions. Participants were asked about time spent watching TV or videos during a typical 24-hour period over the past 12 months. Time spent watching TV or videos was categorized as none, <1 hour, 1–2, 3–4, 5–6,7–8, and ≥ 9 hours
					Total sedentary	In a separate question, participants were also asked to indicate the number of hours spent sitting during a typical 24-hour period over the past 12 months: <3,3–4, 5–6, 7–8, and ⩾ 9 hours. Both measures of inactivity were collapsed as <3, 3–4, 5–6,and ⩾ 7 hours per day

Friedenreich 2010	Cases were Alberta residents, English-speaking, able to complete interview and questionnaire, and did not have another previous cancer except nonmelanoma skin cancer. Controls were identified using random-digit dialing and frequency matched to cases on age (±5 years).	——	Incident, histologically confirmed invasive cases of endometrial cancer were identified directly from the Alberta Cancer Registry	——	Occupational sedentary	Lifetime occupational sedentary activity was estimated using a validated questionnaire. The patterns of physical activity were recorded by the interviewer including the age started, age ended, number of months per year, weeks per month, days per week and hours per day that each activity was performed so that the frequency and duration of these activities is determined.
Arem 2011	English-speaking, Connecticut residents diagnosed with primary endometrial cancer. Population-based controls were identified using random-digit dialing (RDD) and were frequency matched on age.	——	——	——	Total sedentary	Time seated watching multimedia or sitting at work was calculated as hours per week from self-report in the two to five years before interview
Hunter 2020	Participants of UK Biobank cohort without been diagnosed with malignant cancer (excluding non-melanoma skin cancer), and have completed self-report screen time assessment.	7.6 (1.4) years	Uterus cancer identified from national cancer registries (ICD-10: C54; ICD-9: 182)	——	Recreational sedentary	Television (TV) viewing time: "In a typical DAY, how many hours do you spend watching TV?" Daily recreational computer use time: "In a typical DAY, how many hours do you spend using the computer? (Do not include using a computer at work)." Daily total recreational screen time: self-reported time spent watching TV, and time spent using the computer outside of work
Miyata 2021	Japanese inhabitants participated in municipal health screening	14.8 years	Cancer registries or local major	——	Recreational sedentary	Television (TV) viewing (< 1, 1 to < 2, 2 to < 3, 3 to < 4, ⩾ 4hr/day)

	examinations with completed questionnaires and no history of cancer or uterine surgery at enrolment.		hospital records coded according to the ICD-10: C54		Occupational sedentary	Occupational activity was classified according to the position during work (mainly sitting, mainly standing, moving)

Note: Table values are mean (SD) for continuous variables; ICD, International Classification of Disease; * studies not included in the meta-analysis.

Table S4. Detailed data underlying the meta-analysis.

Table S4-1. Detailed data for overall sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Domain	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI
Gierach	2009	Total	Cohort study	North America	≥ 5000	≥ 500	1.56 (1.22, 1.99)	Not adequate	Good	No	No
Arem	2011	Total	Case-control study	North America	≥ 5000	≥ 500	1.52 (1.07, 2.16)	Adequate	Fair	No	Yes
Dosemeci	1993	Occupational&/Leisure-time	Case-control study	Asia	< 5000	< 500	0.50 (0.10, 4.40)	Not adequate	Fair	No	No
Shu	1993	Occupational&/Leisure-time	Case-control study	Asia	< 5000	< 500	1.20 (0.70, 2.00)	Not adequate	Fair	No	yes
Olson	1997	Occupational&/Leisure-time	Case-control study	North America	< 5000	< 500	0.93 (0.55, 1.56)	Adequate	Good	No	Yes
Moradi	2000	Occupational&/Leisure-time	Case-control study	Europe	< 5000	≥ 500	1.32 (1.08, 1.60)	Not adequate	Good	No	Yes
Weiderpass	2001	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	≥ 500	1.30 (1.10, 1.50)	Not adequate	Fair	No	No
Furberg	2003	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	< 500	1.48 (0.97, 2.20)	Adequate	Good	Yes	Yes
Matthews	2005	Occupational&/Leisure-time	Case-control study	Asia	< 5000	≥ 500	0.93 (0.67, 1.30)	Not adequate	Fair	No	Yes
Friedenreich	2010	Occupational&/Leisure-time	Case-control study	North America	< 5000	≥ 500	1.28 (0.89, 1.83)	Not adequate	Fair	No	Yes
Miyata	2021	Occupational&/Leisure-time	Cohort study	Asia	≥ 5000	< 500	2.15 (1.13, 4.09)	Adequate	Good	Yes	Yes
Friberg	2006	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	< 500	1.22 (0.95, 1.57)	Not adequate	Good	Yes	No
Patel	2008	Occupational&/Leisure-time	Cohort study	North America	≥ 5000	< 500	1.40 (1.03, 1.89)	Adequate	Good	No	No
Hunter	2020	Occupational&/Leisure-time	Cohort study	Europe	≥ 5000	≥ 500	0.57 (0.31, 1.03)	Not adequate	Fair	No	Yes

Table S4-2. Detailed data for occupational sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI	Additional adjustment for BMI
Dosemeci	1993	Case-control study	Asia	< 5000	< 500	0.50 (0.10, 4.40)	Not adequate	Fair	No	No	
Shu	1993	Case-control study	Asia	< 5000	< 500	1.20 (0.70, 2.00)	Not adequate	Fair	No	Yes	
Olson	1997	Case-control study	North America	< 5000	< 500	0.93 (0.55, 1.56)	Adequate	Good	No	Yes	
Moradi	2000	Case-control study	Europe	< 5000	≥ 500	1.32 (1.08, 1.60)	Not adequate	Good	No	Yes	
Weiderpass	2001	Cohort study	Europe	≥ 5000	≥ 500	1.30 (1.10, 1.50)	Not adequate	Fair	No	No	
Furberg	2003	Cohort study	Europe	≥ 5000	< 500	1.64 (0.95, 2.84)	Adequate	Good	Yes	Yes	
Matthews	2005	Case-control study	Asia	< 5000	≥ 500	0.93 (0.67, 1.30)	Not adequate	Fair	No	Yes	
Friberg	2006	Cohort study	Europe	≥ 5000	< 500	1.03 (0.76, 1.39)	Not adequate	Good	Yes	No	0.99 (0.73, 1.34)
Friedenreich	2010	Case-control study	North America	< 5000	≥ 500	1.28 (0.89, 1.83)	Not adequate	Fair	No	Yes	
Miyata	2021	Cohort study	Asia	≥ 5000	< 500	2.17 (1.04, 4.56)	Adequate	Good	Yes	Yes	

Table 4-3. Detailed data for leisure-time sedentary behaviour and endometrial cancer underlying the meta-analysis.

Author	Year	Study design	Study area	Sample size	Number of cases	RR (95%CI)	Adjustment of confounding factors	Study quality	Adjustment for physical activity	Adjustment for BMI	Additional adjustment for BMI
Furberg	2003	Cohort study	Europe	≥ 5000	< 500	1.27 (0.69, 2.32)	Adequate	Good	Yes	Yes	
Friberg	2006	Cohort study	Europe	≥ 5000	< 500	1.80 (1.14, 2.83)	Not adequate	Good	Yes	No	1.66 (1.05, 2.61)
Patel	2008	Cohort study	North America	≥ 5000	< 500	1.40 (1.03, 1.89)	Adequate	Good	No	No	1.18 (0.87, 1.59)
Gierach	2009	Cohort study	North America	≥ 5000	≥ 500	1.66 (1.20, 2.88)	Not adequate	Good	No	No	1.21 (0.87, 1.67)
Hunter	2020	Cohort study	Europe	≥ 5000	≥ 500	0.57 (0.31, 1.03)	Not adequate	Fair	No	Yes	
Miyata	2021	Cohort study	Asia	≥ 5000	< 500	2.10 (0.57, 7.71)	Adequate	Good	Yes	Yes	

Table S5. Newcastle-Ottawa quality assessment scale for cohort study.

Source	Selection				Comparability	Outcome			Total Stars
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	
Hunter 2020	1	1	-	1	1	1	1	-	6
Miyata 2021	1	1	-	1	2	1	1	1	8
Gierach 2009	1	1	-	1	1	1	1	1	7
Patel 2008	1	1	-	1	1	1	1	1	7
Friberg 2006	1	1	-	1	2	1	1	1	8
Furberg 2003	1	1	1	1	2	1	1	1	9
Weiderpass 2001	1	1	1	-	-	1	1	-	5

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. For comparability in our analysis, a study can be awarded one star for controlling for age; Two stars for also controlling for physical activity.

Table S6. Newcastle-Ottawa quality assessment scale for case-control study.

Source	Selection				Comparability	Exposure			Total Stars
	Is the Case Definition Adequate?	Representatives of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of Exposure	Same Method of Ascertainment for Cases and Controls	Non-Response Rate	
Arem 2011	1	1	1	-	1	-	1	-	5
Friedenreich 2010	1	1	1	1	1	-	1	-	6
Matthews 2005	1	1	1	-	1	-	1	-	5
Moradi 2000	1	1	1	1	1	1	1	-	7
Olson 1997	1	1	1	1	1	-	1	1	7
Shu 1993	1	1	1	-	1	-	1	-	5
Dosemeci 1993	-	1	-	1	1	1	1	1	6

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. For comparability in our analysis, a study can be awarded one star for controlling for age; Two stars for also controlling for physical activity.

Table S7. Adjusted confounders of the included studies in systematic review.

Publication		Number of confounders	Adjusted confounders	How to deal with obesity/BMI (particular attention to potential intermediator BMI)
Author	Year			
Dosemeci	1993	3	Age, smoking and socioeconomic status (based on income and education levels)	——
Shu	1993	4	Age, number of pregnancies, BMI, caloric intake	Adjusted in the multivariate model
Zheng*	1993	——	Age-specific and sex specific person-years estimated in each occupation category	——
Olson	1997	9	Age, education, BMI, diabetes, smoking, parity, age at menarche, menopausal status, and use of unopposed estrogen.	Adjusted in the multivariate model
Moradi*	1998	4	Age at follow-up, place of residence, calender year of follow-up, and socio-economic status	——
Moradi	2000	8	Age, parity, age at last birth, BMI 1 year prior to data collection, use of oral contraceptives, use of hormone replacement therapy, smoking, and age at menopause	Adjusted in the multivariate model
Weiderpass	2001	3	Mean number of children, mean age at first birth, and turnover rate	——
Furberg	2003	9	age, geographical region, height, BMI, recreational or occupational activity and smoking at baseline and parity. Also considered blood pressure and serum glucose	Adjusted in the multivariate model
Matthews	2005	12	Age, age at menarche, menopausal status and age, number of pregnancies, oral contraceptive use, current smoking, ever drinking, family history of cancer, education, height, and BMI	Adjusted in the multivariate model
Friberg	2006	9	Age in months, parity, history of diabetes, total fruit and vegetable, education, and work/occupation, walking/bicycling, household work, leisure time activity, and leisure time inactivity (watching TV/sitting) simultaneously	Additionally adjusted for BMI
Patel	2008	9	Age, age at menarche, age at menopause, duration of oral contraceptive use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal hormone therapy use	Additionally adjusted for BMI
Gierach	2009	7	Age, race, smoking status, parity, ever use of oral contraceptives, age at menopause, hormone therapy formulation	Additionally adjusted for BMI
Friedenreich	2010	6	Age, BMI, waist circumference, age at menarche, hypertension, and number of pregnancies of ⩾ 20 weeks gestation	Adjusted in the multivariate model

Arem	2011	8	Age, BMI, race, number of live births, menopausal status, oral contraceptive use, hypertension, and smoking status	Adjusted in the multivariate model
Hunter	2020	15	Age, sex, ethnicity, deprivation index, education, fruit and vegetable intake, BMI, smoking status, and alcohol intake, hormone therapy use, oral contraceptive use, number of live births, age at menarche, age at menopause, hysterectomy status	Adjusted in the multivariate model
Miyata[7]	2021	13	Age, BMI, weight change since age 20, history of diabetes, history of hypertension, age at menarche, menstrual presence, parity, smoking status, alcohol consumption, occupational activity, hours of physical exercise, walking, and television viewing	Adjusted in the multivariate model

Note: BMI, body mass index. * studies not included in the meta-analysis.

Table S8. Influence analysis of sedentary behaviour and endometrial cancer (given named study is omitted).

Occupational domain		Leisure-time domain	
Study omitted	Estimate (95% CI)	Study omitted	Estimate (95% CI)
Dosemeci 1993	1.23 (1.10, 1.38)	Furberg 2003	1.35 (0.93-1.95)
Shu 1993	1.22 (1.08, 1.38)	Friberg 2006	1.24 (0.86-1.79)
Olson 1997	1.24 (1.11, 1.39)	Patel 2008	1.31 (0.85-2.03)
Moradi 2000	1.19 (1.04, 1.37)	Gierach 2009	1.26 (0.86-1.86)
Weiderpass 2001	1.19 (1.03, 1.38)	Hunter 2020	1.53 (1.24-1.87)
Furberg 2003	1.21 (1.08, 1.36)	Miyata 2021	1.30 (0.93-1.82)
Matthews 2005	1.27 (1.15, 1.40)	Combined	1.34 (0.98-1.83)
Friberg 2006	1.26 (1.12, 1.41)		
Friedenreich 2010	1.21 (1.06, 1.38)		
Miyata 2021	1.22 (1.11, 1.35)		
Combined	1.22 (1.09, 1.37)		

Table S9. Results of meta-regression analyses on individual study characteristics for studies included in the meta-analysis of the association between sedentary behaviour and the risk of endometrial cancer.

Covariates	N	RR	95% CI		I^2	Tau^2	Ratio of RR	95% CI		*P*
Model with no covariates	14	1.28	1.14	1.43	34.8%	0.0000	-	-	-	-
Domain*										
Total	2	1.55	1.27	1.89	29.3%	0.0004	1.00	Reference		
Occupational	10	1.22	1.09	1.37			0.80	0.60	1.07	0.12
Leisure-time	6	1.34	0.98	1.83			0.89	0.62	1.28	0.51
Study design										
Cohort study	7	1.33	1.13	1.58	36.8%	0.0027	1.00	Reference		
Case-control study	7	1.22	1.05	1.41			0.91	0.72	1.17	0.44
Study area										
Asia	4	1.20	0.78	1.83	36.0%	0.0000	1.00	Reference		
Europe	5	1.24	1.05	1.46			1.14	0.78	1.68	0.47
North America	5	1.41	1.22	1.63			1.26	0.84	1.91	0.24
Sample size										
< 5000	6	1.19	1.03	1.37	32.7%	0.0028	1.00	Reference		
≥ 5000	8	1.35	1.17	1.57			1.15	0.90	1.47	0.24
Number of cases										
< 500	7	1.30	1.12	1.51	39.8%	0.0036	1.00	Reference		
≥ 500	7	1.25	1.06	1.47			0.99	0.75	1.29	0.91
Study quality				1.47						
Fair	7	1.14	0.93	1.41	33.4%	0.0049	1.00	Reference		
Good	7	1.37	1.22	1.53			1.14	0.90	1.46	0.25
Adjustment of confounding factors										
Not adequate	9	1.22	1.07	1.40	35.4%	0.0014	1.00	Reference		
Adequate	5	1.42	1.18	1.72			1.13	0.85	1.50	0.36
Adjustment for physical activity										
No	11	1.25	1.10	1.42	39.1%	0.0094	1.00	Reference		
Yes	3	1.41	1.08	1.84			1.10	0.78	1.55	0.55
Adjustment for BMI										
No	5	1.34	1.20	1.49	37.0%	0.0029	1.00	Reference		
Yes	9	1.21	1.01	1.46			0.92	0.72	1.17	0.46

Meta-regression models are fitted assuming random effects that allow for between-study variability. I-squared (%) representing variation due to heterogeneity; Tau-squared representing estimate of between-study variance.

*Number of studies exceeds in total as some research presented risk estimates separately for total sedentary, occupational, leisure-time domain.