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Night shift work, sleep duration and endometrial cancer risk: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2)

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ABSTRACT

Data on the role of circadian related factors in the etiology of endometrial cancer are scarce. We collected individual data on night shift work or daily sleep duration from 7,207 cases and 22,027 controls participating in 11 studies from the Epidemiology of Endometrial Cancer Consortium (E2C2). Main analyses were performed among postmenopausal women: 6,335 endometrial cancer cases and 18,453 controls. Using individual data, study-specific odd ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated with logistic regression and pooled analyses were conducted using random-effects meta-analyses. A non-significant inverse association was observed between endometrial cancer and night shift work (OR=0.89, 95%CI=0.72–1.09; I^2=0.0%, $P_{heterogeneity}$=0.676). Associations did not vary by shift type (permanent or rotating), or duration of night work. Categorizations of short (<7h) or long (≥9h) sleep duration were not associated with endometrial cancer risk (OR$_{short}$=1.02, 95%CI=0.95–1.10; I^2=55.3%, $P_{heterogeneity}$=0.022; OR$_{long}$=0.93, 95%CI=0.81–1.06;

I^2=11.5%, $P_{\text{heterogeneity}}$=0.339). No associations were observed per 1-h increment of sleep (OR=0.98, 95% CI=0.95–1.01; I^2=46.1%, $P_{\text{heterogeneity}}$=0.063), but an inverse association was identified among obese women (OR=0.93, 95%CI=0.89–0.98 per 1-h increment; I^2=12.7%, $P_{\text{heterogeneity}}$=0.329). Overall, these pooled analyses provide evidence that night shift work and sleep duration are not strong risk factors for endometrial cancer in postmenopausal women.

Abbreviations

BMI	Body Mass Index
CECS	Connecticut Endometrial Cancer Study
CI	Confidence Interval
CTS	California Teachers Study
DRMA	Dose Response Meta-Analyses
EDGE	Estrogen, Diet, Genetics and Endometrial Cancer
E2C2	Epidemiology of Endometrial Cancer Consortium
HAW	Hawaii Endometrial Cancer Study
IARC	International Agency for Research on Cancer
MEC	Multiethnic Cohort
NHS	Nurses' Health Study
NIH-AARP	NIH-AARP Diet and Health Study
NLCS	Netherlands Cohort Study
OR	Odds Ratio
PECS	Polish Endometrial Cancer Study
SCCS	Southern Community Cohort Study
Screenwide	Minimally invasive detection of endometrial and ovarian cancers

1. Introduction

Endometrial cancer is the most common gynecological tumor in developed countries, and the disease burden is expected to increase in coming years, due in part to aging populations and increasing rates of obesity [1,2]. Endometrial cancer is an estrogen-dependent cancer [3, 4]. Known factors associated with endometrial cancer risk include postmenopausal estrogen-only hormone use [5], parity [6], age at last birth [7], age at menarche [8], oral contraceptive use [9], obesity [10, 11], physical activity [12], type 2 diabetes [13], smoking [14], and coffee consumption [15], in part through their hormone-modulating effects.

Sleep plays a crucial role in promoting both physical and mental well-being [16]. Some studies have shown that women with shorter sleep durations have lower urinary melatonin levels, potentially due to a greater exposure to light at night [17]. In addition to its role in regulating sleep, melatonin has been proposed to have anti-cancer properties [18–21]. Melatonin impacts multiple cancer-associated phenomena by promoting apoptosis, inhibiting abnormal metabolism and growth, preventing genomic instability, reducing inflammation, among others [22,23]. Moreover, melatonin may also block the estrogen receptor (ER)α and influence the production of estradiol via enzyme aromatase [24]. The inhibition of melatonin leads to the abnormal release of testosterone and estrogen, which is hypothesized to influence the development hormone-related cancers, such as prostate, endometrial, ovarian, uterine, and breast cancer [25]. Several studies have examined the possible association between sleep duration and cancer risk, with discordant results. In particular, some studies have reported positive associations between sleep duration and skin, lung colorectal, breast, and ovarian cancers [26–31]; other studies found negative associations for colorectal, lung, breast, stomach, prostate and ovarian cancers [29, 30,32–37], while others studies did not find significant associations for prostate, skin, breast and endometrial cancers [17,31,38–43].

Systematic reviews and meta-analyses have evaluated the association between sleep duration and risk of different cancers, mostly reporting null results, except for an association between long sleep duration and increased risk of colorectal cancer [44,45]. These discrepancies might be due to different study designs, measurement and assessment definitions of sleep exposures, and the presence of confounding [46].

Night work refers to the involvement of work during the regular sleeping hours of the general population [47]. The potential health effects of night work have significant implications for public health, as it is a frequent component of industrial development and around 20% of employees in Europe are estimated to work during the night [48]. In 2019, the International Agency for Research on Cancer (IARC) classified night shift work as probably carcinogenic to humans (Group A2) [47], on the basis of limited evidence from epidemiologic studies and sufficient evidence from animal models. The biological plausibility underlying this relationship may be partly explained by alterations in the light–dark schedule resulting in changes in serum melatonin [49]. Several studies have examined the association between night shift work and different cancer risks but have yielded inconsistent results. Some studies found a positive association between night shift work and breast [50–54], prostate [52,55–57] and colorectal cancer [58], while other studies did not find this association [59–65]. Confounding has been proposed as a contributing factor to explain discrepancies between studies, as non-day shift workers differ from day workers in various aspects, including lower physical activity and different dietary habits, among others [66]. In addition, the positive associations described above were mostly related with long-term night shift work, while meta-analyses typically evaluate associations between any night shift work ever and each cancer type. Consequently, the potential risk of long-term night work may not be well characterized in many meta-analyses [65]. Accordingly, a pooled analysis of detailed individual data on night shift work attempted to address some of these concerns and reported positive associations with breast cancer, especially among premenopausal women and with long-term night shift work [67].

The role that sleep duration or night shift work play in endometrial cancer is poorly understood, with few studies reporting discordant results. Three studies [68–70] have evaluated the potential link between night shift work and endometrial cancer risk, two of them [69,70] report null associations. However, the Nurses' Health Study (NHS) I [68] reported an increased risk of endometrial cancer among long-term rotating night workers (>20 years). On the other hand, four studies have investigated the association between sleep duration and endometrial cancer risk, with no significant associations [31,35,41,70].

We conducted the first pooled analyses of individual-level data on sleep duration and night shift work and risk of endometrial cancer. These analyses involved 11 epidemiologic studies participating in the Epidemiology of Endometrial Cancer Consortium (E2C2) with detailed individual information on potential confounding factors.

2. Methods

2.1. Participating studies

Epidemiological studies with data on night shift work or sleep duration were identified through the E2C2 [71] (Fig. 1). Eleven studies, including six cohort studies analyzed with a nested case-control design and five case-control studies, conducted between 1976 and 2021 across the US and Europe contributed individual data to these pooled analyses, with a total of 7,207 cases and 22,027 controls. The six cohort studies

sampled with a nested case-control design were: California Teachers Study (CTS) [72], Multiethnic Cohort (MEC) [73], Nurses' Health Study (NHS) [74], NIH-AARP Diet and Health Study (NIH-AARP) [75], Netherlands Cohort Study (NLCS) [76], and Southern Community Cohort Study (SCCS) [77]. The five case-control studies were: Connecticut Endometrial Cancer Study (CECS) [78], Estrogen, Diet, Genetics and Endometrial Cancer (EDGE) [79], Hawaii Endometrial Cancer Study (HAW) [80], Polish Endometrial Cancer Study (PECS) [81], and Minimally invasive detection of endometrial and ovarian cancers (Screenwide) [70]. Each study provided information regarding tumor characteristics, demographic variables, covariates, and risk factors. Data from four of the E2C2 studies have been previously used to separately report associations between night shift work [68,70], sleep duration [31,35,70], and endometrial cancer. Table 1 outlines studies' designs and main characteristics.

2.2. Exposure assessment

Data on covariates were collected from baseline questionnaires in most cohort studies, except for the NHS study, which used information from follow-up cycles. Similarly, data on main exposure variables, night shift work and sleep duration, were obtained from baseline questionnaires, except for the NHS and NIH-AARP studies, which were collected on questionnaires administered after baseline. Cases diagnosed before the exposure data collection were excluded from the analyses (N=232, Table 1). The reference dates for case-control studies were based on the date of diagnosis for cases and the date of interview for controls.

Sleep duration was defined as the number of hours usually slept at the corresponding reference date, although definitions were not homogenous across studies (Table 1). Three studies provided information separately for weekdays and weekends (Screenwide, CECS and SCCS), therefore data corresponding to weekdays were used in main analyses. We followed National Sleep Foundation's sleep time duration recommendations [82] for sleep duration categorization. In particular, the reference category for sleep duration was defined as 7h–8.9h for all

studies except for CTS (collected sleep duration in different categories), which was defined as 7h–9.9h, and the short and the long sleep duration categories were defined as sleep duration categories below or above the reference category, respectively.

For night shift work, the reference group (never night workers) consisted of workers who had never worked at night. Women who indicated their sole employment was as a housewife were excluded from these analyses (N=38). We investigated the type of night shift rotation, distinguishing between those who always rotated and those who did not (either permanent night or a combination of permanent and rotating night shifts). Regarding the total duration of night shift work in their entire life, we categorized night shift workers into two groups: those who worked less than ten years and those who worked ten or more years. We classified women aged ≥55 years with missing data on menopausal status as postmenopausal. Type I histologic subtypes included endometrioid, mucinous, adenocarcinoma in adenomatous polyp, adenocarcinoma not otherwise specified and adenocarcinoma with squamous differentiation. Type II histologic subtypes included serous, clear cell, mixed cell, small cell, squamous cell, adenosarcoma, mixed Mullerian and carcinosarcoma. Other histologic subtypes were not categorized into either type.

2.3. Statistical analyses

We restricted our main analyses to women who were postmenopausal at their respective study baselines (6,335 cases and 18,453 controls) in an attempt to reduce heterogeneity and make the research findings easier to interpret, given the complex interaction between sleep exposures and hormones among pre and postmenopausal women.

A two-stage methodology was employed to estimate odds ratios (OR) and their corresponding 95% confidence intervals (CI) between endometrial cancer and the night work and sleep variables. Two-stage methodology was used in order to quantify heterogeneity and graphically examine study-specific estimates. In particular, using individual data within each study and for every exposure, we computed ORs with
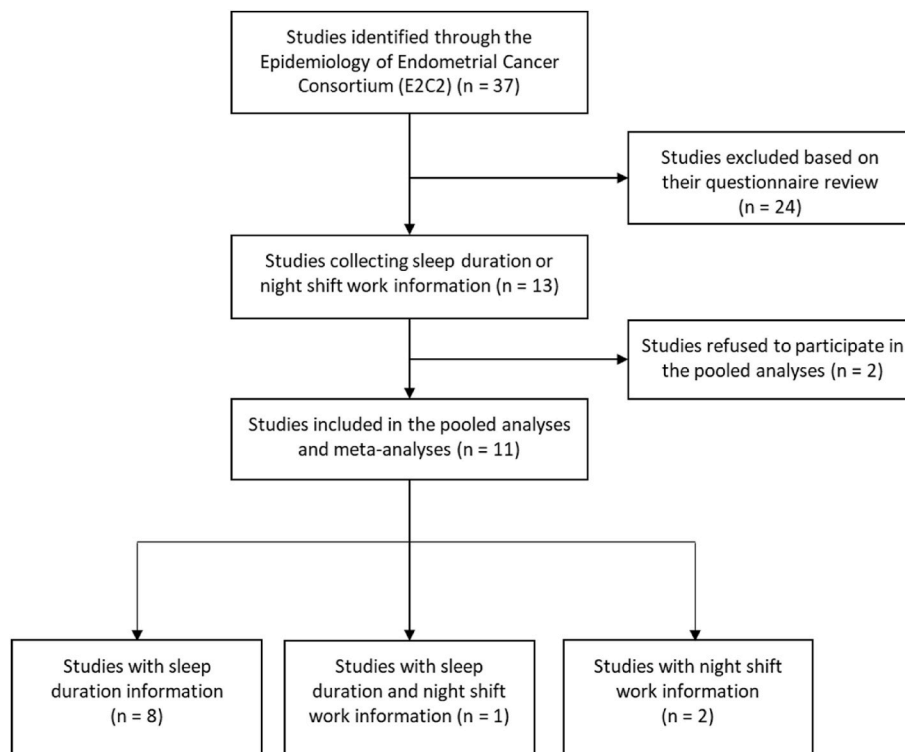

Fig. 1. Flow diagram.

Table 1
Characteristics of the studies participating in the pooled analyses.

Study	Study design	Location	Recruitment Period	Matching Factors	Risk Factors	Controls	Cases
California Teachers Study (CTS)[a]	Cohort	California	1995–1996	Birth year, cohort entry, race, area	Sleep duration[e]	5172	1293
Multiethnic Cohort (MEC)[a]	Cohort	Hawaii, California	1993–1996	Birth year, cohort entry, race, area	Sleep duration[e]	5616	1404
Nurses' Health Study (NHS)[b]	Cohort	11 US states	1976	Birth year, race	Night shift work[f]	1641	650
NIH-AARP Diet and Health Study (NIH-AARP)[c]	Cohort	6 states & 2 metropolitan areas	1995–1996	Birth year, cohort entry, race, area	Sleep duration[g]	4698	1156
Netherlands Cohort Study (NLCS)[a]	Cohort	Netherlands	1986	Birth year, cohort entry	Sleep duration[h]	896	450
Southern Community Cohort Study (SCCS)[a]	Cohort	12 Southern states, US	2002–2009	Birth year, race, recruitment source	Sleep duration[e,i]	224	56
Connecticut Endometrial Cancer Study (CECS)[d]	Case-control	Connecticut	2004–2009	Age (5-year group)	Sleep duration[g,i]	664	666
Estrogen, Diet, Genetics and Endometrial Cancer (EDGE)[d]	Case-control	New Jersey	2001–2005	Age (5-year group)	Night shift work	466	469
Hawaii Endometrial Cancer Study (HAW)[d]	Case-control	Hawaii	1988–1993	Age (+- 2.5 years), ethnicity	Sleep duration[h]	511	332
Polish Endometrial Cancer Study (PECS)[d]	Case-control	Poland	2000–2003	Age (+- 5 years), site	Sleep duration[h]	1921	551
Minimally invasive detection of endometrial and ovarian cancers (Screenwide)[d]	Case-control	Catalonia, Spain	2017–2021	Age (5-years group, hospital controls)	Night shift work and sleep duration[g,i]	218	180

[a] These studies collected covariates and risk factors at the baseline questionnaire.
[b] In this study, covariates were obtained in follow-up cycles in which cases were diagnosed and sleep duration was obtained 12 years after the baseline questionnaire (171 cases diagnosed before the sleep duration information was asked were dropped from the analyses).
[c] In this study, covariates were obtained from the baseline questionnaire and sleep duration was obtained 1 year after the baseline questionnaire (61 cases diagnosed before the sleep duration information collection were dropped from the analyses).
[d] These studies collected covariates and risk factors 6–12 months before date of diagnosis for cases and date of interview for controls.
[e] These studies did not specify if naps were included in the definition of sleep duration.
[f] Participants were asked how many years in total they had worked rotating night shift, defined as working at least three nights per month, but permanent night work was not mentioned. However, due to the definition of rotating night shift, all participants reporting rotating night shift work in this study were classified as having exposure to night work in the ever/never analyses.
[g] These studies excluded nap time from the total sleep duration time.
[h] These studies included nap time from the total sleep duration time.
[i] These studies provided information separately for weekdays and weekends, therefore data corresponding to weekdays were used in main analyses.

their corresponding 95% CIs using unconditional logistic regression, adjusting for age (continuous), race (white, others), body mass index (BMI) (<25, 25–29.9, ≥30), use of oral contraceptives (ever, never), parity (0, 1, 2, 3+) and smoking (never, past, current). Then, random-effects models were used to calculate pooled estimates from these study-specific ORs using the DerSimonian & Laird method [83]. Heterogeneity between studies was assessed using the I^2 statistic and p-value for heterogeneity using the Mantel-Haenszel method [84]. Furthermore, we performed dose response meta-analyses (DRMA) to inspect the linearity of associations with sleep duration. We considered the midpoint of each sleep duration category as the dose. When the longest category was open-ended, we assumed that the open-ended interval length had the same length as the adjacent interval. Potential nonlinear dose response relationships between sleep duration and endometrial cancer were examined by using restricted cubic splines with 5 knots at percentiles 1%, 25%, 50%, 75% and 99% distribution, following Zhan et al. (2017) methodology [85]. We conducted a DRMA using the Greenland and Longnecker method [86] to calculate pooled OR and 95% CI for 1-h increment of sleeping. Additionally, we investigated whether the studies considered nap time in the total hours count of sleep per day or not. We reviewed the related questions in each study's questionnaire and classified sleep definitions as follows: three studies excluded nap time from the total sleep duration time (NIH-AARP, CECS and Screenwide), in other three studies nap time was part of the total sleep duration time per day (NLCS, HAW and PECS), while three other studies did not specify it clearly in their questionnaires (CTS, MEC and SCCS) (Table 1).

Sensitivity analyses included analyses by study design (cohort vs case-control), histology (type I vs type II), and BMI (non-obese <30 BMI vs obese ≥30 BMI). We followed the same two-stage methodology employed for the main analysis but stratifying individual data by the above-mentioned variables. We performed likelihood-ratio tests for the interaction between main exposure variables and study design and BMI. In these sensitivity analyses, Firth's logistic regression was employed for cell frequencies lower than five. We also performed sensitivity analyses excluding individual studies from the models one by one, to ensure that the risk estimates were not dependent on any specific study.

3. Results

A total of 5,543 cases and 16,697 controls contributed to the sleep duration analyses, and 959 cases and 1,937 controls contributed to the night shift work analyses. Characteristics of cases and controls are described in Table 2. Cases were older, had a higher BMI, were less likely to be smokers, and users of postmenopausal hormones and oral contraceptives, and were more likely to be nulliparous, and to have diabetes and hypertension, in comparison with the controls (Table 2). Descriptive characteristics among controls by night shift work and by sleep duration can be found in Supplemental Table S1 and Supplemental Table S2, respectively. Among controls, ever night workers were younger, had higher educational level, were more likely to be ever smokers, postmenopausal hormones, and oral contraceptives users, and to have diabetes than never night workers (Supplemental Table S1). Also, in comparison with individuals with short or long sleep, those who slept between 7h and 8.9h were slightly younger, more likely to be white, had higher education level, were less likely to be obese or to use postmenopausal hormones, and less likely to have hypertension (Supplemental Table S2).

3.1. Night work

During their lifetime, 298 cases (31.1%) and 900 controls (46.6%)

Table 2
Overall number (%) of controls and cases among postmenopausal women.

Total	Control		Cases		p-value[a]
	N	(%)	N	(%)	
	18448	100	6331	100	
E2C2 study center					<0.001
Screenwide	185	(1.0)	172	(2.7)	
EDGE	397	(2.2)	394	(6.2)	
NHS	1350	(7.3)	391	(6.2)	
CTS	3504	(19.0)	1133	(17.9)	
CECS	549	(3.0)	595	(9.4)	
HAW	343	(1.9)	241	(3.8)	
MEC	5134	(27.8)	1310	(20.7)	
NLCS	868	(4.7)	435	(6.9)	
NIH-AARP	4660	(25.3)	1091	(17.2)	
PECS	1306	(7.1)	531	(8.4)	
SCCS	152	(0.8)	38	(0.6)	
Age[b]					<0.001
≤60	5252	(28.5)	1584	(25.0)	
61–69	7417	(40.2)	2486	(39.3)	
≥70	5779	(31.3)	2261	(35.7)	
Race					0.001
White	14558	(78.9)	5113	(80.8)	
Others	3846	(20.8)	1189	(18.8)	
Educational level					0.006
High school or below	5959	(32.3)	2202	(34.8)	
Some college	4851	(26.3)	1610	(25.4)	
College or above	5964	(32.3)	2006	(31.7)	
BMI					<0.001
<25	7893	(42.8)	1877	(29.6)	
25–29.99	6179	(33.5)	1895	(29.9)	
≥30	3849	(20.9)	2422	(38.3)	
Smoking status					<0.001
Never	9420	(51.1)	3668	(57.9)	
Past	6113	(33.1)	2041	(32.2)	
Current	2647	(14.3)	551	(8.7)	
Number of live births					<0.001
0	2740	(14.9)	1305	(20.6)	
1	2263	(12.3)	854	(13.5)	
2	5052	(27.4)	1776	(28.1)	
3 or more	8282	(44.9)	2366	(37.4)	
Age at menarche					<0.001
<11	873	(4.7)	422	(6.7)	
11–12	7290	(39.5)	2645	(41.8)	
13–14	7684	(41.7)	2555	(40.4)	
≥15	2386	(12.9)	627	(9.9)	
Use of any PMH					<0.001
Ever	8203	(44.5)	2427	(38.3)	
Never	9754	(52.9)	3752	(59.3)	
Use of oral contraceptives					<0.001
Ever	7462	(40.4)	2303	(36.4)	
Never	10645	(57.7)	3914	(61.8)	
Diabetes					<0.001
No	17103	(92.7)	5580	(88.1)	
Yes	1320	(7.2)	735	(11.6)	
Hypertension					<0.001
No	10898	(59.1)	3355	(53.0)	
Yes	5592	(30.3)	2530	(40.0)	
Night shift work (NSW)[c]					<0.001
Never	1018	(52.7)	644	(67.3)	
Ever	900	(46.6)	298	(31.1)	
Duration of NSW[c]					<0.001
Never NSW	1018	(52.7)	644	(67.3)	
<10 years	703	(36.4)	215	(22.5)	
≥10 years	192	(9.9)	79	(8.3)	
Type of shift[d]					0.572
Never NSW	492	(84.5)	491	(86.7)	
Permanent NSW	49	(8.4)	40	(7.1)	
Rotating (never permanent)	23	(4.0)	19	(3.4)	
Sleep duration (Weekdays)[e,f]					0.264
Short (<7h)	5239	(31.4)	1764	(31.8)	
Ref. (7h-8.9h)	10360	(62.0)	3385	(61.0)	
Long (≥9h)	1098	(6.6)	394	(7.1)	
Sleep duration (Weekend)[g]					0.635
Short (<7h)	255	(28.8)	236	(29.3)	
Ref. (7h-8.9h)	506	(57.1)	467	(58.0)	
Long (≥9h)	123	(13.9)	99	(12.3)	

BMI = Body mass index, PMH = Postmenopausal hormone use.
Numbers do not always add up due to missing data. Missing values are below 5%, except for education and hypertension which are below 10%.
[a] Chi squared calculated without missing values.
[b] Age at diagnosis for cases and at interview for controls.
[c] Includes Screenwide, EDGE and NHS studies (1932 controls and 957 cases).
[d] Includes Screenwide and EDGE studies (582 controls and 566 cases).
[e] Includes Screenwide, CTS, CECS, HAW, MEC, NLCS, NIH-AARP, PECS and SCCS studies (16701 controls and 5546 cases).
[f] For the CTS study the reference category corresponds to 7–9.9h, and the category 'long' corresponds to ≥10h.
[g] Includes Screenwide, CECS and SCCS studies (886 controls and 805 cases).

had ever performed night shift work. After adjustment for potential confounders, a non-significant inverse association was observed between endometrial cancer and ever working in night shifts (OR=0.89, 95%CI=0.72-1.09; I^2=0.0%, $P_{\text{heterogeneity}}$=0.676; Table 3). This inverse association did not vary by duration of night shift work (OR=0.88, 95% CI=0.70-1.11; I^2=0.0%, $P_{\text{heterogeneity}}$=0.478, for <10 years of night shift work and OR=0.99, 95%CI=0.73-1.36; I^2=0.0%, $P_{\text{heterogeneity}}$=0.374, for ≥10 years of night shift work, compared with never night work) or type of night shift work (OR=0.85, 95%CI=0.52-1.37; I^2=0.0%, $P_{\text{heterogeneity}}$=0.481, for permanent night shift work and OR=0.70, 95% CI=0.36-1.37; I^2=0.0%, $P_{\text{heterogeneity}}$=0.450, for rotating night work, compared with never night work; Table 3).

3.2. Sleep duration

The overall OR, comparing the short category with the reference category of sleep duration, was 1.02 (95%CI=0.95-1.10) with significant heterogeneity across studies (I^2=55.3%, $P_{\text{heterogeneity}}$=0.022; Fig. 2). An OR=0.93 (95%CI=0.81-1.06) was observed for the long category compared with the reference category (I^2=11.5%, $P_{\text{heterogeneity}}$=0.339; Fig. 2). The DRMA revealed an inverse association with endometrial cancer at longer duration of sleep. However, only CTS contained data for a category of sleep duration ≥ 10h, and when it was excluded in sensitivity analyses, the slope of estimates did not reveal a clear pattern (Supplemental Fig. 1). Therefore, we also modelled sleep duration as a linear relationship, and the pooled estimate was OR=0.98, 95%CI=0.95-1.01, per 1-h increment of sleep (I^2=46.1%, $P_{\text{heterogeneity}}$=0.063; Fig. 3). We also modelled sleep duration as a linear relationship, considering if sleep duration considered napping time, and a 5% reduction in risk per each hour increment was observed in the studies that excluded napping from the total sleep duration (OR=0.95, 95%CI=0.91-1.00 for 1-h of sleep increment), although not significant heterogeneity was observed regardless of whether sleep duration included napping time or not ($P_{\text{heterogeneity}}$=0.164; Fig. 4).

3.3. Sensitivity analyses

Stratified analyses revealed a significant interaction (p-interaction=0.0021) between endometrial cancer and sleep duration by BMI, although the effect measures appeared relatively small (OR=0.93, 95% CI=0.89-0.98 for 1-h of sleep increment, I^2= 12.7%, $P_{\text{heterogeneity}}$=0.329 among obese participants, and OR=1.01, 95%CI=0.98-1.05; I^2=51.8%, $P_{\text{heterogeneity}}$=0.035 among non-obese; Supplemental Table S3). Stratified analyses on night shift work and sleep duration by study design did not reveal heterogeneity (Supplemental Table S4). Night shift work was not associated with endometrial cancer in analyses stratified by histologic subtype. Associations between sleep duration and type I tumors were near null in magnitude, while positive associations with both short and long sleep durations were suggested for type II tumors but did not reach statistical significance (Supplemental Table S5).

Table 3
Associations between night shift work and endometrial cancer.

Night shift work	Controls	Cases	OR	95% CI	I^2	$P_{heterogeneity}$ [a]
Never	1018	644	Ref.			No. Centers = 3
Ever	900	298	0.89	0.72–1.09	0.00%	0.575
Duration of night shift work (years)						
Never	1018	644	Ref.			No. Centers = 3
<10 years	703	215	0.88	0.70–1.11	0.00%	0.478
≥10 years	192	79	0.99	0.73–1.36	0.00%	0.374
Type of night shift work						
Never	492	491	Ref.			No. Centers = 2
Permanent	49	40	0.85	0.52–1.37	0.00%	0.481
Rotating (never permanent)	23	19	0.70	0.36–1.37	0.00%	0.456

Adjusted for age (continuous), race (white, others), body mass index (<25, 25-29.99, ≥30), use of oral contraceptive (ever, never), parity (0, 1, 2, +3) and smoking (never, past, current).

[a] P-heterogeneity test evaluates the statistical significance of the variation in study outcomes between different studies.
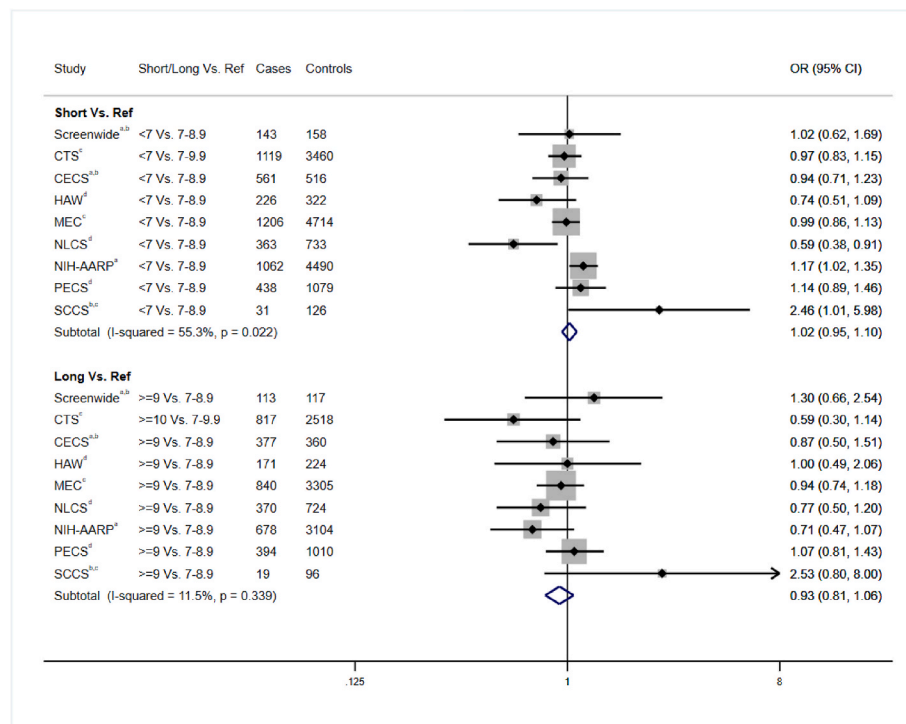
Fig. 2. Forest plot associations between short and long sleep duration and endometrial cancer risk.
Adjusted for age (continuous), race (white, others), body mass index (<25, 25–29.99, ≥30), use of oral contraceptives (ever, never), parity (0, 1, 2, +3) and smoking status (never, past, current).
[a] In these studies napping time was excluded from sleep duration.
[b] These studies provided information separately for weekdays and weekends. Data corresponding to weekdays were used here.
[c] In these studies napping time was not specified.
[d] In these studies napping time was included in sleep duration.

4. Discussion

4.1. Overall findings

These are the first pooled analyses investigating endometrial cancer risk in relation to sleep duration and night shift work. We used individual data from 11 epidemiological studies included in the E2C2 and found limited evidence supporting an association between night shift work or sleep duration and endometrial cancer risk in postmenopausal women. Specifically, after accounting for potential confounding factors, we found no statistically significant association between endometrial cancer and ever working in night shifts, and associations did not vary by type (permanent or rotating) or duration of night shift work. Furthermore, we did not observe clear associations between sleep duration and endometrial cancer risk; modest associations with sleep duration were suggested among obese women, but confidence intervals were imprecise. Taken together, our findings suggest that night shift work and sleep duration are not major risk factors for endometrial cancer in postmenopausal women.

4.2. Night shift work

The role of circadian disruption is an area of emerging interest in cancer etiology. Literature suggests a link between night shift work and increased risk of cancer [47,50–53,55–58]. However, the role of night work in endometrial cancer etiology has been scarcely assessed. To date, only three studies have reported the association between night shift work and endometrial cancer [68–70]: data from two of these studies [68,70] were included in the present pooled analyses. In accordance with our findings, null results were found in a large Swedish cohort [69] and in a Spanish case-control study [70]. However, a significant increased risk of endometrial cancer among long-term (>20 years) rotating night workers was reported in the NHS [68]. However, when we performed the first step analyses with individual NHS data on night work duration in our pooled analyses, we somewhat observed this pattern, although it was not statistically significant: the different analysis (cohort study vs nested case-control design in the present study) and the different confounder adjustments (age in the published analyses vs age, race, BMI, use of oral contraceptives, parity and smoking in the present analyses) may explain this statistical discrepancy.
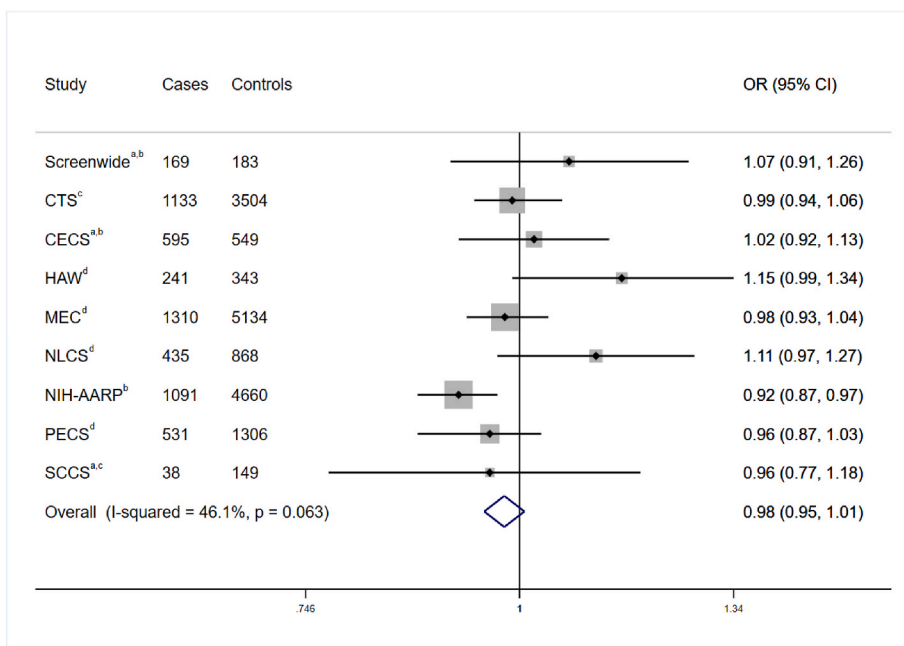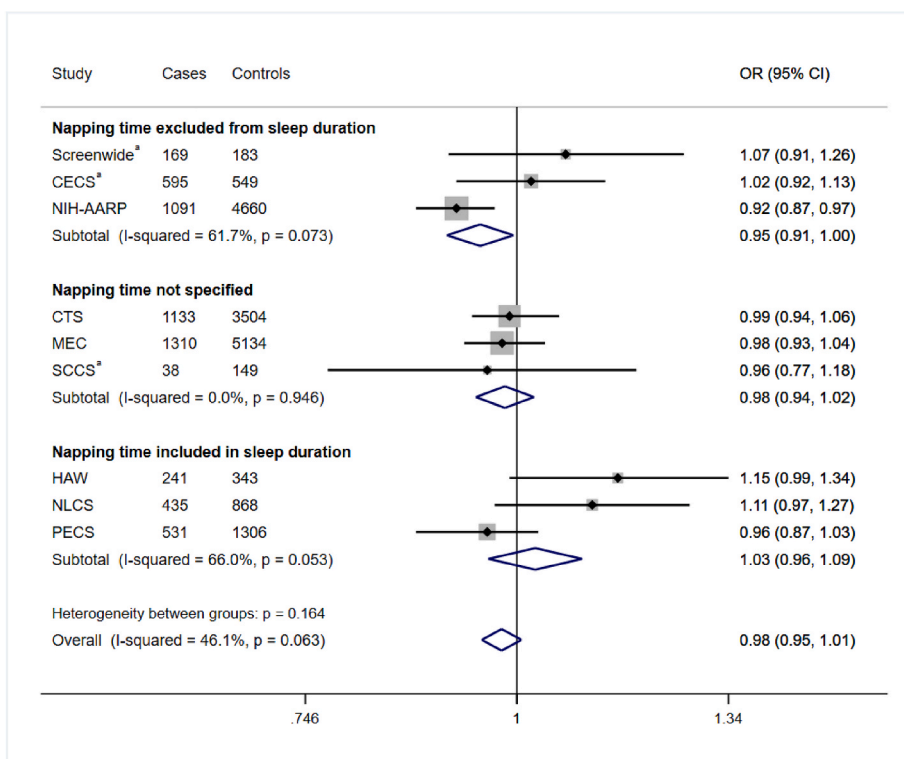
Fig. 3. Forest plot associations between sleep duration (1-h of sleep increment) and endometrial cancer risk.

Adjusted for age (continuous), race (white, others), body mass index (<25, 25–29.99, ≥30), use of oral contraceptives (ever, never), parity (0, 1, 2, +3) and smoking status (never, past, current).

[a] These studies provided information separately for weekdays and weekends. Data corresponding to weekdays were used here.

[b] In these studies napping time was excluded from sleep duration.

[c] In these studies napping time was not specified.

[d] In these studies napping time was included in sleep duration.

Fig. 4. Forest plot associations between sleep duration (1-h of sleep increment) and endometrial cancer risk according to nap information.

Adjusted for age (continuous), race (white, others), body mass index (<25, 25–29.99, ≥30), use of oral contraceptives (ever, never), parity (0, 1, 2, +3) and smoking status (never, past, current).

[a] These studies provided information separately for weekdays and weekends, data corresponding to weekdays were used here.

4.3. Sleep duration

We observed null associations between sleep duration and endometrial cancer risk overall, in accordance with previous literature [31,35, 41,70]. These studies [31,35,70], except one [41], were included in the present analyses, plus data from six other studies [73,76–78,80,81] with unpublished data on sleep duration. Our stratified analyses by BMI showed a significant inverse association between sleep duration and endometrial cancer among obese women that warrants further investigation. A potential biological mechanism that could explain this

association might be that the increased melatonin levels observed in individuals who sleep for extended durations [17] may potentially offset the impact of the circulating estrone levels typically increased in post-menopausal women with obesity [87]. Only one previous study evaluated the association between sleep duration and endometrial cancer among obese women. However, this study did not observe this association, possibly due to being underpowered for stratified analyses [41].

The total sleep duration per day may vary depending on whether it is taken all at once or split between night and napping time. Our results slightly varied depending on the inclusion of napping time in the total

amount of sleep duration. Melatonin levels may differ among individuals who sleep for the same number of hours a day but have different distributions of sleep across the day. This could be particularly relevant in older populations who commonly experience nighttime sleep problems and compensate it by taking daytime naps.

4.4. Mechanistic studies and other factors

Both sleep duration and night shift work have been associated with differences in the circulating levels of melatonin and of several sex hormones across the menstrual cycle [17,88]. In particular, exposure to light at night during night shift work has been related with the suppression of serum melatonin levels [49,89]. Similarly, shorter duration of sleep has also been associated with decreased melatonin urinary levels [17]. Plenty of *in vivo* and *in vitro* studies demonstrated significant anti-tumor effect of melatonin using basic research approaches [47]. In particular, melatonin can be involved in different aspects of cancer development, including apoptosis and anti-growth signaling stimulation, inflammation, angiogenesis, and it may alter sex hormone levels [22,23]. Thus, the exposure of light at night due to sleep deprivation or night shift work can disrupt melatonin production and lead to a decrease in its levels in serum [49]. This reduction in melatonin levels could potentially contribute to an increased risk of cancer [54,90,91]. Moreover, exposure to light at night may also be biologically related to the complex neuroendocrine-immune system that governs functions such as cell proliferation, immune defense, energy metabolism, and adaptation to daily stressors [90,92–94]. Therefore, when sleep is disrupted, these processes can be adversely affected, potentially leading to an increased risk of cancer and other health issues [49,95]. On the other hand, circulating estrogens and estrogen metabolites have been repeatedly associated with endometrial cancer [3,4], while progestogens provide protection against the proliferative effects of estrogens on the endometrium [96]. During menopause, the levels of circulating sex steroid hormones, particularly estradiol, dramatically decline due to the depletion of the ovarian follicular reserve [97]. Thus, the timing between age at menopause and circadian exposures may also be crucial in relation to endometrial cancer risk. However, the complex relationship between hormonal factors and circadian disruption is an understudied area in the postmenopausal period when endometrial cancer typically occurs.

The chronotype of participants may also influence the relationship between night work, sleep duration and endometrial cancer. Chronotype refers to an individual's natural preference for the timing of daily activities [98]. Circadian disruption occurs when the timing of daily activities is misaligned with one's intrinsic chronotype, leading to potential health issues. The evidence suggests that older rotating shift workers with early chronotypes may be less adapted to working night shifts, whereas day work may be more compatible with earlier chronotypes [99]. Chronotype in relation to endometrial cancer has been rarely assessed. A positive association between endometrial cancer and an evening chronotype was observed in the CTS [100], while this association was not observed in the Screenwide study [70]. However, none of the studies evaluated the influence of chronotype in the relationship between sleep factors and endometrial cancer.

4.5. Strengths and limitations

To our knowledge, these are the first pooled analyses to evaluate the possible association between night shift work, sleep duration and endometrial cancer risk. The strengths of these analyses include the relatively large sample size, in particular for sleep duration analyses. However, given that the role of circadian disruption is an area of emerging interest in cancer etiology, only three studies had data on night work, which may have limited the power to detect an association. In addition, complete work history was only available for one study [70], which hampered the characterization of exposure to night work.

We counted with detailed individual information on potential confounding factors, such as age, race, BMI, use of oral contraceptives, parity, and smoking status, although residual confounding cannot definitively be excluded. Moreover, individual data allowed us to perform stratified analysis based on BMI, study type and cancer type. We lacked data on sleep quality, stress levels or chronotype, which may also influence the association between sleep duration and risk of endometrial cancer. Another limitation is the inclusion of women in economically developed nations, but not from other parts of the world where the incidence of endometrial cancer, as well as the prevalence of night shift work and sleep habits, may differ. Furthermore, relevant data on rotational speed, number of consecutive nights, and other significant biological markers that may influence melatonin levels were not available in this study. These limitations underscore the need for future investigations to thoroughly explore these aspects. This, in turn, will contribute to a more comprehensive understanding of the relation between sleep duration, night shift work, and the risk of endometrial cancer. Also, we cannot discard a reverse causality between sleep duration and endometrial cancer in case-control studies. However, we did not observe statistically significant differences by study design (cohort vs case-control studies), which suggest that this may have not played a large role in our study. Recall bias may influence results from case-control studies, as the data was self-reported.

4.6. Conclusion

In conclusion, these data do not support the idea that night shift work and sleep duration are strong risk factors for endometrial cancer in postmenopausal women. Future prospective studies with detailed sleep characterization, including napping time and sleep quality, chronotype and night shift work information, or even measurement of melatonin urine levels, would provide valuable additional insight into the relationship between night work, sleep duration, and endometrial cancer.

Author contributions

Laura Costas conceived the study. Jon Frias-Gomez conducted the primary statistical analysis and Yolanda Benavente and Laura Costas provided statistical expertise. Laura Costas and Jon Frias-Gomez took the lead in writing the manuscript. All authors are representatives from individual studies within E2C2 and assisted the project by providing data and suggesting revisions during the analyses and manuscript editing process. All authors of this paper have read and approved the final version submitted.

Ethics approval and consent to participate

All studies contributing data to these analyses had the relevant

institutional review board approval from each country, in accordance with the Declaration of Helsinki, and all participants provided informed consent.

Practice points

1. Light exposure at night due to night work or sleep deprivation disrupts the circadian rhythm and is associated to a decreased melatonin level.
2. Melatonin has shown several oncostatic properties.
3. In 2019, the International Agency for Research on Cancer (IARC) classified night shift work as a probable carcinogen.
4. The association between sleep duration, night shift work and endometrial cancer has yielded conflicting findings.
5. Night shift work and sleep duration may not strongly impact endometrial cancer risk in postmenopausal women, according to these pooled analyses of 11 studies.

Research agenda

1. **Include diverse populations**: Further research should aim to include women from diverse populations worldwide to determine if the relationship between sleep factors, night shift work, and endometrial cancer risk varies across different regions and populations.
2. **Explore the influence of chronotype:** Future studies could benefit from assess chronotype and its influence on the association between sleep duration, night shift work, and endometrial cancer risk.
3. **Measure melatonin levels in urine**: Measuring melatonin levels in urine directly, adjusted for creatinine concentration, could provide valuable insights into the relationship between melatonin, sleep duration, night shift work, and endometrial cancer risk.
4. **Conduct prospective studies with detailed sleep information:** Future prospective research would benefit from including measures of sleep quality assessments, chronotype data, and objective measures of sleep, such as wearable devices, to obtain more accurate and comprehensive data on sleep factors and their association with endometrial cancer risk.

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101848.

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