Epidemiology
Open Access

Sanni et al., Epidemiol 2016, 6:2
DOI: 10.4172/2161-1165.1000229

Review Article Open Access

Risk Factors (Excluding Hormone Replacement Therapy) for Endometrial Hyperplasia: A Systematic Review

Omolara B Sanni[1*], Andrew T Kunzmann[1], Liam J Murray[1], W Glenn McCluggage[2] and Helen G Coleman[1]

[1]*Cancer Epidemiology & Health Services Research Group, Centre for Public Health, Queen's University Belfast, Northern Ireland*
[2]*Department of Pathology, Belfast Health and Social Care Trust, Northern Ireland*

Abstract

To conduct a systematic review of risk factors associated with the development of Endometrial Hyperplasia (EH).

Data sources

Ovid MEDLINE, EMBASE and Web of Science databases were searched from inception to 30 June 2015.

Study eligibility

Fifteen observational studies that reported on EH risk in relation to lifestyle factors (n=14), medical history (n=11), reproductive and menstrual history (n=9) and measures of socio-economic status (n=2) were identified. Pooled relative risk estimates and corresponding 95% confidence intervals (CI) were able to be derived for EH and Body Mass Index (BMI), smoking, diabetes and hypertension, using random effects models comparing high versus low categories.

Results

The pooled relative risk for EH when comparing women with the highest versus lowest BMI was 1.82 (95% CI 1.22–2.71; n=7 studies, I2=90.4%). No significant associations were observed for EH risk for smokers compared with non-smokers (RR 0.88, 95% CI 0.66-1.17; n=3, I2=0.0%), hypertensive versus normotensive women (RR 1.51, 95% CI 0.72–3.15; n=5 studies, I2=79.1%), or diabetic versus non-diabetic women (RR 1.77, 95% CI 0.79–3.96; n=5 studies, I2=31.8%) respectively although the number of included studies was limited. There were mixed reports on the relationship between age and risk of EH. Too few studies reported on other factors to reach any conclusions in relation to EH risk.

Conclusions

A high BMI was associated with an increased risk of EH, providing additional rationale for women to maintain a normal body weight. No significant associations were detected for other factors and EH risk, however relatively few studies have been conducted and few of the available studies adequately adjusted for relevant confounders. Therefore, further aetiological studies of endometrial hyperplasia are warranted.

Keywords: Endometrial hyperplasia; Endometrial cancer; Risk factors

Introduction

Endometrial Hyperplasia (EH) is a condition that is characterised by abnormal growth of the endometrium lining the uterus [1-3]. This condition is more prevalent among peri-menopausal and post-menopausal women [4]. While previously EH was classified into simple or complex EH, with or without atypia [2], the 2014 World Health Organisation classification simplifies this into EH without atypia and atypical hyperplasia [5]. Atypical hyperplasia is less common than other types, and results from observational studies suggest that it is the type which is more associated with the risk of progression to endometrial cancer [1-3]. The endometrial cancers which develop from EH are so-called type 1 endometrial cancers of endometrioid type [6].

The risk of progression for EH to endometrial cancer has been reported from a large population-based nested case-control study including 7,947 enrolees at a prepaid health plan in the USA. In that study, atypical EH was associated with a 14-fold increased risk of endometrial cancer, while the risk of progression for simple EH and complex (non-atypical) EH were significantly lower [7].

Given the potential for neoplastic progression, treatment options for EH include hysterectomy, and hormonal therapies; occasionally 'watchful waiting' is adopted for EH without atypia [8]. The need for such interventions, and potential psychological distress for women following an EH diagnosis [9]. highlight the importance of preventing EH where possible. Identification of modifiable risk factors for EH would enable women to make lifestyle changes that could reduce risk of this condition, and subsequent cancer risk [10]. EH, especially EH without atypia, develops as a consequence of excessive or prolonged exposure to oestrogen [11-13], and an imbalance between oestrogen and progesterone levels which usually occur as a result of insufficient progesterone in comparison with oestrogen level in a woman's system [13], For premenopausal women, the balance between these hormones changes during a woman's menstrual cycle each month. After menopause, the ovaries stop producing these hormones, but a small amount of oestrogen can be synthesized from androgen by the

***Corresponding author:** Omolara Sanni, Centre for Public Health, Institute of Clinical Sciences, Block B, Queen's University Belfast, Royal Victoria Hospital, Grosvenor Road, Belfast, Northern Ireland, Tel: 009 44 7476101022; E-mail: osanni01@qub.ac.uk

Received February 15, 2016; **Accepted** March 04, 2016; **Published** March 11, 2016

Citation: Sanni OB, Kunzmann AT, Murray LJ, McCluggage WG, Coleman HG (2016) Risk Factors (Excluding Hormone Replacement Therapy) for Endometrial Hyperplasia: A Systematic Review. Epidemiol 6: 229. doi:10.4172/2161-1165.1000229

enzyme aromatase [14]. Given the predominant role of hormones in the development of EH, a Cochrane review on hormone therapy in postmenopausal women which included 45 trials and 38,702 participants found that unopposed oestrogen is associated with an increased risk of EH with relative risks of 3.20 (95% CI 2.02 – 5.26) and 10.09 (95% CI 4.90 – 20.80) for moderate and high doses of oestrogen respectively, although this increased risk was not observed with low doses of hormone replacement therapy (HRT) use [13].

Similar to known risk factors for endometrial cancer [15], it is possible that demographic and modifiable factors such as age, parity, oral contraceptive use, body fatness, physical activity, smoking and co-morbidities may play an aetiological role in the development of EH [1,12,16]. The aim of this systematic review and meta-analyses is to quantify the association between risk factors (excluding HRT, since this is incorporated in a Cochrane review 13 and development of EH.

Materials and Methods

Search strategy

Three electronic databases namely MEDLINE (US National Library of Medicine, Bethesda, Maryland), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands), and Web of Science (Thomson Reuters, USA) were systematically searched from inception up to 30 June 2015 for relevant studies that included one or more keyword(s) or Medical Subject Heading from each of the following groups of terms:

(i) endometrial hyperplasia, simple endometrial hyperplasia, complex endometrial hyperplasia, complex hyperplasia with atypia, simple hyperplasia with atypia, complex atypical endometrial hyperplasia, simple atypical endometrial hyperplasia;

(ii) risk factor(s), causality, association, predisposing factor(s), predisposing factor(s), parity, obesity, history of diabetes, ethnicity, race, socio-economic status, occupation, education, oral contraceptive use, tamoxifen use, NSAID use, aspirin use, age at first birth, miscarriage history, age at menarche, alcohol, smoking, PCOS, polycystic ovarian syndrome, family history of cancer, personal history of cancer, medications, BMI, body mass index, waist circumference, body weight, diet, body fatness, waist-hip ratio, physical activity, use of fertility treatments.

Review articles and animal studies were excluded and no language restriction was applied.

Data extraction

Titles and abstracts for potentially relevant articles were independently screened by two of three reviewers (OS, LM and HC). Then two reviewers (OS and HC) independently screened full text articles for the remaining studies to identify relevant studies that meet the pre-set inclusion criteria for the systematic review:

(i) Participants: Women aged 18 and above.

(ii) Interventions: Measurement of risk factors (excluding HRT) in the study population.

(iii) Comparators: Women without a diagnosis of EH.

(iv) Outcome: Risk of EH.

The full text of the remaining articles were independently screened by two reviewers (OS and HC) to identify relevant studies that meet the pre-set inclusion criteria for the systematic review. Articles reporting on less than 10 cases of EH were excluded from the review. Meetings were held between three reviewers (LJ, HC, OS) to resolve any discrepancies. The full protocol for this review can be found at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016569#.VRfpRJMe5ME. Relevant information about study design, number of cases, controls or cohort size, menopausal status of the study population, age, and method used to diagnose EH, control definition, method used to measure exposure and adjusted confounders were extracted from full text articles. The Newcastle Ottawa Scale coding manual was used to assess quality of each study. Some studies reported EH risk as part of a combined EH and endometrial cancer risk estimate, and were retained for inclusion in the systematic review, and sensitivity analysis conducted removing such studies from overall pooled estimates. Studies that compared risk between different types of EH, and not in comparison with a true control group that did not have EH, were excluded. Attempts were made to retrieve additional information where required from a number of authors via e-mail contact [17-22].

Statistical analysis

Statistical analyses were conducted with STATA version 13 (StataCorp, College Station, TX, USA). Unadjusted and maximally adjusted relative risk (RR) estimates and corresponding 95% confidence intervals (CI) were extracted from published articles where possible. Random-effects models were used to derive pooled RRs [23] and CI. It was decided a priori to perform meta-analyses where at least three studies had reported risk estimates for a particular risk factor. When applying these criteria we were able to conduct meta-analyses of EH risk comparing high versus low for body mass index (BMI), smoking, hypertension, and diabetes.

Sensitivity analyses were conducted for EH risk in relation to BMI and diabetes removing individual studies; this was not possible for other risk factors as too few studies reported these. Sub-group analysis was performed where possible for EH with or without atypia in relation to BMI, diabetes and hypertension. We also assessed heterogeneity of studies included in meta-analyses using the I2 statistic [24,25]; I2 values of 25%, 50% and 75% are typically interpreted as low, moderate and high heterogeneity respectively. We investigated the likelihood of publication bias using the Egger's test [26,27]. Combined RR were calculated before entry into final meta-analyses for studies that reported separate EH risk estimates only by different types of EH or different age categories. Specifically, one study reported separate EH risk estimates for complex EH and atypical EH [28].

Results

After application of our search strategy in the three databases, and removal of duplicates, a total of 2,890 titles and abstracts were reviewed in the first instance to determine potentially relevant studies for inclusion. After title and abstract review, 79 full text articles and abstracts were reviewed, and 15 full text articles were retained in the review (Figure 1). Included articles assessed lifestyle factors, menstrual history, age, medical history, reproductive history and socio-economic factors and their relationship with risk of developing EH.

Lifestyle factors

BMI

Eight studies examined BMI and risk of EH [12,28-34]. Four were case-control studies [12,28,30,32], two were cohort studies [31,34] and two were cross-sectional studies [29,33]. Characteristics of these studies are fully described in Table 1.

Six studies [12,28,29,32-34] provided or allowed unadjusted RRs

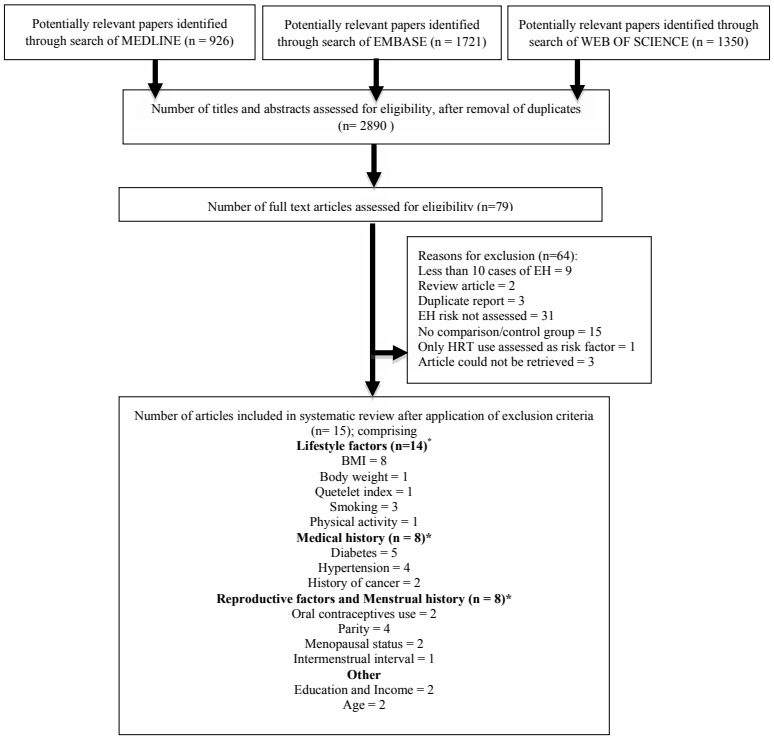

Figure 1: Flow diagram of study selection.

to be calculated, and the pooled RR for EH when comparing women with the highest versus lowest BMI was 1.84 (95%CI: 1.18-2.88) with I2 62.9%. Results from seven studies [12,28-31,33,34] were pooled to derive maximally adjusted EH risk estimates for the highest versus the lowest category of BMI. As shown in Figure 2, high BMI was significantly associated with an increased EH risk (RR 1.82, 95%CI: 1.22-2.71) with an I2 of 90.4%. Egger's test showed no significant evidence of publication bias (p=0.18). Heterogeneity remained consistently high after removal of individual studies, this may be due to the variability of adjusted confounders across studies (Table 2). Only the exclusion of Balbi et al. [30] reduced heterogeneity somewhat and markedly affected results. This study investigated simple EH risk only, and sub-group analysis between BMI and EH without atypia resulted in a non-significant positive association (RR 1.27, 95%CI 0.49-3.59) (Table 3).

Other body fatness measures

Two studies have investigated other body fatness measures and EH risk, as summarised in Tables 1 and

One study among premenopausal women with abnormal menstrual bleeding reported a significant 7–fold increased risk for complex atypical EH and endometrial carcinoma combined (OR 7.3, 95%CI 3.2–16.8), comparing body weight >90kg versus <90kg [35].

In a further study, the Quetelet index was reported to be significantly higher in postmenopausal EH cases, compared with controls, leading to an increased risk (OR 3.8, 95%CI 1.27–11.40) when comparing >2.9 versus ≤2.9. In contrast, a protective effect for premenopausal women was noted (OR 0.25, 95% CI 0.07–0.95) [36].

Smoking

Two population-based [28,37,38] and one hospital-based 12 case-control studies examined the relationship between smoking and risk of EH. Descriptions of study characteristics are shown in Table 4.

Results from these three studies were pooled to derive an unadjusted EH risk estimate of 0.98 (95%CI 0.64-1.49) with I2 45.7% for smokers compared with non-smokers. Adjusted pooled risk estimate was 0.88 (95%CI 0.66-1.17) with 0% heterogeneity for smokers when compared with non-smokers (Figure 3).

The moderate heterogeneity among studies disappeared after adjusting for confounders. However, only one study adjusted for HRT, and two adjusted for BMI as shown in Table 4.

Physical activity

One Italian hospital-based case-control study 30 reported non-significant increased risk of EH (OR 1.38 95%CI 0.50–3.77) among women who reported high levels of physical activity (≥60 minutes 3 times/week) when compared with those who reported lower levels of physical activity (Tables 1 and 4).

Medical history

Diabetes

Five studies evaluated the relationship between diabetes and EH risk. Three were hospital-based case-control [12,30,34], one was a population-based case-control,28 and one was a prospective cohort study [39]. Characteristics of the studies are shown in Table 5.

Three studies [12,28,38] were included in meta-analysis in order to derive unadjusted pooled EH risk estimate for diabetic versus

Author, Year, Location	Study design	No. Cases	No. Controls/ cohort size	Menopausal status	Age, years (range) Cases/ Controls	Case definition including EH type	Method of diagnosis	Control definition	Method of measuring body fatness	Adjusted confounders	Quality scale score (max. 9)
Body Mass Index											
Balbi et al. (2012) [29], Italy	Hospital-based case-control	167	282	Pre-menopausal	40-55	Simple EH	Confirmed by 1 pathologist	Women attending gynaecologic unit of 2 hospitals for menstrual irregularities	Interview, medical history, general physical examination	Age, hypertension, diabetes, physical activity	7
Cheung et al. (2001) [30], Canada	Case-control	45	36	Pre-menopausal	23-41/21-39	Simple or complex EH with or without atypia	Histologically confirmed by pathologist	Consecutive women with PCOS and infertility due to anovulation	Not reported	Age, endometrial thickness, average inter-menstrual interval, menses biopsy interval, last OC use.	5
Cymbaluk et al.(2006) [31], Poland	Hospital-based case-control	14	46	Post -menopausal	56.3/54.8[1]	EH with atypia	Curettage or hysteroscopy	Obese postmenopausal women referred for post-menopausal bleeding	Not reported	Not reported	4
Epplein et al.(2008) [27], USA	Population-based case-control	45	446	Pre- and post-menopausal	≥ 18	Complex EH or EH with atypia	Histologically confirmed by 3 pathologists	Randomly selected from the same health plan as cases	Not reported	Menopausal status, parity	7
Ricci et al.(2002) [12] Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Shan et al. (2014) [28] China	Cross-sectional	194	39	Pre-menopausal	18-35	Simple or complex EH with or without atypia	Histologically confirmed by at least 2 pathologists	Not reported	Height and weight measured to calculate BMI	Pregnancy, severe infection, CVD, breast cancer, reproductive cancers , HRT use, age, menopause	7
Topcu et al.(2014) [33], Turkey	Retrospective cohort	13	203	Pre- and postmenopausal	41-69/ 40-84	EH with or without atypia	Histologically confirmed	Not reported	Not reported	Not reported	7
Viola et al. (2007) [32], Brazil	Cross-sectional	10	177	Pre- and postmenopausal	18-70	Simple or complex EH with or without atypia	Not reported	Not reported	Weight and height measured to calculate BMI	Steroid hormone use, tamoxifen use, history of ovarian or endometrial tumour, history of endometriosis	6
Quetelet Index											
Kreiger et al. (1986) [35], Canada	Population-based case-control	149	248	Pre- and post-menopausal	40-74	Adenomatous hyperplasia	Confirmed by 3 pathologists	Randomly selected from same neighbourhood as cases	Not reported	Menopausal status	6
Body weight											
Farquhar et al. (1999) [34], New Zealand	Retrospective cohort	46	1033	Pre-menopausal	17-50	Simple or complex EH with or without atypia	Histologically confirmed by pathologist	Not reported	Patient record review	Not reported	4

Table 1: Characteristics of studies included in the systematic review of Endometrial Hyperplasia and risk factor: body fatness.

	Number of studies included	References	Pooled risk estimate (95% CI)	I-squared (%)	p-value
Body mass index					
Unadjusted	6	(12,27-30,32)	1.84 (1.18 – 2.88)	62.9	0.02
Adjusted, excluding Balbi et al. [29]	6	(12,27,28,30,32,33)	1.20 (0.97 – 1.49)	60.8	0.03
Adjusted, excluding Ricci et al. [12]	6	(27-30,32,33)	1.88 (1.21 – 2.93)	91.9	0
Adjusted, excluding Epplein et al. [27]	6	(12,28-30,32,33)	1.78 (1.16 – 2.74)	91.6	0
Adjusted, excluding Cheung et al. [30]	6	(12,27-29,32,32)	2.29 (1.10 – 4.74)	88.6	0
Adjusted, excluding Shan et al. [28]	6	(12,27,29,30,32,33)	2.21 (0.96 – 5.07)	91.8	0
Adjusted, excluding Viola et al. [32]	6	(12,27-30,33)	1.78 (1.19 – 2.67)	91.9	0
Adjusted excluding Topcu et al. [33]	6	(12,27-30,32)	1.80 (1.19 – 2.71)	91.9	0
EH without atypia only	3	(12,27,28)	1.27 (0.49 – 3.59)	0	0.9
Smoking					
Unadjusted	3	(12,27,36)	0.98 (0.64 – 1.49)	45.7	0.16
Diabetes					
Unadjusted	3	(12,27,38)	1.43 (0.79 – 2.57)	0	0.96
Adjusted, excluding Ricci et al. [12]	4	(27,29,33,38)	1.48 (0.47 – 4.64)	46.3	0.13
Adjusted, excluding Balbi et al. [29]	4	(12,27,33,38)	1.89 (0.82 – 4.37)	40.6	0.17
Adjusted, excluding Epplein et al. [27]	4	(12,29,33,38)	2.31 (1.10 – 4.85)	11.6	0.34
Adjusted, excluding Gol et al. [38]	4	(12,27,29,33)	1.89 (0.64 – 5.52)	43.8	0.15
Adjusted, excluding Topcu et al. [33]	4	(12,27,29,38)	1.37 (0.66 – 2.82)	0	0.43
EH without atypia only	3	(12,27,38)	1.32 (0.31 – 5.70)	0	0.78
Hypertension					
Unadjusted	3	(12,27,39)	1.33 (0.76 – 2.30)	68.5	0.04
Atypical EH only	3	(27,38,39)	1.92 (0.57 – 6.53)	70.3	0.04
EH without atypia only	3	(12,27,38)	1.17 (0.39 – 3.45)	0	0.96

Table 2: Summary of unadjusted, subgroup and sensitivity analyses excluding individual studies from meta-analyses.

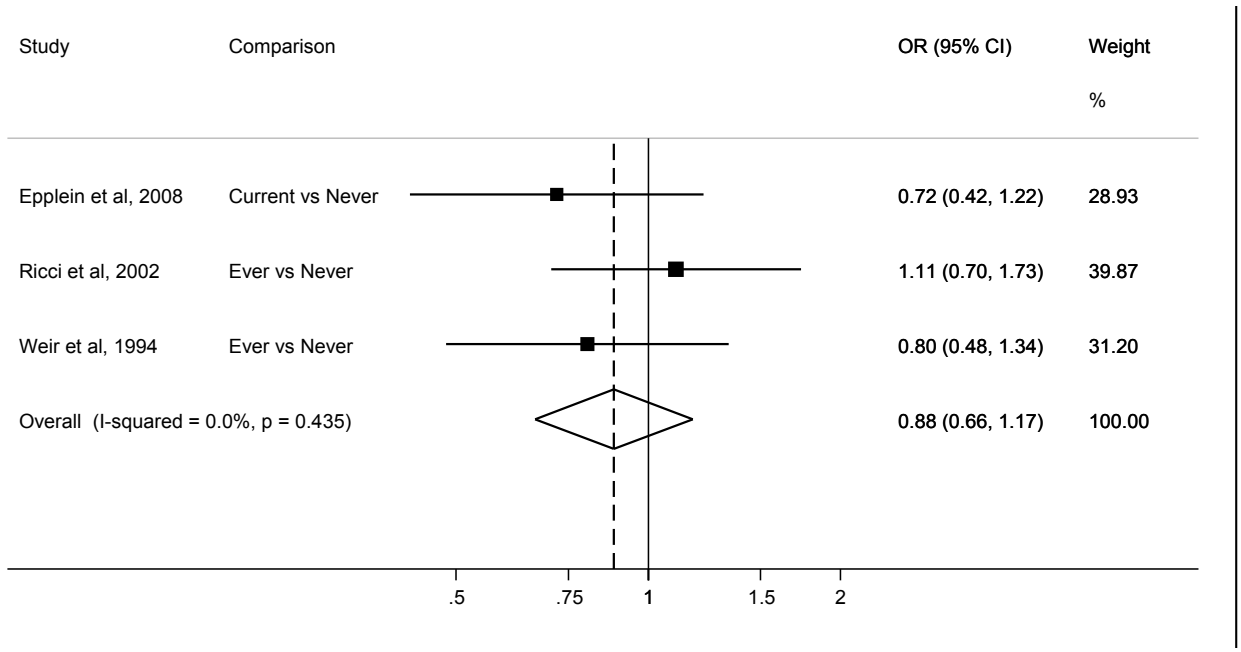

Figure 2: Adjusted meta-analysis for highest versus lowest category of BMI and EH risk.

non-diabetic women (RR 1.43, 95%CI 0.79–2.57; I2=0%). Five studies [12,28,30,34,38] were included in meta-analyses to derive adjusted pooled EH risk estimate (RR 1.77, 95%CI 0.79–3.96; I2=31.8%), as shown in Figure 4. Egger's test showed no significant evidence of publication bias (p=0.34).

While risk estimates remained non-significant for the most part of sensitivity analyses, a significant positive association was observed when the study by Epplein et al. [28] was excluded. Heterogeneity however ranged from low to moderate throughout. Sub-group analysis by EH type showed non-significant positive association between EH without atypia and diabetes (RR 1.32, 95%CI 0.31-5.70) (Table 2). Two studies reported adjusting for BMI while none adjusted for HRT use as shown in Table 5.

Risk factor	No. of studies	References	Study design	Summary of results
Body weight	1	34	Retrospective cohort	n=1 study reported increased risk of complex EH with atypia amongst women weighing ≥90kg when compared with women weighing <90kg.
Quetelet index	1	35	Population-based case-control	n=1 study reported significant higher waist-hip ratio in EH cases when compared with controls.
Physical activity	1	29	Hospital-based case-control	n=1 study reported non-significant increased risk of EH amongst women who reported higher levels of physical activity.
History of cancer	2	12,34	1 hospital-based case-control, 1 retrospective cohort study	n=1 study reported non-significant 20% reduced risk of EH amongst women with a family history of EC. n=1 study reported significant increased risk of EH amongst women with a family history of EC or colon cancer
Oral contraceptive use	2	12,27	1 population-based case-control, 1 hospital-based case-control	n=1 study reported a reduced risk of complex and atypical EH amongst women used OC 6months prior to abnormal vaginal bleeding. n=1 study reported non-significant increased risk of EH amongst women who had ever used OC compared with never-users.
Parity	2	12,27	1 population-based case-control, 1 hospital-based case-control	n=1 study reported significant reduced risk of EH amongst women who had given birth to 3 or more children in comparison with women who had never given birth. n=1 study reported non-significant increase in risk of EH amongst women who had given birth to 2 or more children in comparison with nulliparous women.
Nulliparity	2	34,37	1 hospital-based case-control, 1 retrospective cohort study	n=1 study reported significant increased risk of EH or EC amongst nulliparous women in comparison with multiparous women. n=1 study reported significant increased risk of EH amongst nulliparous women in comparison with multiparous women
Menopausal status	2	12,28	1 hospital-based case-control, 1 cross-sectional study	n=1 study reported a non-significant reduced risk of non-atypical EH among post-menopausal women when compared with pre-menopausal women but non-significant increased risk of atypical EH was reported for postmenopausal women compared with pre-menopausal women. n=1 study reported a significant reduced risk of complex amongst post-menopausal women in comparison with pre- and peri-menopausal women.
Education and Income	2	12,35	1 hospital-based case-control, 1 population-based case-control study	n=1 study reported higher level of education amongst EH cases compared with controls. n=1 study reported higher income for EH cases compared with controls.
Age	2	12,37	2 hospital-based case-control studies	n=1 study reported significant increased risk of EH or EC amongst women ≥70 years compared with women 49-59 years old. n=1 study reported non-significant reduced risk of EH amongst women ≥65years in comparison with women <45years old.

Table 3: Summary of results for risk factors for EH for which meta-analyses were not possible.

Hypertension

Four studies [12,28,30,39] reported on hypertension in relation to EH risk. Characteristics of the studies are shown in Table 5.

Three studies [12,28,39] were included in meta-analysis to derive an unadjusted pooled risk estimate of OR 1.33 (95%CI 0.76–2.30; I2=68.5%), and four studies [12,28,30,39] were included in meta-analysis to derive adjusted pooled risk estimate of OR 1.51 (95%CI 0.72–3.15; I2=79.1%) for hypertensive versus normotensive women (Figure 5). Egger's test showed no significant evidence of publication bias (p=0.28).

Sub-group analyses showed non-significant positive associations between atypical EH (RR 1.92 95%CI 0.57-6.53) and EH without atypia (RR 1.17 95%CI 0.39-3.45) (Table 2) and hypertension status; only the latter showed reduced heterogeneity. Two studies adjusted for BMI while one reported adjusting for HRT as shown in Table 5.

Family History of cancer

Women with a family history of endometrial cancer were reported by Ricci et al. [12] to have around 20 percent reduced risk of developing EH , although not statistically significant (OR 0.8 95% CI 0.2 –2.6). Another study found women with abnormal bleeding who had a family history of colon cancer or endometrial cancer to be more likely to develop endometrial cancer or complex EH with atypia (OR 9.1, 95%CI 2.2 – 37.1;OR 5.8, 1.1 – 28.6, respectively) [35]. (Tables 1 and 5). None of the studies reported adjusting for BMI or HRT use as shown in Table 5.

Reproductive factors

Oral contraceptive use

Two studies [12,40] examined the relationship between oral contraceptive use and the risk of developing EH (Table 6). One population-based case-control study reported a reduced risk of complex and atypical EH among women who had used OC 6 months before presenting with abnormal bleeding (OR 0.2, 95%CI 0.0–0.6) after

Author, Year, Location	Study design	No. Cases	No. Controls/ cohort size	Menopausal status	Age, years (range) Cases/ Controls	Case definition including EH type	Method of diagnosis	Control definition	Method of measuring body fatness	Adjusted confounders	Quality scale score (max. 9)
Smoking											
Epplein et al.(2008) [27], USA	Population-based case-control	45	446	Pre- and post-menopausal	≥ 18	Complex EH or EH with atypia	Histologically confirmed by 3 pathologists	Randomly selected from the same health plan as cases	Medical record review	Menopausal status, BMI, parity	7
Ricci et al.(2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Weir et al.(1994) [36], Canada	Population-based case-control	177	530	Pre- and post-menopausal	40-74	Adenomatous hyperplasia	Histologically confirmed by 3 pathologists	Randomly selected from same neighbourhood as cases	Interview	Age, obesity, oestrogen use	6
Physical activity											
Balbi et al.(2012) [29], Italy	Hospital-based case-control	167	282	Pre-menopausal	40-55	Simple EH	Confirmed by 1 pathologist	Women attending gynaecologic unit of 2 hospitals for menstrual irregularities	Interview, medical history, general physical examination	Age, hypertension, BMI, diabetes	7

Table 4: Characteristics of studies included in the systematic review of Endometrial Hyperplasia and risk factor: smoking and physical activity.

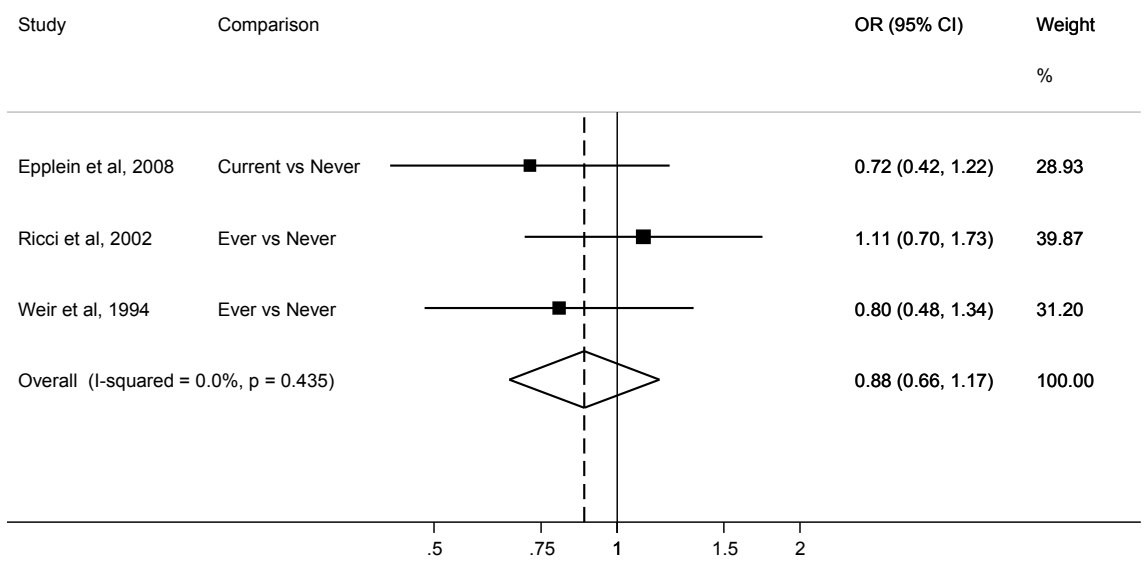

Figure 3: Adjusted meta-analysis for highest versus lowest category of smoking and EH risk.

adjusting for BMI. However, a non-significant increased risk of EH was found in another study among women who had ever used OC versus those who had never used OC (OR 1.6, 95%CI 0.9–2.8) [12] (Table 1). The authors further assessed OC use and EH risk by duration of use and consistently found non-significant increased risks when they compared women who had used OC for more than 5 years, 13–60 months, 12 years or less with never users (OR 1.2, 95%CI 0.4–3.4;OR 1.4, 95%CI 0.5–3.6; and OR 2.0, 0.9–4.3, respectively). It should however be noted that BMI or HRT use was not adjusted for in the latter as shown in Table 6.

Parity

When comparing women who had given birth to two or more babies with nulliparous women, Ricci et al. [12] found an almost significant 2-fold (OR 1.8, 95%CI 0.9–3.6) increase in risk of complex EH (Table 1) after adjusting for age and education [12]. In contrast, Epplein et al. [28], found significant reduced risk (OR 0.29, 95% CI 0.07–0.51) of EH among women who had given birth to three or more babies when compared with nulliparous women, after adjusting for BMI [28].

Two studies which compared nulliparous women with multiparous women found a significant increased risk of EH in nulliparous women (OR 3.7, 95%CI 1.2-10.9) 35 and (OR 2.8, 95% CI 1.3-6.1) (after adjusting for prior use of oestrogen) [41], respectively. Meta-analysis was not performed for these four studies, summarised in Table 6, due

Author, Year, Location	Study design	No. Cases	No. Controls/ cohort size	Menopausal status	Age, years (range) Cases/ Controls	Case definition including EH type	Method of diagnosis	Control definition	Method of measuring medical history	Adjusted confounders	Quality scale score (max. 9)
Diabetes											
Balbi et al.(2012) [29], Italy	Hospital-based case-control	167	282	Pre-menopausal	40-55	Simple EH	Confirmed by 1 pathologist	Women attending gynaecologic unit of 2 hospitals for menstrual irregularities	Interview, medical history, general physical examination	Age, BMI, physical activity	7
Epplein et al.[27] (2008) [27], USA	Population-based case-control	45	446	Pre- and post-menopausal	≥ 18	Complex EH or EH with atypia	Histologically confirmed by 3 pathologists	Randomly selected from the same health plan as cases	Medical record review	Menopausal status, BMI, parity	7
Gol et al.(2001) [38], Turkey	Cohort	30	556	Post-menopausal	52.5±6.6	EH with or without atypia	Confirmed by pathologist	Not reported	Not reported	Not reported	5
Ricci et al.(2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Topcu et al.(2014) [33], Turkey	Retrospective cohort	13	203	Pre- and postmenopausal	41-69/ 40-84	EH with or without atypia	Histologically confirmed	Not reported	Not reported	Not reported	7
Hypertension											
Balbi et al.(2012) [29], Italy	Hospital-based case-control	167	282	Pre-menopausal	40-55	Simple EH	Confirmed by 1 pathologist	Women attending gynaecologic unit of 2 hospitals for menstrual irregularities	Interview, medical history, general physical examination	Age, BMI, physical activity	7
Epplein et al.(2008) [27], USA	Population-based case-control	45	446	Pre- and post-menopausal	≥ 18	Complex EH or EH with atypia	Histologically confirmed by 3 pathologists	Randomly selected from the same health plan as cases	Medical record review	Menopausal status, BMI, parity	7
Ricci et al. (2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Vorgias et al. (2005) [39], Greece	Hospital-based case-control	60	45	Post-menopausal	48-83	Dilatation and curettage	Not reported	Women who underwent D&C at a tertiary cancer hospital	Blood pressure ≥150/100 mmHg, or daily use of antihypertensive medications	HRT use, obesity, tamoxifen use	5

Table 5: Characteristics of studies included in the systematic review of Endometrial Hyperplasia and risk factor: medical history (diabetes, hypertension).

Author, Year, Location	Study design	No. Cases	No. Controls/ cohort size	Menopausal status	Age, years (range) Cases/ Controls	Case definition including EH type	Method of diagnosis	Control definition	Method of measuring medical history	Adjusted confounders	Quality scale score (max. 9)
Reproductive factors											
Epplein et al. (2009) [39], USA	Population-based case-control	45	462	Pre- and post-menopausal	≥ 18	Complex EH or EH with atypia	Histologically confirmed by 3 pathologists	Randomly selected from the same health plan as cases	Dispensed prescription record	Age, race, ZIP code, years enrolled in Group Health, BMI, diabetes, hypertension, smoking	7
Farquhar et al. (1999) [34], New Zealand	Retrospective cohort	46	1033	Pre-menopausal	17-50	Simple/complex EH with/without atypia	Histologically confirmed by pathologist	Not reported	Patients' records	Not reported	4
Feldman et al. (1995) [40], USA	Hospital-based case-control	16	151	Pre- and postmenopausal	61.4/56.0[2]	Complex EH	Pathologic diagnosis	Women who received benign diagnosis following biopsy for abnormal vaginal bleeding	Structured questionnaire, interview	Age ≥70,prior use of oestrogen,hypertension, diabetes,menopause, nulliparity,history of non-breast cancer,quetelet index	5
Ricci et al.(2002), [12] Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected from hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Menstrual history											
Cheung et al. (2001) [30], Canada	Case-control	45	36	Pre-menopausal	23-41/ 21-39	Simple or complex EH with or without atypia	Histologically confirmed by pathologist	Consecutive women with PCOS and infertility due to anovulation	Not reported	Age, endometrial thickness, average inter-menstrual interval, menses biopsy interval, last OC use.	5
Ricci et al.(2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age, education	5
Shan et al.(2014), [28] China	Cross-sectional	194	39	Pre-menopausal	18-35	Simple or complex EH with or without atypia	Histologically confirmed by at least 2 pathologists	Not reported	Height and weight measured to calculate BMI	Pregnancy, severe infection, CVD, history of breast cancer, malignancies in the reproductive system, HRT use, age, BMI	7

Table 6: Characteristics of studies included in the systematic review of Endometrial Hyperplasia and risk factor: reproductive factors (oral contraceptive use and parity) and menstrual history (menopausal status and age at menopause).

[1]Investigated oral contraceptive use and parity

[2]Mean

[3]Investigated menopausal status and age at menopause

[4]Investigated menopausal status

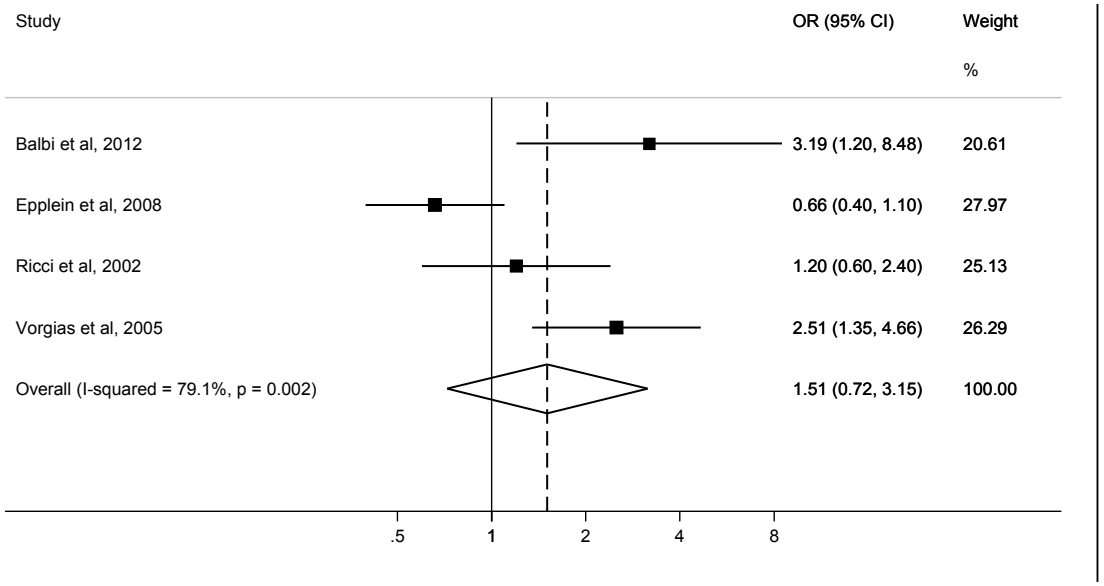

Figure 4: Adjusted meta-analysis comparing women with hypertension with normotensive women in relation to EH risk.

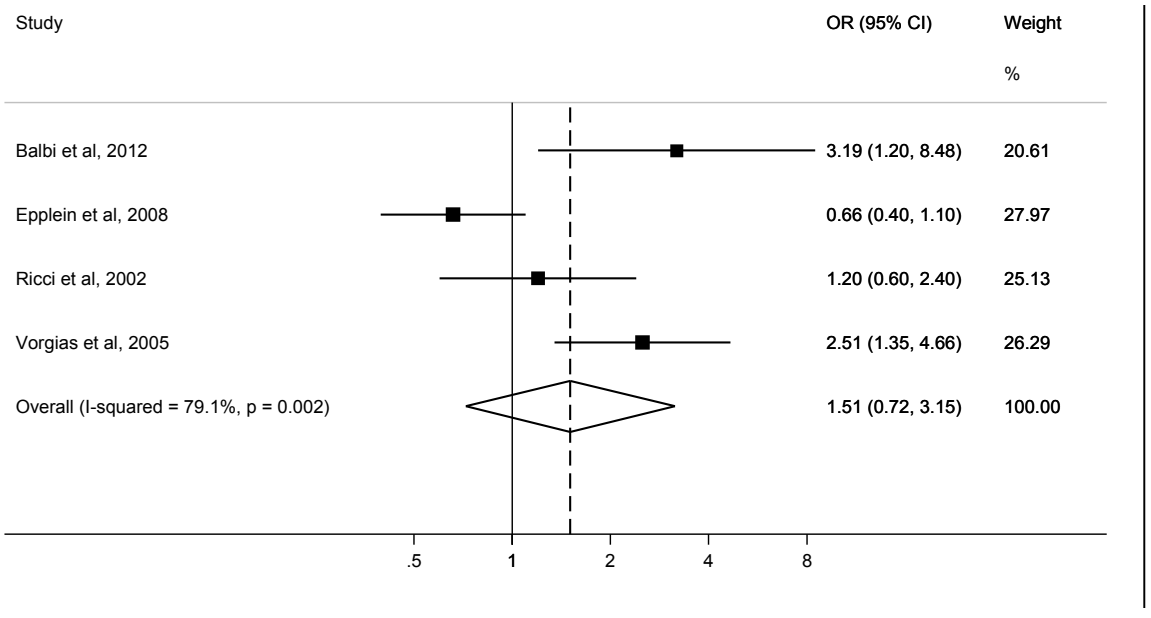

Figure 5: Adjusted meta-analysis comparing women with hypertension with normotensive women in relation to EH risk.

to differences in the reference groups analysed. While two studies Farquhar et al and Feldman et al used multiparous women as reference group, Epplein et al and Ricci et al. [12] used nulliparous women as reference group.

Menstrual history

Menopausal status

Two hospital-based case-control studies [12,29] evaluated menopausal status in relation to EH risk (Table 6). One study among Chinese women 29 found that postmenopausal women were less likely to develop EH without atypia (OR 0.65, 95%CI 0.17–2.50) but they were more likely to develop EH with atypia (OR 2.40, 95%CI 0.43–13.27) when compared with premenopausal women, although these estimates did not achieve statistical significance. Similarly, another study 12 also reported a significant reduced risk of complex EH among postmenopausal women in comparison with pre- and peri-menopausal women (OR 0.2, 95%CI 0.1–0.5). The authors also found a non-significant 20% increased risk of complex EH among women who reported menopause at ≥53 years versus <50 years at menopause [12] (Table 1). One of the studies reported adjusting for BMI and HRT use as shown in Table 6. One further study suggested that polycystic

Author, Year, Location	Study design	No. Cases	No. Controls/ cohort size	Menopausal status	Age, years (range) Cases/ Controls	Case definition including EH type	Method of diagnosis	Control definition	Method of measuring medical history	Adjusted confounders	Quality scale score (max. 9)
Age											
Feldman et al.(1995) [40], USA	Hospital-based case-control	16	151	Pre- and post-menopausal	61.4/56.0[1]	Complex EH	Pathologic diagnosis	Women who received benign diagnosis following biopsy for abnormal vaginal bleeding	Structured questionnaire, interview	Prior use of oestrogen, hypertension, diabetes, menopause, nulliparity, history of non-breast cancer, quetelet index	6
Ricci et al.(2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Education	5
Socio-economic status											
Kreiger et al.(1986) [35], Canada	Population-based case-control	149	248	Pre- and post-menopausal	40-74	Adenomatous hyperplasia	Confirmed by 3 pathologists	Randomly selected from same neighbourhood as cases	Self-reported	Menopausal status	6
Ricci et al.(2002) [12], Italy	Hospital-based case-control	129	258	Pre- and post-menopausal	35-74	Complex EH	Histologically confirmed	Non hysterectomized women selected form hospitals covering the same area as cases	Self-reported, Questionnaire	Age	5

Table 7: Characteristics of studies included in the systematic review of Endometrial Hyperplasia and risk factor: Age and Socio-economic status (income and education).

ovarian syndrome patients with longer intermenstrual intervals have a significant increased risk of developing EH (OR 1.43, 95%CI 1.78-1.15) after adjusting for confounders including last oral contraceptive use [31].

Other factors

Age

Two hospital-based case-control studies reported risk estimates for age with regards to EH [12,41]. Characteristics and results from these studies are shown in Tables 1 and 7 . One study reported a significant increased risk of EH or EC amongst women ≥70 years old versus women 49-59 years old after adjusting for confounders including prior use of oestrogen, and another study reported a non-significant decreased risk of EH amongst women ≥65 years old versus <45 years old. Meta–analyses were not conducted because only two studies [12,41] provided risk estimates for age in relation to development of EH, reports from the studies were mixed (Table 1). One of the studies adjusted for quetelet index, a measure of body fatness as shown in .

Socio-economic status

Two studies [12,36] examined education and income in relation to EH risk (Table 7). In one study, a positive association was observed among women who had ≥12 compared with <7 years of education (OR 2.8 95% CI 1.70–4.80).

Similarly, women who earned ≥$30,000 were found to have higher chances of developing EH when they were compared with women who earned less than $30,000 in a Canadian study (Table 1). The observed association was significant for premenopausal women (OR 1.85, 95%CI 1.16 – 2.96) but not for postmenopausal women (OR 1.15, 95%CI 0.78 – 1.69) [36]. Neither of the studies reported adjusting for HRT use or BMI as shown in Table 7.

Comment

Main findings

In this novel systematic review of risk factors for EH (excluding hormone replacement therapies), meta-analyses suggested a significant positive association between increased BMI and risk of EH; no significant associations were detected between smoking, hypertension or diabetes and EH risk in pooled analyses of a limited number of studies. However, there was paucity of high quality, consistent evidence for the aforementioned and other factors in the review. There was also inadequate adjustment for relevant confounders, namely HRT and BMI, in some of the included studies.

The importance of pooling risk estimates is demonstrated by the expected finding that higher BMI is positively associated with EH compared with lower BMI, considering that only three out of six studies which reported a positive association between BMI and EH risk showed statistical significance. EH is an oestrogen-driven disease. From a biologically plausible viewpoint, it is well known that oestrogen can be synthesized from adipose tissue, this increases the level of circulating oestrogen which in turn stimulates growth of the endometrium. Reduction in high heterogeneity which occurred when the study of simple EH 30 was excluded during sensitivity analyses suggests that the relationship between BMI and EH may differ according to the presence of atypia. Due to the role of body fatness in the development of EH and endometrial cancer, it is important for women to maintain a healthy weight [15].

Pooled analysis of studies that investigated hypertension showed non-significant positive association between hypertension and EH risk. Some authors have reported that hypertension is positively associated with EH 40 or endometrial cancer [42]. However, this association was found among overweight or obese women compared with lean women [42], this observation should therefore be viewed with caution as it is likely to be confounded, considering the association between obesity and hypertension. Hypertension has previously been linked to insulin-like growth factor 1 (IGF-1), and measures of body fatness such as waist-hip ratio and obesity were reported to be higher among hypertensive patients than controls [43,44]. IGF-1 is known to be related to cell growth and cancer progression [45].

We found a non-significant increased EH risk among diabetic versus non-diabetic women. Although the mechanism for a potential association between diabetes and EH is not very clear, diabetes has been linked to IGF-1 [46]. Low levels of IGF-1were found to be positively associated with diabetes after adjusting for confounders including BMI [46]. In a rat model, Type 1 diabetes was also been shown to induce EH development, potentially mediated by oestrogen receptor alpha and p16 expression [47]. Several authors have reported overweight/obesity as one of the most important modifiable risk factors for diabetes [48,49]. Despite the well-known relationship between obesity and diabetes, few of the studies included in our meta-analysis adequately adjusted for this confounder.

Meta-analysis of three studies showed no association between tobacco smoking and risk of EH. An earlier literature review suggested that smoking has an anti-oestrogenic effect, which can reduce the rate of androgen-oestrogen conversion [50]. Smoking has also been linked to early menopause [51-53]. Women who undergo menopause early are less exposed to oestrogen than women who are older at menopause. However, smoking has been consistently linked to the development of many neoplastic conditions and is certainly not advised [54,55]. It is plausible that known carcinogenic effects of smoking may be countered by the aforementioned anti-oestrogenic effect, explaining the observed null association for tobacco smoking and EH risk.

One study reported a non-significant increased EH risk for women with self-reported higher levels of physical activity compared to those who reported lower levels of physical activity. However, as with all self-reported information of desirable lifestyle factors, this result should be interpreted with caution. Physical activity has previously been shown to be protective against endometrial carcinoma, given that physical activity may modulate metabolism, and excretion of endogenous sex hormones such as oestrogen which is also known to be responsible for development of EH [56]. Interestingly the previously described EH diabetic rat model did observe a significant reduction in oestrogen-receptor alpha and p16 expression for those rats undertaking aerobic exercise [48].

Contrasting results were reported for parity and EH risk by individual studies included in this review, although the majority reported protective effects of child-bearing for EH risk. Nulliparity is known to be associated with an increased risk of endometrial cancer [57] - a possible mechanism for this is that during pregnancy, a woman is exposed to larger amounts of progesterone as opposed to oestrogen. Contrasting reports were also observed for the two studies investigating OC use and EH risk. It should however be noted that OC usage has consistently been found to reduce EC risk among users when compared with non-users [58,59]. Biologically, this is related to the low dose of oestrogen in relation to progestin contained in OC, which inhibits endometrial proliferation [60,61].

A significant decreased risk of complex EH was reported among postmenopausal versus pre- and peri-menopausal in an Italian study. Conversely, findings from a further study included in our review suggesting an increased risk of atypical EH among postmenopausal versus premenopausal women, which may indicate that HRT use, a well-known risk factor for EH, has more of a propensity to invoke atypical than non-atypical EH. We however did not assess use of HRT in this review due to an earlier Cochrane review which assessed the effects of different hormone therapy regimens on the postmenopausal endometrium. The reviewers found unopposed oestrogen to be associated with increased risk of all types of EH at all doses, in line with the existing literature. Although the reviewers did not perform sub-group analysis for the different types of EH, they found no difference in the risk of EH in women who took low dose oestrogen combined with progestogen compared with controls who took placebo [13].

It is notable that one study reported an increased risk of complex EH in women with higher versus lower level of education while another reported the same association amongst women with higher versus lower income. Measures of social class have been implicated in the development of neoplasms due to the differing medical attention seeking behaviour of the different groups [62,63].

Finally, two studies in the review suggest a link between family history of endometrial or colon cancer in relation to EH risk. This points to a shared genetic or environmental risk factor in EH development. Families with a history of Lynch syndrome have been found to have between 1.5–3 fold increased risk of developing endometrial cancer [64]. Indeed endometrial cancer is more common than colonic cancer in patients with Lynch syndrome.

Strengths and limitations

This is the first systematic review examining the risk factors (excluding HRT use) for EH, the review has a number of strengths and limitations. A major strength of this review was the evaluation of three databases and the robust methodology and adherence to a previously published protocol. This included the strict exclusion of several studies that included simple EH cases in control groups. Although several studies that were included reported on EH combined with other outcomes such as benign endometrial polyps and/or carcinoma, we were careful to consider those separately in our interpretations, as their risk estimates would be distorted. We were also able to perform sub-group analyses for atypical and non-atypical EH in relation to BMI, diabetes and hypertension. Importantly, our collective assessment of EH risk factors has highlighted the general paucity of data available for this condition, but does suggest that EH could be potentially prevented through maintenance of normal body weight.

Limitations of this systematic review largely relate to insufficient data which would have been helpful in increasing precision of risk estimates for the different risk factors evaluated. Pooled risk estimates could not be derived for important risk factors such as age, parity and menopausal status due to insufficient number of studies (<3) providing risk estimates, in accordance with our protocol. Also, many hospital-based studies were included, which limits applicability of results to the general population. In addition, very few studies adjusted for HRT use and BMI in their statistical models. HRT use is known to play a significant role in the development of EH, its use at all doses in the treatment of menopausal symptoms has been found to be associated with an increased risk of EH [65]. It is still plausible that additional risk factors may exist for EH and could be identified in future, high-quality studies.

The relationship between a high BMI and EH cannot be overemphasized as is shown in this review. Notably, no studies evaluated nutrition or dietary factors in relation to EH risk, even though several aspects of diet, for example coffee and high glycaemic load intake, have been associated with endometrial cancer risk [15]. We hope that this review stimulates further work in this area in an effort to identify more modifiable, preventative factors for EH.

Conclusions

In conclusion, body fatness was found to be associated with an increased risk of EH, therefore women should be encouraged to maintain a normal body weight. No significant associations were detected for other factors and EH risk. However, relatively few studies have been conducted and further aetiological studies which might help identify other non-modifiable risk factors for EH are warranted.

Funding

OS is being funded by a QUB International PhD studentship

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