Endometrial thickness and cancer risk in asymptomatic postmenopausal women: Defining evidence-based cut-offs by systematic review and diagnostic meta-analysis

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Received October 8, 2025; Accepted May 19, 2026

DOI: 10.3892/etm.2026.13307

Abstract. Endometrial carcinoma (EC) is the sixth most common malignancy among women worldwide and predominantly affects postmenopausal individuals. Transvaginal ultrasonography (TVUS) provides a non-invasive method for assessing endometrial thickness (ET); however, the optimal ET threshold for guiding endometrial sampling in asymptomatic postmenopausal women remains controversial. Establishing evidence-based ET cut-offs is essential to balance early detection of premalignant and malignant lesions against unnecessary invasive procedures, patient anxiety and healthcare costs. The aim of the present study was to evaluate the risk of EC and atypical endometrial hyperplasia (AEH) across different TVUS-measured ET thresholds in asymptomatic postmenopausal women and to identify the ET cut-off that provides the most clinically appropriate balance between sensitivity and specificity. A systematic review and diagnostic test accuracy meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies Standards for Reporting Diagnostic Accuracy guidelines. Comprehensive searches of PubMed, EMBASE, Scopus, Cochrane Library and gray literature sources were performed through June 2025. Studies enrolling asymptomatic postmenopausal women with TVUS-assessed ET and histopathological confirmation were included. A total of 20 studies comprising 9,193 women met the eligibility criteria. Pooled analyses included sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratios and summary receiver operating characteristic (SROC) curves. Subgroup analyses were performed according to ET thresholds of 3.0-5.9, 6.0-9.9, 10.0-13.9 and ≥14.0 mm. An ET ≥3.0 mm was associated with a significantly increased risk of AEH or EC (risk ratio 3.84; 95% confidence interval 2.95-5.11). Lower ET thresholds (3.0-5.9 mm) demonstrated the highest pooled sensitivity (0.79) with acceptable specificity (0.71), whereas thresholds ≥14 mm demonstrated markedly reduced sensitivity (0.23) despite higher specificity (0.89). Intermediate thresholds showed favorable diagnostic accuracy but demonstrated greater variability across studies. SROC and ROC analyses suggested that an ET threshold of ~5 mm provides the most clinically pragmatic balance between sensitivity and specificity for guiding endometrial sampling in asymptomatic postmenopausal women. TVUS-measured ET is a clinically valuable predictor of EC and AEH in asymptomatic postmenopausal women. An ET threshold of ~5 mm appeared to provide the most appropriate balance between early detection and avoidance of unnecessary biopsies. Integration of ET assessment with clinical risk factors may further improve individualized patient management and prevention-oriented diagnostic strategies.

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Key words: endometrial thickness, transvaginal ultrasonography, postmenopausal, endometrial carcinoma, atypical hyperplasia, diagnostic test accuracy, risk stratification

Introduction

Endometrial carcinoma (EC) is the sixth most common malignancy among women worldwide, with an estimated 417,000 new cases and 97,000 deaths reported in 2020 (1). The disease predominantly affects postmenopausal women, particularly those between 60 and 65 years of age. Menopause is associated with marked hormonal alterations, including declines in circulating estrogen and progesterone levels, which influence endometrial physiology (2). Persistent unopposed estrogen exposure, whether endogenous or exogenous, together with metabolic conditions such as obesity and diabetes mellitus, may promote abnormal endometrial proliferation and carcinogenesis (3,4). Established risk factors for EC include

nulliparity, late menopause, obesity and prolonged unopposed estrogen therapy, whereas parity and long-term combined oral contraceptive use appear protective (5,6).

In clinical practice, EC is commonly suspected in postmenopausal women presenting with vaginal bleeding or increased endometrial thickness (ET) detected on transvaginal ultrasonography (TVUS) (7,8). However, the optimal management of asymptomatic postmenopausal women with incidentally detected endometrial thickening remains controversial (9). Applying the same low threshold used in symptomatic patients may reduce specificity and lead to unnecessary biopsies, patient anxiety, procedural complications and increased healthcare costs (10,11). By contrast, for symptomatic women with postmenopausal bleeding, several professional societies, including the American College of Obstetricians and Gynecologists, the Society of Radiologists in Ultrasound, the Society of Gynecologic Oncology and the British Gynaecological Cancer Society, recommend an ET threshold of ~4 mm to guide endometrial sampling, as the likelihood of malignancy below this cut-off is considered markedly low (8,12-15).

Early decision-analytic studies suggest that higher ET thresholds may be more appropriate for asymptomatic women. Smith-Bindman *et al* (12) reported that an ET >11 mm was associated with an estimated malignancy risk of 6-7%, comparable with the cancer risk observed in symptomatic women with an ET threshold of 5 mm. Subsequent evidence has supported the use of intermediate thresholds. Alcázar *et al* (13) in a systematic review and meta-analysis, demonstrated that higher ET cut-offs (6-9.9, 10-13.9 and ≥14 mm) notably improved specificity, although at the expense of sensitivity. Similarly, Giannella *et al* (14) suggested that an ET threshold of ~8 mm may provide a clinically useful balance between sensitivity and specificity for detecting atypical hyperplasia or carcinoma in asymptomatic postmenopausal women. Additional cohort studies and case series have further explored optimal ET thresholds by correlating ultrasonographic findings with histopathological outcomes and clinical risk factors. Recent investigations by Liang *et al* (16) (2025), Cruz García *et al* (17) (2023), Quaranta *et al* (18) (2023) and Sayyah-Melli *et al* (19) (2025), and previous observational studies by Ghoubara *et al* (20) (2018) and Yasa *et al* (21) (2016) have provided further evidence regarding risk stratification and clinically relevant ET cut-offs in asymptomatic postmenopausal women (15-22). Other systematic reviews (23,24) have proposed that thresholds of 11-12 mm may improve specificity and support more conservative management in women with lower baseline risk, thereby potentially reducing unnecessary invasive procedures. Furthermore, several contemporary clinical guidelines now recommend considering ET thresholds of ~11 mm in asymptomatic women, particularly when combined with additional ultrasonographic findings or patient-specific risk factors (25,26).

Given these evolving and occasionally conflicting data, several guideline committees have begun to differentiate diagnostic strategies according to symptom status, recommending either higher ET thresholds or integration of additional clinical risk factors when evaluating asymptomatic postmenopausal women (27). Nevertheless, uncertainty remains regarding the threshold that best balances sensitivity and specificity while minimizing both missed malignancies and unnecessary invasive procedures. This ongoing debate underscores the need for robust systematic reviews and diagnostic meta-analyses to clarify risk estimates, optimize diagnostic thresholds, and support evidence-based prevention and early detection strategies for EC.

Therefore, the present systematic review and diagnostic meta-analysis aimed to evaluate the risk of EC and atypical endometrial hyperplasia (AEH) across different TVUS-measured ET thresholds in asymptomatic postmenopausal women using evidence derived from observational studies (16-22,28-40). In addition, recognizing the inherent trade-off between sensitivity and specificity, the present study sought to determine the ET threshold that provides the most clinically appropriate balance for recommending endometrial sampling, thereby improving early detection of EC and AEH while minimizing unnecessary interventions, patient burden and healthcare costs.

Materials and methods

Study design. The present investigation was conducted as a systematic review and diagnostic test accuracy (DTA) meta-analysis. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines (41), as well as the Standards for Reporting Diagnostic Accuracy (STARD) framework (42). The present review protocol was developed a priori to predefine the study objectives, eligibility criteria, screening methodology, data extraction process and statistical analysis plan.

Data sources and search strategy. A comprehensive literature search was performed across multiple electronic databases, including PubMed, (https:/pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), EMBASE (https://www.embase.com/) and the Cochrane Library (https://www.cochranelibrary.com), from database inception through June 2025. No language, date or geographic restrictions were applied.

To maximize retrieval sensitivity, combinations of controlled vocabulary terms [Medical Subject Headings (MeSH) and Emtree terms], keywords and Boolean operators were used. MeSH search terms included variations of 'endometrial carcinoma', 'endometrial cancer', 'atypical endometrial hyperplasia', 'asymptomatic postmenopausal women', 'transvaginal ultrasonography' and 'endometrial thickness'. The detailed search strategy for each database is presented in Table I.

To minimize publication bias, additional searches were conducted in the Cumulative Index to Nursing and Allied Health Literature (CINAHL; https://www.ebsco.com/products/research-databases/cinahl-complete), the Allied and Complementary Medicine Database (AMED; https://ovidsp.ovid.com/), and relevant gray literature repositories. Ongoing or unpublished studies were identified through ClinicalTrials.gov (https://clinicaltrials.gov/), the Cochrane Central Register of Controlled Trials (CENTRAL; https://www.cochranelibrary.com/central), and the World Health Organization International Clinical Trials Registry Platform (ICTRP; https://trialsearch.who.int/). Furthermore, the reference lists of

Table I. Database search strategy.

Scopus	i) ('Endometrial cancer' or 'endometrial neoplasms' or 'uterine cancer' or 'endometrial carcinoma' or 'uterine neoplasms' or 'endometrial tumor' or 'uterine tumor') and ('postmenopausal' or 'menopause' or 'postmenopause' or 'perimenopause' or 'climacteric') ii) ('Observational studies' or 'cohort studies' or 'case-control studies' or 'cross-sectional studies' or 'retrospective studies' or 'prospective studies' or 'longitudinal studies' or 'epidemiologic studies' or 'population-based studies') iii) i AND iii
PubMed	i) ('Endometrial cancer' or 'endometrial neoplasm' or 'uterine cancer' or 'endometrial carcinoma' or 'uterine neoplasm*' or 'endometrial tumor' or 'uterine tumor') and ('postmenopause' or 'menopause*' or 'perimenopause' or 'climacteric') ii) ('Observational study' or 'cohort stud*' or 'case-control stud*' or 'cross-sectional stud*' or 'retrospective stud*' or 'prospective stud*' or 'longitudinal stud*' or 'epidemiologic stud*' or 'population-based stud*') iii) i AND iii
Embase	i) ('Endometrial cancer'/exp or 'endometrial neoplasm'/exp or 'uterine cancer'/exp or 'endometrial carcinoma'/exp or 'uterine neoplasm'/exp or 'endometrial tumor'/exp or 'uterine tumor'/exp) and ('ostmenopause'/exp or 'menopause'/exp or 'perimenopause'/exp or 'climacteric'/exp) ii) ('Observational study'/exp or 'cohort analysis'/exp or 'case-control study'/exp or 'cross-sectional study'/exp or 'retrospective study'/exp or 'prospective study'/exp or 'longitudinal study'/exp or 'epidemiologic study'/exp or 'population-based study'/exp iii) i AND iii
Cochrane Library	i) ('Endometrial cancer'):ti,ab,kw or ('endometrial neoplasms'):ti,ab,kw or ('uterine cancer'):ti,ab,kw or ('endometrial carcinoma'):ti,ab,kw or ('uterine neoplasms'):ti,ab,kw or ('endometrial tumor'):ti,ab,kw or ('uterine tumor'):ti,ab,kw and ('postmenopausal'):ti,ab,kw or ('menopause'):ti,ab,kw or ('perimenopause'):ti,ab,kw or ('climacteric'):ti,ab,kw ii) ('Observational studies'):ti,ab,kw or ('cohort studies'):ti,ab,kw or ('case-control studies'):ti,ab,kw or ('cross-sectional studies'):ti,ab,kw or ('retrospective studies'):ti,ab,kw or ('prospective studies'):ti,ab,kw or ('longitudinal studies'):ti,ab,kw iii) i AND iii
CINAHL	i) (MH 'endometrial cancer' or MH 'endometrial neoplasms' or 'uterine cancer' or 'endometrial carcinoma' or MH 'uterine neoplasms' or 'endometrial tumor' or 'uterine tumor') and (MH 'postmenopause' or MH 'menopause' or 'perimenopause' or 'climacteric') ii) (MH 'observational studies' or MH 'cohort studies' or MH 'case-control studies' or MH 'cross-sectional studies' or 'retrospective studies' or 'prospective studies' or 'longitudinal studies' or mh 'epidemiologic studies' or 'population-based studies') iii) i AND ii

MeSH, Medical Subject Headings (PubMed); Emtree, controlled vocabulary used in Embase; MH, CINAHL Subject Heading (CINAHL Headings); exp, explosion of a controlled vocabulary term; ti, title; ab, abstract; kw, keyword.

all included studies and relevant review articles were manually screened to identify additional eligible publications.

Eligibility criteria. Studies were considered eligible if they met the following criteria: i) Enrolled asymptomatic postmenopausal women undergoing endometrial evaluation using TVUS; ii) reported diagnostic accuracy outcomes, including sensitivity, specificity, predictive values, likelihood ratios or related diagnostic performance measures, using histopathological confirmation as the reference standard; iii) evaluated one or more ET thresholds for predicting EC and/or AEH; and iv) employed observational study designs, including prospective or retrospective cohort, cross-sectional or diagnostic accuracy studies.

Studies were excluded if they met any of the following criteria: i) Included premenopausal or perimenopausal women, women receiving tamoxifen, hormone replacement therapy, aromatase inhibitors or selective estrogen receptor modulators; ii) included women with a history of postmenopausal bleeding; iii) reported only prevalence or risk estimates without extractable diagnostic accuracy outcomes; iv) were non-original articles, including reviews, editorials, conference abstracts, letters or commentaries; and v) did not provide sufficient data to construct 2x2 contingency tables or calculate diagnostic performance measures.

Study selection and data extraction. A total of two reviewers independently screened all titles and abstracts identified

through the literature search. Full-text articles considered potentially eligible were subsequently assessed in detail according to the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion and consensus or, when necessary, by consultation with a third reviewer.

A standardized data extraction form was developed to ensure consistency across studies. Extracted variables included: Study characteristics (country, design, duration and setting); participant demographics (sample size, age distribution, menopausal duration and ethnicity/race when available); imaging characteristics (ET thresholds evaluated, TVUS measurement techniques and operator details); index test characteristics (TVUS protocols); reference standards (histopathological findings from biopsy, hysteroscopy, curettage or surgical specimens); and diagnostic accuracy outcomes, including sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios and diagnostic odds ratios. Information related to methodological quality and risk of bias was also collected.

Extracted data were synthesized qualitatively and quantitatively. Pooled diagnostic performance estimates were calculated across predefined ET threshold categories. In addition to summarize diagnostic accuracy measures, threshold selection was interpreted in the context of the clinical trade-off between false-positive and false-negative findings to identify clinically meaningful ET cut-offs for recommending endometrial sampling in asymptomatic postmenopausal women. When published reports lacked sufficient detail, attempts were made to contact corresponding authors to obtain missing or unpublished data.

Risk of bias assessment. To ensure methodological rigor, the quality of all included studies was independently assessed by three reviewers using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) framework (43). This validated instrument evaluates four domains: Patient selection, index test, reference standard and flow and timing. Each domain was assessed for risk of bias, while the first three domains were additionally evaluated for concerns regarding applicability. Risk-of-bias judgments were categorized as 'low risk', 'some concerns' or 'high risk' in accordance with QUADAS-2 guidance. Any discrepancies between reviewers were resolved through discussion and consensus. If disagreement persisted, a fourth reviewer adjudicated the final decision.

Primary and secondary outcomes. The primary outcomes of the present systematic review and diagnostic meta-analysis were: i) The risk of EC and AEH across TVUS-ET thresholds reported in the included studies; and (ii) the DTA of TVUS at each ET threshold. DTA performance was assessed using diagnostic odds ratio (DOR) (44), pooled sensitivity and specificity (45,46) and the area under the summary receiver operating characteristic curve (AUC-SROC) (47). Secondary diagnostic measures included positive likelihood ratio (PLR) and negative likelihood ratio (NLR) (48,49).

In addition to pooled statistical performance, ET threshold selection was interpreted in the context of clinical applicability, with particular emphasis on balancing early lesion detection against the risk of unnecessary invasive procedures in asymptomatic postmenopausal women.

Data extraction and statistical analysis. Data regarding true-positives (TPs), true-negatives (TNs), false-positives (FPs) and false-negatives (FNs) were extracted directly from the included studies whenever available. When raw diagnostic data were not explicitly reported, they were reconstructed into 2x2 contingency tables using standard diagnostic test formulas derived from reported sensitivity and specificity estimates (50-52). Specifically, sensitivity was calculated as TP/(TP + FN) and specificity as TN/(TN + FP). When the total number of diseased and non-diseased participants was available, TP and TN were estimated from the reported sensitivity and specificity values, respectively, using the formulas: TP=Sensitivity x (TP + FN) and TN=Specificity x (TN + FP). Corresponding FN and FP values were then derived as FN=(TP + FN) - TP and FP=(TN + FP) - TN. If studies reported multiple ET thresholds, each threshold was analyzed separately.

Comparisons between lower and higher ET thresholds were performed by stratifying studies according to predefined ultrasound cut-off categories. A bivariate random-effects model (53) was used to calculate pooled sensitivity and specificity estimates for each ET subgroup. The diagnostic odds ratio was additionally estimated using the DerSimonian-Laird random-effects approach (54), while SROC curves and corresponding AUC values were used to summarize overall diagnostic performance across studies (55). Forest plots of paired sensitivity and specificity values were generated to illustrate interstudy variability and threshold-specific diagnostic performance (56-58).

To ensure adequate statistical power and improve comparability across studies, ET thresholds were grouped into predefined subcategories: 3.0-5.9, 6.0-9.9, 10.0-13.9 and ≥14.0 mm, consistent with previously published literature and clinical threshold classifications. The final clinically relevant ET threshold was determined by jointly considering pooled sensitivity, specificity, likelihood ratios, DOR, AUC-SROC performance, interstudy consistency and the clinical implications of false-negative vs. false-positive findings.

Heterogeneity among studies was assessed using the Higgins I^2 statistic, with values ranging from 0% (no heterogeneity) to 100% (maximum heterogeneity) (59). Publication bias was evaluated using Deeks' funnel plot asymmetry test; $P<0.05$ was considered to indicate a statistically significant difference (60). Because ethnicity-specific diagnostic data were inconsistently reported across studies, stratified meta-analysis according to ethnicity could not be reliably performed.

All statistical analyses were conducted using Stata version 14.1 (StataCorp LP) with the MIDAS module for diagnostic accuracy meta-analysis (61). Review Manager version 5.4 (Nordic Cochrane Centre) was used to generate paired sensitivity-specificity forest plots and SROC visualizations (62).

Results

Study selection. A comprehensive literature search initially identified 190 potentially relevant publications (Fig. 1). Following a rigorous multistep screening process, 20 studies

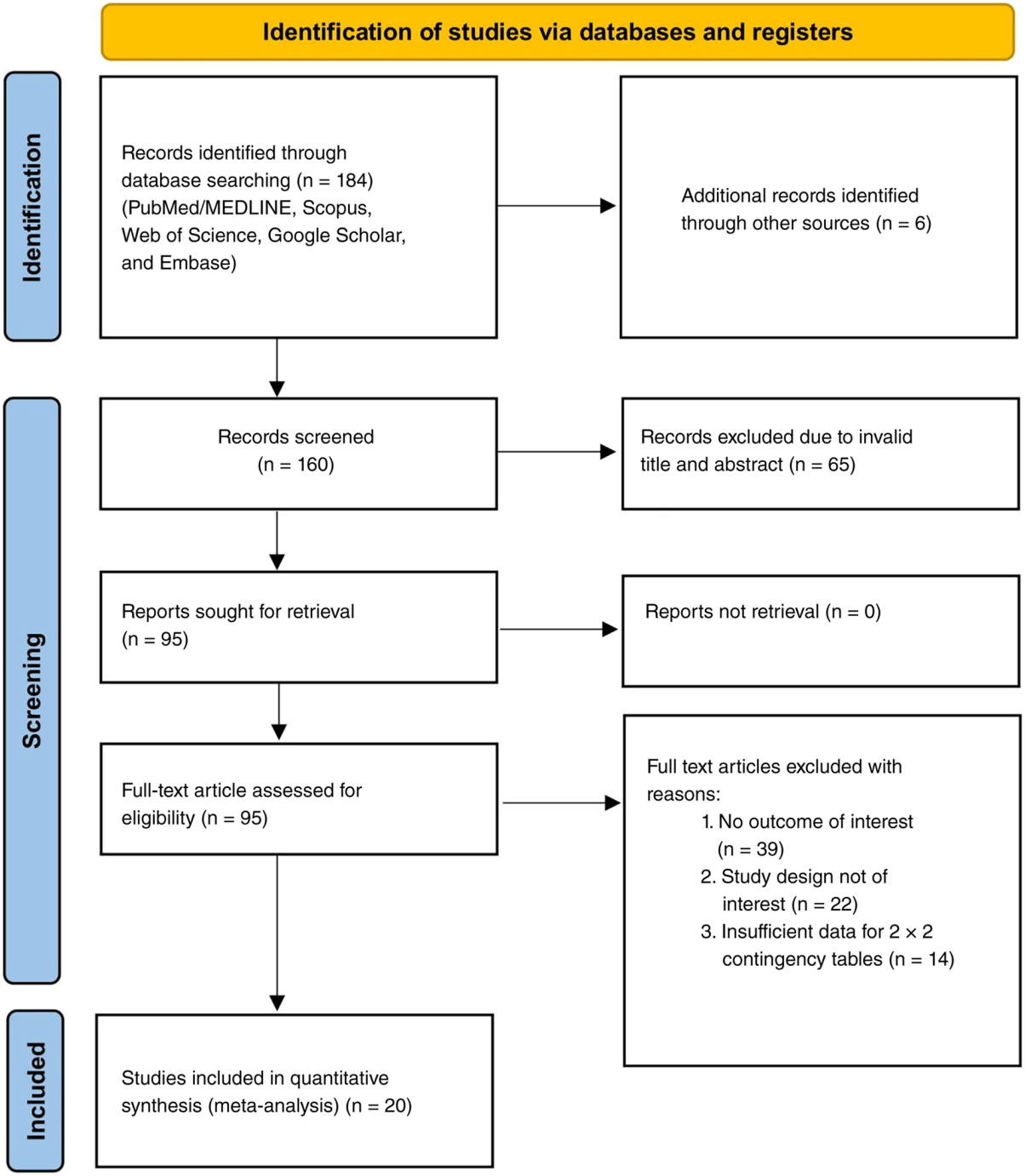

Figure 1. PRISMA flow diagram illustrating the study selection process.

ultimately met the predefined eligibility criteria and were included in the final diagnostic meta-analysis. Collectively, these studies encompassed 9,193 asymptomatic postmenopausal women who underwent TVUS) with subsequent histopathological confirmation through endometrial biopsy or related sampling procedures.

During the screening process, 30 duplicate records were removed, 65 studies were excluded following title and abstract screening because they were not relevant to the objectives of the present study, 39 studies lacked the predefined diagnostic outcomes of interest, 22 did not meet the required methodological design criteria and 14 failed to provide sufficient data for construction of 2x2 contingency tables. This stringent selection process ensured inclusion of studies with extractable diagnostic accuracy data and histopathological confirmation, thereby strengthening the reliability and consistency of the pooled estimates.

Study characteristics. Marked heterogeneity was observed in the methodological designs and ET threshold definitions across the included studies (Table II). A total of 15 studies evaluated a single ET cut-off, whereas five studies assessed multiple thresholds, thereby permitting comparative analysis across a broader range of diagnostic criteria. In all included

Table II. Characteristics of the included studies.

Author, year	Journal of publication	Country	Study design	Patients studied	Endometrial biopsy technique	Duration, years	Primary outcomes	Secondary outcomes	Endometrial thickness thresholds, mm	(Refs.)
Famuyide *et al*, 2014	Journal of minimally invasive gynecology	United States of America	Monocentric retrospective study	154	In-office hysteroscopy, endometrial biopsy	4	Endometrial cancer risk	Diagnostic accuracy, endometrial thickness	10	(28)
Garcia *et al*, 2023	Journal of obstetrics and gynecology	Spain	Monocentric retrospective study	267	In patient hysteroscopy	4	Endometrial cancer risk	Diagnostic accuracy, endometrial thickness	5-10, 11-15, >15	(17)
Ghoubara *et al*, 2018	Journal of obstetrics and gynecology	United Kingdom	Monocentric retrospective study	1,995	Pipette or office hysteroscopy	4	Endometrial cancer risk	Diagnostic accuracy	10	(20)
Guven *et al*, 2004	European Journal of Gynaecological Oncology	Turkey	Monocentric retrospective study	97	Pipelle or dilation and curettage	2	Endometrial cancer risk	Diagnostic accuracy	5	(29)
Gouveia *et al*, 2007	Revista da Associação Médica Brasileira	Brazil	Monocentric retrospective study	47	In-office hysteroscopy, pipelle biopsy	2	Endometrial cancer risk	Diagnostic accuracy, cut off differences	5	(30)
Hefler *et al*, 2018	Archives of gynecology and obstetrics	Austria	Multicentric prospective study	900	In-office hysteroscopy, endometrial biopsy	4	Endometrial cancer risk	Diagnostic accuracy, endometrial thickness	10, 12, 15, 20	(31)
Jiang *et al*, 2019	BMC women's health	China	Monocentric prospective study	234	In-office hysteroscopy, endometrial biopsy	2	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	11	(32)
Jokubkiene *et al*, 2016	Ultrasound in obstetrics and gynecology	Sweden	Monocentric prospective study	96	In patient hysteroscopy	2	Endometrial cancer risk, intracavity lesion number	Diagnostic accuracy, saline contrast sonohysterography	14	(33)
Kasraeian *et al*, 2011	Climacteric	Iran	Monocentric prospective study	259	In-office hysteroscopy, endometrial biopsy	1	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	5	(34)

Table II.Continued.

Author, year	Journal of publication	Country	Study design	Patients studied	Endometrial biopsy technique	, Duration years	Primary outcomes	Secondary outcomes	Endometrial thickness thresholds, mm	(Refs.)
Li *et al*, 2019	Medicine (Baltimore)	United States of America	Monocentric retrospective study	2,898	In-office hysteroscopy, endometrial biopsy	10	Endometrial cancer risk	Diagnostic accuracy	11	(35)
Liang *et al*, 2025	Journal of minimally invasive gynecology	China	Monocentric retrospective study	415	In-office hysteroscopy, endometrial biopsy	10	Endometrial cancer risk	Diagnostic accuracy	10.5	(16)
Louie *et al*, 2016	International journal of Gynecology and obstetrics	United States of America	Monocentric retrospective study	435	In patient hysteroscopy	5	Endometrial cancer risk	Diagnostic accuracy, endometrial thickness	14	(36)
Laiyemo *et al*, 2016	Journal of obstetrics and gynecology	United Kingdom	Monocentric retrospective study	63	In-office hysteroscopy, endometrial biopsy	2	Endometrial cancer risk	Diagnostic accuracy	11	(37)
Ozelic *et al*, 2019	Obstetrics and gynecology science	Turkey	Monocentric ret6rospective study	266	In-patient hysteroscopy	1	Endometrial cancer risk	Diagnostic accuracy, endometrial thickness	6, 11, 16, 21	(38)
Paraskevaidis *et al*, 2002	Anticancer research	Greece	Monocentric prospective study	59	In-office hysteroscopy, endometrial biopsy	2	Endometrial cancer risk	Diagnostic accuracy	3, 4, 6, 8	(39)
Seckin *et al*, 2016	Journal of clinical ultrasound	Turkey	Monocentric prospective study	328	Pipelle or Dilation & Curettage	2	Endometrial cancer risk, best cut off	Diagnostic accuracy	11	(40)
Sayyah-melli *et al*, 2025	Journal of obstetrics and gynecology of India	Iran	Monocentric retrospective study	84	In-office hysteroscopy, endometrial biopsy	1	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	5	(19)

Table II. Continued.

Author, year	Journal of publication	Country	Study design	Patients studied	Endometrial biopsy technique	Duration, years	Primary outcomes	Secondary outcomes	Endometrial thickness thresholds, mm	(Refs.)
Quaranta *et al*, 2023	Cureus	United Kingdom	Monocentric retrospective study	136	In-office hysteroscopy, endometrial biopsy	1	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	4	(18)
Xue *et al*, 2022	World journal of clinical cases	China	Monocentric retrospective study	184	In-office hysteroscopy, endometrial biopsy	1	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	5	(22)
Yasa *et al*, 2016	Archives of gynecology and obstetrics	Turkey	Monocentric retrospective study	276	In-office hysteroscopy, endometrial biopsy	10	Endometrial cancer risk	Diagnostic accuracy, cut-off differences	8, 12	(21)

studies, TVUS served as the primary screening modality and diagnostic findings were validated using histopathological examination of biopsy or surgical specimens.

Endometrial sampling techniques varied substantially among studies. Hysteroscopy was the most frequently used approach, reported in 18 of 20 studies (90%). Other studies utilized dilation and curettage (D&C), Pipelle aspiration biopsy or aspiration biopsy techniques. This procedural diversity reflects real-world clinical practice and may enhance the external validity and generalizability of the findings.

The investigated ET thresholds ranged from 3.0 to 21.0 mm. A total of seven studies evaluated thresholds <6.0 mm, primarily aimed at maximizing sensitivity for early lesion detection. A total of three studies investigated intermediate thresholds (6.0-9.9 mm), whereas 10 studies assessed thresholds between 10.0 and 13.9 mm. Additionally, five studies evaluated thresholds ≥14.0 mm, which generally favored specificity at the expense of sensitivity.

The included studies represented geographically diverse populations from North America, Europe, Asia and South America. However, ethnicity-diagnostic outcomes were inconsistently reported, precluding reliable subgroup meta-analysis according to race or ethnicity.

Risk of bias. The methodological quality of the included studies was evaluated using the QUADAS-2 instrument. Overall, the majority of studies demonstrated low risk of bias or only some concerns, with minimal applicability concerns across the assessed domains, thereby supporting the robustness of the pooled diagnostic estimates (Figs. 2 and 3). However, two studies [Liang *et al* (16) (2025); Seckin *et al* (40) (2016)] were judged to have some concerns, primarily related to patient selection and interpretation of the index test, respectively. In addition, one study [Hefler *et al* (31) (2018)] was assessed as having a high risk of bias, particularly within the domains of patient selection, index test methodology, and applicability concerns, which may have influenced the reliability of its reported diagnostic accuracy estimates. Overall, the relatively low proportion of studies with high risk of bias supports the methodological credibility and internal consistency of the present diagnostic meta-analysis.

Publication bias. Potential publication bias was assessed using Deeks' funnel plot asymmetry test. No statistically significant asymmetry was observed across the predefined ET threshold subgroups: <5.9 mm (P=0.41), 6.0-9.9 mm (P=0.18), 10.0-13.9 mm (P=0.11) and ≥14.0 mm (P=0.23) (Fig. 4). These findings suggest that selective reporting and preferential publication of favorable diagnostic outcomes were unlikely to have substantially influenced the pooled estimates or the overall conclusions of the meta-analysis. The absence of significant publication bias further strengthens confidence in the reliability and reproducibility of the synthesized diagnostic performance results.

Synthesis of results. Analysis of ET cut-offs demonstrated that an ultrasonographic threshold of ≥3.0 mm in asymptomatic postmenopausal women was associated with a markedly increased likelihood of AEH or EC on histopathological

Figure 2. Traffic light plot depicting the risk of bias assessment across individual studies.

evaluation, with a pooled risk ratio (RR) of 3.84 (95% CI, 2.95-5.11; I^2=34%) compared with women with ET <3.0 mm. Elevated risk persisted across higher ET thresholds, with pooled RRs of 3.18 (95% CI, 2.95-3.43; I^2=0%) for 3.0-5.9 mm, RR was 3.87 (95% CI, 2.36-6.35; I^2=16%) for 6.0-9.9 mm, the RR was 4.04 (95% CI, 3.34-4.90; I^2=23%) for 10.0-13.9 mm and the RR was 4.27 (95% CI, 3.15-5.79; I^2=50%) for ≥14.0 mm. No statistically significant differences in pooled RR estimates were identified among the ET subgroups (P=0.658) (Fig. 5).

DTA meta-analysis demonstrated clinically important trade-offs between sensitivity and specificity across different ET thresholds. For the 3.0-5.9 mm subgroup, pooled sensitivity was highest, whereas specificity remained acceptable (sensitivity 0.79; 95% CI 0.36-0.86; specificity 0.71; 95% CI 0.59-0.81). Corresponding likelihood ratios included a PLR of 2.3 (95% CI, 1.8-3.5) and an NLR of 0.28 (95% CI, 0.05-0.91), yielding a DOR of 11 (95% CI, 2-39) and an AUC of 0.83 (95% CI, 0.71-0.89).

At ET thresholds of 6.0-9.9 mm, sensitivity declined (0.64; 95% CI 0.20-0.07), whereas specificity improved (0.85; 95% CI 0.68-0.99), resulting in a PLR of 3.2 (95% CI, 1.8-6.0), NLR of 0.62 (95% CI, 0.39-0.98), DOR of 5.4 (95% CI, 3-14) and an AUC of 0.75 (95% CI, 0.70-0.81). For the 10.0-13.9 mm

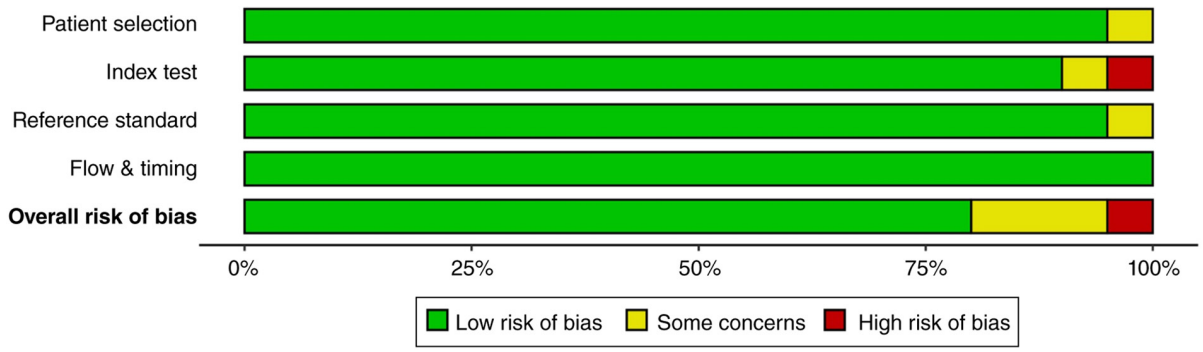

Figure 3. Summary plot of overall risk of bias assessment for included studies.

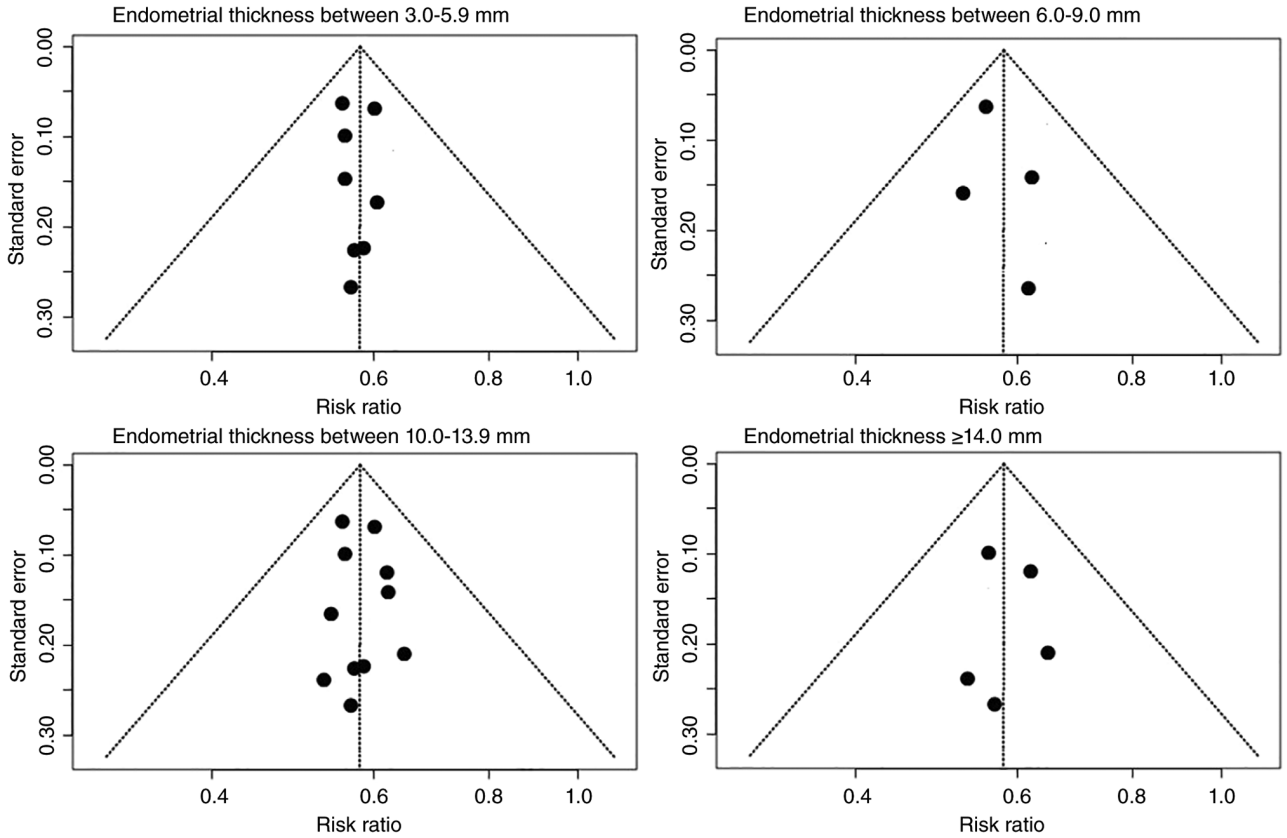

Figure 4. Deeks' funnel plot evaluating potential publication bias.

subgroup, pooled sensitivity was 0.77 (95% CI, 0.50-0.91) and specificity was 0.82 (95% CI, 0.65-0.96), with corresponding PLR and NLR values of 4.0 (95% CI, 1.4-8.9) and 0.36 (95% CI, 0.20-0.75), respectively. This subgroup yielded a DOR of 11 (95% CI, 3-54) and an AUC of 0.88 (95% CI, 0.71-0.92).

By contrast, ET thresholds ≥14.0 mm demonstrated substantially poorer diagnostic performance, with sensitivity declining markedly to 0.23 (95% CI, 0.10-0.31) despite a relatively high specificity of 0.89 (95% CI, 0.74-0.99). This threshold category corresponded to a PLR of 2.4 (95% CI, 1.0-4.2), an NLR of 0.88 (95% CI, 0.79-0.99), a comparatively low DOR of 1.9 (95% CI, 1.2-5.9) and the lowest AUC value (0.39, 95% CI, 0.31-0.58) (Fig. 6).

Overall, lower and intermediate ET thresholds demonstrated superior diagnostic performance compared with high thresholds. Although the 10.0-13.9 mm subgroup showed favorable AUC and DOR estimates, these thresholds demonstrated greater variability across studies and less consistent sensitivity estimates. By contrast, lower thresholds, particularly 3.0-5.9 mm, more consistently maintained high sensitivity while preserving acceptable specificity, thereby reducing the likelihood of missed AEH or EC cases.

As ET thresholds increased, sensitivity progressively declined, resulting in a greater risk of false-negative findings and underdiagnosis of premalignant or malignant lesions, whereas gains in specificity were comparatively modest. Confidence intervals for SROC curves overlapped across several threshold categories, suggesting no statistically significant superiority of one subgroup over another; however, the

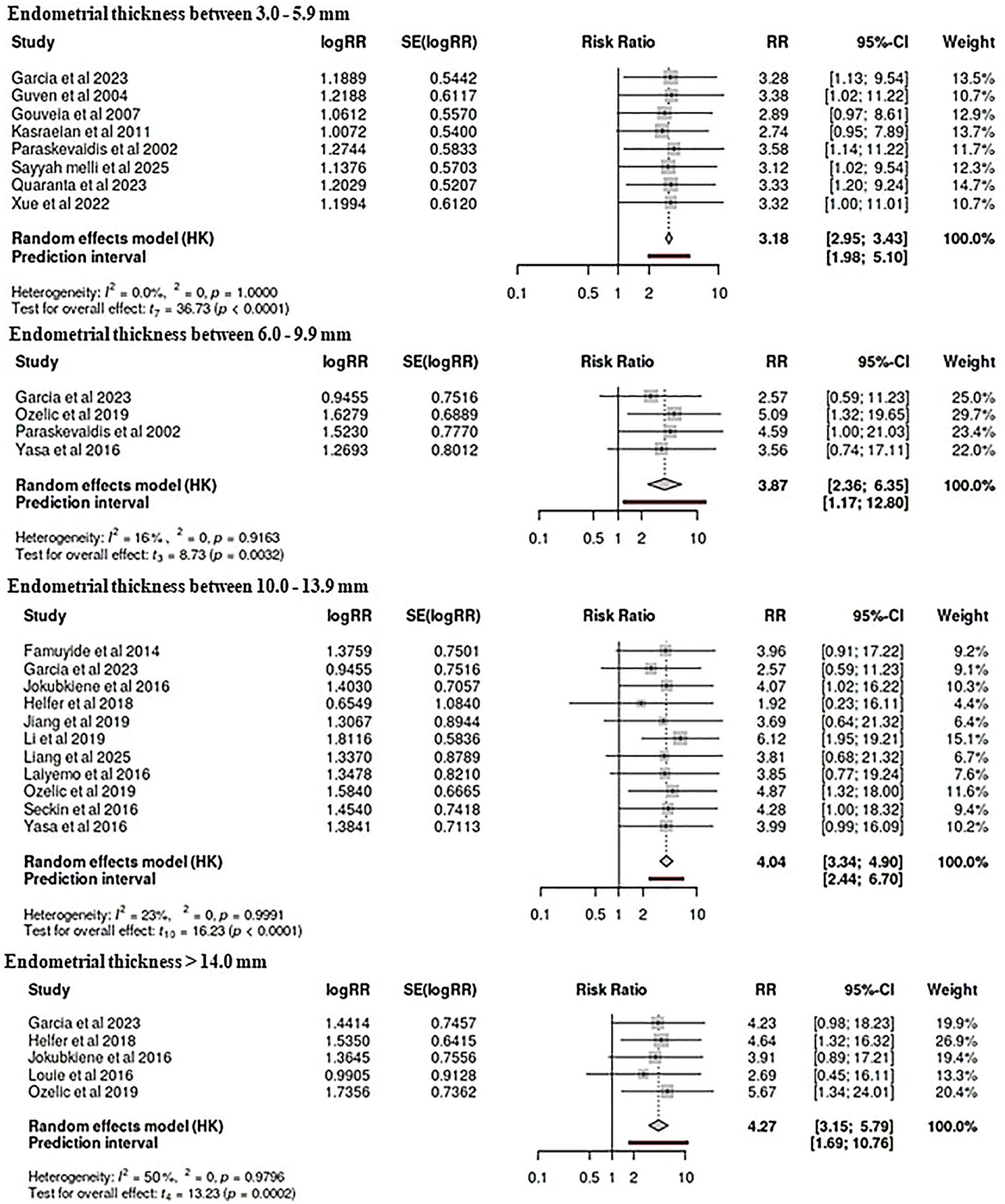

Figure 5. Forest plot of risk ratios for endometrial carcinoma or atypical endometrial hyperplasia. RR. Risk ratio; CI, confidence interval.

≥14 mm threshold consistently demonstrated inferior diagnostic accuracy and limited clinical utility (Fig. 7).

Taken together, these findings support the clinical relevance of lower ET thresholds for early detection strategies in asymptomatic postmenopausal women and provide additional justification for considering an ET cut-off of ~5 mm as a pragmatic balance between sensitivity and specificity.

Discussion

The present comprehensive systematic review and meta-analysis evaluated the diagnostic utility of ET measurements obtained by TVUS for detecting EC and AEH in asymptomatic postmenopausal women. By synthesizing evidence from 20 rigorously selected studies involving 9,193 women, the present

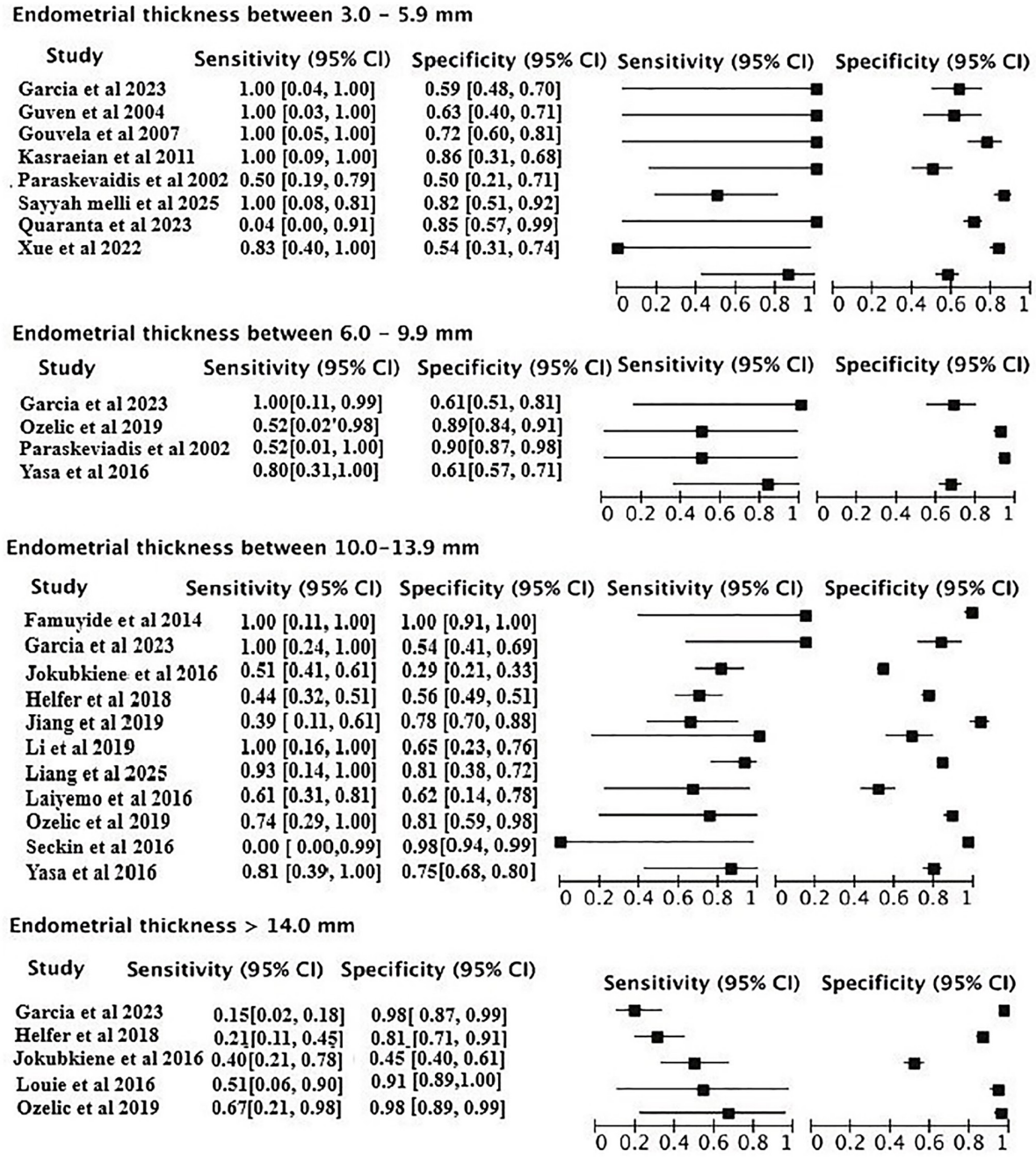

Figure 6. Forest plot of pooled sensitivity and specificity estimates across different endometrial thickness thresholds.

analysis provides a detailed assessment of how varying ET thresholds influence risk stratification and diagnostic accuracy in this population.

The present findings demonstrated that even minimal increases in ET were associated with a markedly elevated risk of AEH and EC. Specifically, an ET ≥3.0 mm conferred a 3.84-fold higher risk compared with women with ET <3.0 mm, underscoring that subtle ultrasonographic endometrial changes may carry clinically meaningful implications even in asymptomatic postmenopausal women. Notably, the increased risk persisted across all evaluated ET thresholds, with no statistically significant differences in pooled RRs among subgroups. These observations reinforce the role of ET as a robust marker of endometrial pathology and are consistent with previous studies by Yu *et al* (63), Zhang *et al* (64) and Su *et al* (65), which similarly highlighted the predictive significance of modest ET elevations in postmenopausal populations.

DTA analyses demonstrated clinically notable trade-offs between sensitivity and specificity across ET thresholds. Lower thresholds (3.0-5.9 mm) demonstrated the highest pooled sensitivity (0.79), although specificity was modestly lower (0.71), indicating that these thresholds may be preferable for early lesion detection while minimizing the probability of missed AEH or EC cases. Intermediate thresholds (6.0-9.9 and 10.0-13.9 mm) maintained relatively favorable diagnostic performance, with AUC values ranging from 0.75 to 0.88, supporting their potential clinical utility in selected settings where higher specificity is desirable. Conversely, thresholds ≥14 mm demonstrated markedly reduced sensitivity (0.23), despite modestly improved specificity (0.89),

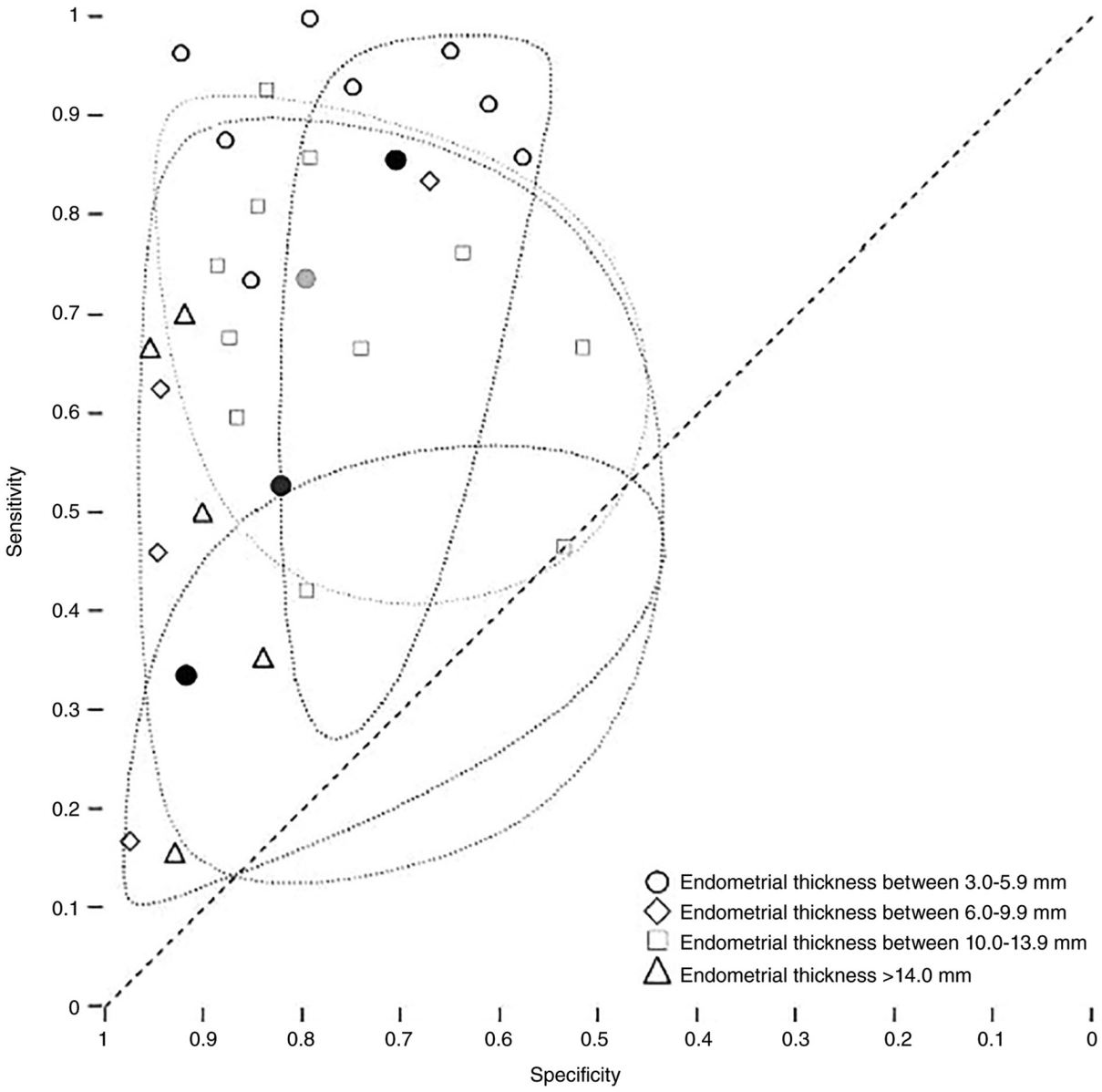

Figure 7. Summary receiver operating characteristic (SROC) curve for endometrial thickness thresholds.

indicating that reliance on markedly high ET cut-offs may lead to substantial underdiagnosis of premalignant and malignant lesions.

Although the 10.0-13.9 mm subgroup demonstrated favorable AUC and DOR estimates, selection of an optimal clinical threshold should not rely exclusively on summary diagnostic statistics. The thresholds within this subgroup showed greater variability across studies and less consistent sensitivity estimates compared with lower ET categories. From a clinical perspective, minimizing false-negative findings is particularly important in asymptomatic postmenopausal women because delayed diagnosis may permit progression of premalignant lesions or early-stage carcinoma. Therefore, lower ET thresholds provide an important advantage by improving early detection rates, even at the expense of a moderate increase in false-positive results and potentially unnecessary biopsies.

Taken together, the present findings suggest that an ET threshold of ~5 mm provides the most clinically pragmatic balance between sensitivity and specificity for guiding endometrial sampling in asymptomatic postmenopausal women. This threshold maintained relatively high sensitivity while preserving acceptable specificity and demonstrated greater consistency across studies compared with higher threshold categories. Moreover, the use of a 5 mm cut-off may support earlier diagnosis of EC and AEH, thereby contributing to prevention of disease progression and facilitating timely clinical intervention.

The findings of the present meta-analysis also have notable implications for clinical practice and prevention-oriented strategies. Incorporation of TVUS-based ET assessment into individualized risk stratification models may facilitate earlier identification of asymptomatic women at increased risk for EC or AEH, particularly among patients with obesity, diabetes mellitus, prolonged estrogen exposure or other established risk factors (4,7,12,29,30). Earlier histopathological evaluation in appropriately selected patients may improve opportunities

for early diagnosis and treatment, potentially reducing disease-related morbidity and improving long-term outcomes. At the same time, the present findings emphasize the importance of avoiding indiscriminate invasive sampling in women with markedly low-risk ET measurements, thereby reducing unnecessary procedures, healthcare costs and patient anxiety.

Collectively, these findings underscore the importance of balancing sensitivity, specificity and clinical applicability when establishing ET thresholds for endometrial evaluation in asymptomatic postmenopausal women.

The observed heterogeneity in endometrial sampling methods, primarily hysteroscopy, with a smaller proportion of studies utilizing D&C or Pipelle biopsy, reflects real-world variability in contemporary clinical practice. Notably, the predictive value of ET thresholds remained relatively consistent across these procedural approaches, thereby enhancing the external validity and generalizability of the pooled findings.

The present data further demonstrated that women with an ET ≥5 mm had a substantially increased risk of EC and AEH compared with those with ET <5 mm. Specifically, the incidence of EC and AEH was 1.54 and 1.23%, respectively, among women with ET ≥5 mm, compared with 0.32 and 0.47% among those with ET <5 mm. ROC analyses suggested that an ET threshold of ~5 mm provides a clinically appropriate balance between sensitivity and specificity for detecting AEH and EC. Lower thresholds (such as 3 mm) improve sensitivity but may substantially increase false-positive findings, thereby potentially exposing women to unnecessary invasive procedures and anxiety. By contrast, higher thresholds (such as ≥10 mm) improve specificity but reduce sensitivity, increasing the risk of missed diagnoses and delayed intervention.

Notably, although intermediate thresholds such as 10.0-13.9 mm demonstrated favorable summary diagnostic statistics, these thresholds were associated with greater interstudy variability and less consistent sensitivity estimates. Consequently, reliance solely on higher ET cut-offs may compromise early lesion detection in asymptomatic women. From a prevention and early diagnosis perspective, the clinical consequences of false-negative findings may outweigh the burden associated with additional biopsies generated by lower thresholds. Therefore, an ET cut-off of ~5 mm appears to represent the most pragmatic and clinically applicable threshold for guiding endometrial sampling in asymptomatic postmenopausal women.

Integrating ET measurements into routine clinical evaluation may improve risk stratification for endometrial malignancies in asymptomatic postmenopausal women. In particular, incorporation of TVUS-based ET assessment into individualized prevention and surveillance strategies may facilitate earlier diagnosis of premalignant lesions and early-stage EC before the onset of symptoms. Women with ET ≥5 mm should be considered for endometrial sampling to exclude malignancy; however, clinical judgment remains essential, and patient-specific factors such as age, obesity, diabetes mellitus, hormonal exposure, family history and overall comorbidity burden should be incorporated into individualized decision-making.

Previous studies have similarly explored the relationship between ET and endometrial pathology. Kaur and Qadri (66) reported that an ET threshold of 10.5 mm yielded a sensitivity of 100% and specificity of 78.3% for predicting EC and AEH in asymptomatic women; however, the improved specificity was achieved at the expense of reduced sensitivity in broader clinical settings, potentially increasing the likelihood of missed diagnoses. By contrast, the present meta-analysis supports the use of a lower ET threshold of ~5 mm, which demonstrated a more balanced trade-off between sensitivity and specificity while reducing the risk of both false-positive and false-negative outcomes. These findings further support the concept that ET, when interpreted within an appropriate clinical context, represents a robust and clinically valuable predictor of endometrial pathology.

The included studies represented populations from multiple geographic regions and ethnic backgrounds; however, ethnicity-specific diagnostic outcomes were inconsistently reported, preventing reliable subgroup meta-analysis according to ethnicity. Future multicenter studies involving diverse populations are therefore needed to determine whether optimal ET thresholds differ across ethnicity and to improve the generalizability of evidence-based recommendations.

Future research should aim to refine ET threshold recommendations through integration of additional clinical risk factors, including age, body mass index, hormonal exposure, metabolic disease and genetic predisposition. Prospective studies utilizing standardized TVUS protocols and uniform histopathological validation are needed to reduce methodological heterogeneity and improve precision of diagnostic performance estimates. Additionally, future investigations should evaluate the clinical utility, cost-effectiveness and prevention-related impact of ET-based screening and surveillance strategies in asymptomatic postmenopausal populations. Development of predictive models incorporating ET together with clinical, imaging, and laboratory parameters may further improve individualized risk stratification and patient outcomes.

The present systematic review and diagnostic meta-analysis is strengthened by the inclusion of a comparatively large number of diagnostic accuracy studies relative to earlier reviews on this topic. The inclusion of only studies with histopathological confirmation and extractable diagnostic accuracy data enhanced methodological rigor and improved the reliability of pooled estimates. Furthermore, exclusion of studies involving patients receiving hormone replacement therapy, tamoxifen, aromatase inhibitors or selective estrogen receptor modulators minimized important sources of confounding, given the recognized effects of these therapies on endometrial thickness measurements and endometrial morphology. Additional strengths include the use of predefined eligibility criteria, adherence to PRISMA-DTA and STARD reporting recommendations, application of the QUADAS-2 framework for risk-of-bias assessment, and stratified evaluation of multiple ET threshold categories to facilitate clinically meaningful comparisons across diagnostic cut-off ranges.

Nevertheless, several limitations should be acknowledged. The relatively low prevalence of EC and AEH among asymptomatic postmenopausal women contributed to wider confidence intervals around certain sensitivity estimates and may partly explain interstudy variability in diagnostic performance. Variability in ET thresholds, ultrasound protocols, operator expertise, histopathological sampling techniques,

and study populations may also have contributed to methodological heterogeneity across the included studies.

Although intermediate ET thresholds such as 10.0-13.9 mm demonstrated favorable summary diagnostic statistics, considerable variability across studies limited definitive identification of a universally optimal cut-off. Consequently, the recommendation of a ~5 mm threshold should be interpreted as a clinically pragmatic rather than absolute threshold, intended to balance early detection against the risk of unnecessary invasive procedures. Another notable limitation is that ethnicity-specific diagnostic outcomes were inconsistently reported across studies, precluding reliable subgroup analyses according to racial or ethnic background. Therefore, potential differences in optimal ET thresholds among diverse populations could not be adequately evaluated. In addition, most included studies originated from high-income countries, which may limit the global generalizability of the findings to lower-resource healthcare settings. Finally, type II ECs, which may develop in the absence of substantial endometrial thickening, remain difficult to detect using TVUS-based ET assessment alone and therefore represent an important diagnostic limitation of ET-guided screening strategies.

In conclusion, the present systematic review and diagnostic meta-analysis demonstrated that ET measured by TVUS is a clinically valuable marker for identifying the risk of EC and AEH in asymptomatic postmenopausal women. Although variations in ET thresholds influenced diagnostic performance, the present findings indicate that sensitivity progressively declines as higher thresholds are applied, whereas specificity correspondingly improves.

Lower ET cut-offs (particularly 3.0-5.9 mm) provided the greatest sensitivity for detecting AEH and EC, thereby reducing the likelihood of missed diagnoses. However, lower thresholds may also increase false-positive findings and contribute to unnecessary biopsies, patient anxiety and additional healthcare costs. Conversely, ET thresholds ≥14 mm demonstrated substantially reduced sensitivity and were associated with a considerable risk of underdiagnosis, missing a large proportion of premalignant and malignant lesions. Although intermediate thresholds (10.0-13.9 mm) demonstrated favorable summary diagnostic accuracy estimates, these thresholds showed greater variability across studies and less consistent sensitivity compared with lower threshold categories. Therefore, threshold selection should not rely exclusively on summary statistical performance but also consider clinical implications related to early detection and prevention of disease progression.

Taken together, the available evidence suggests that an ET threshold of ~5 mm provides the most clinically pragmatic balance between sensitivity and specificity for guiding endometrial sampling in asymptomatic postmenopausal women. This threshold may facilitate earlier diagnosis of EC and AEH while limiting excessive invasive procedures in low-risk patients. The findings of the present meta-analysis further support the integration of ET assessment into individualized clinical risk stratification and prevention-oriented strategies, particularly for women with obesity, diabetes mellitus, prolonged estrogen exposure or other established EC risk factors. Nevertheless, patient management should remain individualized and incorporate clinical history, comorbidities, ultrasonographic features, and overall risk profile.

Beyond diagnostic accuracy alone, careful consideration of cost-effectiveness, patient anxiety, healthcare resource utilization and ethical implications remains essential when developing evidence-based strategies for evaluating incidental endometrial thickening in asymptomatic postmenopausal women. Future prospective multicenter studies involving ethnically diverse populations and standardized imaging protocols are needed to further refine clinically applicable ET thresholds and improve global generalizability of these recommendations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YS and HW conceptualized and designed the study. TQ analyzed the data. NL and MW collected the data and assisted in the data analysis. NL and MW drafted and edited the manuscript. YS and TQ confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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