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Risk of endometrial cancer in asymptomatic postmenopausal women in relation to ultrasonographic endometrial thickness. Systematic review and diagnostic test accuracy meta-analysis.

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Condensation

An ultrasonographic endometrial thickness between 3.0 and 5.9 mm as the threshold for endometrial sampling seems the most accurate for endometrial malignancy detection in asymptomatic postmenopausal women

Short title

Endometrial thickness thresholds and risk for malignancy

AJOG at a Glance

Why was this study conducted? To evaluate the risk of endometrial carcinoma and atypical endometrial hyperplasia in postmenopausal women without vaginal bleeding relative to endometrial thickness thresholds used in previous trials to guide endometrial histopathologic assessment.

What are the key findings? Using ultrasonographic endometrial thickness, a threshold between 3.0 and 5.9 mm showed the highest sensitivity, while a threshold over 14.0 mm had highest specificity. Summary point analysis showed increased chances of failing to diagnose endometrial carcinoma or atypical hyperplasia using an endometrial thickness threshold of 10.0-13.9 mm.

What does this study add to what is already known? The use of a lower ultrasonographic endometrial threshold (3.0-5.9 mm) to recommend performing endometrial sampling maximizes balances for diagnostic accuracy and should be considered for further endometrial evaluation in asymptomatic postmenopausal women.

Abstract

Objective: To evaluate the risk of endometrial carcinoma (EC) and atypical endometrial hyperplasia (AEH) in asymptomatic postmenopausal women in relation to the endometrial thickness (ET) measured by transvaginal ultrasonography (TVS) stratified by threshold categories used for performing subsequent endometrial sampling and histologic evaluation.

Data sources: MEDLINE, Scopus, ClinicalTrials.gov, Scielo, EMBASE, the Cochrane Library at the CENTRAL Register of Controlled Trials, LILACS, conference proceedings and international controlled trials registries were searched without temporal or geographical or language restrictions.

Study eligibility criteria: Studies were selected if they had a cross-over design evaluating the risk for AEH and EC in postmenopausal asymptomatic women and calculated the diagnostic accuracy of TVS thresholds (at least 3.0 mm) confirmed by histopathological diagnosis.

Study appraisal and synthesis methods: We conducted a systematic review and diagnostic test accuracy meta-analysis according to PRISMA-DTA and SeDATE guidelines. ET thresholds were grouped as follows: from 3.0 mm to 5.9 mm; between 6.0 and 9.9 mm; between 10.0 and 13.9 mm; and equal or greater than 14.0 mm. Quality assessment was performed using QUADAS-2 tool. Publication bias was quantified by Deek funnel plot test. Co-primary outcomes were risk for AEH or EC according to ET and diagnostic accuracy of each threshold group.

Results: A total of 18 studies provided the data of 10,334 women who were all included in the final analysis. Overall, at an ET threshold of at least 3.0 mm, the risk for AEH or EC was increased three-fold relative to women below the cut-off (relative risk (RR) 3.77, 95% confidence interval (CI) 2.26 to 6.32, I2=74%). Similar degrees of risk were reported for thresholds between 3.0 and 5.9 mm (RR 5.08, 95% CI 2.26 to 11.41, I2=0%), 6.0 and 9.9 mm (RR 4.34, 95% CI 1.68 to 11.23, I2=0%), 10.0 and 13.9 mm (RR 4.11, 95% CI 1.55 to 10.87, I2=86%) and over 14.0 mm (RR 2.53, 95% CI 1.04 to 6.16, I^2=78%) with no significant difference among subgroups (p=0.885). Regarding diagnostic accuracy, the pooled sensitivity decreased from thresholds below 5.9 mm (0.81, 95% CI 0.49 to 0.85) to above 14.0 mm (0.28 95% CI 0.18 to 0.40) Meanwhile, specificity increased from 0.70 (95% CI

0.61 to 0.78) for ET between 3.0 mm and 5.9 mm to 0.86 (95% CI 0.71 to 0.94) when the ET is 14.0 mm or greater.

For 3.0-5.9 mm and 10.0-13.9 mm thresholds, the highest diagnostic odds ratio of 10 (95% CI 3 to 41) and 11 (95% CI 2 to 49), with an area under curve of 0.81 (95% CI 0.77 to 0.84) and 0.82 (95% CI 0.79 to 0.86) respectively were retrieved.

The summary point analysis revealed that, compared to the other subgroups, the 3.0-5.9 mm cut off point was placed higher in the summary receiver operator curve space, indicating increased EC or AEH diagnosis using these cut-offs.

Conclusions: Both low and high ET thresholds in postmenopausal asymptomatic women seem equally effective in detecting EC and AEH. However, although using a 3.0 to 5.9 mm cut off results in lower specificity, the offsetting improvement in sensitivity may justify using this cut off for further endometrial evaluation in patients with suspected endometrial malignancy.

PROSPERO registration: CRD42021241857

Keywords: Endometrial cancer; Atypical Endometrial Hyperplasia; Transvaginal ultrasonography; Endometrial thickness; Cut-off.

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1. Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy diagnosed in developed countries [1]. It should be suspected in women presenting with postmenopausal bleeding, or with a thickened endometrium visualized by transvaginal ultrasonography (TVS) [2].

In the presence of postmenopausal bleeding (PMB), several guidelines recommend using a sonographic cut-off value of 4.0 or 5.0 mm to recommend further investigation of the endometrium [3, 4]. When the endometrial thickness (ET) is below these thresholds, the risk of endometrial carcinoma is considered to be less than 1% [5]. More rarely, some patients diagnosed with uterine premalignant or malignant pathology are asymptomatic and do not present with PMB [6, 7]. In contrast to the guidelines on the management of women with postmenopausal bleeding, there is no clear consensus regarding when to screen for endometrial cancer in asymptomatic women with increased endometrial thickness. Accordingly, it is appropriate to explore thresholds for evaluating postmenopausal women with endometrial thickening to prompt endometrial tissue sampling in order to increase the diagnostic accuracy avoiding the risk of failure to diagnose EC when present [8-10].

Postmenopausal patients may be incidentally diagnosed with a thickened endometrium in the absence of PMB when performing a pelvic ultrasound for other gynecologic indications or abdominal/pelvic complaints [11]. If applying the same ultrasonographic thresholds for ET currently recommended for symptomatic patients with PMB for further endometrial investigation to asymptomatic patients, these cutoffs would likely result in lower specificity, with increased cost and inconvenience for millions of women worldwide [12, 13].

Early insights for this issue were proposed by Smith-Bindman et al. in 2004 [14]. Their decision-analysis based on a theoretical cohort concluded that for asymptomatic postmenopausal patients an endometrial biopsy should be carried out when the transvaginal ultrasonographic ET is of at least 11.0 mm. They demonstrated that ET values above this threshold have a malignancy risk of 6.7%, which is comparable to the prevalence of endometrial cancer for women with postmenopausal bleeding where ET is 5.0 mm (7.3%) or greater, a cutoff that remains a widely accepted threshold for recommending endometrial biopsy in symptomatic women [14]. Since Smith-Bindman's 2004 research, several diagnostic accuracy studies have been conducted to determine the ideal sonographic threshold warranting biopsy for the early diagnosis of EC in asymptomatic women.

2. Objective

The aim of this systematic review and diagnostic meta-analysis was to determine the risk for EC and AEH relative to the different ET thresholds by TVS reported in the literature. Recognizing tradeoffs between sensitivity and specificity, an additional goal was to determine what ET would be the ideal balance for performing endometrial tissue sampling in asymptomatic postmenopausal women with increased ultrasonographic ET to increase the diagnostic accuracy for EC and balance costs.

3. Methods

We conducted a systematic review and diagnostic test accuracy (DTA) meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) [15] and Synthesizing Evidence from Diagnostic Accuracy Tests (SeDATE) guidelines [16] on studies with a cross-over design that evaluated the risk for AEH and EC in postmenopausal asymptomatic women and estimated the diagnostic accuracy of ultrasonography by comparing TVS ET thresholds with histopathological diagnosis. The research protocol was designed a priori, defining methods for the literature screening, inclusion and exclusion criteria before article examination, data extraction, tabulation, and analysis. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021241857) on April 09, 2021.

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a. Data sources and search strategy

Electronic databases (MEDLINE, Scopus, Scielo, EMBASE, LILACS) were searched from inception of each database without temporal limits and covered articles as early as March 1997, and as recently as May 2021. Search terms used were the following text words and Medical Subject Headings (MeSH): “endometrial carcinoma” or “atypical hyperplasia”, and “asymptomatic” and “ultrasonography”.

We also searched CINAHL, PsycINFO and AMED to retrieve other relevant papers and reduce publication bias. To capture further data, Clinicaltrials.gov, Cochrane Central Register of Controlled Trials and WHO International Clinical Trials Registry Platform

(ICTRP) were also searched. Moreover, to search for abstracts of international and national conferences, the grey literature (NTIS, PsycEXTRA) was screened. In addition, the reference lists of all eligible papers and related reviews were examined to further screen for studies not included by electronic searches.

No language or geographic location restriction was applied. Commentaries, letters to the editor, editorials, and reviews were excluded from the search.

The electronic searches and the eligibility of the involved studies were independently evaluated by two authors (G.R. and S.G.V.). If disagreement arose, a third reviewer (P.D.F.) helped resolve questions of eligibility.

b. Study selection and data extraction

Studies were selected if they enrolled asymptomatic postmenopausal women who were evaluated for endometrial pathology by TVS and reported diagnostic accuracy data. As tests of diagnostic accuracy, included studies inherently had a crossover design where women served as their own controls.

Studies including premenopausal and/or perimenopausal women, studies including women taking tamoxifen, hormonal therapy (HT), aromatase inhibitors, or any other selective estrogen receptor modulator or therapies with known effects on the endometrium were excluded, as well as studies including women with active or a history of postmenopausal bleeding. In addition, studies not reporting diagnostic accuracy data, but only risk and/or prevalence of EC or AEH were also excluded.

The index test was TVS performed prior to endometrial sampling. The reference test used was the histopathological analysis of endometrial biopsy specimens acquired from the same patient. Endometrial sampling was performed by means of any available technique to provide adequate endometrial tissue sample.

The abstraction forms were created specifically for this DTA meta-analysis. Key characteristics recorded included: patient descriptors, study duration, setting, ultrasonographic ET evaluated, features of the cohort and ET, outcomes evaluated, mean follow-up length, results, and quality elements.

All the abstracts were screened, reviewed, and classified by two authors (G.R., S.G.V.) independently. The concordance for plausible relevance was accomplished by consensus; the same two authors performed a full-text assessment of the eligible studies and independently extracted significant data about the characteristics and the outcomes of interest described in the study. All the inconsistencies were discussed by the reviewers and consensus was reached by asking a third author (T.P.M.). If necessary, other unpublished data was obtained by establishing direct contact with the authors of the original papers whenever the methodology indicated that additional outcome data were reported.

c. Assessment of risk of bias

The methodology of the included studies was analyzed by 3 authors (L.D.C., S.H. and P.D.F.) through a qualitative instrument for data collection (Quality Assessment Tool for Diagnostic Accuracy Studies−2; QUADAS- 2; University of Bristol, Bristol, United Kingdom), as recommended by the Agency for Healthcare Research and Quality [17]. This tool consists of 4 domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing. All domains are assessed for risk of bias, and the first 3 domains are assessed for applicability concerns by indicating a low, high, or unclear risk

The assessment of risk of bias was independently judged by three authors (L.D.C, J.P.P., S.H.). The disagreement was resolved by discussion with a fourth reviewer (P.D.F.).

d. Primary and secondary Outcomes

The co-primary outcomes for this meta-analysis were the risk for EC and AEH according to each ET threshold for recommending subsequent endometrial sampling, outlined by included studies, and DTA of TVS for each threshold using the following statistics: diagnostic odds ratio (DOR), area under curve (AUC) of the summary receiver operator curve (SROC) and summary estimates of the sensitivity and specificity. The secondary outcomes were the positive likelihood ratio (PLR) and negative likelihood ratio (NLR).

e. Data extraction and Statistical analysis

Statistical parameters— including true positive (TP), true negative (TN), false positive (FP), and false negative (FN)— were directly extracted from the study, and, if not available, they were calculated and arranged in a 2 x 2 table; for these circumstances, we used the following formulas: sensitivity = TP/(TP + FN) and specificity = TN/(FP + TN).

When multiple ultrasonographic cut-offs were used in a single study, data were reported and analyzed for each included threshold.

Subsequently, to evaluate differences between lower and higher ET thresholds, we performed the analysis based on the ultrasonographic measurement of ET used as threshold in qualified papers.

For each ET at the prespecified threshold, to calculate the overall DTA, we used the bivariate model according to Reitsma [15]. We evaluated the DOR through the DerSimonian-Laird random-effects model and the AUC of the SROC. The SROC curve and its derived AUC have been recommended to represent the performance of a diagnostic test, based on data from a meta-analysis [18]. SROC curve represents the relationship between sensitivity and specificity across involved studies. The AUC ranges from 1 for a perfect diagnostic test that correctly identifies all cases and non-cases of a known pathology, to 0 for a test which is never able to correctly diagnose disease [18]. We then obtained paired forest plots, showing the variation in accuracy between studies for sensitivity and specificity. The PLRs and NLRs were calculated through summary estimates of the sensitivity and specificity.

The bivariate method of Reitsma uses logistic regression on the TP, TN, FP, and FN values reported in the studies. We constructed SROCs and plotted confidence regions for each [18]. The average operating point for each test was identified on each curve, and pooled sensitivities and specificities were computed. In cases of insufficient data for estimating all variables, we simplified the SROC model by assuming a symmetrical shape to the SROC curve. We assessed the significance of the difference in test performance by using a likelihood ratio test comparing models with and without covariate terms for accuracy at equivalent thresholds levels.

According to the available literature [14, 19, 20] and to apply the bivariate model, which requires a minimum of four datasets to run the analysis, threshold subgroups were divided as follows: ET between 3 and 5.9 mm; ET between 6.0 and 9.9 mm; ET between 10.0 and 13.9 mm; ET equal or greater than 14.0 mm.

Heterogeneity was assessed using the Higgins I^2 index in which 0% means no heterogeneity and 100% represents the highest degree of heterogeneity [21]. Publication bias was assessed using the Deek funnel plot asymmetry test for each outcome and each subgroup, and a p-value <.05 was considered to reflect significant publication bias. For all data analyses, Stata 14.1 (StataCorp LLC, College Station, TX) with a *MIDAS* package was used to calculate risk ratios (RR), DORs and AUCs and Review Manager 5.3 (The Nordic Cochrane Centre 2014, Copenhagen, Denmark) was used both to generate paired forest plots of sensitivity and specificity and to draw SROC curves.

4. Results

a. Study selection

We identified and evaluated 466 initial studies (Figure 1). Of these, 18 studies involving 10,334 patients, who underwent sequential TVS followed by histopathological analysis through endometrial biopsy, were considered for inclusion in this meta-analysis (Table 1). We excluded 283 articles as duplicates, 17 for not providing diagnostic accuracy data for at least one ET threshold, 9 studies for including women with PMB and 2 trials for not excluding women treated with hormone replacement therapy (HRT) or tamoxifen.

b. Study characteristics

Among the 18 included studies, 14 analyzed a single cut-off [12, 20, 22-33] while 4 [19, 34-36] evaluated multiple cut-offs (Table 1). All studies used a crossover comparison in which ultrasonographic endometrial thickness was compared with subsequent endometrial biopsy followed by histopathological examination. For endometrial sampling, 11 out of 18 studies (61%) used hysteroscopy, while the rest of the trials involved dilation & curettage (D&C), Pipelle, Vabra, Endocyte or Karman/aspiration biopsy techniques (Table 1).

The ET thresholds evaluated by the 18 studies ranged from 3.0 mm to 21.0 mm. Eight studies [26, 29-32, 34, 35] evaluated an ET threshold below 6.0 mm. Four studies [28, 33-36] investigated a threshold between 6.0 and 9.9 mm. Ten studies [12, 19, 20, 22-25, 34-36] considered an ET cut off between 10.0 and 13.9 mm, and three studies [19, 27, 36] performed a DTA analysis for thresholds at or above 14.0 mm.

c. Risk of bias

The methodological assessment of the included reports according to the Quality Assessment Tool for Diagnostic Accuracy Studies−2 is presented in Supplemental Figures 1 and 2. Overall, low scores relative to risk of bias and applicability concerns were achieved for the vast majority of the included papers. Only one study was considered at high risk for bias and applicability of findings issues by the authors.

The Deek funnel plot asymmetry test was performed to evaluate the publication bias among the eligible studies. We found no significant publication bias in this meta-analysis for the under 5.9 mm (p = 0.38), between 6.0 and 9.9 mm (p=0.27), between 10.0 and 13.9 mm (p=0.07) and equal to or greater than 14.0 mm (p=0.17) thresholds.

d. Synthesis of results

An ultrasonographic ET threshold for recommending endometrial sampling of at least 3.0 mm in asymptomatic postmenopausal women resulted in a three-fold increased risk of finding AEH or EC at subsequent endometrial biopsy (RR 3.77, 95% CI 2.26 to 6.32, I2=74%) compared to asymptomatic women with an ET below the 3.0 mm. This increased risk was also observed for ET thresholds between 3.0 mm and 5.9 mm (RR 5.08, 95% CI 2.26 to 11.41, I2=0%), between 6.0 mm and 9.9 mm (RR 4.34, 95% CI 1.68 to 11.23, I2=0%), between 10.0 mm and 13.9 mm (RR 4.11, 95% CI 1.55 to 10.87, I2=86%) and 14.0 mm or greater (RR 2.53, 95% CI 1.04 to 6.16, I^2=78%) (Figure 2). Overall, there were no significant risk differences among the cut-off subgroups (p=0.885).

When DTA meta-analysis was performed, the pooled sensitivity, specificity, PLR, and NLR of TVS at a threshold for ET to subsequent endometrial biopsy between 3.0 mm and 5.9 mm were 0.81 (95% CI 0.49 to 0.85), 0.70 (95% CI 0.61 to 0.78), 2.7 (95% CI 2.0 to 3.7), 0.26 (95% CI 0.08 to 0.86), with a DOR of 10 (95% CI 3 to 41) and an AUC of 0.81 (95% CI 0.77 to 0.84)

Conducting DTA meta-analysis for ET thresholds between 6.0 mm and 9.9 mm resulted in a sensitivity of 0.53 (95% CI 0.27 to 0.77), a specificity of 0.82 (95% CI 0.64 to 0.92), while PLR and NLR were 3.0 (95% CI 1.6 to 5.6) and 0.58 (95% CI 0.35 to 0.94) respectively. Pooled DOR was 5 (95% CI 2 to 13), with an AUC of 0.71 (95% CI 0.67 to 0.75).

When analyzing the accuracy of ET thresholds between 10.0 mm and 13.9 mm, pooled sensitivity was 0.74 (95% CI 0.54 to 0.87), while a specificity of 0.80 (95% CI 0.62 to 0.91), PLR of 3.6 (95% CI 1.6 to 8.4) and NLR of 0.33 (95% CI 0.16 to 0.70) were retrieved. Moreover, the DOR was 11 (95% CI 2 to 49), with an AUC of 0.82 (95% CI 0.79 to 0.86).

Lastly, an ET equal or greater than 14.0 mm obtained a sensitivity of 0.28 (95% CI 0.18 to 0.40), with a specificity of 0.86 (95% CI 0.71 to 0.94), a PLR of 2.0 (95% CI 1.1 to 3.7) and NLR of 0.84 (95% CI 0.75 to 0.94), resulting in a DOR of 2 (95% CI 1 to 5) with an AUC of 0.45 (95% CI 0.41 to 0.50).

At the lowest threshold (from 3.0 to 5.9 mm) pooled sensitivity reached the highest value, though pooled specificity was slightly lower (0.70) than for higher thresholds (0.82, 0.8, and 0.86 respectively), as also depicted by forest plots for sensitivity and specificity (figure 3). As the threshold increased, pooled sensitivity decreased (fewer endometrial biopsies were performed, failing to diagnose some patients with AEH or EC) and specificity slightly increased (figure 4). However, while the other SROC curves demonstrated similar pathways, the curve design for an ET threshold greater than 14 mm showed the lowest diagnostic accuracy. The summary sensitivity and specificity points with 95% CI confidence bands for each threshold subgroup is displayed in figure 5.

A clear overlap of the confidence bands for each one of the ET thresholds subgroups was present, showing no statistically significant differences between the investigated ET subgroups. However, the summary point for an ET equal or greater than 14.0 mm was positioned lower in the SROC space (Figure 5), suggesting that a worse diagnostic accuracy is expected when choosing higher cut-offs due to low sensitivity and the lowest AUC (0.45), relative to 3.0 to 5.9 mm, 6.0 to 9.9 mm, and 10.0 to 13.9 mm cut-offs (0.81, 0.71 and 0.82 respectively).

5. Comment

a. Principal findings

This systematic review and meta-analysis demonstrates that the risk for EC and AEH in postmenopausal asymptomatic women with an incidental ultrasonographic finding of ET of 3.0 mm or greater is three-fold higher when compared to postmenopausal asymptomatic women with an ultrasound ET under the 3.0 mm threshold to perform endometrial sampling

with histopathologic examination. This suggests it is higher yield to perform endometrial sampling with histopathologic examination in women with these findings. However, no significant risk differences were found compared to higher ultrasonographic thresholds for ET. Regarding the DTA analysis, choosing an ultrasonographic ET threshold between 3.0 mm and 5.9 mm when deciding to sample the endometrium to screen for EC demonstrated higher sensitivity, while DOR and AUC were similar between 3.0-5.9 mm and 10.0-13.9 mm. The highest specificity was obtained with a TVS ET threshold equal to or greater than 14.0 mm, but this was associated with much lower sensitivity. Summary point analysis demonstrated the < 6.0 mm cut off point to be higher in the SROC space, showing that despite a lower specificity, there were reduced chances of missing the EC or AEH diagnosis using these cut-offs values.

b. Comparison with existing literature

The prognosis of EC in asymptomatic postmenopausal women is similar to the cancer prognosis of women presenting with vaginal bleeding. However, screening of asymptomatic women for EC or AEH is currently not recommended, and when a thickened endometrium is incidentally found in asymptomatic patients, recommended ET thresholds to prompt endometrial tissue sampling are not well defined. Though a low ET threshold is less likely to miss EC, the associated high number to treat for EC or AEH detection can have meaningful implications for cost and patient experience [37]. In addition, the study based on a theoretical cohort by Smith-Bindman et al. [14] and the UKCTOCS study [37] reported that adopting an ET threshold value above 10.0 mm or 12.0 mm seemed to be a promising way to reduce the number of excessive second-level examinations, while, consequentially, improving the early detection of cases of endometrial malignancy.

However, data retrieved in our meta-analysis showed no differences in the risk for EC or AEH between low and high ET thresholds. Moreover, the use of higher ET thresholds to recommend further endometrial investigation in asymptomatic postmenopausal women, although increasing the specificity of TVS to diagnose EC, decreased the number of women undergoing endometrial tissue sampling, therefore lowering the overall sensitivity of the diagnostic test (Figure 3).

Office hysteroscopy reduces cost and complexity relative to scheduling at risk postmenopausal women to blind dilation and curettage performed in the operating room under general anesthesia [38, 39]. The enhanced accuracy inherent to directly visualized

biopsy of pathology is an important consideration, particularly when the majority of studies used hysteroscopic sampling as the reference test. In-office hysteroscopic endometrial biopsy facilitates identification of cornual pathology, which would be more likely to be missed when blind sampling disproportionately assesses the posterior midline of an anteflexed uterus. The enhanced sensitivity relative to blind office sampling and the lower cost relative to a D&C in the operating room should be considered when considering modern thresholds for endometrial sampling. Several studies have confirmed the cost-effectiveness of in-office hysteroscopic guided endometrial biopsy under direct visualization in the management of postmenopausal women with EC [40] as well as other intrauterine conditions [41, 42]. Despite the fact that a visual approach should be preferred to blind techniques, in poor resource settings, the use of an in-office Pipelle biopsy remains an inexpensive, and worldwide available technique to assess for uterine malignancy without surgery when a suspicious ET is ultrasonographically measured [43].

Considering the number of biopsies performed in included studies, lowering the cut-off to a minimum ET of 3 mm could result in 44.8% of women having endometrial biopsies. However, false positives for potential cancer create a meaningful emotional burden, and this rate could be meaningfully reduced if secondary screening were implemented for a cut-off of 4 or 5 mm, where only 12.7% or 9.5% of women require additional evaluation. Since this degree of reassessment is comparable to the 11.3% seen in the United States after cervical cancer screening [44], this seems an already acceptable rate for gynecologic malignancy, though risk factors and cost-effectiveness considerations may further refine decision making.

For this reason, to maximize the diagnostic accuracy, even if ET should be considered first line prior to performing endometrial tissue sampling to discover EC or AEH, a more accurate prediction model should include common risk factors (age, body mass index, HT use, personal and family history for gynecological and colorectal cancers) as well as other minor factors to improve sensitivity and avoid performing lower yield endometrial biopsies. However, evidence about a wider and more inclusive prediction model is lacking, since only few models have been developed for asymptomatic women [45].

c. Strengths and limitations

A strength of this study is the high number of studies included for DTA analysis. A previous meta-analysis by Breijer et al. [46] from 2012 noted the paucity of diagnostic accuracy trials for ultrasonographic diagnosis of asymptomatic endometrial malignancies. To date, several

new studies have been added to the literature, enhancing statistical power and confidence in the available scientific evidence, as well as justifying an updated meta-analysis. Moreover, to improve validity, we restricted the analysis to only studies evaluating the diagnostic accuracy of sonographic ET, avoiding the inclusion of trials without a reference test or without reporting the number of true negatives. Another strength worth highlighting is the exclusion of studies involving cohorts of women receiving hormone therapy or tamoxifen, considering the drug's impact on the endometrial thickness and, as a consequence, biasing the results of the meta-analysis.

Though there are meaningful strengths to this meta-analysis, several limitations should be acknowledged. First, though multiple studies were included in the data synthesis, since EC and AEH had low prevalence in the evaluated studies, the 95% CI's for the pooled sensitivity are wide, reflecting inconsistency among studies. Second, there were discrepancies among the number of ET cut-offs evaluated by the included trials, since 3 studies investigated the accuracy of multiple thresholds on the same cohort of women. Moreover, all the included studies had inherently a cross-over design and the associated inherent limitations should be applied to the results of this meta-analysis. Specifically, a carry-over from the results of the first diagnostic examination on the effect of the endometrial sampling could be applicable, therefore increasing the number of incorrect diagnoses. Another limitation is related to the analysis of sensitivity and specificity for each ET threshold subgroup, in which the evaluated CIs were wide in amplitude for both the parameters. This limitation should be linked to the low incidence of EC and AEH in all the included studies, to the different ethnicities involved in the studies, to the presence of interobserver variability (as in each study more than one operator oversaw the ultrasonographic examinations), and to the technical advances in both ultrasonographic imaging and endometrial sampling techniques across 24 years of scientific progress, which have been increasing the diagnostic accuracy for EC over time. Additionally, only one study was carried in out in a low-income environment, hindering broader generalizability. Lastly, it should be acknowledged that about 10% of endometrial malignancies are type 2, non-endometrioid, adenocarcinomas, which are related to endometrial atrophy and not to increased ET. In such cases, standard TVS cannot be useful as a predictive tool for asymptomatic women [46].

d. Conclusions and implications

This systematic review and DTA meta-analysis showed limited differences in diagnosing EC or AEH in asymptomatic postmenopausal patients with incidental finding of ET when using multiple threshold groups. Sensitivity decreases with increased thresholds while specificity increases when shifting from lower to higher cut-offs. Though use of a threshold between 3.0 mm and 5.9 mm had the highest sensitivity, this should be balanced with cost and patient convenience as screening protocols when deciding which asymptomatic postmenopausal women with increased endometrial thickness should have subsequent biopsy. Given that a 14.0 mm or greater threshold for screening for EC or AEH in asymptomatic women misses 72% of cases, a lower cut-off likely will achieve better balances for efficacy, economics, and patient preference. On the other hand, it also should be acknowledged that use of an excessively low threshold will come with meaningful financial and psychological costs. The emotional burden inherent to following up potential malignancy can take a substantive toll on patients. There are ethical implications to minimizing such burdens, particularly when these false positives are found in asymptomatic women undergoing EC and AEH screening.

Authors' Contributions

S.G.V. and G.R designed the study and reviewed the manuscript; P.D.F. and L.C. searched the literature, extracted data and revised the manuscript; S.H. and L.D.C. performed statistical analyses; T.P.M., L.A.P., P.T., S.H. and J.C. critically revised the manuscript; J.P.P., J.T. and A.D.S.S. interpreted data and drafted the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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633 **Figures and Tables legend**

634 **Figure 1**. Flow chart of studies identified for diagnostic accuracy meta-analysis

635 **Figure 2**. Relative risk for endometrial carcinoma or atypical hyperplasia in asymptomatic
636 postmenopausal women according to endometrial thickness

637 **Figure 3**. Pooled sensitivity and specificity plots for endometrial thickness thresholds

638 **Figure 4**. SROC curves for endometrial thickness thresholds

639 **Figure 5**. Summary points on SROC curves spaces for endometrial thickness thresholds.

640 **Supplemental Figure 1**. Summary of Risk of Bias and Applicability Concerns according to
641 QUADAS-2 score

642 **Supplemental Figure 2**. Detailed Risk of Bias and Applicability Concerns for each included
643 study according to QUADAS-2 score

644 **Table 1**. Main characteristics of studies included in diagnostic accuracy meta-analysis

645 **Table 2**. Inclusion and exclusion criteria

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MEDLINE (accessed through PubMed)

("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("diagnostic imaging"[MeSH Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasonography"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasonographies"[All Fields]) AND ((("thicken"[All Fields] OR "thickened"[All Fields] OR "thickening"[All Fields] OR "thickenings"[All Fields] OR "thickens"[All Fields]) AND ("endometrium"[MeSH Terms] OR "endometrium"[All Fields] OR "endometriums"[All Fields])) OR ("endometrial neoplasms"[MeSH Terms] OR ("endometrial"[All Fields] AND "neoplasms"[All Fields]) OR "endometrial neoplasms"[All Fields] OR ("endometrial"[All Fields] AND "cancer"[All Fields]) OR "endometrial cancer"[All Fields]) OR (("atypic"[All Fields] OR "atypical"[All Fields] OR "atypicalities"[All Fields] OR "atypicality"[All Fields] OR "atypically"[All Fields] OR "atypicals"[All Fields] OR "atypism"[All Fields] OR "atypisms"[All Fields]) AND ("hyperplasia"[MeSH Terms] OR "hyperplasia"[All Fields] OR "hyperplasias"[All Fields])))

EMBASE

asymptomatic AND ('ultrasonography'/exp OR ultrasonography) AND ('thickened endometrium' OR (thickened AND ('endometrium'/exp OR endometrium)) OR 'endometrial cancer'/exp OR 'endometrial cancer' OR (endometrial AND ('cancer'/exp OR cancer)) OR 'atypical hyperplasia'/exp OR 'atypical hyperplasia' OR (atypical AND ('hyperplasia'/exp OR hyperplasia)))

SCOPUS

TITLE-ABS-KEY (asymptomatic AND ultrasonography AND (thickened AND endometrium OR endometrial AND cancer OR atypical AND hyperplasia))

Cochrane at CENTRAL

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

CINAHL / PsycINFO / AMED / PsycExtra (accessed through EBSCO – IDEM for Italian Universities)

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia) AND Cerca anche nel testo completo degli articoli; Applica argomenti equivalenti

Scielo.br

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

LILACS

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

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Clinicaltrials.gov / ICTRP (accessed through CENTRAL)

asymptomatic AND ultrasonography AND (thickened endometrium OR endometrial cancer OR atypical hyperplasia)

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Study, year	Design	Duration	Location	Patients	Primary Outcome	Secondary outcomes	Endometrial thickness thresholds	Endometrial biopsy technique
Hefler, 2018 [18]	Multicentric Prospective	2015-2018	Austria	900	Endometrial cancer risk	Endometrial thickness	10.0 mm 12.0 mm 15.0 mm 20.0 mm	In-office hysteroscopic endometrial biopsy
Ozelci, 2019 [35]	Monocentric Retrospective	2012-2013	Turkey	266	Endometrial cancer risk	Endometrial thickness	6.0 mm 11.0 mm 16.0 mm 21.0 mm	In-patient hysteroscopy
Ghoubara, 2018 [19]	Monocentric Retrospective	2011-2015	UK	1995	Endometrial cancer risk	Diagnostic accuracy	10. mm	Pipelle or office hysteroscopy
Li, 2019 [21]	Monocentric Retrospective	2006-2016	USA	2898	Endometrial cancer risk	Diagnostic accuracy	11.0 mm	In-office hysteroscopic endometrial biopsy
Famuyide, 2014 [12]	Monocentric Retrospective	2007-2011	USA	154	Endometrial cancer rate	NA	10.0 mm	In-office hysteroscopic endometrial biopsy
Jiang, 2019 [22]	Monocentric Prospective	2013-2015	China	234	Diagnostic accuracy	Cut-off differences	11.0 mm	In-office hysteroscopic endometrial biopsy
Laiyemo, 2015 [23]	Monocentric Retrospective	2008-2010	UK	63	Diagnostic accuracy	Endometrial cancer risk	11.0 mm	In-office hysteroscopic endometrial biopsy
Seckin, 2016 [24]	Monocentric Prospective	2012-2014	Turkey	328	Best cut-off	Diagnostic accuracy for asymptomatic women	11.0 mm	Pipelle or D&C
Jokubkiene, 2016 [25]	Monocentric Prospective	2008-2010	Sweden	96	Intracavitary lesion number	SCSH attempt	5.0 mm	In-patient hysteroscopic surgery

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Louie, 2016 [26]	Monocentric Retrospective	2008-2013	USA	435	Malignant pathology threshold for endometrial thickness	Risk of cancer/AEH	14.0 mm	Hysteroscopy
Fleischer, 2001 [27]	Multicentric Prospective	1998-2000	EU-USA	1792	Idoxifene safety	Endometrial cancer risk	6.0 mm	Aspiration biopsy
Kasraeian, 2011 [28]	Monocentric Prospective	2009-2010	Iran	259	Cut off value	Diagnostic accuracy	5.0 mm	In-office hysteroscopic endometrial biopsy
Yasa, 2016 [34]	Monocentric Retrospective	2003-2012	Turkey	276	Cut off value	Endometrial cancer prevalence	8.0 mm 12.0 mm	In-office hysteroscopic endometrial biopsy
Cohen, 1999 [29]	Monocentric Prospective	1996-1998	USA	60	EC and AEH prevalence	Diagnostic accuracy	5.0 mm	Unspecificed or endocyte
Gouveia, 2007 [30]	Monocentric retrospective	NR	Brazil	47	EC and AEH prevalence	Diagnostic accuracy	5.0 mm	Pipelle biopsy
Guven, 2004 [31]	Monocentric retrospective	NR	Turkey	97	EC-BMI correlation	Diagnostic accuracy	5.0 mm	D&C
Paraskevaidis, 2002 [32]	Monocentric prospective	2000	Greece	59	Diagnostic accuracy	Mean endometrial thickness	9.0 mm	Karman biopsy
Tsuda, 1997 [33]	Monocentric retrospective	NR	Japan	375	Diagnostic accuracy	EC and AEH prevalence	3.0 mm 4.0 mm 6.0 mm 8.0 mm	Endocyte

NR, not reported.

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Study, year	Inclusion criteria	Exclusion criteria
Hefler, 2018 [18]	Asymptomatic postmenopausal women with an endometrium larger than 3 mm	Use of tamoxifen, known HNPCC
Ozelci, 2019 [35]	Postmenopause and symptoms anbsence. Endometrial thickness equal to or greater than 6 mm (double layer) without any symptoms	Premenopausal and perimenopausal women, patients on HRT, and patients with a history uterine malignancy; tamoxifen use.
Ghoubara, 2018 [19]	Postmenopausal women with incidental finding of ET >4 mm in the absence of bleeding.	NA
Li, 2019 [21]	Endometrial thickness ≥5 mm in asymptomatic postmenopausal women	NA
Famuyide, 2014 [12]	Postmenopausal women with>4mm endometrial thickness on ultrasound and without uterine bleeding	NA
Jiang, 2019 [22]	Postmenopausal endometrium ≥5 mm or uterine cavity lesion without history of postmenopausal bleeding	AUB
Laiyemo, 2015 [23]	Postmenopausal women with thickened endometrium and without postmenopausal nleeding	NA
Seckin, 2016 [24]	Asymptomatic thickened endometrium (>5 mm).	Abnormal vaginal bleeding, HRT or tamoxifen use
Jokubkiene, 2016 [25]	Postmenopause and no systemic or local HRT with absence of symptoms	Current hormonal treatment for breast cancer; history of irregular menstruation or abnormal vaginal bleeding either before or after menopause; gynecological surgery on the uterus, ovaries or Fallopian tubes (including sterilization) other than cone biopsy, loop electrosurgical excision procedure, dilatation and curettage, Cesarean section or surgical termination of pregnancy; hormonal therapy obscuring time of menopause.
Louie, 2016 [26]	Menopausal, no history of postmenopausal bleeding, and had an endometrial thickness of at least 4 mm.	History of endometrial hyperplasia or carcinoma, tamoxifen use, oral or transdermal hormone replacement therapy, endometrial ablation, hereditary cancer syndrome.
Fleischer, 2001 [27]	Postmenopausal women who had not undergone hysterectomy	History of endometrial abnormality, undiagnosed vaginal bleeding, oral or vaginal HRT within 6 months of use, use of therapies that interact with the estrogen, history of breast cancer.
Kasraeian, 2011 [28]	Non-bleeding women who were referred to the outpatient clinics for routine follow-ups or other gynecologic problems, including pruritus and dysuria.	AUB, history of endometrial pathologies, including cancer or hyperplasia, and co-existing malignancies, hormone replacement therapy, tamoxifen and raloxifene.

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Yasa, 2016 [34]	Asymptomatic postmenopausal patients	(1) AUB; (2) history of endometrial pathologies such as hyperplasia or cancer; (3) history or current use of hormone replacement therapy; (4) use of raloxifene and/or tamoxifen.
Cohen, 1999 [29]	Asymptomatic postmenopausal women (	Presence of active uterine bleeding
Gouveia, 2007 [30]	Asymptomatic postmenopausal patients	Women with history of AUB or using HRT
Guven, 2004 [31]	Asymptomatic postmenopausal patients	BMI over 30
Paraskevaidis, 2002 [32]	Unselected asymptomatic postmenopausal women	NR
Tsuda, 1997 [33]	Amenorrhea for at least 1 year,	HRT usage

ET: endometrial thickness; NR: not reported; HRT: hormone replacement therapy; AUB: abnormal uterine bleeding

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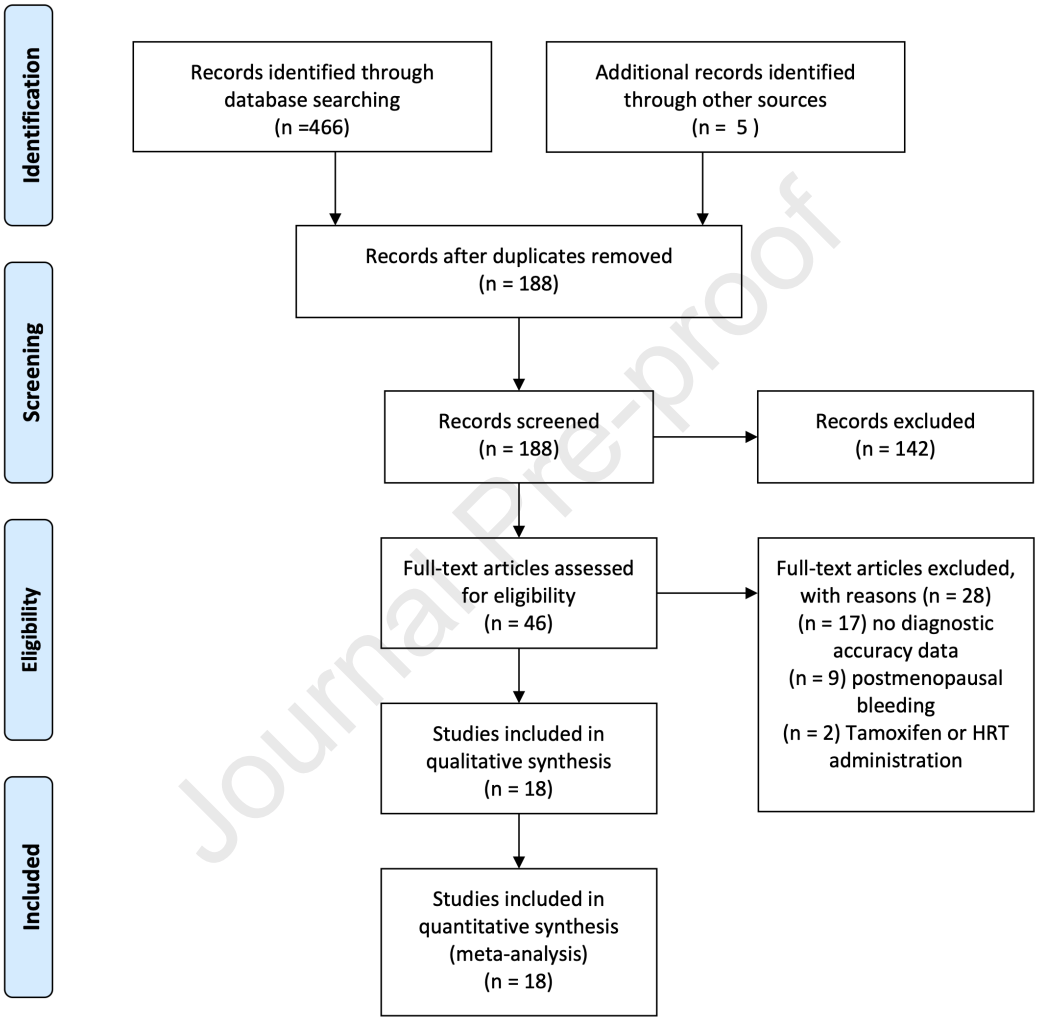
PRISMA 2009 Flow Diagram



Journal Pre-proof

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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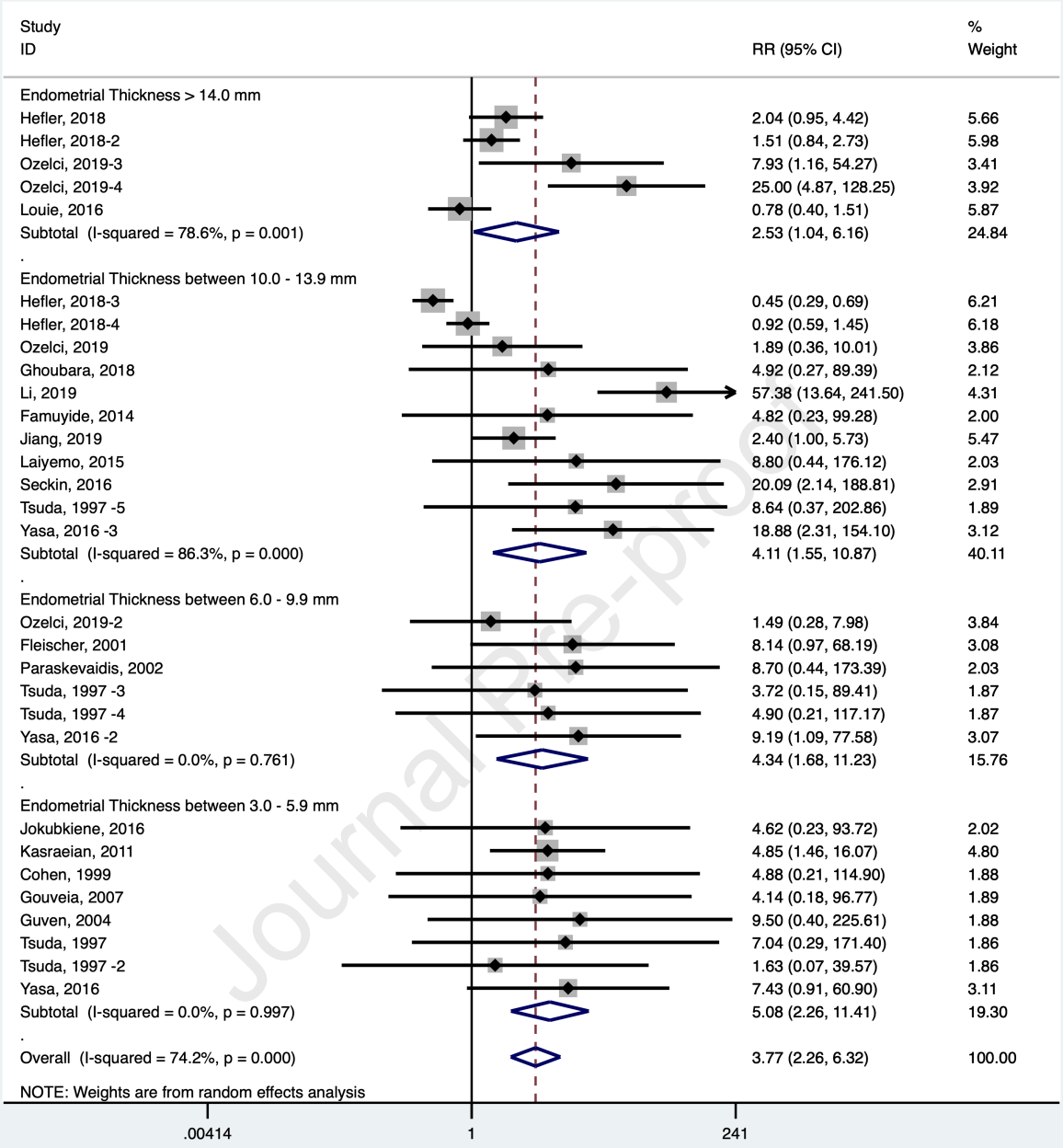

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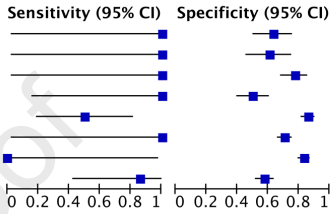
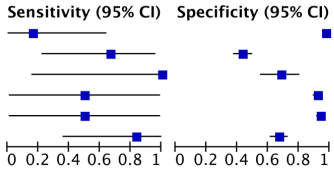
Endometrial thickness between 3.0 – 5.9 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Cohen, 1999	1	22	0	38	5.0	1.00 [0.03, 1.00]	0.63 [0.50, 0.75]
Gouveia, 2007	1	18	0	28	5.0	1.00 [0.03, 1.00]	0.61 [0.45, 0.75]
Guven, 2004	1	22	0	75	5.0	1.00 [0.03, 1.00]	0.77 [0.68, 0.85]
Jokubkiene, 2016	2	47	0	47	5.0	1.00 [0.16, 1.00]	0.50 [0.40, 0.60]
Kasraeian, 2011	5	36	5	218	5.0	0.50 [0.19, 0.81]	0.86 [0.81, 0.90]
Tsuda, 1997	1	110	0	264	3.0	1.00 [0.03, 1.00]	0.71 [0.66, 0.75]
Tsuda, 1997 -2	0	63	1	311	4.0	0.00 [0.00, 0.97]	0.83 [0.79, 0.87]
Yasa, 2016	6	114	1	155	4.0	0.86 [0.42, 1.00]	0.58 [0.51, 0.64]



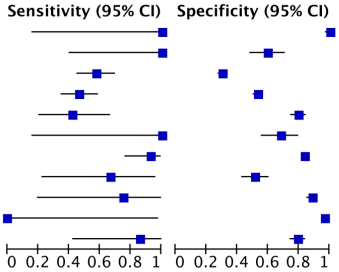
Endometrial thickness between 6.0 – 9.9 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Fleischer, 2001	1	41	5	1475	6.0	0.17 [0.00, 0.64]	0.97 [0.96, 0.98]
Ozelci, 2019	4	148	2	114	6.0	0.67 [0.22, 0.96]	0.44 [0.37, 0.50]
Paraskevaidis, 2002	2	18	0	39	9.0	1.00 [0.16, 1.00]	0.68 [0.55, 0.80]
Tsuda, 1997 – 4	1	30	1	344	6.0	0.50 [0.01, 0.99]	0.92 [0.89, 0.95]
Tsuda, 1997 -3	1	23	1	351	8.0	0.50 [0.01, 0.99]	0.94 [0.91, 0.96]
Yasa, 2016 -2	5	89	1	181	8.0	0.83 [0.36, 1.00]	0.67 [0.61, 0.73]



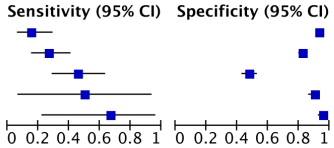
Endometrial thickness between 10.0–13.9 mm

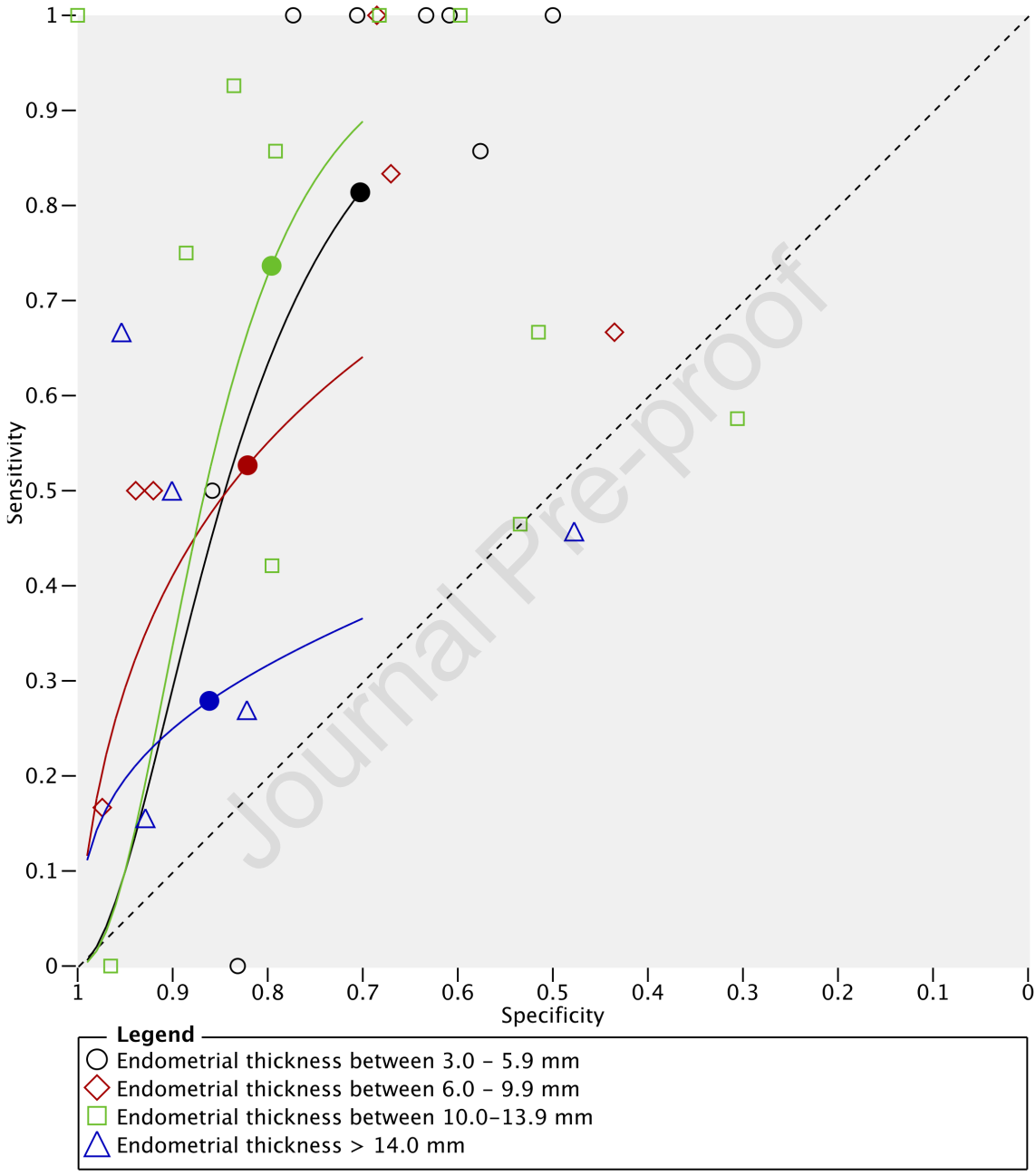
Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Famuyide, 2014	2	0	0	107	10.0	1.00 [0.16, 1.00]	1.00 [0.97, 1.00]
Ghoubara, 2018	4	31	0	46	10.0	1.00 [0.40, 1.00]	0.60 [0.48, 0.71]
Hefler, 2018 -2	38	572	28	252	10.0	0.58 [0.45, 0.70]	0.31 [0.27, 0.34]
Hefler, 2018 -3	33	386	38	443	12.0	0.46 [0.35, 0.59]	0.53 [0.50, 0.57]
Jiang, 2019	8	54	11	210	11.0	0.42 [0.20, 0.67]	0.80 [0.74, 0.84]
Laiyemo, 2015	2	20	0	43	11.0	1.00 [0.16, 1.00]	0.68 [0.55, 0.79]
Li, 2019	25	463	2	2353	11.0	0.93 [0.76, 0.99]	0.84 [0.82, 0.85]
Ozelci, 2019 -2	4	64	2	68	11.0	0.67 [0.22, 0.96]	0.52 [0.43, 0.60]
Seckin, 2016	3	37	1	287	11.0	0.75 [0.19, 0.99]	0.89 [0.85, 0.92]
Tsuda, 1997 -5	0	13	1	361	10.0	0.00 [0.00, 0.97]	0.97 [0.94, 0.98]
Yasa, 2016 -3	6	56	1	213	4.0	0.86 [0.42, 1.00]	0.79 [0.74, 0.84]



Endometrial thickness > 14.0 mm

Study	TP	FP	FN	TN	Threshold (mm)	Sensitivity (95% CI)	Specificity (95% CI)
Hefler, 2018	7	61	38	794	20.0	0.16 [0.06, 0.29]	0.93 [0.91, 0.94]
Hefler, 2018 -4	14	151	38	697	15.0	0.27 [0.16, 0.41]	0.82 [0.79, 0.85]
Louie, 2016	16	210	19	192	14.0	0.46 [0.29, 0.63]	0.48 [0.43, 0.53]
Ozelci, 2019 -3	2	26	2	236	16.0	0.50 [0.07, 0.93]	0.90 [0.86, 0.93]
Ozelci, 2019 -4	4	12	2	248	21.0	0.67 [0.22, 0.96]	0.95 [0.92, 0.98]





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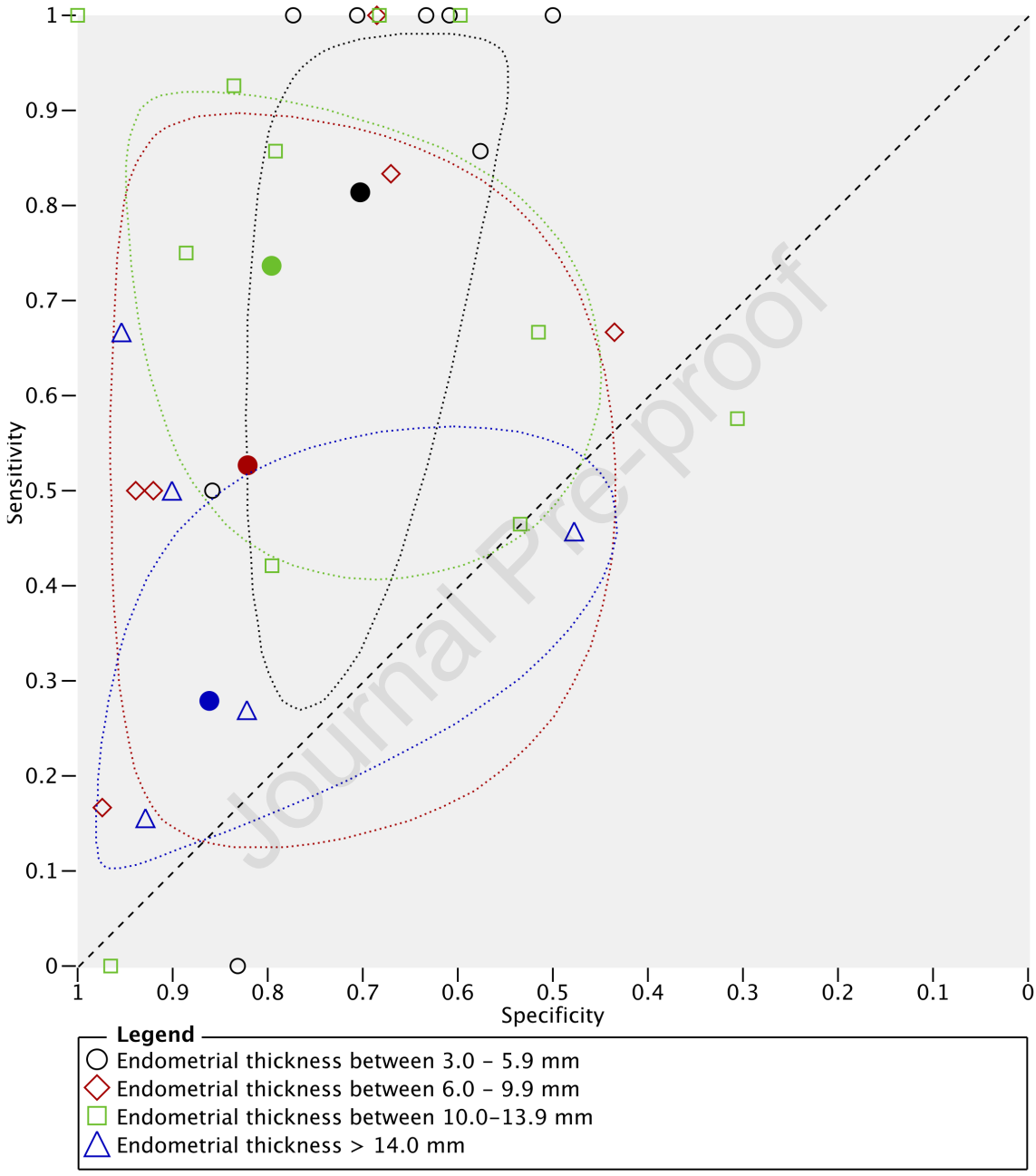

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