BMC Endocrine Disorders

SYSTEMATIC REVIEW Open Access

Prevalence of subclinical hypothyroidism in polycystic ovary syndrome and its impact on insulin resistance: a systematic review and meta-analysis

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Abstract

Background Although recent studies indicate a high prevalence of subclinical hypothyroidism (SCH) in women with polycystic ovary syndrome (PCOS), the reported prevalence rates vary widely. Therefore, we conducted this study to estimate the pooled prevalence of SCH among women with PCOS. Additionally, emerging evidence suggests that SCH may negatively impact insulin resistance in PCOS. Thus, we examined its effect on insulin resistance indices as our secondary objective.

Methods We searched PubMed, Web of Science, Scopus, and Embase from their inception to February 25, 2024. Observational studies reporting the prevalence of SCH among women with PCOS were included. Joanna Briggs Institute's (JBI) critical appraisal checklist for prevalence studies was adopted for the risk of bias assessment. The random-effects model was employed to estimate the pooled prevalence with its 95% confidence intervals (CI). The weighted mean difference (WMD) was used to compare the insulin resistance indices between PCOS patients with and without SCH.

Results Twenty-nine studies comprising 5765 women with PCOS were included. The meta-analysis demonstrated that 19.7% (95% CI: 16.1%; 23.5%) of women with PCOS have SCH. PCOS patients with SCH had significantly higher HOMA-IR (WMD = 0.78, 95% CI: 0.34; 1.22) and fasting insulin (WMD = 2.38, 95% CI: 0.34; 4.42) levels than those without SCH. Differences in fasting plasma glucose and 2-hour postprandial glucose did not reach statistical significance.

Conclusion This systematic review and meta-analysis found that approximately 20% of women with PCOS have SCH. This underscores the need for regular thyroid function testing in these patients. The prevalence of SCH is influenced by the TSH cut-off used for diagnosis, highlighting the need for establishing a standardized TSH cut-off value. Furthermore, SCH significantly elevates the HOMA-IR index and fasting insulin levels, highlighting its potential impact on insulin resistance. Whether these metabolic changes are clinically important and put these individuals at higher risk of developing type 2 diabetes mellitus and cardiovascular disease requires further investigation.

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Systematic review registration number in PROSPERO CRD42024510798.
Clinical trial number Not applicable.
Keywords Subclinical hypothyroidism, Polycystic ovary syndrome, PCOS, Prevalence, Insulin resistance, Meta-analysis

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder among women of reproductive age, affecting 5 to 15% of this population [1, 2]. According to the Rotterdam criteria, a PCOS diagnosis requires at least two of the following: oligo-anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound [3]. The 2023 international evidence-based guideline for the assessment and management of PCOS now recommends that anti-Mullerian hormone (AMH) can be used as an alternative to ultrasound for diagnosis [4]. In addition to its well-known reproductive manifestations, PCOS is closely associated with metabolic disturbances, including obesity, dyslipidemia, and insulin resistance [5]. Up to 70% of women with PCOS have insulin resistance, substantially increasing their risk of type 2 diabetes mellitus (T2DM) later in life. The body's decreased insulin sensitivity triggers compensatory hyperinsulinemia. This hyperinsulinemia leads to androgen overproduction. It also increases the amount of free androgen by lowering sex hormone-binding globulin (SHBG) levels, thereby exacerbating hyperandrogenism and PCOS symptoms [6, 7].

Subclinical hypothyroidism (SCH), a milder form of hypothyroidism, is another common endocrine disorder. It is thought to affect 4 to 10% of the adult population. As with most thyroid diseases, women are more likely to be affected [8, 9]. SCH is defined as elevated serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) within the reference range [10]. Though often asymptomatic, as the term "subclinical" suggests, research over the past decade has highlighted its potential adverse effects. Many studies have shown its negative impact on lipid profile, insulin sensitivity, and reproductive health [11–13]. An animal study showed that hypothyroidism leads to hyperandrogenemia and the formation of ovarian cysts, which are the main characteristics of PCOS [14]. Additionally, thyroid hormones stimulate the production of SHBG in the liver. The reduced SHBG levels in the hypothyroid state may exacerbate the vicious cycle between low SHBG, hyperandrogenemia, and hyperinsulinemia observed in PCOS [15]. Furthermore, SCH can impair insulin sensitivity by reducing intracellular glucose utilization and inhibiting GLUT4 translocation to the cell membrane [16]. Notably, it has been suggested that lower thyroid function, even in the euthyroid range, predisposes individuals to higher glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) levels [17]. Therefore, the coexistence of SCH with PCOS might have a compounding negative effect on insulin resistance and put these individuals at higher risk of T2DM and cardiovascular diseases later in life.

Three meta-analyses have explored the impact of SCH on lipid profiles and insulin resistance in women with PCOS. The most recent one, published in 2021, observed significantly higher LDL, triglyceride, and total cholesterol levels in those with both conditions, alongside a significant decrease in HDL [18]. Other reviews reported relatively similar findings except for LDL levels, which did not show a significant difference [19, 20]. However, the results concerning insulin resistance were inconclusive and somewhat contradictory. Two meta-analyses noted a significant increase in the HOMA-IR index of women with both conditions. Conversely, another meta-analysis found no difference in HOMA-IR levels between PCOS subjects with and without SCH [18–20].

Researchers have reported a very wide range for the prevalence of SCH among women with PCOS. Some studies reported its prevalence to be less than 10%, while others found it to be as high as 40% [21–24]. A recently published narrative review highlighted that SCH is at least two times more common in women with PCOS compared to unselected women [25]. Given the wide range of prevalence reported in original studies and the lack of a systematic review and meta-analysis on this topic, the primary objective of this study was to estimate the pooled prevalence of SCH in women with PCOS. Additionally, given the inconclusive and controversial findings of the previous meta-analyses, we aimed to elucidate its impact on insulin resistance as our secondary objective. Although this systematic review is based on observational studies, our findings could provide a basis for future clinical trials and the development of clinical guidelines to determine whether thyroid replacement therapy in women with both SCH and PCOS could lead to improved metabolic outcomes.

Methods

Protocol registration

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [26]. This study was conducted following a predetermined protocol, which was registered in the International

Prospective Register of Systematic Reviews (PROSPERO) on March 2, 2024, with the registration number CRD42024510798.

Search strategy

A comprehensive literature search was conducted across PubMed, Embase, Scopus, and Web of Science databases with a restriction to English-language publications. No publication date restriction was set (from inception until February 25, 2024). We used MeSH terms, Embase, the free-text method, and expert opinion to identify all the relevant search terms for hypothyroidism, SCH, and PCOS. Supplementary Material Table S1 outlines detailed search strategies for each database. We also hand-searched the reference lists of the included studies and relevant review articles to identify additional eligible studies.

Inclusion and exclusion criteria

Observational studies reporting SCH prevalence among individuals with PCOS were eligible to be included. Only peer-reviewed English-language studies were eligible. The exclusion criteria are as follows: (1) Conference papers, case reports, case series, animal studies, review articles, and clinical trials; (2) Studies lacking prevalence data; (3) Studies with a small sample size (fewer than 30 women with PCOS); (4) Studies that included (i) pregnant, postpartum, or lactating mothers (ii) patients with a prior history of thyroid surgery or radiotherapy to the head and neck (iii) patients who were under treatment with levothyroxine or drugs that alter thyroid function (iv) patients with central hypothyroidism (v) patients with renal or liver failure (vi) cancer cases.

Study selection

All records retrieved from the databases were imported into Endnote software. After removing the duplicate records, two reviewers (SS and MS) independently screened the studies based on their titles and abstracts. The same two reviewers then examined the remaining relevant studies in full text against the inclusion and exclusion criteria. Disagreements in the selection process were resolved through discussion. In cases of persistent disagreements, a third expert's opinion (MF) was sought.

Data extraction

Two reviewers (MP and SS) independently extracted the following data into a predefined Excel sheet: first author, publication year, country, study design, total number of PCOS cases, mean and standard deviation (SD) of age and BMI, PCOS diagnostic criteria, number of PCOS cases diagnosed with SCH, and the normal upper limit of TSH. Additionally, the number, mean, and SD for the following variables were extracted for PCOS cases with and without SCH: HOMA-IR, fasting insulin, fasting plasma glucose (FPG), and 2-hour postprandial glucose. Any discrepancies between the reviewers were resolved through discussion. If disagreements persisted, a third expert's (MH) opinion was sought to resolve the conflict.

Risk of bias assessment

We conducted the quality assessment of the included studies using the Joanna Briggs Institute's (JBI) critical appraisal checklist for prevalence studies [27]. The JBI checklist consists of nine questions evaluating various aspects of methodological quality. Since the checklist does not provide a cut-off score, we categorized studies based on the following criteria: 1 to 4 indicated a high risk of bias, 5 to 6 moderate risk of bias, and 7 to 9 low risk of bias. Two authors (AS and SM-T) independently assessed the quality of the studies. Disagreements between reviewers were resolved by discussion. In cases of unresolved disagreements, a third expert's (MH) opinion was asked.

Statistical analysis

The meta-analysis was performed using R version 4.4.0. We used the metaprop function from the meta package to calculate the pooled prevalence and its 95% confidence interval (CI) [28]. The inconsistency index (I^2) was used to assess the degree of statistical heterogeneity. $I^2 < 25\%$, $25\% \leq I^2 \leq 50\%$, and $I^2 > 50\%$ were defined as low, moderate, and high statistical heterogeneity, respectively. Given the high methodological and statistical heterogeneity across the studies, we used the random-effects model. The weighted mean difference (WMD) was chosen as the effect size to compare the insulin resistance indices between PCOS patients with and without SCH. The metacont function from the meta package employing the Hartung-Knapp adjustment method for the random-effects model was used to calculate the pooled WMD along with its 95% CI [29, 30].

We performed subgroup analyses based on the following variables (continuous variables were categorized) to investigate the potential sources of heterogeneity: study design, risk of bias, sample size, publication year, mean age of patients, mean BMI of patients, and TSH cut-off used for the diagnosis of SCH. Differences between groups were examined using the *p*-value of the test for subgroup differences.

Publication bias was assessed using funnel plots (for analyses including at least ten studies), as well as the Begg and Egger tests. If asymmetry was observed in the funnel plot or any of the Begg or Egger tests indicated the potential presence of publication bias, Duval and Tweedie's trim-and-fill method was applied to assess the impact of publication bias on our findings [31–33]. The leave-one-out sensitivity analysis was conducted to evaluate the

robustness of pooled estimates by sequentially excluding one study at a time and re-estimating outcomes. Statistical significance was defined as a p-value < 0.05 for all the statistical tests.

Results

Study selection and study characteristics

The comprehensive search across four electronic databases yielded 2371 records. After removing duplicate results, 1437 studies were screened based on their titles and abstracts. Subsequently, 108 relevant studies were eligible for full-text examination. Six studies did not have retrievable full-texts. Of the remaining 102 studies, 74 were excluded for the following reasons: 31 lacked prevalence data; 28 were reviews, conference papers, case reports, clinical trials, or animal studies; 9 met exclusion criteria; and 6 had sample sizes smaller than thirty women with PCOS. One additional study was identified from the reference lists. Ultimately, 29 observational studies were included in this systematic review and meta-analysis. The literature search results and study selection process are illustrated in detail through a PRISMA flow diagram (Fig. 1).

The detailed characteristics of the included studies are summarized in Table 1. Of the 29 studies, 21 were carried out in Asia, 5 in Europe, 2 in South America, and 1 in North America. Regarding study design, 20 were cross-sectional, and 9 were case-control studies. The publication dates ranged from 2009 to 2024. Since our primary objective was to assess the prevalence of SCH, all 29 studies reported its prevalence among PCOS subjects and were included in the meta-analysis. In terms of our secondary outcome, eleven studies compared the HOMA-IR index and FPG between PCOS subjects with and without SCH. Nine studies conducted this comparison for fasting insulin and six for 2-hour postprandial glucose levels.

Quality assessment

The average JBI score of the included studies was 4.96 ± 1.54. Five studies were classified as having a low risk of bias. Fourteen were classified as moderate, and ten as high risk of bias. Detailed quality assessment results for each study are provided in Table S2.

Meta-analysis

Primary outcome

The overall pooled prevalence of SCH across all 29 studies, with a total of 5765 PCOS subjects, was 19.7% (95% CI: 16.1%; 23.5%). The heterogeneity across studies was high (I^2 = 92%). Prevalence rates varied significantly, with the lowest rate reported at 4% and the highest at 46.9%. The forest plot illustrating these findings is depicted in Fig. 2.

Subgroup analysis was performed based on the following variables: study design, risk of bias, publication year, sample size, mean age of patients, mean BMI of patients, and TSH cut-off used for diagnosing SCH. The purpose of subgroup analysis was to investigate potential sources of heterogeneity and possible causes for different prevalence rates. None of the variables were identified as sources of heterogeneity. Our subgroup analysis demonstrates that the TSH cut-off value was the only factor that could explain the wide range of prevalence across the studies. The pooled prevalence of SCH was 16.1% (95%CI: 11.9%; 20.8%) in studies with upper reference limits of 4-5.5 vs. 28.6% (95% CI: 21.6%; 36.3%) in studies with upper reference limits of 2.5-4 (P-value of test for subgroup differences = 0.003) (Fig. 3). Subgroup analysis results are presented in Table 2 and Fig. S1.

Secondary outcomes

Regarding insulin resistance, the pooled WMD of 0.78 (95% CI: 0.34; 1.22) indicated a significantly higher HOMA-IR index in PCOS cases with SCH compared to those without SCH (Fig. 4). Similarly, fasting insulin levels were significantly higher in the SCH group, with a pooled WMD of 2.38 (95% CI: 0.34; 4.42) (Fig. 5). However, the pooled WMD for FPG was 1.66 (95% CI: -0.06; 3.37), which did not reach statistical significance (Supplementary Material Fig. S2). Likewise, the pooled WMD for 2-hour postprandial glucose was 10.1 (95% CI: -3.49; 23.69), also failing to reach statistical significance (Fig. S3). Table 3 provides a comparison of our results with those of previous meta-analyses.

Publication bias and sensitivity analysis

We observed a symmetrical funnel plot for the prevalence of SCH in women with PCOS (Fig. S4). Additionally, the results of the Begg (p = 0.159) and Egger (p = 0.347) tests suggested that publication bias is unlikely to affect our findings. Similarly, the funnel plots for the WMD and its standard error for HOMA-IR and FPG (Fig. S5) also appeared symmetrical. For these secondary objectives, the Begg and Egger tests were also not significant (Table S3). The leave-one-out sensitivity analysis showed that the pooled prevalence of SCH remains stable when omitting any of the studies (Fig. S6).

Discussion

Data from the National Health and Nutrition Survey (NHANES) and the Colorado Thyroid Prevalence Study suggest that SCH affects approximately 4 to 10% of the general population [58, 59]. Our systematic review and meta-analysis, synthesizing data from 29 studies, demonstrate that 19.7% of women with PCOS have SCH, a rate considerably higher than in the general population. Supporting our findings, a systematic review and

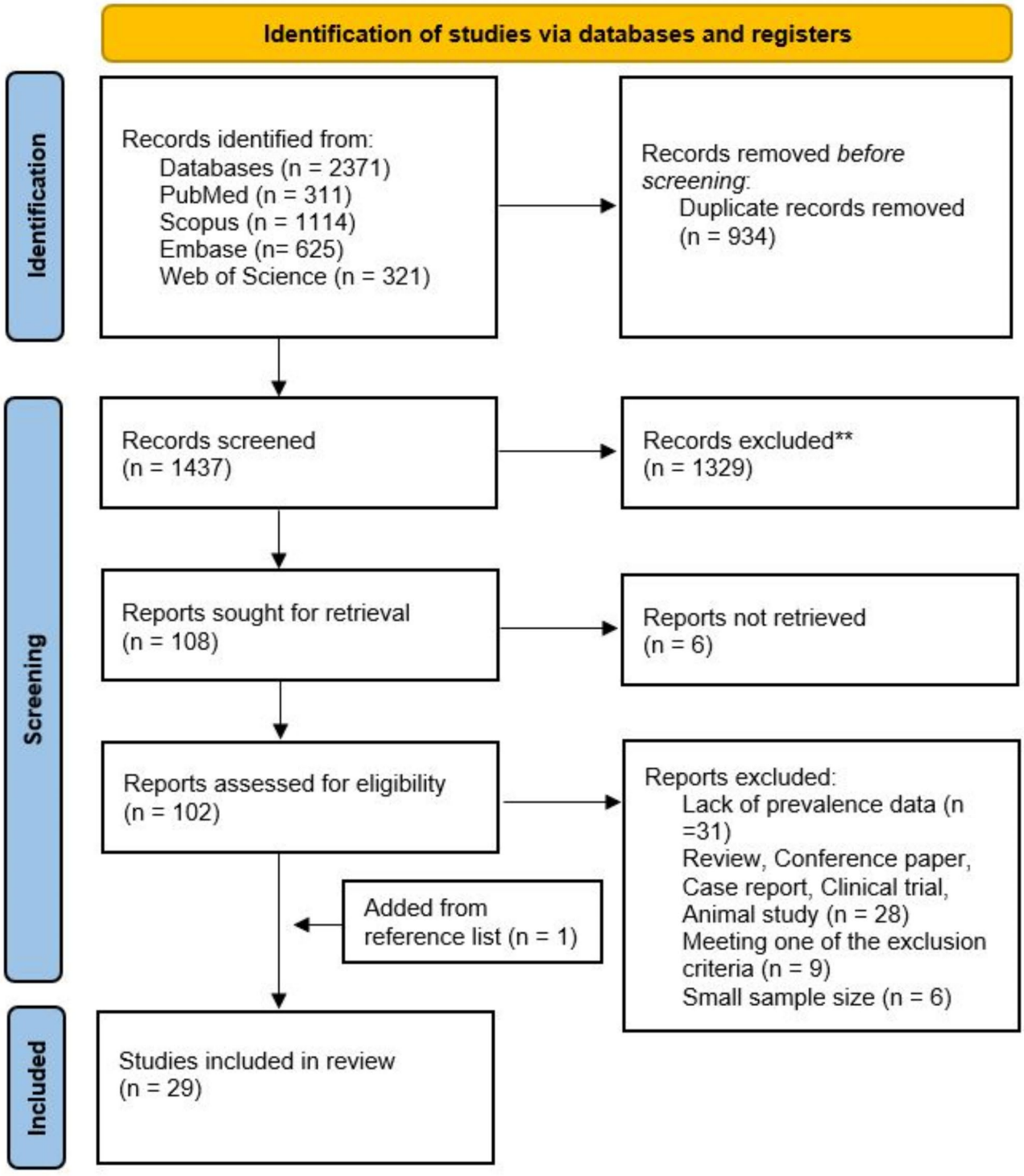

Fig. 1 PRISMA flow diagram of the study selection process

meta-analysis reported that women with PCOS are more likely to have SCH, with an odds ratio of 2.87. When limiting the analysis to studies that used a TSH cut-off of ≥ 4 mIU/L for SCH diagnosis, women with PCOS were 3.59 times more likely to have SCH compared to the control group [60]. According to existing literature, the association between PCOS and thyroid disorder goes beyond just SCH. A systematic review involving 13 studies found that autoimmune thyroiditis is nearly three times more common in women with PCOS in comparison to healthy

Table 1 Main characteristics of the included studies

Author	Year	Country	Study design	Number of PCOS patients	PCOS diagnostic criteria	Age Mean ± SD	BMI Mean ± SD	SCH (+/-)	Normal TSH upper limit (mIU/ml)	Risk of bias
Anebaracy [34]	2024	India	Cross-sectional	40	Rotterdam	23.47 ± 6.87	23.21 ± 3.07	6/34	NR	High
Bedaiwy [35]	2018	USA	Cross-sectional	137	Rotterdam	28.72	31.46	30/107	2.5	Moderate
Benetti-Pinto [36]	2013	Brazil	Cross-sectional	168	Rotterdam	24.19 ± 5.78	33.45 ± 8.23	19/149	4.5	Moderate
Cakir [37]	2022	Turkey	Cross-sectional	96	Rotterdam	24.08 ± 5.98	NR	33/63	2.5	High
Dittrich [13]	2009	Germany	Cross-sectional	103	Rotterdam or NIH	28.45 ± 6.67	28.78 ± 7.69	33/70	2.5	Moderate
Enzevaei [38]	2014	Iran	Cross-sectional	75	Rotterdam	26 ± 4.2	25.49 ± 4.27	19/56	3.75	Moderate
Fatima [39]	2020	Pakistan	Cross-sectional	90	Rotterdam	23.81 ± 4.59	28.04 ± 4.72	31/59	2.5	Moderate
Ganie [40]	2011	India	Case-control	353	NIH	23.5 ± 4.92	25.3 ± 4.2	62/291	5	Low
Ganvir [41]	2017	India	Cross-sectional	60	Rotterdam	19 ± 4.84	26.42 ± 4.59	16/44	NR	High
Garelli [42]	2013	Italy	Case-control	113	Rotterdam	24 ± 6.3	23.5 ± 7.35	13/100	NR	High
Huang [43]	2014	China	Cross-sectional	428	Rotterdam	27.21 ± 6.37	26.03 ± 5.67	60/368	5	Moderate
Kamrul-Hasan [44]	2020	Bangladesh	Cross-sectional	465	Rotterdam	22.52 ± 5.38	26.63 ± 5.12	50/415	5	Moderate
Lu [23]	2016	China	Cross-sectional	196	Rotterdam	25.56 ± 3.5	25.05 ± 4.76	92/104	2.5	Low
Mehra [45]	2023	India	Cross-sectional	68	Rotterdam	24 ± 3.25	23.4 ± 2.84	16/52	4.25	Moderate
Morgante [46]	2013	Italy	Case-control	151	Rotterdam	32.2 ± 6.5	24.9 ± 5.9	51/100	2.5	Moderate
Nanda [47]	2014	India	Cross-sectional	196	NR	27.28 ± 10.56	NR	15/181	4.25	High
Nayak [48]	2020	India	Cross-sectional	287	Rotterdam	22.45 ± 5.51	24.91 ± 5.7	58/229	4.2	Low
Naz [49]	2022	Pakistan	Cross-sectional	77	Rotterdam	29 ± 9.2	NR	9/68	5.5	High
Novais [50]	2015	Brazil	Cross-sectional	65	Rotterdam	27.8 ± 6.9	34.8 ± 8.9	11/54	4.5	Moderate
Pan [51]	2023	China	Cross-sectional	1059	Rotterdam	28 (median) (26–30) IQR	NR	211/848	2.5	Moderate
Raj [24]	2021	Pakistan	Case-control	200	NR	23.23 ± 3.13	25.12 ± 2.51	87/113	5	High
Rojhani [52]	2023	Iran	Cross-sectional	207	Rotterdam	30.7 ± 7.5	26.6 ± 5.5	24/183	5.06	Low
Saeed [53]	2023	Saudi arabia	Cross-sectional	200	Rotterdam	33.5 ± 10.13	33.57 ± 9.56	30/170	4.94	Low
Sinha [54]	2013	India	Case-control	80	Rotterdam	22.7 ± 5.3	24.68 ± 3.07	18/62	NR	High
Tagliaferri [55]	2016	Italy	Case-control	154	Rotterdam	(18–36) range	(16.6–52) range	22/132	2.8	Moderate
Trakakis [21]	2017	Greece	Case-control	280	Rotterdam	24 (median) (12–44) range	24 (median) (16–50) range	21/259	4	Moderate
Vardhan [22]	2023	India	Cross-sectional	100	Rotterdam	25.62 ± 4.08	NR	4/96	NR	High
Yasar [56]	2016	Turkey	Case-control	217	Rotterdam	24.92 ± 6.03	28.45 ± 7.01	45/172	NR	High
Yu [57]	2016	China	Case-control	100	Rotterdam	27.4 ± 5.4	31.2 ± 8.3	27/73	4.25	Moderate

IQR: interquartile range, NIH: National Institute of Health, NR: not reported, PCOS: polycystic ovary syndrome, SCH: subclinical hypothyroidism, SD: standard deviation, TSH: thyroid-stimulating hormone

controls [61]. Additionally, another systematic review and meta-analysis revealed that women with PCOS have a nearly threefold higher chance of having positive thyroid peroxidase antibody (TPOAb) and a twofold higher chance of positive thyroglobulin antibody compared to controls [62]. In line with these findings, another systematic review and meta-analysis demonstrated that women with PCOS are at increased risk of Hashimoto's thyroiditis (HT), with an odds ratio of 2.28 [63]. Since HT is the primary cause of SCH and can initially present in euthyroid or SCH stages, it is plausible that some cases of SCH represent early, undiagnosed stages of HT [64].

Since SCH is defined biochemically, the upper reference limit of TSH is a critical factor to consider. The conventional threshold for TSH is around 4-5.5 mIU/L. Nevertheless, the question of whether to reduce this upper limit remains a topic of continuous debate. There are numerous arguments for and against lowering this upper limit, but they are beyond the scope of this discussion [8]. A recent study with a large sample size demonstrated that lowering the normal upper limit from 4.1 mIU/L to 2.5 mIU/L led to a threefold increase in the prevalence of SCH [65]. Based on the recommendations of the American Thyroid Association (2011) and Endocrine Society guidelines and evidence of adverse pregnancy outcomes at TSH levels above 2.5 mIU/L [66–68], some studies used a TSH cut-off of 2.5 mIU/L. Accordingly, we performed a subgroup analysis based

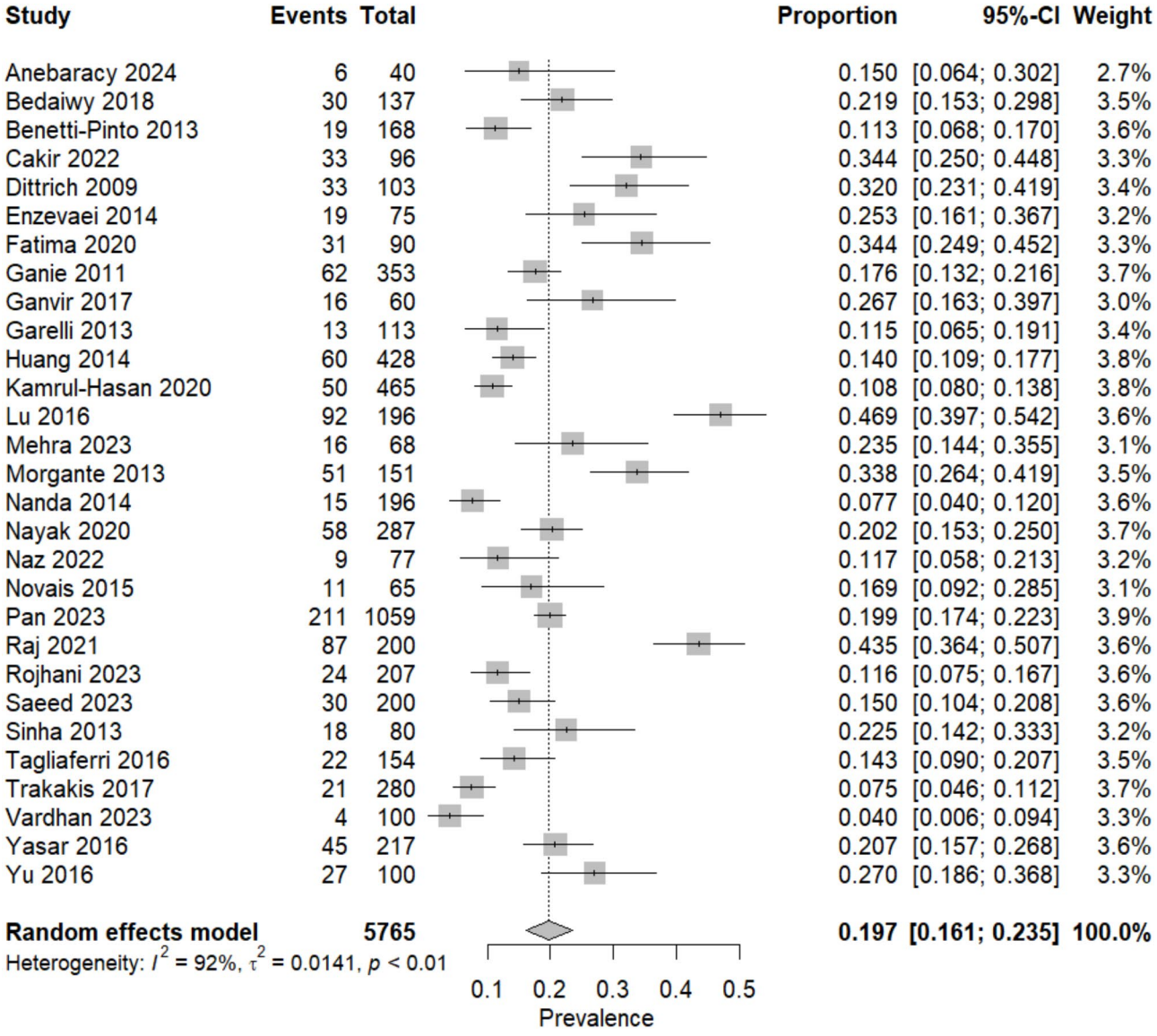

Fig. 2 Forest plot showing the pooled prevalence of subclinical hypothyroidism

on these differing cut-off values. As expected, studies using TSH upper limits of 2.5-4 mIU/L revealed a significantly higher pooled prevalence of 28.6% compared to those using the upper limits of 4-5.5 mIU/L, which had a pooled prevalence of 16.1% (p-value of test for subgroup differences = 0.003). Even with the conventional upper limit, SCH prevalence in women with PCOS is considerably higher than in women of the same age, indicating a possible association between the two conditions.

Insulin resistance, a key factor in the pathophysiology of PCOS, exacerbates the hyperandrogenism state by having direct effects on androgen production and indirect effects by suppressing SHBG production, which subsequently leads to higher free androgen levels [69]. Although the hyperinsulinemic-euglycemic clamp is the gold standard for detecting insulin resistance, its complex procedure limits its use in practice [70]. There are multiple insulin resistance indices that can be easily calculated from fasting levels of insulin and blood glucose. HOMA-IR is the most widely used index and is calculated as fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [71, 72]. Our study demonstrated that the HOMA-IR index is significantly higher in cases with concurrent SCH. This finding aligns with two other meta-analyses, which also reported a significant increase in the HOMA-IR of PCOS patients with SCH [18, 19]. On the contrary, another meta-analysis did not note a significant difference in HOMA-IR levels between these two groups of PCOS patients [20]. Fasting insulin was also higher in the presence of SCH. Future studies are required to confirm if this difference in HOMA-IR and fasting insulin is clinically meaningful. Our findings regarding FPG and 2-hour

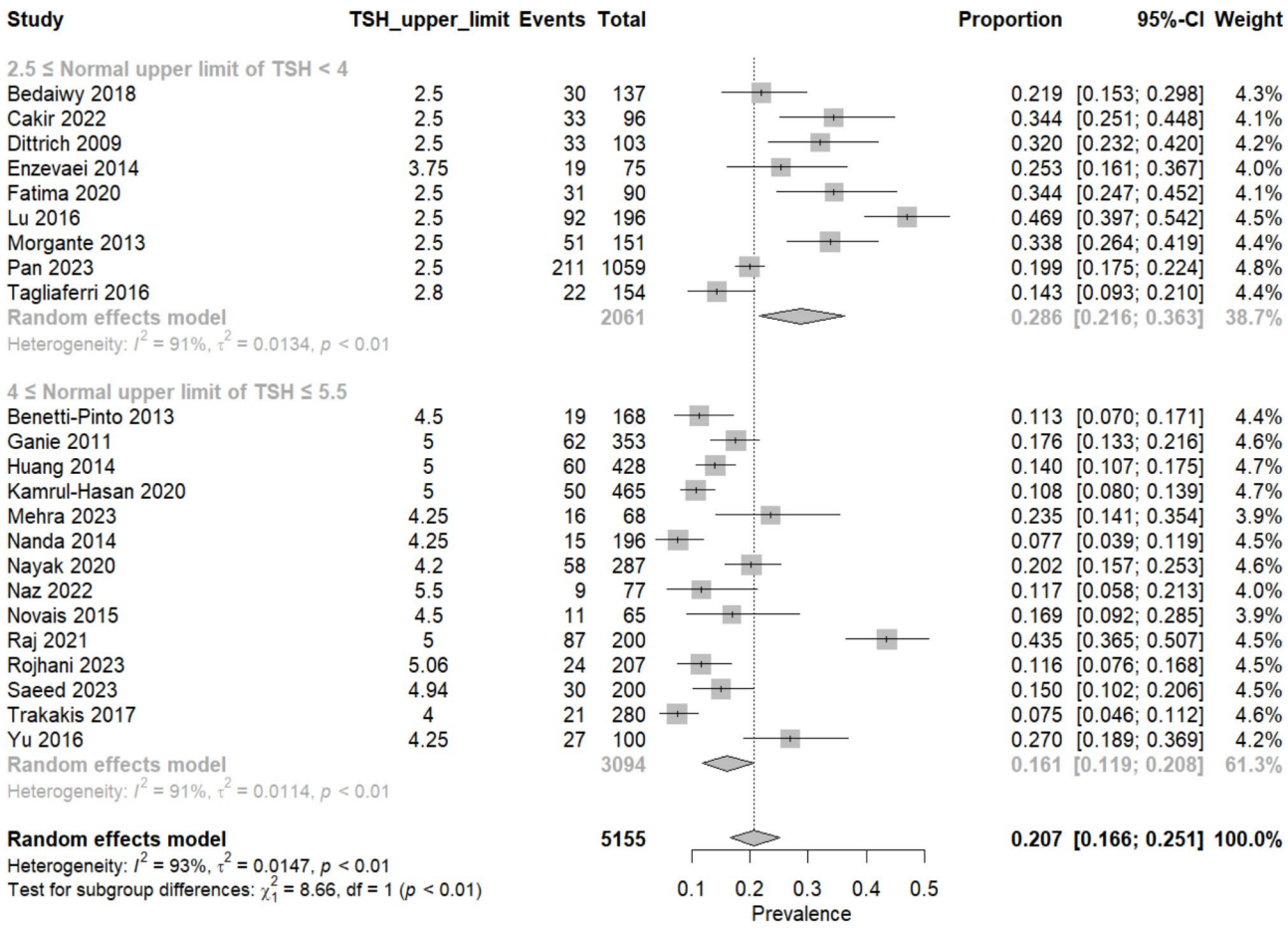

Fig. 3 Pooled prevalence of subclinical hypothyroidism with subgroup analysis by TSH upper limit

Table 2 Subgroup analysis

Subgroup variable		No of studies	Prevalence (%) (95% CI)	*P*-value of Cochran's Q test for heterogeneity	I^2 (%)	*P*-value of test for subgroup differences
Publication year	≥ 2020	12	19.2 (13.8, 25.3)	0.000	92.4	0.839
	< 2020	17	20.0 (15.1, 25.4)	0.000	91.4	
Risk of bias	Low	5	21.3 (11.9, 32.5)	0.000	95.1	0.931
	Moderate	14	19.7 (15.5, 24.3)	0.000	88.9	
	High	10	18.5 (10.7, 27.8)	0.000	92.8	
Study design	Cross-sectional	20	19.0 (14.9, 23.5)	0.000	90.9	0.660
	Case-control	9	21.1 (13.8, 29.4)	0.000	93.3	
Sample size	≥ 150	15	18.5 (13.8, 23.7)	0.000	94.5	0.439
	< 150	14	21.2 (16.0, 26.9)	0.000	81.3	
Mean age	≥ 25	14	19.4 (14.2, 25.2)	0.000	92.5	0.810
	< 25	14	20.4 (15.0, 26.4)	0.000	91.6	
Mean BMI	≥ 25	16	22.5 (17.0, 28.5)	0.000	92.9	0.418
	< 25	7	18.4 (11.3, 26.7)	0.000	89.1	
Upper reference limit of TSH	2.5 ≤ upper limit < 4	9	28.6 (21.6, 36.3)	0.000	90.7	0.003
	4 ≤ upper limit ≤ 5.5	14	16.1 (11.9, 20.8)	0.000	90.8	
All studies		29	19.7 (16.1, 23.5)	0.000	91.5	-

BMI: body mass index, CI: confidence interval, I^2: inconsistency index, SCH: subclinical hypothyroidism, TSH: thyroid-stimulating hormone

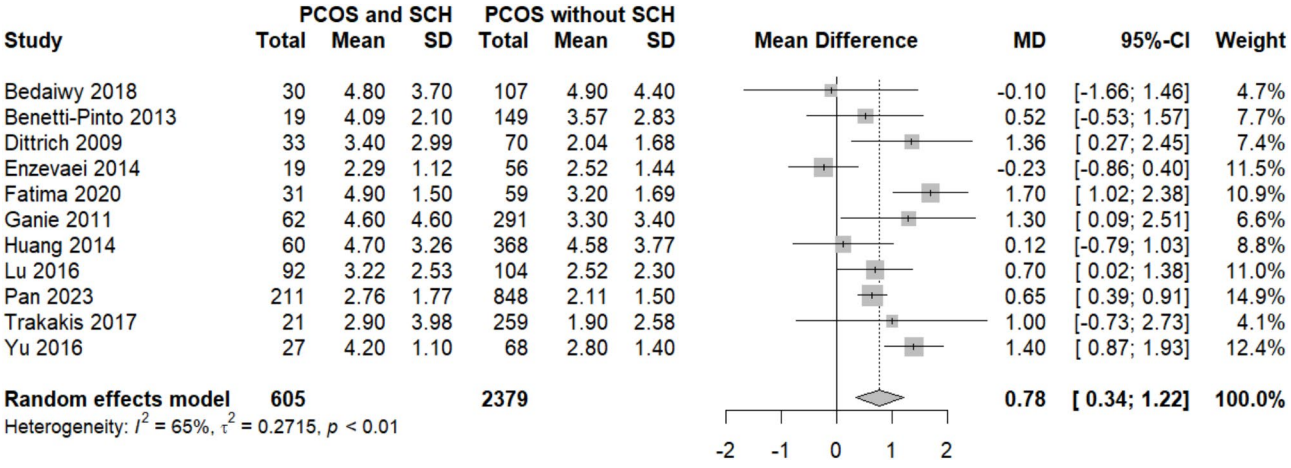

Fig. 4 Forest plot showing the weighted mean difference of HOMA-IR between patients with and without subclinical hypothyroidism

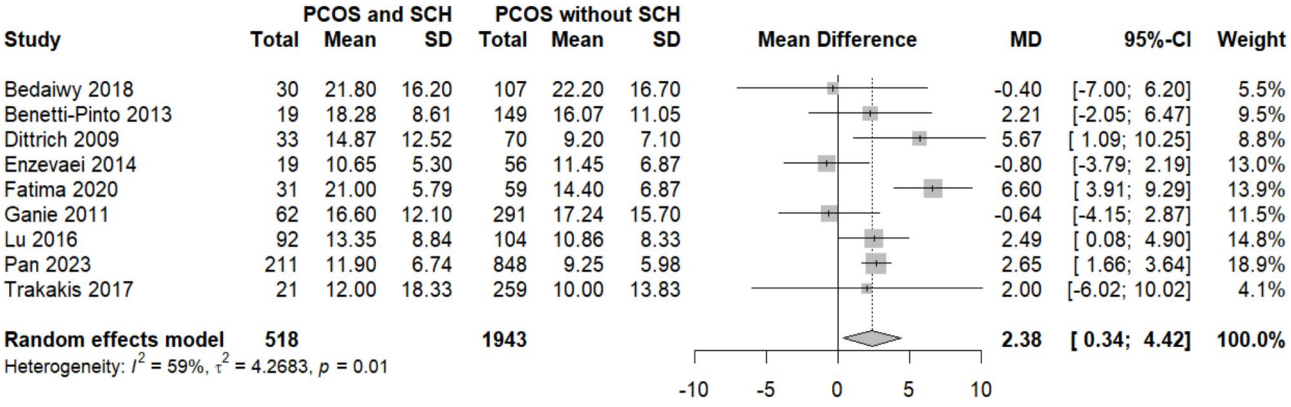

Fig. 5 Forest plot showing the weighted mean difference of fasting insulin levels between patients with and without subclinical hypothyroidism

Table 3 Comparison of findings from previous and current meta-analyses

Study	HOMA-IR WMD (95% CI)	Fasting insulin WMD (95% CI)	FPG WMD (95% CI)	2 h-PPG WMD (95% CI)	Comment
Pergialiotis (2017) [19]	0.82 (0.15, 1.50)	NR	1.62 (-0.71, 3.94)	NR	HOMA-IR was significantly higher in the SCH-PCOS group. FPG and 2 h-PPG were not different.
de Medeiros[a] (2017) [20]	0.16 (-0.48, 0.80)	0.18 (CI is not reported)	0.11 (0.02, 0.20)	NR	FPG was significantly higher in the SCH-PCOS group. HOMA-IR and fasting insulin were not different.
Xing[b] (2021) [18]	0.48 (0.26, 0.71)	NR	0.21 (0.08, 0.35)	-0.04 (-0.11, 0.19)	HOMA-IR and FPG were significantly higher in the SCH-PCOS group. 2 h-PPG was not different.
Current meta-analysis	0.78 (0.34, 1.22)	2.38 (0.34, 4.42)	1.66 (-0.06, 3.37)	10.10 (-3.49, 23.69)	HOMA-IR and fasting insulin were significantly higher in the SCH-PCOS group. FPG and 2 h-PPG were not different.

a: This study used the SCH-PCOS group as the reference. The signs of the WMD and 95% CI were reversed to ensure comparability with other studies. b: This study reported standardized mean difference instead of mean difference. CI: confidence interval, FPG: fasting plasma glucose, HOMA-IR: homeostatic model assessment of insulin resistance, NR: not reported, PCOS: polycystic ovary syndrome, SCH: subclinical hypothyroidism, WMD: weighted mean difference, 2 h-PPG: 2-hour postprandial glucose

postprandial glucose did not reach statistical significance. Nonetheless, considering the limited number of studies and wide confidence intervals, our findings are not conclusive. Unfortunately, other insulin resistance indices, such as QUICKI and Matsuda, were underreported in the literature, precluding us from performing meta-analyses on these indices.

The primary pathophysiological mechanisms by which PCOS and SCH contribute to insulin resistance are different. In PCOS, increased serine phosphorylation of insulin receptor substrate-1 (IRS-1) inhibits PI3-K

activation, impairing downstream insulin signaling pathways [73]. Hyperandrogenism, a hallmark of PCOS, can directly impair insulin signaling in skeletal muscle and adipose tissue. High androgen levels promote visceral fat accumulation, which is strongly associated with insulin resistance. It also reduces adiponectin production, which has insulin-sensitizing effects [73, 74]. In SCH, while not fully understood, impaired insulin sensitivity is primarily attributed to reduced intracellular glucose utilization, inhibition of GLUT 4 translocation, and decreased glycogen synthesis [16, 18]. Additionally, hepatic endoplasmic reticulum stress, via activation of the IRE1α/XBP-1 pathway, has been suggested to play a pivotal role in inducing insulin resistance in SCH [75]. Furthermore, TSH itself can activate the toll-like receptor 4 (TLR4)-mediated inflammatory pathway, further disrupting insulin signaling in hepatic tissue [76]. However, there are similar pathophysiological mechanisms by which both conditions promote insulin resistance. Both SCH and PCOS are associated with chronic low-grade inflammation, marked by increased levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which can impair insulin signaling pathways [76–78]. Additionally, reduced SHBG levels seen in both conditions lead to higher amounts of free androgens, which is a key contributor to insulin resistance in women with PCOS [15, 55, 79]. These shared mechanisms underscore the potential synergistic adverse effect of SCH and PCOS on insulin sensitivity.

PCOS management depends on factors like symptom severity and the patient's pregnancy plans. For most patients, combined oral contraceptives (COCs) are the first-line pharmacological therapy. When COCs are contraindicated or not preferred, metformin is considered an alternative treatment. Metformin, an insulin sensitizer, is particularly beneficial for women with PCOS who have insulin resistance, T2DM, and metabolic risk factors. It is also used as adjuvant therapy with letrozole and clomiphene citrate for ovulation induction [4, 80, 81]. In recent years, many studies have investigated metformin's effect on thyroid function tests. Except for one study, which observed no significant difference in thyroid function tests following metformin therapy [82], other studies found that metformin significantly lowers TSH without notable changes in thyroid hormone levels [83–85]. Three studies, specifically on women with PCOS, observed similar TSH-lowering effects, while thyroid hormones remained unchanged [86–88].

SCH can be classified into mild (TSH < 10 mIU/L) or severe (TSH > 10 mIU/L). Almost all guidelines recommend thyroid replacement therapy when the serum TSH concentrations are above ten due to a higher risk of cardiovascular disease and an increased chance of progression to overt hypothyroidism [89–91]. However, there is no firm consensus regarding the treatment of mild SCH. Most guidelines and expert opinions do not encourage thyroid replacement therapy for most cases of mild and asymptomatic SCH. Treatment is generally considered for individuals with positive TPOAb, pregnant women or those planning to become pregnant, and patients with cardiovascular risk factors [10, 89, 91, 92]. Although PCOS is not currently recognized as an indication for treating SCH [25], many women with PCOS have obesity, dyslipidemia, and insulin resistance, which are major cardiovascular risk factors [5]. Furthermore, a systematic review and meta-analysis, including 12 randomized controlled trials, showed that treatment with levothyroxine in patients with SCH causes a significant reduction in LDL and total cholesterol. Their results remained consistent even in trials that enrolled only mild cases of SCH [93].

Similar to overt hypothyroidism, patients with SCH are at increased risk of hyperprolactinemia, a known cause of ovulatory dysfunction and infertility. It is estimated that around 20 to 30% of individuals with SCH experience hyperprolactinemia, which often resolves with thyroid replacement therapy [94, 95]. Furthermore, a recent meta-analysis found a significant increase in prolactin levels of women with concurrent PCOS and SCH compared to those with PCOS alone [18]. These findings further support the potential benefits of levothyroxine treatment for women with both conditions. Additionally, long-term use of COCs, the first-line pharmacological treatment for PCOS, is associated with a fourfold increased risk of hypothyroidism, according to a large-scale NHANES study [96]. Given these considerations, future clinical guidelines should assess whether PCOS should be recognized as an indication for treating SCH.

Another important aspect to consider is the potential impact of SCH on PCOS symptoms. Oligo-anovulation is a key component of the PCOS diagnostic criteria and one of its most important clinical features [4]. Hyperprolactinemia, commonly seen in SCH, is strongly associated with oligo-anovulation and infertility [97]. However, studies comparing menstrual irregularities in PCOS patients with and without SCH report no significant differences [13, 21, 40]. With respect to hyperandrogenism-related symptoms, namely acne and hirsutism, it is plausible that SCH may worsen these symptoms due to reduced levels of SHBG, which increase the free form of androgens [15, 55]. However, the findings of clinical research on this topic are controversial. Lu et al. reported a significantly higher Ferriman-Gallwey score among patients with both PCOS and SCH compared to those with PCOS only [23]. Conversely, another study noted a lower rate of hirsutism among those with concurrent PCOS and SCH [44]. Most studies, however, found no significant difference in the prevalence of hirsutism and

acne when comparing PCOS patients with and without SCH [13, 21, 38]. Further research on this aspect is needed to draw a firm conclusion.

This study has several strengths. To our knowledge, it is the first systematic review and meta-analysis assessing the pooled prevalence of SCH in PCOS patients. The large number of included studies and extensive data extraction allowed for subgroup analyses based on seven variables. Notably, subgroup analysis demonstrated that the TSH cut-off value used for SCH diagnosis is a critical factor influencing SCH prevalence. This finding highlights the need for a standardized cut-off value to harmonize research findings and minimize over or underdiagnosis. None of the funnel plots or Begg and Egger tests indicated that our findings were influenced by publication bias. Moreover, the leave-one-out sensitivity analysis supports the robustness of our results. This study has several methodological limitations. Firstly, non-English studies were not included. Secondly, the quality assessment identified 24 studies as having a moderate or high risk of bias. Additionally, most studies had non-random sampling methods, which might have introduced selection bias by including more severe cases that sought medical care. There are also several analytical limitations. Despite conducting rigorous subgroup analyses based on seven variables, none were identified as sources of statistical heterogeneity. The observed high heterogeneity may partly stem from variations in the distribution of PCOS phenotypes among studies as well as differences in other characteristics such as ethnicity and iodine status. The use of different thyroid function test kits is likely to be another factor contributing to this high heterogeneity. The limited number of studies reporting SCH prevalence across different PCOS phenotypes prevented us from performing a meta-analysis to estimate the prevalence for each phenotype. Lastly, due to the limited number of studies and wide confidence intervals, the findings regarding 2-hour postprandial glucose and FPG are not conclusive. These limitations should be considered when interpreting our findings.

Conclusion

This study demonstrates that around 20% of women with PCOS have SCH, highlighting the importance of regular thyroid function testing in these patients. We found that the prevalence of SCH is significantly influenced by the TSH cut-off used for diagnosis. This underscores the need for a standardized TSH cut-off value to ensure consistency across studies and reduce the risk of over- or underdiagnosis. Moreover, women with both PCOS and SCH had significantly higher HOMA-IR and fasting insulin levels compared to those with PCOS alone, indicating a potential exacerbation of insulin resistance. Future cohort studies are needed to assess the long-term risks of T2DM and cardiovascular disease in these patients. Additionally, clinical trials with sufficient follow-up periods are essential to aid future guidelines in deciding whether PCOS should be considered an indication for treating SCH.

Abbreviations

BMI	Body mass index
CI	Confidence interval
COCs	Combined oral contraceptives
FPG	Fasting plasma glucose
FT4	Free thyroxine
HOMA-IR	Homeostatic model assessment of insulin resistance
HT	Hashimoto's thyroiditis
I^2	Inconsistency index
IL-6	Interleukin-6
IQR	Interquartile range
IRS-1	Insulin receptor substrate-1
JBI	Joanna briggs institute
NHANES	National health and nutrition survey
NIH	National institute of health
NR	Not reported
PCOS	Polycystic ovary syndrome
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
SCH	Subclinical hypothyroidism
SD	Standard deviation
SHBG	Sex hormone-binding globulin
T2DM	Type 2 diabetes mellitus
TLR4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-α
TPOAb	Thyroid peroxidase antibody
TSH	Thyroid-stimulating hormone
WMD	Weighted mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01896-2.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
MH and MF conceptualized and designed the study. AS and SM-T developed the search strategy. SS and MS screened the studies. MP and SS extracted the data. SM-T and AS assessed the risk of bias. MH and MF supervised the study and resolved disagreements. APA and AS conducted the statistical analysis. AS, SM-T, and APA wrote the manuscript text, and all other authors critically reviewed and revised it. All authors read and approved the final manuscript.

Funding
No funding was received.

Data availability
Availability of data and materials: The dataset supporting the results of this systematic review and meta-analysis was extracted from previously published studies and is presented within the manuscript and supplementary material.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 26 October 2024 / Accepted: 6 March 2025
Published online: 19 March 2025

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