

Is There an Association Between Hypothyroidism and Sexual Dysfunction: A Systematic Review and Cumulative Analysis



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ABSTRACT

Introduction: Many investigators have found a detrimental effect on sexual functioning developed by hypothyroidism in both sexes, but a cumulative analysis has not been conducted.

Aim: This study aims to summarize and quantify the association between overt or subclinical hypothyroidism and the risk of sexual dysfunction (SD) through a meta-analysis.

Methods: 4 electronic databases were systematically searched. The quality of evidence was rated by the GRADE approach. This meta-analysis was registered on the PROSPERO (ID: CRD42020186967).

Main Outcome Measure: The strength of the relationship between overt/subclinical hypothyroidism and SD was quantified by presenting the relative risk (RR) with its 95% confidence interval (CI).

Results: 7 studies involving 460 patients with hypothyroidism and 2,143 healthy controls were included in this meta-analysis. Among the 7 included studies, 2 studies were provided the data of both overt and subclinical hypothyroidism. Pooled results from 4 included studies investigating overt hypothyroidism indicated that overt hypothyroidism led to significant SD in both sexes (RR = 2.26, 95% CI: 1.42 to 3.62, $P = 0.001$), while synthetic RR of 5 eligible studies reporting subclinical hypothyroidism failed to find a positive association between subclinical hypothyroidism and SD (RR = 1.3, 95% CI: 0.85 to 1.99, $P = 0.229$), irrespective of gender (all $P > 0.05$). Subgroup analyses revealed that women with overt hypothyroidism rather than men with overt hypothyroidism were correlated with a significant higher risk of SD. The quality of evidence in the study of overt hypothyroidism and subclinical hypothyroidism was considered low and moderate, respectively.

Conclusion: SD is a devastating problem in female patients with clinical hypothyroidism but unsusceptible in either women or men with subclinical hypothyroidism. Clinicians should be aware of these phenomena and manage the sufferers accordingly in clinical practice. More rigorous studies are still needed to validate this evidence.

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INTRODUCTION

Sexual dysfunctions (SD), which has traditionally included disorders of interest or desire, arousal, and inhibited orgasm, are a complex process and highly prevalent disorders for female and male in worldwide. It was suggested that the prevalence of new female sexual difficulty is 36% at 12-month follow-up.¹ The incidence of ED, a common type of male SD, was observed in 31.7% of eligible men at a 5-year follow-up.² Epidemiologic researches have shown that endocrine disease, age, cardiovascular disease, urinary tract infections, chronic health problems, and general health play a key role in the development of female and male SD.³ However, the exact role of the endocrine disease is still not completely unclear. Recent studies have shown that

hypothyroidism was associated with sexual health in both women and men.^{4,5}

Hypothyroidism can be separated into overt or subclinical based on its severity. Overt hypothyroidism is a common and multifactorial clinical disorder associated with numerous diseases and aging due to the elevated pituitary thyrotropin (TSH) concentrations and low level of free triiodothyronine (FT3) and free thyroxine/tetraiodothyronine (FT4),⁶ while subclinical hypothyroidism is defined by low levels of TSH with normal FT4 and FT3 concentrations.⁷ According to the U.S. National Health and Nutrition Examination Survey III, the prevalence of hypothyroidism was 4.6% (0.3% of overt and 4.3% of subclinical). Hypothyroidism was found to affect more women than men (ratio: 5–8: 1).⁸ A common cause of hypothyroidism is iodine deficiency. While in iodine-sufficient populations, chronic autoimmune thyroiditis (Hashimoto thyroiditis) is the most common etiological factor of hypothyroidism.⁹ Undiagnosed or untreated hypothyroidism potentially has profound adverse effects that is, weight gain, fatigue, constipation, cold intolerance, and menstrual irregularities.^{10,11}

Hypothyroidism also has been associated with uterine hyperplasia and inflammation, a low fertility potential of females and reduction of steroidogenesis and spermatogenesis in males.^{12,13} Besides, over the last decade, accumulating evidence has emerged showing that patients with hypothyroidism are more likely to have SD in both sexes.¹⁴ Carani et al¹⁵ reported that men with hypothyroidism are more inclined to suffer from SD than the healthy controls, such as hypoactive sexual desire (64.3% vs 17.6%), delayed ejaculation (DE) (64.3% vs 2.9%), and erectile dysfunction (ED) (64.3% vs 14.7%). Similarly, Nikoobakht et al¹⁶ found that the International Index of Erectile Function score in male with hypothyroidism was significantly decreased. For female subjects, Oppo et al¹⁷ suggested that all female sexual function index (FSFI) domain scores were significantly reduced in hypothyroidism women. Of note, with the restoration of the euthyroid state, a significant improvement in FSFI domain scores in women and erectile function in men when the restoration of the euthyroid state was achieved.^{17,18}

Despite the results of some studies indicating hypothyroidism may have an adverse effect on female and male sexual functioning, the association between hypothyroidism and the risk of SD remains controversial. Corona et al¹⁹ found that there was no association between hypothyroidism and erectile function after adjusting for potential confounders. Data from Bates et al²⁰ revealed that the impact of subclinical hypothyroidism on sexual functioning was less clear. As a result, we speculate that there may be a positive association between overt hypothyroidism and risk of SD, while no link is presented in subclinical hypothyroidism and SD. In this study, we have reviewed all of the relevant studies and subsequently conducted the quantified results via a meta-analysis so that to answer the above scientific questions.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this systematic review and meta-analysis (Supplementary Table 1). Besides, we have registered this meta-analysis on the PROSPERO (ID: CRD42020186967, <http://www.crd.york.ac.uk/PROSPERO>).

Data Sources and Search strategy

A comprehensive systematic literature search of the potential related studies was employed in MEDLINE (PubMed), EMBASE (OVID), Cochrane Library, and the PsychINFO databases from inception to May 2020. The searching was limited to the English language and human subjects. To identify the eligible studies, we used the keyword searching in the PubMed database, and the searching strategy is: ((((((("Erectile Dysfunction"[Mesh]) OR sexual function) OR sexual dysfunction) OR "Sexual Dysfunctions, Psychological"[Mesh]) OR "Sexual Dysfunction, Physiological"[Mesh]) OR Impotence) AND (((((((("Hypothyroidism"[Mesh]) OR (Hypothyroidisms)) OR (Primary Hypothyroidism)) OR (Hypothyroidism, Primary)) OR (Primary Hypothyroidisms)) OR (Secondary Hypothyroidism)) OR (Hypothyroidism, Secondary)) OR (Secondary Hypothyroidisms)) OR (Central Hypothyroidism)) OR (Central Hypothyroidisms)) OR (Hypothyroidism, Central)). Besides, we also attempted to detect additional potential studies by manual inspection of the reference lists of the related studies.

Assessments of Hypothyroidism and SD

Definitions of overt hypothyroidism, subclinical hypothyroidism, and SD were according to the international classification of diseases codes (ICDs). The diagnosis of overt hypothyroidism was generally followed by increasing serum concentration of TSH and reducing concentrations of FT3 and FT4, while subclinical hypothyroidism was confirmed by elevated serum TSH concentrations and normal free thyroid hormone levels. SD is diagnosed by the common use methods of the validated instruments, such as the International Index of Erectile Function-5 and International Index of Erectile Function-15 for men and FSFI for women.

Study Selection

Inclusion. Any studies reporting the prevalence of SD in patients with overt/subclinical hypothyroidism along with a normal control group were potentially considered eligible. The inclusion criteria were followed by the Patient, Intervention, Comparison, Outcome, and Study design (PICOS) evidence. The scientific question guiding for the present study was: whether patients with overt hypothyroidism or/and subclinical hypothyroidism have a significantly higher risk of SD than the

healthy control group? The components for the PICOS evidence in this study was: male or female subjects with SD or sexual disorders (P); a history of overt/subclinical hypothyroidism (I); compared with the healthy normal men or women (C); the diagnosis of SD (O); any study designs were accepted (S). Furthermore, any studies reporting the relative risk (RR), hazard ratio (HR), or odds ratios (OR) with its 95% confidence intervals (CI) or providing sufficient data to calculate these effect sizes were also included. Though subclinical hypothyroidism is not considered to be “clinical hypothyroidism” condition due to those sufferers were asymptomatic or mild symptoms, we also investigated the association between subclinical hypothyroidism and SD because of its high prevalence around the world. It has clinical significance to better illuminate this issue.

Exclusion. The exclusion criteria in the current study were: (i) those studies failed to provide the data of the normal control group; (ii) the study type was case report, review, editorial, and comment, etc.; (iii) previous publications or the duplicated data of the same clinical trials; (iv) animal experiments.

Data Extraction

Two investigators independently assessed the eligibility of the potential studies and extracted the following relevant data based on a standardized data collection form, including the first author's name, the year of publication, study regions, study design, gender, age of the patients, the number of SD in the study group and the control group, ascertainment of overt hypothyroidism and subclinical hypothyroidism, assessment of SD, type of SD.

Quality Assessment

The cross-sectional study quality methodology checklist was conducted to rate the methodological quality of the eligible cross-sectional studies, which contained 11 items and the conformity gained with 1 star (low quality = 0–3 stars, moderate quality = 4–7 stars, high quality = 8–11 stars). The Newcastle-Ottawa Quality Assessment Scale (NOS) for the case-control studies and the cohort studies was employed to evaluate the methodological quality of these studies. This scale includes 9 domains and the conformity is assigned with 1 score, while the score of 0–3, 4–6, and 7–9 was considered to the low quality, moderate quality, and high quality, respectively. Any ambiguities were resolved by discussion or the third author.

The grading of recommendations assessment, development, and evaluation profiler (GRADE-pro, version: 3.6, McMaster University and Evidence Prime Inc.) Working Group was used to calculate the absolute estimates of the risk of SD in patients with overt hypothyroidism or subclinical hypothyroidism and rank the overall quality of the evidence.

Risk of Bias Assessment. The risk of bias for each eligible study was evaluated using the software Review Manager 5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen; Denmark). The results were showed as risk of bias summary and risk of bias graph.

Meta-analyses

This meta-analysis aims to answer the overarching scientific question: is SD more prevalent in subjects with overt hypothyroidism or subclinical hypothyroidism than those without hypothyroidism (the healthy normal individuals)? The strength of the relationship between overt/subclinical hypothyroidism and SD was quantitatively pooled by calculating the overall RR with its 95% CI. The combined effects were estimated by the Z test, and the P values < 0.05 were considered to statistically significant. I^2 statistic and the Cochrane Q statistic were used to evaluate the heterogeneity across the studies, while $I^2 > 50\%$ indicated substantial heterogeneity, and P value of Q test < 0.10 was regarded to be significant. Considering a high likelihood of between-study variance for differences in study designed and the demographic across the included studies, a random-effect model rather than a fixed-effects model was used in this study. Sensitivity analyses were conducted to detect the potential origin of between-study heterogeneity. The publication bias test was presented by both Begg's rank-correlation test and Egger's regression asymmetry test. The above-mentioned statistical analyses were conducted with STATA version 13.0 software (Stata Corp LP, College Station, Texas).

RESULTS

Characteristics of Included Studies

Figure 1 shows the search flowchart for detecting potential studies. In the initial database search, we have identified a total of 423 publications. After removing 416 records for various reasons, 7 studies^{21–27} ultimately met our predefined inclusion criteria. A total of 2,703 individuals were involved, while the hypothyroidism cases were 460 (overt: 114; subclinical: 346). Among the 7 included studies, 5 studies^{21,23,25–27} solely reported the cases of overt hypothyroidism or subclinical hypothyroidism, while 2 included studies^{22,24} reported both overt hypothyroidism and subclinical hypothyroidism, resulting in 4 studies related to overt hypothyroidism and 5 studies related to subclinical hypothyroidism. There are 2 cross-sectional studies^{21,25} and 5 case-control studies^{22–24,26,27} published from 2006 to 2018. The mean age of the individuals in the 7 included studies ranged from 29 ± 4 to 39 ± 5 years. The study region of these eligible studies was conducted in Italy,^{21,23} Turkey,²² Poland,^{24,26} Korea,²⁵ and China²⁷. The clinical characteristics of the 7 eligible studies were summarized in Table 1.

Study Quality, Quality of the Evidence, and Risk of Bias. The overall quality of the 7 included studies was

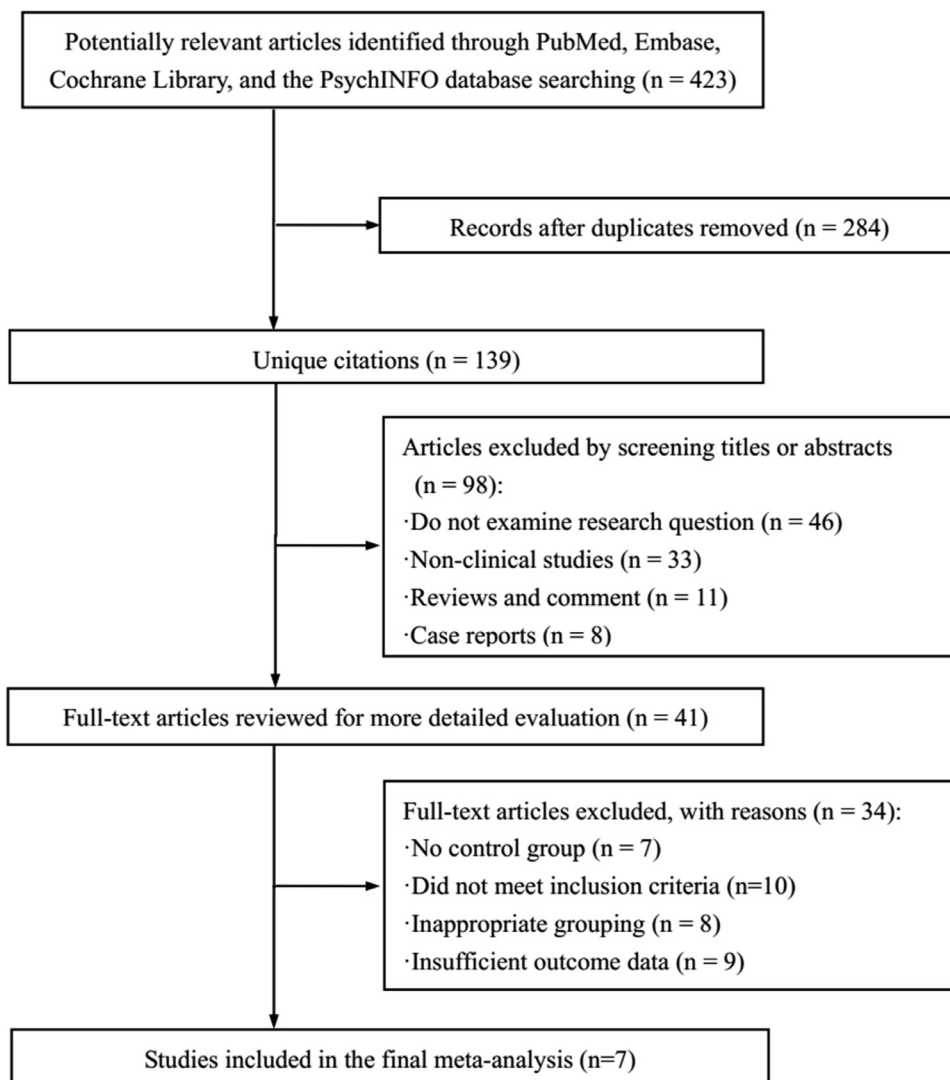


Figure 1. Flow chart of study selection.

considered to medium. Among these studies, 3 studies^{23,25,27} were rated to high methodological quality (43%) and the other 4 were regarded as moderate methodological quality (57%) (Supplementary Table 2 and Supplementary Table 3).

As shown in Table 2, according to the results calculated by GRADE approach, the rate of events of SD on average in overt hypothyroidism patients and the general population was 63 per 114 (55.3%) and 48 per 194 (24.7%), respectively. The absolute effect of overt hypothyroidism on SD was 312 more per 1,000 (from 104 more to 648 more) and the GRADE Working Group grades of evidence was low. In the studies of subclinical hypothyroidism, the rate of events of SD in subclinical hypothyroidism individuals and the healthy control subjects was 152 per 346 (43.9%) and 916 per 1,949 (47.0%), respectively. The absolute effect of subclinical hypothyroidism on SD was 141 more per 1000 (from 70 fewer to 465 more) and the GRADE evidence was rated to moderate.

As displayed in Supplementary Figure 1, all the included studies were classified as “high risk” due to none of these trials were randomized controlled trial designed.

Meta-analysis. 4 studies^{21–24} reported data from overt hypothyroidism, for a total of 114 patients with overt hypothyroidism and 194 subjects in the control group. The pooled results revealed that overt hypothyroidism patients had a remarkably higher risk of SD than the general population with the combined RR of 2.26 (95% CI: 1.42–3.62, $P = 0.001$). No statistical heterogeneity was found in this pooled effect with an I^2 of 30.3% ($P = 0.231$). In the present study, we have further conducted a meta-analysis based on male and female participants separately (Supplementary Figure 2). Pooled result from 2 studies reporting male subjects revealed that there was no significant positive association between overt hypothyroidism and SD (RR = 3.27, 95% CI: 0.66–16.17, $P = 0.147$; heterogeneity: $I^2 = 67%$, $P = 0.082$).

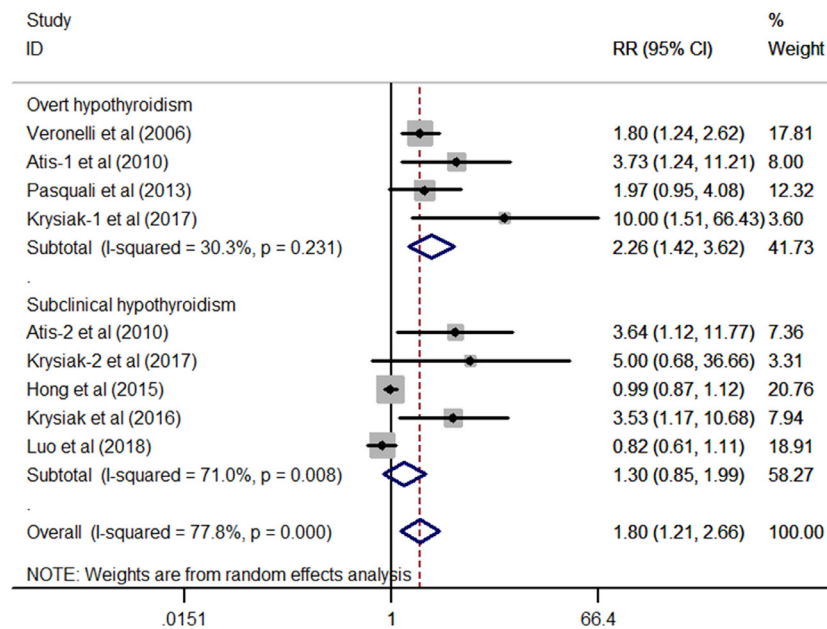


Figure 2. Forest plots of the meta-analysis of the eligible studies on the association between hypothyroidism and sexual dysfunction in both sexes.

Nevertheless, pooled RR derived from 2 included studies reporting female individuals indicated that overt hypothyroidism was significantly associated with an increased risk of SD (RR= 2.39, 95% CI: 1.31–4.39, $P = 0.005$) and no substantial heterogeneity was identified ($I^2 = 0.0\%$, $P = 0.342$) (Figure 2).

When focused on those studies investigating the subclinical hypothyroidism in both sexes, synthetic RR from 5 included studies^{22,24,25–27} with a total of 2,395 individuals indicated that there was no significant association between subclinical hypothyroidism and the risk of SD (RR = 1.3, 95% CI: 0.85–1.99, $P = 0.229$; heterogeneity: $I^2 = 71\%$, $P = 0.008$). In addition, we also performed a meta-analysis on subclinical hypothyroidism by separating male and female (Supplementary Figure 3). In line with the results from both sexes, the combined RR from the included studies reporting either males or females indicated that no significant association between subclinical hypothyroidism and SD was observed (male: RR = 5.0, 95% CI: 0.68–36.66, $P = 0.113$; female: RR = 1.2, 95% CI: 0.79–1.81, $P = 0.387$) (Figure 2).

Sensitivity Analysis. We performed sensitivity analyses to explore the potential sources of heterogeneity and incoherence across the included studies. As shown in Figure 3 and Table 3, sensitivity analysis for the study of overt hypothyroidism indicated that there was no substantial change in the new combined RR after omitting any of the 4 included studies. The RR ranged from 1.95 (95% CI: 1.42–2.68, $P < 0.001$) to 3.05 (95% CI: 1.42–6.56, $P = 0.004$). However, we have observed a remarkable change of the heterogeneity across these studies, the I^2 varied in a range of 0–53.4%. The $I^2 = 0\%$ was obtained after

eliminating Krysiak-1's study,²⁴ which indicated this study might be the potential source of the heterogeneity.

When further evaluating the influence of a single study on the overall RR and heterogeneity in those studies reporting subclinical hypothyroidism, the results revealed that both the new overall pooled RR and heterogeneity did not exhibit a substantial change after omitting any of the 5 included studies. All the newly calculated RR did not support the positive association between subclinical hypothyroidism and SD. The RR ranged from 1.08 (95% CI: 0.75–1.58, $P = 0.673$) to 2.34 (95% CI: 0.89–6.21, $P = 0.086$) and the I^2 ranged from 65.4% ($P = 0.034$) to 78.2% ($P = 0.003$). The above results demonstrated that no single study dominated the overall combined RR and heterogeneity in those studies investigating subclinical hypothyroidism.

Publication Bias

As displayed in Figure 4 with the funnel plots, both Begg's rank correlation test and Egger's linear regression yielded no significant publication bias across the 4 included studies investigating overt hypothyroidism (Begg's, $P > |z| = 0.089$; Egger, $P > |t| = 0.056$, 95% CI: -0.13 to 3.98) (Figure 4A, 4B) and the 5 included reporting subclinical hypothyroidism (Begg's, $P > |z| = 0.806$; Egger, $P > |t| = 0.113$, 95% CI: -0.78 to 4.41) (Figure 4C, 4D).

DISCUSSION

More and more clinical researches have confirmed that thyroid disorders are associated with a detrimental effect on the quality of life, affecting both physiological and psychological conditions. In 1995, Jannini et al²⁸ published the first review

Table 1. Characteristics of the included studies

Study	Study design	Gender	Mean age (years)	Study group case/total	Control group case/total	Assessment of hyperthyroidism	Assessment of SD; type of SD
The 4 included studies that reported the prevalence of SD in patients with overt hypothyroidism:							
Veronelli [21] 2006 Italy	Cross- sectional	Male	S: 35–81 C: 30–76	30/55	33/109	TSH levels	IIEF-5; ED
Atis-1 [22] 2010 Turkey	Case – control	Female	S: 37.04 ± 7.08 C: 39.30 ± 5.52	14/25	3/20	TSH, FT3, and FT4 levels	FSFI; the 6 sub-domains of FSFI
Pasquali [23] 2013 Italy	Case – control	Female	S: 39.7 ± 8.7 C: 39.2 ± 12.4	9/22	11/53	TSH level higher than normal value with FT4 below the normal value	FSFI; The 6 sub-domains of FSFI
Krysiak-1 [24] 2017 Poland	Case – control	Male	S: 38 ± 5 C: 34 ± 7	10/12	1/12	Thyrotropin levels above 20 mU/L and free thyroid hormone levels below the lower limit of the normal laboratory range	IIEF-15, ED
The five included studies that reported the prevalence of SD in patients with subclinical hypothyroidism:							
Atis-2 [22] 2010 Turkey	Case – control	Female	S: 38.90 ± 5.72 C: 39.30 ± 5.52	6/11	3/20	The subclinical hypothyroidic women with TSH value >10 mU/L	FSFI; The 6 sub-domains of FSFI
Krysiak-2 [24] 2017 Poland	Case – control	Male	S: 35 ± 6 C: 34 ± 7	5/12	1/12	Thyrotropin levels more than 4.5 mU/L, but below 20 mU/L and normal free thyroid hormone levels	IIEF-15, ED
Hong [25] 2015 Korea	Cross- sectional	Female	S: 46–55 C: 47–56	93/138	648/948	Elevated serum TSH concentrations (>4.1 μIU/mL) with normal FT4	FSFI; The 6 sub-domains of FSFI
Krysiak [26] 2016 Poland	Case – control	Female	S: 31 ± 5 C: 29 ± 4	10/17	3/18	Thyrotropin levels in the range between 4.5 and 10 mU/L and free thyroid hormone levels within the reference range	FSFI; the 6 sub-domains of FSFI
Luo [27] 2018 China	Case – control	Female	S: 39.2 ± 7.6 C: 38.5 ± 7.7	38/168	261/951	TSH, FT3, and FT4 levels	FSFI; the 6 sub-domains of FSFI

C = control group: the healthy general population; ED = erectile dysfunction; FSFI = female sexual function index; FT3 = free triiodothyronine; FT4 = free thyroxin/tetraiodothyronine; IIEF-5 = International Index of Erectile Dysfunction; IIEF-15 = International Index of Sexual Function-15; S = study group: patients with hyperthyroidism; SD = sexual dysfunction; TSH = thyroid-stimulating hormone.

Table 2. GRADE-profiler summary of evidence for the effects of hypothyroidism and sexual dysfunction

No. of studies	Quality assessment				Other considerations	No. of patients		Effect		Quality	Importance	
	Design	Risk of bias	Inconsistency	Indirectness		Imprecision	Hypothyroidism	Control	Relative(95% CI)			Absolute
Sexual dysfunction (assessed with: TSH, FT3, and FT4 levels) 4 studies reporting overt hypothyroidism	Observational studies	Serious*	No serious inconsistency ^f	Serious ^f	No serious imprecision	Strong association [§] dose response gradient	63/114 (55.3%)	48/194 (24.7%)	RR= 2.26 (1.42 to 3.62)	312 more per 1000 (from 104 more to 648 more)	⊕⊕⊕⊕ LOW	CRITICAL
5 studies reporting subclinical hypothyroidism	Observational studies	Serious*	Serious [†]	No serious indirectness	No serious imprecision	Very strong association [‡] increased effect for RR ~1**	152/546 (43.9%)	916/1,949 (47.0%)	RR= 1.3 (0.85 to 1.99)	141 more per 1000 (from 70 fewer to 465 more)	⊕⊕⊕⊕ MODERATE	CRITICAL

* Selection bias, performance bias, and detection bias have been identified in a few studies.

[†] Most of included studies (3/4) investigating the association between overt hypothyroidism and sexual dysfunction have confirmed such a significant relationship.

[‡] The potential mechanism of overt hypothyroidism-induced sexual dysfunction is still under debate.

[§] The combined effects were derived from 4 eligible studies with a total of 308 participants, which increasing the study sample.

^{||} People with free thyroid hormone levels below the lower limit of the normal laboratory range have a significant higher risk to develop sexual dysfunction, while those with free thyroid hormone levels within the reference range are comparable to the general population.

[¶] In the 5 included studies investigating subclinical hypothyroidism, there are 2 studies showing a positive association between subclinical hypothyroidism and sexual dysfunction, while the remainder studies failed to find such a relationship.

^{‡‡} The combined effects were derived from 5 eligible studies with a total of 2395 participants, which dramatically increasing the study sample.

** Some included studies managed to adjust the common confounding factors, which increased the effect of evidence. CI = confidence interval; RR = relative risk; FT3 = free triiodothyronine; FT4 = free thyroxine; TSH = thyroid-stimulating hormone. GRADE Working Group grades of evidence: *high quality*: Further research is very unlikely to change our confidence in the estimate of effect. *Moderate quality*: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low quality*: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. *Very low quality*: We are very uncertain about the estimate.

that summarized all the evidence related to the topic of thyroid disease and the risk of SD. Since then, mounting studies were conducted to illuminate the impact of thyroid disease on human sexual functioning. Hyperthyroidism and hypothyroidism are common disorders causing by thyroid derangements. Clinical hypothyroidism is characterized by increased serum TSH and reduced serum FT3 and FT4, while subclinical hypothyroidism is featured by elevated serum TSH concentrations with normal FT3 and FT4. In the present study, we have managed to better explore the association between clinical/subclinical hypothyroidism and the risk of SD in both sexes which are still controversial among different studies.

Based on this meta-analysis, pooled RR from 4 included studies providing the data of overt hypothyroidism demonstrated that the prevalence of SD in both sexes was significantly higher among patients with overt hypothyroidism compared to the healthy normal subjects. Those patients with overt hypothyroidism were at 2.26-fold higher risk of SD than the general population. Results from GRADEpro indicated that the rate of events of SD on an average in overt hypothyroidism patients and the healthy individuals were 55.3–24.7%, respectively. Heterogeneity analysis revealed no substantial heterogeneity was found across these 4 studies. Further sensitivity analyses indicated that the quantification of the risk for SD in overt hypothyroidism individuals remained dramatically higher in all of the remaining studies, which suggested that the combined effects presented in this study were stable.

Based on the subgroup analysis, we should also note that women with overt hypothyroidism rather than men with overt hypothyroidism were correlated with a significant higher risk of SD. There are two explanations for this phenomenon. First, only 2 studies were included when separately analyzed with male subjects^{21,24} or female subjects,^{22,23} each of the included study might dominate the overall RR after pooling. We could not judge which independent analysis was more reliable due to the limited eligible studies. Second, the sample size among these studies was variable. For example, in the 2 eligible studies^{21,24} reporting male participants, the sample size ranged from 24 (Krysiak et al's study²⁴) to 164 (Veronelli et al's study²¹), which was considered to be the potential source of the heterogeneity. Therefore, our findings should be interpreted with caution because of the limited eligible studies and the various sample size across any studies.

Different from the case of overt hypothyroidism, synthetic RR from 5 eligible studies reporting subclinical hypothyroidism did not support such a positive association between subclinical hypothyroidism and SD regardless of gender (RR = 1.3, 95% CI: 0.85–1.99, $P = 0.229$). The rate of events of SD in patients with subclinical hypothyroidism and the general population was 43.9–47.0%, respectively. In the subgroup analysis, no significant association between subclinical hypothyroidism and SD was detected in those included studies reporting either males or females (male: RR = 5.0, 95% CI: 0.68–36.66, $P = 0.113$;

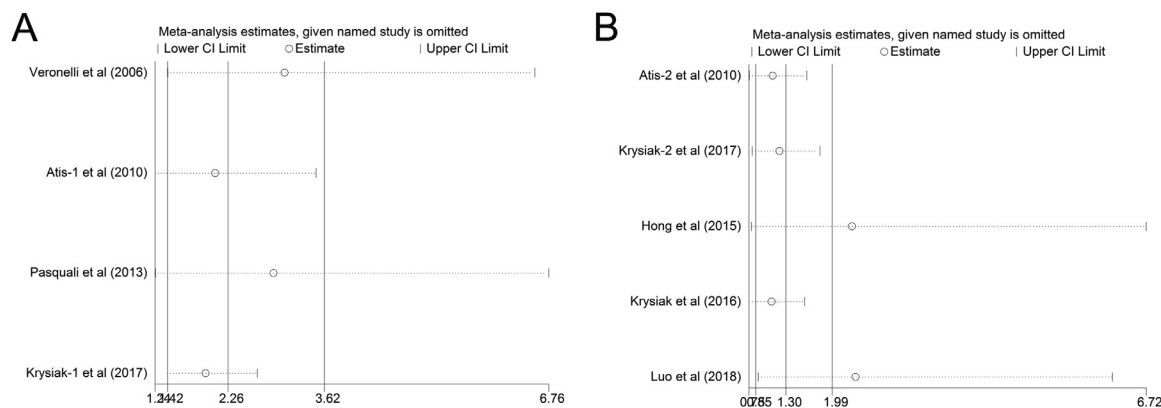


Figure 3. Forest plot for sensitivity analysis.

Table 3. Sensitivity analysis after each study was excluded by turns

Study omitted	RR (95% CI) for remainders, <i>P</i>	Heterogeneity	
		<i>I</i> ²	<i>P</i>
Overt hypothyroidism:			
Veronelli et al (2006) [21]	3.05 (1.42, 6.56), <i>P</i> = 0.004	30.7%	0.236
Atis-1 et al (2010) [22]	2.09 (1.24, 3.50), <i>P</i> = 0.005	34.1%	0.219
Pasquali et al (2013) [23]	2.90 (1.25, 6.76), <i>P</i> = 0.013	53.4%	0.117
Krysiak-1 et al (2017) [24]	1.95 (1.42, 2.68), <i>P</i> < 0.001	0.0%	0.469
Subclinical hypothyroidism:			
Atis-2 et al (2010) [22]	1.10 (0.75, 1.61), <i>P</i> = 0.627	66.7%	0.029
Krysiak-2 et al (2017) [24]	1.20 (0.79, 1.81), <i>P</i> = 0.387	73.3%	0.011
Hong et al (2015) [25]	2.29 (0.78, 6.72), <i>P</i> = 0.131	78.2%	0.003
Krysiak et al (2016) [26]	1.08 (0.75, 1.58), <i>P</i> = 0.673	65.4%	0.034
Luo et al (2018) [27]	2.34 (0.89, 6.21), <i>P</i> = 0.086	75.1%	0.007

CI = confidence interval; RR = relative risk.

female: RR = 1.2, 95% CI: 0.79–1.81, *P* = 0.387). Substantial heterogeneity (*I*² = 71%) was identified across these 5 relevant studies. Different ages of the participants, sample size, study design, geographical area, duration of subclinical hypothyroidism, and varied characteristics of the subjects could all be partly responsible for the substantial heterogeneity in those studies investigating subclinical hypothyroidism. Sensitivity analyses on the subclinical hypothyroidism further confirmed there was no positive relationship between subclinical hypothyroidism and SD (*P* > 0.05 for all). Such analyses yielded negligible changes in the results of RR and the GRADE-profiler indicated a moderate quality of evidence, thereby emphasizing the robustness of our study.

Though overt hypothyroidism is significantly associated with SD in both men and women, the exact mechanism of clinical hypothyroidism on SD is not completely clarified. Some recent studies have shown that several associated factors have been implicated. Hypothyroidism-induced decreased thyroid hormone levels were significantly correlated with female SD. Data from Oppo et al¹⁷ indicated that all FSFI domains, in women with overt hypothyroidism, were closely correlated with serum

FT4 and inversely with serum TSH. In the same study, corresponding therapy could normalize sexual desire, satisfaction, and pain in hypothyroid women. Similarly, Carani et al¹⁵ also demonstrated that half of DE patients with overt hypothyroidism were resolved after thyroid hormone normalization. Hence, hypothyroidism should be excluded in each patient presenting with DE, and if present a corresponding hormone therapy might improve hypothyroidism-induced SD.

Clinical hypothyroidism may cause SD by regulating the hypothalamus–pituitary–thyroid axis. This axis lies in parallel to the hypothalamus–pituitary–gonadal axis. As aforementioned, overt hypothyroidism is characterized by increased TSH and thyrotropin-releasing hormone, which increases the production of prolactin (PRL). Consequent hyperprolactinemia can lead to reduced testosterone by suppressing the mammary expression of GnRH,²⁹ having an indirect effect on ED and the enhancement of dopamine metabolism in specific brain areas having a direct effect on male and female SD.^{30,31} Corona et al³² reported that a severely reduced libido was significantly associated with the higher PRL level. Similarly, the study conducted by Krysiak et al²⁴ also showed that patients with overt

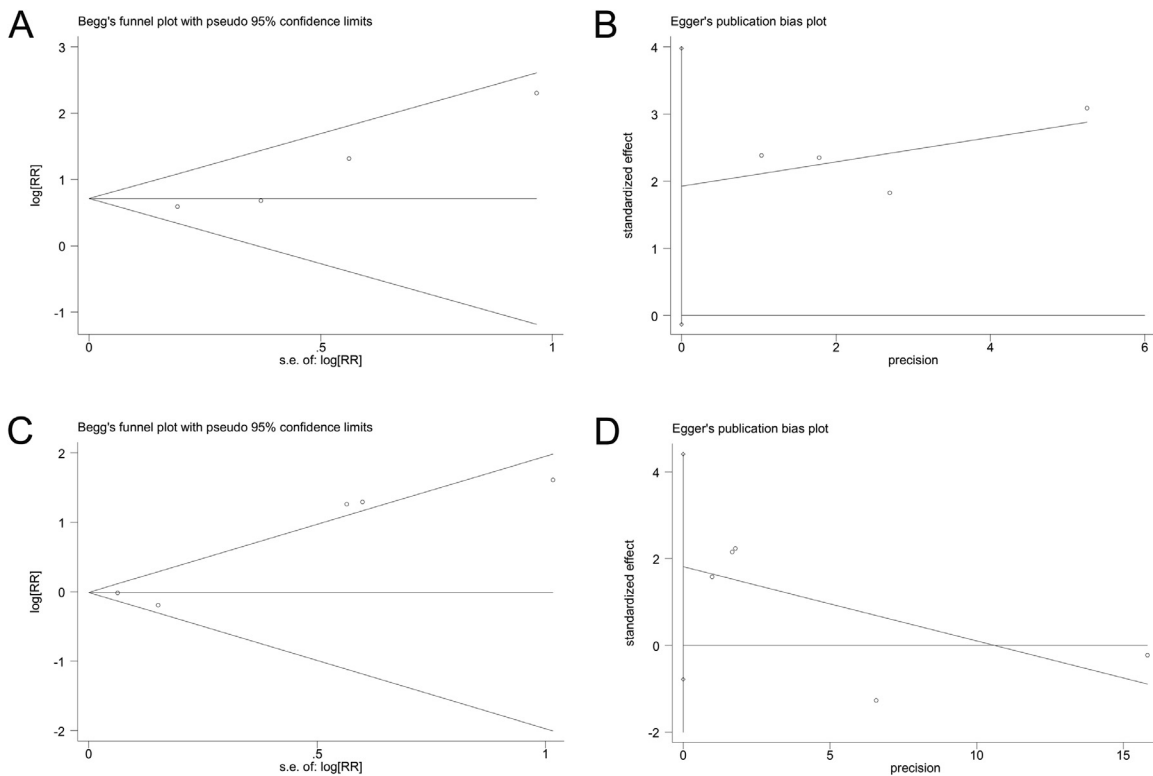


Figure 4. Begg's and Egger's tests to detect publication bias.

hypothyroidism have higher prolactin levels than that of healthy controls, and prolactin levels have a negative association with erection and sexual satiety in men. However, the relationship between hypothyroidism and ED remains controversial. A large study involving 2,146 sample size demonstrated no effect of hyperprolactinemia on ED.³²

Tian et al.³³ demonstrated the expression level of nitric oxide of endothelial was inhibited by elevated TSH. Yildirim et al.³⁴ found that penile smooth muscle in hypothyroid rabbits was less relaxing than control groups.

Also, hypothyroidism-induced atherosclerosis and its complications are important causes for female and male SD. Krysiak et al.⁵ reported that hypothyroidism might decrease blood flow and contributed to the development of female SD by inducing local atherosclerosis. Recent studies also have described a significant association between atherosclerosis and ED.^{35,36} A large study conducted by Park et al.³⁷ found that a lowed FT4 level was significantly associated with a high risk of atherosclerosis in men and women. Another study involving 5,608 subjects showed that antithyroid antibodies are closely associated with chronic inflammation, which causes endothelial dysfunction and atherosclerosis.³⁸ Veronelli et al.³⁹ suggested that the presence of antithyroid antibodies was negatively correlated with the FSFI score. Consequently, hypothyroidism might decrease vaginal, clitoral, and penile engorgement by inducing local atherosclerosis and led to the development of female and male SD.

Moreover, overt hypothyroidism was also associated with depression, irritability, and anxiety, which all undoubtedly contributed to SD in both men and women.^{14,26,40,41} Romero et al.⁴² reported that the prevalence of anxiety in hypothyroid patients was 63–65%, and a higher incidence of thyroid dysfunction has been found in patients with depressive disorders. Krysiak et al.²⁴ demonstrated that the presence of hypothyroidism was significantly associated with depression in males. A large study involving 1,298 middle-aged women conducted by Guimaraes et al.⁴³ also indicated the close relationship between hypothyroidism and depressive symptoms. Siegmann et al.⁴⁰ reported that the prevalence of depression and anxiety is higher in patients with hypothyroidism than those without hypothyroidism. A recent study showed that patients with ED have a higher risk of psychoses and depression than patients without ED.⁴⁴ Another study also reported that the prevalence of patients with major depression has been estimated to be 35–69%.⁴⁵ Hypothyroidism-induced depression causes SD might due to a decrease in brain serotonin content, overactivity in the hypothalamic-pituitary-adrenal axis, and increased secretion of proinflammatory cytokines.²⁴ As a consequence, a screening for SD should be recommended when handling hypothyroidism patients which are accompanied by depression, irritability, and anxiety symptoms. A test for thyroid hormone is advisable in SD patients with these psychological disorder symptoms. Of note, however, there was not consistency in the association between hypothyroidism and depression and anxiety. Yu et al.⁴⁶ demonstrated that hypothyroidism could decrease depression and anxiety symptoms and the

anxiety and depression behaviors were increased in the hypothyroid rats after treatment with levothyroxine.

Furthermore, metabolic syndrome might also have some effects on the association between hypothyroidism and SD. Metabolic syndrome is defined as having at least three of the following conditions: increased fasting blood glucose, abdominal obesity, elevated serum triglycerides, high blood pressure, and low serum high-density lipoprotein. All these conditions have been implicated in the pathogenesis of SD.^{47–49} Numerous studies indicate that there is a close relationship between metabolic syndrome and hypothyroidism regardless of overt or subclinical.^{50–52} Therefore, there might be also an association between hypothyroidism and SD. Udenze et al⁵³ reported that patients with metabolic syndrome had a significantly lower FT3 levels, namely hypothyroidism. And they also observed that those patients were at high risk of hypertension and hyperglycemia, both of which might contribute to the development of SD. A cross-sectional population-based study conducted by Mehran et al⁵⁴ showed that overt hypothyroidism was correlated with the development of abdominal obesity and hypertriglyceridemia, both of which were considered to independently induce SD.⁵⁵ Based on the above evidence, patients with hypothyroidism, especially in those complicating with metabolic syndrome, are at high risk of SD. The comorbidities that is, cardiovascular disease and type 2 diabetes, may play roles in this pathogenesis. However, some investigators even failed to find a significant association between metabolic syndrome and hypothyroidism.⁵⁶ Therefore, more studies are still needed to better illustrate the exact role of metabolic syndrome on the association between hypothyroidism and SD.

In contrast, subclinical hypothyroidism, affecting more women than men, is not related to female sexual dysfunction (FSD). Hong et al²⁵ demonstrated that there was no difference in the total FSFI score and FSD between subclinical hypothyroidism patients and the control group. In line with Hong et al's findings, Luo et al²⁷ also suggested that subclinical hypothyroidism was not the risk factor for FSD in women. In a more previous study, Atis et al²² had an interesting finding. They observed that FSD was significantly higher in women with subclinical hypothyroidism with TSH values over 10 mU/L when compared to the healthy control group of women, while the prevalence of FSD was comparable between subclinical hypothyroidism women with TSH values less than 10 mU/L and the control subjects. Krysiak et al²⁶ failed to observe the elevated circulating prolactin levels and the changed domain FSFI scores in patients with subclinical hypothyroidism. It is known that the thyroid hormone is higher than overt hypothyroidism but lower than normal individuals in subclinical hypothyroidism patients. The reason why subclinical hypothyroidism does not induce FSD might due to the decreased level of thyroxine is not high enough to change the prolactin and to cause depression. However, Atis et al²² reported that a significant percentage of women with subclinical

hypothyroidism had SD. So far, the association between subclinical hypothyroidism and FSD is still unclear. It needs more studies to explore this association. For male subjects, studies that investigated the relationship between subclinical hypothyroidism and SD in men are scarce. The reasons why no positive association between subclinical hypothyroidism and male SD are similar to that in female subjects, referring to the disease degree. Subclinical hypothyroidism did not significantly affect the clinical symptoms, circulating gonadal hormone levels, and psychological states of the sufferers, thereby yielding negligible changes in the sexual functioning of men. This undiscovered topic of the association between subclinical hypothyroidism and male SD is waiting for more investigators to explore it.

To our knowledge, this is the first study to have shown that the association between overt hypothyroidism and the risk of SD in both sexes. In addition, we also found that lack of association between subclinical hypothyroidism and SD in both genders. However, several inherent limitations in this meta-analysis must be acknowledged when interpreting of our results. First, though no statistical heterogeneity was observed in the included studies that investigated the overt hypothyroidism ($I^2 = 30\%$), substantial heterogeneity was detected in those studies reporting subclinical hypothyroidism ($I^2 = 71\%$). Substantial heterogeneity among these studies might be related to the basis of methodological (i.e., study design, inclusion and exclusion criteria, assessment for SD) and clinical variation (i.e., mean age, sample size, geographic location, disease duration/severity, and comorbidities). Second, all the 7 included studies were observational designed, suggesting that the direction of causality between overt/substantial hypothyroidism and the potential risk of SD must be interpreted with caution. Third, in the current study, we did not further analyze the female and male subjects separately by reason of only 2 included studies reporting the male individuals which may induce great heterogeneity and bias. Fourth, the results from this meta-analysis are based on the limited included studies and small sample of participants. Given the above limitations, further well-designed cohorts with large sample are still warranted to better illuminate the relationship between overt/substantial hypothyroidism and the sexual functioning in both sexes.

CONCLUSIONS

In alignment with clinical observations, this study empirically indicated that overt hypothyroidism and the risk of SD in both sexes are associated, while no positive association between subclinical hypothyroidism and SD was found. Our study reminds the clinicians that should be aware of the detrimental effects on sexual functioning developed by overt hypothyroidism in clinical practice. Based on the current evidence, though subclinical hypothyroidism is limited to impairing sexual function, more studies are still needed to validate it.

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STATEMENT OF AUTHORSHIP

Author Contributions: Conceptualization, M.S. and S.Z.; methodology, X.L. and Z.Z.; software, W.Y.; validation, M.S. and S.Z.; formal analysis, R.D. and X.M.; investigation, W.X.; writing—original draft preparation, M.S. and S.Z.; writing—review and editing, M.L. and J.C. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIALS

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