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Lack of associations between thyroid dysfunction and obstructive sleep apnea-hypopnea syndrome
A meta-analysis

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Abstract

Background: Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a comprehensive syndrome with endocrine and metabolic complications. This review aims to explore the correlation between thyroid hormone levels and the severity of OSAHS in patients.

Methods: The protocol for this meta-analysis has been registered on PROSPERO. Searches were carried out from the inception of the databases to July 18, 2023, utilizing 6 databases (PubMed, CNKI, EMBASE, Web of Science, Cochrane Library, China Biology Medicine, and Wanfang). Standardized mean difference (SMD) and correlation coefficients were used as the effect size measures. Additionally, random effects or fixed effects models were used for pooled analysis. Moreover, data were statistically evaluated with the help of STATA 11.0 and R 4.1.3.

Results: This study included 23 articles that satisfied the pre-defined criteria. The prevalence of hypothyroidism and subclinical hypothyroidism in OSAHS patients was 6% and 8%, whereas hyperthyroidism had a prevalence of 2%. Moreover, thyroid hormone levels in OSAHS individuals exhibited no significant difference relative to healthy subjects. Subgroup analysis based on disease severity also established no significant changes in thyroid hormone levels between OSAHS individuals and controls. There was no significant correlation between the Apnea-Hypopnea Index (AHI) and free triiodothyronine (FT3), serum thyroid stimulating hormone (TSH), and free thyroxine (FT4) levels.

Conclusion: The prevalence of thyroid dysfunction is relatively low in OSAHS individuals. Thyroid hormone levels show no significant difference between OSAHS patients and healthy subjects. Furthermore, there is no significant correlation between AHI and serum TSH, FT3, and FT4 levels. Based on existing data, the relationship between OSAHS and thyroid function remains controversial, and further in-depth research is warranted to validate the connection and elucidate the underlying mechanisms.

Abbreviations: AHI = apnea-hypopnea index, FT3 = free triiodothyronine, FT4 = free thyroxine, OSAHS = obstructive sleep apnea-hypopnea syndrome, SMD = standard mean difference, TSH = thyroid stimulating hormone.

Keywords: meta-analysis, obstructive sleep apnea-hypopnea syndrome, thyroid dysfunction, thyroid hormone, thyroid stimulating hormone

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a prevalent sleep disorder marked by recurrent, partial, or complete episodes of breathing pauses owing to an obstruction of the upper airway during sleep, thereby causing intermittent low blood oxygen saturation.[1,2] Globally, there are close to one billion individuals with OSAHS, with China having the highest number, followed by the United States, Brazil, and other countries.[3] Recent data depict the prevalence of moderate to severe OSAHS as 49.7% in males and 23.4% in females, with an apnea-hypopnea index (AHI) of 15 events every hour as the standard.[4–6] Typical clinical symptoms of OSAHS include recurrent sudden awakenings, morning headaches, increased nocturia, snoring during sleep, and daytime sleepiness.[7] Nevertheless, individuals often overlook these symptoms and lack effective time management techniques. OSAHS is also a comprehensive syndrome related to endocrine and metabolic complications,

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The datasets generated during and/or analyzed during the current study are publicly available.

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thereby severely impacting the survival and quality of life for individuals with OSAHS. Previous studies have shown that OSAHS is a significant independent factor for hypertension, diabetes, dyslipidemia, coronary heart disease and other diseases.[8,9]

Being a primary hormone, thyroid hormones contribute immensely to metabolism, development, and growth.[10] The maintenance of normal human thyroid function relies on mediating the rate of thyroid hormone secretion as well as the delicate interactions between different metabolic procedures that the hormones undergo in peripheral tissues.[11] Some researchers also suggest that OSAHS may influence the hypothalamic-pituitary-adrenal axis due to intermittent hypoxia and sleep disturbances.[12] Furthermore, research has demonstrated that OSAHS can elevate the incidence of hypothyroidism, whereas hypothyroidism can also elevate the incidence of OSAHS.[13–17] Hypothyroidism is believed to induce sleep-breathing disorders through various hypothetical mechanisms. This includes obesity due to decreased basal metabolic rate, pharyngeal stenosis due to submucosal glycosaminoglycan deposition, pharyngeal dilator muscle dysfunction, and central respiratory depression.[18] During conditions such as stroke, myocardial infarction, sepsis, or trauma, individuals commonly experience hypoxia, leading to changes in thyroid hormone metabolism.[19–21] Hypoxia can result in reduced levels of circulating triiodothyronine, known as the nonthyroidal illness syndrome, which is closely associated with the prognosis of cardiovascular and cerebrovascular diseases.[22–27] However, chronic intermittent hypoxia caused by OSAHS differs from sustained hypoxia. Additionally, there is evidence suggesting a relationship between OSAHS and thyroid cancer.[28] Nevertheless, certain studies have established that OSAHS is not related to thyroid function.[29,30] While other studies have reported opposite results.[31,32] In conclusion, the link between OSAHS and thyroid function is yet to be comprehended, and the specific mechanisms underlying their association have not been fully elucidated so far.

In order to further elucidate the link between OSAHS and thyroid function, a meta-analysis was conducted to assess the variations in thyroid function in the non-OSAHS group versus the OSAHS group. As per the existing literature, this meta-analysis incorporates the most accessible literature studies. Additionally, for the first time, this study performed a combined analysis of the correlation coefficients between AHI and free triiodothyronine (FT3), serum thyroid stimulating hormone (TSH), and free thyroxine (FT4), aiming to better understand the link between OSAHS and thyroid function.

2. Materials and Methods

2.1. Database retrieval and literature selection

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines,[33] a rigorous review and meta-analysis of the included literature were carried out. The databases Web of Science, PubMed, and EMBASE were systematically searched for published articles on the link between OSAHS and thyroid function, both locally and internationally. Chinese articles were searched in the Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, and China Biology Medicine (CBM) Database. The search was conducted using MeSH terms and keyword combinations. These search terms were used: ("sleep apnea" OR "obstructive sleep apnea syndrome" OR "nocturnal hypoxia" OR "sleep apnea, obstructive" OR "OSA" OR "syndrome, obstructive sleep apnea" OR "nocturnal hypoxemia" OR "obstructive sleep apnea" OR "obstructive sleep apnea") AND ("thyroid function" OR "FT4" OR "FT3" OR "TPOAb" OR "TSH" OR "TgAb" OR "thyroid gland function tests"). Articles published before July 15, 2023 were included in the database search. Additionally, the reference lists of relevant publications were reviewed to detect any potentially missing studies. Finally, this meta-analysis was registered on https://www.crd.york.ac.uk/PROSPERO/ with the registration number CRD42023446676.

2.2. Inclusion and exclusion criteria

Two researchers independently screened publications with the help of the citation management system EndNote 20. After initially screening potential articles as per titles and abstracts, the full texts were read to ascertain their final inclusion or exclusion. We performed our meta-analysis based on PICOS (participants, interventions, controls, outcomes and studies) rules.

- Participants: all patients with OSAHS.
- Interventions: Thyroid hormone levels were carried out by chemiluminescence method or other accepted methods.
- Controls: all controls were reported controls that had no obvious respiratory diseases.
- Outcomes: all participants were clearly reported the status of thyroid hormone levels, including TSH, FT3, FT4, TT3, TT4, anti-TPO, anti-Tg.
- Studies: all studies were case-control, cross-sectional study, or cohort studies.

The disease incidence and severity were quantified using the respiratory disturbance index, AHI, and clinical diagnosis of OSAHS, indicated by the International Classification of Diseases (ICD) diagnostic codes. OSAHS severity was quantified with the help of conventional criteria. Subjects were diagnosed with OSAHS according to polysomnography (PSG) criteria (adults: AHI ≥ 5/h; children: AHI ≥ 1/h).[34] Conference abstracts, academic papers, and other types of gray literature that met the above criteria were also included. However, reviews, animal experiments, letters, and case reports were excluded from the analysis.

2.3. Data extraction

Data were extracted from each publication by 3 researchers, followed by standardization into a common electronic spreadsheet format. Moreover, the extracted data constituted all relevant information, such as the first author name, sample size, publication year, study design type, exposures and interventions, statistical techniques, control variables, and thyroid function measurement items.

2.4. Literature quality assessment

The methodological quality of the included literature was ascertained using the Cross-Sectional Study Quality Assessment Tool recommended by the Agency for Healthcare Research and Quality (AHRQ).[35] Each item was assigned a "0" if the answer was "No" or "Unclear," and a "1" if the answer was "Yes." The quality rating of the articles was categorized as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11. As for case-control and cohort studies, the Newcastle-Ottawa Scale[36] was used for evaluation, including 3 categories: selection of study groups (4 items, total score 4), comparability of groups (3 items, total score 3), and assessment of outcome/exposure (2 items, total score 2). Studies were classified as high quality (total score 7–9), moderate quality (total score 4–6), or low quality (total score 0–3).

2.5. Ethical review

Meta-analyses are a form of research that analyses previous research data without requiring ethical approval.

2.6. Statistical analysis

The data were collected, summarized, and analyzed with the aid of Stata software (11.0) and R software (ver. 4.1.3).

Normalization was applied for continuous variables, and they were expressed as Standardized Mean Differences (SMDs) with a confidence of 95% (95% CI). The connections between AHI in patients with OSAHS and TSH/FT3/FT4 were explored in this study by employing Spearman Coefficients of Correlation (CORs). The standard error, which depends on the significance of the rank COR, shows that Spearman product-moment COR is independent of the distribution of the sample. Resultantly, every COR value was compared with a Fisher transformation. An analysis was carried out wherein transformed values were applied as input, and the CORs were reconverted. Furthermore, the correlation of AHI with TSH/FT3/FT4 was evaluated with the aid of Pearson COR. Several papers have established an approach for transforming Pearson COR to Spearman COR with the help of the given formula:

$$r_s = \frac{6}{\pi}\sin^{-1}\frac{r}{2}$$

Herein Spearman CORs and Pearson CORs are represented by r_s and r, respectively.[37] The heterogeneity of the data was determined with the help of chi-square tests and Cochran Q tests. $I^2 \geq 50\%$ and $I^2 < 50\%$ indicated a high and low heterogeneity across various studies, respectively. Where the studies showed no heterogeneity, the random- and fixed-effects models were employed. To carry out subgroup analyses, the overall population was segregated into groups according to severity. Additionally, 1 study was eliminated at a time to observe the influence of every study on the overall effect size as part of the sensitivity analysis. Egger tests aided the detection of any publication bias.

3. Results

3.1. Literature search and inclusion

Overall, 1058 relevant studies were retrieved from the databases. After removing duplicates, 367 studies were further screened. Following this, 647 studies were found to be irrelevant publications based on abstracts and titles and, thus, were discarded. Hence, only 44 studies remained. The inclusion and exclusion criteria aided the exclusion of another 21 publications. Concerning the remaining literature, included 8 reviews, 4 letters to the editor, 5 studies with unavailable data, and 4 animal studies. Hence, 23 publications[12,31,32,38–57] were selected for the meta-analysis. Among them, 12 articles demonstrated the prevalence of hypothyroidism in OSAHS, 5 articles reported the prevalence of subclinical hypothyroidism in OSAHS, and 3 articles reported the prevalence of hyperthyroidism in OSAHS. Additionally, 14 articles compared the differences in thyroid function between OSAHS patients and healthy controls. Thyroid function indicators included TSH, FT3, FT4, Total-triiodothyronine (TT3), Total thyroxine (TT4), anti-thyroid peroxidase (anti-TPO), and anti-thyroid globulin (anti-Tg). Furthermore, 6 articles reported the correlation between AHI and TSH, 6 articles reported the correlation between AHI and FT3, and 6 articles reported the correlation between AHI and FT4. The literature screening procedure is illustrated in Figure 1. Table 1 and Table 2 gives the basic information on the findings of the literature that was included.

3.2. Prevalence of hypothyroidism in OSAHS patients

A total of 12 studies mentioned the number of OSAHS individuals with hypothyroidism. Therefore, a meta-analysis was carried out on these studies involving 3023 individuals with OSAHS and 182 hypothyroidism-positive individuals. The findings of this meta-analysis revealed that the overall prevalence of hypothyroidism in individuals with OSAHS was around 6% (95% CI, 0.04–0.08, $P < .001$, Figure 2A).

3.3. Prevalence of subclinical hypothyroidism in OSAHS patients

Five studies mentioned the number of OSAHS individuals with subclinical hypothyroidism. These studies included 797 OSAHS patients and 59 subclinical hypothyroidism-positive individuals. A meta-analysis was carried out using these articles, and the results established that the overall prevalence of subclinical hypothyroidism in individuals with OSAHS was 7% (95% CI, 0.03–0.12, $P = .002$, Figure 2B).

3.4. Prevalence of hyperthyroidism in OSAHS patients

Three studies mentioned the number of OSAHS individuals with hyperthyroidism. These studies included 1212 OSAHS patients and 37 hyperthyroidism-positive individuals. A meta-analysis of these articles was subsequently carried out, and the findings revealed the overall prevalence of hyperthyroidism in individuals with OSAHS as 2% (95% CI, 0.001–0.048, $P = .01$, Figure 2C).

3.5. Difference in TSH Levels in individuals with OSAHS versus healthy subjects

In total, 14 studies reported data on serum TSH levels in individuals with OSAHS versus healthy subjects. The meta-analysis established no significant variation in serum TSH in OSAHS individuals versus healthy subjects (SMD = –0.01, 95% CI, –0.14 to 0.12, $P = .873$)(Fig. 3A). Following this, subgroup analysis was carried out as per the disease severity parameter (AHI value) to investigate the influence of disease severity on serum TSH levels in patients. However, the results of the subgroup analysis (at 95% CI for all groups) indicated no significant variation in serum TSH among the mild group (SMD = –0.11, CI –0.24 to 0.06, $P = .214$) (Fig. 3A), moderate group (SMD = –0.03, CI –0.21 to 0.14, $P = .702$), severe group (SMD = 0.08, CI –0.08 to 0.25, $P = .323$) (Fig. 3A), and mixed group (SMD = 0.06, CI –0.41 to 0.53, $P = .808$) (Fig. 3A).

3.6. Difference in FT3 levels in individuals with OSAHS versus healthy subjects

In total, 13 studies reported data on serum FT3 levels in individuals with OSAHS versus healthy subjects. The meta-analysis revealed no significant variation in serum FT3 in OSAHS individuals versus healthy subjects (SMD = 0.09, 95% CI, –0.04 to 0.23, $P = .163$) (Fig. 3B). Subgroup analysis (at 95% CI for all groups) based on disease severity was also performed. The findings of this analysis established no significant variation in serum FT3 levels among the mild group (SMD = –0.11, CI –0.24 to 0.03, $P = .115$) (Fig. 3B), moderate group (SMD = 0.08, CI –0.16 to 0.32, $P = .520$), severe group (SMD = 0.13, CI –0.07 to 0.34, $P = .211$), and mixed group (SMD = 0.09, CI –0.04 to 0.23, $P = .209$) (Fig. 3B).

3.7. Difference in FT4 levels in individuals with OSAHS versus healthy subjects

In total, 14 studies reported data on serum FT4 levels in individuals with OSAHS versus healthy subjects. Overall, OSAHS individuals had elevated serum TT4 levels relative to healthy subjects (SMD = –0.18, 95% CI, –0.33 to –0.02, $P = .025$) (Fig. 3C). Subgroup analysis (at 95% CI for all groups) based on disease severity depicted no significant variation in serum FT4 levels in OSAHS individuals versus healthy subjects in the mild group (SMD = –0.19, CI –0.43 to 0.05, $P = .124$), moderate group (SMD = –0.22, CI –0.50 to 0.07, $P = .135$), severe group (SMD = –0.12, CI –0.49 to 0.26, $P = .540$), and mixed group (SMD = –0.18, CI –0.54 to 0.17, $P = .307$) (Fig. 3C).

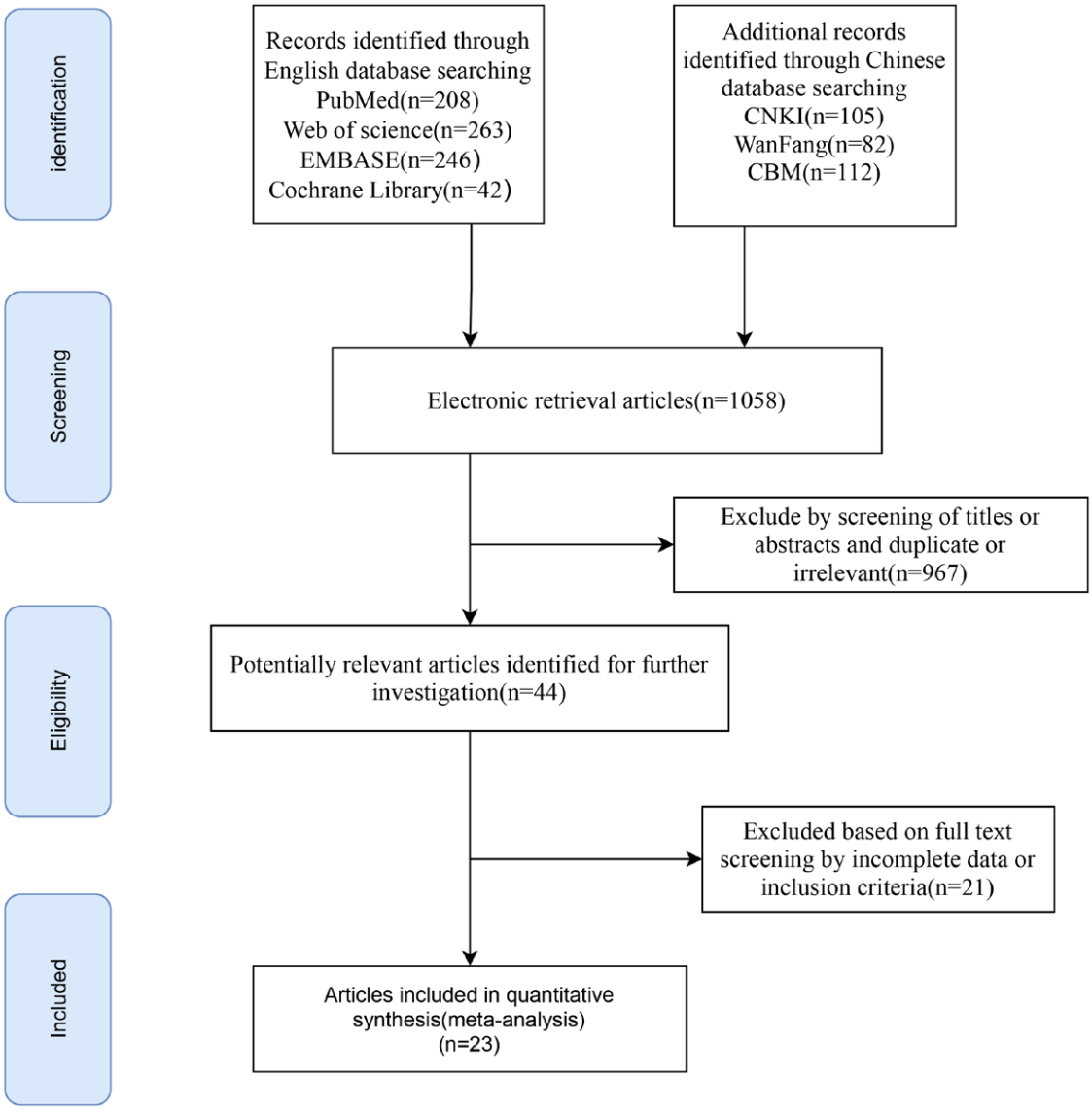

Figure 1. Literature screening flow chart.

3.8. Difference in TT3 levels between OSAHS patients and healthy controls

Two studies published data on serum TT3 levels in individuals with OSAHS versus healthy subjects. Overall, no significant variation was observed in serum TT3 levels in OSAHS individuals versus healthy subjects (SMD = −0.03, 95% CI, −0.15 to 0.08, $P = .558$) (Fig. 3D). Subgroup analysis (at 95% CI for all groups) based on disease severity also reported no significant variation in serum TT3 levels in OSAHS individuals versus healthy subjects in the moderate group (SMD = −0.09, CI −0.27 to 0.10, $P = .366$) and severe group (SMD = −0.01, CI −0.19 to 0.17, $P = .907$) (Fig. 3D).

3.9. Difference in TT4 levels between OSAHS patients and healthy controls

Two studies revealed data on serum TT4 levels in individuals with OSAHS versus healthy subjects. Overall, OSAHS individuals had elevated serum TT4 levels relative to healthy subjects (SMD = −0.03, 95% CI, −0.15 to 0.08, $P = .014$) (Fig. 3E). Subgroup analysis (at 95% CI for all groups) based on disease severity established no significant variation in serum TT4 levels in OSAHS individuals versus healthy controls in the moderate group (SMD = −0.42, CI −0.97 to 0.12, $P = .130$) and severe group (SMD = −0.26, CI −0.61 to 0.09, $P = .149$) (Fig. 3E).

3.10. Difference in anti-TPO (thyroid peroxidase) levels between OSAHS patients and healthy controls

Two studies published data on serum anti-TPO levels in individuals with OSAHS versus healthy subjects. Nevertheless, no significant variation was detected in serum anti-TPO in OSAHS individuals versus healthy subjects (SMD = 0.01, 95% CI, −0.30 to 0.33, $P = .939$) (Fig. 4A). Subgroup analysis based on disease severity revealed no significant variation in serum anti-TPO levels in individuals with OSAHS versus healthy subjects in the moderate group (SMD = 0.20, CI −0.08 to 0.48, $P = .168$) and severe group (SMD = −0.02, CI −0.71 to 0.66, $P = .947$) (Fig. 4A).

3.11. Difference in anti-Tg levels in individuals with OSAHS versus healthy subjects

Two studies provided data on serum anti-Tg levels in individuals with OSAHS versus healthy subjects. No significant

Table 1

Characteristics of included studies.

First author	Yr	Study design	Sample size		Country	Sample type	Mean age (yr)		AHRQ/NOS	Thyroid hormone indicators (Case vs Control)	Mean BMI (kg/m^2)	
			Case	Control			Case	Control			Case	Control
Bahammam SA	2011[38]	Cohort study	271	76	Saudi Arabia	Serum	48.7	40.8	NOS (7)	TSH, FT4	37.7	33.7
Bielicki P	2016[39]	Cohort study	813	NA	Poland	Serum	54.3	NA	NOS (5)	NA	33.1	NA
Kapur VK	1998[40]	Cross-sectional study	336	NA	USA	Serum	>18	NA	AHRQ (7)	NA	NA	NA
Lin CC	1992[41]	Cohort study	65	NA	China	Serum	48.5	NA	NOS (5)	NA	NA	NA
Miller CM (female)	2003[42]	Cohort study	118	NA	USA	Serum	55.3	NA	NOS (7)	NA	36.5	NA
Ozcan KM	2014[43]	Cohort study	203	NA	Turkey	Serum	49.95	NA	NOS (6)	NA	30.7	NA
Takeuchi S	2014[44]	Case-control study	147	9	Japan		52.9	53.6	NOS (7)	TSH, FT3, FT4	27.1	26.8
Wang L(male)	2022[45]	Cross-sectional study	400	NA	China	Serum	43.53	NA	AHRQ (8)	NA	30.78	NA
Wang L(female)	2022[45]	Cross-sectional study	173	NA	China	Serum	43.21	NA	AHRQ (8)	NA	33.99	NA
Resta O	2004[46]	Cross-sectional study	78	NA	Italy	Serum	50.3	NA	AHRQ (7)	NA	36.2	NA
Mete Ta	2013[12]	Cross-sectional study	50	32	Turkey	Serum	46.58	46.94	AHRQ (8)	TSH, FT3, FT4, anti-TPO, anti-Tg	32.21	32.02
Mete Tb	2013[12]	Cross-sectional study	50	32	Turkey	Serum	47.64	46.94	AHRQ (8)	TSH, FT3, FT4, anti-TPO, anti-Tg	32.79	32.02
Mete Tc	2013[12]	Cross-sectional study	50	32	Turkey	Serum	47.4	46.94	AHRQ (8)	TSH, FT3, FT4, anti-TPO, anti-Tg	33.68	32.02
Sakellaropoulou AV	2011[11]	Cohort study	44	NA	Greece	Serum	7.8	NA	NOS (8)	NA	18.2	NA
Bruyneel M	2019[49]	Cohort study	280	NA	Belgium	Serum	56.4	NA	NOS (8)	NA	32.8	NA
Li N	2016[31]	Cross-sectional study	373	144	China	Serum	45.69	42.39	AHRQ (8)	TSH, FT3, TT3, TT4, FT4	28.3	26.62
Winkelman JW	1996[48]	Cohort study	243		USA	Serum	43.9	NA	NOS (6)	NA	NA	NA
Shi Y (elderly population)	2023[32]	Case-control study	686	52	China	Serum	42.1	38.92	NOS (8)	TSH, FT3, FT4, TT3, TT4, anti-TPO, anti-Tg	28.5	26.96
Shi Y (non-elderly population)	2023[32]	Case-control study	107	8	China	Serum	67.35	65.88	NOS (8)	TSH, FT3, FT4, TT3, TT4, anti-TPO, anti-Tg	26.7	28.09
Zheng YW (obesity)	2020[50]	Case-control study	50	50	China	Serum	55.32	51.94	NOS (6)	TSH, FT3, FT4	30.85	30.12
Zheng YW (non-obesity)	2020[50]	Case-control study	50	50	China	Serum	52.02	52.83	NOS (6)	TSH, FT3, FT4	21.52	23.77
Huang ZQa	2020[51]	Case-control study	29	36	China	Serum	63.45	65.06	NOS (6)	TSH, FT3, FT4	26.45	25.45
Huang ZQb	2020[51]	Case-control study	30	36	China	Serum	64.37	65.06	NOS (6)	TSH, FT3, FT4	27.01	25.45
Huang ZQc	2020[51]	Case-control study	30	36	China	Serum	64.53	65.06	NOS (6)	TSH, FT3, FT4	29.95	25.45
Wu YH	2010[52]	Case-control study	33	30	China	Serum	47.1	46.3	NOS (5)	TSH, FT3, FT4	NA	NA
Zhang XQa	2017[53]	Case-control study	56	110	China	Serum	48.06	45.98	NOS (6)	TSH, FT3, FT4	27.45	26.89
Zhang XQb	2017[53]	Case-control study	47	110	China	Serum	46.03	45.98	NOS (6)	TSH, FT3, FT4	28.38	26.89
Zhang XQc	2017[53]	Case-control study	49	110	China	Serum	46.47	45.98	NOS (6)	TSH, FT3, FT4	29.72	26.89
Bozkurt NCa	2012[54]	Cross-sectional study	59	59	Turkey	Serum	47.3	44	AHRQ (8)	TSH, FT3, FT4	28.8	27
Bozkurt NCb	2012[54]	Cross-sectional study	61	59	Turkey	Serum	47.9	44	AHRQ (8)	TSH, FT3, FT4	30.5	27
Bozkurt NCc	2012[54]	Cross-sectional study	66	59	Turkey	Serum	47.9	44	AHRQ (8)	TSH, FT3, FT4	33.6	27
Feng HW	2015[55]	Case-control study	35	35	China	Serum	6.47	6.81	NOS (7)	TSH, FT3, FT4	22.58	22.49
Sriphrapradang Ca	2019[56]	Cross-sectional study	74	48	Thailand	Serum	53.8	49.5	AHRQ (9)	TSH, FT3, FT4	28.3	26
Sriphrapradang Cb	2019[56]	Cross-sectional study	43	48	Thailand	Serum	54.8	49.5	AHRQ (9)	TSH, FT3, FT4	27.8	26
Sriphrapradang Cc	2019[56]	Cross-sectional study	23	48	Thailand	Serum	52.4	49.5	AHRQ (9)	TSH, FT3, FT4	33	26
Zhang M(obesity)	2012[57]	Case-control study	30	30	China	Serum	43.35	39.87	NOS (7)	TSH, FT3, FT4	30.06	31.22
Zhang M(non-obesity)	2012[57]	Case-control study	10	10	China	Serum	44.02	41.23	NOS (7)	TSH, FT3, FT4	24.18	25.37

a = mild, AHRQ = Agency for Healthcare Research and Quality, anti-Tg = anti-thyroid globulin, anti-TPO = anti-thyroid peroxidase, b = moderate, c = severe, NA = not available, NOS = Newcastle-Ottawa Scale.

Table 2

The number of hypothyroidism, subclinical hypothyroidism and Hyperthyroidism.

First author	Yr	Hypothyroidism (n)	Subclinical hypothyroidism (n)	Hyperthyroidism (n)	Pearson/Spearman correlation coefficients
Bahammam SA (male)	2011[38]	6	13	NA	NA
Bahammam SA (female)	2011[38]	21	14	NA	NA
Bielicki P	2016[39]	38	NA	31	NA
Kapur VK	1998[40]	17	NA	NA	NA
Lin CC	1992[41]	2	NA	NA	NA
Miller CM (female)	2003[42]	11	NA	NA	NA
Ozcan KM	2014[43]	26	22	NA	NA
Takeuchi S	2014[44]	3	1	0	R1 = 0.131, R2 = 0.073, R3 = −0.128
Wang L(male)	2022[45]	16	NA	NA	NA
Wang L(female)	2022[45]	11	NA	NA	NA
Resta O	2004[46]	9	NA	NA	NA
Mete T	2013[12]	13	6	NA	R1 = −0.047
Sakellaropoulou AV	2011[11]	5	3	NA	NA
Winkelman JW	1996[48]	4	NA	6	NA
Bruyneel M	2019[49]	NA	NA	NA	R1 = 0.065, R3 = −0.06
Li N	2016[31]	NA	NA	NA	R1 = 0.104
Shi Y (non-elderly)	2023[32]	NA	NA	NA	R1 = 0.01, R2 = 0.294, R3 = 0.054
Shi Y(elderly)	2023[32]	NA	NA	NA	R1 = 0.122, R2 = 0.061, R3 = −0.139

NA = not applicable, R1 = correlation coefficient between AHI and TSH, R2 = correlation coefficient between AHI and FT3, R3 = correlation coefficient between AHI and FT4.

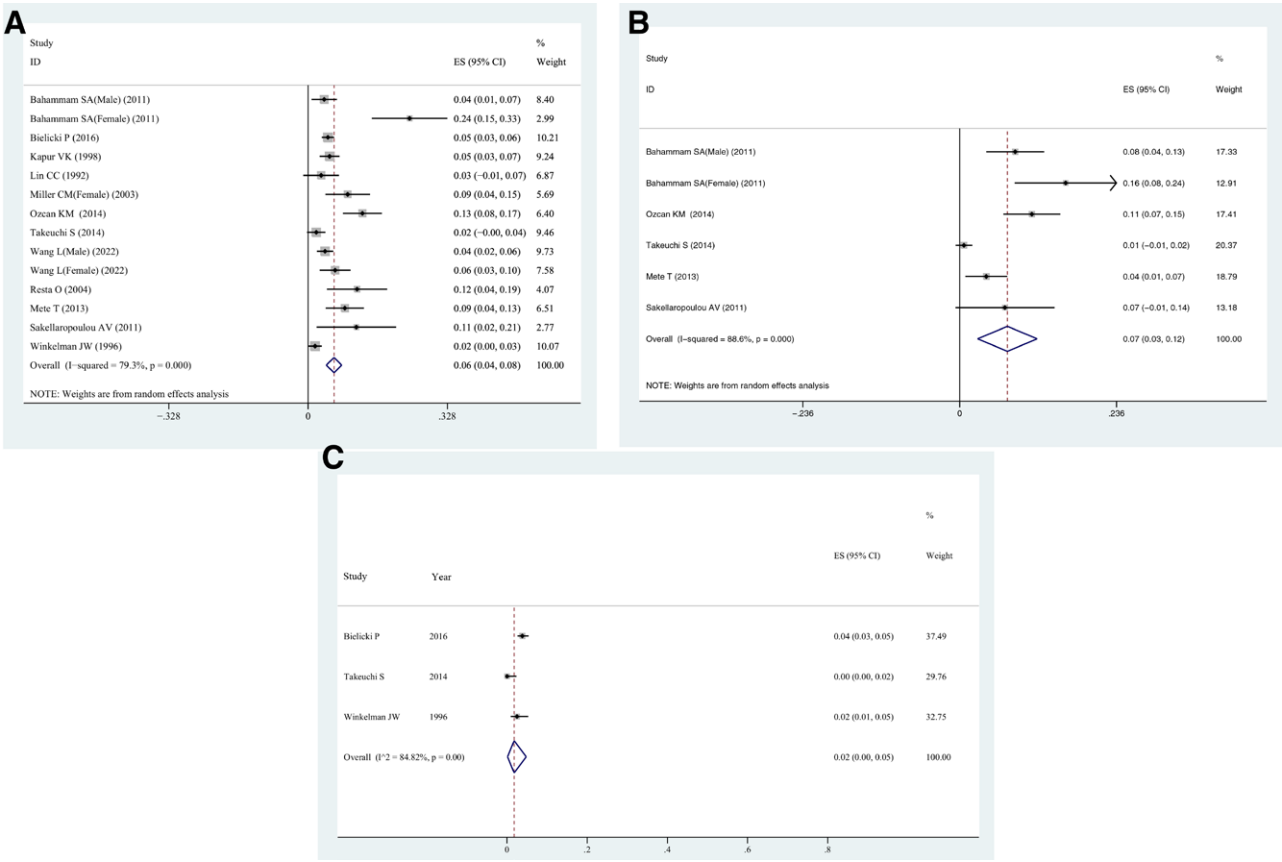

Figure 2. The incidence rate for thyroid dysfunction in patients with OSAHS. (A) hypothyroidism, (B) subclinical hypothyroidism, (C) hyperthyroidism. OSAHS = obstructive sleep apnea-hypopnea syndrome.

variation was observed in serum anti-Tg levels in OSAHS individuals versus healthy subjects (SMD = −0.04, 95% CI, −0.21 to 0.13, $P = .619$) (Fig. 4B). Furthermore, subgroup analysis based on disease severity revealed no significant variation in serum anti-Tg levels in OSAHS individuals versus healthy subjects in the moderate group (SMD = 0.10, CI −0.23 to 0.44, $P = .552$) and severe group (SMD = −0.14, CI −0.37 to 0.08, $P = .217$) (Fig. 4B).

3.12. Sensitivity analysis and publication bias

No studies were revealed by the sensitivity analysis to have potential heterogeneity sources. Moreover, publication bias was evaluated with the help of the Egger test, based on which (TSH: $P = .458$, FT3: $P = .536$, FT4: $P = .05$, TT3: $P = .056$, TT4: $P = .103$, anti-TPO: $P = .717$, anti-Tg: $P = .328$) (Figure 5A,B,C,D,E,F,G). The meta-analysis was deemed as not significantly affected by publication bias.

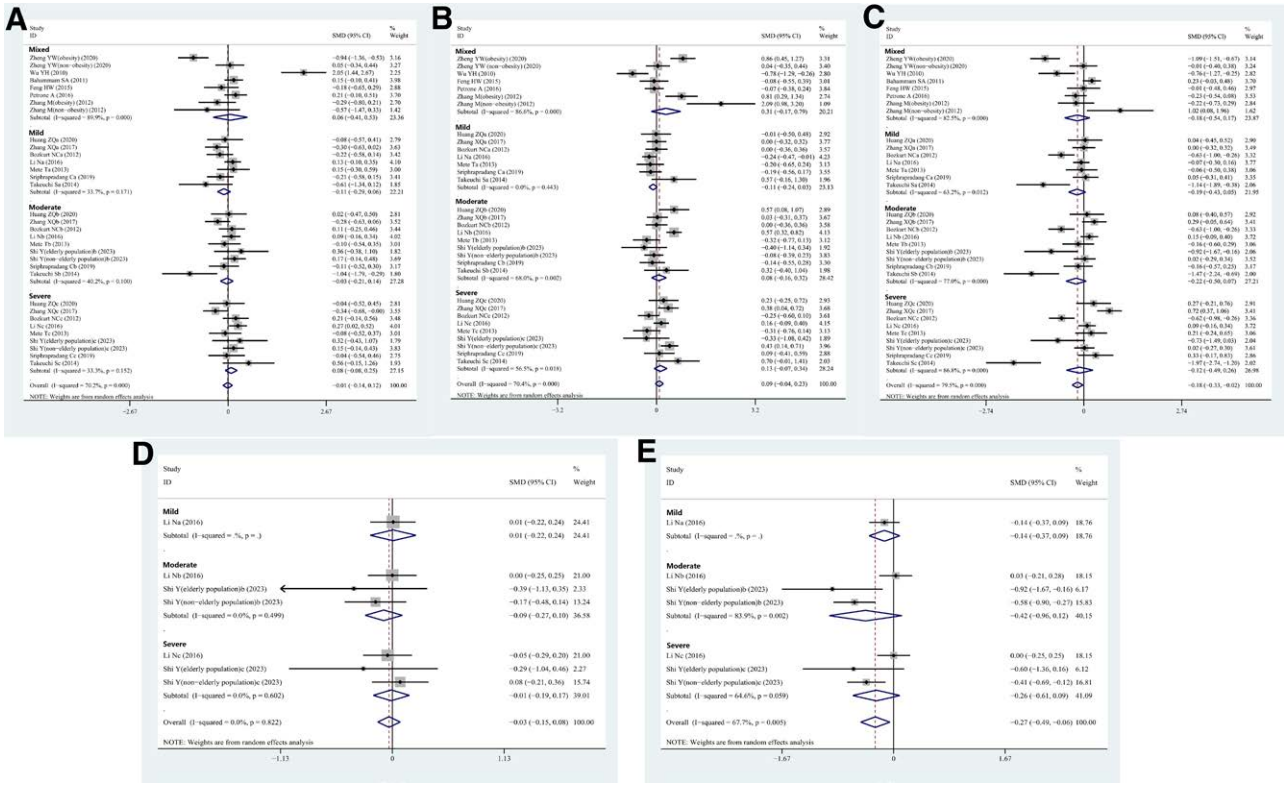

Figure 3. Forest plot of comparison of thyroid hormone between OSAHS and controls. (A) TSH, (B): FT3, (C): FT4, (D): TT3, (E): TT4. anti-Tg = anti-thyroid globulin, anti-TPO = anti-thyroid peroxidase, FT3 = free triiodothyronine, FT4 = free thyroxine, TSH = thyroid stimulating hormone, TT3 = total-triiodothyronine, TT4 = total thyroxine.

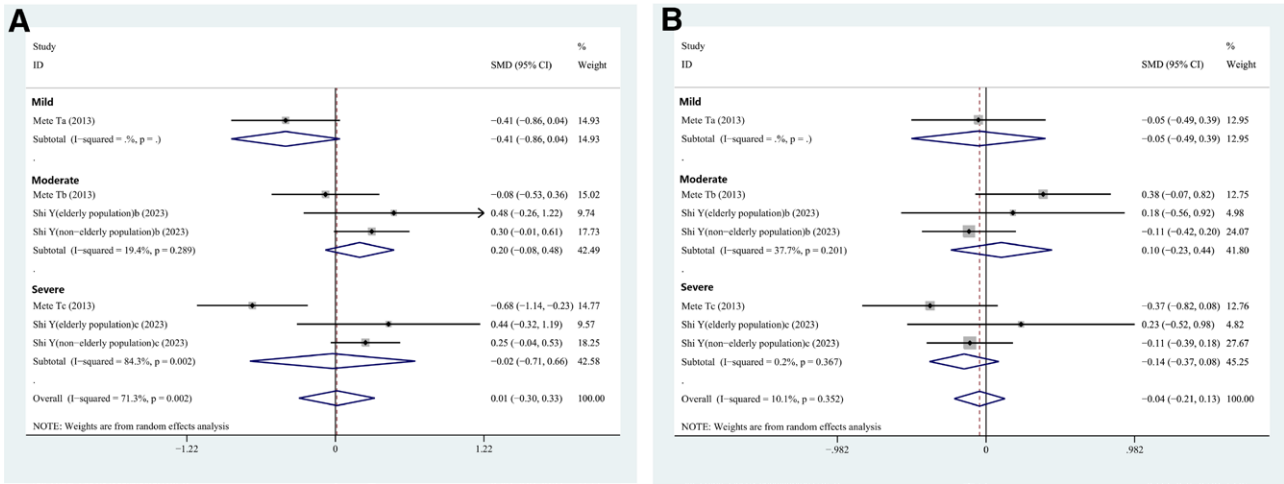

Figure 4. Forest plot of comparison of anti-TPO and anti-Tg between OSAHS and controls. (A) anti-TPO, (B): anti-Tg. anti-TPO = anti-thyroid peroxidase, anti-Tg = anti-thyroid globulin, OSAHS = obstructive sleep apnea-hypopnea syndrome.

3.13. Relationship between AHI and TSH, FT3, and FT4 levels

Six articles revealed the Spearman or Pearson correlation coefficients between AHI and TSH (Table 2). AHI aided in ascertaining the severity of OSAHS. Moreover, the "meta" R package aided the execution of a meta-analysis for TSH levels in the included populations and AHI. However, no significant correlation was observed between serum TSH and AHI, with an effect value of 0.05 (95% CI, 0.01 to 0.10, $P = .038$) (Fig. 6A). Additionally, 3 studies revealed the Spearman or Pearson correlation coefficients between AHI and FT3. Nevertheless, the meta-analyzed correlation coefficients exhibited no significant correlation between serum FT3 and AHI (ZCOR = 0.16, 95% CI, −0.01 to 0.33, $P = .058$) (Fig. 6B). Additionally, 4 studies reported the Spearman or Pearson correlation coefficients between AHI and FT4. However, the meta-analyzed correlation coefficients showed no significant correlation between serum FT4 and AHI (ZCOR = −0.05, 95% CI, −0.15 to 0.05, $P = .066$) (Fig. 6C).

4. Discussion

This research employed a meta-analysis approach to quantitatively explore the association of thyroid function with OSAHS.

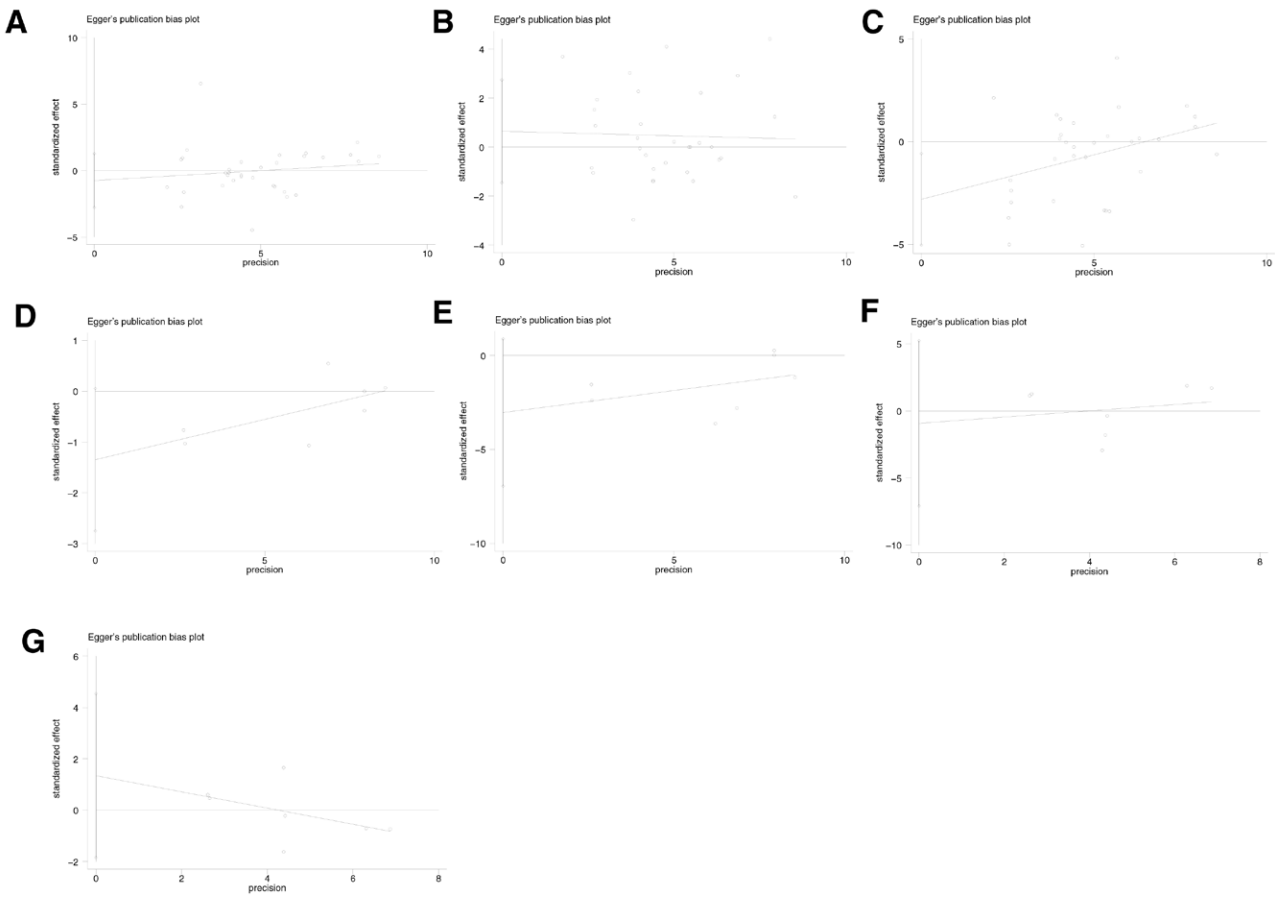

Figure 5. The Egger funnel plot of publication bias. (A) TSH, (B): FT3, (C): FT4, (D): TT3, (E): TT4. FT3 = free triiodothyronine, TSH = thyroid stimulating hormone, FT4:free thyroxine, TT3 = total-triiodothyronine, TT4 = total thyroxine.

A total of 23 articles, encompassing 1000 individuals with OSAHS and 1000 healthy individuals, met the specified inclusion criteria. Three main findings were observed in this study. Firstly, the prevalence of subclinical hypothyroidism, hypothyroidism, and hyperthyroidism in OSAHS patients was found to be 8%, 6%, and 2%, which is in line with previous literature reports.[13,14,17] Secondly, in the overall population, OSAHS patients did not exhibit significant alterations in several key thyroid function indicators (FT3, TT4, FT4, TT3, TSH, anti-TPO, anti-Tg) when compared to healthy non-OSAHS individuals, except for FT4 and TT4. Subgroup analysis based on disease severity further supported these results, as no significant variations were observed in serum FT3, TSH, FT4, anti-TPO, TT4, TT3, and anti-Tg levels in healthy subjects versus individuals with OSAHS. Lastly, no significant correlation was found between AHI and serum TSH, FT3, and FT4.

Thyroid dysfunction is associated with many changes in pulmonary physiology.[58] Clinical investigators have observed that OSAHS and hypothyroidism share several common clinical features, such as daytime sleepiness, slow reaction time, and memory decline. These features are commonly seen in both conditions. In hypothyroidism, these symptoms are attributed to reduced sympathetic nervous system activation and decreased basal metabolic rate. As for OSAHS, these symptoms arise from recurrent nocturnal episodes of breathing cessation leading to intermittent hypoxia, elevated carbon dioxide levels, frequent arousals, and disrupted sleep structure.[59,60] Additionally, OSAHS patients often exhibit signs of obesity, increased neck circumference, or retrognathia, thereby indicating narrow pharyngeal airways. In hypothyroidism, the deposition of glycosaminoglycans and proteins in the soft tissues of the upper airway and skin can also lead to pharyngeal narrowing. Moreover, the neurological alterations and reduction in basal metabolic rate in hypothyroid patients can result in weight gain and changes in the control of pharyngeal dilator muscles. This further contributes to similar symptoms and signs observed in OSAHS.[17,61,62] It has been reported that 25% to 35% of hypothyroid patients may experience nighttime breathing abnormalities, including choking, snoring, and in severe cases, respiratory pauses/hypopnea events.[16,62] Thyroid dysfunction is a contributing factor to OSAHS, but it may also indirectly lead to OSAHS through associations with metabolic syndrome (manifested by obesity), cardiovascular issues, and neuromuscular issues.[49] However, there is still controversy regarding whether there are variations in thyroid function in OSAHS patients versus healthy individuals in current research. Further investigations are required to better understand the complex link between thyroid function with OSAHS.

The prevalence of thyroid dysfunction in individuals with OSAHS often raises the question of whether routine screening for thyroid function is necessary for OSAHS patients. The findings of this study indicate that both hypothyroidism and hyperthyroidism have relatively low prevalence rates in OSAHS patients. Some researchers have also established that the hypothyroidism prevalence in individuals with OSAHS is comparable to the general population.[39,42] In a study by Bahammam et al,[38] the prevalence of newly diagnosed clinical hypothyroidism in individuals with OSAHS was found to be low at 0.4%, whereas the subclinical hypothyroidism prevalence was relatively higher at 11.1%. However, the results of this study differ from those of Bahammam et al,[38] potentially due to the influence of ethnic, environmental, and socio-economic factors.The authors

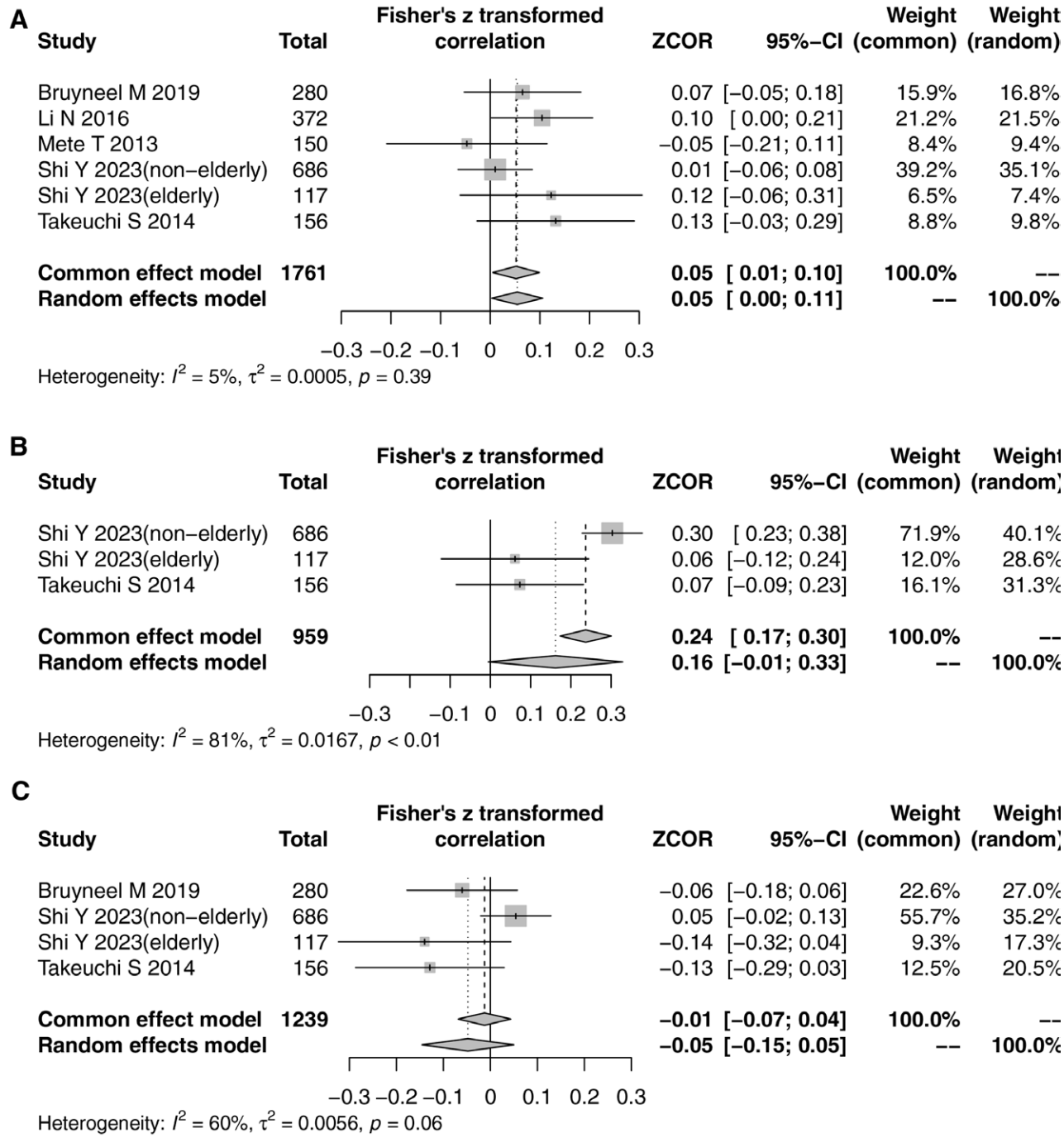

Figure 6. Funnel plot of effect sizes measured as correlations between AHI and TSH, FT3 and FT4. (A) TSH, (B): FT3, (C): FT4. FT3 = free triiodothyronine, TSH = thyroid stimulating hormone, FT4 = free thyroxine, TT3 = total-triiodothyronine, TT4 = total thyroxine.

propose that the low prevalence of diagnosed clinical hypothyroidism and hyperthyroidism in individuals with OSAHS is not sufficient to justify routine screening unless there are symptoms or signs raising suspicion of thyroid dysfunction. Although subclinical hypothyroidism appears relatively common in the OSAHS population, the necessity for routine screening remains controversial. This is because the influence of subclinical hypothyroidism on OSAHS and the potential benefits of treatment for OSAHS patients with subclinical hypothyroidism is not yet well-established. Additionally, further research is warranted to elucidate these aspects.

Bielicki et al[39] pointed out that while hypothyroidism may be a contributing factor in some OSAHS patients, the majority of OSAHS patients have normal thyroid function. Hence, treating thyroid disorders may not necessarily alleviate sleep symptoms. In fact, Bruyneel et al[49] and several others have demonstrated that there is no significant variation in FT4 and TSH levels between moderate and severe OSAHS patients. This suggests that the level of the thyroid hormone may not be indicative of OSAHS severity. Moreover, Mete et al[12] evaluated 150 individuals diagnosed with OSAHS based on polysomnography and established no significant correlation between thyroid hormone levels and the severity of OSAHS. The results of this meta-analysis also suggest that no significant variations were detected in thyroid hormone levels in individuals with OSAHS versus healthy subjects. The analysis of the reasons behind this

finding indicates that thyroid dysfunction may affect the severity of OSAHS, as higher TSH levels are linked to a higher risk of developing OSAHS.[48] Nevertheless, this does not necessarily mean that OSAHS can directly influence thyroid function. The lack of a significant correlation between thyroid hormone levels and the severity of OSAHS is supported by both the individual analyses of disease severity and the combined analysis of correlation coefficients in this study. While there are numerous hypotheses and speculations about the impact of OSAHS on thyroid function, several studies have indicated that oxidative stress and inflammatory responses exert a strong influence on the structure and function of thyroid tissue.[63,64] OSAHS patients experiencing long-term intermittent hypoxia and excessive oxidative stress may hinder the autophagic response, preventing it from compensating for cell damage caused by oxidative stress. The increased reactive oxygen species (ROS) levels may further exacerbate thyroid injury.[65] However, these hypotheses are primarily based on basic laboratory experiments and lack of confirmation from large-scale clinical cohort studies. Consequently, the level of thyroid dysfunction does not reliably forecast the severity of OSAHS. Additionally, the severity of OSAHS may have only a subtle influence on the level of the thyroid hormone.

Some researchers have proposed that thyroid hormone replacement therapy is not able to decrease the AHI in OSAHS patients. For instance, research by Misiolek et al[66] on a series of individuals receiving replacement therapy found that snoring intensity decreased, but the respiratory disturbance index did not show significant changes. Additionally, there was no significant improvement in the lowest oxygen saturation during sleep. The correlation between thyroid-stimulating hormones and age is well-known, which can potentially be a confounding factor in this study. Another research by Shi et al[32] suggested that in non-elderly populations, the progression of OSAHS may lead to an increase in thyroid hormones (particularly FT3), but this effect may not be observed in the elderly. However, the age span of the participants in this meta-analysis was wide, thereby making it difficult to conduct a sub-group analysis based on age. Furthermore, as the incidence of obesity is high in populations with both OSAHS and hypothyroidism, obesity is considered a confounding factor for both conditions.[67–69] Therefore, in these individuals, the coexistence of OSAHS and thyroid dysfunction may be merely an associated phenomenon related to obesity. Hence, there might not be a direct correlation between OSAHS and thyroid function. In future research, more studies focusing on specific populations (such as the elderly, females, children, and obese individuals) should be included to fully comprehend the link between thyroid hormone levels and OSAHS.

Compared to previous meta-analyses,[16,17] this study includes more recently published high-quality research, thus resulting in more reliable findings. Secondly, previous reviews focused on differences in sleep monitoring indicators between the hypothyroid and non-hypothyroid groups among OSAHS patients. However, this review specifically examines the variations in thyroid function in individuals with OSAHS versus healthy subjects. Moreover, this study also performs a meta-analysis on the prevalence of hypothyroidism, subclinical hypothyroidism, and hyperthyroidism in OSAHS patients. Therefore, it provides some evidence for clinicians on whether routine thyroid function screening is necessary for individuals with OSAHS.

The current research has certain limitations that must be acknowledged. Firstly, the analytical models used in this study did not consider covariates such as gender, age, iodine nutrition status, and body mass index. This could lead to heterogeneity. Additionally, most of these studies did not consider confounding factors, and age was a key confounder. It is well-known that TSH increases with age,[70] and variations observed across different age groups may influence the results. Nevertheless, the age range of participants in all included articles was wide, with the average age ranging from 7 to 68. There is only 1 study[47] involved children with OSAHS. Shi et al study differentiated data regarding the elderly population and the non-elderly population.[32] Thus, further research is needed with a focus on including more children or elderly patients to ascertain whether OSAHS affects thyroid hormone levels in these specific populations. Moreover, the diagnostic methods for hypothyroidism were inconsistent among the included studies. This may have affected the accuracy of the true sample size for hypothyroidism. Lastly, owing to the absence of effective longitudinal cohort studies in this analysis, a causal relationship cannot be established between OSAHS and thyroid dysfunction. The biological mechanisms underlying the lack of significant variations in thyroid hormone levels in individuals with OSAHS versus healthy individuals still require extensive validation via basic experimentation.

5. Conclusion

The meta-analysis of various observational studies indicates a lower incidence of thyroid dysfunction in OSAHS individuals. Thyroid hormone levels were not significantly different in individuals with OSAHS versus healthy individuals. Additionally, no significant correlation exists between AHI and serum TSH, FT3, and FT4 levels. The relationship between OSAHS and thyroid function remains controversial, as per the available data. Therefore, further research is required to establish the connection between these 2 conditions and further elucidate their underlying mechanisms.

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