Association between rheumatoid arthritis and thyroid dysfunction: A meta-analysis and systematic review

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Objective: Rheumatoid arthritis (RA) is an autoimmune disorder. Multiple studies have investigated the risk of thyroid dysfunction in patients with RA but have reached conflicting conclusions. This systematic review aimed to determine whether patients with RA are at higher risk of thyroid dysfunction.

Methods: We comprehensively reviewed online literature databases, including PubMed, Scopus, Embase, and the Cochrane Library, from their respective inception dates to March 25, 2022. Studies that provided data on at least one case of thyroid dysfunction in RA patients and their controls were included. Based on these data, we calculated pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for thyroid dysfunction in RA and non-RA patients.

Results: Twenty-nine studies met the inclusion criteria, involving a total of 35,708 patients with RA. The meta-analysis showed that, compared with non-RA patients, RA patients had an increased risk of developing thyroid dysfunction, particularly hypothyroidism (OR 2.25, 95% CI 1.78–2.84).

Subgroup analysis suggested that study type and sample source of control group were the source of heterogeneity.

Conclusions: Patients with RA are at increased risk of developing thyroid dysfunction, especially hypothyroidism. Routine biochemical examination of thyroid function in RA patients should be strengthened. Larger prospective studies are needed to explore the causal relationship between RA and thyroid dysfunction, and to investigate the impact of thyroid dysfunction on RA disease activity, drug efficacy, and medication safety.

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KEYWORDS
rheumatoid arthritis, subclinical hyperthyroidism, subclinical hypothyroidism, thyroid dysfunction, immune system

Abbreviations: CI, confidence interval; NOS, Newcastle–Ottawa Scale; OR, odds ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AITD, autoimmune thyroid disease; TSH, thyroid-stimulating hormone; T₃, triiodothyronine; T₄, thyroxine; fT₃, free triiodothyronine; fT₄, free thyroxine.
Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by systemic inflammation, persistent synovitis, and autoantibodies (particularly against citrullinate peptides and rheumatoid factors) (1). With repeated episodes of joint inflammation, the normal structure of the joint is destroyed, ultimately resulting in reduced mobility and increased disability (2). In addition, many RA patients also present with extraarticular clinical symptoms (3). Recently, a meta-analysis (4) determined that the global prevalence of RA was approximately 0.46% over the past 40 years. Moreover, RA has been found to be potentially associated with a variety of autoimmune diseases, including thyroid dysfunction (5). Thyroid dysfunction mainly includes hyperthyroidism, hypothyroidism, subclinical hyperthyroidism and subclinical hypothyroidism. Autoimmune thyroid disease (AITD), which mainly includes Hashimoto’s thyroiditis and Graves’ disease, is the most common cause of various thyroid dysfunction and is manifested by the production of antibodies against thyroid peroxidase, thyroglobulin or thyrotropin receptor autoantigens (6, 7). In addition to clinical manifestations, laboratory tests are more important in the definition of several thyroid diseases. Common test indicators include thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (fT3), free thyroxine (fT4) (8). The range of reference values given by different experimental equipment and detection kits varies to a certain extent, but the trend of indicator change has been widely recognized (9, 10). Hypothyroidism and hyperthyroidism can be divided into overt and subclinical stages. Based on hormone levels, hyperthyroidism and hypothyroidism are defined as excessive and insufficient thyroid hormones, respectively (11). Most thyroid diseases and rheumatoid arthritis are chronic diseases, and unfortunately, early signs of thyroid dysfunction are not specific and are often overshadowed by clinical manifestations of other diseases in the absence of biochemical tests of thyroid function (12). Thyroid dysfunction can be detrimental to health and, if left undiagnosed or treated, can have serious adverse consequences and, in exceptional cases, can be fatal (12).

Findings from studies on the risk of thyroid dysfunction in RA patients are conflicting (13). For example, a study by McCoy et al. (14) concluded that RA patients did not have significantly increased risk of hypothyroidism as compared with non-RA patients (14). Graves’ disease is the most common cause of hyperthyroidism and has a high comorbidity rate with RA (15). Considering the accumulation of evidence, we conducted a systematic review and meta-analysis to assess whether patients with RA are at a higher risk of the four major thyroid dysfunctions. We also used subgroup analysis to investigate the influence of control group origin, study type, regions, and publication date on the results of the overall analysis, as well as to explore sources of heterogeneity.

Methods

Search strategy

A systematic review and a meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (16). We searched PubMed, Scopus, Embase, and the Cochrane Library databases, for all eligible studies, regardless of language, from their respective inception dates to 25 March 2022. The search terms used were “Thyroid Dysfunction,” “Thyroid Diseases,” “Hypothyroidism,” “Hyperthyroidism,” and “Arthritis, Rheumatoid” (please see appendix eTable 1 for the complete search strategy). This study is registered on PROSPERO, number CRD42022331142.

Inclusion and exclusion criteria

A Population, Intervention, Comparator, Outcome and Study design (PICOS) scheme was used to clarify our research objectives. Our meta-analysis was designed to answer the question: does rheumatoid arthritis increase the risk of thyroid dysfunction? Representatives of the PICOS regimen as follows: patients with RA (P); comparison with non-RA, non-systemic lupus erythematosus (SLE), or healthy subjects (C); the diagnosis of thyroid dysfunction (O); observational studies (S). In our meta-analysis, patients with thyroid dysfunction mainly included hyperthyroidism, hypothyroidism, subclinical hypothyroidism, and subclinical hyperthyroidism.

Studies that up to the following standards were incorporated in this meta-analysis: Observational studies that included RA and non-RA controls provided the number of samples in both groups and provided the number or prevalence of thyroid dysfunction in each group. Patients who met the American College of Rheumatology diagnostic criteria for RA or the European League Against Rheumatism classification criteria, or who had at least one documented rheumatoid arthritis diagnosis in the medical records of hospitals and medical databases, were included in the study. In addition, to be included in this study, at least one case of hypothyroidism, subclinical hypothyroidism, hyperthyroidism, or subclinical hyperthyroidism had to be detected in RA patients and/or controls. To test whether the findings are common across countries, we did not restrict the language used to publish the articles.

We excluded reviews, editorials, case reports, comments, books, etc. Studies without available abstracts or complete manuscripts were also excluded. If there was duplication in the study population among studies, only the latest article was included. Given that a strong association between thyroid disease and systemic lupus erythematosus has been reported for more than 50 years (17), studies with SLE patients as controls were also excluded.
Data extraction and quality assessment

Two reviewers (Y.L. and H.M.) independently fetched the data from eligible papers and then combined the data. Disagreements were settled through discussion to consensus. We extracted the following basic information and outcome-related data from studies that up to our inclusion criteria: year of publication, the name of the first author, nationality of the author, average duration of RA, study design, the number of cases and controls, the mean age and sex ratio among RA and non-RA patients, methodological quality of the study, and number of people with thyroid dysfunction. We focused on the statistical results of the four types of thyroid dysfunction in the RA group and the control groups. We preferentially extracted the raw data in the study report, and if the study did not provide the raw data, the prevalence value provided by the study was used for calculation. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the included literature (18). The overall score is 9, with 7-9 being high quality, 4-6 being medium quality, and 0-3 being low quality.

Statistical analysis

The association strength between RA and four types of thyroid dysfunction was calculated, expressed by the odds ratio (OR), with the corresponding 95% confidence interval (CI), using the sample sizes of RA and control groups as well as the statistical results of four types of thyroid dysfunction. OR > 1 indicates that RA increases the risk of thyroid dysfunction, OR = 1 indicates that there is no correlation between RA and thyroid dysfunction, and OR < 1 indicates that RA patients have a reduced risk of thyroid dysfunction.

P < 0.05 was recognized statistically significant. We used the I^2 statistic and y^2 test to assess the heterogeneity of the pooled ORs (P < 0.1 considered statistically significant). I^2 ≤ 25% indicated that heterogeneity was insignificant, I^2 < 50% indicated low heterogeneity, 1^2 between 50% and 75% indicated medium heterogeneity, and I^2 > 75% indicated high heterogeneity (19).

When the pooled OR was calculated, if I^2 > 50%, the random effect model was used for sensitivity analysis and subgroup analysis; if I^2 < 50%, the fixed-effect model was adopted (20). Egger’s test, Funnel plot, and Begg’s test were used to evaluate whether publication bias existed. P < 0.05 indicated that the detected publication bias was statistically significant, and the impact of potential publication bias was further assessed using the Duval and Tweedie non-parametric modified trim-and-fill method (21). All statistical analyses were accomplished using Stata V.16.0 software.

Results

Literature search results and study characteristics

A preliminary search of four electronic databases, PubMed, Scopus, Embase, and the Cochrane Library, yielded 9,746 articles, including 1,549 PubMed articles, 5,378 Embase articles, 2,673 Scopus articles, and 146 Cochrane Library articles. After removing duplicates, 6,287 records remained. Two authors (Y.L. and H.M.) scanned the titles and abstracts of these articles as a preliminary screen and selected 156 articles that appeared eligible for inclusion. Further, the two authors then read the full text of these articles respectively. If there were disputes about inclusion of any of these papers, a third author (Z.C.) made the final decision. Finally, 29 studies (5, 11, 13, 14, 22-46) that met all inclusion criteria were absorbed in the meta-analysis. Figure 1 shows the detailed screening steps.

Table 1 describes the general characteristics of the literature included in our meta-analysis. Twenty-nine studies met the inclusion criteria, involving 35,708 RA patients and 149,421 non-RA controls. Among them, 15 studies (5, 11, 13, 22, 24, 25, 27, 31, 33, 34) provided (37-40, 45) prevalence values for hyperthyroidism, 12 provided (5, 11, 22, 24, 31, 33, 34, 36, 37, 42, 44, 45) prevalence values for subclinical hyperthyroidism, 26 provided (5, 11, 13, 14, 22-31, 33-41, 43, 45, 46) prevalence values for hypothyroidism, and 17 provided (5, 11, 14, 22, 24, 31-34, 36-39, 42-45) prevalence values for subclinical hypothyroidism. The NOS checklist was used to evaluate the quality of studies, and 7 studies (24.13%) assessed as high quality, and 18 studies (62.07%) identified as medium quality.

Synthesis of results

RA and hyperthyroidism

Fifteen studies (5, 11, 13, 22, 24, 25, 27, 31) recorded the prevalence of hyperthyroidism in RA and control groups (33, 34, 37–40, 45). However, in 5 literatures (27, 31, 33, 34, 45), there is no information on hyperthyroidism in RA patients or controls.

We executed a statistical analysis on the remaining 10 studies (Figure 2A). The risk of developing hyperthyroidism in RA patients was observably higher than in control groups (OR 1.65, 95% CI 1.24–2.19). Among the studies reporting statistically significant differences, some extremes occurred, such as in the study by Al-Awadhi et al. (39) suggested that RA patients had a higher risk of hyperthyroidism, while the study of Mahagna et al. (13) found that RA patients had a relatively low risk of hyperthyroidism.
TABLE 1 Characteristic of basic information.

| Author, year | Country | Total patients with RA | Age of RA (mean year ± SD) | Sex ratio of RA (M/F) | Duration of RA (mean year ± SD) | Source of control group | Number of control group | Study design | Quality score |
|--------------|---------|------------------------|----------------------------|-----------------------|-------------------------------|-------------------------|--------------------------|--------------|--------------|
| E. Deseatnicova, 2022 (22) | Moldova | 59 | 54.2 ± 9.6 | NA | 9.6 ± 5.6 | Non-RA control | 48 | cross-section research | 1 |
| Nazary, K, 2021 (5) | Afghanistan | 400 | 36 ± 08 | 159/241 | 0 | Non-RA control | 400 | case-control study | 7 |
| Yadav, B., 2019 (23) | India | 493 | 47 ± 12 | 68/425 | 3.97 ± 3.93 | Osteoarthritis patients | 165 | cross-section research | 5 |
| Saqre, I. M., 2019 (24) | Egypt | 60 | 41 ± 10.5 | 17/43 | 8.6 ± 4.1 | Health control | 60 | case-control study | 6 |
| Li, Q., 2019 (11) | China | 65 | 59.58 ± 11.64 | 13/52 | 7.12 ± 8.58 | Health control | 550 | case-control study | 8 |
| Mahagna, H., 2018 (13) | Israel | 11782 | 61.1 ± 17.0 | 2879/9103 | NA | Non-RA control | 57973 | cross-section research | 4 |
| Huang, C. M., 2018 (25) | China | 18267 | 53.6 ± 13.9 | 3945/14322 | NA | Non-RA control | 73068 | case-control study | 6 |
| Guy, A., 2018 (26) | Israel | 15 | 56.27 ± 13.35 | 1/14 | NA | Health control | 32 | case-control study | 3 |
| Figueroa-Sánchez, 2019 (27) | Mexico | 78 | 42.75 ± 12.15 | 13/65 | 4.74 ± 6.04 | Health control | 81 | cross-section research | 6 |

(Continued)
| Author, year | Country | Total patients with RA | Age of RA (mean year ± SD) | Sex ratio of RA patients (M/F) | Duration of RA (mean year ± SD) | Source of control group | Number of control group | Study design | Quality score |
|--------------|---------|------------------------|----------------------------|-------------------------------|--------------------------------|------------------------|------------------------|--------------|--------------|
| El Achek, M. A., 2018 (28) | Tunisia | 111 | 51.04[18-80] | 17/94 | 6.54[0-29] | Ankylosing spondylitis patients | 60 | case-control study | 2 |
| Posselt, R. T., 2017 (29) | Brazil | 210 | 53.7 ± 10.45 | 19/191 | 11.1 ± 8.9 | Health control | 141 | cross-sectional research | 6 |
| Tascilar, K., 2016 (30) | Canada | 1357 | 63.7 ± 9.4 | 539/818 | 3.26 | Non-RA control | 13570 | case-control study | 6 |
| El-saadany, H., 2014 (31) | Egypt | 40 | 29.1 ± 6.1 | 0/40 | NA | Healthy female control | 20 | case-control study | 5 |
| Gomez, R., 2013 (32) | Colombia | 86 | 56.4 | 9/77 | NA | Arthropy and fibromyalgia patients | 86 | case-control study | 5 |
| Acay, A., 2014 (33) | Turkey | 80 | 48.09 ± 10.25 | 17/63 | NA | Health control | 122 | cross-sectional research | 4 |
| McCoy, S. S., 2012 (14) | USA | 650 | 55.8 ± 15.7 | 202/448 | 7.9 ± 5.2 | Non-RA control | 650 | cohort study | 7 |
| Mousa, A. A., 2012 (34) | Egypt | 217 | 36.3 ± 12.8 | 43/174 | NA | Health control | 120 | case-control study | 6 |
| Fatima, F., 2010 (35) | India | 800 | 46.15 ± 13.37 | 132/668 | 4.9 ± 5.50 | Non-RA control | 800 | case-control study | 5 |
| Mobini, M., 2011 (36) | Iran | 80 | 51.4 ± 12 | 4/76 | NA | Osteoarthritis patients | 80 | case-control study | 5 |
| Przygodzka, M., 2009 (37) | Poland | 100 | 54 ± 12.2 | 0/100 | 12.3 | Non-RA control | 55 | case-control study | 7 |
| Haghighi, A., 2009 (38) | Iran | 75 | NA | 5/70 | NA | mechanical low back pain or osteoarthritis patients | 66 | case-control study | 2 |
| Al-Awadhi, A. M., 2008 (39) | Kuwait | 177 | 38.3 ± 12.8 | 37/140 | NA | Health control | 577 | cross-sectional research | 5 |
| Andonopoulos, A. P., 1996 (40) | Greece | 101 | 57.9 ± 13.5 | 29/72 | 8.3 ± 7.7 | Osteoarthritis patients | 70 | case-control study | 7 |
| Shiroky, J. B., 1993 (41) | Canada | 119 | NA | 28/91 | NA | Osteoarthritis or primary fibromyalgia patients | 108 | case-control study | 7 |
| Antonelli, A., 2000 (42) | Italy | 91 | 59 ± 16 | 1/91 | 9 ± 7 | Healthy female control | 180 | case-control study | 6 |
| Al-Awadhi, A. M., 1999 (43) | Kuwait | 48 | 47 ± 11 | 5/43 | NA | Non-inflammatory rheumatic diseases patients | 90 | case-control study | 7 |
| Innocencio, R. M., 2004 (44) | Brazil | 25 | 49 ± 13 | 7/18 | 18 ± 11 | Healthy blood donors | 113 | case-control study | 4 |

(Continued)
RA and subclinical hyperthyroidism

After excluding two studies (31, 44), in which subclinical hyperthyroidism was not found in any subjects, the prevalence of subclinical hyperthyroidism in RA patients and controls was calculated in a total of 10 studies (5, 11, 22, 24, 33, 34, 36, 37, 42, 45) (Figure 2B). The pooled OR was 2.13 (95%CI 1.25–3.63) (P < 0.05), indicating that RA patients had more than twice the risk of subclinical hyperthyroidism as non-RA subjects, which was statistically significant. Due to low heterogeneity (I² = 0.0%, P = 0.743), a fixed-effect model was used for statistical analysis.

RA and hypothyroidism

In the study conducted by Acay et al. (33), neither group included any cases of hypothyroidism. We thus conducted a combined analysis of the remaining 25 studies (5, 11, 13, 14, 22–28, 31, 34–41, 43, 45, 46) (Figure 2C). Due to the high I² value (I² = 75.7%), a random-effects model was applied. The pooled OR was 2.25 (95%CI 1.78–2.84) (P > 0.05). Our statistical results indicated that RA patients had a higher risk of hypothyroidism than of the other three types of thyroid dysfunction.

RA and subclinical hypothyroidism

A pooled analysis of 17 studies (5, 11, 14, 22, 24, 31–34, 36–39, 42–45) involving the association between RA and subclinical hypothyroidism was performed. The pooled OR was 2.18 (95% CI 1.32–3.61) (P < 0.05), indicating that the risk of subclinical hypothyroidism in RA patients was significantly higher than that in controls (Figure 2D), with an I² value of 63.8% (P < 0.001); thus, we used a random effects model.

Subgroup analyses

In addition to the pooled analysis of the risk of developing subclinical hyperthyroidism in patients with RA, there was significant heterogeneity in the pooled analysis of the other
three types of thyroid dysfunctions. To further explore possible sources of heterogeneity and to determine whether specific factors influence the risk intensity for thyroid dysfunction among RA patients, we performed subgroup analyses by control group origin, study type, geographic region, and publication date. As shown in Table 2, the subgroup analysis showed that the origin of controls was the source of heterogeneity in the risk of hyperthyroidism, and the study type was the source of heterogeneity in the risk of subclinical hypothyroidism. Region and publication date did not significantly contribute to heterogeneity.

### Sensitivity analysis

Sensitivity analysis was carried out by removing each of the studies consecutively to verify the reliability and stability of the pooled results, observe the effect of individual results on the overall analysis, and look for possible sources of heterogeneity.

Sensitivity analyses were performed for association of RA and four thyroid dysfunctions. If the pooled results suggested an increased risk of thyroid dysfunction even after exclusion of any study, the pooled analysis was considered robust. As shown in Figure 3, when sensitivity analysis was performed on the pooled results of studies related to subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism, the combined OR remained within the overall 95% CI range after the exclusion of any study, indicating that the statistical data were robust and reliable. However, in the sensitivity analysis of hyperthyroidism-related studies, the combined OR did not remain within the 95% CI range of the overall OR after excluding the studies of Mahagna et al. (13) or Huang et al. (25), and these two studies were considered to have an impact on the overall efficacy. Heterogeneity was significantly reduced after we excluded these two articles (P = 0.186, I² = 30.5%). Therefore, the two studies were considered to represent a source of heterogeneity. Without the two studies, the combined OR of the remaining studies was 3.03 (95%CI 1.33–6.91, P = 0.008).

### Publication bias

To detect whether publication bias existed, we created funnel plots, and conducted Begg’s and Egger’s tests. Typically, precise studies or studies with large numbers of subjects appear at the top of a funnel plot, while less precise studies or studies with fewer subjects appear at the bottom (21). As shown in Figure 4, these plots showed that there was no significant bias in these studies except for the abnormal funnel plot associated with RA and hypothyroidism (Figure 4C). The detection of publication bias was also confirmed in Egger’s test (eTable 2).

### Table 2: Subgroup analysis of region, year of Publication, study design, and control group origin.

| Region       | Hyperthyroidism OR, 95% CI | 1³%, P | Subclinical hyperthyroidism OR, 95% CI | 1³%, P | Hypothyroidism OR, 95% CI | 1³%, P | Subclinical hypothyroidism OR, 95% CI | 1³%, P |
|--------------|---------------------------|--------|--------------------------------------|--------|---------------------------|--------|--------------------------------------|--------|
| Europe       | 1.43 (0.47, 4.38)         | 0.00%  | 2.53 (0.97, 6.58)                    | 0.00%  | 3.92 (1.33, 11.57)        | 14.2%  | 1.61 (0.84, 3.10)                    | 0.00%  |
| Asia         | 1.68 (1.22, 2.30)         | 75.3%  | 1.91 (0.85, 4.27)                    | 24.3%  | 2.54 (1.82, 3.54)         | 84.8%  | 3.17 (1.31, 7.70)                    | 0.00%  |
| Africa       | 5.17 (0.24, 10.01)        | –      | 2.09 (0.72, 6.05)                    | 32.4%  | 5.51 (1.64, 18.58)        | 0.00%  | 3.11 (0.39, 4.48)                    | 0.00%  |
| Americas     | –                         | –      | –                                    | –      | 1.56 (1.05, 2.34)         | 69.0%  | 2.41 (83.3%, 1.54, 10.80)            | 0.00%  |
| Year of Publication | 2011-2022 | 63.8% | 2.11 (1.17, 3.83)                    | 0.00%  | 1.84 (1.45, 2.33)         | 76.5%  | 1.49 (0.86, 2.60)                    | 0.00%  |
| Study design | Case-control study 1.70 (1.52, 1.89) | 0.00% | 1.91 (0.67, 3.33)                    | 0.00%  | 3.72 (2.56, 5.40)         | 44.0%  | 4.43 (1.78, 11.03)                   | 0.00%  |
| Cross-section research | 4.46 (0.53, 37.74) | 77.2% | 3.50 (0.93, 13.15)                  | 0.00%  | 2.62 (1.89, 4.00)         | 71.3%  | 1.88 (1.15, 3.08)                    | 0.00%  |
| Control group origin | Non-RA control 1.48 (1.23, 1.79) | 41.2% | 1.78 (0.85, 3.75)                    | 0.00%  | 1.76 (1.42, 2.19)         | 74.0%  | 1.76 (0.86, 3.61)                    | 0.00%  |
| Health control | 9.75 (3.12, 30.48) | 0.00% | 2.58 (1.20, 5.54)                    | 0.00%  | 5.68 (2.65, 12.19)        | 59.0%  | 2.82 (1.33, 5.96)                    | 0.00%  |

I³ indicates the level of heterogeneity. RA, rheumatoid arthritis.
Publications bias detected by funnel plot on the risk of thyroid dysfunction in RA patients.

(A) Publications bias detected by funnel plot on the risk of hyperthyroidism in RA patients.

(B) Publications bias detected by funnel plot on the risk of subclinical hyperthyroidism in RA patients.

(C) Publications bias detected by funnel plot on the risk of hypothyroidism in RA patients.

(D) Publications bias detected by funnel plot on the risk of subclinical hypothyroidism in RA patients.
We attempted to evaluate the impact of publication bias on the aggregate results by making use of the trim-and-fill method (21). After four iterations, nine potential studies were added, and the results showed that publication bias had little impact on the stability of the results (eFigure 1).

Discussion

This meta-analysis involved 35,708 RA patients and 149,421 control subjects. Our meta-analysis of 29 selected papers on the association between RA and thyroid dysfunction revealed a strong correlation between RA and thyroid dysfunction, particularly hypothyroidism. This yielded a pooled OR of 2.25 (95% CI 1.78–2.84) (Figure 2). In addition, RA was closely associated with subclinical hypothyroidism (low thyroid stimulating hormone [TSH], high free thyroxine [FT4]), hypothyroidism (high TSH, low FT4), subclinical hyperthyroidism (low TSH, normal FT4), subclinical hypothyroidism (high TSH, normal FT4) (49, 50).

Thyroid dysfunction mainly discussed in this meta-analysis included hyperthyroidism (low thyroid stimulating hormone [TSH], high free thyroxine [FT4]), hypothyroidism (high TSH, low FT4), subclinical hyperthyroidism (low TSH, normal FT4), subclinical hypothyroidism (high TSH, normal FT4) (49, 50). Because the clinical manifestations of thyroid disease are highly variable and usually nonspecific, the diagnosis of thyroid dysfunction relies primarily on laboratory biochemical tests (49). Although many studies have assessed the risk of thyroid dysfunction in patients with RA, their conclusions have been inconsistent, perhaps due to differences in the populations and geographical regions across studies (51). For example, Nazary et al. compared thyroid function in 400 newly diagnosed RA patients with matched controls and found a higher prevalence of thyroid dysfunction in RA patients (25.2% vs. 11.5%; P value = 0.00001). However, McCoy et al. (14) found that the incidence of hypothyroidism in RA patients was not significantly increased compared with non-RA patients (14). Unfortunately, many studies have not investigated these four types of thyroid dysfunction. Therefore, given the accumulation of evidence, we here performed a systematic review and meta-analysis to address whether patients with RA are at higher risk of developing the four major thyroid disorders.

We performed a meta-analysis of the 29 included articles. Using the four types of thyroid dysfunction as categorical variables, the risk of thyroid dysfunction in RA patients increased to varying degrees, but the comprehensive analysis results also showed high heterogeneity. Subgroup analysis showed that the origin of control groups was the source of heterogeneity in the risk of hyperthyroidism, and study type was the source of heterogeneity for that of subclinical hypothyroidism in the correlation analysis.

When the control group consisted of healthy individuals, RA patients had a higher risk of hyperthyroidism compared with other non-RA patients. This suggests the need for further research into the relationship between thyroid dysfunction and other diseases. Such as the use of chemotherapy drugs as a systemic treatment for breast cancer increases the risk of thyroid dysfunction (52). In turn, a meta-analysis two years ago suggested that hyperthyroidism was associated with prostate, thyroid and breast cancers, compared with those with normal thyroid function (53). A Mendelian randomization study last year also provided further evidence of a causal link between thyroid disease and breast cancer risk (54). Subgroup analyses revealed that geographic region and year of publication were not the main sources of heterogeneity. However, subgroup analysis found that only studies conducted in Asia showed statistically significant differences between the RA group and the control group in terms of the prevalence of hyperthyroidism and subclinical hypothyroidism. In contrast, a subgroup analysis of hyperthyroidism and subclinical hyperthyroidism showed that the difference in the prevalence of these disorders between the RA and control groups was only statistically significant in the last decade compared with earlier studies. We speculated that this finding might be due to variations in detection device sensitivity, diagnostic thresholds, and iodine intake (Table 2) (49). The specific reasons need to be explored in future studies.

In the sensitivity analysis of the primary variable, the combined results after excluding studies showed that the risk of developing thyroid dysfunction in RA patients remained significant, indicating that our findings were robust. However, in the sensitivity analysis of hyperthyroidism, after excluding the studies of Mahagna et al. (13) and Huang et al. (25), the combined OR value fluctuated greatly. Moreover, after excluding these two articles, heterogeneity was significantly reduced (P = 0.186, I² = 30.3%). Therefore, they may be one of the main sources of heterogeneity. The retrospective cohort study by Huang et al. focused on the risk of hearing loss in patients with RA, not thyroid dysfunction. The relevant information could only be extracted from their baseline data. In addition, Huang et al.’s study included only newly diagnosed RA patients and excluded patients with a history of hearing loss, which may have confounded the data on the prevalence of thyroid dysfunction. Mahagna et al. used a cross-sectional study with inherent limitations and low methodological quality scores. Both studies used large databases and had large sample sizes compared to the other studies. However, irrespective of whether these two studies were included, the combined OR values suggested an increased risk of hyperthyroidism in RA patients. To provide more convincing evidence, more prospective studies are needed to more accurately assess the association between RA and thyroid disease. Although the funnel plot and Egger's test indicated
that there was indeed publication bias in meta-analysis of RA association with hypothyroidism, our combined results were proven to be robust by the trim-and-fill method, and that reporting bias did not significantly affect the results.

The underlying mechanisms of thyroid dysfunction in patients with RA are unclear (51). Thyroid dysfunction often occurs in autoimmune thyroid disease (AITD), particularly in Hashimoto’s thyroiditis and Graves’s disease. Moreover, it is now generally accepted that RA and AITD are caused by multiple factors, such as genetic susceptibility and environmental factors (55, 56). We found that patients with RA had a higher risk of developing hypothyroidism than other types of thyroid dysfunction. We hypothesized that the immunogenicity related to hyperthyroidism was lower than that related to hypothyroidism. The vast majority of hypothesized that the immunogenicity related to hyperthyroidism found that patients with RA had a higher risk of developing thyroid dysfunction, both primary and secondary, and their classification is complex. The lack of restriction on etiology is also part of the limitation of our meta-analysis. However, thyroid dysfunction is most common in autoimmune thyroid diseases, especially Graves’s disease and Hashimoto’s thyroiditis. Future studies are needed to more accurately compare the relationship between different thyroid diseases and RA (50, 57).

Our meta-analysis confirmed that RA patients have a high incidence of thyroid dysfunction, and routine biochemical testing of thyroid function in RA patients is reasonable. This not only enables the potential thyroid diseases of RA patients to be detected and treated in a timely manner, but more importantly, the therapeutic drugs for RA may aggravate the thyroid diseases, and the detection of thyroid function is helpful to clinicians for rational drug use (5). Common drugs used to treat RA, such as glucocorticoids (63) and leflunomide (64), interfere with thyroid function, whereas tumor necrosis factor inhibitors improve thyroid function in RA patients with hypothyroidism (65). It is suggested that the effects of various drugs related to the treatment of RA on thyroid function and the influence of thyroid dysfunction on the early treatment effect of RA should be studied more comprehensively (66). Compared with RA patients with negative thyroid autoantibodies, RA patients with positive thyroid autoantibodies had younger onset age and higher disease activity (67). Therefore, thyroid function should be tested regularly in younger RA patients. The close association between thyroid dysfunction and RA suggests a common pathogenic mechanism and potential therapeutic targets, which deserve further exploration.
Conclusion

This meta-analysis revealed that RA patients have a higher prevalence of thyroid dysfunction, especially hypothyroidism. We conclude that it is reasonable to promote routine biochemical testing of thyroid function in patients with RA regardless of the presence or absence of obvious suspicious clinical manifestations, and vice versa. Our findings suggest that rheumatologists should screen RA patients for thyroid function and refer to endocrinologists to determine effective strategies for preventing and treating thyroid dysfunction. Furthermore, since RA may share a common pathogenesis with most AITDs that cause thyroid dysfunction, there may also be corresponding treatment options. More potential mechanisms and treatment options should be explored in future studies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

YJL, ZC, and SL contributed to the conception and design of the systemic review. YJL and H-BM drafted and finalized the manuscript. ZC, H-BM, and SL revised the manuscript and provided critical advice on the content of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1015516/full#supplementary-material

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