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The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis

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Running title: A meta-analysis of AITD and psoriasis

Abstract

Objective Psoriasis is a chronic inflammatory disease with autoimmune etiology. A possible link between psoriasis and autoimmune thyroid disease (AITD) has been suggested in some studies with inconsistent findings. This meta-analysis aims to

determine the association between psoriasis and AITD and to provide better advice for the management of psoriasis.

Methods The electronic search was conducted through PubMed, EMBASE, PubMed, EMBASE, and the Cochrane Library. Two independent reviewers screened the articles, and then the third independent reviewer conducted the final review. The Mantel-Haenszel method was applied to perform the meta-analysis using the Stata 15.0 software. Odds ratio (OR) and 95% confidence intervals (CI) were pooled to compare the prevalence of AITD in psoriasis and control groups.

Results Ten available studies with data on 253,173 patients with psoriasis and 1,376,073 controls were included. Meta-analysis showed that patients with psoriasis had a higher prevalence of AITD (OR = 1.46, 95% CI: 1.28 - 1.67, Z = 5.51, p <0.001), especially loss-of-function disorder of the thyroid gland. Both TgAb positive rate (OR = 1.76, 95% CI: 1.28 - 2.43, Z = 3.47, p = 0.001) and TPOAb positive rate (OR = 1.77, 95% CI: 1.31 - 2.40, Z = 3.68, p <0.001) were also increased in the psoriasis group compared to the control group.

Conclusions Our study indicated that the comorbid prevalence of AITD was significantly increased in patients with psoriasis. Thyroid-related examinations should be considered as a part of routine evaluations in patients with psoriasis.

PROSPERO registration number CRD42020206005

Keywords: Psoriasis, Thyroid, Immunology

Strengths and limitations of this study

This is the first meta-analysis focusing on the risk of AITD for psoriasis patients, which included hypothyroidism, hyperthyroidism, subclinical hypothyroidism, subclinical

hyperthyroidism, Hashimoto's thyroiditis, Graves' disease, TgAb and TPOAb.

All studies included had moderate to high quality and representative, and published in recent years.

The heterogeneity in the pooled data cannot be ignored, and couldn't improve by subgroup analysis.

INTRODUCTION

Psoriasis is a chronic inflammatory disease with autoimmune etiology, affecting approximately 125 million people around the world[1 2]. The skin lesions of psoriasis occur mainly on the scalp, trunk, and exterior surfaces of the limbs, and manifest as erythema, plaques, and scales[3]. Apart from the impaired appearance and intense pruritus of the skin lesions, various comorbidities have a significant impact on the quality of life in patients with psoriasis[4 5]. Among the comorbidities, autoimmune thyroid disease (AITD) has been characterized in patients with psoriasis. For patients with psoriasis who also develop complications, their management requires extra attention[6]. Therefore, understanding the risk of other diseases on psoriasis has important clinical significance.

Autoimmune thyroid disease (AITD) is an inflammatory disease of the thyroid gland with the presence of thyroid autoantibodies, lymphocytic infiltration of thyroid parenchyma, and even thyroid dysfunction[7]. Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the two main clinical subtypes of AITD. GD is characterized by hyperthyroidism and the presence of thyroid-stimulating hormone receptor antibodies (TRAb) in serum, while HT is characterized by hypothyroidism and the presence of thyroid peroxidase antibodies (TPOAb) or Thyroglobulin antibodies (TgAb) in serum[8].

Psoriasis and AITD share some common pathophysiological features, such as Th1-predominant adaptive immune reaction[7]. Hence, the relationship between AITD and psoriasis has been hypothesized and studied. In 2006, Antonelli *et al.* first reported that the prevalence of AITD in patients with psoriatic arthritis was significantly higher than in the general population[9]. However, the study reported by Tsai *et al*. pointed that the

association between psoriasis and AITD was limited[10]. In recent years, several observational studies regarding the association between psoriasis and AITD were published in succession, but the results of the studies were inconsistent[11-16]. In addition, Karadag *et al.* reported that the commonly administered acitretin treatment for psoriasis system treatment affects the levels of free T4 (thyroid hormone)[17]. To address this discrepancy, we designed and performed a meta-analysis with the existing evidence to assess the relationship between psoriasis and AITD, and to provide guidance on clinical management of psoriasis.

METHODS

Search strategy

The literature search was conducted through PubMed, EMBASE, and the Cochrane Library for relevant studies published before August 24th, 2020. Detailed literature-search strategies of the databases are presented in Table 1.

Inclusion and exclusion criteria

The inclusion criteria for the studies included in our analysis were the following: (1) The prevalence of AITD in patients with psoriasis/psoriatic arthritis and non-psoriasis were studied; (2) The study was a cohort study, case-control study, or cross-sectional study; (3) The observed indicators were at least one of the following outcomes: the prevalence of hypothyroidism, hyperthyroidism, HT, GD, or the positive rate of TPOAb, TgAb, or TRAb; (4) The number of patients with psoriasis and the control group should be over 50. Drug-related studies, animal studies, reviews, and conference abstracts were excluded from our analysis.

Data extraction

The specific process for analyzing the studies generated from the search was as follows: record screening and data extraction were performed by two independent authors (XC Zhang and SH Zhang) according to the above retrieval strategy. The following information in the included studies were extracted: the name of the first author, year of publication, country of origin, study design, sample size, the definition of psoriasis and AITD, gender ratio, and mean age.

Quality assessment

The Newcastle-Ottawa Scale (NOS)[18] was used to assess the quality of the included cohort and case-control studies, and the tools recommended by the Agency for Healthcare Research and Quality (AHRQ)[19] were used for the cross-sectional studies.

Data synthesis and analysis

The meta-analysis was performed using the Stata 15.0 software. We used the Odds ratio (OR) and 95% Confidence Intervals (CI) to describe the differences between groups. The statistical difference was considered significant when $p < 0.05$. The Mantel-Haenszel method was used for data analysis. The inconsistency index (I^2) was used to evaluate heterogeneity as follows: $I^2 \leq 25\%$, no heterogeneity; $25\% \leq I^2 \leq 50\%$, mild heterogeneity; $50\% < I^2 \leq 75\%$, moderate heterogeneity; $I^2 > 75\%$, severe heterogeneity. A fixed effects model was applied if $I^2 \leq 50\%$ and the random effects model was applied when $I^2 > 50\%$. Publication bias was assessed by Funnel chart and Egger's test (Publication bias was considered when $p < 0.05$). Sensitivity Analysis was performed to assess the stability of the meta-analysis by omitting one study in each turn. The flow

chart was drawn in Adobe Illustrator, and the forest charts, funnel charts, and Egger's test charts were drawn by Stata 15.0 software.

Patient and public involvement

There were not patients or the public involved in this review.

RESULTS

Search results

After removing duplicate results, we identified 3217 published studies in the initial search. After screening the titles and abstracts, 16 studies underwent further screening. After full-text screening, 10 studies[2 9-16 20] that met the inclusion criteria were included in the final analysis (figure. 1).

Study characteristics

The basic characteristics of the included studies are shown in Tables 2 and 3. A total of 253,173 patients with psoriasis and 1,376,073 control patients were included in the analysis. Four studies were from Asia, and six were from Europe and North America. Two of the studies were cohort studies, seven were case-controlled studies, and one was a cross-sectional study.

Prevalence of AITD in patients with psoriasis

Ten studies provided available data on the prevalence of AITD in patients with psoriasis. The meta-analysis showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.46, 95% CI: 1.28 - 1.67, Z = 5.51, p <0.001), and the heterogeneity was moderate (I^2 = 70.6%, p <0.001). Subgroup analyses by study type indicated that the prevalence of AITD was significantly higher in the case-control

study strata (OR = 1.40, 95% CI: 1.18 - 1.67, Z = 3.88, p <0.001) and the cross-section study strata (OR = 2.11, 95% CI: 1.55-2.88, Z = 4.72, p <0.001), but not in the cohort study strata (OR = 1.55, 95% CI: 0.95 - 2.54, Z = 1.76, p = 0.079) (figure. 2).

Sensitivity analysis and publication bias

The combined effects after removal of any one study were all within the confidence interval of the total combined effect (figure. 3A). Therefore, the results of the analysis were reliable and stable. The funnel chart for the publication bias is shown in Figure. 3B. The results of Egger's test suggested no significant publication bias was evident (p = 0.066, figure. 3C).

Psoriasis and thyroid function status

Patients with psoriasis had a significantly higher prevalence of hypothyroidism than the controls (OR = 1.44, 95% CI: 1.34 - 1.55, Z = 9.44, p <0.001) and no significant heterogeneity was observed (I^2 = 0.0%, p = 0.679). Patients with psoriasis had a higher prevalence of hyperthyroidism than the controls (OR = 1.20, 95% CI: 1.11 - 1.30, Z = 4.76, p <0.001). No significant heterogeneity was observed (I^2 = 0.0%, p = 0.512, figure. 4A-B).

Additionally, a higher prevalence of subclinical hypothyroidism and subclinical hyperthyroidism was observed in patients with psoriasis compared with the controls (Subclinical hypothyroidism: OR = 2.17, 95% CI: 0.27 - 17.72, Z = 0.72, p = 0.470. Subclinical hyperthyroidism: OR = 2.66, 95% CI: 0.74 - 9.56, Z = 1.50, p = 0.132). However, the difference was not statistically significant (Supplementary figure. 1 A-B).

Psoriasis and specific autoimmune thyroid diseases

The prevalence of HT in patients with psoriasis and in the controls was 0.209% and 0.199%, respectively, while the prevalence of GD in patients with psoriasis and in the controls was 0.443% and 0.405%, respectively. The prevalence of HT was significantly higher in patients with psoriasis than the controls (OR = 1.68, 95% CI: 1.48 - 1.92, Z = 7.86, p <0.001) and the heterogeneity was mild (I^2 = 37.3%, p = 0.188). However, the heterogeneity of GD in these studies was too severe (I^2 = 92.7%, p <0.001), so the OR (OR = 1.02, 95% CI: 0.65 - 1.60, Z = 0.07, p = 0.943) had no reference value (figure. 4C, figure. 5A).

Psoriasis and thyroid serological antibodies

The positive rate of TgAb was significantly higher in patients with psoriasis than the controls (OR = 1.76, 95% CI: 1.28 - 2.43, Z = 3.47, p = 0.001) and no significant heterogeneity was observed (I^2 = 14.3%, p = 0.323). The positive rate of TPOAb was significantly higher in patients with psoriasis than the controls (OR = 1.77, 95% CI: 1.31 - 2.40, Z = 3.68, p <0.001) and the heterogeneity was mild (I^2 = 45.0%, p = 0.122). Since no studies have been published about the positive rate of TRAb in patients with psoriasis, only TgAb and TPOAb were analyzed (figure. 5B-C).

Heterogeneity analysis

According to the results of the funnel plot, three studies outside the funnel plot were removed and the meta-analysis was conducted again. The results of the second analysis also showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.30, CI: 1.18-1.43, Z = 5.46, p <0.001) and the heterogeneity was

mild (I^2 = 46.8%, p = 0.080) The source of heterogeneity in the study of Antonelli *et al*. was that all the patients were patients with psoriatic arthritis, and the prevalence of AITD in patients with psoriatic arthritis may be higher than that of patients with psoriasis[21]. The source of heterogeneity in the study by Peluso *et al.* may have been due to the control group bring comprised of hospital staff rather than the general population[2]. The source of heterogeneity in the study of Kiguradze *et al.* may lie in the fact that it was a cross-sectional study[13]. These three studies were not excluded because they had little effect on the final results of the analysis.

DISCUSSION

To our knowledge, this is the first meta-analysis focusing on the risk of AITD for psoriasis patients. While the study by Khan SR *et al.* is the first meta-analysis of studies on the association between AITD and the risk of psoriasis incidence[22]. We summarized all available evidence on the association between psoriasis and AITD. Our meta-analysis found that the prevalence of AITD, and particularly HT, was higher in patients with psoriasis than the control individuals. Additionally, elevated positive rates of TgAb and TPOAb were also observed in patients with psoriasis. Collectively, a positive association between psoriatic disease and AITD can be indicated. Considering that psoriasis is a type of discosmetic dermatosis that is easy to be concerned about, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD. As such, we recommend that patients with psoriasis receive a thyroid-related examination at their first visit, as well at regular follow-ups to assess thyroid function. By promoting early diagnosis and treatment of AITD, patients

may be able to avoid thyroid dysfunction.

Main findings

The primary finding of this meta-analysis is the increased prevalence of AITD in the population of patients with psoriasis. However, moderate heterogeneity was observed. We hypothesize that the inconsistency of the study designs was the major source of heterogeneity. When the subgroup analysis according to different study designs was conducted, the heterogeneity in each subgroup was reduced, and the results remained positive. According to the definition of the study designs, an accurate cause-effect relationship can only be demonstrated in the cohort studies. In the present study, three types of study designs were included in the meta-analysis, including cohort, case controlled, and cross-sectional studies. Therefore, the results should be interpreted with caution. Additionally, it has been demonstrated that the prevalence of HT in patients with psoriasis is elevated compared with the controls. HT, a main clinical subtype of AITD, is generally accompanied by hypothyroidism. An elevated frequency of hypothyroidism was also observed in patients with psoriasis. Taken together, the current data indicates that psoriasis may be closely associated with the loss-of-function disorder of the thyroid gland.

Common pathogenesis of psoriasis and AITD

Abnormal immunological reaction and underlying genetic risk are two indispensable factors responsible for triggering psoriasis and AITD. These two diseases share some autoimmune processes and susceptibility genes, which may explain the concurrence of psoriasis and AITD. The predominant Th1 immune reaction has been

observed in patients with psoriasis[23 24], such as Th1 infiltration in involved tissues, and high serum levels of Th1-prototype chemokines and cytokines (TNF-α, IFN-γ, and CXCL10), all of which are present in AITD[25-27]. Additionally, Th17-mediated immune disorder has also been observed in psoriasis and AITD[28 29]. Several predisposing genetic alleles or regions are shared by the two diseases. For example, the genetic data from 265 families with two or more autoimmune disorders have shown that the PTPN22-R620W allele has a remarkable association with HT and a mild association with psoriasis[30 31]. Additionally, other SNP variations in the PTPN22 gene have been demonstrated to be indicators for evaluating the risk of psoriasis[32]. IL12B has been generally recognized as a psoriasis susceptibility gene[33], an upstream variation of which was found to affect the phenotype of AITD in men[34].

Implications for practice

It has been reported that the administration of acitretin, a common drug for the treatment of psoriasis, can lead to the reduction of free T4 (thyroid hormone) levels in patients with psoriasis[17]. The finding suggests that patients with psoriasis should have thyroid-related examinations regularly while undergoing acitretin treatment. In addition, propylthiouracil (PTU), a drug used to inhibit thyroid hormone synthesis, has been found to be effective in the treatment of psoriasis[35]. Based on the above findings, it is recommended that the treatment options be adjusted once patients with psoriasis are diagnosed with comorbid AITD.

Limitations

This meta-analysis contains several limitations. First, the meta-analysis included

studies with different study designs. Given this, we conducted a subgroup analysis of each study design. However, the heterogeneity did not improve, suggesting that different study designs were not the main source of heterogeneity. Second, the diagnostic criteria of psoriasis and AITD, gender ratio, and course of disease varied from study to study, but meta-analysis regression was meaningless due to the small number of articles included in our study. Additionally, the included studies were conducted in different regions, so the influence of geographical location, living habits, and drug use may also affect the prevalence of AITD in the population, resulting in discordance. Therefore, further large-scale and high-quality prospective studies are still required to validate our findings.

CONCLUSIONS

The present meta-analysis revealed that AITD was more prevalent in patients with psoriasis than in the general population, especially loss-of-function disorder of the thyroid gland. Moreover, patients with psoriasis were found to have elevated positive rates of TPOAb and TgAb compared to the control individuals. Accordingly, we recommend that every dermatologist be conscious of this association and suggest those thyroid-related examinations, such as thyroid function test and analysis of thyroid antibodies, be included in the routine tests for patients with psoriasis.

Contributors XZ and SZ carried out the extraction of reference data, meta-analysis, and wrote manuscripts, RW and PZ supported and assisted the manuscripts, YS and SL reviewed and suggested the manuscripts. All authors were involved in finalizing the

manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As this is a meta-analysis ethics approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. No additional data are available.

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Figure legend:

Figure 1 Flowchart for study screening

Figure 2 Forest plot of the association between psoriasis and autoimmune thyroid

disease

Figure 3 Sensitivity analysis and publication bias

Figure 4 A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

Figure 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

Database	Retrieval strategy
PubMed	((((((((((Thyroid[Title/Abstract]) OR (Thyroiditis[Title/Abstract])) OR (Hashimoto Thyroiditis[Title/Abstract])) OR (Graves Disease[Title/Abstract])) OR (Hyperthyroidism[Title/Abstract])) OR (Hypothyroidism[Title/Abstract])) OR (TgAb[Title/Abstract])) OR (TPOAb[Title/Abstract])) OR (TRAb[Title/Abstract])) OR (Endocrine Comorbidities[Title/Abstract])) OR (Autoimmune diseases[Title/Abstract])) AND ((psoriasis[Title/Abstract]) OR (psoriatic[Title/Abstract]))
Cochrane	(((Psoriasis) OR psoriatic) OR Pustulosis of Palms) AND (((((((Thyroid) OR Thyroiditis) OR Thyroiditides) OR Hashimoto Disease) OR Graves Disease) OR Hyperthyroidism) OR Hypothyroidism)). Then chose "Trials"
Embase	(thyroid:ab,ti OR thyroiditis:ab,ti OR 'hashimoto thyroiditis':ab,ti OR 'graves disease':ab,ti OR hyperthyroidism:ab,ti OR hypothyroidism:ab,ti OR tgab:ab,ti OR tpoab:ab,ti OR trab:ab,ti OR 'endocrine comorbidities':ab,ti OR 'autoimmune diseases':ab,ti) AND (psoriasis:ab,ti OR psoriatic:ab,ti)

Table 1 Database source and retrieval strategy.

TPOAb: Thyroid peroxidase antibody; TgAb: Thyroglobulin antibody; TRAb: Thyroid stimulating hormone receptor antibody.

Study (Author)	Year	Country	Study design	No.Patients	No.Controls	Patients, % male	Patients, mean age
Antonelli *et al.*	2006	Italy	Case-control	80	400	45	57
Tsai *et al.*	2011	China	Case-control	51800	207200	61.6	46.4
Peluso *et*	2011	Italy	Case-	108	318	47.2	39.9

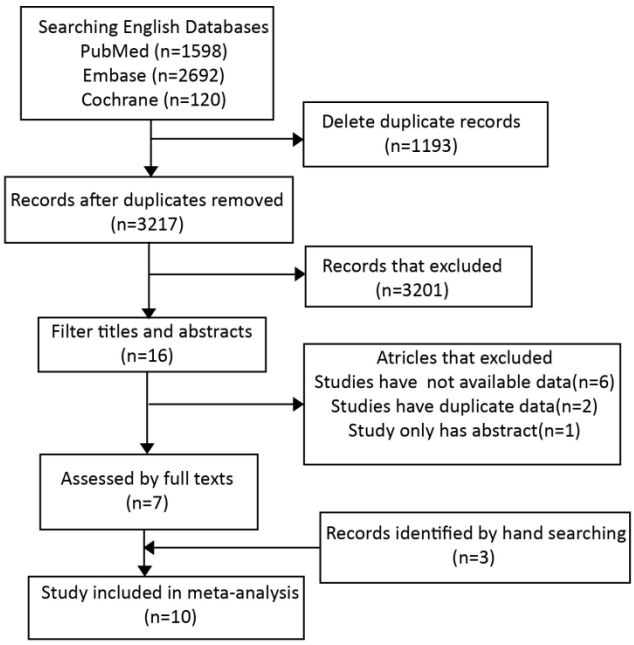
al.			control				
Wu *et al.*	2012	American	Case-control	25341	126705	51.6	48.9
Vassilatou *et al.*	2017	Greece	Case-control	114	286	50.9	52.7
Kiguradze *et al.*	2017	Greece	Cross-sectional	9654	846961	NA	NA
Haddad *et al.*	2017	Israel	Case-control	3161	31610	46.6	58.4
Fallahi *et al.*	2017	Italy	Cohort	97	97	47.4	56
Alidrisi *et al.*	2019	Iraq	Case-control	56	54	41.1	43.05
Wang *et al.*	2019	China	Cohort	162842	162842	59.35	45

Table 2 Characteristics of the included studies

Study (Author)	Definition of psoriasis	Definition of AITD	NOS score
Antonelli *et al.*	PsA was diagnosed by the criteria of Vasey and Espinoza	AITD was diagnosed by serum levels of thyroid stimulating hormone and TgAb and TPOAb	7
Tsai *et al.*	Ps was diagnosed by clinical examination	AITD was diagnosed by clinical examination	6
Peluso *et al.*	PsA was diagnosed by the Classification of Psoriatic Arthritis study group criteria	AITD was diagnosed by serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL, and Thyroid ultrasonography	7
Wu *et al.*	Ps was diagnosed by clinical diagnosis	AITD was diagnosed by clinical diagnosis	7
Vassilatou *et al.*	Ps was diagnosed by clinical examination	AITD was diagnosed by serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL	7
Kiguradze *et al.*	Ps was diagnosed by clinical diagnosis	AITD was diagnosed by clinical diagnosis	6
Haddad *et al.*	Ps was diagnosed by clinical diagnosis	AITD was diagnosed by clinical diagnosis	6
Fallahi *et al.*	PsA was diagnosed by the criteria of Vasey and Espinoza	AITD was diagnosed by serum levels of TgAb or TPOAb > 100 IU/mL	6
Alidrisi *et*	Ps was diagnosed by clinical	AITD was diagnosed by serum levels of	6

al.	diagnosis	TgAb > 115 IU/mL or TPOAb > 34 IU/mL	
Wang *et al.*	Ps was diagnosed by at least 2 outpatient visits or 1 hospital admission	AITD was diagnosed by at least 2 outpatient visits or 1 hospital admission	8

Table 3 Characteristics of the included studies (2)



Flowchart for study screening

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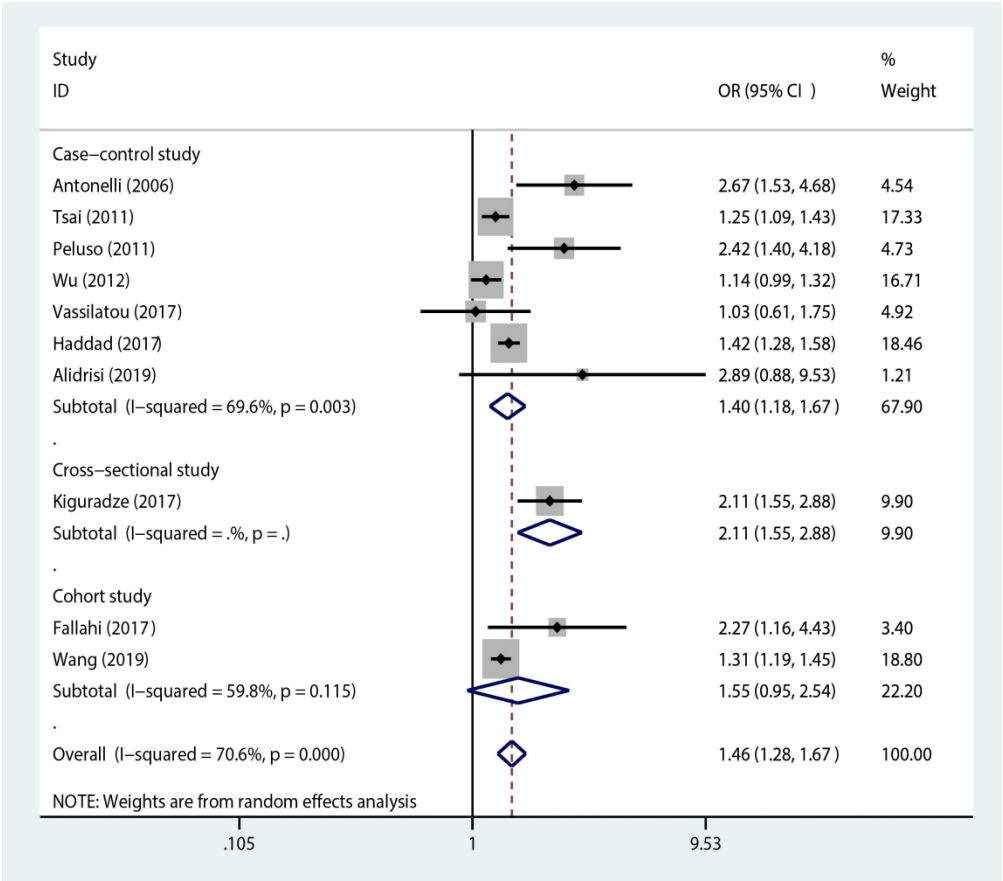
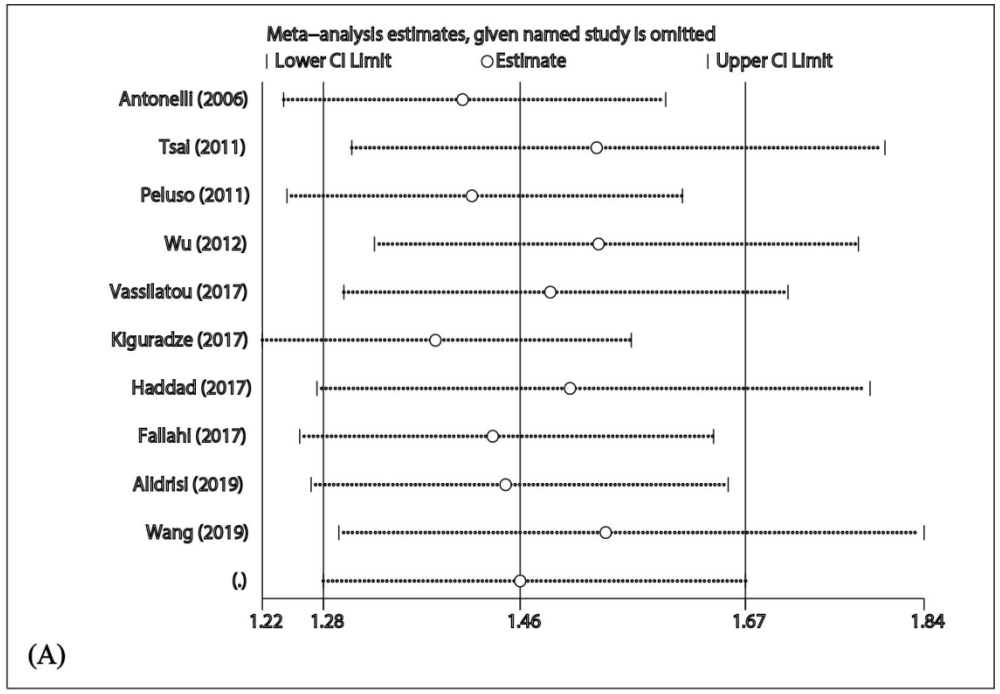
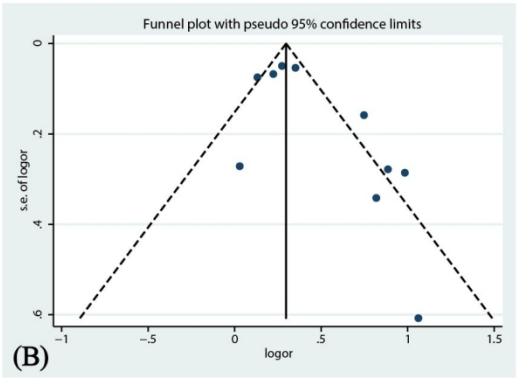
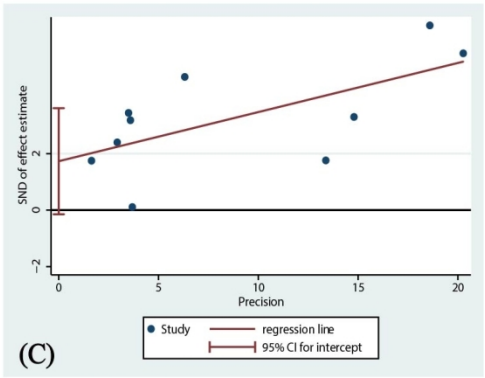


Forest plot of the association between psoriasis and autoimmune thyroid disease

215x189mm (300 x 300 DPI)

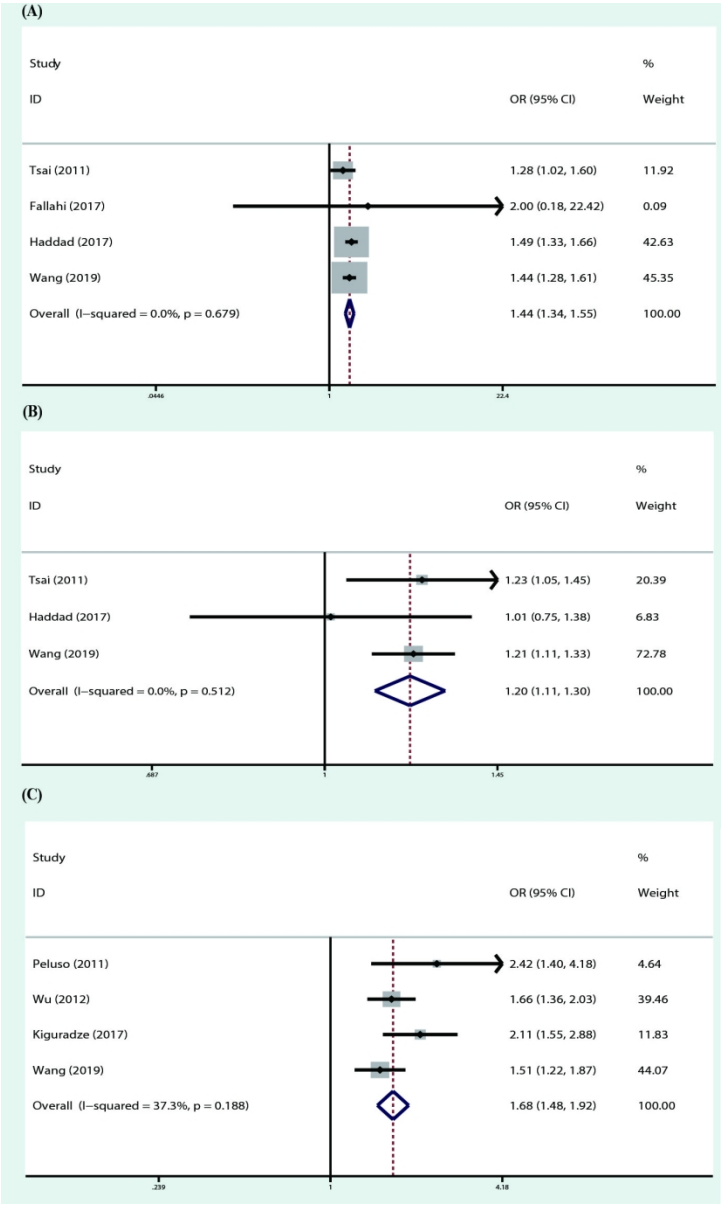






Sensitivity analysis and publication bias

141x150mm (300 x 300 DPI)



A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

117x195mm (300 x 300 DPI)

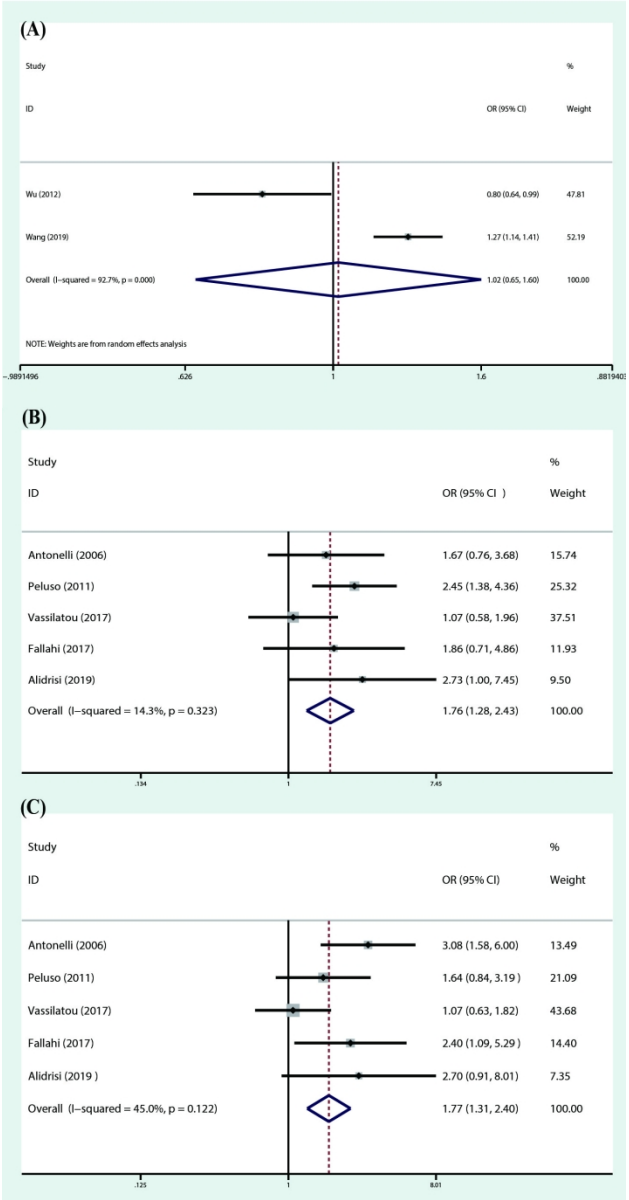
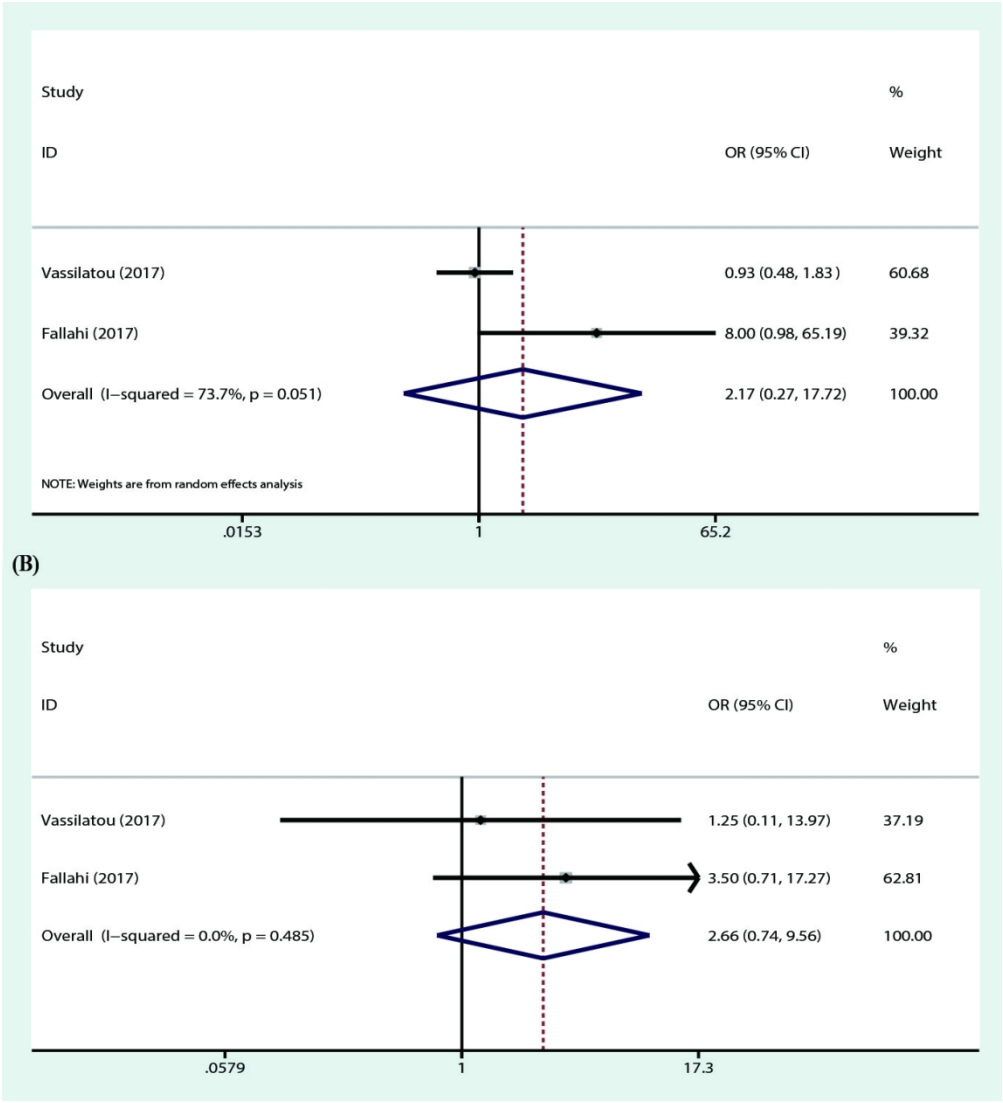


Fig. 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

124x237mm (300 x 300 DPI)



117x129mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5, Table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6, Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6, Figure 1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Table 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Table 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7 - 10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figure 2 - 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7, 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Figure 3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8, Figure 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8, Figure 3

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	×
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	×
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2 - 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8 - 9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	×
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	×
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 1

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

PRISMA 2020 Checklist

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The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis

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Secondary Subject Heading:	Dermatology, Immunology (including allergy)
Keywords:	Thyroid disease < DIABETES & ENDOCRINOLOGY, IMMUNOLOGY, Psoriasis < DERMATOLOGY

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The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis

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Running title: A meta-analysis of AITD and psoriasis

Abstract

Objective Psoriasis is a chronic inflammatory disease with autoimmune etiology. A possible link between psoriasis and autoimmune thyroid disease (AITD) has been suggested in some studies with inconsistent findings. This meta-analysis aims to determine the association between psoriasis and AITD.

Design A Meta-analysis of observational studies.

Data sources PubMed, EMBASE, Scopus, and the Cochrane Library were searched up to November 1st, 2021.

Eligibility criteria for selecting studies We included non-randomized studies, each with over 50 cases in every group, focusing on the rate of comorbidity between psoriasis and AITD.

Data extraction and synthesis Two independent reviewers screened the articles and extracted data. The restricted maximum-likelihood was applied to perform the meta-analysis. Odds ratio (OR) and 95% confidence intervals (CI) were pooled to compare the prevalence of AITD in psoriasis and control groups. Heterogeneity was assessed with I^2 statistic. The Newcastle-Ottawa Scale (NOS) and Agency for Healthcare Research and Quality (AHRQ) were applied for quality assessment. The risk of bias was assessed with ROBINS-I.

Results Eleven available studies with data on 253,313 patients with psoriasis and 1,376,533 controls were included. Meta-analysis showed that patients with psoriasis had a higher prevalence of AITD (OR = 1.76, 95% CI: 1.35 - 2.28, Z = 4.25, p <0.01), especially loss-of-function disorder of the thyroid gland. Both TgAb positive rate (OR = 1.98, 95% CI: 1.27 - 3.10, Z = 3.00, p <0.01) and TPOAb positive rate (OR = 2.15, 95% CI: 1.31 - 3.52, Z = 3.05, p <0.01) were also increased in the psoriasis group compared

to the control group.

Conclusions Our study indicates that the rate of co-occurring AITD was significantly increased in patients with psoriasis. It suggests that the increased risk of AITD should be concerned in patients with psoriasis.

PROSPERO registration number CRD42020206005

Keywords: Psoriasis, Thyroid, Immunology

Strengths and limitations of this study

This is the first meta-analysis focusing on the risk of AITD for psoriasis patients, which included hypothyroidism, hyperthyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, Hashimoto's thyroiditis, Graves' disease, TgAb positivity and TPOAb positivity.

All studies included were of moderate to high quality and were representative. All studies were published in recent years.

The heterogeneity in the pooled data cannot be ignored, and was not improved by subgroup analysis. However, meta-regression analysis identified the differences of sample size and scope of research on AITD among these studies as the potential sources of heterogeneity.

INTRODUCTION

Psoriasis is a chronic inflammatory disease with autoimmune etiology, affecting approximately 125 million people around the world.[1] The skin lesions of psoriasis occur mainly on the scalp, trunk, and exterior surfaces of the limbs, and manifest as erythema, plaques, and scales.[2] Apart from the impaired appearance and intense pruritus of the skin lesions, various comorbidities have a significant impact on the quality of life in patients with psoriasis.[3 4] Among the comorbidities, autoimmune thyroid disease (AITD) has been characterized in patients with psoriasis. For patients with psoriasis who also develop complications, their management requires extra attention.[5] Therefore, understanding the risk of other diseases on psoriasis has important clinical significance.

Autoimmune thyroid disease (AITD) is an inflammatory disease of the thyroid gland with the presence of thyroid autoantibodies, lymphocytic infiltration of thyroid parenchyma, and even thyroid dysfunction.[6] Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the two main clinical subtypes of AITD. GD is characterized by hyperthyroidism and the presence of thyroid-stimulating hormone receptor antibodies (TRAb) in serum, while HT is characterized by hypothyroidism and the presence of thyroid peroxidase antibodies (TPOAb) or Thyroglobulin antibodies (TgAb) in serum.[7]

Psoriasis and AITD share some common pathophysiological features, such as Th1-predominant adaptive immune reaction.[6] Hence, the relationship between AITD and psoriasis has been hypothesized and studied. In 2006, Antonelli *et al.* first

reported that the prevalence of AITD in patients with psoriatic arthritis was significantly higher than in the general population.[8] However, the study reported by Tsai *et al*.[9] pointed that the association between psoriasis and AITD was limited. In recent years, several observational studies regarding the association between psoriasis and AITD were published in succession, but the results of the studies were inconsistent.[10-16] In addition, Karadag *et al.* reported that the commonly administered acitretin treatment for psoriasis system treatment affects the levels of free T4 (thyroid hormone).[17] To address this discrepancy, we designed and performed a meta-analysis with the existing evidence to assess the relationship between psoriasis and AITD and provide guidance on the clinical management of psoriasis.

METHODS

Search strategy

The literature search was conducted through PubMed, EMBASE, Scopus, and the Cochrane Library for relevant studies published before November 1st, 2021. Detailed literature-search strategies of the databases are presented in Table 1.

Inclusion and exclusion criteria

The inclusion criteria for the studies included in our analysis were the following: (1) The prevalence of AITD in patients with psoriasis/psoriatic arthritis and non-psoriasis were studied; (2) The study was a cohort study, case-control study, or cross-sectional study; (3) The observed indicators were at least one of the following outcomes: the prevalence of hypothyroidism, hyperthyroidism, HT, GD, or the positive rate of TPOAb, TgAb, or TRAb; (4) The number of patients with psoriasis

and the control group should be over 50. Drug-related studies, animal studies, reviews, and conference abstracts were excluded from our analysis.

Data extraction

The specific process for analyzing the studies generated from the search was as follows: record screening and data extraction were performed by two independent authors (X Zhang and S Zhang) according to the above retrieval strategy. In case of dispute, the third author(R Wu) would reassess and reach an agreed decision after discussion. The following information in the included studies was extracted: the name of the first author, year of publication, country of origin, study design, sample size, the definition of psoriasis and AITD, gender ratio, and mean age.

Quality assessment

The Newcastle-Ottawa Scale (NOS)[18] was used to assess the quality of the included cohort and case-control studies. The quality of the study was scored by three dimensions: selection, comparability, and exposure/outcome. Studies that achieved 0-3, 4-6, 7-9 scores were considered of low, moderate and high qualities respectively. Additionally, the tools recommended by the Agency for Healthcare Research and Quality (AHRQ)[19] were used for the cross-sectional studies. Eleven items were included in AHRQ. The study would get one point if the answer "Yes", otherwise no point was got. Studies achieved: 0-3, 4-7,and 8-11 points were considered of low, moderate and high qualities respectively. Moreover, the ROBINS-I was used to assess the risk of bias.[20] The assessments were carried by two authors (X Zhang and S Zhang), and checked by the third author(R Wu).

The meta-analysis was performed using the Stata 16.0 software. We used the odds ratio (OR) and 95% confidence intervals (CI) to describe the differences between groups. The statistical difference was considered significant when $p < 0.05$. The prediction interval was used to explore the prevalence of AITD in individuals with psoriasis. The I^2 statistic was used to evaluate heterogeneity as follows: $I^2 \leq 25\%$, no heterogeneity; $25\% \leq I^2 \leq 50\%$, mild heterogeneity; $50\% < I^2 \leq 75\%$, moderate heterogeneity; $I^2 > 75\%$, severe heterogeneity. The random effects model was applied throughout the analyses. Publication bias was assessed by funnel plot and Egger's test (Publication bias was considered when $p < 0.1$). Sensitivity analysis was performed to assess the stability of the meta-analysis by omitting one study in each turn. Univariate meta-regression analysis was used to investigate the sources of heterogeneity. The flow chart was drawn in Adobe Illustrator, and the forest plots, funnel plots, and Egger's test charts were drawn by Stata 16.0 software.

Patient and public involvement

There were not patients or the public involved in this review.

RESULTS

Search results

After removing duplicate results, we identified 6380 published studies in the initial search: 6377 studies were included by searching through databases and three studies were harvested by manually searching the references of relevant studies. After screening the titles and abstracts, the remaining 42 studies underwent further full-text screening. Eventually, 11 studies[8-16 21 22] that met the inclusion criteria were included

in the final analysis (figure. 1).

Study characteristics

The basic characteristics of the included studies are shown in Tables 2 and 3. A total of 253,313 patients with psoriasis and 1,376,533 control patients were included in the analysis. Two of the studies were cohort studies, eight were case-controlled studies, and one was a cross-sectional study.

Quality of studies

Overall, five studies were of high qualities and six of moderate ones (Table 3). In the studies checked with NOS (n=10), five studies were considered of moderate qualities because the control groups were not from the same community. The only cross-sectional study checked with AHRQ was a moderate quality study due to confounding controlling was not clear. Based on ROBINS-I, all included studies had moderate risk in overall bias (Table 4).

Prevalence of AITD in patients with psoriasis

Eleven studies provided available data on the prevalence of AITD in patients with psoriasis. The meta-analysis showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.76, 95% CI: 1.35 - 2.28, Z = 4.25, p <0.01). The prediction interval ranged from 0.79 to 2.73, and the heterogeneity was severe ($I^2 = 92.72\%$).

Heterogeneity analysis

To investigate potential sources of heterogeneity, we firstly performed a subgroup analysis by types of study design. The high rate of comorbidity between

psoriasis and AITD was also observed in the cross-sectional study strata (OR = 2.12, 95% CI: 1.55 - 2.89), and in the case-control study strata (OR = 1.75, 95% CI: 1.23 - 2.48, Z = 3.14, p <0.01) but with heterogeneity remaining severe (figure. 2), which indicated that inconsistency of the study designs was not the source of high heterogeneity.

We further conducted a meta-regression analysis to explore the reason for between-study heterogeneity. Seven variables were included in the regression model, covering average age, sex ratio, nation (China or other counties), race (Caucasian or non-Caucasian), sample size, clinical types of psoriasis (psoriasis vulgaris or psoriatic arthritis), and scope of research on AITD (all studies were divided into two categories: the one focusing on the loss-of-function disorder of the thyroid gland alone; another one focusing on both the loss-of-function disorder and hyperfunction disorder of the thyroid gland). When the criterion was set as p<0.1, sample size (β = -0.40, *S.E.* = 0.20, p = 0.07) and scope of research on AITD (β = 0.45, *S.E.* = 0.15, p = 0.02) were the potential sources of high heterogeneity.

Besides, we removed three studies[8 13 21] outside the funnel plot and then conducted the meta-analysis again. The results of the reanalysis also showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.34, CI: 1.20-1.50, Z = 5.07, p <0.01), but with moderate heterogeneity (I^2 = 57.30%). The results indicated that these three studies might also contribute to on severe heterogeneity of previous analysis. The source of heterogeneity in the study of Antonelli *et al*. was that all the patients were patients with psoriatic arthritis,[8] and the

prevalence of AITD in patients with psoriatic arthritis may be higher than that of patients with psoriasis.[23] The source of heterogeneity in the study by Peluso *et al.* may have been due to the control group being comprised of hospital staff rather than the general population.[21] The source of heterogeneity in the study of Kiguradze *et al.* may lie in the fact that it was a cross-sectional study.[13] These three studies were not excluded because they had little effect on the final results of the analysis.

Sensitivity analysis and publication bias

Omission of either of the included studies did not significantly change the confidence interval of the combined effect (figure. 3A). Therefore, the results of the analysis were reliable and stable. The funnel plot for the publication bias is shown in figure. 3B. The results of Egger's test showed significant publication bias (p = 0.036, figure. 3C). There was a possibility of exaggerating the association between psoriasis and AITD.

Psoriasis and thyroid function status

Patients with psoriasis had a higher prevalence of hypothyroidism than the controls (OR = 1.21, 95% CI: 1.12 - 1.30, Z = 4.80, p <0.01) and no significant heterogeneity was observed (I^2 = 0.00%). Patients with psoriasis had a higher prevalence of hyperthyroidism than the controls (OR = 1.20, 95% CI: 1.12 - 1.30, Z = 4.78, p <0.01) and no significant heterogeneity was observed (I^2 = 0.00%, figure. 4A-B).

Additionally, a higher prevalence of subclinical hypothyroidism and subclinical hyperthyroidism was observed in patients with psoriasis compared with the controls

(Subclinical hypothyroidism: OR = 2.24, 95% CI: 0.26 - 19.13, Z = 0.74, p = 0.46. Subclinical hyperthyroidism: OR = 2.66, 95% CI: 0.70 - 10.07, Z = 1.44, p = 0.15). However, the difference was not statistically significant (Supplementary figure. 1 A-B).

Psoriasis and specific autoimmune thyroid diseases

The prevalence of HT in patients with psoriasis and the controls was 0.215% and 0.199%, respectively. In comparison, the prevalence of GD in patients with psoriasis and the controls was 0.443% and 0.405%, respectively. The prevalence of HT was significantly higher in patients with psoriasis than the controls (OR = 1.88, 95% CI: 1.50 - 2.35, Z = 5.47, p <0.01) and the heterogeneity was moderate (I^2 = 55.98%). The prevalence of GD was also higher in patients with psoriasis than the controls (OR = 1.02, 95% CI: 0.65 - 1.60, Z = 0.07, p = 0.94) and the heterogeneity was severe (I^2 = 92.78%). However, the difference was not statistically significant (figure. 4C, figure. 5A).

Psoriasis and thyroid serological antibodies

No studies provided data on the positive rate of TRAb in patients with psoriasis, so we only included TgAb and TPOAb in the meta-analysis (figure. 5B-C).The positive rate of TgAb was significantly higher in patients with psoriasis than the controls (OR = 1.98, 95% CI: 1.27 - 3.10, Z = 3.00, p <0.01) and the heterogeneity was mild (I^2 = 41.54%). The positive rate of TPOAb was significantly higher in patients with psoriasis than the controls (OR = 2.15, 95% CI: 1.31 - 3.52, Z = 3.05, p <0.01) and the heterogeneity was moderate (I^2 = 56.27%).

DISCUSSION

To our knowledge, this is the first meta-analysis focusing on the risk of AITD for psoriasis patients. The study by Khan *et al.* is the first meta-analysis of studies on the association between AITD and the incidence risk of psoriasis.[24] By summarizing all available evidence on the association between psoriasis and AITD, we found that the prevalence of AITD, particularly HT, was higher in patients with psoriasis than the control individuals. Additionally, elevated positive rates of TgAb and TPOAb were also observed in patients with psoriasis. As psoriasis is a type of discosmetic dermatosis and therefore likely to be of concern, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD. As such, we recommend that patients with psoriasis receive a thyroid-related examination when they have suspicious AITD-related symptoms. By promoting early diagnosis and treatment of AITD, patients may be able to avoid thyroid dysfunction.

Main findings

The primary finding of this meta-analysis is that the prevalence of AITD is increased in patients with psoriasis compared with the general population. However, severe heterogeneity was observed. In order to determine whether or not the inconsistency of the study designs was the primary source of heterogeneity, the subgroup analysis based on different study designs was conducted. However, the heterogeneity was not limited by subgroup analysis; hence the heterogeneity in this meta-analysis was not caused by inconsistency of the study design. Through further meta-regression analysis, we found that the differences in sample size and scope of

research on AITD among these studies might explain the high level of between-study heterogeneity. Furthermore, the heterogeneity was improved when we focused on the link of psoriasis with specific clinical characters of AITD, such as hypothyroidism, hyperthyroidism, and the positivity rate of autoantibodies.

According to the definition of the study designs, an accurate cause-effect relationship can only be demonstrated in cohort studies. The present study included three types of study designs, including cohort, case-controlled, and cross-sectional studies. Therefore, the results should be interpreted with caution. Additionally, it has been demonstrated that the prevalence of HT in patients with psoriasis is elevated compared with the controls. HT, a main clinical subtype of AITD, is generally accompanied by hypothyroidism. An elevated frequency of hypothyroidism was also observed in patients with psoriasis. Taken together, the current data indicates that psoriasis may be closely associated with the loss-of-function disorder of the thyroid gland.

Common pathogenesis of psoriasis and AITD

Both Abnormal immunological reactions and underlying genetic risk can contribute to the pathogenesis of psoriasis and AITD.[25 26] These two diseases share some autoimmune processes and susceptibility genes, which may explain the concurrence of psoriasis and AITD. The predominant Th1 immune reaction has been observed in patients with psoriasis,[27 28] such as Th1 infiltration in involved tissues, and high serum levels of Th1-prototype chemokines and cytokines (TNF-α, IFN-γ, and CXCL10), all of which are present in AITD.[29-32] Additionally, Th17-mediated

immune disorder has also been observed in psoriasis and AITD.[33 34] The two diseases share several predisposing genetic alleles or regions. For example, the genetic data from 265 families with two or more autoimmune disorders have shown that the PTPN22-R620W allele has a remarkable association with HT and a mild association with psoriasis.[35] Additionally, other SNP variations in the PTPN22 gene have been demonstrated to be indicators for evaluating the risk of psoriasis.[36 37] IL12B has been generally recognized as a psoriasis susceptibility gene,[38] an upstream variation of which affects the phenotype of AITD in men.[39]

Implications for practice

Owing to no access to the information on drug application not provided by original researches, drug exposure may be a source of residual confounding in the present study and a potential risk factor for concurrence of psoriasis and AITD, apart from the reasons mentioned above. β-blocker, used to control thyrotoxicosis-related symptoms, has been implicated in induction or exacerbation of psoriasis.[40 41] In addition, it has been reported that the administration of acitretin, a common drug for the treatment of psoriasis, can lead to the reduction of free T4 (thyroid hormone) levels in patients with psoriasis.[17] Therefore, once the patients develop suspicious symptoms after these treatments, diagnostic investigation and intervention should be considered as early as possible to avoid the exacerbation. On the other hand, the treatment for AITD and psoriasis can be mutually beneficial. For example, propylthiouracil (PTU), a drug used to inhibit thyroid hormone synthesis, has been effective in the treatment of psoriasis.[42] Based on the above findings, it is

recommended that the treatment options be adjusted once patients with psoriasis are diagnosed with comorbid AITD.

Limitations

There are several limitations to this meta-analysis. First, the meta-analysis included studies with different study designs. Given this, we conducted a subgroup analysis of each study design, which also showed that the patients with psoriasis had an increased prevalence of AITD in the cross-sectional study strata and the case-control study strata. Second, there is considerable heterogeneity in the present study. Subgroup analysis and meta-regression analysis helped us to identify the potential sources of the heterogeneity. However, there are likely to be other unknown reasons responsible for the heterogeneity. Thirdly, the lack of information on drug application made drug exposure a confounding factor. Therefore, further large-scale and high-quality prospective studies are still required to validate our findings.

CONCLUSIONS

The present meta-analysis revealed that AITD was more prevalent in patients with psoriasis than in the general population, especially loss-of-function disorder of the thyroid gland. Moreover, patients with psoriasis were found to have elevated positive rates of TPOAb and TgAb compared to the control individuals. Accordingly, we recommend that every dermatologist be conscious of this association and suggest necessary examinations and intervention be considered as soon as possible when patients with psoriasis have suspicious AITD-related symptoms.

Contributors XZ and SZ carried out the extraction of reference data, meta-analysis,

and wrote manuscripts, RW and PZ supported and assisted the manuscripts, YS and SL reviewed and suggested the manuscripts. All authors were involved in finalizing the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As this is a meta-analysis ethics approval was not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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Figure legend:

Figure 1 Flowchart for study screening

Figure 2 Forest plot of the association between psoriasis and autoimmune thyroid disease

Figure 3 Sensitivity analysis and publication bias

Figure 4 A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

Figure 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

Database	Retrieval strategy
PubMed	((((((((((Thyroid[Title/Abstract]) OR (Thyroiditis[Title/Abstract])) OR (Hashimoto Thyroiditis[Title/Abstract])) OR (Graves Disease[Title/Abstract])) OR (Hyperthyroidism[Title/Abstract])) OR (Hypothyroidism[Title/Abstract])) OR (TgAb[Title/Abstract])) OR (TPOAb[Title/Abstract])) OR (TRAb[Title/Abstract])) OR (Endocrine Comorbidities[Title/Abstract])) OR (Autoimmune diseases[Title/Abstract])) AND ((psoriasis[Title/Abstract]) OR (psoriatic[Title/Abstract]))
Embase	(thyroid:ab,ti OR thyroiditis:ab,ti OR 'hashimoto thyroiditis':ab,ti OR 'graves disease':ab,ti OR hyperthyroidism:ab,ti OR hypothyroidism:ab,ti OR tgab:ab,ti OR tpoab:ab,ti OR trab:ab,ti OR 'endocrine comorbidities':ab,ti OR 'autoimmune diseases':ab,ti) AND (psoriasis:ab,ti OR psoriatic:ab,ti)
Scopus	((TITLE-ABS-KEY (thyroiditis) OR TITLE-ABS-KEY (hashimoto AND thyroiditis) OR TITLE-ABS-KEY (graves AND disease) OR TITLE-ABS-KEY (hyperthyroidism) OR TITLE-ABS-KEY (hypothyroidism) OR TITLE-ABS-KEY (tgab) OR TITLE-ABS-KEY (tpoab) OR TITLE-ABS-KEY (trab))) AND (TITLE-ABS-KEY (psoriasis) OR TITLE-ABS-KEY (psoriatic))
Cochrane	(((Psoriasis) OR psoriatic) OR Pustulosis of Palms) AND (((((((Thyroid) OR Thyroiditis) OR Thyroiditides) OR Hashimoto Disease) OR Graves Disease) OR Hyperthyroidism) OR Hypothyroidism)). And chose literature published up to "2021/11/01". Then chose “Trials”

Table 1 Database source and retrieval strategy.

TPOAb: Thyroid peroxidase antibody; TgAb: Thyroglobulin antibody; TRAb: Thyroid stimulating hormone receptor antibody.

Study (Author)	Year	Country	Study design	No.Patients	No.Controls	Patients, % Female	Patients, mean age
Antonelli *et al.*	2006	Italy	Case-control	80	400	45	57
Tsai *et al.*	2011	China	Case-control	51800	207200	38.5	46.4
Peluso *et al.*	2011	Italy	Case-control	108	318	52.8	39.9
Wu *et al.*	2012	American	Case-control	25341	126705	48.4	48.9
Vassilatou *et al.*	2017	Greece	Case-control	114	286	49.1	52.7
Kiguradze *et al.*	2017	Greece	Cross-sectional	9654	846961	NA	NA
Haddad *et al.*	2017	Israel	Case-control	3161	31610	53.4	58.4
Fallahi *et al.*	2017	Italy	Cohort	97	97	47.4	56
Alidrisi *et al.*	2019	Iraq	Case-control	56	54	58.9	43.05
Wang *et al.*	2019	China	Cohort	162842	162842	45.5	45
Valduga *et al.*	2021	Valduga	Case-control	60	60	66.7	54.5

Table 2 Characteristics of the included studies

Study (Author)	Definition of psoriasis	Definition of AITD	NOS score
Antonelli *et al.*	The criteria of Vasey and Espinoza	Serum levels of thyroid stimulating hormone and TgAb and TPOAb	7
Tsai *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 242.9x, 244.9x	6
Peluso *et al.*	Classification of Psoriatic Arthritis study group criteria	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL, and Thyroid ultrasonography	7
Wu *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 242.0, 245.2	7
Vassilatou *et al.*	Moll and Wright criteria	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL	7
Kiguradze *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 245.2	6*
Haddad *et al.*	Clinical diagnosis from Clalit Health Services	Clinical diagnosis from Clalit Health Services	6
Fallahi *et al.*	Criteria of Vasey and Espinoza	Serum levels of TgAb or TPOAb > 100 IU/mL	6
Alidrisi *et al.*	Clinical diagnosis from Endocrine and Metabolism Center	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL	6
Wang *et al.*	ICD-9-CM code 696.0	ICD-9-CM code 242, 242.0, 244, 246	8
Valduga *et al.*	Clinical diagnosis and measured by Psoriasis Area and Severity Index (PASI)	Hypothyroidism was detected, or when they need for thyroid hormone replacement therapy or positive of TPOAb with or without TgAb	6

Table 3 Characteristics of the included studies (2)

*This was a score based on the AHRQ evaluation.

ICD-9-CM: The International Classification of Diseases, Ninth Revision, Clinical Modification

Study(Author)	Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Antonelli *et al.*	2006	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Tsai *et al.*	2011	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Peluso *et al.*	2011	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Wu *et al.*	2012	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk
Vassilatou *et al.*	2017	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kiguradze *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk
Haddad *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Fallahi *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Alidrisi *et al.*	2019	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Wang *et al.*	2019	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Valduga *et al.*	2021	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk

Table 4 Risk of bias for the 11 included studies based on the ROBINS-I tool

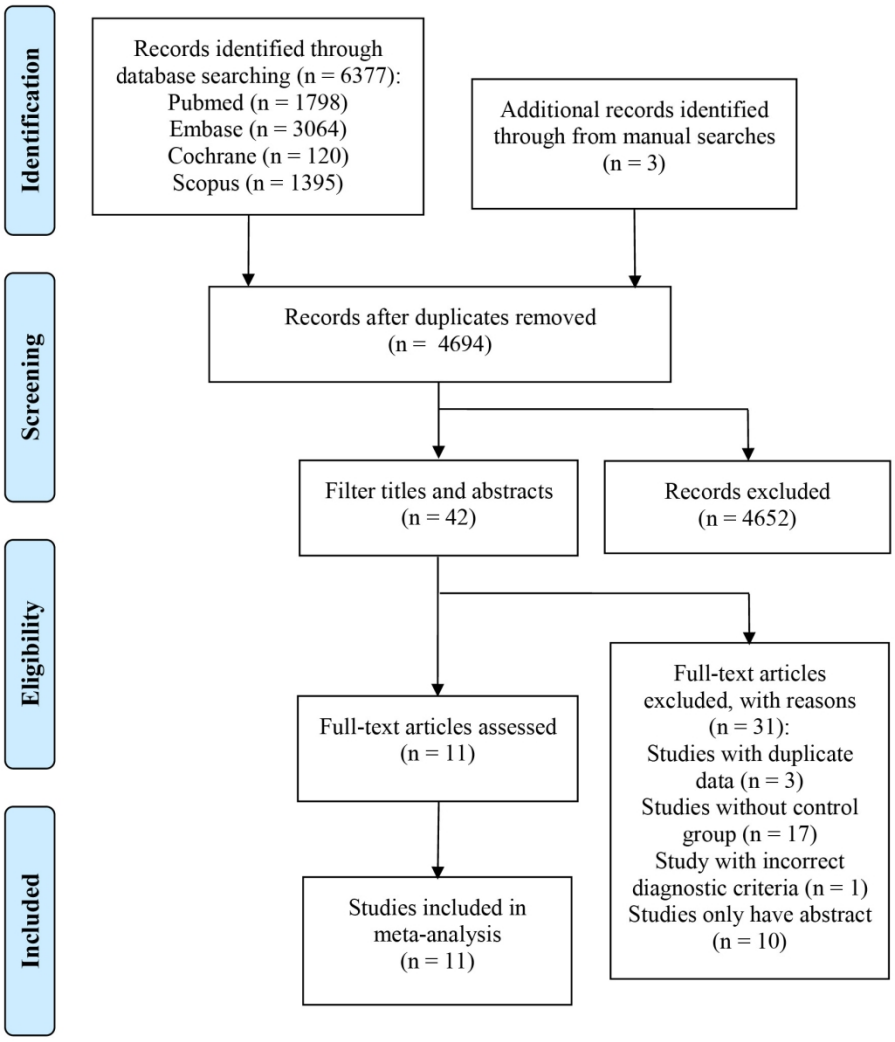


Figure 1 Flowchart for study screening

164x200mm (300 x 300 DPI)

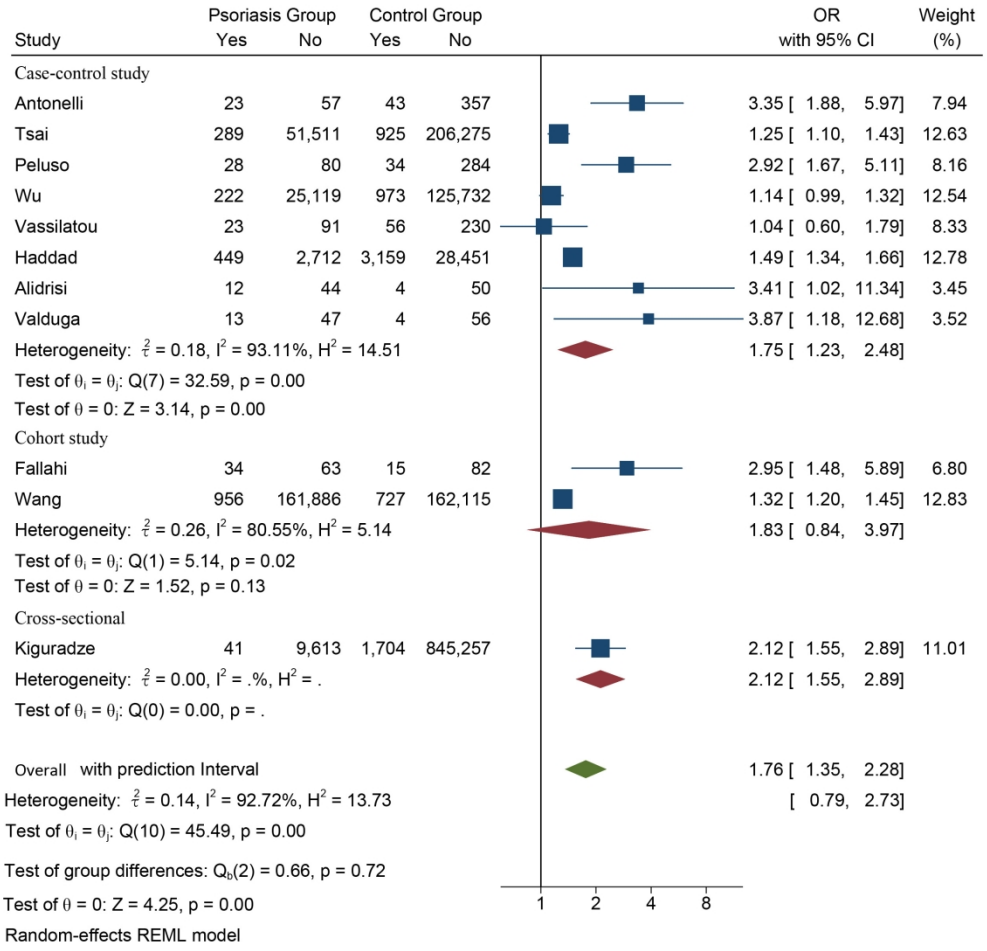


Figure 2 Forest plot of the association between psoriasis and autoimmune thyroid disease

215x206mm (300 x 300 DPI)

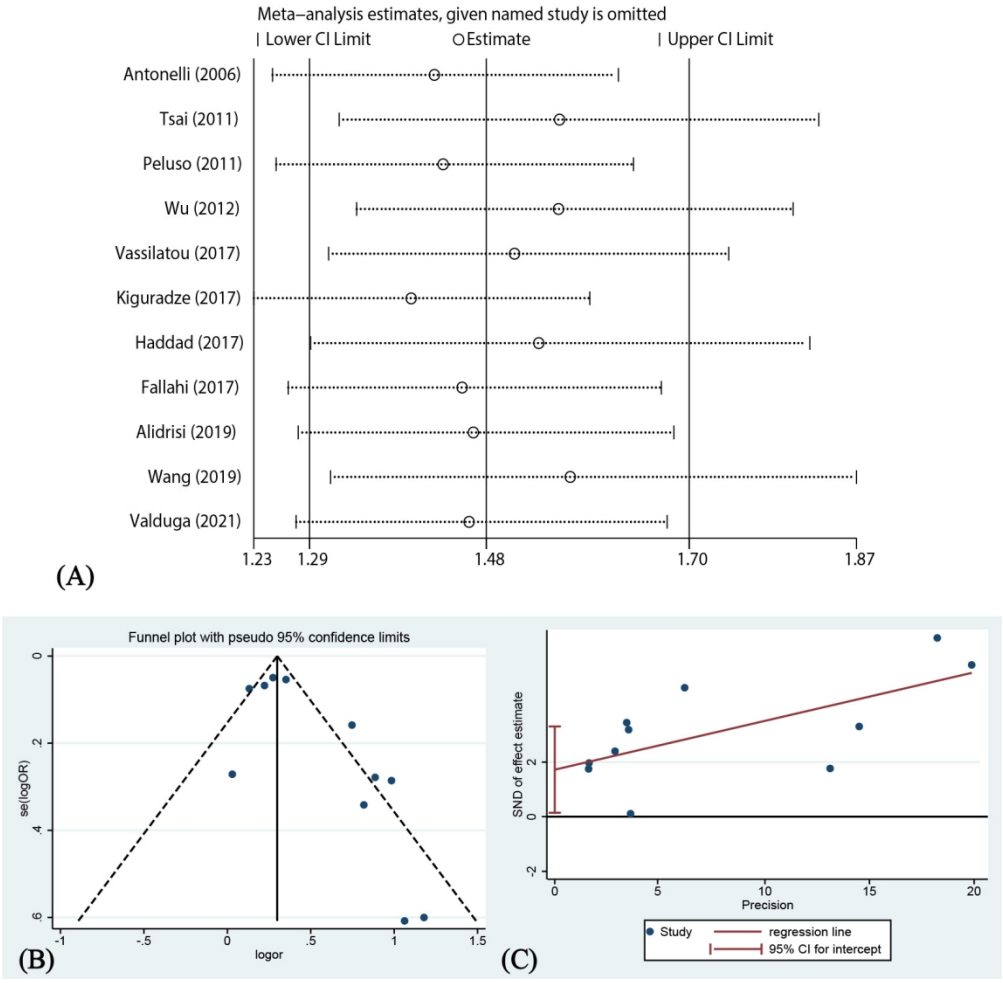


Figure 3 Sensitivity analysis and publication bias

141x138mm (300 x 300 DPI)

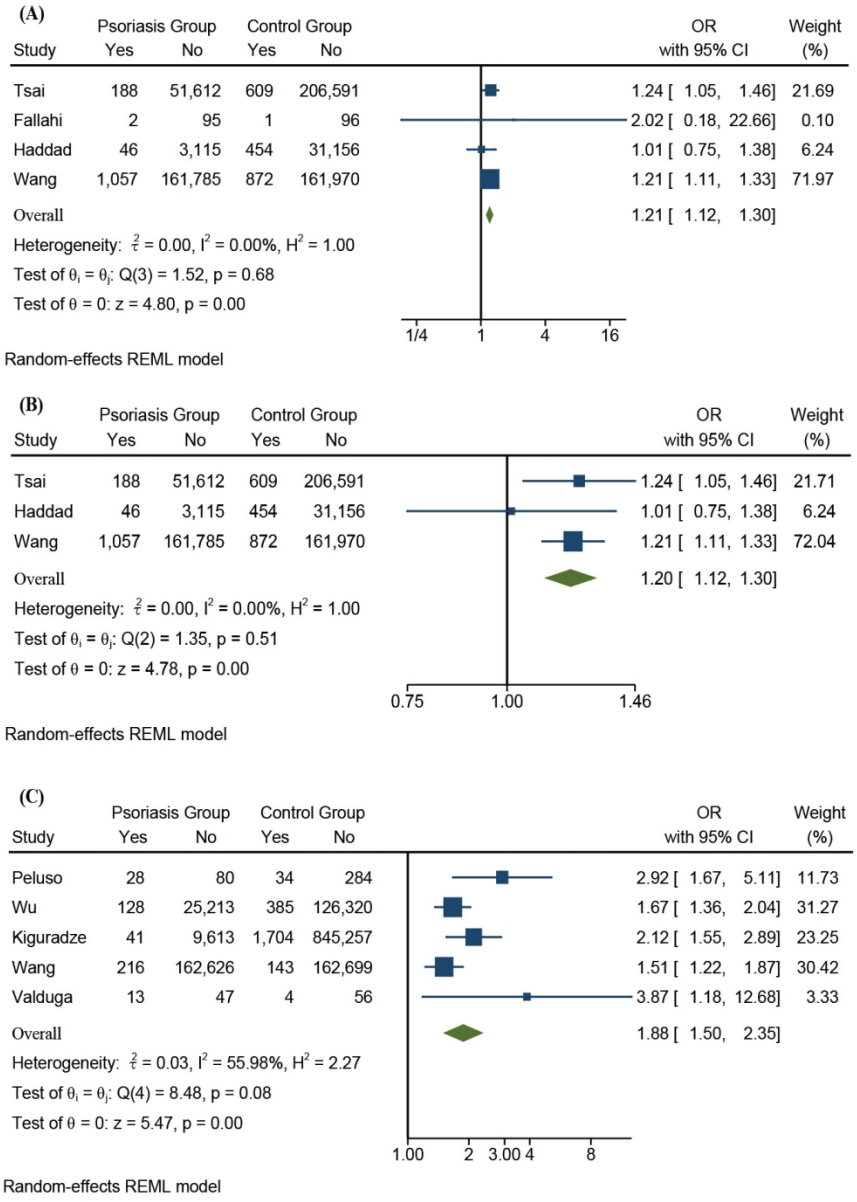


Figure 4 A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

117x162mm (300 x 300 DPI)

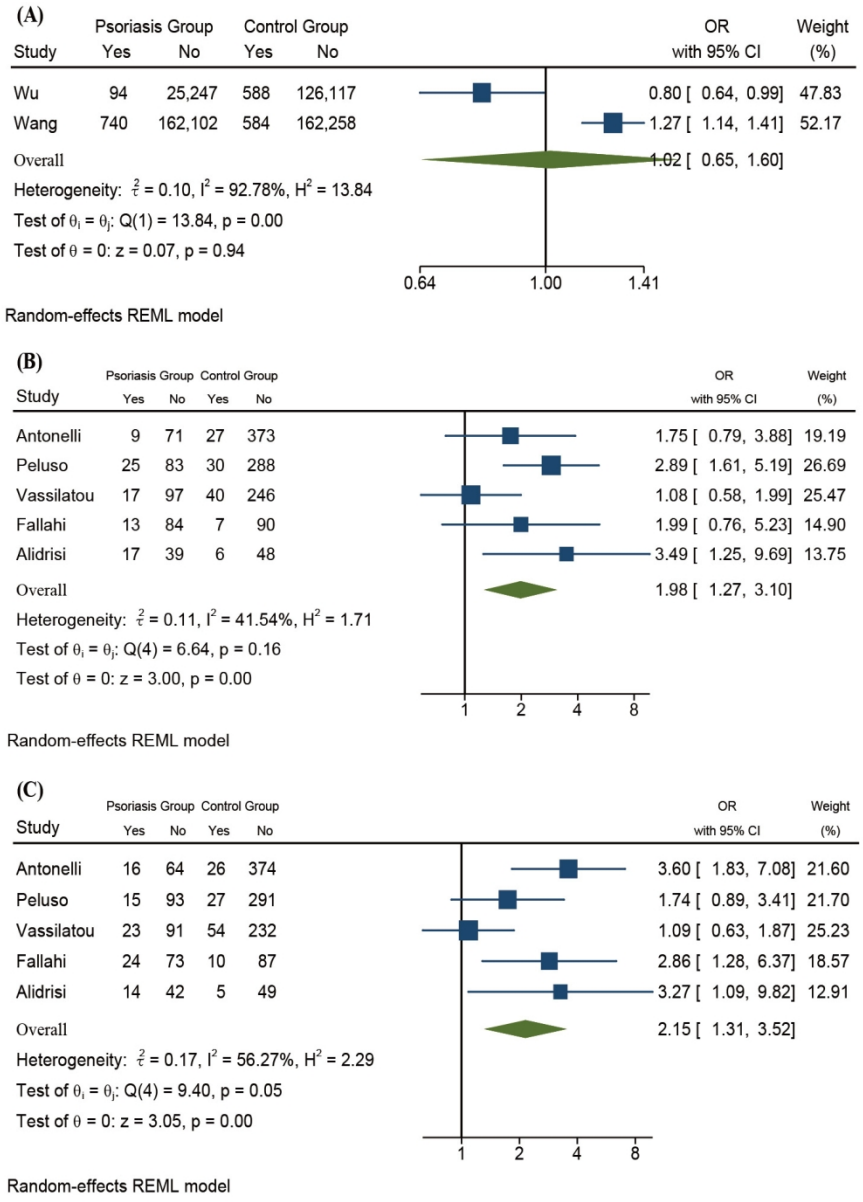
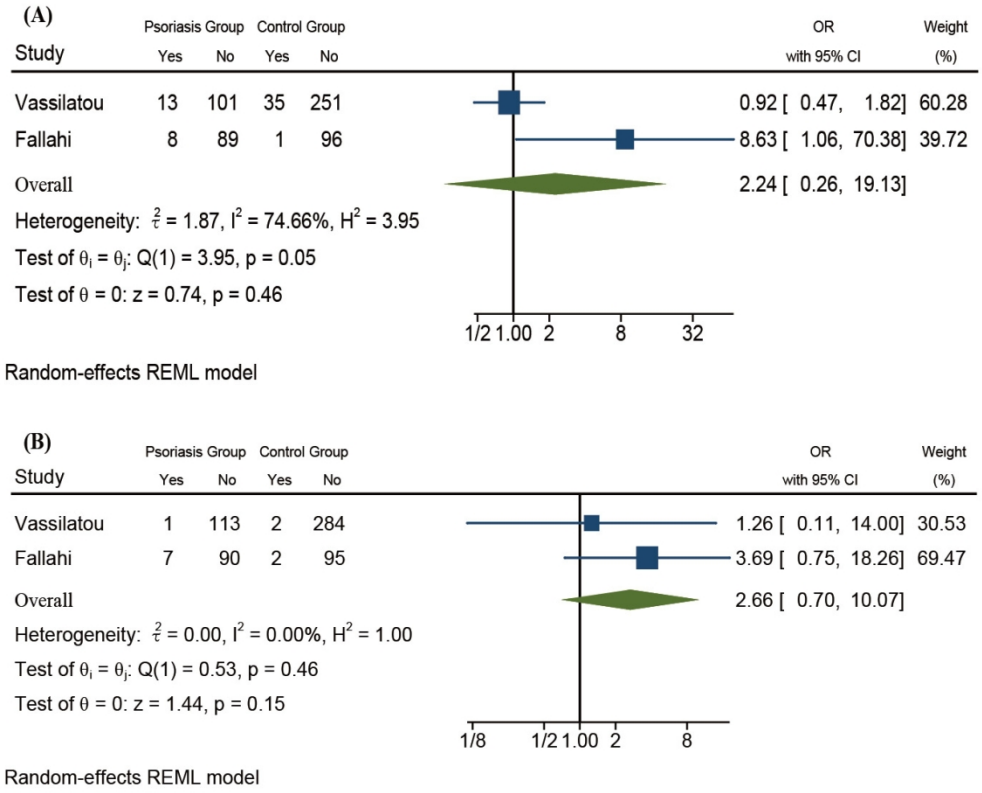


Figure 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

123x169mm (300 x 300 DPI)



117x97mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a meta-analysis.	1
ABSTRACT			
Abstract	2	The abstract included Objective, Design, Data sources, Eligibility criteria for selscting studies, Data extraction and synthesis, Results, Conclusions, PROSPERO registration number .	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5, Table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7, Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7, 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8,10,11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13,14
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	×
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	×
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	×

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The prevalence of autoimmune thyroid disease in patients with psoriasis: a meta-analysis

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Running title: A meta-analysis of AITD and psoriasis

Abstract

Objective Psoriasis is a chronic inflammatory disease with autoimmune etiology. A possible link between psoriasis and autoimmune thyroid disease (AITD) has been suggested in some studies with inconsistent findings. This meta-analysis aims to determine the association between psoriasis and AITD.

Design A Meta-analysis of observational studies.

Data sources PubMed, EMBASE, Scopus, and the Cochrane Library were searched up to November 1st, 2021.

Eligibility criteria for selecting studies We included non-randomized studies, each with over 50 cases in every group, focusing on the rate of comorbidity between psoriasis and AITD.

Data extraction and synthesis Two independent reviewers screened the articles and extracted data. The restricted maximum-likelihood was applied to perform the meta-analysis. Odds ratio (OR) and 95% confidence intervals (CI) were pooled to compare the prevalence of AITD in psoriasis and control groups. Heterogeneity was assessed with I^2 statistic. The Newcastle-Ottawa Scale (NOS) and Agency for Healthcare Research and Quality (AHRQ) were applied for quality assessment. The risk of bias was assessed with ROBINS-I.

Results Eleven available studies with data on 253,313 patients with psoriasis and 1,376,533 controls were included. Meta-analysis showed that patients with psoriasis had a higher prevalence of AITD (OR = 1.76, 95% CI: 1.35 - 2.28, Z = 4.25, p <0.01), especially loss-of-function disorder of the thyroid gland. Both TgAb positive rate (OR = 1.98, 95% CI: 1.27 - 3.10, Z = 3.00, p <0.01) and TPOAb positive rate (OR = 2.15, 95% CI: 1.31 - 3.52, Z = 3.05, p <0.01) were also increased in the psoriasis group compared

to the control group.

Conclusions Our study indicates that the rate of co-occurring AITD was significantly increased in patients with psoriasis. It suggests that the increased risk of AITD should be concerned in patients with psoriasis.

PROSPERO registration number CRD42020206005

Keywords: Psoriasis, Thyroid, Immunology

Strengths and limitations of this study

This is the first meta-analysis focusing on the risk of AITD for psoriasis patients, which included hypothyroidism, hyperthyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, Hashimoto's thyroiditis, Graves' disease, TgAb positivity and TPOAb positivity.

All studies included were of moderate to high quality and were representative. All studies were published in recent years.

The heterogeneity in the pooled data cannot be ignored, and was not improved by subgroup analysis. However, meta-regression analysis identified the differences of sample size and scope of research on AITD among these studies as the potential sources of heterogeneity.

INTRODUCTION

Psoriasis is a chronic inflammatory disease with autoimmune etiology, affecting approximately 125 million people around the world.[1] The skin lesions of psoriasis occur mainly on the scalp, trunk, and exterior surfaces of the limbs, and manifest as erythema, plaques, and scales.[2] Apart from the impaired appearance and intense pruritus of the skin lesions, various comorbidities have a significant impact on the quality of life in patients with psoriasis.[3 4] Among the comorbidities, autoimmune thyroid disease (AITD) has been characterized in patients with psoriasis. For patients with psoriasis who also develop complications, their management requires extra attention.[5] Therefore, understanding the risk of other diseases on psoriasis has important clinical significance.

Autoimmune thyroid disease (AITD) is an inflammatory disease of the thyroid gland with the presence of thyroid autoantibodies, lymphocytic infiltration of thyroid parenchyma, and even thyroid dysfunction.[6] Graves' disease (GD) and Hashimoto's thyroiditis (HT) are the two main clinical subtypes of AITD. GD is characterized by hyperthyroidism and the presence of thyroid-stimulating hormone receptor antibodies (TRAb) in serum, while HT is characterized by hypothyroidism and the presence of thyroid peroxidase antibodies (TPOAb) or Thyroglobulin antibodies (TgAb) in serum.[7]

Psoriasis and AITD share some common pathophysiological features, such as Th1-predominant adaptive immune reaction.[6] Hence, the relationship between AITD and psoriasis has been hypothesized and studied. In 2006, Antonelli *et al.* first

reported that the prevalence of AITD in patients with psoriatic arthritis was significantly higher than in the general population.[8] However, the study reported by Tsai *et al*.[9] pointed that the association between psoriasis and AITD was limited. In recent years, several observational studies regarding the association between psoriasis and AITD were published in succession, but the results of the studies were inconsistent.[10-16] In addition, Karadag *et al.* reported that the commonly administered acitretin treatment for psoriasis system treatment affects the levels of free T4 (thyroid hormone).[17] To address this discrepancy, we designed and performed a meta-analysis with the existing evidence to assess the relationship between psoriasis and AITD and provide guidance on the clinical management of psoriasis.

METHODS

Search strategy

The literature search was conducted through PubMed, EMBASE, Scopus, and the Cochrane Library for relevant studies published before November 1st, 2021. Detailed literature-search strategies of the databases are presented in Table 1.

Inclusion and exclusion criteria

The inclusion criteria for the studies included in our analysis were the following: (1) The prevalence of AITD in patients with psoriasis/psoriatic arthritis and non-psoriasis were studied; (2) The study was a cohort study, case-control study, or cross-sectional study; (3) The observed indicators were at least one of the following outcomes: the prevalence of hypothyroidism, hyperthyroidism, HT, GD, or the positive rate of TPOAb, TgAb, or TRAb; (4) The number of patients with psoriasis

and the control group should be over 50. Drug-related studies, animal studies, reviews, and conference abstracts were excluded from our analysis.

Data extraction

The specific process for analyzing the studies generated from the search was as follows: record screening and data extraction were performed by two independent authors (X Zhang and S Zhang) according to the above retrieval strategy. When disagreements could not be resolved through consensus by the two authors, these were referred to the third author(R Wu) and resolved through discussion. The following information in the included studies was extracted: the name of the first author, year of publication, country of origin, study design, sample size, the definition of psoriasis and AITD, gender ratio, and mean age.

Quality assessment

The Newcastle-Ottawa Scale (NOS)[18] was used to assess the quality of the included cohort and case-control studies. The quality of the study was scored on three dimensions: selection, comparability, and exposure/outcome. Studies that achieved 0-3, 4-6, 7-9 scores were considered of low, moderate and high quality respectively. Additionally, the tools recommended by the Agency for Healthcare Research and Quality (AHRQ)[19] were used for the cross-sectional studies. Eleven items were included in AHRQ. The study was assigned one point if the answer “Yes”, otherwise no points were assigned. Studies that achieved 0-3, 4-7, and 8-11 points were considered of low, moderate and high quality respectively. Moreover, the ROBINS-I was used to assess the risk of bias.[20] The assessments were carried by two authors (X

Zhang and S Zhang), and checked by the third author(R Wu).

The meta-analysis was performed using Stata 16.0 software. We used odds ratios (OR) and 95% confidence intervals (CI) to describe the differences between patients with and without psoriasis. Differences were considered statistically significant when $p < 0.05$. The prediction interval was used to explore the prevalence of AITD in individuals with psoriasis. The I^2 statistic was used to evaluate heterogeneity as follows: $I^2 \leq 25\%$, no heterogeneity; $25\% \leq I^2 \leq 50\%$, mild heterogeneity; $50\% < I^2 \leq 75\%$, moderate heterogeneity; $I^2 > 75\%$, severe heterogeneity. The random effects model was applied throughout the analyses. Publication bias was assessed by funnel plot and Egger's test (Publication bias was considered when $p < 0.1$). Sensitivity analysis was performed to assess the stability of the meta-analysis by omitting one study in each turn. Univariate meta-regression analysis was used to investigate the sources of heterogeneity. The flow chart was drawn in Adobe Illustrator, and the forest plots, funnel plots, and Egger's test charts were drawn by Stata 16.0 software.

Patient and public involvement

No patients or members of the public were involved in this review.

RESULTS

Search results

After removing duplicate results, we identified 6380 published studies in the initial search: 6377 studies were included by searching through databases and three studies were harvested by manually searching the references of relevant studies. After screening the titles and abstracts, the remaining 42 studies underwent further full-text

screening. Eventually, 11 studies[8-16 21 22] that met the inclusion criteria were included in the final analysis (figure. 1).

Study characteristics

The basic characteristics of the included studies are shown in Tables 2 and 3. A total of 253,313 patients with psoriasis and 1,376,533 control patients were included in the analysis. Two of the studies were cohort studies, eight were case-controlled studies, and one was a cross-sectional study.

Quality of studies

Overall, five studies were of high quality and six of moderate ones (Table 3). In the studies checked with NOS (n=10), five studies were considered of moderate quality because the control groups were not from the same community. The only cross-sectional study checked with AHRQ was a moderate quality study as the method for control of confounding was not clear. Based on ROBINS-I, all included studies had moderate risk in overall bias (Table 4).

Prevalence of AITD in patients with psoriasis

Eleven studies provided available data on the prevalence of AITD in patients with psoriasis. The meta-analysis showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.76, 95% CI: 1.35 - 2.28, Z = 4.25, p <0.01). The prediction interval ranged from 0.79 to 2.73, and the heterogeneity was severe (I^2 = 92.72%).

Heterogeneity analysis

To investigate potential sources of heterogeneity, we firstly performed a

subgroup analysis by types of study design. The high rate of comorbidity between psoriasis and AITD was also observed in the cross-sectional study strata (OR = 2.12, 95% CI: 1.55 - 2.89), and in the case-control study strata (OR = 1.75, 95% CI: 1.23 - 2.48, Z = 3.14, p <0.01) but with heterogeneity remaining severe (figure. 2), which indicated that inconsistency of the study designs was not the source of high heterogeneity.

We further conducted a meta-regression analysis to explore the reason for between-study heterogeneity. Seven variables were included in the regression model, covering average age, sex ratio, nation (China or other counties), race (Caucasian or non-Caucasian), sample size, clinical types of psoriasis (psoriasis vulgaris or psoriatic arthritis), and scope of research on AITD (all studies were divided into two categories: one focusing on the loss-of-function disorder of the thyroid gland alone and the other focusing on both the loss-of-function disorder and hyperfunction disorder of the thyroid gland). When the statistical significance was set as p<0.1, sample size (β = -0.40, *S.E.* = 0.20, p = 0.07) and scope of research on AITD (β = 0.45, *S.E.* = 0.15, p = 0.02) were the potential sources of high heterogeneity.

We removed three studies[8 13 21] outside the funnel plot and then conducted the meta-analysis again. The results of the reanalysis also showed that patients with psoriasis had a higher prevalence of AITD than the controls (OR = 1.34, CI: 1.20-1.50, Z = 5.07, p <0.01), but with moderate heterogeneity (I^2 = 57.30%). The results indicated that these three studies may have contributed to severe heterogeneity in the previous analysis. The source of heterogeneity in the study of Antonelli *et al*. was that

all the patients were patients with psoriatic arthritis,[8] and the prevalence of AITD in patients with psoriatic arthritis may be higher than that of patients with psoriasis.[23] The source of heterogeneity in the study by Peluso *et al.* may have been due to the control group being comprised of hospital staff rather than the general population.[21] The source of heterogeneity in the study of Kiguradze *et al.* may lie in the fact that it was a cross-sectional study.[13] These three studies were not excluded because they had little effect on the final results of the analysis.

Sensitivity analysis and publication bias

Omission of either of the included studies did not significantly change the confidence interval of the combined effect (figure. 3A). Therefore, the results of the analysis were considered reliable and stable. The funnel plot for the publication bias is shown in figure. 3B. The results of Egger's test showed significant publication bias (p = 0.036, figure. 3C). There was a possibility of exaggerating the association between psoriasis and AITD.

Psoriasis and thyroid function status

Patients with psoriasis had a higher prevalence of hypothyroidism than the controls (OR = 1.21, 95% CI: 1.12 - 1.30, Z = 4.80, p <0.01) and no significant heterogeneity was observed (I^2 = 0.00%). Patients with psoriasis had a higher prevalence of hyperthyroidism than the controls (OR = 1.20, 95% CI: 1.12 - 1.30, Z = 4.78, p <0.01) and no significant heterogeneity was observed (I^2 = 0.00%, figure. 4A-B).

Additionally, a higher prevalence of subclinical hypothyroidism and subclinical

hyperthyroidism was observed in patients with psoriasis compared with the controls (Subclinical hypothyroidism: OR = 2.24, 95% CI: 0.26 - 19.13, Z = 0.74, p = 0.46. Subclinical hyperthyroidism: OR = 2.66, 95% CI: 0.70 - 10.07, Z = 1.44, p = 0.15). However, the difference was not statistically significant (Supplementary figure. 1 A-B).

Psoriasis and specific autoimmune thyroid diseases

The prevalence of HT in patients with psoriasis and the controls was 0.215% and 0.199%, respectively. In comparison, the prevalence of GD in patients with psoriasis and the controls was 0.443% and 0.405%, respectively. The prevalence of HT was significantly higher in patients with psoriasis than the controls (OR = 1.88, 95% CI: 1.50 - 2.35, Z = 5.47, p <0.01) and the heterogeneity was moderate (I^2 = 55.98%). The prevalence of GD was also higher in patients with psoriasis than the controls (OR = 1.02, 95% CI: 0.65 - 1.60, Z = 0.07, p = 0.94) and the heterogeneity was severe (I^2 = 92.78%). However, the difference was not statistically significant (figure. 4C, figure. 5A).

Psoriasis and thyroid serological antibodies

No studies provided data on the positive rate of TRAb in patients with psoriasis, so we only included TgAb and TPOAb in the meta-analysis (figure. 5B-C).The positive rate of TgAb was significantly higher in patients with psoriasis than the controls (OR = 1.98, 95% CI: 1.27 - 3.10, Z = 3.00, p <0.01) and the heterogeneity was mild (I^2 = 41.54%). The positive rate of TPOAb was significantly higher in patients with psoriasis than the controls (OR = 2.15, 95% CI: 1.31 - 3.52, Z = 3.05, p

<0.01) and the heterogeneity was moderate (I^2 = 56.27%).

DISCUSSION

To our knowledge, this is the first meta-analysis focusing on the risk of AITD for psoriasis patients. The study by Khan *et al.* is the first meta-analysis of studies on the association between AITD and the incidence risk of psoriasis.[24] By summarizing all available evidence on the association between psoriasis and AITD, we found that the prevalence of AITD, particularly HT, was higher in patients with psoriasis than the control individuals. Additionally, elevated positive rates of TgAb and TPOAb were also observed in patients with psoriasis. As psoriasis is a type of discosmetic dermatosis and therefore likely to be of concern, patients with psoriasis are more likely to be active about seeing a doctor regarding their condition than patients with AITD. As such, we recommend that patients with psoriasis receive a thyroid-related examination when they have suspicious AITD-related symptoms. By promoting early diagnosis and treatment of AITD, patients may be able to avoid thyroid dysfunction.

Main findings

The primary finding of this meta-analysis is that the prevalence of AITD is increased in patients with psoriasis compared with the general population. However, severe heterogeneity was observed. In order to determine whether or not the inconsistency of the study designs was the primary source of heterogeneity, the subgroup analysis based on different study designs was conducted. However, the heterogeneity was not limited by subgroup analysis; hence the heterogeneity in this meta-analysis was not caused by inconsistency of the study design. Through further

meta-regression analysis, we found that the differences in sample size and scope of research on AITD among these studies might explain the high level of between-study heterogeneity. Furthermore, the heterogeneity was improved when we focused on the link of psoriasis with specific clinical characters of AITD, such as hypothyroidism, hyperthyroidism, and the positivity rate of autoantibodies.

According to the definition of the study designs, an accurate cause-effect relationship can only be demonstrated in cohort studies. The present study included three types of study designs, including cohort, case-controlled, and cross-sectional studies. Therefore, the results should be interpreted with caution. Additionally, it has been demonstrated that the prevalence of HT in patients with psoriasis is elevated compared with the controls. HT, a main clinical subtype of AITD, is generally accompanied by hypothyroidism. An elevated frequency of hypothyroidism was also observed in patients with psoriasis. Taken together, the current data indicates that psoriasis may be closely associated with the loss-of-function disorder of the thyroid gland.

Common pathogenesis of psoriasis and AITD

Both abnormal immunological reactions and underlying genetic risk can contribute to the pathogenesis of psoriasis and AITD.[25 26] These two diseases share some autoimmune processes and susceptibility genes, which may explain the concurrence of psoriasis and AITD. The predominant Th1 immune reaction has been observed in patients with psoriasis,[27 28] such as Th1 infiltration in involved tissues, and high serum levels of Th1-prototype chemokines and cytokines (TNF-α, IFN-γ,

and CXCL10), all of which are present in AITD.[29-32] Additionally, Th17-mediated immune disorder has also been observed in psoriasis and AITD.[33 34] The two diseases share several predisposing genetic alleles or regions. For example, the genetic data from 265 families with two or more autoimmune disorders have shown that the PTPN22-R620W allele has a remarkable association with HT and a mild association with psoriasis.[35] Additionally, other SNP variations in the PTPN22 gene have been demonstrated to be indicators for evaluating the risk of psoriasis.[36 37] IL12B has been generally recognized as a psoriasis susceptibility gene,[38] an upstream variation of which affects the phenotype of AITD in men.[39]

Implications for practice

As information relating to patient medications was not provided by in the original research, drug exposure may be a source of residual confounding in the present study and a potential risk factor for concurrence of psoriasis and AITD, apart from the reasons mentioned above. β-blocker, used to control thyrotoxicosis-related symptoms, has been implicated in induction or exacerbation of psoriasis.[40 41] In addition, it has been reported that the administration of acitretin, a common drug for the treatment of psoriasis, can lead to the reduction of free T4 (thyroid hormone) levels in patients with psoriasis.[17] Therefore, once the patients develop suspicious symptoms after these treatments, diagnostic investigation and intervention should be considered as early as possible to avoid the exacerbation. On the other hand, the treatment for AITD and psoriasis can be mutually beneficial. For example, propylthiouracil (PTU), a drug used to inhibit thyroid hormone synthesis, has been

effective in the treatment of psoriasis.[42] Based on the above findings, it is recommended that the treatment options be adjusted once patients with psoriasis are diagnosed with comorbid AITD.

Limitations

There are several limitations to this meta-analysis. First, the meta-analysis included studies with different study designs. Given this, we conducted a subgroup analysis of each study design, which also showed that the patients with psoriasis had an increased prevalence of AITD in the cross-sectional study strata and the case-control study strata. Second, there is considerable heterogeneity in the present study. Subgroup analysis and meta-regression analysis helped us to identify the potential sources of the heterogeneity. However, there are likely to be other unknown reasons responsible for the heterogeneity. Thirdly, the lack of information on drug application made drug exposure a confounding factor. Therefore, further large-scale and high-quality prospective studies are still required to validate our findings.

CONCLUSIONS

The present meta-analysis revealed that AITD was more prevalent in patients with psoriasis than in the general population, especially loss-of-function disorder of the thyroid gland. Moreover, patients with psoriasis were found to have elevated positive rates of TPOAb and TgAb compared to the control individuals. Accordingly, we recommend that every dermatologist be conscious of this association and suggest necessary examinations and intervention be considered as soon as possible when patients with psoriasis have suspicious AITD-related symptoms.

Contributors XZ and SZ carried out the extraction of reference data, meta-analysis, and wrote manuscripts, RW and PZ supported and assisted the manuscripts, YS and SL reviewed and suggested the manuscripts. All authors were involved in finalizing the manuscript.

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Figure legend:

Figure 1 Flowchart for study screening

Figure 2 Forest plot of the association between psoriasis and autoimmune thyroid disease

Figure 3 Sensitivity analysis and publication bias

Figure 4 A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

Figure 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

Database	Retrieval strategy
PubMed	((((((((((Thyroid[Title/Abstract]) OR (Thyroiditis[Title/Abstract])) OR (Hashimoto Thyroiditis[Title/Abstract])) OR (Graves Disease[Title/Abstract])) OR (Hyperthyroidism[Title/Abstract])) OR (Hypothyroidism[Title/Abstract])) OR (TgAb[Title/Abstract])) OR (TPOAb[Title/Abstract])) OR (TRAb[Title/Abstract])) OR (Endocrine Comorbidities[Title/Abstract])) OR (Autoimmune diseases[Title/Abstract])) AND ((psoriasis[Title/Abstract]) OR (psoriatic[Title/Abstract]))
Embase	(thyroid:ab,ti OR thyroiditis:ab,ti OR 'hashimoto thyroiditis':ab,ti OR 'graves disease':ab,ti OR hyperthyroidism:ab,ti OR hypothyroidism:ab,ti OR tgab:ab,ti OR tpoab:ab,ti OR trab:ab,ti OR 'endocrine comorbidities':ab,ti OR 'autoimmune diseases':ab,ti) AND (psoriasis:ab,ti OR psoriatic:ab,ti)
Scopus	((TITLE-ABS-KEY (thyroiditis) OR TITLE-ABS-KEY (hashimoto AND thyroiditis) OR TITLE-ABS-KEY (graves AND disease) OR TITLE-ABS-KEY (hyperthyroidism) OR TITLE-ABS-KEY (hypothyroidism) OR TITLE-ABS-KEY (tgab) OR TITLE-ABS-KEY (tpoab) OR TITLE-ABS-KEY (trab)) AND (TITLE-ABS-KEY (psoriasis) OR TITLE-ABS-KEY (psoriatic))
Cochrane	(((Psoriasis) OR psoriatic) OR Pustulosis of Palms) AND (((((((Thyroid) OR Thyroiditis) OR Thyroiditides) OR Hashimoto Disease) OR Graves Disease) OR Hyperthyroidism) OR Hypothyroidism)). And chose literature published up to "2021/11/01". Then chose “Trials”

Table 1 Database source and retrieval strategy.

TPOAb: Thyroid peroxidase antibody; TgAb: Thyroglobulin antibody; TRAb: Thyroid stimulating hormone receptor antibody.

Study (Author)	Year	Country	Study design	No.Patients	No.Controls	Patients, % Female	Patients, mean age
Antonelli *et al.*	2006	Italy	Case-control	80	400	45	57
Tsai *et al.*	2011	China	Case-control	51800	207200	38.5	46.4
Peluso *et al.*	2011	Italy	Case-control	108	318	52.8	39.9
Wu *et al.*	2012	American	Case-control	25341	126705	48.4	48.9
Vassilatou *et al.*	2017	Greece	Case-control	114	286	49.1	52.7
Kiguradze *et al.*	2017	Greece	Cross-sectional	9654	846961	NA	NA
Haddad *et al.*	2017	Israel	Case-control	3161	31610	53.4	58.4
Fallahi *et al.*	2017	Italy	Cohort	97	97	47.4	56
Alidrisi *et al.*	2019	Iraq	Case-control	56	54	58.9	43.05
Wang *et al.*	2019	China	Cohort	162842	162842	45.5	45
Valduga *et al.*	2021	Valduga	Case-control	60	60	66.7	54.5

Table 2 Characteristics of the included studies

Study (Author)	Definition of psoriasis	Definition of AITD	NOS score
Antonelli *et al.*	The criteria of Vasey and Espinoza	Serum levels of thyroid stimulating hormone and TgAb and TPOAb	7
Tsai *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 242.9x, 244.9x	6
Peluso *et al.*	Classification of Psoriatic Arthritis study group criteria	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL, and Thyroid ultrasonography	7
Wu *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 242.0, 245.2	7
Vassilatou *et al.*	Moll and Wright criteria	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL	7
Kiguradze *et al.*	ICD-9-CM code 696.0	ICD-9-CM codes 245.2	6*
Haddad *et al.*	Clinical diagnosis from Clalit Health Services	Clinical diagnosis from Clalit Health Services	6
Fallahi *et al.*	Criteria of Vasey and Espinoza	Serum levels of TgAb or TPOAb > 100 IU/mL	6
Alidrisi *et al.*	Clinical diagnosis from Endocrine and Metabolism Center	Serum levels of TgAb > 115 IU/mL or TPOAb > 34 IU/mL	6
Wang *et al.*	ICD-9-CM code 696.0	ICD-9-CM code 242, 242.0, 244, 246	8
Valduga *et al.*	Clinical diagnosis and measured by Psoriasis Area and Severity Index (PASI)	Hypothyroidism was detected, or when they need for thyroid hormone replacement therapy or positive of TPOAb with or without TgAb	6

Table 3 Characteristics of the included studies (2)

*This was a score based on the AHRQ evaluation.

ICD-9-CM: The International Classification of Diseases, Ninth Revision, Clinical Modification

Study(Author)	Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Antonelli *et al.*	2006	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Tsai *et al.*	2011	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Peluso *et al.*	2011	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Wu *et al.*	2012	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk
Vassilatou *et al.*	2017	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kiguradze *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk
Haddad *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Fallahi *et al.*	2017	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Alidrisi *et al.*	2019	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Wang *et al.*	2019	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Valduga *et al.*	2021	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk

Table 4 Risk of bias for the 11 included studies based on the ROBINS-I tool

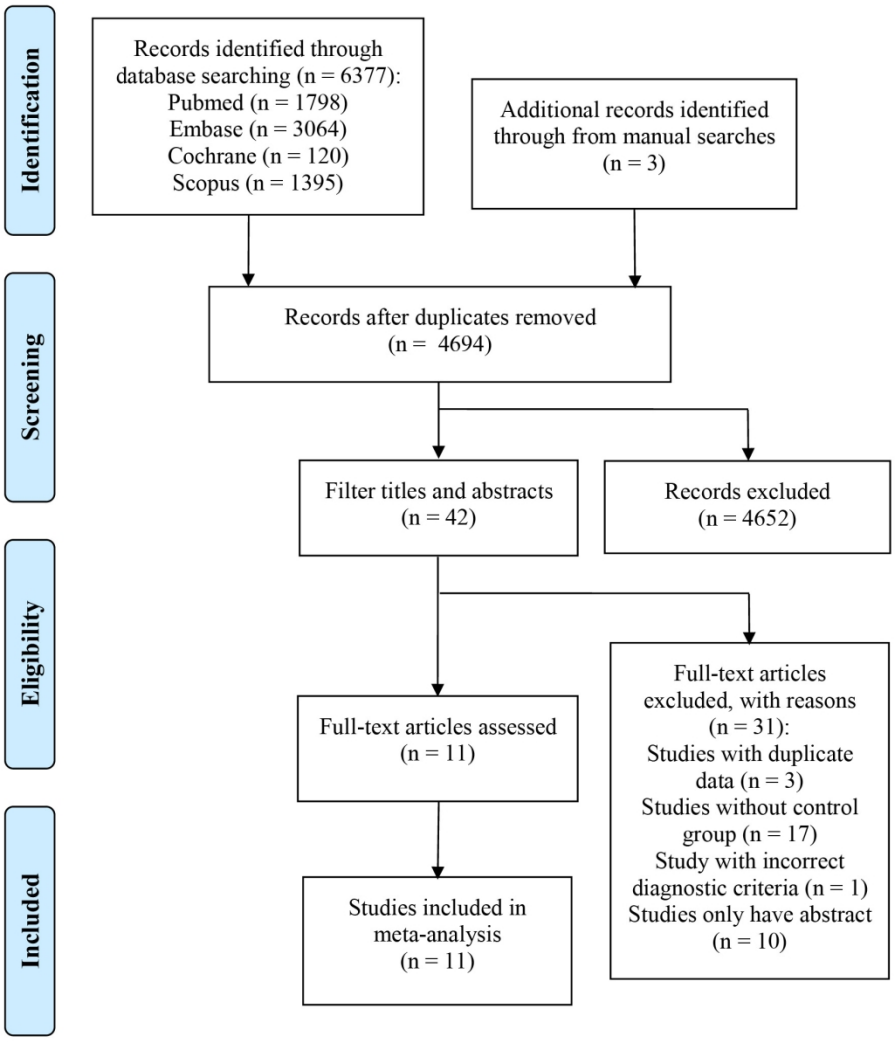


Figure 1 Flowchart for study screening

164x200mm (300 x 300 DPI)

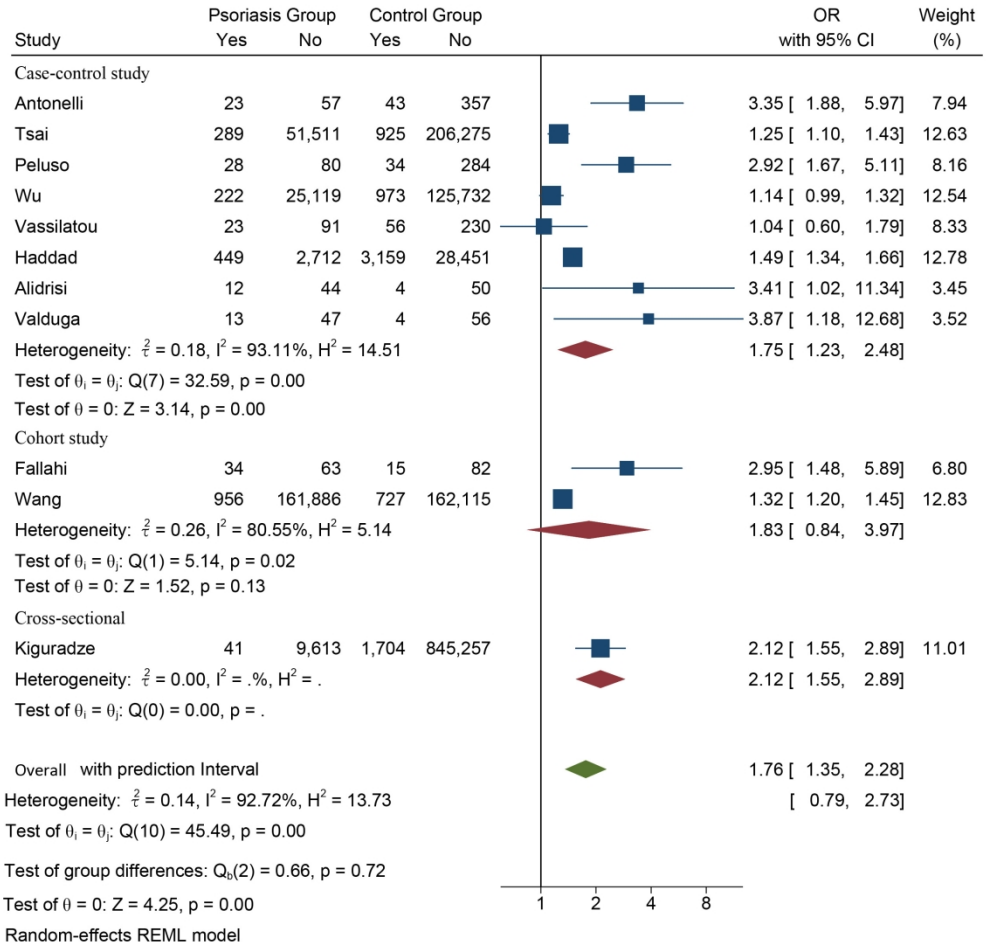


Figure 2 Forest plot of the association between psoriasis and autoimmune thyroid disease

215x206mm (300 x 300 DPI)

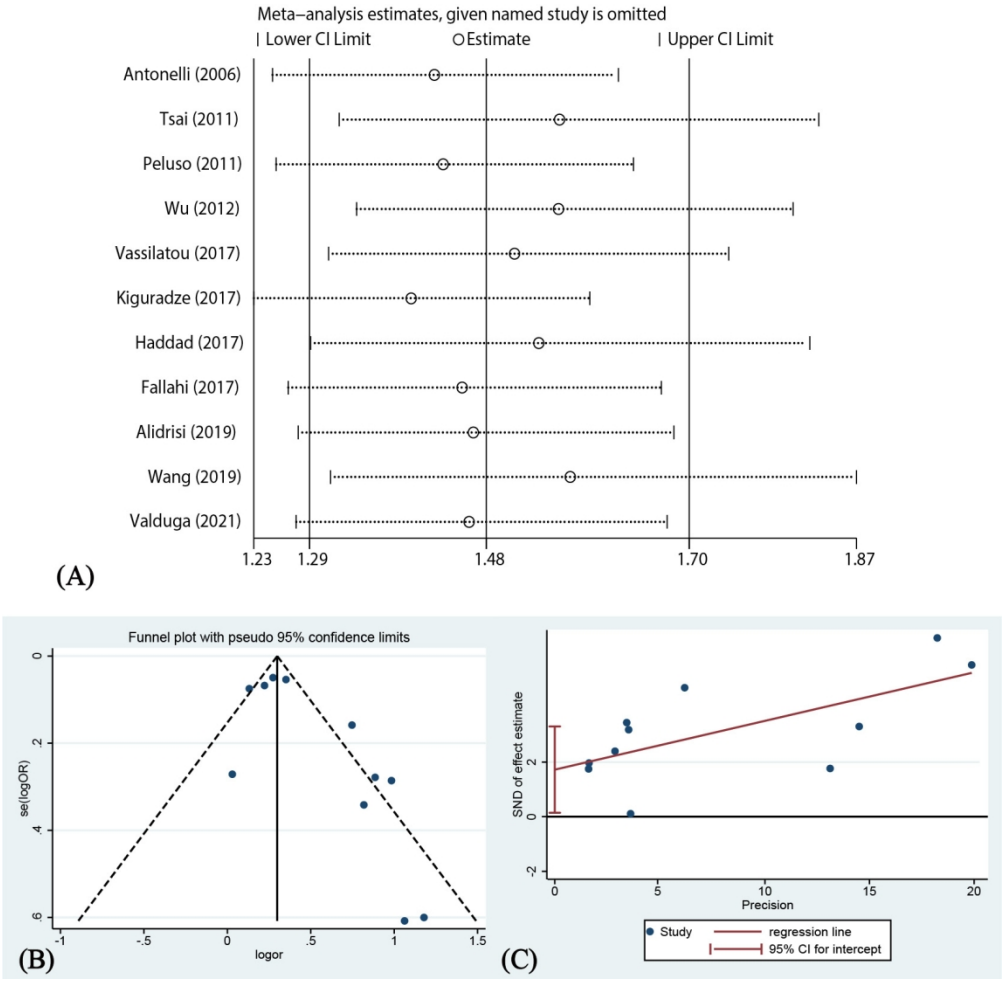


Figure 3 Sensitivity analysis and publication bias

141x138mm (300 x 300 DPI)

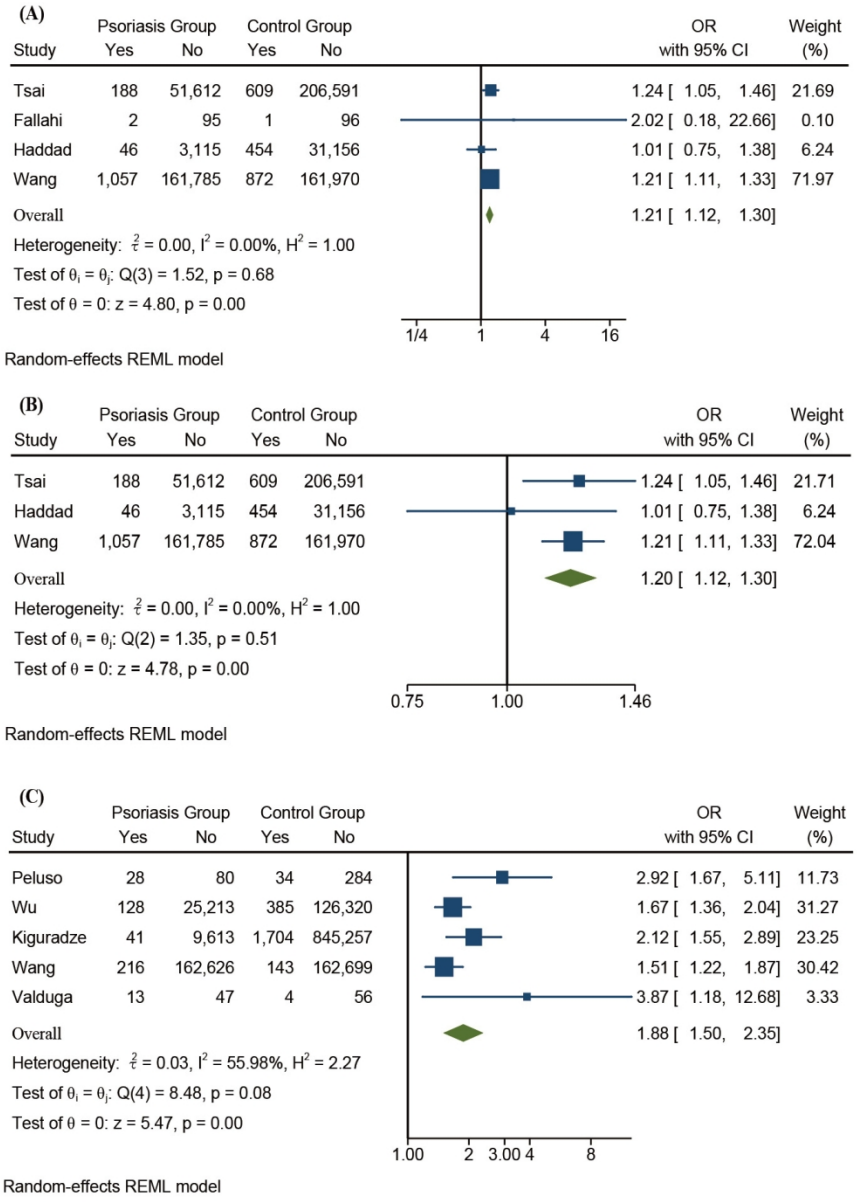


Figure 4 A: Forest plots of psoriasis and hypothyroidism B: Forest plots of psoriasis and hyperthyroidism C: Forest plots of psoriasis and HT

117x162mm (300 x 300 DPI)

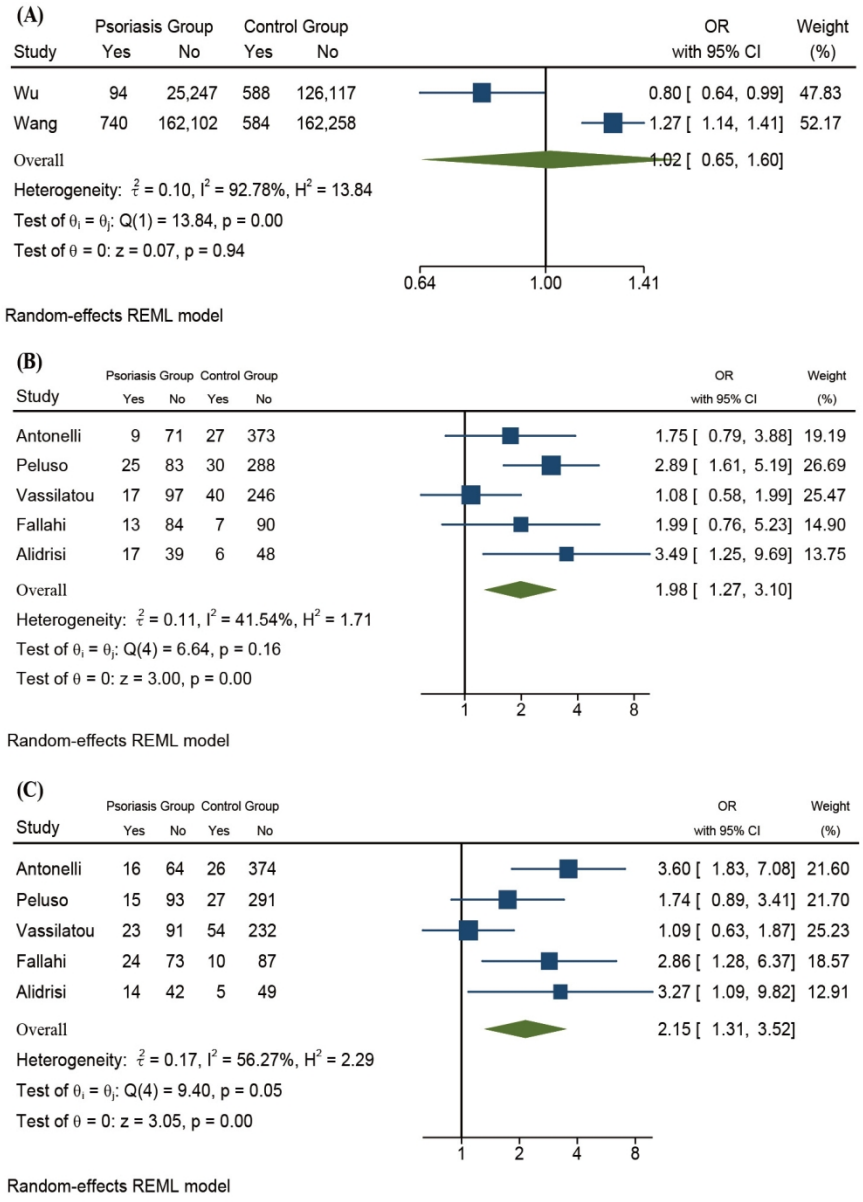
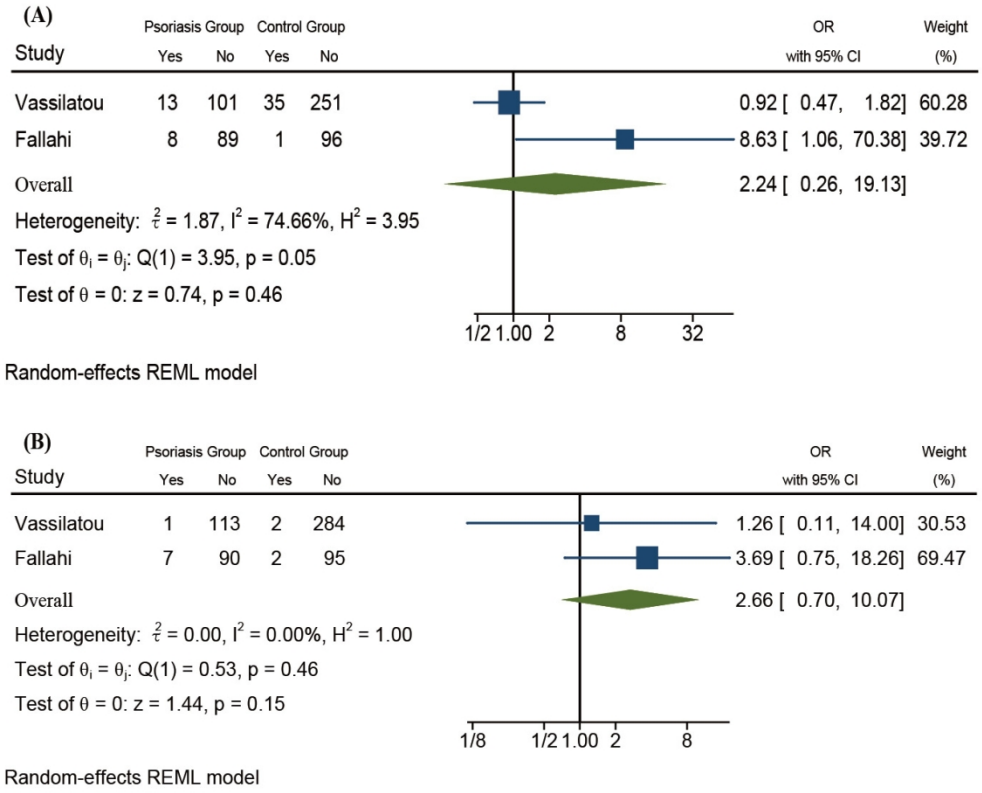


Figure 5 A: Forest plots of psoriasis and GD B: Forest plots of psoriasis and TgAb C: Forest plots of psoriasis and TPOAb

123x169mm (300 x 300 DPI)



117x97mm (300 x 300 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a meta-analysis.	1
ABSTRACT			
Abstract	2	The abstract included Objective, Design, Data sources, Eligibility criteria for selscting studies, Data extraction and synthesis, Results, Conclusions, PROSPERO registration number .	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5, Table 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	7, Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7, 8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8,10,11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Figure 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13,14
	23b	Discuss any limitations of the evidence included in the review.	15
	23c	Discuss any limitations of the review processes used.	15
	23d	Discuss implications of the results for practice, policy, and future research.	15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	×
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	×
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	×

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi:

PRISMA 2020 Checklist

10.1136/bmj.n71

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