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META-ANALYSIS

Increased risk of thyroid autoimmunity in rheumatoid arthritis: a systematic review and meta-analysis

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Abstract Thyroid autoimmunity, which is the most common immune-mediated disease, is frequently together with other organ- as well as nonorgan-specific autoimmune disorders. Meanwhile, rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disorder that mainly results in cartilage destruction as well as synovial joint inflammation, and both the adaptive and innate immune responses involve in the progression of this disease. Considering that autoimmune elements may be common characteristics of thyroid autoimmunity and RA, it is likely that both disorders may coexist within some patients. A great number of studies have researched whether an association between thyroid autoimmunity and RA exists; however, the results of these studies have been inconsistent. Most of these studies have included relatively small sample sizes, which have rendered them insufficiently powerful to determine whether there is a relationship between RA and thyroid autoimmunity. The main objective of this meta-analysis was to provide reliable estimates of the extent of any association between thyroid autoimmunity and RA by combining the primary data from all related studies. Literature databases, including the Embase, Medline, Web of Science, Chinese Wanfang, and CBM databases, were searched for studies published from January 1980 to May 2014, with a language restriction of English and Chinese. A total of 1,021 RA cases and 1,500 healthy controls were included in this study. From these data, the odds ratios (OR) and the corresponding 95 % confidence intervals (95 % CI) were calculated. The results of the meta-analysis showed that the prevalence of thyroid autoantibody positivity in patients with RA was higher than that in healthy controls (TgAb: OR 3.17, 95 % CI 2.24–4.49; TPOAb: OR 2.33, 95 % CI 1.24–4.39). The results of this meta-analysis suggest that thyroid autoimmunity is more prevalent in patients with RA than in the control population.

Keywords Thyroid autoimmunity · Rheumatoid arthritis · Meta-analysis

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Introduction

Thyroid autoimmunity is one of the most common immune-mediated diseases [1] and includes disease such as Graves' disease (GD), which is a common autoimmune disorder that mainly results from thyroid-stimulating antibodies [2], and Hashimoto's thyroiditis (HT), which is characterized by a gradual failure of thyroid function, the existence of a goiter as well as T cell infiltration detectable on histological analysis [3]. Thyroid autoimmunity is characterized by the existence of autoantigens like thyroglobulin (Tg), thyroid peroxidase (TPO), and so on, which may play crucial roles in the loss of self-tolerance resulting in disease pathogenesis [4]. Furthermore, thyroid autoimmunity may lead to infiltration of thyroid by T cells and B cells which are the cellular parts of adaptive immune response [5]. The T or B lymphocytic response prevails that can influence the manifested pathology [6]. It has also been suggested that increased oxidative stress is likely to be associated with thyroid autoimmunity [7]. While the exact pathogenesis of thyroid autoimmunity is unknown, recent studies have indicated that the complex interplay

between environmental, genetic, and endogenous factors is indispensable to initiate thyroid autoimmunity [8].

Rheumatoid arthritis (RA) is a chronic immune-mediated disorder of unknown pathogenesis that primarily affects the diarthrodial joints. The characteristics of RA etiology are synovial proliferation and inflammation together with cartilage erosion as well as bone loss [9]. RA is a multifactorial autoimmune disease whose pathogenesis involves different cell types. For example, macrophages, T and B lymphocytes, endothelial cells, osteoclasts, and fibroblasts have all been indicated in participating the production of proinflammatory cytokines, autoantibodies and, ultimately, bone erosions [10]. Because autoimmunity plays a crucial role in the etiology of RA, an association between this disorder and thyroid autoimmunity may exist.

A great number of studies have researched the relationship between thyroid autoimmunity and RA by investigating the prevalence of thyroid autoantibodies, including thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb); however, the results of these studies have been inconsistent. Furthermore, most of these studies examined a relatively small sample size and were thus not powerful enough to determine whether an association between RA and thyroid autoimmunity existed. The aim of this meta-analysis was to provide reliable estimates of the extent of any association between thyroid autoimmunity and RA using combined primary data from all related studies.

Materials and methods

Literature and search strategy

A systematic search for eligible studies published from January 1980 to May 2014 was conducted using the Embase, Medline, Web of Science, Chinese Wanfang, and CBM databases, with language restriction to English and Chinese. The key words used were "rheumatoid arthritis" or "RA", combined with the terms "thyroid autoimmunity" or "autoimmune thyroid diseases", and the studies were filtered for those containing human subjects. Additionally, the reference lists of the retrieved studies were examined to identify additional eligible articles. The studies were selected by two independent reviewers, and the relevance of the articles was assessed using a hierarchical approach based on the title, abstract, and full manuscript. The studies selected by the two reviewers were compared, and disagreements were resolved by consensus.

The preliminary search using the above-mentioned terms yielded 1,892 potential articles. The authors read the abstracts of these publications and identified 439 publications that appeared to contain relevant data. The full text of these 439 publications was then read and examined for the presence of suitable data. This process identified 13 studies that were appropriate for further analysis based on our inclusion criteria.

Inclusion criteria

The studies eligible for inclusion in this meta-analysis met all of the following criteria: (1) the relationship between thyroid autoimmunity and RA was evaluated by assaying for the presence of TgAb and TPOAb, (2) a case–control design was used, and (3) the data provided for cases and healthy controls were sufficient to allow us to analyze the odds ratio (OR) with a 95 % confidence interval (CI) as well as a *P* value.

Data extraction

The following information was taken out from each study: first author, publication year, geographical location of the study population, number of cases and controls, and number of cases and controls positive for each type of thyroid autoantibody. This information was carefully taken out from all eligible publications, and the analysis was performed independently by two authors. Any disagreement was settled by discussion between the authors, and if a consensus could not be reached, another investigator resolved the disagreement.

Assessment of risk of bias in the included studies

Two investigators performed quality assessments of the included studies using the Newcastle–Ottawa Scale [11]. The Newcastle–Ottawa Scale is a risk of bias assessment tool for observational studies that has been recommended by the Cochrane Collaboration [12]. Each included study was judged in three broad categories using the "star system" as follows: the selection of study groups, the comparability of their cases and controls, and the ascertainment of exposure for the cases and controls. When a study met the criteria of a scale item, that study was assigned one star. The exception was the comparability category, for which a study could receive a maximum of two stars. The scores on the Newcastle–Ottawa Scale ranged from zero to nine stars. In this meta-analysis, studies that received seven or more stars were considered high quality, those receiving four to six stars were considered medium quality, and those receiving three or less stars were considered low quality. As our meta-analysis focused on the relationship between RA and thyroid autoimmunity, we defined the "no history of disease (endpoint)" scale item as "no history of RA." Furthermore, we created a funnel plot to analyze potential publication bias. The assessments of the studies by both

investigators were compared, and disagreement was resolved by consensus.

Statistical analysis

The relationship between thyroid autoimmunity and RA was evaluated by calculating the OR and the corresponding 95 % CI. The significance of the OR was determined using a Z test ($P < 0.05$ was judged statistically significant), and the extent of inter-study heterogeneity was determined using Cochrane's Q test ($P < 0.1$ was considered statistically significant). The selection of using a random effects model or a fixed effects model to calculate the OR was according to the heterogeneity. When the I^2 value >50 % indicated that heterogeneity existed across studies, so the random effects model was adopted for the meta-analysis; otherwise, the fixed effects model was selected. Publication bias was investigated using Begg's test, and all statistical analyses were performed using STATA Version 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Characteristics of the included studies

Thirteen relevant studies with a case–control design that investigated the association between thyroid autoimmunity and RA by assaying for thyroid autoantibodies and that met the study inclusion criteria were identified. The detailed procedure used to include or exclude articles is presented in Fig. 1. We chose these eligible articles to perform our meta-analysis, and as a result, our meta-analysis included 1,021 RA cases and 1,500 healthy controls. The characteristics of each article included are summarized in Table 1.

The quality of the included studies was assessed according to the Newcastle–Ottawa Scale guidelines for case–control studies. 11 studies were evaluated to be high quality, 2 were evaluated to be medium quality, and none were considered to be low quality. Overall, according to the suggested criteria for Selection, Comparability, and Exposure categories of the Newcastle–Ottawa Scale, the studies included in this meta-analysis were of acceptable quality.

Meta-analysis results

A summary of our meta-analysis results regarding the association between RA and thyroid autoimmunity, after incorporating data from all eligible studies, is provided in Table 2. The data were categorized according to the types of thyroid autoantibodies that were examined. The prevalence of positivity of each antibody in patients with RA was compared to that in healthy controls (TgAb: OR 3.17, 95 % CI 2.24–4.49; TPOAb: OR 2.33, 95 % CI 1.24–4.39). The meta-analysis results indicated that patients with RA were more likely to be positive for thyroid autoantibodies than the individuals in healthy control group.

Because the included studies examined a geographically diverse set of study populations, a subgroup analysis was performed based on the different continents from which the study subjects were drawn. For this analysis, the subjects in all of the included studies were divided into Asian, African, American, and European populations. The results of the subgroup analysis showed a positive relationship between TgAb and RA in the Asian, African, and European populations (OR 2.25, 95 % CI 1.23–4.11, OR 5.40, 95 % CI 1.10–26.61, and OR 3.57, 95 % CI 2.27–5.62, respectively), but not in the American population (OR 4.38, 95 % CI 0.17–113.31). A positive association between TPOAb positivity and RA was observed in the Asian and African populations (OR 2.75, 95 % CI 1.24–6.13 and OR 5.67, 95 % CI 1.43–22.41, respectively) but was not observed in either the American or the European population (OR 0.45, 95 % CI 0.02–11.55 and OR 2.21, 95 % CI 0.81–6.02, respectively). The forest plots for the frequency of TgAb and TPOAb positivity in patients with RA compared with that in healthy controls are shown in Fig. 2.

Sensitivity analysis

To investigate the influence of each individual study on the overall meta-analysis estimate, a sensitivity analysis was performed by omitting one study and calculating the pooled OR for the remaining studies sequentially; this analysis showed the influence of each individual data to the pooled OR. A study was considered to be excessively influential if the pooled OR excluding that study was not within the 95 % CI of the overall analysis. The ORs resulting from the sensitivity analysis did not differ substantially from our original estimates, indicating that our statistics were relatively credible and stable.

Publication bias

To determine whether potential publication bias existed in the reviewed literature, a funnel plot was constructed, and Begg's test was conducted. The funnel plot is a comparatively straightforward method of determining whether publication bias is present, and Begg's test is used to statistically examine the symmetries of the plots. The relative symmetry of the distributions indicated that there was no significant publication bias (Fig. 3). Similarly, the consequences of Begg's test did not suggest the existence of publication bias (TgAb: $Pr > |z| = 0.837$; TPOAb: $Pr > |z| = 0.348$), as all $Pr > 0.05$.

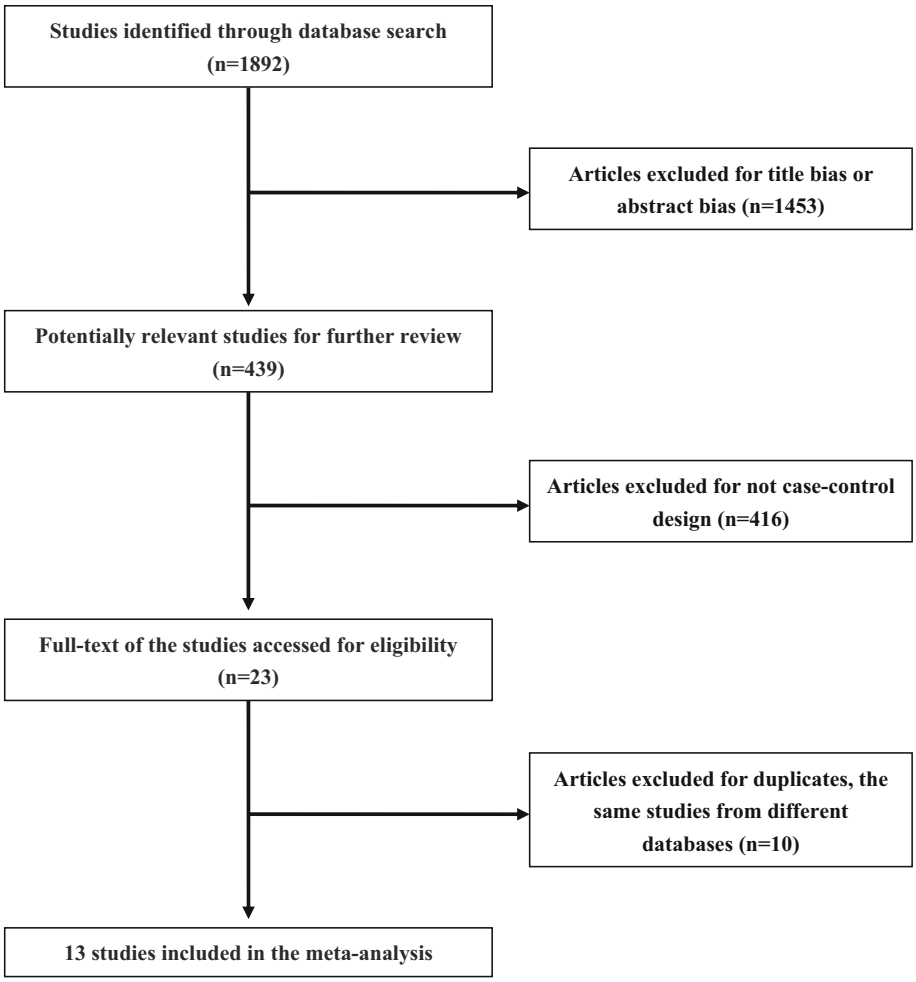

Fig. 1 Flow charts showing the detailed procedure for the inclusion or exclusion of studies. Thirteen independent studies were included in this meta-analysis

Table 1 General characteristics of the articles included in this meta-analysis

Author	Year	Region	Continent	Thyroid antibodies	RA cases (n/N)	Healthy controls (n/N)
Bianchi et al. [13]	1993	Italy	European	TgAb	9/107	2/52
Xu et al. [14]	1995	China	Asian	TgAb	2/32	0/35
Andonopoulos et al. [15]	1996	Greece	European	TPOAb	13/101	6/70
Staykova et al. [16]	2000	Bulgaria	European	TgAb	55/175	3/72
Tunc et al. [17]	2004	Turkey	Asian	TgAb, TPOAb	0/30, 2/30	2/53, 2/53
Kramer et al. [18]	2005	Brazil	American	TgAb, TPOAb	1/20, 0/20	0/28, 1/28
Kostić et al. [19]	2006	Serbia	European	TgAb, TPOAb	3/24, 5/24	1/34, 2/34
Antonelli et al. [20]	2006	Italy	European	TgAb, TPOAb	20/112, 29/112	27/400, 26/400
Pamuk et al. [21]	2007	Turkey	Asian	TgAb, TPOAb	13/64, 19/64	9/64, 6/64
Al-Awadhi et al. [22]	2008	Kuwait	Asian	TgAb	10/177	6/577
Przygodzka et al. [23]	2009	Poland	European	TgAb, TPOAb	12/100, 15/100	5/55, 10/55
Başkan et al. [24]	2010	Turkey	Asian	TgAb, TPOAb	2/39, 1/39	2/40, 2/40
El-saadany et al. [25]	2014	Egypt	African	TgAb, TPOAb	15/40, 20/40	2/20, 3/20

TgAb thyroglobulin antibody, *TPOAb* thyroid peroxidase antibody, *n* number of individuals with positive antibodies, *N* total number of individuals with RA disease or healthy controls

Table 2 Meta-analysis of the association between RA and thyroid autoimmunity

Type of antibody	Eligible studies	OR (95 % CI)	*P* value	Heterogeneity test	Effect model
TgAb	12	3.17 (2.24–4.49)	0.000	P–H = 0.246, I^2 = 20.2 %	Fixed
Asian	5	2.25 (1.23–4.11)	0.008	P–H = 0.187, I^2 = 35.1 %	Fixed
African	1	5.40 (1.10–26.61)	0.038	–	Fixed
American	1	4.38 (0.17–113.31)	0.373	–	Fixed
European	5	3.57 (2.27–5.62)	0.000	P–H = 0.151, I^2 = 40.6 %	Fixed
TPOAb	9	2.33 (1.24–4.39)	0.009	P–H = 0.020, I^2 = 56.0 %	Random
Asian	3	2.75 (1.24–6.13)	0.013	P–H = 0.268, I^2 = 24.1 %	Fixed
African	1	5.67 (1.43–22.41)	0.013	–	Fixed
American	1	0.45 (0.02–11.55)	0.628	–	Fixed
European	4	2.21 (0.81–6.02)	0.123	P–H = 0.004, I^2 = 77.4 %	Random

TgAb thyroglobulin antibody, *TPOAb* thyroid peroxidase antibody

Discussion

Autoimmune diseases are usually diagnosed in the light of classification criteria. However, these diseases share similar subphenotypes, including symptoms and signs, nonspecific autoantibodies as well as other immune changes, which are tend to taxonomic problems [26]. There is an accepted opinion that different autoimmune disorders may coexist in the same individual and in families, although this hypothesis has only been studied in small groups of patients with autoimmune thyroid disease [27]. Thyroid autoimmunity, the most common immune-mediated disease, is frequently together with other organ as well as nonorgan-specific autoimmune disorders [28], and all forms of thyroid autoimmunity are associated with the presence of serum thyroglobulin (Tg) and thyroid peroxidase (TPO) antibodies [29]. The evaluation of thyroid autoantibody titers is required for the laboratory diagnosis of thyroid autoimmunity, and the serum levels of thyroid autoantibodies that exceed or are equal to the upper level of the normal interval represent the minimum criteria for the diagnosis of thyroid autoimmunity. RA is a chronic immune-mediated inflammatory disorder that mainly results in cartilage destruction as well as synovial joint inflammation [30], and both the adaptive and innate immune responses involve in the progression of RA [31]. Because autoimmune elements may be common characteristics of thyroid autoimmunity and RA, it is likely that both diseases may coexist within some patients. The potential association between thyroid autoimmunity and RA deserves particular attention because it may help in the planning of preventive as well as therapeutic strategies.

Several studies have evaluated the association between RA and thyroid autoimmunity, but the results of these studies have been inconsistent. Moreover, most of these studies used a relatively small sample size, which limited their power to detect whether an association between RA and thyroid autoimmunity existed. Our meta-analysis quantitatively evaluated whether an association exists between thyroid autoimmunity and RA. Thirteen independent, relevant articles with case–control designs were involved in our meta-analysis and assessed. The consequences of this meta-analysis indicated that the prevalence of thyroid autoantibodies in patients with RA was significantly higher than in the control group. The results of a subgroup analysis by geographic location showed that the study subjects with RA who were drawn from Asian, African, and European populations were more likely to be TgAb positive, but those drawn from American population were not. There was a positive relationship between TPOAb positivity and RA in Asian and African populations, but this association was not observed in either American or European population, suggesting a possible role for geography-driven diversity in genetic backgrounds and living environments. Further investigation of disease-specific genetic variations may contribute to revealing the actual association between thyroid autoimmunity and RA in the American population. Another possible reason for this difference may be that only one study addressed the association between thyroid autoimmunity and RA in an American population, resulting in insufficient statistical power to explore the real association between these diseases in this population.

The main objective for conducting this meta-analysis was to elucidate the association between thyroid autoimmunity and RA using statistical methods. However, there were some limitations to our meta-analysis. First, several relevant studies were not involved in this meta-analysis due to the incomplete raw data or other limitations of the publications. Second, in the subgroup analysis, the number of studies examining African and American populations was relatively small; thus, there was insufficient statistical

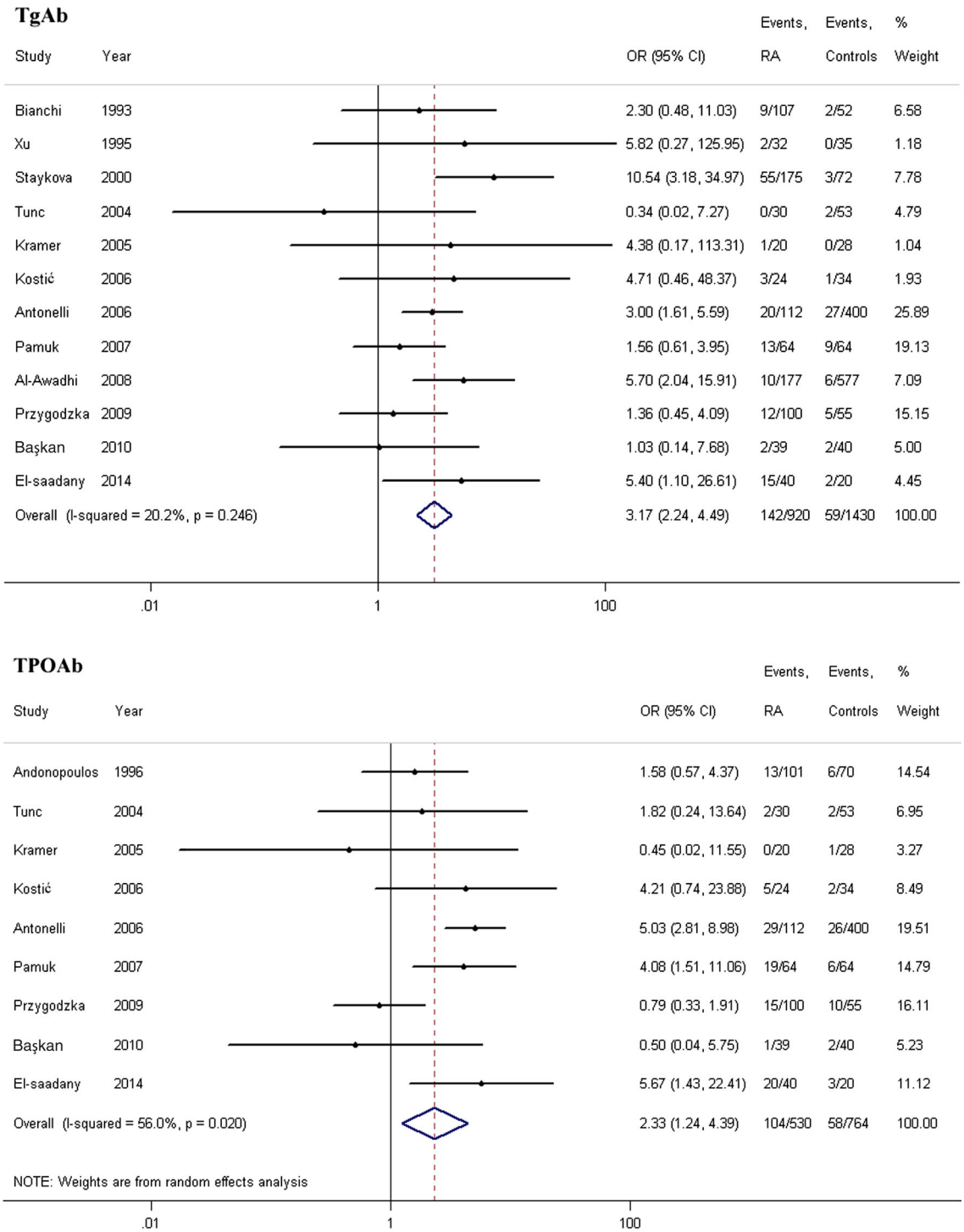

Fig. 2 Forest plots for the frequency of TgAb and TPOAb positivity in patients with RA compared with healthy controls. The diamond represents the pooled OR and 95 % CI

power to evaluate the level of association in these groups to a desired level of accuracy. Third, because of the lack of consistent criteria for categorizing thyroid function between different countries, this meta-analysis only addressed the relationship between RA and thyroid autoantibodies. Consequently, these meta-analysis consequences should be interpreted with caution.

In conclusion, the consequences of this meta-analysis support the hypothesis that the prevalence of thyroid autoantibodies in patients with RA is higher than in healthy

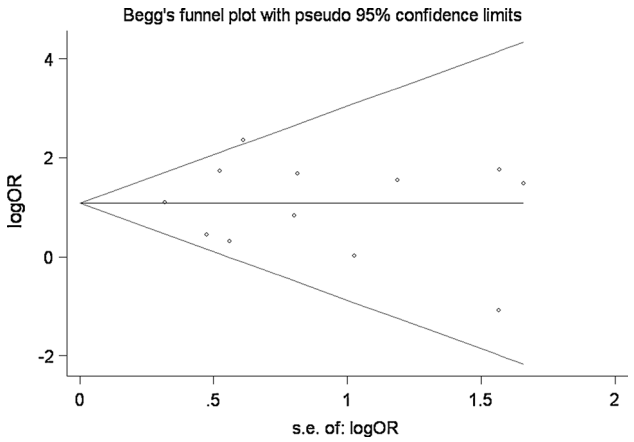

Fig. 3 Begg's funnel plot for testing the publication bias of the association between RA and the risk of thyroid autoimmunity associated with studies detecting TgAb positivity. Each point represents an individual study of the indicated association. The *horizontal line* indicates the effect size

controls, which suggests that RA may be associated with elevated thyroid autoimmunity risk.

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Conflict of interest The authors declare that there is no conflict of interest.

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