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Review

Thyroid disorders in patients with myasthenia gravis: A systematic review and meta-analysis

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ABSTRACT

Background: Our purpose was to determine the prevalence of thyroid disorders in myasthenia gravis (MG) or whether MG was associated with an increased risk of thyroid disorders.

Methods: Pubmed, Embase, Web of Science, Cochrane database, Google Scholar and the Chinese Biomedical Databases were searched about the relationship between thyroid disorders and myasthenia gravis up to November 30, 2018, without language restrictions. The prevalence and relative risk (RR) for thyroid disorders were pooled by the R and STATA software.

Results: 39 papers with 24,927 MG patients were ultimately included for analysis in this meta-analysis. The pooled estimate of thyroid autoimmunity prevalence in MG patients was 10.1% (95%CI 6.7%–15.1%). Subgroups in patients with thyroid autoimmunity showed the prevalence of positive TGAb was the highest in MG patients (12.6%, 95%CI 8.1%–19.1%), followed by GD (6.0%, 95%CI 4.2%–8.5%), HT (4.6%, 95%CI 1.9%–10.5%). Moreover, the pooled estimated prevalence of thyroid dysfunction in MG patients was 6.8% (95%CI 4.6%–9.8%). After stratification, the results showed the prevalence of hyperthyroidism and hypothyroidism in MG cases were 5.6% (95%CI 3.9%–8.0%) and 2.6% (95%CI 1.7%–4.1%), respectively. In addition, meta-analysis of 2 studies showed that MG was significantly associated with the increased risk of thyroid autoimmunity (OR = 2.86; 95%CI 1.54–5.28, P = .001).

Conclusions: This systemic review and meta-analysis provides reliable evidence that thyroid disorders are prevalent in MG, especially TGAb positivity, GD, hyperthyroidism, and HT, and MG is associated with increased risk for thyroid autoimmunity.

1. Introduction

It is well-known that thyroid autoimmunity and the accompanied thyroid dysfunction are the most common disorders in thyroid gland. Thyroid autoimmunity, also known as autoimmune thyroid disease (AITD), is caused by the development of autoimmunity against thyroid antigens and defined by positive antibodies, including thyroid stimulating hormone receptor antibody (TRAb), thyroid peroxidase (TPOAb) antibody and thyroglobulin antibody (TGAb). The general prevalence of thyroid autoimmunity in population is about 1%–5% [1]. There are three major phenotypes of thyroid autoimmunity such as Graves' disease (GD) triggered hyperthyroidism, hypothyroidism due to Hashimoto's thyroiditis (HT), and euthyroid patients with positive antithyroid antibodies [2,3]. Thyroid autoimmunity is a polygenic and organ specific disorder caused by a combination of genetic susceptibility in conjunction with immune and environmental factors [4]. One factor and single gene cannot sufficient to explain the etiology of this disease. It is very vital to further study and uncover the pathogenesis of thyroid autoimmunity and its consequent dysfunction in thyroid.

MG is a neuromuscular disease with muscle weakness and abnormal fatigability, caused by a defective transmission of the nerve impulse to muscles [5]. MG is mediated by the production of antibodies, like the antibody against acetylcholine receptor (AchR), muscle-specific kinase antibody (MuSK) and agrin receptor low-density lipoprotein receptor-related protein-4 antibody (LRP4) [6]. MG and thyroid autoimmunity share some commonalities, for example, they are both organ-specific, antibody-mediated, and involved ocular myopathy and exophthalmos [7].

Meanwhile, thyroid disorders are more frequent associated with MG

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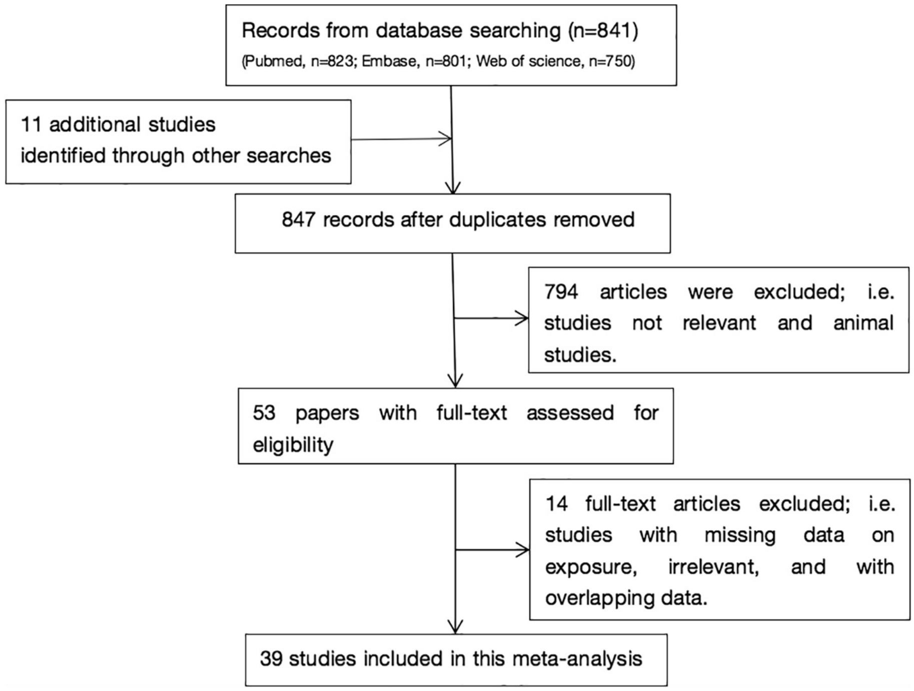

Fig. 1. Flow chart of study selection in the meta-analysis.

compared with other autoimmune diseases [8], but the prevalence of thyroid diseases varies among different studies. Thus, a systemic review and meta-analysis was conducted by us to assess the prevalence and risk of thyroid disorders among MG patients. And this research was on the basis of PRISMA statement [9].

2. Methods

2.1. Search strategy

A systematic computer-assisted search was done by two independent individuals (Song RH and Yao QM) and disagreements were resolved by discussion. Pubmed, Embase, Web of Science, Cochrane database, Google Scholar and the Chinese Biomedical Database were searched up to November 30, 2018. The search strategy in this study was as follows: ((myasthenia gravis)) AND (AITD OR AITDs OR autoimmune thyroid OR Graves' disease OR thyrotoxicosis OR hyperthyroidism OR Grave's orbitopathy OR Graves' ophthalmopathy OR hypothyroidism OR Hashimoto's thyroiditis OR thyroiditis OR Hashimoto's disease)). Any language or publication period was not restricted while searching.

2.2. Inclusion and exclusion criteria

Eligible papers should satisfy the following inclusion criteria: 1) case-control studies, cross-sectional studies and cohort studies; 2) comparability of the risk of thyroid disorders between MG patients and controls, or providing the prevalence of thyroid disorders in patients with MG; 3) outcomes of thyroid disorders analyzed in original papers were hyperthyroidism, hypothyroidism or AITD or antibodies positivity; 4) providing complete data to calculate the prevalence of thyroid disorders in MG cases or risk estimates of thyroid disorders with MG, including relative risk (RR) and odds ratio (OR). Review, case reports, animal studies, guidelines or studies including overlapping data or without usable data were all excluded.

2.3. Outcomes selection

The outcomes included the risk of thyroid dysfunction (hypothyroidism or hyperthyroidism) and thyroid autoimmunity (AITD, GD, HT, TPOAb positivity, TGAb positivity).

2.4. Data extraction

Two investigators assessed the selected articles independently. The data extracted included: i) study characteristics: the first author, publication year, design types, location); ii) participant characteristics: number of subjects, subgroups; iii) outcomes: types of thyroid diseases.

2.5. Quality assessment

The Newcastle-Ottawa scale (NOS) was carried out to estimate the quality of observational studies [10]. 4 points were utilized to evaluate the participant selection (sample size and representativeness), 2 points were awarded for the exposure evaluation, and 3 points were used for assessment of outcome and cofounders. Studies with 4 or fewer score were assigned to have low quality, and those with 5 or more score were considered to have high quality.

2.6. Statistical analysis

The pooled prevalence of thyroid disorders in MG was used by R 3.2.3 software. And the pooled RR or OR with corresponding 95%CI were used to evaluate MG on the risk of thyroid autoimmunity and dysfunction. Heterogeneity assessment was carried on using the I^2 test, and $I^2 > 50\%$ was considered with high heterogeneity [11]. Simultaneously, the random-effects model was assigned to calculate the pool data while the obvious heterogeneity exist [12]. We used Begg's test and Egger's test to statistically assess the potential publication bias [13]. Statistical analyses of the association between thyroid disorders and MG were conducted by STATA 12.0 (StataCorp, College Station, TX). And *P*-value under the level of 0.05 with two-side was considered with statistically significance.

Table 1
Characteristics of included studies in the meta-analysis.

Study	Design	Country	Study period	Number (MG)	Outcomes	Quality
Tanovska [48]	Cross-sectional	Republic of Macedonia	10 years	127	Hyperthyroidism, Hypothyroidism	6
Lin [47]	Cohort	Taiwan	2000–2002	7965	Thyrotoxicosis, Chronic lymphocytic thyroiditis, Acquired Hypothyroidism	7
Cordts [45]	Cohort	Germany	NA	100	GD , HT	7
Kubiszewska [46]	Cross-sectional	Poland	2009–2012	343	GD , HT , antithyroid antibodies	6
Meng [44]	Cohort	China	2004–2013	106	Thyroid function-abnormal, TGAb or TMAb positive	8
Tamer [43]	Cross-sectional	Turkey	2007–2012	75	AITD	6
Yeh [42]	Case-control	Taiwan	2008–2011	1689	GD , HT	6
Evoli [41]	Cohort	Italy	2–40 years	984	Thyroid disease	7
Maharaj [40]	Cross-sectional	Trinidad and Tobago	30 months	38	Thyroid disease	8
Klein [39]	Case-control	Germany	1981–2004	473	Thyroiditis, TGAb and/or TPOAb	8
Nakata [38]	Cross-sectional	Japan	2005–2009	166	GD , HT	7
Huang [51]	Cross-sectional	southern China	1987–2009	2154	Hyperthyroidism, Hypothyroidism	6
Chen [7]	Cross-sectional	Taiwan	1999–2009	1482	AITD, antibody-positive thyroid disease	6
Sri-udomkajorn [37]	Cohort	Thailand	1995–2009	119	Hyperthyroidism, Hypothyroidism	6
Leeamornsiri [36]	Cross-sectional	Thailand	1994–2004	96	Hyperthyroidism, Hypothyroidism	8
Mamarabadi [35]	Cross-sectional	Iran	2006–2007	58	Hyperthyroidism, Hypothyroidism	7
Boumendil [34]	Cross-sectional	France	2002–2007	15	Hashimoto thyroiditis	7
Kanazawa [33]	Cohort	Japan	1986–2005	142	GD , HT	6
Ramagopalan [32]	Case-control	Canada	1993–2007	5031	AITD	7
Toth [31]	Cross-sectional	Canada	1983–2004	109	GD , HT	6
Téllez-Zenteno [52]	Cohort	Mexico	1987–2000	198	Hyperthyroidism, Hypothyroidism	7
Ratanakorn [53]	Cross-sectional	Thailand	1969–1990	291	HT	7
Weissel [30]	Cohort	Austria	1–4 years	74	Hyperthyroidism, Hypothyroidism	8
Lavrnić [29]	Cross-sectional	Serbia	1983–1992	124	Thyroid diseases	7
Lindner [28]	Cohort	Germany	1958–1989	79	Hyperthyroidism	8
Zhang [27]	Cross-sectional	Chinese	NA	644	GD , HT	9
Marinó [26]	Cross-sectional	Italy	1980–1995	129	AITD	7
Takeuchi [25]	Cross-sectional	Japan	NA	11	HT, TAO	8
Christensen [24]	Cross-sectional	Denmark	1975–1989	432	Hyperthyroidism	9
Yu [23]	Cross-sectional	Hong Kong	1975–1987	262	AITD	7
Wong [22]	Cross-sectional	Hong Kong	NA	103	GD	8
Itoh [21]	Cross-sectional	Japan	30 years	253	GD	7
Thorlacius [20]	Cross-sectional	Norway	NA	48	Thyroiditis	6
Monden [19]	Cross-sectional	Japan	NA	277	GD , HT	8
De Assis [18]	Cross-sectional	Portuguese	NA	304	Hyperthyroidism, Hypothyroidism	8
Kiessling [17]	Cross-sectional	German	NA	52	Hyperthyroidism, Hypothyroidism	9
Kiessling [17]	Case-control	German	NA	104	Thyrotoxicosis, hypothyroidism	9
Garlepp [15]	Cross-sectional	Austria	NA	230	Hyperthyroidism, Hypothyroidism, TGAb	8
Aarli [14]	Cross-sectional	Norway	NA	40	Thyrotoxicosis	8

Table 2
Meta-analysis of the prevalence of thyroid disorders in MG patients.

Analyses	No. of studies	Number	Events	I^2	Prevalence	95% CI
Dysfunction	19	12,633	542	93%	0.068	0.046–0.098
Hyperthyroidism	13	3695	222	75%	0.056	0.039–0.080
Hypothyroidism	16	12,016	282	79%	0.026	0.017–0.041
thyroid autoimmunity	21	19,231	1020	97%	0.101	0.067–0.151
GD	13	5699	305	88%	0.060	0.042–0.085
HT	14	13,363	241	98%	0.046	0.019–0.105
TGAb	2	144	18	0%	0.126	0.081–0.191

3. Results

3.1. Results of the literature search

The detailed process of the literature selection is presented in Fig. 1. In total, 841 studies were initially searched, then, another 11 articles were added through other searching strategy, like manual retrieval. Then 847 researches were left after duplicated ones removed. Subsequently, 794 entries were excluded, which were irrelevant to the meta-analysis or animals after careful reading of the titles and abstracts. Additionally, among the remained 53 articles, another 14 trials were excluded for such reasons: missing data on exposure, irrelevant or overlapping results and outcomes. In final, 39 papers were ultimately included for analysis in this study [7,14–48].

3.2. Study characteristics

As shown in Table 1, a summary of the characteristics (the first author, publication year, design, country or region, study period, numbers of MG patients, outcomes and quality assessment score) of 39 studies included in the meta-analysis. A total population of 24,927 subjects with MG were included in each trail ranged from 11 to 7965 individuals. This research comprised of 3 case-control ones, 26 cross-sectional ones and 10 cohort studies.

3.3. Prevalence of thyroid autoimmunity in MG patients

As presented in Table 2, Fig. 2, the pooled estimate of thyroid autoimmunity prevalence in patients with MG was 10.1% (95%CI 6.7%–15.1%). Subgroup in patients with thyroid autoimmunity showed

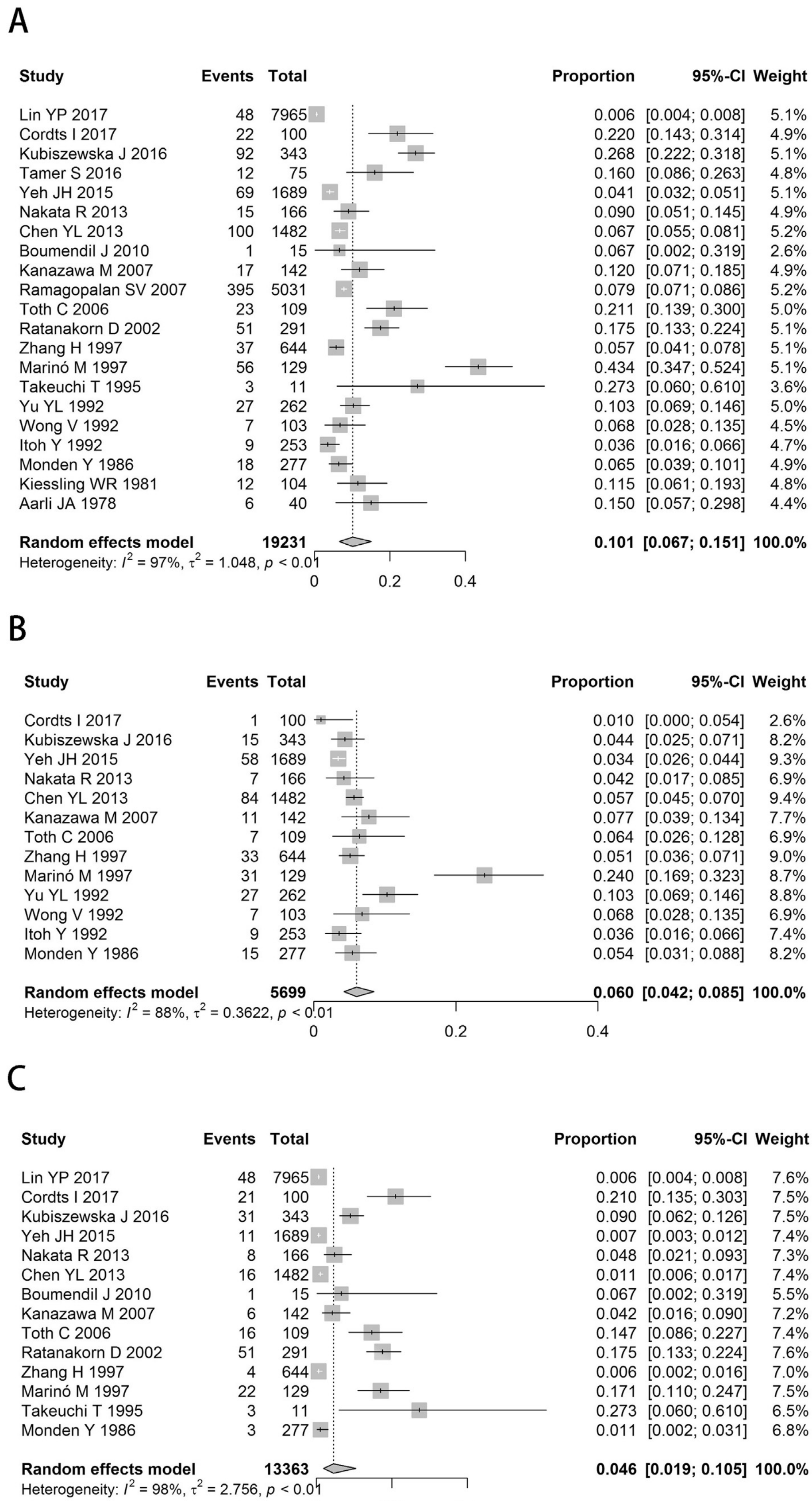

Fig. 2. The pooled prevalence of thyroid autoimmunity in MG using the meta-analysis. A. The pooled prevalence of thyroid autoimmunity in MG. B. The pooled prevalence of GD in MG. C. The pooled prevalence of HT in MG.

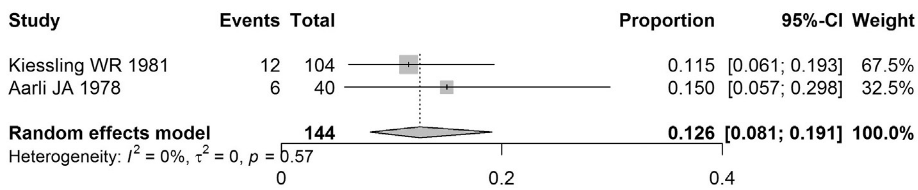

Fig. 3. The pooled prevalence of TGAb positivity in MG using the meta-analysis.

the prevalence of positive TGAb was the highest in MG patients (12.6%, 95%CI 8.1%–19.1%), followed by GD (6.0%, 95%CI 4.2%–8.5%) and HT (4.6%, 95%CI 1.9%–10.5%), which were showed in Fig. 2 and Fig. 3.

3.4. Prevalence of thyroid dysfunction in MG patients

The pooled estimated prevalence of thyroid dysfunction in MG patients was 6.8% (95%CI 4.6%–9.8%), which was displayed in Table 2 and Fig. 4. After stratification, the results showed the prevalence of hyperthyroidism and hypothyroidism in MG cases were 5.6% (95%CI 3.9%–8.0%) and 2.6% (95%CI 1.7%–4.1%), respectively, so the hyperthyroidism showed a higher prevalence than hypothyroidism.

3.5. MG and thyroid disorders

AS shown in Fig. 5, meta-analysis of 2 studies showed that MG was significantly associated with the increased risk of thyroid autoimmunity (OR = 2.86; 95%CI 1.54–5.28, P = .001).

4. Discussion

AITD and myasthenia gravis are a group of heterogeneous diseases resulting from loss of immune tolerance to autoantigens [49]. Up to 5% of the whole population is suffered by one or more autoimmune disorders, and the prevalence of this kind disease is predominant higher in women. For patients with one autoimmune disease, they are prone to have another or more autoimmune diseases, which implies they may have common pathogenesis to some extent, including genetic, environmental factors or immunological, hormonal elements [49,50]. There have been many studies reported the increased prevalence of thyroid disorders in myasthenia gravis (MG) and MG being associated with an increased risk of thyroid disorders. Nevertheless, the reported results are not in line with each other. For example, it is reported that MG patients have an increased incidence of thyroid autoimmunity, and the frequency varies from 3.3% to 18.9% [18,44]. Herein, we reviewed the above articles and made a meta-analysis on the prevalence and the association between MG and thyroid disorders.

Our meta-analysis of 39 papers with 24,927 MG patients showed the pooled estimated the prevalence of thyroid autoimmunity in 10.1% of MG patients: positive TGAb was predominant, followed by GD and HT. Moreover, we also demonstrated the whole prevalence of thyroid autoimmunity accompanied thyroid dysfunction including hyperthyroidism and hypothyroidism in MG patients was 6.8%. In addition, meta-analysis of 2 studies showed that MG increased the risk of thyroid autoimmunity by 186%. That the prevalence of thyroid disease accompanying MG varies in reported series of papers may be due to the different methods used to identify thyroid diseases, different sample size or various study population. Therefore, our current meta-analysis synthesized the above data, and obtain a relatively reliable result. Finally, our study confirmed that thyroid disorders in MG patients are more prevalent than in the general population, which is consistent with the previously published studies [33].

Thyroid immunity and its accompanied thyroid disorders are prevalent in patients with MG, drawing attention to the possible common basis for their coexistence, as well as the diagnosis and therapeutic strategy of these two diseases. There are strong evidences suggesting thyroid autoimmunity is associated with MG, and the ocular form of MG is in special relationship with thyroid disease [7,33]. Mechanism underlying such overlap has not been fully stated. However, it is noted that clustering of thyroid autoimmunity and MG reflects autoimmunity always playing a key role in the correlation of MG and thyroid disorders, and cross-immune epitopes or autoantigens shared by thyroid gland and eye muscles might be the basis for this association [7,33]. Additionally, common genetic background is also thought to involve in this correlation. For example, HLA-DR3 antigen was found to be related to Graves' disease, simultaneously, other studies found HLA haplotypes take a part in the development of MG onset [31]. This implies the roles of genetic factors between these two diseases worthy further imploring. More importantly, the close connection of thyroid disorders and MG suggests that screening thyroid diseases including thyroid autoantibodies and thyroid function is vital in MG patients, as the therapies for thyroid dysfunction are relatively simple comparing to those for MG and hormone replacement therapy for hypothyroidism in MG cases benefits greatly, almost no side effects.

The sample size in this meta-analysis is large enough to provide a precise estimation of the prevalence of thyroid immunity and accompanied thyroid dysfunction in MG and the relationship between thyroid disorders and MG. Though we conducted this meta-analysis very rigorously, there are still some limitations should be taken into consideration. At first, there were some differences in the included researches, such as the confounding factors, different diagnosis criteria of disease, different methodology in different papers and so on, which may result in the heterogeneity between studies. Considering this, the pooled assessment should be interpreted in a sensible way. Secondly, there still lack of enough prospective cohort studies to evaluate the relationship of thyroid disease and MG. Further prospective cohort researches are needed to confirm our results. Thirdly, a previous study emphasized higher incidence of ocular MG when thyroid autoimmunity presented [26]. We tried to further analyze the relationship between thyroid ophthalmopathy and MG, but the studies on this correlation is too less to synthesize. In future, we hope there will be more researches to concentrate on this topic and more data will be available.

5. Conclusion

This systemic review and meta-analysis provides reliable evidence that thyroid disorders are prevalent in MG, especially TGAb positivity, GD, hyperthyroidism, and HT. Meanwhile, the present study identified that MG is a real risk factor for thyroid autoimmunity.

Contributors

All authors participated in interpreting the data and critically reviewing the paper. Zhang JA and Song RH designed the study and generating hypotheses. Song RH and Yao QM extracted the data. Song RH wrote the first draft of the report and analyzed the data, with support from Wang B, Li Qian and Jia X. Zhang JA helped revising the manuscript.

Source of funding

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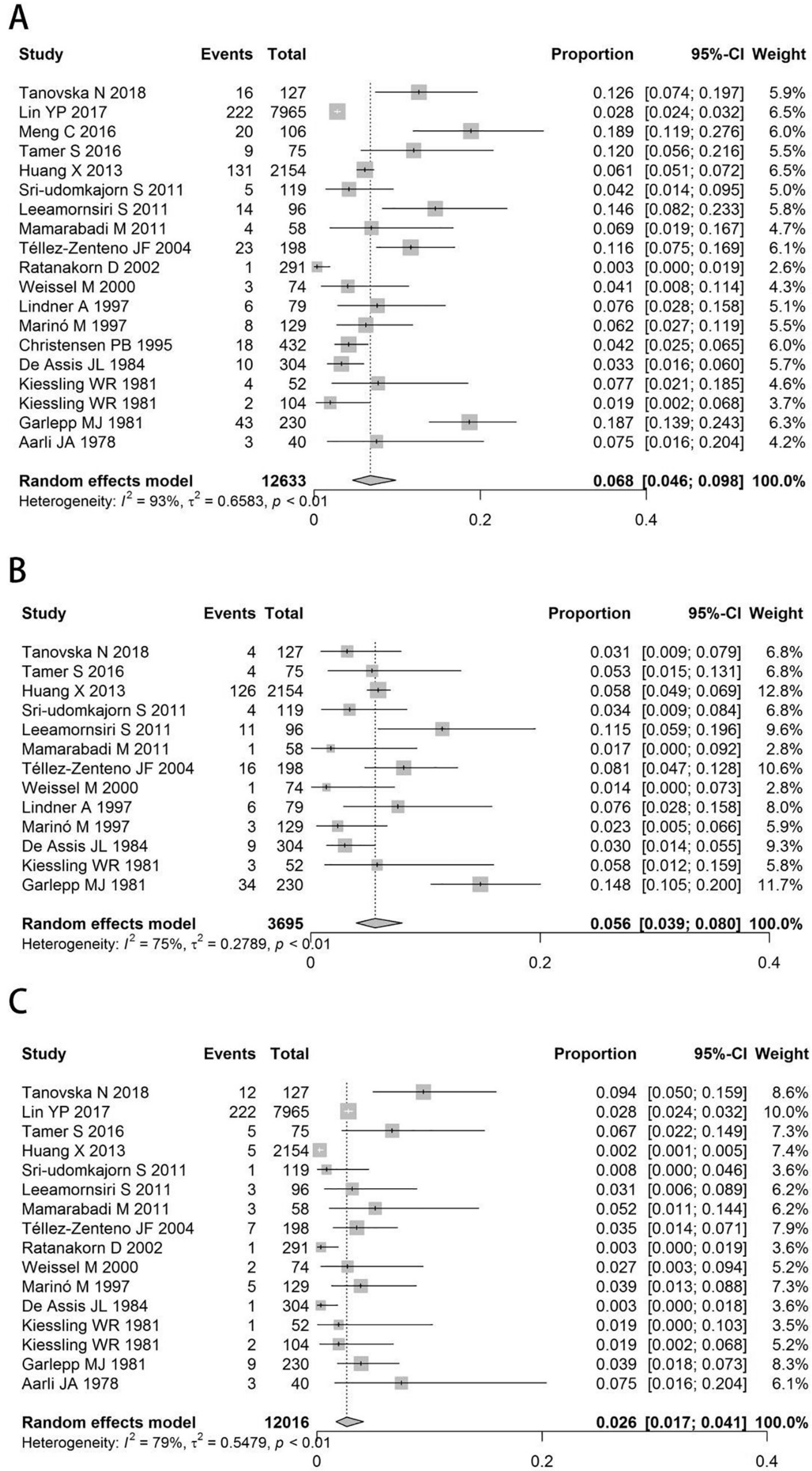

Fig. 4. The pooled prevalence of thyroid dysfunction in MG using the meta-analysis. A. The pooled prevalence of dysfunction in thyroid in MG. B. The pooled prevalence of hyperthyroidism in MG. C. The pooled prevalence of hypothyroidism in MG.

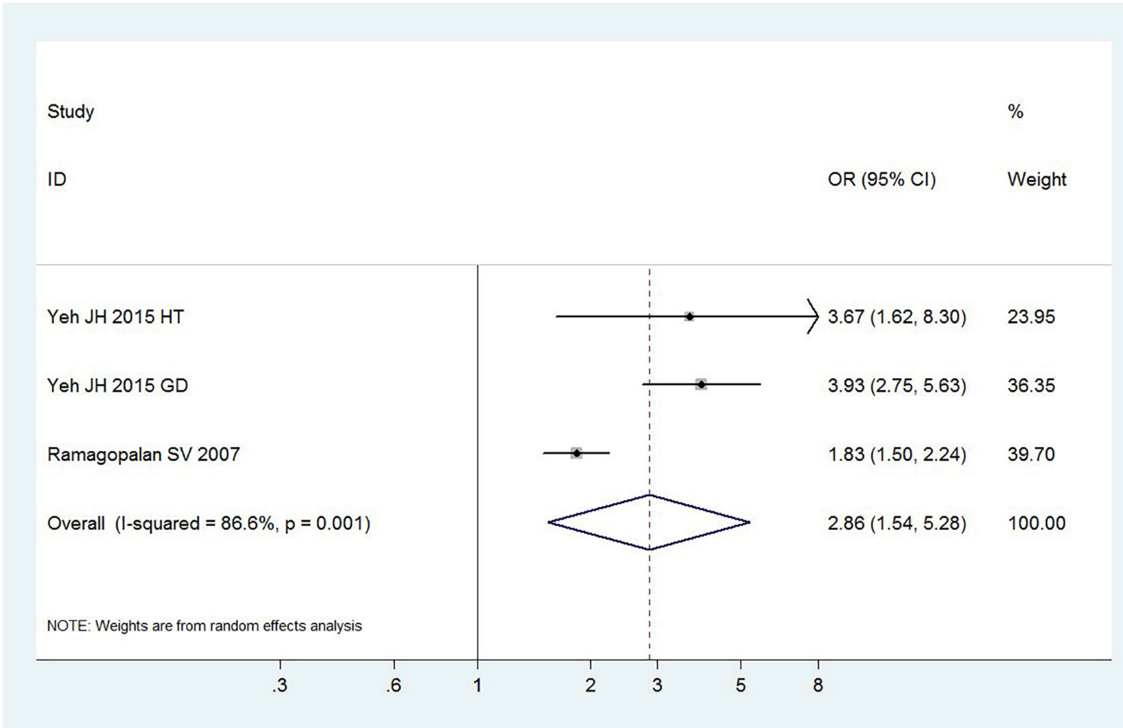

Fig. 5. Meta-analysis of association between thyroid autoimmunity and MG.

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Declaration of Competing Interest

The authors have declared that no competing interests exist.

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