



The Association Between Asthma and Risk of Myasthenia Gravis: A Systematic Review and Meta-analysis

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Abstract

Purpose This study aimed to investigate the association between asthma and risk of myasthenia gravis (MG) using the method of systematic review and meta-analysis.

Methods Potentially eligible studies were identified from Medline and EMBASE databases from inception to July 2020 using search strategy that comprised terms for “Asthma” and “Myasthenia Gravis”. Eligible cohort study must consist of one cohort of individuals with asthma and another cohort of individuals without asthma. Then, the study must report relative risk (RR) with 95% confidence intervals (95% CIs) of incident MG between the groups. Eligible case–control studies must include cases with MG and controls without MG. Then, the study must explore their history of asthma. Odds ratio (OR) with 95% CIs of the association between asthma status and MG must be reported. Point estimates with standard errors were retrieved from each study and were combined together using the generic inverse variance method.

Results A total of 6,835 articles were identified. After two rounds of independent review by five investigators, two cohort studies and three case–control studies met the eligibility criteria and were included into the meta-analysis. Pooled analysis showed that asthma was significantly associated with risk of MG with the pooled risk ratio of 1.38 (95% CI 1.02–1.86). Funnel plot was symmetric, which was not suggestive of publication bias.

Conclusion The current study found a significant association between asthma and increased risk of MG.

Keywords Asthma · Myasthenia gravis · Systematic review · Meta-analysis

Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by skeletal muscle weakness either generalized or localized, more proximal than distal, and nearly always includes eye muscles, with diplopia and ptosis.

Anti-acetylcholine receptor (AChR) antibodies can be detected in serum of approximately 85% of MG patients, while other patients who are seronegative for anti-AChR may have autoantibodies against functionally related molecules, such as muscle-specific tyrosine kinase [1–3]. The reported incidence rate estimates between 5 and 30 cases

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per 100,000 population, with the bimodal age distribution around the age of 30 and 50 years [4]. MG is a multifactorial disease and the onset of the disease likely linked to a combination among immunological, genetic, and environmental factors [5].

Asthma is a chronic inflammatory disorder of the airway that is associated with reversible airflow obstruction, persistent airway hyperreactivity, and airway remodeling. Symptoms may include wheezing, breathlessness, chest tightness, and coughing in particular at night or in the early morning [6, 7]. It is estimated that over 300 million people suffer from asthma, and its prevalence is increasing in both adult and pediatric population [8]. The etiology of asthma is complex and multifactorial. Most asthmatics have type 2 inflammation (T2-high) which is associated with inflammatory cells (eosinophils, mast cells, basophils, Th2 lymphocytes, and immunoglobulin E [IgE]-producing plasma cells) and certain cytokine profiles (IL-4, IL-5 and IL-14) [6, 7]. On the other hand, “non-eosinophilic asthma,” also known as non-type 2 (non-T2 or T2-low) asthma, is less well characterized, where Th1 and Th17 cells, neutrophils, and proteins including IL-1 β , IL-6, IL-8, IL-17A/F, IFN- γ , and TNF- α are implicated in its pathogenesis [9].

Previous epidemiologic studies have reported an association between asthma and a higher risk of other autoimmune diseases, such as systemic lupus erythematosus (SLE) [10], Sjogren’s syndrome [11], and rheumatoid arthritis [12]. The associations were separately explained by different types of immunopathogenic pathway including Th1 and Th2 overexpression [11, 13–15]. Several studies have reported the association between asthma and increased risk of MG [16–20]. Additionally, there were some case reports that showed the association between severity of asthma and MG [21–23]. Nonetheless, the results from existing evidence are markedly inconsistent. Establishing the association between asthma and MG would lead to a better understanding of their pathogenesis. Consequently, it may lead to a better understanding on prevention and management of asthma and MG. The current systematic review and meta-analysis was conducted with the aim to investigate whether patients with asthma had a higher risk of MG by identifying all available studies and summarizing their results together.

Methods

Search Strategy

Publications indexed in Medline and Embase from inception to July 2020 were independently searched by 3 investigators (P.Y., N.C., B.P.). Search terms were derived from terms related to “Asthma” and “Myasthenia gravis.” The detailed

search strategy is demonstrated in the Supplemental Material 1. No language limitation was applied.

Inclusion Criteria

Eligible study must be either cohort or case–control study. Eligible cohort study must consist of one cohort of individuals with asthma and another cohort of comparators without asthma. Then, the study must report relative risk (RR), incidence rate ratio (IRR), hazard risk ratio (HR), or standardized incidence ratio (SIR) with 95% confidence intervals (95% CIs) of incident MG between individuals with asthma versus comparators without asthma. Eligible case–control studies must include cases with MG and controls without MG. Then, the study must explore their history of asthma. Odds ratio (OR) with 95% CIs of the association between presence of asthma and MG must be reported.

Three investigators (P.Y., N.C., B.P.) independently reviewed the eligibility of the retrieved articles. Different opinion was resolved by discussion with the senior investigator (P.U.). Two investigators evaluated the quality of each study (N.C. and P.U.) using the Newcastle–Ottawa quality assessment scale for cohort study and case–control study [24].

Data Extraction

A standardized collection form was applied for data extraction of the following information: last name of the first author, country of the study, study design, publication year, number of participants, recruitment of participants, diagnosis of MG, diagnosis of asthma, follow-up duration, mean age of participants, percentage of male participants, comorbidities of participants, and variables adjusted in multivariate analysis.

Statistical Analysis

Review Manager 5.3 software from the Cochrane Collaboration was used for analysis of data. Point estimates with standard errors were retrieved from each study and were combined together using the generic inverse variance method as described by DerSimonian and Laird [25]. Random-effect model, instead of fixed-effect model, was used as the included studies had different background populations and protocols. The Cochran’s Q test was used to determine the statistical heterogeneity. This statistic is further adjuncted with the I^2 statistic which quantifies the proportion of the total variation across studies, that is from heterogeneity rather than coincidence. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and > 75% represents high heterogeneity [26]. If enough studies were eligible for the

meta-analysis, visualization of funnel plot would be used for investigating the presence of publication bias. If funnel plot was asymmetric, Egger regression and trim-and-fill analyses would be performed to assess whether publication bias had any effect on the result of meta-analysis.

Results

Search Results

A total of 6,835 articles were retrieved from EMBASE and MEDLINE database in which duplicated articles were discarded, leaving 6,368 articles for title and abstract review. After review of title and abstract, 6,336 articles were excluded as they obviously did not meet the eligibility criteria based on study design and type of article, leaving 32 articles for full-length article review. A total of 27 articles were excluded at this stage as the outcome of interest was not reported, leaving five articles that fulfilled the eligibility criteria. Finally, two cohort studies [16, 17] and three case–control studies [18–20] were included in the meta-analysis. Figure 1 demonstrates the search methodology and selection process of this study.

Study Characteristics

The characteristics of the five eligible studies are presented in Tables 1 and 2. All of the studies were published between 2004 and 2019. Two studies were conducted in Taiwan [19, 20], one in Japan [18], one in the United Kingdom [17], and one in Sweden [16]. A total of more than 13 million participants (1,195,163 cases of asthma) were included in the two cohort studies [16, 17], whereas a total of 2,259 cases of MG and 8,477 controls were included in the three case–control studies [18–20]. One study used clinical presentation and compatible laboratory investigation to diagnose MG [18] and the rest used diagnostic codes from administrative database [16, 17, 19, 20]. Similarly, one study used health questionnaire to diagnose asthma [18] and the rest relied on diagnostic codes from administrative database [16, 17, 19, 20].

Association Between Asthma and Risk of Myasthenia Gravis

The meta-analysis found that asthma was associated with risk of MG with the pooled risk ratio of 1.38 (95% CI

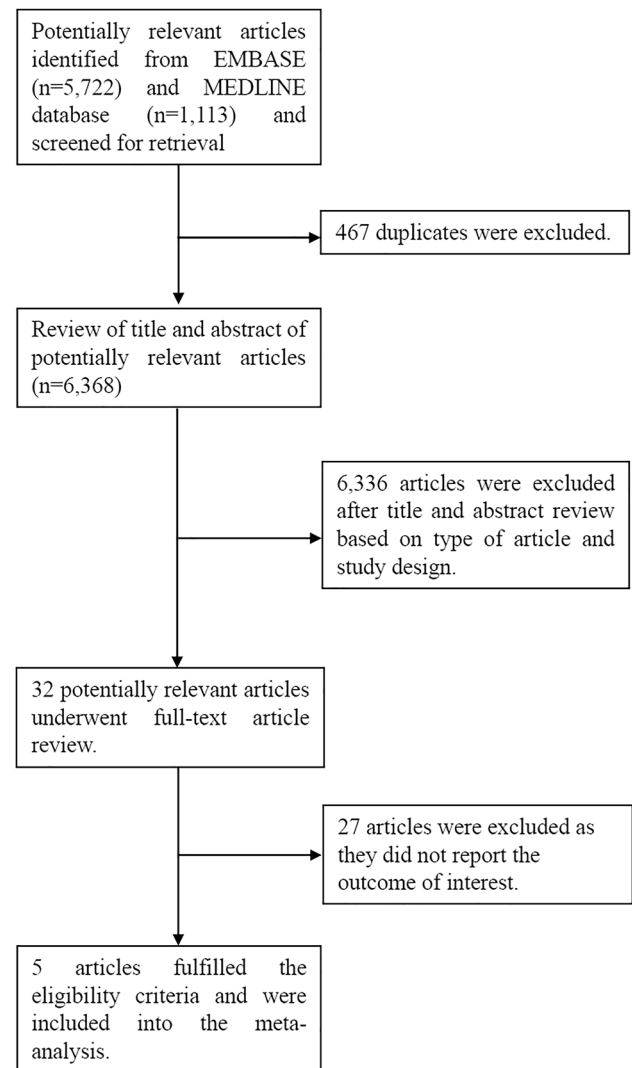


Fig. 1 Study identification and literature review process

1.02–1.86). This meta-analysis had moderate statistical heterogeneity with I^2 of 74% (Fig. 2).

Quality Evaluation

The results of the quality assessment of the included studies are shown in Tables 1 and 2. Three studies were of high quality and two studies were of moderate quality.

Evaluation for Publication Bias

A funnel plot (Fig. 3) was used for assessment for publication bias of the meta-analysis. The funnel plot was fairly symmetric, which is not suggestive of publication bias.

Table 1 Main characteristics of the cohort studies included in the meta-analysis

	Hemminki et al. [16]	Krishna et al. [17]
Country	Sweden	United Kingdom
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2010	2019
Total number of participants	Patients with asthma: 148,295 Comparators: close to 12 million	Patients with asthma: 1,049,868 Comparators: 1,732,480
Recruitment of participants	Patients with asthma were identified from the autoimmune disease database, which is a subset of the national MigMed database at Center for Primary Health Care Research Lund University from 1964 to 2007 The rest of the individuals without asthma in the database served as comparators	Patients with asthma were identified from the Health Improvement Network database from January 1, 1990 to January 17, 2018. This database contained clinical data of approximately 3 million patients recorded by 787 general practitioners across the UK Comparators without asthma were randomly identified from the same database (up to 2 comparators for 1 case). They were matched to cases by age, sex, and general practitioner
Diagnosis of asthma	Presence of diagnostic codes of asthma in the database (ICD-7: 241; ICD-8: 493; ICD-9: 493; ICD-10: J45, J46)	Presence of diagnostic codes of asthma in the database
Diagnosis of MG	Presence of inpatient diagnostic codes of MG in the database according to the different versions of the International Classification of Diseases	Presence of diagnostic codes of MG in the database
Follow-up period	Until hospitalization for MG, death, emigration, or closing date (December 31, 2007)	Until the development of MG, death, emigration, or closing date (January 17, 2018)
Average duration of follow-up (years)	Participants with asthma: N/A Comparators: N/A	Patients with asthma: 4.0 Comparators: 5.5
Average age of participants at index date (years)	Participants with asthma: N/A Comparators: N/A	Patients with asthma: 35.6 Comparators: 38.0
Percentage of female	Participants with asthma: N/A Comparators: N/A	Patients with asthma: 51.3% Comparators: 52.0%
Variables adjusted in multivariate analysis	None	Age, sex, body mass index, ethnicity, townsend deprivation quintile, and smoking status
Newcastle-Ottawa score	Selection: 3 Comparability: 0 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

ICD-7 The International Classification of Disease, 7th Revision, *ICD-8* The International Classification of Disease, 8th Revision, *ICD-9* The International Classification of Disease, 9th Revision, *ICD-10* The International Classification of Disease, 10th Revision, *MG* myasthenia gravis, *N/A* not available

Discussion

The present study is the first systematic review and meta-analysis that summarizes the results of all available cohort and case–control studies that reported the association between asthma and risk of developing MG. The pooled analysis found that patients with asthma had approximately 1.4 times higher odds of MG. The observed association is largely driven by the result from the largest UK study by Krishna et al. [17].

The underlying mechanism of the association between asthma and risk of MG is still unclarified but there are some possible explanations. First, asthma and MG might share some common immunopathogenic pathway. Previous studies showed that MG patients had the overexpression of CD23 in

germinal centers of the thymus and the increase serum level of sCD23. However, the declining of serum level of sCD23 was observed after thymectomy which showed a strong correlation with clinical improvement [27, 28]. CD23, known as a low-affinity receptor for IgE (FcεRII), is involved in the regulation of IgE synthesis, antigen presentation, and B-cell activation [29, 30]. IgE is believed to contribute to T2-high asthmatic manifestation and other allergic condition [31]. In addition, dysregulated CD4 T lymphocyte (Th1, Th2, Th17, Treg) is considered to be involved in the pathogenesis of both asthma, both T2-high and T2-low endotypes, and MG [5, 32].

Second, genetic predispositions for MG and asthma have been well documented and with the strongest association to HLA genes. Based on the current evidence, several traits

Table 2 Main characteristics of the case–control studies included in the meta-analysis

	Murai et al. [18]	Tsai et al. [19]
Country	Japan	Taiwan
Year of publication	2004	2014
Total number of participants	Cases: 160 Controls: 81	Cases: 410 Controls: 1,640
Recruitment of participants	Cases: cases were patients with MG who visited the Department of Neurology, Kyushu University Hospital during April 2000 to July 2003 Controls: controls were neurological normal patients who visited the same department during March 1998 to February 2000	Cases: cases were patients aged 1–18 years with MG who were identified from the Taiwan National Health Insurance Research Database during 1998 to 2011 Controls: controls without MG were randomly selected from the same database Controls were 1:4 matched with cases by sex and index year
Diagnosis of MG	Presence of clinical symptoms with diurnal fluctuation or easy fatigability plus at least one of the following positive tests: (1) Edrophonium test, (2) repetitive nerve stimulation on the facial or median nerves, and (3) measurement of anti-AChR antibody through radioimmunoassay	Presence of diagnostic codes of MG in the database (ICD-9-CM: 358.0)
Diagnosis of asthma	Self-reported through a health questionnaire	Presence of diagnostic codes of asthma in the database (ICD-9: 493 and 494)
Average age of participants (years)	Cases: 52.2 Controls: N/A	Cases: 8.7 Controls: 10.7
Percentage of female	Cases: 67.5% Controls: N/A	Cases: 62.9% Controls: 62.9%
Variables adjusted in multivariate analysis	None	Age, parental occupation, and mutual allergic diseases (allergic conjunctivitis, allergic rhinitis, atopic dermatitis, urticaria)
Newcastle–Ottawa score	Selection: 3 Comparability: 0 Exposure: 2	Selection: 4 Comparability: 2 Exposure: 3
Yeh et al. [20]		
Country	Taiwan	Taiwan
Year of publication	2015	2015
Total number of participants	Cases: 1,689 Controls: 6,756	Cases: 1,689 Controls: 6,756
Recruitment of participants	Cases: cases were patients aged ≥ 20 years with MG who were identified from the dataset of Catastrophic Illness Patient Database from January 1, 2008 to December 31, 2011 Controls: controls without MG were randomly selected from the Longitudinal Health Insurance Database	Cases: cases were patients aged ≥ 20 years with MG who were identified from the dataset of Catastrophic Illness Patient Database from January 1, 2008 to December 31, 2011 Controls: controls without MG were randomly selected from the Longitudinal Health Insurance Database
Diagnosis of MG	Controls were 1:4 matched with cases by age, sex, and index year	Controls were 1:4 matched with cases by age, sex, and index year
Diagnosis of asthma	Presence of diagnostic codes of MG in the database (ICD-9: 358.0)	Presence of diagnostic codes of MG in the database (ICD-9: 358.0)
Average age of participants (years)	Presence of diagnostic codes of asthma in the database (ICD-9:493 and 494) Cases: 51.4 Controls: 51.3	Presence of diagnostic codes of asthma in the database (ICD-9:493 and 494) Cases: 51.4 Controls: 51.3

Table 2 (continued)

	Yeh et al. [20]
Percentage of female	Cases: 56.7% Controls: 56.7%
Variables adjusted in multivariate analysis	Presence of diagnosis of allergic conjunctivitis, allergic rhinitis, atopic dermatitis, urticaria, Hashimoto thyroiditis, Graves' disease, malignancies, diabetes mellitus, cardiovascular disease, and chronic pulmonary disorders
Newcastle–Ottawa score	Selection: 4 Comparability: 2 Exposure: 3
AC/I/R acetylcholine receptor; ICD-9 The International Classification of Disease, 9th Revision, ICD-9-CM The International Classification of Disease, 9th Revision Clinical Modification, MG myasthenia gravis, N/A not available	

of HLA can be characterized in the background of MG by subtype specificity, gender discrepancy, and ethnic and geographical disparity. For example, HLA-B*08, HLA-DRB1, and HLA-DQB1 are present virtually in certain MG subtypes universally [33, 34]. These genes are also shown to be associated with asthma based on genome-wide association studies [35–37]. In addition, TNF- α (gene-related non-classic MHC molecules) also contribute to MG and asthma predisposition [33, 38, 39].

Lastly, asthma and MG may share some common environmental risk factors. Viral infections are important trigger of acute wheezing episodes in infancy and the inception and exacerbation of asthma [40]. They also have been suspected to play a role in MG. Antiviral process can be observed in the MG thymus [41]. Molecular mimicry, cryptic antigens, epitope spreading, bystander activation, and polyclonal activation have all been suggested as mechanisms for the induction of MG by viral agents [42].

This meta-analysis carries some limitations that should be aware of. First, the statistical heterogeneity of the meta-analysis was moderate. Difference in study design and participant characteristics was probably the one of the main reasons for the variation. Second, nearly half of included studies have poor quality based on Newcastle–Ottawa scale. Third, the majority of the included studies relied on diagnosis codes from administrative databases to identify and diagnose asthma and MG with no information on endotype/phenotype or severity [16, 17, 19, 20]. One study relied on self-reported questionnaires to diagnose asthma [18]. Therefore, the completeness of case identification, accuracy of the diagnoses, and subtype/endotype classification of both diseases are limited. Last, the small number of included studies in meta-analysis could jeopardize the validity and the interpretation of the funnel plot.

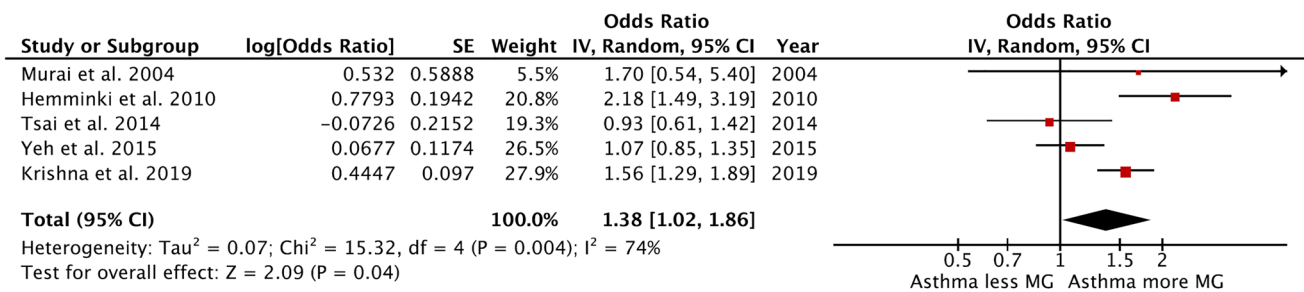


Fig. 2 Forest plot of the meta-analysis of risk of myasthenia gravis in asthma patients

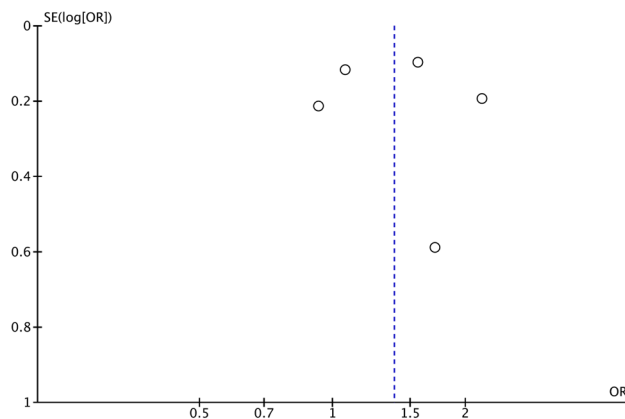


Fig. 3 Funnel plot of the meta-analysis of risk of myasthenia gravis in asthma patients

Conclusion

In summary, this systematic review and meta-analysis revealed a significant association between asthma and higher risk of MG.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00408-021-00444-8>.

Author Contributions All authors had access to the data and a role in writing the manuscript.

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Data Availability All data and materials support the published claims and comply with field standards.

Declarations

Conflict of interest We declare that there is no financial or nonfinancial potential conflict of interest.

References

- Gilhus NE (2016) Myasthenia gravis. *N Engl J Med* 375(26):2570–2581
- Gilhus NE, Verschuuren JJ (2015) Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol* 14(10):1023–1036
- Meriggioli MN, Sanders DB (2012) Muscle autoantibodies in myasthenia gravis: beyond diagnosis? *Expert Rev Clin Immunol* 8(5):427–438
- Hehir MK, Silvestri NJ (2018) Generalized myasthenia gravis: classification, clinical presentation, natural history, and epidemiology. *Neurol Clin* 36(2):253–260
- Berrih-Aknin S, Le Panse R (2014) Myasthenia gravis: a comprehensive review of immune dysregulation and etiological mechanisms. *J Autoimmun* 52:90–100
- Mims JW (2015) Asthma: definitions and pathophysiology. *Int Forum Allergy Rhinol* 5(Suppl 1):S2–6
- Maddox L, Schwartz DA (2002) The pathophysiology of asthma. *Annu Rev Med* 53(1):477–498
- Croissant S (2014) Epidemiology of asthma: prevalence and burden of disease. *Heterogeneity in asthma*. Springer, Boston, pp 17–29
- Sze E, Bhalla A, Nair P (2020) Mechanisms and therapeutic strategies for non-T2 asthma. *Allergy* 75(2):311–325
- Charoenngam N et al (2021) Patients with asthma have a higher risk of systemic lupus erythematosus: a systematic review and meta-analysis. *Clin Rheumatol* 40(2):529–536
- Shen T-C et al (2016) Risk of asthma in patients with primary Sjögren's syndrome: a retrospective cohort study. *BMC Pulm Med* 16(1):152–152
- Charoenngam N et al (2020) Patients with asthma have a higher risk of rheumatoid arthritis: a systematic review and meta-analysis. *Semin Arthritis Rheum* 50(5):968–976
- Hsiao YP et al (2014) Atopic diseases and systemic lupus erythematosus: an epidemiological study of the risks and correlations. *Int J Environ Res Public Health* 11(8):8112–8122
- Jeong HE, Jung SM, Cho SI (2018) Association between rheumatoid arthritis and respiratory allergic diseases in Korean adults: a propensity score matched case-control study. *Int J Rheumatol* 2018:3798124
- Sheen YH et al (2018) Association of asthma with rheumatoid arthritis: a population-based case-control study. *J Allergy Clin Immunol Pract* 6(1):219–226
- Hemminki K et al (2010) Subsequent autoimmune or related disease in asthma patients: clustering of diseases or medical care? *Ann Epidemiol* 20(3):217–222
- Krishna MT et al (2019) Allergic diseases and long-term risk of autoimmune disorders: longitudinal cohort study and cluster analysis. *Eur Respir J* 54(5):1900476

18. Murai H et al (2004) High frequency of allergic conjunctivitis in myasthenia gravis without thymoma. *J Neurol Sci* 225(1–2):27–31
19. Tsai JD et al (2014) Increased subsequent risk of myasthenia gravis in children with allergic diseases. *J Neuroimmunol* 276(1–2):202–206
20. Yeh JH et al (2015) Higher risk of myasthenia gravis in patients with thyroid and allergic diseases: a national population-based study. *Medicine* 94(21):e835
21. Gong P-H et al (2017) Acute severe asthma with thyroid crisis and myasthenia: a case report and literature review. *Clin Respir J* 11(6):671–676
22. Satkunam N, Siddiqi ZA, Vethanayagam D (2014) Severe asthma associated with myasthenia gravis. *Can Respir J*. <https://doi.org/10.1155/2014/914719>
23. Souza-Machado A, Ponte E, Cruz AA (2007) Severe asthma associated with myasthenia gravis and upper airway obstruction. *J Investig Allergol Clin Immunol* 17(4):267–270
24. Wells GA et al (2000) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford
25. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* 7(3):177–188
26. Higgins JP et al (2003) Measuring inconsistency in meta-analyses. *BMJ* 327(7414):557–560
27. Murai H et al (1997) Expression of CD23 in the germinal center of thymus from myasthenia gravis patients. *J Neuroimmunol* 76(1–2):61–69
28. Bansal AS et al (1993) Variations in serum sCD23 in conditions with either enhanced humoral or cell-mediated immunity. *Immunology* 79(2):285–289
29. Gordon J (1992) CD23 and B cell activation. *Clin Exp Allergy* 22(2):199–204
30. Balbino B et al (2018) Approaches to target IgE antibodies in allergic diseases. *Pharmacol Ther* 191:50–64
31. Galli SJ, Tsai M (2012) IgE and mast cells in allergic disease. *Nat Med* 18(5):693–704
32. Robinson DS (2010) The role of the T cell in asthma. *J Allergy Clin Immunol* 126(6):1081–1091
33. Zhong H, Zhao C, Luo S (2019) HLA in myasthenia gravis: from superficial correlation to underlying mechanism. *Autoimmun Rev* 18(9):102349
34. Muñoz-Castrillo S, Vogrig A, Honnorat J (2020) Associations between HLA and autoimmune neurological diseases with autoantibodies. *Auto Immun Highlights* 11(1):2
35. Schoettler N et al (2019) Advances in asthma and allergic disease genetics: Is bigger always better? *J Allergy Clin Immunol* 144(6):1495–1506
36. Shiina T, Inoko H, Kulski JK (2004) An update of the HLA genomic region, locus information and disease associations: 2004. *Tissue Antigens* 64(6):631–649
37. Kontakioti E et al (2014) HLA and asthma phenotypes/endotypes: a review. *Hum Immunol* 75(8):930–939
38. Kang SW et al (2019) Promoter polymorphism (– 308G/A) of tumor necrosis factor-alpha (TNF- α) gene and asthma risk: an updated meta-analysis. *Genet Test Mol Biomark* 23(6):363–372
39. Sun H et al (2018) Associations of tumor necrosis factor- α polymorphisms with the risk of asthma: a meta-analysis. *Exp Mol Pathol* 105(3):411–416
40. Mikhail I, Grayson MH (2019) Asthma and viral infections: an intricate relationship. *Ann Allergy Asthma Immunol* 123(4):352–358
41. Le Panse R, Berrih-Aknin S (2013) Autoimmune myasthenia gravis: autoantibody mechanisms and new developments on immune regulation. *Curr Opin Neurol* 26(5):569–576
42. Gilhus NE et al (2018) Myasthenia gravis and infectious disease. *J Neurol* 265(6):1251–1258

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Supplemental material – Searching strategy

Ovid MEDLINE Database

1. asthma.mp. or exp asthma/
2. exp bronchial hyperreactivity/ or reactive airway disease.mp.
3. reactive airway disease.mp
4. atopic dermatitis.mp. or exp dermatitis, atopic/
5. eczema.mp. or exp eczema/
6. allergic rhinitis.mp. or exp rhinitis, allergic/
7. atopic.mp.
8. atopy.mp.
9. myasthenia gravis.mp. or exp Myasthenia Gravis/
10. neuromuscular junction disorder.mp. or exp Neuromuscular Junction Diseases/
11. rheumatic disease.mp. or exp rheumatic diseases/
12. autoimmune disease.mp. or exp autoimmune diseases/
13. cohort studies.mp. or exp Cohort Studies/
14. comparative study.mp. or exp Comparative Study/
15. follow-up studies.mp. or exp Follow-Up Studies/
16. prospective studies.mp. or exp Prospective Studies/
17. risk factors.mp. or exp Risk Factors/
18. cohort.mp.
19. compared.mp.
20. groups.mp.
21. multivariate.mp.
22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
23. 9 or 10 or 11 or 12
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
25. 22 and 23 and 24

Embase Database

1. 'asthma'/exp OR 'asthma'
2. 'reactive airway disease'/exp OR 'reactive airway disease'
3. 'bronchus hyperreactivity'/exp OR 'bronchus hyperreactivity'
4. 'bronchial hyperresponsiveness'/exp OR 'bronchial hyperresponsiveness'
5. 'atopy'/exp OR 'atopy'
6. 'atopic dermatitis'/exp OR 'atopic dermatitis'
7. 'eczema'/exp OR 'eczema'
8. 'allergic rhinitis'/exp OR 'allergic rhinitis'
9. 'myasthenia gravis'/exp OR 'myasthenia gravis'
10. 'neuromuscular junction disorder'/exp OR 'neuromuscular junction disorder'
11. 'autoimmune disease'/exp OR 'autoimmune disease'
12. 'prospective study'/exp OR 'prospective study'
13. 'controlled study'/exp OR 'controlled study'
14. 'clinical article'/exp OR 'clinical article'
15. 'major clinical study'/exp OR 'major clinical study'
16. cohort
17. compared
18. groups
19. multivariate
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
21. 9 or 10 or 11
22. 12 or 12 or 14 or 15 or 16 or 17 or 18 or 19
23. 20 and 21 and 22