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

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Research Article

Keywords: Asthma, Myasthenia Gravis, Systematic Review, Meta-analysis

Posted Date: February 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-224462/v1>

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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 ... using search strategy that comprised of 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.

Conclusion

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

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. The underlying mechanism is autoantibody binding to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction [1, 2]. The reported incidence rate estimates between 5 to 30 cases per 100,000 population, with the bimodal age distribution around the age of 30 and 50 years [3]. MG is a multifactorial disease and the onset of the disease likely linked to a combination among immunological, genetic and environmental factors [4].

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 [5, 6]. It is estimated that over 300 million people suffer from asthma, and its prevalence is increasing in both adult

and pediatric population [7]. The etiology of asthma is complex and multifactorial. Most asthmatics have type 2 inflammation which is associated with inflammatory cells (eosinophils, mast cells, basophils, Th2 lymphocytes, and immunoglobulin E [IgE]-producing plasma cells) and certain cytokine profiles (interleukin IL-4, IL-5 and IL-14) [5, 6].

Previous epidemiologic studies have reported an association between asthma and a higher risk of other autoimmune diseases, such as Systemic lupus erythematosus (SLE), Sjogren syndrome and rheumatoid arthritis [8–11]. Additionally, several studies have reported the association between asthma and increased risk of MG [12–16]. Nonetheless, the results from existing evidence are markedly inconsistent. 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.

Method

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 [17].

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[18]. 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 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% high heterogeneity[19]. 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 [12, 13] and three case-control studies [14–16] were included in the meta-analysis. Figure 1 demonstrates the search methodology and selection process of this study. The characteristics of all eligible cohort studies and case-control studies were summarized in Table 1 and Table 2, respectively.

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

	Hemminki et al.	Krishna et al. (18)
Country	Sweden	United Kingdom
Study design	Retrospective cohort	Retrospective cohort
Year of publication	2010	2019
Total number of participants	<p>Patients with asthma: 148,295</p> <p>Comparators: close to 12 million</p>	<p>Patients with asthma: 1,049,868</p> <p>Comparators: 1,732,480</p>
Recruitment of participants	<p>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.</p> <p>The rest of the individuals without asthma in the database served as comparators.</p>	<p>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.</p> <p>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.</p>
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)

Abbreviation: 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

	Hemminki et al.	Krishna et al. (18)
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
Abbreviation: 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		

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

	Murai et al.	Tsai et al.
Country	Japan	Taiwan
Year of publication	2004	2014
Total number of participants	Cases: 160 Controls: 81	Cases: 410 Controls: 1,640
Recruitment of participants	<p>Cases: Cases were patients with MG who visited the Department of Neurology, Kyushu University Hospital during April 2000 to July 2003</p> <p>Controls: Controls were neurological normal patients who visited the same department during March 1998 to February 2000.</p>	<p>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</p> <p>Controls: Controls without MG were randomly selected from the same database.</p> <p>Controls were 1:4 matched with cases by sex and index year.</p>
Diagnosis of MG	<p>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</p> <p>facial or median nerves, and 3.) measurement of anti-AChR antibody through radioimmunoassay</p>	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	Cases: 52.2	Cases: 8.7

age of participants (years)	Controls: N/A	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.
Country	Taiwan
Year of publication	2015
Total number of participants	Cases: 1,689 Controls: 6,756
Recruitment of participants	<p>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</p> <p>Controls: Controls without MG were randomly selected from the Longitudinal Health Insurance Database.</p> <p>Controls were 1:4 matched with cases by age, sex and index year.</p>
Diagnosis of MG	Presence of diagnostic codes of MG in the database (ICD-9: 358.0)
Diagnosis of Asthma	Presence of diagnostic codes of asthma in the database (ICD-9: 493 and 494)
Average age of participants (years)	Cases: 51.4 Controls: 51.3
Percentage of female	Cases: 56.7 % Controls: 56.7 %
Variables	Presence of diagnosis of allergic conjunctivitis, allergic rhinitis, atopic dermatitis,

adjusted in multivariate analysis	urticaria, Hashimoto thyroiditis, Graves' disease, malignancies, diabetes mellitus, cardiovascular disease, and chronic pulmonary disorders
Newcastle-Ottawa score	Selection: 4 Comparability: 2 Exposure: 3

Abbreviation: AChR: 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

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

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.

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-time higher odds of MG.

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. Whereas, the declining of serum level of sCD23 were observed after thymectomy which showed a strong correlation with clinical improvement [20, 21]. CD23, known as a low-affinity receptor for IgE (FcεRII), involved in regulation IgE synthesis, antigen presentation and B cell activation [22, 23]. IgE is believed to contribute to asthmatic manifestation and other allergic condition [24]. In addition, the dysregulation of CD4 T lymphocyte (Th1, Th2, Th17, Teg) is also considered to be involved in the pathogenesis of asthma and MG [4, 25].

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 of HLA can be characterized in the

background of MG by subtype specificity, gender discrepancy, ethnic and geographical disparity. For example, HLA-B*08, HLA-DRB1 and HLA-DQB1 present virtually in certain MG subtypes universally [26, 27]. These genes are also shown to be associated with asthma based on genome-wide association studies [28–30]. In addition, TNF- α (gene related non-classic MHC molecules) also contribute to MG and asthma predisposition [26, 31, 32]

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 [33]. They also have been suspected to play role in MG. Antiviral process can be observed in the myasthenia gravis thymus [34]. 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 [35].

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 [12, 13, 15, 16]. One study relied on self-reported questionnaires to diagnose asthma [14]. Therefore, the completeness of case identification, accuracy of the diagnoses of both diseases and MG subtype classification could be limited. Last, the small number of included studies in meta-analysis could jeopardize the validity and the interpretation of the funnel plot.

Conclusion

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

Declarations

Disclosure

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

Funding

Nipith Charoenngam receives the institutional research training grant from the Ruth L. Kirchstein National Research Service Award program from the National Institutes of Health (2 T32 DK 7201-42).

Conflict of interest/competing interest: All the authors declare no conflicts of interest

Availability of data and material: All data and materials support the published claims and comply with field standards.

Code availability: Not applicable

Authors' contributions: All authors had access to the data and a role in writing the manuscript.

Ethics approval: Not applicable

Consent to participate: Not applicable

Consent for publication: Not applicable

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Figures

Figure 1

Study identification and literature review process

Figure 2

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

Figure 3

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

Supplementary Files

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