

Review article

Association between allergies and multiple sclerosis: a systematic review and meta-analysis

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system that expresses a typical type 1 immune response (Th1). Allergies, on the other hand, present with high levels of type 2 (Th2) cytokines. Some authors observed that Th1 and Th2 diseases could coexist in the same subject. Besides its biological plausibility, the association between MS and allergies remains controversial. The aim of this systematic review and meta-analysis was to determine if there is an association between allergic diseases and MS. All clinical and epidemiological studies on patients with MS published up to July 2009, that assessed the association between allergic diseases and MS were reviewed. A total of 1010 articles were retrieved from search, and ten epidemiological studies were included in the analysis. The results showed that there is no evidence supporting an association between allergic diseases (OR: 0.91; CI 95%: 0.68–1.23), asthma (OR: 0.83; CI 95%: 0.48–1.44), allergic rhinitis (OR: 0.81; CI 95%: 0.59–1.12), eczema (OR: 0.93; CI 95%: 0.71–1.23) and MS. Additional prospective studies in this field might help to elucidate the nature of these associations.

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Introduction

In recent decades, there has been special interest in understanding the complex relationship between allergic and autoimmune diseases, and its consequence on disease expression. Until very recently, allergies and autoimmune diseases were considered as distinct and conflicting patterns of immune response. The adaptive immune system is responsible for the immunological memory and recognition of 'non-self' antigens, where T cells and various cytokines and chemokines elicit appropriate effects. A balance in the production of specific cytokines is critical for the development of distinct clones of T helper cells, type 1 or 2 (Th1, Th2), and the deregulation of the immune system may be responsible for the increased incidence of autoimmune disorders and chronic inflammatory

diseases (1). The Th1 response, characterized by the production of interleukin-2 (IL-2) and interferon-gamma (IFN- γ) cytokines, activates cell-mediated immune functions. The Th2 response, produces interleukins 4, 5, 6, 10 and 13 (IL-4, IL-5, IL-6, IL-10 and IL-13), promoting humoral immunity. Th1 and Th2 cells are counter-regulatory. Although it became clear that the distinction between these subsets in humans was considerably less evident than in animal models of diseases, human immune responses were still generally classified as either Th1 or Th2. However, epidemiological and experimental researchers suggest that the Th1–Th2 polarization of immune responses is an oversimplification (2).

Multiple sclerosis (MS) is a chronic and progressive autoimmune disease of the central nervous system (CNS) that expresses a typical

Th1 pattern (3). Allergic diseases, on the other hand, are considered classic examples of Th2 diseases with activation of mast cells, eosinophils, B cells and Immunoglobulin E (IgE) production (4).

Some authors observed that Th1 and Th2 diseases could coexist in the same subject (5, 6). Studies on experimental allergic encephalomyelitis (EAE), an animal model of MS, showed that tumoral necrosis factor-beta (TNF- β) and IFN- γ could have a protective effect, if administrated before clinical manifestations of tissue damage (7, 8). In addition, IFN- γ enhances the Th2 immune response (9). These findings suggest that complex immune interactions can contribute to development of both autoimmune and allergic diseases in the same subject, and these interactions could modify disease progression and interfere with treatment targets (10). Besides its biological plausibility, the association between MS and allergies remains controversial.

The aim of this systematic review and meta-analysis was to determine if there is an association between allergic diseases and MS.

Method

Study selection and search strategy

All clinical and epidemiological studies on patients with MS published up to July 2009, that assessed the association between allergic diseases and MS were reviewed. We searched the MEDLINE database without language restrictions and manually searched article references and bibliographies to identify unpublished data or articles that were not available online.

The descriptors used in electronic search (MEDLINE) were atopy *or* atopic *or* allergy *or* asthma *or* hayfever *or* nasal allergy *or* rhinitis *or* eczema *or* dermatitis *and* multiple sclerosis. A total of 1010 articles that considered the association between MS and allergies were retrieved from search. For this systematic review and meta-analysis, ten epidemiological studies were identified, including five cross-sectional studies (11–15) and five case-control studies (16–20). Reasons for exclusion of studies included the following: the study design did not have a comparison group, outcomes were not comparable, studies did not focus on the clinical association between MS and allergies, reviews and case report papers (Fig. 1).

There was no restriction regarding gender, race or age group. The exposure conditions considered in the analysis were diagnosis of allergies in general, asthma, allergic rhinitis and atopic eczema.

Data extraction and quality assessment

All selected studies were reviewed and if necessary, additional information was requested from their authors. Two researchers independently assessed the eligibility of the studies. The studies considered for analysis were evaluated and scored from 0 to 10, according to the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies (NCO) (21). The final decision to include the article in the analysis was based on total agreement between investigators.

Data analysis

The selected articles were analyzed with the help of the software Comprehensive Meta-analysis V2.

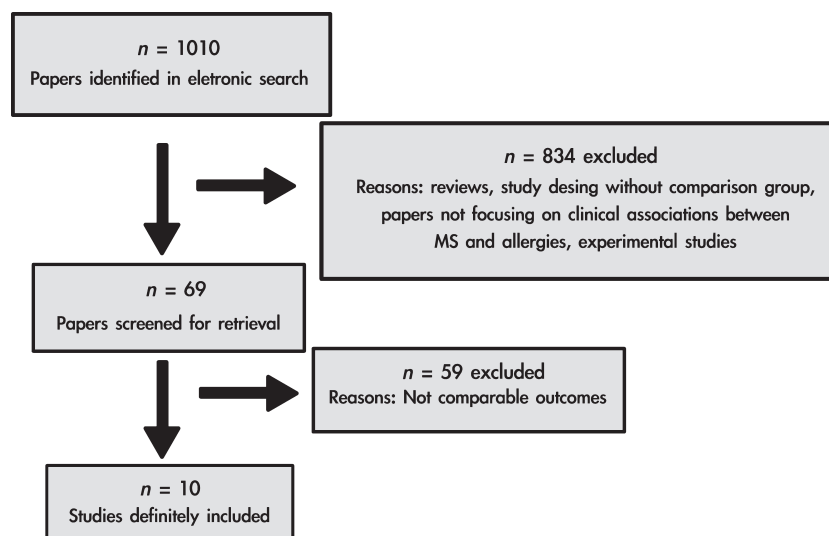


Figure 1. Fluxogram of study selection and reasons for exclusion.

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

Authors	Study design	Population Cases/Controls	Cases Inclusion criteria	Cases Source	Controls Source
Alonso et al. (16) 2006 UK	Case-control	163/1.523	Clinically definite MS	GPRD	GPRD
Ponsonby et al. (18) 2006 Australia	Case-control	136/272	Clinically definite MS At least one grandparent who was born in Tasmania	Residents in Tasmania under the age of 60 years	Randomly selected from electoral rolls
Alonso et al. (17) 2008 USA	Case-control	248/248	Definite or probable MS diagnosis	NHS NHS II	NHS NHS II
Pedotti et al. (19) 2009 Italy	Case-control	345/535	Definite MS diagnosis	RHSR	RHSR
Bergamaschi. (20) 2009 Italy	Case-control	200/200	Definite MS diagnosis	MS centre of the neurological institute in northern-western Italy	General population in northern-western Italy
Oro et al. (13) 1996 USA	Cross-sectional	24/18	Clinically definite MS	Neurology clinics in the Stanford University Hospital	Neurology clinics in the Stanford University Hospital
Neukirch et al. (14) 1997 France	Cross-sectional	610/6926	No reference	MS outpatient clinic in Paris and Montpellier	Randomly selected subjects from electoral rolls in Paris and Montpellier
Kira et al. (11) 1998 Japan	Cross-sectional	60/40	Clinically definite MS	MS clinic of Kyushu University	Healthy volunteers
Tremlett et al. (15) 2002 England	Cross-sectional	320/320	Diagnosis of MS	GPMD	GPMD
Edwards et al. (12) 2004 UK	Cross-sectional	658/252.538	Diagnosis of MS	MS outpatient clinic	General population prevalence

MS, multiple sclerosis; GPRD, General Practice Research Database; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; RHSR, Regional Health Service Register; GPMD, General Practice Morbidity Database.

Table 2 Quality assessment and effect size of each study included in the meta-analysis

Authors	Adjustment	NCO score	Exposure assessments	OR (95% CI)
Alonso et al. (16) 2006 UK	Yes	7	Allergies Asthma Rhinitis Eczema	1.10 (0.77–1.59) 0.88 (0.42–1.86) 1.10 (0.52–2.34) 1.02 (0.58–1.82)
Ponsonby et al. (18) 2006 Australia	Yes	8	Allergies Asthma Rhinitis	1.35 (0.76–2.41) 1.64 (0.99–2.70) 1.07 (0.70–1.63)
Alonso et al. (17) 2008 USA	Yes	7	Allergies Asthma Rhinitis Eczema	1.09 (0.76–1.58) 1.05 (0.58–1.89) 0.86 (0.59–1.26) 1.18 (0.81–1.73)
Pedotti et al. (19) 2009 Italy	Yes	8	Allergies Asthma	0.80 (0.6–1.06) 0.37 (0.22–0.65)*
Bergamaschi. (20) 2009 Italy	Yes	8	Allergies Asthma Rhinitis	0.42 (0.25–0.73)* 0.56 (0.16–1.95) 0.34 (0.19–0.61)*
Oro et al. (13) 1996 USA	No reference	4	Allergies	0.42 (0.11–1.55)
Neukirch et al. (14) 1997 France	No reference	2	Asthma Rhinitis	0.73 (0.53–1.01) 0.68 (0.56–0.83)*
Kira et al. (11) 1998 Japan	No reference	6	Allergies	0.57 (0.23–1.37)
Tremlett et al. (15) 2002 England	No reference	6	Asthma Eczema	0.26 (0.11–0.62)* 0.65 (0.35–1.20)
Edwards et al. (12) 2004 UK	No reference	2	Allergies Asthma Rhinitis Eczema	1.45 (1.13–1.87)* 2.39 (1.79–3.18)* 1.32 (0.78–2.24) 0.76 (0.45–1.29)

NCO, Newcastle-Ottawa Quality Assessment Scale; OR, odds ratio; CI, confidence interval. * $P < 0.05$.

Pooled odds ratio (OR) and their confidence interval (CI) of 95% were calculated using a random-effects model, which allows each of the

studies included to estimate a different effect size. The chi-square test was conducted to evaluate the heterogeneity among the studies, considering a value of $P < 0.05$ to be statistically significant. To assess the degree of heterogeneity, we also used the I^2 test, which describes the percentage of variation in the estimated effect. A value greater than 50% was indicative of substantial heterogeneity. To further examine the robustness of the results, we performed a sensitivity analysis by dropping all the studies that did not controlled for potential confounders.

Results

A total of 10 studies comprising 2764 MS cases and 262,620 controls were included in the analysis. The overall characteristics of these papers are summarized in Tables 1 and 2.

The joint analysis of eight studies comprising 1834 MS cases and 255,374 controls showed that there is not an association between allergic diseases and MS (OR: 0.91; 95% CI: 0.68–1.23) (Fig. 2). When asthma symptoms were analyzed independently from other allergic diseases, such as rhinitis and conjunctivitis, the pooled OR failed to show an association between asthma and MS (OR: 0.83; 95% CI: 0.48–1.44) (Fig. 3). The diagnosis of rhinitis was assessed according to positive symptoms registered in the questionnaires, such as sneezing, rhinorrhea, nasal obstruction and itching. The joint analysis of

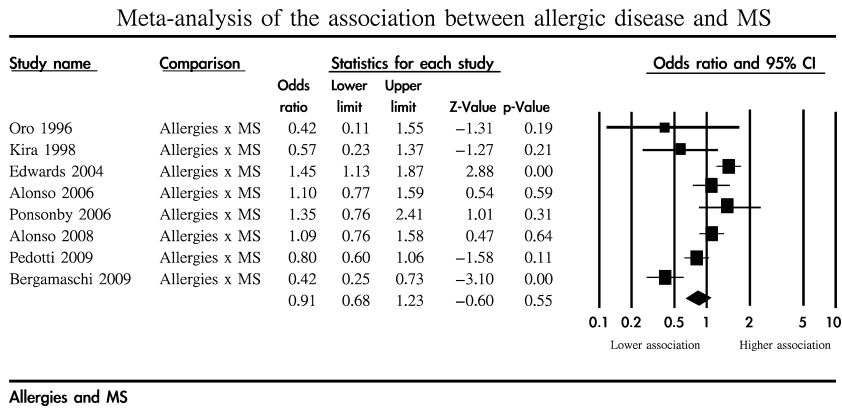


Figure 2. Meta-analysis of the association between allergic disease and MS.

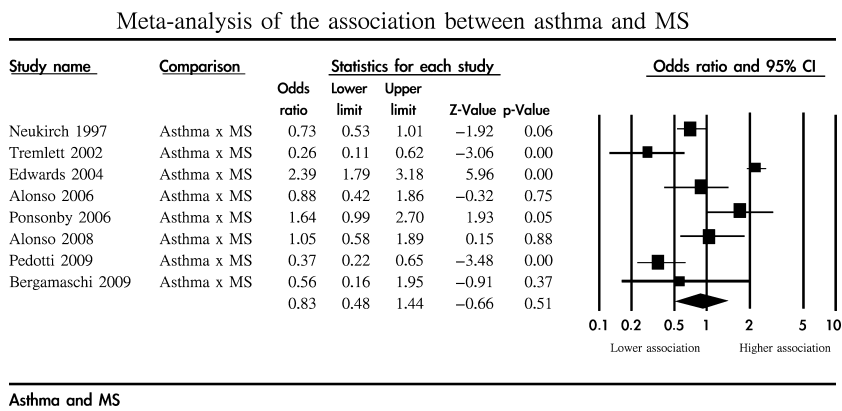


Figure 3. Meta-analysis of the association between asthma and MS.

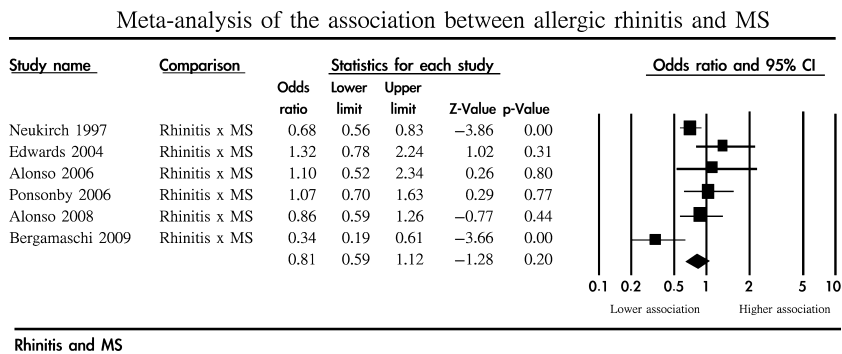


Figure 4. Meta-analysis of the association between allergic rhinitis and MS.

four studies comprising 2015 MS cases and 261705 controls showed no association between rhinitis symptoms and MS (OR: 0.81; 95% CI: 0.59–1.12) (Fig. 4). Four studies comprising 1389 MS cases and 254,629 controls had atopic eczema as the outcome. There was not verified an association between eczema and MS (OR: 0.93; 95% CI: 0.71–1.23) (Fig. 5).

Besides not statistically significant, all analysis showed a trend toward an inverse relationship between allergies MS. We performed a secondary

analysis excluding the studies that did not adjust for potential confounders. The results remained the same, except for the association between eczema and MS, that shifted to a positive relationship (OR: 1.13; 95% CI: 0.83–1.55) (results not showed). A possible explanation would be the high frequency of eczema in younger populations, and adjustment for age tends to strength the inverse association between eczema and MS. There was significant heterogeneity among the studies included in the analy-

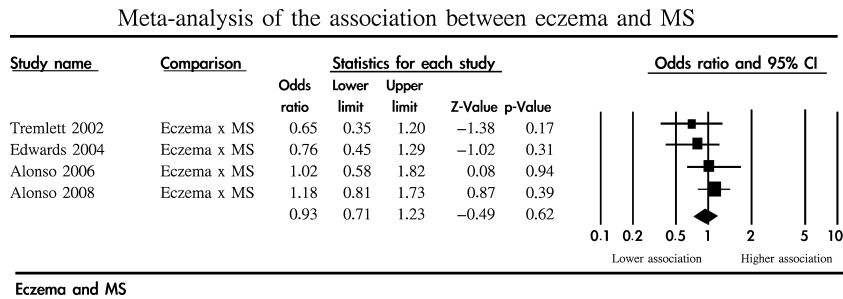


Figure 5. Meta-analysis of the association between eczema and MS.

sis, except for the eczema and MS analysis (I^2 : 0–17%).

Discussion

The results of this systematic review and meta-analysis showed that there is no evidence supporting an association between allergic diseases and MS.

The relationship between diseases with different immune response patterns and their clinical expression has been the impetus for extensive research over the past 20 years. Several attempts at understanding the relationship between autoimmune diseases (Th1) and allergies (Th2) have led to conflicting results. Some epidemiological studies suggest a model in which an atopic phenotype, with the production of the cytokines IL-4, IL-5 and IL-10, protects against autoimmune diseases. Stene & Joner showed that children with atopic dermatitis had a low risk of developing type 1 diabetes (OR: 0.55; 95% CI: 0.35–0.87) (22). Caffarelli et al. observed that diabetic children had significantly less allergic symptoms, compared to non-diabetic controls. Skin prick tests results were similar in both groups (23). Similarly, Sheikh et al. observed a lack of association between atopy and autoimmune diseases such as type 1 diabetes, thyroid diseases and rheumatoid arthritis (OR: 1.01; 95% CI: 0.61–1.67) (24). However, previous allergic history was associated with an increased risk of developing autoimmune diseases (OR: 1.67; $P < 0.001$). In a population-based study, Tirosh et al. verified that some young adults with asthma had lower predispositions for Th1 autoimmune diseases (25). Some authors also reported increased incidences of asthma in patients with diabetes type 1, rheumatoid arthritis and inflammatory bowel disease (6, 26).

The polarized immune responses and cross-regulation mediated by cytokines led to the logical reasoning that the coexistence of diseases with typical Th1 or Th2 immune responses would be unlikely, or even impossible. The apparent imbal-

ance of the immune system, expressed as the clinical onset of allergic or autoimmune diseases (27), may be related to reduced antigenic exposure in early childhood. The inadequate development of regulatory cells (Treg cells) predisposes an individual to hypersensitivity, depending on the prevailing antigenic stimulus. In the last five decades, the prevalence of allergic and autoimmune diseases has increased considerably, especially in industrialized countries and urban areas (28, 29). These observations could be explained by changes in lifestyle that are associated with improved living conditions, hygiene and modification of exposure rates to infectious agents in early childhood. These, in turn, could lead to deregulation of the immune system and clinical manifestations of disease (30). An effective immune response is essential for protection against infections. However, enhanced and misdirected immune reactions may also be responsible for immune-mediated diseases, such as inflammatory bowel disease (IBD), asthma, MS and type 1 diabetes. The observation that these conditions are prevalent in areas with low infection rates, i.e., industrialized and developed countries, raises several questions about the influence of environmental agents on disease susceptibility. MS has a specific geographic distribution, and the risk of developing the disease changes according to immigration factors and age of the immigrant. Areas that experienced an improvement in hygiene and sanitation have increased incidences of asthma and MS (31, 32). Epidemiological observations and experimental researchers attempted to establish a link between parasite exposure, especially helminthes, and protection from immune-mediated diseases. Activation of Treg cells and secretion of IL-10 and TGF- β are involved in immune tolerance. Immune regulatory mechanisms triggered by exposure to helminthes, especially through secretion of IL-10 and TGF- β , may partially explain the protective effect afforded by these infections (33–39). The complexities of immune pathways, the host's individual responses and predisposition, and the dual role of several cytokines during

immune reactivity to some agents only add to the, as yet, unresolved questions.

Recent demonstrations of new regulatory pathways challenged early concepts and prompted the development of new experimental models. A newly described lineage of T-cells, characterized by the production of several inflammatory cytokines, such as interleukin 17 (IL-17), is also responsible for the perpetration of the inflammatory process in the CNS. The production of IL-17 and other signaling molecules contributes to the pathogenesis of several autoimmune diseases including allergic inflammation, rheumatoid arthritis, autoimmune gastritis, inflammatory bowel disease, psoriasis and multiple sclerosis (40). It has been demonstrated that IL-17 could contribute to the pathogenesis of atopic asthma. The expression of IL-17 is enhanced in airways of asthmatic patients and can induce the production of IL-16 and IL-11 by bronchial fibroblasts (41). The interleukin 17-E (IL-17E), actually called interleukin 25 (IL-25), expressed by Th2 murine cells, enhances the secretion of IL-4, IL-5, IL-13 and eotaxins. In animal models, it was demonstrated that the IL-25 induces an allergic inflammation and suppresses the action of Th1 and Th17 cells (42).

In this context, Th1 and Th2 patterns of disease can coexist in the same individual, depending on genetic and environmental factors. However, our results show that there is not an association between MS and allergic diseases. This could be explained by some aspects of respiratory diseases such as asthma, which is classified as non-atopic and atopic asthma, according to the prevailing immune response. Atopic asthma is a Th2-type disease whereas non-atopic asthma shows, mostly, Th17 patterns (43). Besides, considering that the majority of the studies included in the meta-analysis were questionnaire-based and some of them did not controlled for residual confounding, methodological issues may have limit the reliability of these results. The identification of atopic subjects only relied on patient reports or past medical history, may have lead to the possibility of misclassification error, biasing the results.

This study has some limitations, due to methodological problems of the original studies. The absence of prospective studies and the application of different instruments for diagnosing allergies, limit the extrapolation of results. In case-control studies, memory bias can interfere with the results, since patients, compared to their healthy counterparts, are more likely to remember their prior atopic history. Only one of the included studies comprised the possibility of memory bias, and included a control group with a chronic disease

(17). Although we tried to contact authors and localize unpublished data, publication bias may be present. There was significant heterogeneity between the studies included. Missing information on exposure definitions and not adjusting for potential confounding variables may have introduced bias into the results.

Trends on future research on immune-mediated diseases are toward identification of alternative pathways and different patterns of the immune response, with respect to clinical consequences and diseases progression. This may help to recognize and interpret unexpected clinical disease courses and develop new therapeutic strategies with more specific targets, enabling effective intervention.

Conclusion

Based on the results of this systematic review and meta-analysis, there is no evidence supporting an association between allergies and MS.

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