



## Review

# Is a History of Type 1 Allergic Diseases Associated with the Risk of Developing Multiple Sclerosis?

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## ABSTRACT

Multiple Sclerosis (MS) is an autoimmune disorder affecting the central nervous system, characterized by demyelination of the neurons with limited remyelination. There has been a rising trend toward associating a history of allergy with MS. Both MS and type 1 allergies are developed by a hyper-reactive immune system. This is further reinforced by the similar environmental and genetic factors of both diseases. This review examines the association between a history of type 1 allergic diseases and the risk of MS, as well as the influence of study location on the association. A literature search was conducted through the Saudi Digital Library search engine, which includes many databases, such as PubMed and Web of Science; articles addressing the relationship between MS and type 1 allergies were retrieved. In this review, most studies show an inverse or no association between type 1 allergy history and MS. Most articles concluded that the relationship is not statistically significant. One study stated that asthma increases MS risk. Geographical location does not influence MS and allergy association.

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## 1. INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune disorder affecting the central nervous system, characterized by demyelination of the neurons with limited remyelination [1]. MS occurs when the immune system loses one of its unique features, self-tolerance, leading it to mistakenly attack the body's cells and tissues [1]. Development of tolerance arises in through the central and peripheral immune systems. In central tolerance, the thymus and bone marrow participate in the early differentiation of T and B cells, respectively. The cells then leave the central sites, and peripheral tolerance ensures that any remaining self-reactive cells do not cause autoimmune disease [2]. Unfortunately, autoimmune diseases reflect a loss of self-tolerance arising from molecular mimicry, especially after infection [3,4]. Another explanation is epitope spreading, which occurs when self-epitopes are hidden from the immune system, manifested clinically as a relapsing–remitting course like MS [5,6]. When naïve T helper cells lose their self-tolerance, they react to the myelin sheath to develop T Helper 1 (Th1) cells, which produce cytokines, such as tumor necrosis factor-alpha, Interleukin 1 (IL-1), and IL6, which trigger more T cells, macrophages, and Immunoglobulin E (IgE) antibodies from B cells, causing demyelination of the myelin sheath [7,8]. In hypersensitivity type 1, Th2 cells respond to an

originally harmless substance, leading to the production of IgE antibodies, which bind to different antigens, such as dust, food, and pollen, promoting the release and production of proinflammatory mediators and causing the clinical signs and symptoms of allergies [9]. Along with genetic and environmental factors, both MS and allergies are developed by a hyperreactive immune system involving T helper cells.

The relationship between MS and allergies has been tested in many studies, which have concluded that the history of allergies is inversely related to MS risk, and that Th2 allergic cells are protective against MS [10]. Furthermore, low exposure to microbes in childhood increases the risk of developing a hyperreactive immune system for both MS and allergies later [11,12].

The prevalence of MS diagnoses has increased worldwide because of the growing awareness of the disease, its signs, and symptoms, as well as improving diagnostic capability, leading to increased life expectancy. Geographically, MS incidence is higher near the north and south latitudes, which could be attributed to more sophisticated healthcare systems in those areas [13,14]. The prevalence in Saudi Arabia is 25 out of 100,000, which is relatively low [14,15]. Other factors associated with increased risk of MS include smoking [16], vitamin D deficiency [17], and viral infections (e.g., Epstein–Barr virus) [18]. Interestingly, there is a 2–4% risk of developing MS among siblings, 5% risk among dizygotic twins, and 30% among monozygotic twins [19].

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Although MS is a common, disabling disease, minimal data have been collected to study the association between type 1 allergies and MS. Therefore, a literature search was conducted through the Saudi Digital Library search engine, which includes many databases, such as PubMed and Web of Science; articles addressing the relationship between MS and type 1 allergies were retrieved. This short review assesses the association between the history of allergic diseases type 1 and the risk of MS. It will also determine the influence of the geographical locations of studies on the nature of the association.

## 2. MATERIALS AND METHODS

We collected all articles addressing the relationship between MS and type 1 allergies. Articles were retrieved from the Saudi Digital Library and the Google Scholar database. Keywords used in the search engines were Multiple Sclerosis, Allergy, Hypersensitivity, Atopy, and Allergic Diseases. All articles addressing the relationship between MS and type 1 allergies were included. Select articles from the bibliographies were added. Limitations included (1) studies not written in English, (2) conference articles, and (3) unpublished articles. Thirty-three articles were initially retrieved, but with the literature review exclusion criteria, only 15 articles were

incorporated. We read each article thoroughly prior to summarizing its salient points in a Word document. Then, we extracted the data into a table. The table shows the journal's impact factor and the study's name, design, location, inclusion and exclusion criteria, sample size, statistical tests, severity of allergy, types of MS, conclusion, and limitations. No statistical program was used. We excluded articles published in nonindexed journals, articles addressing the association of type 1 allergies with other autoimmune diseases, and articles whose study design had no comparison groups.

## 3. RESULTS

Although one study suggested the possibility of a risk association, six concluded that allergies tend to be inversely associated with MS, and 11 studies indicated no association between allergies and MS. The Odds Ratios (ORs) are shown in Table 1. The asthma OR was associated with a higher risk of developing MS in Australia [20]. Four studies in the UK [21], the USA [22], a meta-analysis [23], and France [24] showed no risk of MS among asthma patients. Two studies in Italy [25,26] concluded that asthma tends to be protective against developing MS. Moreover, respiratory allergies, including asthma and allergic rhinitis, showed an inverse association with MS

**Table 1** | Odds ratio between multiple sclerosis and different types of allergy

| Study, year, site                         | Cases:controls | Types of allergy          | OR (95% CI)      |
|---|----------------|---------------------------|------------------|
| Ponsonby et al. [20], 2006, Australia     | 34:46          | Asthma                    | 1.67 (1.00–2.80) |
|   | 51:98          | Allergic rhinitis         | 1.05 (0.68–1.62) |
|   | 22:34          | All allergies             | 1.36 (0.75–2.47) |
| Ansari et al. [31], 1976, Iran            | 49:85          | Asthma, allergic rhinitis | 0.44 (0.28–0.70) |
|   | 16:53          | Food or drug allergy      | 0.23 (0.12–0.43) |
| Bergamaschi et al. [25], 2009, Italy      | 4:7            | Asthma                    | 0.41 (0.11–1.47) |
|   | 19:47          | Allergic rhinitis         | 0.27 (0.14–0.50) |
| Strandgaard and Jørgensen [32], 1972, USA |                | Asthma, URTI, bronchitis  | 0.38 (0.19–0.77) |
|   |                | All other allergies       | 0.29 (0.18–0.49) |
|   |                | Atopic <sup>a</sup>       | 0.58 (0.38–0.89) |
| Pedotti et al. [26], 2009, Italy          | 36:88          | Nonatopic <sup>b</sup>    | 1.13 (0.79–1.63) |
|   | 70:87          | Allergic rhinitis         | 1.1 (0.5–2.3)    |
| Alonso et al. [21], 2006, UK              | 8:68           | Urticaria                 | 1.2 (0.5–3.2)    |
|   | 5:38           | Asthma                    | 0.9 (0.4–2.0)    |
|   | 8:84           | Eczema                    | 1.1 (0.6–1.9)    |
|   | 14:128         | Other allergies           | 2.5 (0.6–11.3)   |
|   | 3:9            | Pollens                   | 1.0 (0.7–1.3)    |
| Alonso et al. [22], 2008, USA             | 91:409         | House dust                | 1.0 (0.7–1.4)    |
|   | 53:237         | Animal dander             | 1.3 (0.9–1.9)    |
|   | 51:170         | Foods                     | 0.9 (0.6–1.3)    |
|   | 34:173         | Drugs                     | 1.1 (0.8–1.5)    |
|   | 138:539        | Other allergies           | 1.0 (0.7–1.4)    |
|   | 91:384         | Conjunctivitis            | 1.1 (0.7–1.6)    |
|   | 52:216         | Rhinitis                  | 1.0 (0.7–1.4)    |
|   | 93:410         | Asthma                    | 1.1 (0.7–1.8)    |
|   | 27:109         | Hives                     | 1.1 (0.8–1.5)    |
|   | 99:404         | Foods                     | 0.61 (0.31–1.22) |
| Bourne et al. [29], 2017, USA             | 13:37          | Antibiotics               | 2.05 (0.91–4.6)  |
|   | 14:13          | Environmental             | 0.65 (0.4–1.06)  |
|   | 32:80          | Skin allergy              | 0.81 (0.53–1.26) |
|   | 43:84          | Runny nose/puffy eyes     | 0.72 (0.41–1.28) |
|   | 23:53          | Allergic diseases         | 0.91 (0.68–1.23) |
| Monteiro et al. [23], 2011, meta-analysis |                | Asthma                    | 0.83 (0.48–1.44) |
|   |                | Allergic rhinitis         | 0.81 (0.59–1.12) |
|   |                | Eczema                    | 0.93 (0.71–1.23) |
|   |                |                           |                  |

<sup>a</sup>Atopic: asthma, rhinitis, conjunctivitis, atopic eczema/dermatitis syndrome, or food allergy with respiratory allergies. <sup>b</sup>Nonatopic: contact dermatitis, insect bites, medications, or food allergy without respiratory allergies. CI, confidence interval; URTI, upper respiratory tract infections.

in USA, Iran, and Italy [26–28]. Whereas allergic rhinitis showed an inverse association in Iran [27] and Italy [25], no relationship was found in Australia [20], the UK [21], the USA [22], or in a meta-analysis [23]. In two US studies [22,29], a history of food and drug allergies [22] showed no MS risk relation, but in Iran [27], a food or drug allergy history showed an inverse association. Four studies [21,23,26,29] evaluated the risk of developing MS in patients with a history of skin allergies such as urticaria and eczema. None of the studies found a relation.

Six studies in France [24], Italy [25], Northern Italy [26], Iran [27], and the USA [28,29] showed an inverse association between type 1 allergies and MS (Table 2). Respiratory allergy prevalence was significantly low in MS patients in Iran [27], Italy [25], the USA [28], and Northern Italy [26]. Females with respiratory allergies tend to have less risk of developing MS than do males in France ( $p = 0.001$ ) [24]. However, a case-control study (including females only) in the USA [22] concluded that there was no relationship between MS and allergies such as allergic rhinitis and asthma.

Table 3 presents the data, method, results, and limitations of 11 studies that found no relationship between MS and allergies [21–23, 26,28–34]. A large Canadian population-based cohort with 6638 MS participants and 2509 controls was conducted to investigate the relationship between MS and cow milk allergies [34]. No association was found between MS and cow milk allergies during the perinatal period (males,  $p = 0.83$ ; females,  $p = 0.61$ ), early childhood (males,  $p = 0.3$ ; females,  $p = 0.82$ ), or late childhood (males,

$p = 0.51$ ; females,  $p = 0.32$ ). The geographical distribution showed no trends relating allergies and MS.

## 4. DISCUSSION

We aimed to investigate the association between MS and type 1 allergy histories. Most studies addressed an inverse or nonstatistically significant association between type 1 allergy histories and MS.

Hygiene theory has been linked to many autoimmune diseases and allergies, including MS and asthma, emphasizing that early childhood exposure to infections can protect against subsequent autoimmune illnesses [35]. The theory also explains the increased modern prevalence of both disorders, but it has never been proven. Also, one T cell lineage produces IL-17, which induces both allergic inflammation and MS [36–38]. The results of many studies that confirmed the risk association between allergies and MS may have been biased owing to less sophisticated healthcare systems in the past, underdiagnosed allergies in rural populations, and frequent diagnosis of MS patients because of frequent hospital visits with symptoms.

Six studies (Table 2) showed an inverse association between allergies and MS. Th2 cells, which are responsible for type 1 allergies, secrete IL-4, IL-5, and IL-10, which protect against the autoimmunity damage caused by the Th1 cells responsible for MS. With regard to asthma, there are two types, nonatopic (nonallergic) and atopic

**Table 2** Data of case-control studies finding an inverse relation between allergy and MS

| Study, year, site                                      | Sample size                         | Allergy type  | Results   | Notes   |
|--|-------------------------------------|---|---|---|
| Sahraian et al. [27], 2013, Iran                       | 195:195                             | (1) Respiratory tract allergy (RTA)<br>(2) Cutaneous allergy (CA)<br>(3) Food or drug allergy (FDA) and nonspecific agent (including dust, animal dander)                                 | History of allergy and MS ( $p = 0.04$ )<br>RTA (OR = 0.43; 95% CI, 0.28–0.66; $p < 0.001$ )<br>FDA (OR = 0.24; 95% CI, 0.13–0.43; $p < 0.001$ )                                    | 80% female participants.<br>Prevalence of asthma 1:9, allergic rhinitis 49:84<br>No OR of other allergies |
| Neukirch et al. [24], 1997, Paris and Toulouse         | Paris 302:3152<br>Toulouse 308:3774 | Asthma and nasal allergies  | Paris results<br>Nasal allergies, $p = 0.006$<br>Females only<br>(1) Asthma, $p = 0.05$<br>(2) Nasal allergy, $p = 0.001$<br>In Toulouse, association not statistically significant | Did not show Toulouse results   |
| Ren et al. [28], 2017, <sup>a</sup> USA                | 829:2441                            | Respiratory tract allergies: asthma, URTI, and bronchitis   | $p = 0.039$ (OR = 0.38; 0.19, 0.77)   |   |
| Bergamaschi et al. [25], 2009, Italy                   | 200:200                             | (1) At least one allergic respiratory disease (ARD)<br>(2) Asthma<br>(3) Allergic rhinitis  | ARDs (OR = 0.33, $p > 0.001$ )<br>Allergic rhinitis (OR = 0.27, $p > 0.001$ )<br>Asthma (OR = 0.41, $p < 0.169$ )   | Asthma cases = 4; control = 7   |
| Pedotti et al. [26], 2009, <sup>a</sup> Northern Italy | 423:643                             | Asthma, rhinitis, conjunctivitis, atopic eczema/dermatitis syndrome, or (food allergy with respiratory allergies)   | $p = 0.017$   |   |
| Bourne et al. [29], 2017, <sup>a</sup> USA             | 418:271                             | Skin reaction (include rash and eczema), nose or eyes reaction (include swollen eyes and stuffy nose), gastrointestinal reaction (including vomiting and diarrhea) and anaphylactic shock | MS relapse and food allergy, $p = 0.01$   |   |

<sup>a</sup>These studies have results in Table 3. CA = urticaria, angioedema, eczema; RTA = asthma, allergic rhinitis.

**Table 3** | Data of studies finding no relation between allergy and MS

| Study, year, site                                      | Design                              | Sample size  | Allergy type  | p + OR   |
|--|-------------------------------------|--|---|--|
| Ansari et al. [31], 1976, USA                          | Cohort                              | 36:40  | Asthma, hay fever or eczema, or allergy to food, dust, dyes, contrast material, or drugs  | No results in manuscript   |
| Ren et al. [28], 2017, <sup>a</sup> USA                | Case-control                        | 829:2441   | Skin allergy, eye allergy, ear allergy, and other unspecified allergies that are not respiratory  | $p = 0.281$<br>OR = 0.38; 0.19–0.77  |
| Strandgaard and Jørgensen [32], 1972, Denmark          | Cohort                              | 12:12  | Hypersensitivity reaction   | No results in manuscript   |
| Alonso et al. [21], 2006, UK                           | Case-control                        | 163:1523   | Allergic rhinitis, asthma, urticaria/angioedema, eczema, other allergic conditions prior to the index date (date of first Sx of MS)   | OR 1.1; 0.8–1.6  |
| Karimi et al. [33], 2013, Iran                         | Case-control                        | 40:40  | Any allergy manifested as rhinitis conjunctivitis eczema, urticaria, or asthma. Family history of allergy IgE testing   | $p = 1.00$<br>$p = 0.392$ higher EDSS and allergy in MS group<br>$p = 0.776$ MS initial symptoms and allergy   |
| Alonso et al. [22], 2008, USA                          | Case-control                        | Primary: 294:1248<br>Secondary 248:248<br>All participants females | (1) Allergy to pollens, house dust, animal dander, foods, drugs, and other<br>(2) Manifested as conjunctivitis, rhinitis, asthma, hives, and other manifestation                        | OR 1.0; 0.8–1.4  |
| Ramagopalan et al. [34] 2010, Canada                   | Cohort                              | 6638:2509  | Cow milk allergy<br>Perinatal<br>Early childhood up to 3 years<br>Late childhood up to 11 years   | Perinatal: males $p = 0.83$ , females $p = 0.61$<br>Early childhood: males $p = 0.3$ , females $p = 0.82$<br>Late childhood: males $p = 0.51$ , females $p = 0.32$                     |
| Bourne et al. [29], 2017, USA                          | Case-control                        | 418:271  | Skin reaction (include rash and eczema), Nose or eyes reaction (include swollen eyes and stuffy nose), Gastrointestinal reaction (include vomiting and diarrhea) and Anaphylactic shock | Age at onset of MS ( $p = 0.41$ )<br>Sex ( $p = 0.30$ )<br>Race ( $p = 0.06$ )<br>Ethnicity ( $p = 0.54$ )   |
| Monteiro et al. [23], 2011                             | Systematic review and meta-analysis | 2764:262,620   | Allergic disease<br>Asthma<br>Allergic rhinitis<br>Eczema   | Allergic diseases (OR = 0.91; 95% CI, 0.68–1.23)<br>Asthma (OR = 0.83; 95% CI, 0.48–1.44)<br>Allergic rhinitis (OR = 0.81; 95% CI, 0.59–1.12)<br>Eczema (OR = 0.93; 95% CI, 0.71–1.23) |
| Ashtari et al. [30], 2013, Iran                        | Case-control                        | 48:48  | Cow milk allergy  |  |
| Pedotti et al. [26], 2009, <sup>a</sup> Northern Italy | Population-based case-control       | 423:643  | Contact dermatitis, insect bites, medications, or food allergy without respiratory allergies  | $p = 0.503$  |

<sup>a</sup>This study also has results in the inverse association table. EDSS, Expanded Disability Status Scale.

(allergic). Unfortunately, only one study distinguished between the two types and showed an inverse association [27]. Further studies, both longitudinal and experimental, should be conducted to investigate the relationship.

In this short review, the limitations are methodological or attributable to fundamental issues in the collected studies. Methodological limitations include publication bias and the exclusion of non-English papers. With regard to the collected studies themselves, the limitations include the lack of diagnostic criteria for MS and allergies, the low sample size, and the failure to classify allergy severity or types of MS. Cofactors were also not mentioned, such as vitamin D deficiency, family history, ethnicity, and residence.

All studies included a comparison group that could hide genetic susceptibility, resulting in biased results. Thus, we recommend a further longitudinal, cohort study conducted only on people with MS. Also, there is a lack of studies corresponding to the severity and timing of allergic reactions or diseases with the clinical manifestations, course, and severity of MS.

## 5. CONCLUSION

Most studies in this review showed an inverse or a statistically non-significant association between type 1 allergy histories and MS. One study reported that asthma increased MS risk. Furthermore,

geographical location has no influence on the relationship between MS and allergies.

## CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

## AUTHORS' CONTRIBUTION

All authors have contributed to the manuscript and fulfilled the authorship criteria. A. Alfawzan, SA, A. Alswaidan and A. Alkharaan contributes effectively in data collection and writing the first and final draft of the study. HA and A. Almklass were responsible for conception and design of the study, and provided critical revision of the article. All authors approved the final version to be submitted.

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