

Allergy, family history of autoimmune diseases, and the risk of multiple sclerosis

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Objective – Previous reports suggested an association between allergy, autoimmunity, and risk of multiple sclerosis (MS), but results have been inconsistent. The present study assessed the association between history of allergy and autoimmune diseases, and the risk of MS. **Methods** – We conducted a case–control study nested in the Nurses' Health Study (NHS) and NHS II cohorts. A total of 298 women with MS were matched with 1248 healthy controls and 248 women with history of breast cancer. A mailed questionnaire gathered information about history of allergic conditions and autoimmune disorders. **Results** – History of allergy was not associated with MS risk [odds ratio (OR) 1.0, 95% confidence interval (CI) 0.8–1.4]. As expected, cases were more likely to have a positive family history of MS than controls (OR 9.7, 95% CI 6.1–15.3). A modest association was found between family history of other autoimmune diseases and MS risk (OR 1.4, 95% CI 1.0–1.8). We obtained similar results when we used women with breast cancer as comparison group. **Conclusion** – Family history of other autoimmune diseases was associated with a higher MS risk, suggesting a common genetic background or shared environmental triggers. There was no clear association between personal history of allergy and risk of MS.

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Introduction

Because multiple sclerosis (MS) could share common risk factors with other disorders of the immune system, previous studies have evaluated the association between MS and other autoimmune diseases (1–6), or a previous history of allergy (7). Their results suggest a possible link between MS and autoimmune diseases but no association with allergic disorders. Most of these studies, however, had important methodological limitations (potential bias in control selection, self-reported information for exposures of interest, possible confounding by age and sex).

We have therefore assessed the association between previous history of allergic conditions, family history of MS and other autoimmune diseases, and the risk of developing MS, using a case–control study nested in two cohorts of US women: the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II) (8).

Methods

Study population

The NHS was established in 1976 when 121,700 female registered nurses from 11 states, 30–55 years of age, answered a mailed questionnaire about lifestyle items and disease history. The NHS II was established in 1989 when 116,671 female registered nurses from 14 states, 25–42 years of age, answered a similar questionnaire. Follow-up in both studies is conducted through biennial mailed questionnaires, updating information on potential risk factors and ascertaining whether major medical events have occurred.

A specific question on the lifetime occurrence of MS was first included in the 1992 (NHS) and 1991 (NHS II) questionnaires. A question on MS diagnosis within the last 2 years was included in subsequent questionnaires. Most MS cases diagnosed before 1992 in the NHS had already been

reported through an open-ended question on 'other major illness'. For this analysis, we excluded women who had received a diagnosis of MS before they answered the baseline questionnaire.

Case ascertainment, controls selection, and other procedures for this study have been previously reported (8–10), and are briefly summarized below.

Case ascertainment

We requested permission to obtain relevant medical records from all participants who reported a new diagnosis of MS. After obtaining permission, we sent to the treating neurologists a questionnaire on the certainty of the diagnosis (definite, probable, possible, or not MS), clinical history, and laboratory tests. If a neurologist was not involved or did not respond, we mailed the questionnaire to the patient's internist.

When the Poser criteria (11) for the diagnosis of MS were applied to the clinical and laboratory data provided by the treating physician in the questionnaire, more than 90% of all definite and probable diagnoses were confirmed. Therefore, for the purpose of this investigation, we confirmed as cases women who had a diagnosis of definite or probable MS according to their physicians. We considered the categories clinically definite or laboratory-supported definite as definite, and clinically probable or laboratory-supported probable as probable. We decided to use Poser and not McDonald diagnostic criteria because the former were in use at the time the cases were diagnosed.

Cases diagnosed through April 1998 were included in the study. Follow-up was 22 years in the NHS and 9 years in the NHS II.

Selection of controls

For each case, we randomly selected five healthy women, matched on year of birth and study cohort. Cases received a letter inviting them to participate in a study on MS, and controls received a letter inviting them to participate in a study on 'the effect of infectious and immunological factors on the risk of developing chronic diseases'. Exclusion criteria for healthy controls were any report of MS or breast cancer diagnosis (see below) and not being alive at the time of the selection. Also for each case, one woman with breast cancer, matched on year of birth, study cohort, and year of diagnosis, was randomly selected and invited to participate. This second group of controls was included to address the potential bias that may derive from differential recall among women with a serious disease.

Exposure assessment

A questionnaire was mailed to cases and controls. Non-respondents to the first mailing received up to two additional letters (plus questionnaires) emphasizing the importance of their response.

The questionnaire included questions on personal history of allergy to different allergens (pollens, house dust, animal dander, foods, drugs, other) and its clinical manifestations (conjunctivitis, rhinitis, asthma, hives, other). For asthma history, we repeated the analysis using a physician-validated diagnosis of asthma, as reported in a previous publication (12).

The questionnaire also included questions on family history of MS, optic neuritis, and several other autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, hyperthyroidism, and type 1 diabetes).

Other information gathered in the questionnaire and considered in the analyses were latitude of residence at birth, maternal and paternal education, sibship size and previous history of infectious mononucleosis. We used these variables to adjust for potential confounding. We also adjusted for ancestry (Scandinavian, southern European/Mediterranean, other white, or other ancestry) and smoking history, as recorded in the main biennial questionnaire. Results did not change when we adjusted for latitude of residence at age 15.

Statistical analysis

For the results presented here, we included all cases detected in both cohorts through April 1998 and their matched controls. Participants with missing values for some of the covariates used in the analysis were excluded (seven cases and their corresponding controls). We used conditional logistic regression to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). We conducted separate analysis using the healthy controls and the breast cancer controls.

Results

The proportion of invited women who agreed to participate in the study was 94% among MS cases, 88% among healthy controls, and 90% among breast cancer cases. The primary analysis included 294 MS cases (210 definite and 84 probable), and 1248 matched healthy controls. Secondary analyses included 248 MS cases and 248 matched breast cancer cases. Table 1 shows the distribution of potential confounding factors in healthy controls.

Table 1 Distribution of potential confounding factors among healthy controls according to previous history of allergy and family history of autoimmune diseases

	History of allergy		Family history of MS or optic neuritis		Family history of autoimmune diseases other than MS/optic neuritis	
	Yes	No	Yes	No	Yes	No
Age at baseline, mean	37.8	37.9	37.9	37.7	37.5	38.0
Residence in north tier at age 15, %	32.8	33.6	35.9	32.9	34.5	31.8
Scandinavian ancestry, %	5.8	3.9	9.4	4.9	5.2	5.0
Southern European/Mediterranean ancestry, %	15.0	17.7	14.1	16.1	16.5	15.4
Maternal education less than high school, %	29.6	35.4	39.1	31.3	31.4	31.9
Paternal education less than high school, %	39.4	41.2	40.6	40.0	41.0	39.0
Sibship size, mean	3.6	3.6	3.7	3.6	3.8	3.4
Sibship size greater than 3, %	43.2	44.6	48.4	43.4	48.4	39.2
Never-smoker at baseline, %	53.3	48.7	53.1	51.6	50.0	53.3
History of infectious mononucleosis, %	13.2	9.9	7.8	12.3	11.9	12.1
History of allergy, %	100.0	0.0	73.4	64.7	71.2	59.3
Family history of MS or optic neuritis, %	5.8	3.9	100.0	0.0	6.7	3.6
Family history of autoimmune diseases other than MS/optic neuritis, %	53.6	40.5	64.1	48.2	100.0	0.0

Compared with women without history of allergy, a history of allergy was not associated with the risk of MS (OR 1.0, 95% CI 0.8–1.4). Allergy to different allergens or specific allergic manifestations were not associated with MS risk (Table 2). Use of a physician-confirmed diagnosis of asthma instead of the self-reported diagnosis yielded similar results (OR 0.9, 95% CI 0.4–2.3) to those in Table 2.

Compared with no family history of MS or other autoimmune disease, the OR (95% CI) was 9.7 (6.1–15.3) for family history of MS and 1.4 (1.0–1.8) for family history of other autoimmune disease (Table 3). The corresponding OR (95% CI) was 2.4 (1.0–5.8) for family history of systemic lupus erythematosus. The association between

family history of autoimmune diseases and MS risk was similar among those with or without family history of MS (OR 1.5, 95% CI 0.8–2.5 and OR 1.3, 95% CI 1.0–1.8, respectively). Prevalence of first and non-first degree relatives with any autoimmune disease was respectively 48% and 41% among MS cases, and 38% and 25% among controls. When we considered family history of autoimmune disease among first or non-first degree relatives as separate categories, ORs were very similar (data not shown).

Results were comparable when we used breast cancer controls instead of healthy controls (Table 4). For some exposures, however, confidence intervals were wide because of the low number of exposed women.

Table 2 Risk of MS according to previous history of allergy

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR (95% CI)*	OR (95% CI)†
No allergy	99 (33.7)	435 (34.9)	1 (ref.)	1 (ref.)
Any allergy	195 (66.3)	813 (65.1)	1.1 (0.8–1.4)	1.0 (0.8–1.4)
Allergy to:				
Pollens	91 (30.1)	409 (32.8)	1.0 (0.7–1.3)	0.9 (0.7–1.3)
House dust	53 (18.0)	237 (19.0)	1.0 (0.7–1.4)	0.9 (0.6–1.4)
Animal dander	51 (17.4)	170 (13.6)	1.3 (0.9–1.9)	1.3 (0.9–1.9)
Foods	34 (11.6)	173 (13.9)	0.9 (0.6–1.3)	0.8 (0.5–1.3)
Drugs	138 (46.9)	539 (43.2)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
Other	48 (16.3)	186 (14.9)	1.1 (0.8–1.7)	1.0 (0.7–1.5)
Manifested as:				
Conjunctivitis	52 (17.7)	216 (17.3)	1.1 (0.7–1.6)	1.1 (0.7–1.6)
Rhinitis	93 (31.6)	410 (32.9)	1.0 (0.7–1.4)	1.0 (0.7–1.3)
Asthma	27 (9.2)	109 (8.7)	1.1 (0.7–1.8)	1.0 (0.6–1.7)
Hives	99 (33.7)	404 (32.4)	1.1 (0.8–1.5)	1.0 (0.7–1.4)
Other manifestations	91 (31.0)	384 (30.8)	1.0 (0.7–1.4)	1.0 (0.7–1.4)

*Adjusting for matching factors.

†Adjusting additionally for latitude tier at birth (north, middle or south), ancestry (southern European/Mediterranean, Scandinavian, other white, or non-white), maternal education less than high school, paternal education less than high school, smoking status at baseline (never, past, or current), sibship size greater than 3, and previous history of infectious mononucleosis.

Table 3 Risk of MS according to family history of multiple sclerosis and other autoimmune diseases

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR (95% CI)*	OR (95% CI)†
No family history of autoimmune disease	94 (32.0)	613 (49.1)	1 (ref.)	1 (ref.)
Family history of multiple sclerosis	75 (25.5)	51 (4.1)	9.2 (6.0–14.1)	9.7 (6.1–15.3)
Only multiple sclerosis	31 (10.5)	18 (1.4)	11.0 (5.7–21.0)	12.3 (6.2–24.5)
MS and other autoimmune disease	44 (15.0)	33 (2.6)	8.3 (5.0–13.8)	8.4 (4.9–14.5)
No family history of MS, family history of:				
Other autoimmune disease	125 (42.5)	584 (46.8)	1.4 (1.0–1.9)	1.4 (1.0–1.8)
Only one other autoimmune disease	83 (28.2)	394 (31.6)	1.4 (1.0–1.9)	1.3 (0.9–1.8)
Two or more autoimmune diseases	42 (14.3)	190 (15.2)	1.5 (1.0–2.2)	1.5 (1.0–2.2)
Optic neuritis	4 (1.4)	13 (1.0)	1.6 (0.4–5.8)	1.2 (0.3–5.3)
Systemic lupus erythematosus	16 (5.4)	46 (3.7)	2.4 (1.1–5.2)	2.4 (1.0–5.8)
Rheumatoid arthritis	55 (18.7)	243 (19.5)	1.4 (0.9–2.1)	1.3 (0.8–2.0)
Hyperthyroidism	52 (17.7)	239 (19.2)	1.6 (1.1–2.5)	1.6 (1.0–2.6)
Type 1 diabetes	52 (17.7)	277 (22.2)	1.0 (0.7–1.5)	1.0 (0.7–1.6)

CI, confidence interval; MS, multiple sclerosis; OR, odds ratio.

*Adjusting for matching factors.

†Adjusting additionally for latitude tier at birth (north, middle or south), ancestry (southern European/Mediterranean, Scandinavian, other white, or non-white), maternal education less than high school, paternal education less than high school, smoking status at baseline (never, past, or current), sibship size greater than 3, and previous history of infectious mononucleosis.

Table 4 Risk of MS according to personal history of allergy and family history of autoimmune diseases in MS cases vs controls with breast cancer

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR (95% CI)*	OR (95% CI)†
No allergy	84 (33.9)	89 (35.9)	1 (ref.)	1 (ref.)
Any allergy	164 (66.1)	159 (64.1)	1.1 (0.8–1.6)	1.2 (0.8–1.8)
Allergy to:				
Pollens	76 (30.6)	84 (33.9)	1.0 (0.6–1.5)	1.0 (0.6–1.6)
House dust	46 (18.5)	46 (18.5)	1.1 (0.6–1.8)	1.2 (0.6–2.1)
Animal dander	46 (18.5)	39 (15.7)	1.3 (0.7–2.1)	1.4 (0.8–2.5)
Foods	27 (10.9)	21 (8.5)	1.4 (0.7–2.8)	1.6 (0.7–3.5)
Drugs	120 (48.4)	94 (37.9)	1.4 (0.9–2.1)	1.4 (0.9–2.3)
Other	39 (15.7)	32 (12.9)	1.3 (0.7–2.4)	1.2 (0.6–2.4)
Manifested as:				
Conjunctivitis	43 (17.3)	53 (21.4)	0.9 (0.5–1.4)	0.9 (0.5–1.5)
Rhinitis	77 (31.0)	85 (34.3)	1.0 (0.6–1.5)	1.0 (0.6–1.7)
Asthma	25 (10.1)	24 (9.7)	1.1 (0.6–2.0)	1.0 (0.5–2.0)
Hives	83 (33.5)	74 (29.8)	1.2 (0.8–1.9)	1.2 (0.7–2.1)
Other manifestations	78 (31.5)	65 (26.2)	1.4 (0.9–2.1)	1.3 (0.8–2.0)
No family history of autoimmune disease	82 (33.1)	126 (50.8)	1 (ref.)	1 (ref.)
Family history of multiple sclerosis	65 (26.2)	17 (6.9)	5.2 (2.8–9.7)	5.6 (2.9–10.9)
Only multiple sclerosis	27 (10.9)	6 (2.4)	6.9 (2.6–18.6)	7.1 (2.5–20.5)
MS and other autoimmune disease	38 (15.3)	11 (4.4)	4.5 (2.2–9.3)	4.9 (2.2–10.6)
No family history of MS, family history of:				
Other autoimmune disease	101 (40.7)	105 (42.3)	1.4 (1.0–2.1)	1.5 (1.0–2.3)
Only one other autoimmune disease	69 (27.8)	76 (30.7)	1.3 (0.9–2.0)	1.4 (0.9–2.3)
Two or more autoimmune diseases	32 (12.9)	29 (11.7)	1.7 (0.9–3.0)	1.7 (0.9–3.1)
Optic neuritis	3 (1.2)	1 (0.4)	3.0 (0.3–28.8)	14.5 (0.3–614.2)
Systemic lupus erythematosus	14 (5.6)	8 (3.2)	4.0 (0.8–18.8)	4.8 (0.5–44.3)
Rheumatoid arthritis	41 (16.5)	46 (18.5)	1.5 (0.8–2.9)	1.5 (0.6–4.1)
Hyperthyroidism	43 (17.3)	37 (14.9)	2.0 (1.0–4.0)	2.2 (1.0–5.0)
Type 1 diabetes	44 (17.7)	47 (19.0)	1.1 (0.6–2.1)	1.3 (0.6–2.9)

CI, confidence interval; MS, multiple sclerosis; OR, odds ratio.

*Adjusting for matching factors.

†Adjusting additionally for latitude tier at birth (north, middle or south), ancestry (southern European/Mediterranean, Scandinavian, other white, or non-white), maternal education less than high school, paternal education less than high school, smoking status at baseline (never, past, or current), sibship size greater than 3, and previous history of infectious mononucleosis.

Discussion

In this population of US female nurses, we found no association between history of allergic conditions

and the risk of MS. We found a 10-fold increase in MS risk among women with a family history of MS and a 35% increase in MS risk among women with a family history of other autoimmune diseases.

Our investigation has several limitations. Information on exposure was self-reported by study participants, and no formal validation study was conducted to assess its accuracy, although results did not change when we used a validated physician-diagnosis of asthma as exposure instead of self-reported information. Additional evidence of validity for the exposure assessment rests on the high level of health literacy in our study population and the validity of other exposures and outcomes (as diet or high blood pressure) (13, 14), but some degree of misclassification in reported history of allergies or family history of autoimmune diseases cannot be excluded. Also, exposures were ascertained retrospectively, after the diagnosis of MS. This could cause recall bias if women with personal history of a severe health problem remember past exposures more precisely than healthy women. We tried to mitigate this problem by including an additional control group of women with history of breast cancer, but more accurate reporting of family history of MS and other autoimmune diseases among women with MS remains a concern. On the other hand, under our study design, selection bias does not pose an important threat to validity. Cases and controls have been selected from participants in a well-defined cohort, and the response proportion for both groups was similarly high. Finally, our study accounted for potential confounding by age or other exposures as smoking.

Based on our results and those from previous studies (7), a strong link between allergy and MS seems unlikely. Nonetheless, the recent finding of an inverse association between histamine 1 receptor blockers and risk of MS in a British population (7), and the beneficial effect of these drugs in animal models of MS (15–17) suggest that allergy and MS could share some pathophysiological pathways.

The 10-fold increase in the risk of MS in women with family history of this disorder is similar to previous estimates and consistent with the well-established genetic predisposition to MS (18). Although environmental factors clearly contribute to geographical variations in MS incidence, clustering within families is predominantly explained by shared genes (19). On the other hand, the association between family history of other autoimmune disease and MS is much weaker and less well understood. Similarities in gene expression signatures of patients with systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, and MS (20, 21), and results of studies of gene expression in unaffected first-degree relatives of patients with autoimmune diseases suggest that there may be a common

genetic predisposition to autoimmunity (22), but environmental causes could also be important. For instance, convincing evidence exists on the association of Epstein–Barr virus infection with MS (23–25) and with systemic lupus erythematosus (26, 27). Similarly, there are reports showing an inverse association between vitamin D intake and the risk of MS (28), rheumatoid arthritis (29), and type 1 diabetes (30).

A recent systematic review assessing familial co-occurrence of autoimmune diseases (1) suggested the existence of a positive association between type 1 diabetes and MS, based in four published studies (2, 3, 5, 6). The review, however, did not offer convincing evidence to support a link between MS and other autoimmune diseases. Previous reports also found a positive association between other autoimmune disorders, such as inflammatory bowel disease and MS (5, 31), which were not included in the present study.

It has been suggested that family history of autoimmune disease could be associated with a higher risk of familial MS but not sporadic MS (32). In our analyses, however, we found a similar association between autoimmune diseases and MS risk among those with or without family history of MS.

In conclusion, allergy does not seem to be associated with MS, but the higher risk of MS among those with family history of autoimmune diseases suggests the need for further research in this topic.

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