

# Autoimmune disease in first-degree relatives of patients with multiple sclerosis

## A UK survey

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### Summary

Previous studies examining an association with other autoimmune diseases have suggested the existence of a generalized autoimmune diathesis in patients with multiple sclerosis. We investigated the prevalence of autoimmune disease in first-degree relatives of probands with multiple sclerosis using a case-control method. The results show an excess of autoimmune disease within these families, but no significant association was seen with non-autoimmune diseases. The higher risk in multiplex than simplex families suggests an effect of genetic loading. While the increase in risk applies to each autoimmune

disease, autoimmune thyroid disease (and Graves' disease in particular) contributes disproportionately to the excess risk. There was no increase in autoimmune disease within patients with multiple sclerosis themselves when compared with the index controls or population data. We conclude that autoimmune disease is more common in first-degree relatives of patients with multiple sclerosis and hypothesize that common genetic susceptibility factors for autoimmunity co-exist with additional disease specific genetic or environmental factors, which determine clinical phenotype in the individual.

**Keywords:** multiple sclerosis; autoimmune disease; epidemiology; prevalence; familial

### Introduction

Autoimmune disease is characterized by humoral or cell mediated immune response to self-antigen. This may be organ specific or systemic and, given the various overlap syndromes and occurrence of more than one autoimmune disease in the same patient (Sheehan and Stanton-King, 1993), the different phenotypes are thought to represent a spectrum of immune dysregulation (Gordon and Isenberg, 1990). Multiple sclerosis shares many clinical and pathological characteristics of prototypical autoimmune diseases (Hafler and Weiner, 1989).

The majority of autoimmune diseases, including multiple sclerosis, are more common in women and show an increasing prevalence throughout adult life with peak incidence between the ages of 20 and 40 years (Beeson, 1994). A tendency for remission during pregnancy, with a transient deterioration or increased incidence of onset in the puerperium, has been reported for several autoimmune diseases (Mitchell and Bebbington, 1992; Tada *et al.*, 1994; Nelson and Ostensen, 1997), including multiple sclerosis (Confavreux *et al.*, 1998), and each shows a variable response to immunosuppressive therapy. The presence of autoantibodies, usually associated

with other conditions, is well recognized in multiple sclerosis (Spadaro *et al.*, 1999). The significance of this finding is less clear since these autoantibodies are not usually associated with clinical evidence of disease (Baker *et al.*, 1972). The hallmark of multiple sclerosis as an autoimmune disease is the perivascular accumulation of autoreactive T cells (Stinissen *et al.*, 1998).

There are occasional case reports linking multiple sclerosis and autoimmune disease within families (McCombe *et al.*, 1990), and one case-control study looking at the risk of chronic inflammatory disease within the immediate family members of patients with multiple sclerosis (Midgard *et al.*, 1996). This and other studies (Warren and Warren, 1982) suggest an association with diabetes, but others have failed to show any familial link between these disorders (Alter and Sawyer, 1970). However, none of these studies has sufficient sample size to be definitive and each fails to make the distinction between type 1 and type 2 diabetes.

As part of ongoing genetic studies in multiple sclerosis, we have accumulated a large cohort of simplex and multiplex families from throughout the UK. We have conducted a

**Table 1** Population prevalences of autoimmune diseases in the UK

Autoimmune disease	Prevalence (%)	References
Hashimoto's/hypothyroidism*	0.80	(Tunbridge <i>et al.</i> , 1977)
Graves'/hyperthyroidism*	0.65	(Shank, 1976; Tunbridge <i>et al.</i> , 1977)
Rheumatoid arthritis	0.55	(Hochberg, 1990)
Type 1 diabetes mellitus	0.34	(Gatling <i>et al.</i> , 1998)
Pernicious anaemia	0.13	(Scott, 1960)
Systemic lupus erythematosus	0.027	(Hopkinson <i>et al.</i> , 1993; Johnson <i>et al.</i> , 1995)
Myasthenia gravis	0.015	(Robertson <i>et al.</i> , 1998)
Addison's disease	0.009	(Willis and Vince, 1997)
Total	2.52	—

Mean figures are given where more than one reference was available. \*Adult population figure.

retrospective case-control postal questionnaire survey in order to assess whether autoimmune disease is more common in first-degree relatives of probands with multiple sclerosis.

## Methods

Power calculations indicated that 250 cases and 250 controls would be required to demonstrate a twofold increase in the risk of autoimmune disease, with  $\alpha$  (the probability of a false positive, i.e. type 1 error, result) = 0.05 and  $\beta$  (the probability of a false negative, i.e. type 2 error, result) = 0.2, assuming a background prevalence of 2.5% (Table 1) and an average of three relatives per family. A larger sample size was predicted for unequal sample sizes, but this requirement is counteracted by the use of simplex and multiplex families in order to measure dosage effect. Multiplex families were defined as a proband with one or more first-degree relatives having multiple sclerosis. Ethical approval was obtained from the local Cambridge (CREC) and Oxford and Cambridge Regional Ethics Committee (MREC).

The patients were 773 cases referred by members of the Association of British Neurologists from throughout the UK, or those volunteering for participation in research through the Multiple Sclerosis Society of Great Britain and Northern Ireland, and Brunel University. Inclusion criteria were a confirmed diagnosis of multiple sclerosis made by a consultant neurologist, Caucasian origin and living parents born in the UK. Probands were excluded if they failed to meet the Poser criteria for a diagnosis of clinically definite (Poser *et al.*, 1983), laboratory-supported definite or laboratory-supported probable multiple sclerosis (categories A–C). All multiple sclerosis probands were visited to establish the diagnosis and record clinical details. Confirmation of the diagnosis was made using medical records, and where applicable, results of MRI, visual evoked potentials and CSF examination were obtained.

The autoimmune diseases selected for study are the most prevalent of those with recognized associated autoantibodies (Patrick, 1993). Their overall population prevalence in the UK is 2.5% (Table 1). Psoriasis was also considered as a putative T-cell mediated autoimmune disease (Barker, 1998) but analysed separately. Crohn's disease and ulcerative colitis

were investigated because of previous reports linking these diseases with individuals having multiple sclerosis (Rang *et al.*, 1982) and their families (Minuk and Lewkonja, 1986; Sadovnick *et al.*, 1989).

Non-autoimmune diseases were considered in order to control for reporting bias. 'Heart attack' was included in the list of conditions, and age of onset of a disease was requested allowing a differentiation to be made between type 1 and type 2 diabetes, so that type 2 would provide a further non-autoimmune control. The cut-off was made at 30 years, recognizing that this is arbitrary and that some cases of later onset diabetes are also autoimmune in nature. Atopic asthma was included as an 'immunological' control condition; there are reports linking atopy with multiple sclerosis (Frovig *et al.*, 1967), although this is unconfirmed and others have found a reduced prevalence in patients with multiple sclerosis (Oro *et al.*, 1996).

Two identical questionnaires, one to be completed by the proband and the other by a control, were distributed. A reminder letter was sent to non-responders after 2 months. Controls were selected by the probands from a choice of spouse, partner, carer or friend. The questionnaire requested information about the list of specific autoimmune and non-autoimmune conditions in parents and siblings. Information about offspring was not requested because of ethical issues relating to informed consent in those aged under 18 years. Since the rate of autoimmune disease in childhood is low, this group would be relatively uninformative. Relevant information regarding each condition was provided and it was requested that all living relatives be asked directly about these conditions and for information from memory on deceased relatives. Where there was any doubt about a particular relative, participants were instructed to reply in the affirmative, so as to increase the likelihood of including all positive diagnoses. Informed consent for participation in the study was obtained from all index cases and controls.

On receipt of completed questionnaires all living relatives said to have one of the listed conditions were contacted to request confirmation from their general practitioner. A repeat mail-shot was sent to non-responders after a further 2 months. Consent to release of medical information was obtained and further specific details relating to asthma (atopy, age of onset



and smoking history) and thyroid disease (previous surgery, thyroxine replacement therapy and specific diagnoses) were requested. It was therefore possible to distinguish atopic asthma from non-atopic asthma and primary hypothyroidism and hyperthyroidism from other secondary causes of thyroid disease. Atopic asthma was defined as asthma beginning before the age of 20 years, asthma with atopic features (hay fever or eczema) commencing before the age of 30 years, or asthma with atopic features prior to the age of 50 years in persons who had never been smokers. For the purposes of analysis, primary hypothyroidism and hyperthyroidism were assumed to have an autoimmune basis and were included with Hashimoto's thyroiditis and Graves' disease, respectively. The majority of cases with primary hyperthyroidism are due to Graves' disease, but the remainder usually also have an autoimmune basis (predominantly Hashimoto's thyroiditis).

General practitioners were contacted to confirm or refute each diagnosis. Three options were given: 'yes', the diagnosis is correct; 'no', this person has never had this disease; or 'uncertain', it is not possible to confirm or deny this diagnosis based on personal knowledge and the available medical records. Only affirmative responses have been included in the analysis. Demographic details and all diagnostic data were entered into a specifically created Microsoft® Access database, such that positive diagnoses were entered three times: initial notification, relatives' verification and general practitioner confirmation. Thus, encoding errors were minimized.

To explore under-reporting of autoimmune diseases within the control families, a randomly chosen, apparently unaffected, member of every third responding family was contacted. This individual was asked to confirm their date of birth, number of relatives in the family and whether they had ever been diagnosed with any of the specified conditions.

Statistical analysis was carried out using the proportion of families in whom one or more relatives had the specified condition. A  $\chi^2$  test for trend ( $\chi^2_{\text{trend}}$ ) was used to test for dose effect of genetic loading between control, simplex and multiplex families with unitary weighting (Fleiss, 1981). The  $\chi^2$  test was used for comparisons between two groups and the odds ratio, which very closely approximates to the relative risk in large samples, used to calculate the sibling risk. The age- and sex-adjusted prevalence figure for autoimmune disease in control relatives was calculated using the UK mid-census estimates for 1997 (Matheson and Pullinger, 1999).

## Results

### Response rates

The overall response rates for usable questionnaires were 375 of 647 (58%) for controls and 571 of 753 (76%) for cases. A breakdown of recruitment and reasons for exclusion are given in Fig. 1. Analysis of the non-responding cases revealed that they were twice as likely to have an incomplete address (e.g. missing postcode) and were more likely to have

been originally visited for other aspects of genetic research more than 4 years prior to the postal survey. This suggests that many of the non-responders may never have received the questionnaires due to inadequate postal details or through having moved since originally being recruited. Disease severity did not influence the likelihood of response and this may reflect the option that the questionnaire be completed, if necessary, by another relative or carer on behalf of the proband. In total, the survey included 3439 relatives of 946 index cases and controls. Thirty-two half-siblings were excluded from the analysis. One thousand individuals were contacted regarding positive diagnoses, of whom 879 replied.

### Diagnostic confirmation

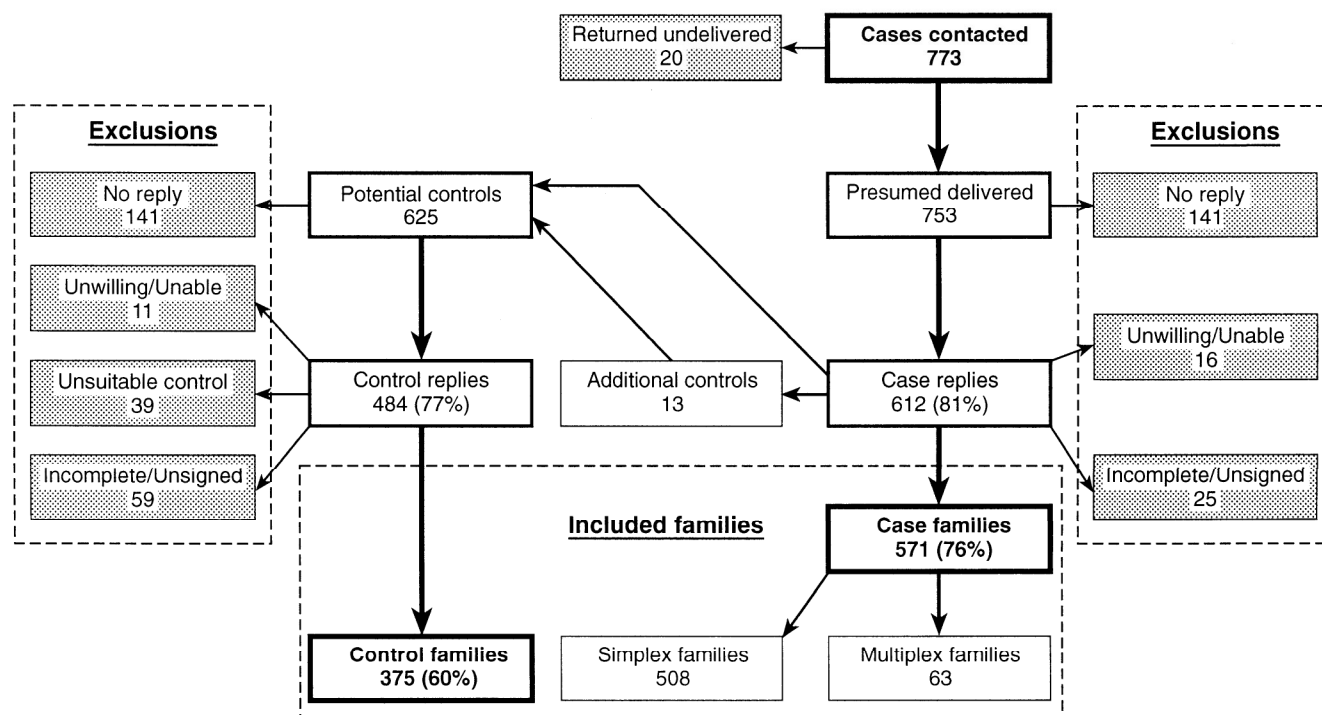
The number of general practitioners contacted was 799, of whom 722 responded. It was therefore possible to confirm the diagnosis of autoimmune disease through general practitioners in 78% of living affected relatives. The figure for all diagnoses was 75%. The positive predictive value of diagnoses in living relatives initially reported by the index case or control for each condition is listed in Table 2. With the exception of rheumatoid arthritis, pernicious anaemia and ulcerative colitis, reliable reporting figures of 70% or more were seen and rates were similar for case and control relatives. The confusion of rheumatoid arthritis with osteoarthritis was predictable and explains the positive predictive value of less than 50% in both cases and controls.

### Demographics of families

Of the 571 index cases, criteria for Poser category A were met in 513 (89.8%), category B in 32 (5.6%) and category C in 26 (4.6%). There were 140 males and 431 females (ratio 1 : 3). Disability scores (from the expanded disability status scale) ranged from 0 to 9.5, with 217 having scores less than 4, 274 from 4 to 7, and 80 greater than 7. A relapsing–remitting course was reported in 339 (59.4%), with 180 (31.5%) having secondary progressive disease and 52 (9.1%) primary progressive disease. These figures accord well with previously reported cross-sectional surveys of patients with multiple sclerosis (Miller *et al.*, 1992).

The index controls were spouses or partners in 73%. Of the control relatives, 22% were no longer living as opposed to only 2% of case relatives. Deceased relatives were included in the analysis, except where otherwise stated. There were 375 control, 508 simplex and 63 multiplex families. The 11% frequency of multiple sclerosis cases with a co-affected first-degree relative is consistent with UK population figures (Robertson *et al.*, 1996).

There was a co-affected sibling in 49 of the multiplex families. Because of the way in which these families were identified (i.e. affected sibling pair), they were predictably larger. The 49 co-affected siblings have therefore been excluded so as to avoid any potential bias from including siblings with multiple sclerosis and concurrent autoimmune



**Fig. 1** Summary of recruitment and reasons for exclusion of case and control families. Controls were deemed unsuitable if they themselves had multiple sclerosis (1), were a blood relative of the index case (30) or non-Caucasian (8). ‘Additional controls’ refers to instances where more than one control family was supplied by the same index case.

**Table 2** Positive predictive value for each condition

Diagnosis	Cases (%)	Controls (%)
Multiple sclerosis	87	100
Thyroid disease	85	88
Rheumatoid arthritis	32	41
Diabetes (type 1 and 2)	94	97
Pernicious anaemia	45	100
Systemic lupus erythematosus	67	N/A
Psoriasis	55	78
Crohn’s disease	80	100
Ulcerative colitis	55	64
Asthma	74	87
Myocardial infarction	74	68
Overall	70	78

Proportion of notified diagnoses in living relatives confirmed by general practitioners. N/A = not applicable.

disease (in fact only one of the 49 had an autoimmune disease) and to equilibrate the sibship sizes. The mean ages of relatives, the sibship sizes and sex distribution for siblings were comparable between the three groups (Table 3). The figure of 2.5 for the mean number of offspring per family is slightly higher than the population figure for mothers 40 years ago of just over 2 (Harris, 1997). This difference may merely reflect the fact that, by the very nature of this study, no families without children were included. When sibling numbers for one-third of the control families were checked with a second family member, five additional siblings were identified. When extrapolated to the entire set of control families, this only constitutes an error of 1% in the number

**Table 3** Details of family members

Relative	Control	Simplex	Multiplex
Mean age of relatives (range) in years			
Index	42.8 (19–68)	40.7 (19–60)	40.0 (21–56)
Mother	68.4 (28–95)	67.7 (42–92)	65.7 (42–85)
Father	67.3 (33–90)	70.2 (33–93)	68.6 (48–93)
Sister	42.2 (17–84)	39.4 (7–61)	36.9 (8–63)
Brother	41.4 (1–67)	39.2 (21–56)	37.6 (1–52)
All (excluding index)	55.6 (1–95)	55.6 (7–93)	55.8 (1–93)
Sibship size and proportion of sisters			
Sibship size	1.63	1.65	1.51
Sisters (%)	45	51	54

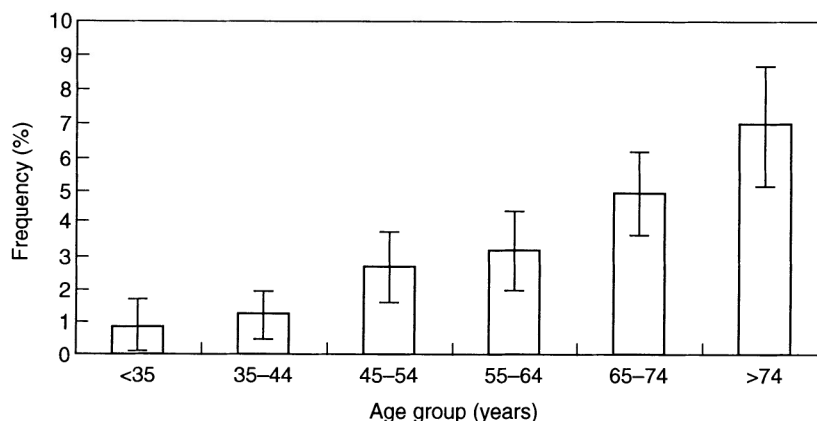
Sibship size refers to the mean number of siblings for each family type.

of control relatives. Seven control relatives also had a diagnosis of multiple sclerosis, which was confirmed in all six of the living cases. These families remained in the analysis as controls.

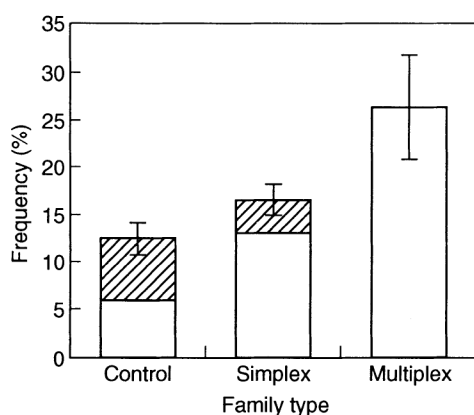
**Autoimmune disease in control relatives**

The prevalence data for autoimmune disease in all control relatives are summarized by age in Fig. 2. These give an age- and sex-adjusted prevalence of 2.3% for the selected autoimmune diseases in the control relatives, which compares well with the predicted population figure of 2.5%. Ninety-one of 117 unaffected control relatives who were contacted





**Fig. 2** Age-specific prevalence of selected autoimmune diseases in control relatives ( $n = 1315$ ). Error bars show the standard error.

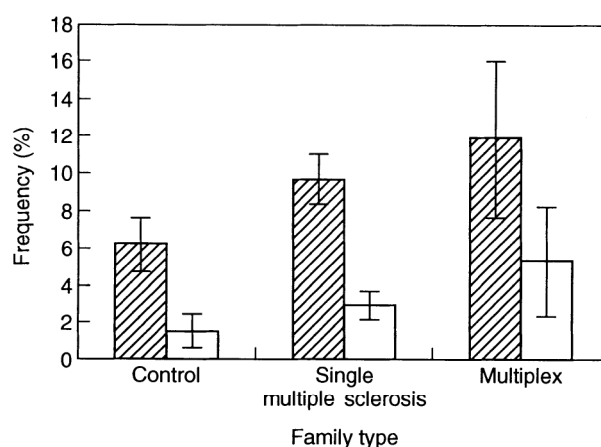


**Fig. 3** Prevalence rates based on one or more relatives having any of the selected autoimmune diseases. ‘Confirmed’ (white bars) refers to the diagnosis in one or more of these affected relatives having been verified by the general practitioner; unconfirmed = striped bars. Error bars show the standard error for the combined data.

responded. None reported suffering from any of the listed autoimmune diseases, confirming that under-reporting was not a significant problem.

### Autoimmune disease in case and control families

The number of families where one or more relatives had one of the selected autoimmune diseases was 44 of 375 (11.7%) in control families, 80 of 508 (15.7%) in simplex families and 16 of 63 (27%) in multiplex families ( $\chi^2_{\text{trend}} = 8.95$ ,  $P = 0.003$ ). Figure 3 shows this result graphically and also demonstrates the proportion of families in which at least one relative with a diagnosis of autoimmune disease was confirmed by the general practitioner. The result for the control families is slightly higher than that predicted by the population data ( $3.5 \times 2.5\% = 8.8\%$ ) and reflects the mean age of 56 years seen for all relatives. To remove any potential bias due to disparity in the sibship size, sibling sex distribution or proportion of deceased parents, the prevalences of

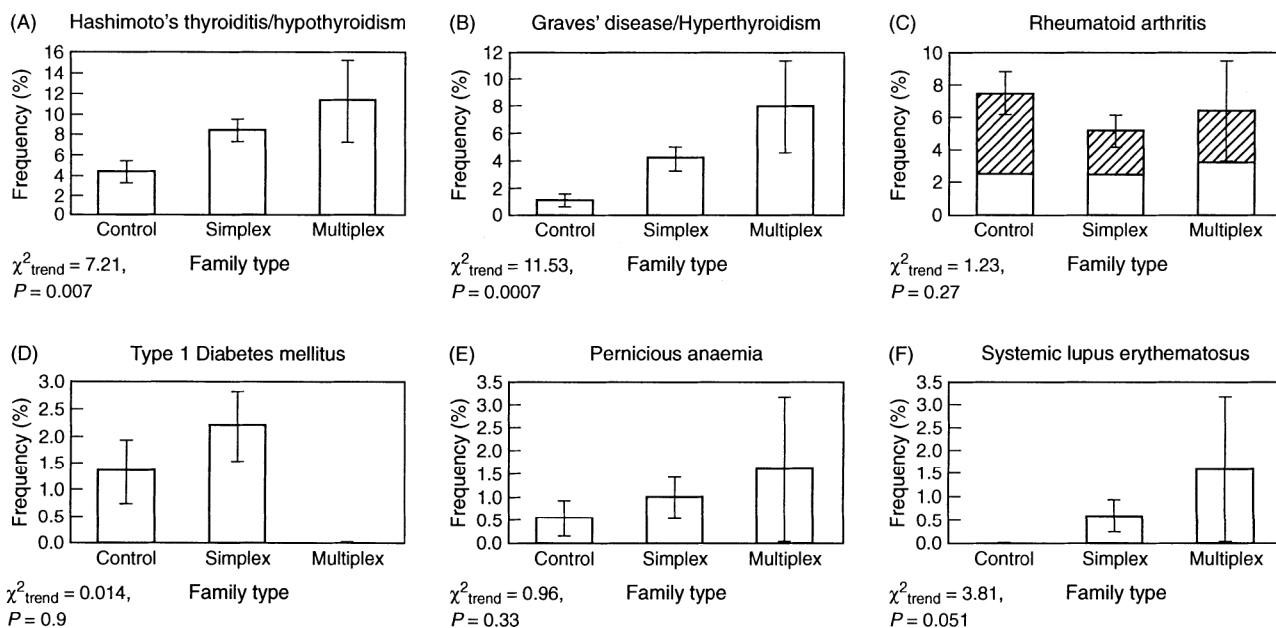


**Fig. 4** Autoimmune disease in living parents. Error bars show the standard error. Striped bars = mothers; white bars = fathers.

autoimmune disease in living mothers and living fathers were calculated separately (Fig. 4). These data combined also show a statistically significant relationship ( $\chi^2_{\text{trend}} = 4.06$ ,  $P = 0.04$ ).

The association with all autoimmune disease was seen for each individual condition (Fig. 5). The relationships for Hashimoto’s disease/autoimmune hypothyroidism and Graves’ disease/autoimmune hyperthyroidism reach statistical significance in their own right, with Graves’ disease/primary hyperthyroidism appearing to contribute the largest effect. The result for systemic lupus erythematosus just fails to reach significance at the 5% level ( $P = 0.051$ ).

In the case of rheumatoid arthritis, deceased relatives account for half of the unconfirmed control families and diagnostic confirmation rates are generally low for all family types (Fig. 5C). In view of the low positive predictive value of around 40% for rheumatoid arthritis seen in living relatives, it is reasonable to presume that a fair proportion of these unconfirmed rheumatoid arthritis diagnoses are incorrect and mistaken for osteoarthritis. If rheumatoid arthritis is excluded from the analysis, the result becomes more significant ( $P = 0.000035$ ) indicating that our quoted  $P$ -value is likely to be



**Fig. 5 (A–F)** Frequency of individual autoimmune diseases. Error bars show the standard error. (C) The proportion of confirmed (white) and unconfirmed (striped) cases with rheumatoid arthritis. Error bars and hypothesis test statistic are based on combined data.

a conservative estimate. This result remains significant even when the non-responding case families are included on the basis that they had no autoimmune disease ( $\chi^2_{\text{trend}} = 8.49$ ,  $P = 0.0036$ ).

There were no type 1 diabetic relatives in the multiplex families where one or two might have been expected. Only two cases of myasthenia gravis were reported, one in a deceased control relative and the second in a living case relative in whom the general practitioner was 'uncertain' about the diagnosis; this individual was excluded. No cases of Addison's disease were reported.

### Sibling risk for autoimmune disease

The number of siblings with one or more autoimmune diseases was 10 of 565 (1.8%) for controls and 30 of 982 (3.1%) for cases. The sex-adjusted sibling ( $\lambda_s$ ) risk is 1.65 (95% confidence interval, 1.0–3.4).

### Other conditions in families

Psoriasis showed a similar trend to the selected antibody associated autoimmune diseases (Fig. 6A). Inflammatory bowel disease showed no association with multiple sclerosis (Fig. 6B). The non-autoimmune control diseases, myocardial infarction and type 2 diabetes mellitus, and asthma showed no familial relationship with multiple sclerosis (Fig. 6C–E).

### Autoimmune disease in index cases and controls

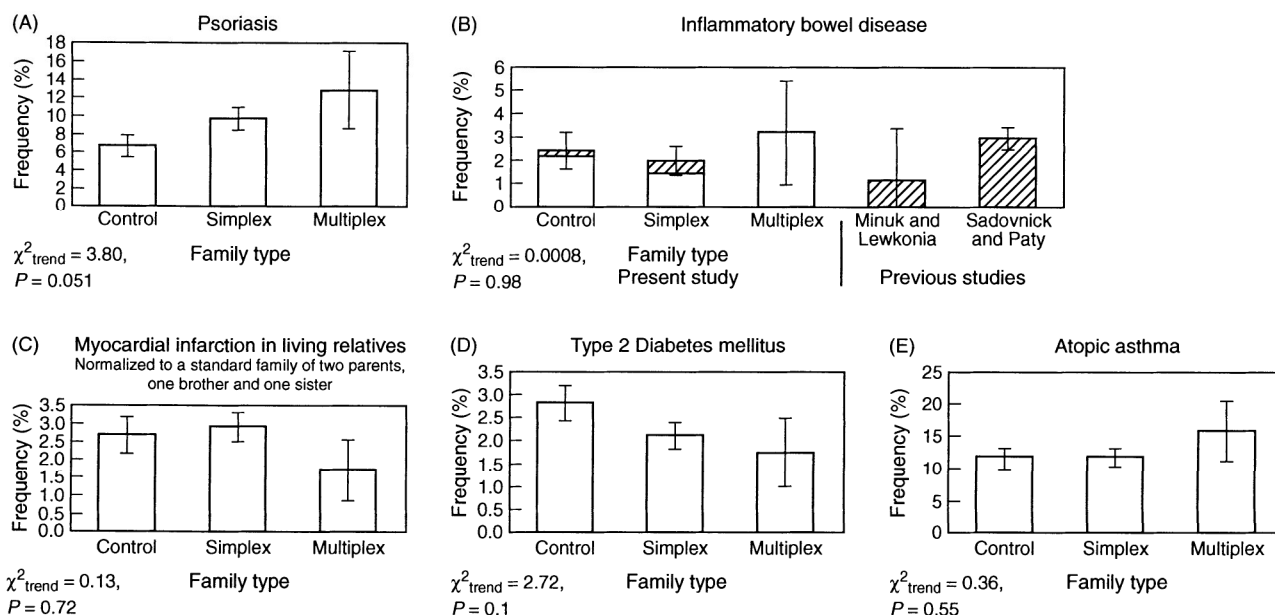
An estimate of prevalence for autoimmune disease in index cases and controls would require several thousand participants

carefully matched for age and sex. However, calculated sex-adjusted prevalence rates for autoimmune disease were 2% in the index cases and 2.73% in the index controls ( $Z = 0.74$ ,  $P = 0.46$ ). These figures are comparable with a population prevalence of 2.5% for these autoimmune diseases in the UK. The figures for individual conditions are listed in Table 4 and most agree with population data. The numbers of cases and controls make interpretation of the apparently lower rate of autoimmune disease in cases impossible, but do at least indicate that there has been no bias towards autoimmune disease in the cases who responded. There were no cases of pernicious anaemia, systemic lupus erythematosus, myasthenia gravis or Addison's disease among the index cases and controls.

### Discussion

Here we show an increased risk of other autoimmune diseases in the relatives of patients with multiple sclerosis. This study was large with high response rates and diagnostic confirmation, and used a conservative family based method of statistical analysis. The sex distributions of the index cases and controls are clearly influenced by the use of spouses/partners as controls. However, these individuals were not used for the primary analysis and only their relatives were included. Fears that men may be less diligent in reporting family history data were not born out, as the frequencies of all conditions studied in the control families match published figures for the UK population, and random sampling for under-reporting of autoimmune disease failed to identify missed cases in the control families. In a condition which predominantly affects women, such as multiple sclerosis, cases will tend to come from families with a higher proportion





**Fig. 6 (A–E)** Frequency of other diseases. Error bars show the standard error. **(B)** The proportion of unconfirmed (striped) and confirmed (white) cases for inflammatory bowel disease. Error bars and hypothesis test statistic are based on combined data for present data only. Because heart disease was frequently reported as a cause of death in deceased relatives, and could not always be validated only living relatives have been analysed for myocardial infarction, and families normalized to a structure of two parents, one brother and one sister.

**Table 4** Sex-adjusted prevalences in index cases and controls

Condition	Cases (%)	Controls (%)	Population (%)	Reference
Hashimoto's/hypothyroidism	0.4	1.2	0.8	(Tunbridge <i>et al.</i> , 1977)
Graves'/hyperthyroidism	0.5	0.0	0.7	(Shank, 1976; Tunbridge <i>et al.</i> , 1977)
Rheumatoid arthritis	0.2	1.4	0.6	(Hochberg, 1990)
Type 1 diabetes mellitus*	0.7	0.3	0.3	(Gatling <i>et al.</i> , 1998)
Psoriasis	2.8	3.4	3.7	(Brandrup and Green, 1981)
Type 2 diabetes mellitus	0.4	0.0	1.5	(Gatling <i>et al.</i> , 1998)
Asthma	6.5	7.1	6.5	(Ertle and London, 1998)
Inflammatory bowel disease*	0.5	1.1	0.4	(Bernstein <i>et al.</i> , 1999)
Myocardial infarction	0.5	0.8	N/A	–

\*Not sex-adjusted.

of daughters, and this effect is further increased in affected sibling pair families. In addition, the sex distribution of the index cases does have a subtle effect on the sibship sex distribution, with women tending to have a slightly higher proportion of sisters and vice versa for men. However, variations in the sibship sex distribution observed in the present study would not account for differences in the rates of autoimmune disease seen in the three sets of relatives, particularly as it is the parents who contribute the largest effect. We therefore conclude that the antibody associated autoimmune diseases studied are more frequent among first-degree relatives of patients with multiple sclerosis than well-matched controls, whereas non-autoimmune diseases show no such relationship. In addition, the data indicate increasing genetic load for autoimmune disease among members of multiplex families. However, the overall risk of other autoimmune diseases observed in relatives of our patients

with multiple sclerosis is small, suggesting that genetic factors responsible for this apparent autoimmune diathesis contribute only a small part to genetic susceptibility in multiple sclerosis. Since  $\lambda_s$  for multiple sclerosis is approximately 20, the figure of 1.65 attributable to the risk of non-specific autoimmunity indicates that disease specific genetic factors are more significant.

Autoimmune thyroid disease shows the strongest effect, but this may reflect the high prevalence compared with other autoimmune conditions. Using different methodology, without control data, a recent French study found a lower overall rate of autoimmune disease in first-degree relatives of patients with multiple sclerosis than in our study, but also reported a high prevalence of Graves' disease (Heinzlef *et al.*, 1999). This finding is of particular interest since a proportion of patients with multiple sclerosis treated with interferon- $\beta$  (Rotondi *et al.*, 1998) and one-third of patients receiving

Campath-1H (Coles *et al.*, 1999) develop Graves' disease. This suggests a specific relationship between Graves' disease and multiple sclerosis, although the mechanism is not yet understood. The finding of no relatives with type 1 diabetes in the multiplex families may have arisen purely by chance, but could indicate a specific relationship between type 1 diabetes and multiple sclerosis: a higher genetic load predisposing towards multiple sclerosis may be relatively protective against autoimmune diabetes. For example, the class 2 major histocompatibility complex allele HLA-DR2, which is clearly associated with multiple sclerosis (Corradu *et al.*, 1998), is protective in type 1 diabetes mellitus (Noble *et al.*, 1996) in northern Europeans.

Psoriasis shows a similar trend of genetic loading in simplex and multiplex families and this confirms the previously reported increased risk of psoriasis within multiple sclerosis families (Midgard *et al.*, 1996). It would therefore seem reasonable to include psoriasis in the list of autoimmune diseases linked with multiple sclerosis. In contrast, we found no association with inflammatory bowel disease. This result is in contrast to previous studies (Minuk and Lewkonja, 1986; Sadovnick *et al.*, 1989) which report a higher than expected prevalence of inflammatory bowel disease in relatives of patients with multiple sclerosis. However, these studies calculated the risk of an individual developing both conditions from published population prevalence figures, but not the family risk. The finding of inflammatory bowel disease in 1.13% (Minuk and Lewkonja, 1986) and 2.94% (Sadovnick *et al.*, 1989) of families, if restricted to parents and siblings, is within the confidence intervals for our results in both case and control families. Taken together, these results provide no evidence supporting an increased prevalence of inflammatory bowel disease within first-degree relatives of patients with multiple sclerosis.

Although not a primary objective of this survey, we found no evidence for an increased risk of autoimmune disease within multiple sclerosis probands. This is consistent with previous larger series looking specifically at this relationship (De Keyser, 1988; Wynn *et al.*, 1990). The finding of an increased familial rate of autoimmune disease without a corresponding increase in patients with multiple sclerosis seems counterintuitive. However, this finding is compatible with the hypothesis that while a number of shared genotypes may underlie genetic predisposition to autoimmunity, the specific phenotype in individual family members is determined by disease specific genes or external factors, and that to some extent these phenotypic determinants may be mutually exclusive. This interpretation was the conclusion of a previous study of familial autoimmunity (Bias *et al.*, 1986).

Most autoimmune diseases are thought to arise from somatic events or environmental factors affecting individuals who are genetically predisposed (Heward and Gough, 1997); this model is supported by the results of twin studies (Leslie and Hawa, 1994). The majority of autoimmune diseases also have a recognized HLA association. However, these disease associations are specifically different (Heward and Gough,

1997). Genome screens for type 1 diabetes mellitus (Todd and Farrall, 1996), systemic lupus erythematosus (Gaffney *et al.*, 1998), rheumatoid arthritis (Cornelis *et al.*, 1998) and multiple sclerosis (Ebers *et al.*, 1996; Haines *et al.*, 1996; Sawcer *et al.*, 1996; Kuokkanen *et al.*, 1997) have failed to identify any common loci. However, clustering of non-major histocompatibility complex candidate susceptibility loci for these conditions has already been noted (Becker *et al.*, 1998). Since there is a definite familial recurrence risk for multiple sclerosis and other autoimmune diseases, it is logical to consider combined linkage studies or to perform a meta-analysis of the available independent genome screens to identify loci which confer susceptibility to autoimmunity independent of the disease phenotype.

### Acknowledgements

We wish to thank general practitioners from the UK, Australia, Cyprus, France, Holland, Spain and the USA who provided information for this survey. We thank members of the Association of British Neurologists for referring patients. This study was supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland, the Medical Research Council and the Wellcome Trust.

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*Received November 1, 1999. Revised January 4, 2000.  
Accepted January 17, 2000*