Barnett MH, Williams DB, Day S, Macaskill P, McLeod JG (2003) "Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study" *Journal of Neurological Sciences*, 213, 1-6.

A significant increase in prevalence over time, although it is not clear the extent to which this reflects better case ascertainment or differential migration of people from high risk populations (Hammond et al, 1987; Hammond et al, 1988b). Prevalence in Newcastle has risen by 272% for females and 74% for men from 1961 to 1996 (Barnett et al, 2003). The rise was attributed to increased incidence, particularly among females, and to increased survival rates. The 1996 study of prevalence in the ACT found unexpectedly high levels of MS, compared to results then available (1981) of prevalence in Newcastle, a city of similar latitude. Subsequent publication of MS prevalence in Newcastle (Barnett et al, 2003) during 1996 in fact shows very similar results between the two cities at the later date.

ELSEVIER

Journal of the Neurological Sciences 213 (2003) 1–6

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study

M.H. Barnett[a,b], D.B. Williams[c], S. Day[a,b], P. Macaskill[d], J.G. McLeod[a,b,*]

[a] *Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, NSW 2006, Australia*
[b] *Department of Medicine, University of Sydney, Sydney, NSW 2006, Australia*
[c] *Department of Neurology, John Hunter Hospital, Newcastle, NSW, Australia*
[d] *Department of Public Health, University of Sydney, Sydney, NSW, Australia*

Received 26 November 2002; received in revised form 25 March 2003; accepted 4 April 2003

Abstract

The prevalence of multiple sclerosis (MS) in Newcastle, Australia increased significantly between 1961 and 1981 and the incidence of the disease also increased between the decades 1950–1959 and 1971–1981. The present study sought to determine whether there has been a further increase in the frequency of MS in the subsequent 15 years, and to examine the potential factors underlying this change. The incidence, prevalence and clinical profile of multiple sclerosis were therefore re-examined in Newcastle, Australia in 1996 using comparable diagnostic criteria and methods to those employed in studies in the same region in 1961 and 1981. There has been a significant progressive increase in prevalence from 19.6 to 59.1 per 100,000 population and a significant increase in incidence from 1.2 to 2.4 per 100,000 population from 1961 to 1996. The most pronounced increase in prevalence was in females and in the age-group over 60 years, and there was also an increased incidence in females aged 20–29 years. There was little change in the age of disease onset, but duration of disease in females had increased substantially. The significant increase in prevalence is attributed to increased incidence, particularly in females; and to increased survival. Although such trends in prevalence have been observed in the Northern Hemisphere, this is the first such study in the Southern Hemisphere to show a longitudinal increase in prevalence and incidence over a period of this duration.

Keywords: Multiple sclerosis; Australia; Epidemiology; Prevalence; Incidence

1. Introduction

The prevalence of multiple sclerosis (MS) in three Australian cities (Newcastle, Perth and Hobart) increased significantly between 1961 and 1981 and the incidence of the disease also increased between the decades 1950–1959 and 1971–1981 [1]. The present study sought to determine whether there was a further increase in the frequency of the disease over the subsequent 15 years. Using diagnostic criteria and methods comparable to those employed in the previous studies, we therefore undertook a point prevalence survey in Newcastle for 8 August 1996, the date of a national census, and determined the incidence of MS in Newcastle in the decade 1986–1996. The clinical profile of MS in 1996 was also compared with that in 1981 [2].

2. Materials and methods

The city of Newcastle is situated on the Hunter river at latitude 32°52′S, longitude 151°49′E. It lies on the eastern coast of New South Wales approximately 160 km north of Sydney, and encompasses an area of 205 km^2. The population was 142,574, 135,207 and 133,686 on the prevalence days in 1961, 1981 and 1996, respectively.

The major sources for case ascertainment were as follows:

1. The diagnostic index of the John Hunter Hospital, the major teaching hospital of the University of Newcastle.
2. Practising doctors. There were six neurologists practising in the Newcastle area on the prevalence day. A circular

* Corresponding author. Department of Medicine, University of Sydney, Sydney, NSW 2006, Australia. Tel.: +61-2-9351-3385; fax: +61-2-9351-4018.
E-mail address: jmcl7953@mail.usyd.edu.au (J.G. McLeod).

0022-510X/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0022-510X(03)00122-9

was sent to all neurologists and general practitioners requesting the name, most recent address, approximate date of diagnosis and hospital where notes might be found of any patients known to them either currently or in the past in whom the likely diagnosis was MS. Follow up procedures included a second mailing of this letter if no reply was received to the first and personal telephone calls were also made in some instances.

3. The New South Wales Multiple Sclerosis Society records.
4. Patients included in the 1981 survey [1].
5. Patients included in a trial of beta-interferon, commenced in 1994 [3,4].

Details of doctors' records and hospital admission notes were transferred to a standard protocol form designed to facilitate entry of information into a computerised database. All patients were examined by a neurologist. All patients in whom a diagnosis of MS was considered to be correct were classified according to the diagnostic criteria of Rose et al. [5] into clinically definite, probable or possible groups. As in the previous surveys, laboratory results (e.g. cerebrospinal fluid (CSF) analysis, evoked potential studies and magnetic resonance imaging (MRI)) were not considered in the allocation of individual patients to particular diagnostic categories. The disability status of each patient on prevalence day was assessed according to the Kurtzke disability status scale (DSS) employed in the previous studies. Approval for the study was obtained from the Hunter Area Research Ethics Committee.

2.1. Definitions

Crude prevalence was defined as the ratio of persons with an acceptable diagnosis of MS living in the study area on the prevalence date of 8th August 1996, a national census day, to the total number of persons in the same area on the same day and was expressed per 100,000 population. The crude prevalence of MS on both prevalence days was age-standardized to the distribution of the total Australian population on 8th August 1996 by the direct method. In addition, the crude MS prevalence data from 1961 and 1981 were age-standardised to the same population distribution to facilitate direct comparison.

Crude incidence was calculated from the number of cases in the study area on 8th August 1996 in whom onset of symptoms occurred during the decade mid-1986 to mid-1996, and is expressed per 100,000 person years using the 1991 Newcastle census data as the denominator. The incidence data was age standardised using the direct method to the distribution of the Australian population on 8th August 1996. The crude incidence data for the decade mid-1971 to mid-1981 was age standardised to the same population to facilitate direct comparison.

Age-specific incidence data for the 1950–1959 period was not available, and thus incidence data for this period was not age-standardised.

2.2. Statistical methods

Confidence intervals for crude prevalence and incidence may be computed using the relationship between the Poisson and chi-squared distributions [6]. A generalization of this approach was used to calculate confidence intervals for the standardised rates [7]. Poisson regression [6] was used to test for a trend in prevalence across years by fitting year as a continuous variable. Poisson regression was also used to test for a difference in incidence between the decades 1971–1981 and 1986–1996.

The chi-squared statistic was used to test for association between categorical variables. Analysis of variance was used to test for differences between means. The Mann Whitney U and Kruskall–Wallis (non-parametric) tests were used to compare medians for two or more groups respectively when normality could not be assumed.

3. Results

3.1. Case ascertainment

All patients had been examined and were notified by a neurologist. 44% of the patients were also identified from records of the Multiple Sclerosis Society; 33% had been included in the 1981 epidemiological survey [1]; 21% were ascertained from hospital records; 15% were notified by general practitioners; and 4% were known from the beta-interferon trial. The average number of sources reporting each case was 2.2.

3.2. Diagnostic classification

In 1996, the proportion of patients with definite MS was 81% ($n=64$); with probable MS 18% ($n=14$); and with possible MS 1% ($n=1$). There was no significant change in the distribution of diagnostic categories between 1961 and 1996 ($\chi^2=6.66$, 4 *df*, $P=0.16$) (data not shown). The Allison and Millar criteria [8] were used for the 1961 data, and their 'probable', 'early probable' and 'possible' categories have been considered equivalent to the 'definite', 'probable' and 'possible' categories of Rose et al. [5].

3.3. Prevalence

The prevalence for all persons with MS in 1996 was 59.1 per 100,000 persons, the highest ever reported in the Newcastle region. In addition, age-standardisation of the crude prevalence figures extracted from the previously published 1961 and 1981 data[1] revealed an almost linear increase over the period. Based on the Poisson regression model adjusted for age, this trend was statistically significant ($\chi^2=25.1$, 1 *df*, $P<0.001$). Crude and age-standardised rates were not appreciably different (Table 1). The mean age on the prevalence day was 50.9 years in 1996. The ratio of

Table 1
Age-specific and age-standardised prevalence rates by sex and for all persons Newcastle 1961 1996[a]

Age group (years)	1961						1981						1996					
	Males		Females		All persons		Males		Females		All persons		Males		Females		All persons	
	n	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000	*n*	Prevalence/ 100,000
0 9	0		0		0		0		0		0		0		0		0	
10 19	2	9.4	2	9.7	4	9.6	0		1	9.3	1	4.5	0		0		0	
20 29	3	28.7	5	50.1	8	39.2	3	24.2	3	26.9	6	25.5	2	17.0	3	26.0	5	21.4
30 39	5	49.4	5	49.3	10	49.3	4	47.8	7	86.6	11	66.9	7	69.5	9	92.5	16	80.8
40 49	3	37.1	3	38.0	6	37.5	4	58.6	9	130.7	13	94.8	3	34.3	14	165.8	17	98.9
50 59	0		0		0		4	47.5	7	81.7	11	64.8	5	79.0	14	221.5	19	150.2
60 69	0		0		0		2	30.6	6	78.2	8	56.8	3	55.9	10	161.3	13	112.4
70+	0		0		0		0		1	14.1	1	8.8	2	31.3	7	71.9	9	55.8
Total	13	18.3 (19.0)	15	21.0 (22.4)	28	19.6 (20.6)	17	25.5 (27.0)	34	49.5 (53.2)	51	37.7 (40.3)	22	33.7 (33.1)	57	83.7 (83.4)	79	59.1 (58.6)
95% CI		10.1 32.5		12.4 37.0		13.7 29.9		15.3 43.2		36.2 75.2		29.6 53.4		20.6 50.2		62.9 108.4		46.3 73.2

[a] Figures in parentheses are age-standardised to the 1996 Australian population.

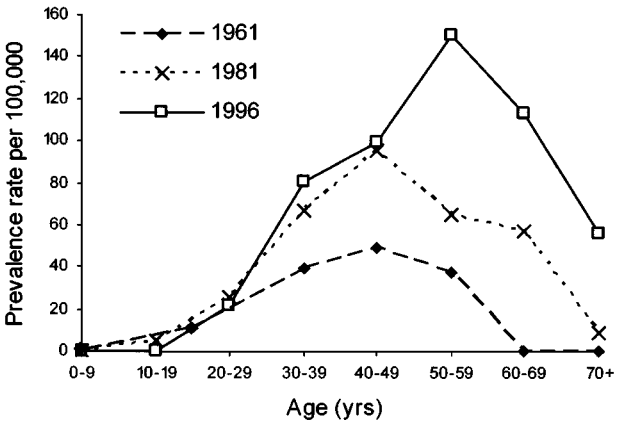

Fig. 1. Comparison between age-specific prevalence rates (all persons) 1961–1996.

females:males consistently increased throughout the study period, from 1.5 in 1961 to 2.0 and 2.6 in 1981 and 1996, respectively. The age-standardised prevalence in females rose by 272% between 1961 and 1996 (trend $\chi^2 = 24.5$, 1 *df*, $P < 0.001$), and in males by 74% (trend $\chi^2 = 2.6$, 1 *df*, $P = 0.11$).

Age-specific prevalence rates by sex for each study year are shown in Table 1 and Fig. 1. The age-specific prevalence rose to a peak in the 5th decade in 1961 and 1981, shifting to the 6th decade for both sexes by 1996. The prevalence of patients with MS in the 7th decade and beyond rose from 0 in 1961 to 35.4 and 79.4 per 100,000 in 1981 and 1996, respectively. This represents a 125% increase in prevalence in this age group between 1981 and 1996, during which time the total prevalence rose by only 57%. A similar trend is observed in the proportion of MS patients over 60 years of age, which increased from 0% in 1961 to 17.6% and 27.8% in 1981 and 1996, respectively; the percentage of the total population in this age group underwent a moderate increase only, from 13.5% in 1961 to 18.9% and 20.8% in 1981 and 1996, respectively.

3.4. Incidence

Incidence rates in the decades 1950 to 1959, mid-1971 to mid-1981, and mid-1986 to mid-1996 are compared in

Table 2
Incidence rate per 100,000 person years in the decades 1950 to 1959, mid-1971 to mid-1981 and mid-1986 to mid-1996[a]

	Cases with onset	Census population[b]	Average annual incidence	95% CI
1950–1959	17	137,428	1.2	–
1971–1981	29	138,719	2.1 (2.3)	1.55–3.37
1986–1996	33	131,303	2.4 (2.5)	1.68–3.47

[a] Figures in parentheses are age-standardised to the 1996 Australian population.

[b] Census population taken at mid-point of each decade studied (1954, 1976 and 1991).

Table 3
Age-specific incidence rates in the decades mid-1971 to mid-1981 and mid-1986 to mid-1996 by sex and for all persons[a]

Age group (years)	1971–1981						1986–1996					
	Males		Females		All persons		Males		Females		All persons	
	n	Incidence/ 100,000	*n*	Incidence/ 100,000	*n*	Incidence/ 100,000	*n*	Incidence/ 100,000	*n*	Incidence/ 100,000	*n*	Incidence/ 100,000
0–9	0	–	0	–	0	–	0	–	0	–	0	–
10–19	2	1.62	2	1.66	4	1.64	0	–	0	–	0	–
20–29	6	5.24	6	5.64	12	5.43	2	1.73	7	6.27	9	3.96
30–39	2	2.64	5	6.73	7	4.66	6	6.13	5	5.35	11	5.75
40–49	4	5.10	2	2.50	6	3.79	0	–	4	5.12	4	2.56
50–59	0	–	0	–	0	–	1	1.67	4	6.48	5	4.11
60–69	0	–	0	–	0	–	1	1.53	2	2.74	3	2.17
70+	0	–	0	–	0	–	0	–	0	–	0	–
Total	14	2.05 (2.20)	15	2.13 (2.49)	29	2.09 (2.34)	10	1.56 (1.52)	22	3.27 (3.36)	32	2.44 (2.45)
95% CI		1.21–3.79		1.34–4.03		1.55–3.37		0.74–2.85		2.07–5.02		1.68–3.47

[a] Figures in parentheses are age-standardised to the 1996 Australian population.

Table 2. There was a substantial and statistically significant increase in the overall crude incidence over the periods ranging from 1950 to 1996 (trend $\chi^2 = 5.67$, $P = 0.017$). The age-standardised incidence rate in females and all persons rose between the two decades 1971–1981 and 1986–1996, but did not change significantly in males (Table 3). The age-standardised F:M incidence ratio rose from 1.1 to 2.2 between the two decades ($P = 0.18$). In addition, the peak incidence rate in males shifted from the 3rd to the 4th decade, while that in females shifted from the 4th to the 3rd decade (Table 3). The age-specific incidence data for all persons is illustrated in Table 3, from which it may be seen that there has been a marked increase in the incidence of MS in groups aged over 50 years.

3.5. Clinical profile

The mean age at disease onset in 1996 was 33.8 years in males and 34.1 years in females. The age-specific distribution of disease onset for 1996 is shown in Fig. 2. The peak age of onset for all persons and females occurs in the age group 21–25 years, but there is a bimodal distribution evident in both sexes, with a later peak at 36–40 years. There was no significant change in age of disease onset between 1981 and 1996.

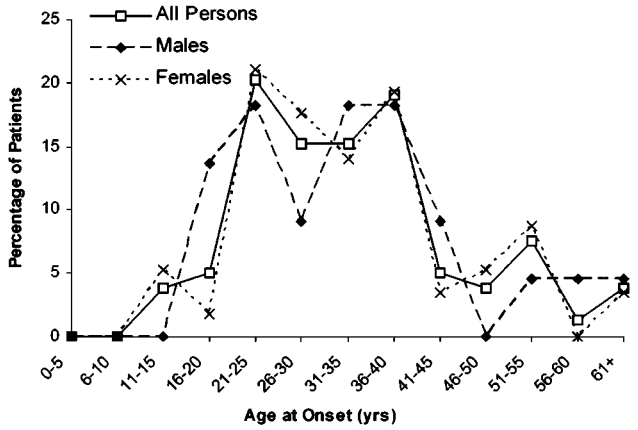

Fig. 2. Distribution of ages at disease onset by half-decades for male, female and all patients in 1996.

Median disease duration in women increased from 12 (range 1–47 years) in 1981 to 16 years (range 1–48 years) in 1996 ($P = 0.72$); and in males fell from 12 to 10 years ($P = 0.63$). The proportion of female patients with disease duration of 30 years or more increased from 10.8% to 21.1% between 1981 and 1996 ($\chi^2 = 1.67$, $P = 0.20$), while that of male patients fell from 15.4% to 9.1% ($\chi^2 = 0.32$, $P = 0.57$).

There was no significant association between sex and clinical course ($\chi^2 = 0.33$, 1 *df*, $P = 0.85$). On the 1996 prevalence day, 63.3% of patients had relapsing–remitting, 16.4% secondary progressive and 20.3% primary progressive disease. There was a significant association between disease course in 1996 and age of onset ($F_{2,76} = 3.36$, $P = 0.04$). Patients with a relapsing remitting course had the youngest mean age of onset at 32 ± 10.3 years, while those with progressive disease from the outset were afflicted at the older mean age of 40.7 ± 14.7 years. The peak age of onset in patients with relapsing–remitting disease and relapsing–remitting disease becoming progressive was 21–25 years, compared with 36–40 years in those with progressive disease from outset.

There was a significant association between disease course (RR, RR-P, P) and median level of disability ($P < 0.001$). Patients with secondary progressive MS had a median Kurtzke Disability Status Score (DSS) of 7, the greatest of the clinical subtypes. Patients with progressive disease were significantly more disabled (median DSS = 6) than the combined RR and RR-P group (median DSS = 3) ($P = 0.015$). The median DSS in males, females and all persons did not substantially change between 1981 and 1996.

4. Discussion

This study shows a further significant increase in MS prevalence compared with earlier studies carried out in

Newcastle, Australia. The prevalence of MS in Newcastle in 1996 of 59.1 per 100,000 is very close to that determined in the Australian Capital Territory on the same prevalence date [9]. The increase in prevalence reflects similar trends observed in several studies carried out in the Northern Hemisphere [10–18]. The population size in Newcastle of approximately 135,000 is small enough, given the available resources, to ensure thorough case ascertainment, and is large enough to avoid the potential pitfalls of case clustering. The use of identical diagnostic criteria and methods of case ascertainment employed in the previous 1981 Newcastle MS epidemiological study justifies their direct comparison after appropriate age standardisation. Comparison with the 1961 prevalence and incidence data is limited somewhat by use of the Allison and Millar [8] classification in that study, and the use of the more recently developed criteria [5] in both subsequent surveys. The older criteria are, however, considered to be more inclusive; their use would tend to have exaggerated the 1961 estimates and thereby to have diminished the increase in prevalence and incidence found in the present study [19].

Increased incidence in females is likely to have contributed in part to the increased female prevalence found in 1996 compared with 1981. Median duration of disease also increased substantially from 1981 to 1996 in females and may have played a role in the prevalence findings in this group.

The possibility that better case ascertainment contributed to the increased incidence and prevalence figures cannot be excluded. Resurvey of an area for a second or subsequent time increases the prevalence yield because of improved awareness in the at-risk population [10]. This finding is principally due to benign or early cases being missed in the initial survey. Recent improvements in MS therapy, particularly the introduction of the interferons in the 1990s, have heightened public awareness of the disease and may have brought patients to medical attention earlier. Although modern investigatory techniques such as MRI were not included in the diagnostic criteria used, their availability may have had a similar effect, consistent with the finding that a greater proportion of patients with shorter disease duration (<10 years) were included in the recent study years. A dominant contribution of females to increasing prevalence, as well as an increasing female:male ratio with serial surveys, has been previously noted [20] and may indicate a diagnostic bias in females [11], but this fact alone is unlikely to account for our findings. The stable proportion of immigrants in Newcastle (12.1% in 1961 vs. 12.2% in 1996) also makes it unlikely that a change in population genetic susceptibility to disease contributed to the increased incidence/prevalence. Rather, sharp changes in incidence, and therefore prevalence, point toward an undetermined environmental or socio-economic factor.

Both increased incidence and survival contributed significantly to the increased prevalence of MS found in several previous epidemiological studies carried out in the Northern hemisphere. In these reports, increased incidence has been attributed to changes in local aetiological factors. Several serial MS epidemiological studies in Scandanavia have shown a trend to increasing incidence, particularly in counties situated on the coastline; incidence in other regions has, however, appeared to fluctuate [14]. Incidence in the province of Nuoro, Sardinia, has increased in each half-decade from 1955–1959 to 1990–1995, and this trend was confirmed for both sexes [12]. By contrast, incidence of MS in the present study increased in females between the study decades 1971–1981 and 1986–1996, but did not change significantly in males. Such discrepancies may in part reflect differing methodologies, particularly case ascertainment sources, between MS surveys and should be interpreted with caution. Nevertheless, a substantial rise in total MS incidence has been shown in several populations in both the northern and now southern hemispheres. Interestingly, the incidence of other diseases with a probable autoimmune basis has increased over the same period [21]. Pooled data suggest that the incidence of Type I diabetes, for example, has increased by 3% annually between 1960 and 1996 [22]. The condition is not fraught by the diagnostic pitfalls and ascertainment biases which affect epidemiological studies of multiple sclerosis.

The present paper confirms a steady and significant rise in MS prevalence and incidence from 1961 to 1996, and is the first such study in the Southern Hemisphere to corroborate this trend over a prolonged period. The homogeneity of the population studied on each occasion and the application of identical study methods suggest a true increase in prevalence, which we attribute to increased incidence in females and increased survival in the MS population of Newcastle.

Acknowledgements

The authors are grateful to the Newcastle neurologists, Professor J.T. Holland and Drs. David Floate, Keith Burton, Jeffrey Blackie and Michael Katekar without whose patience and support the study would not have been possible.

References

[1] Hammond SR, McLeod JG, Millingen KS, Stewart-Wynne EG, English D, Holland JT, et al. The epidemiology of multiple sclerosis in three Australian cities: Perth, Newcastle and Hobart. Brain 1988; 111(Pt 1):1–25.

[2] Hammond SR, English D, de Wytt C, Maxwell IC, Millingen KS, Stewart-Wynne EG, et al. The clinical profile of MS in Australia: a comparison between medium- and high-frequency prevalence zones. Neurology 1988;38:980–6.

[3] PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. PRISMS. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352: 1498–504.

[4] Li DK, Zhao GJ, Paty DW. Randomized controlled trial of interferon-

beta-1a in secondary progressive MS: MRI results. Neurology 2001; 56:1505–13.
[5] Rose AS, Ellison GW, Myers LW, Tourtellotte WW. Criteria for the clinical diagnosis of multiple sclerosis. Neurology 1976;26:20–2.
[6] Armitage P, Berry G. Statistical methods in medical research. Oxford: Blackwell; 1994.
[7] Dobson AJ, Kuulasmaa K, Eberle E, Scherer Y. Confidence intervals for weighted sums of Poisson parameters. Stat Med 1991;10:457–62.
[8] Allison RD, Millar JHD. Prevalence and familial incidence of disseminated sclerosis. (A report to the Northern Ireland Hospitals Authority on the results of a three-year survey). Ulster Med J 1954;23:5–27.
[9] Simmons RD, Hall CA, Gleeson P, Everard G, Casse RF, O'Brien ED. Prevalence survey of multiple sclerosis in the Australian capital territory. Intern Med J 2001;31:161–7.
[10] Compston DA. Methods of genetic epidemiology in multiple sclerosis. In: Compston DA, editor. McAlpine's multiple sclerosis. London: Churchill Livingstone; 1998. p. 45–61.
[11] Forbes RB, Wilson SV, Swingler RJ. The prevalence of multiple sclerosis in Tayside, Scotland: do latitudinal gradients really exist? J Neurol 1999;246:1033–40.
[12] Granieri E, Casetta I, Govoni V, Tola MR, Marchi D, Murgia SB, et al. The increasing incidence and prevalence of MS in a Sardinian province. Neurology 2000;55:842–8.
[13] Grimaldi LM, Salemi G, Grimaldi G, Rizzo A, Marziolo R, Lo PC, et al. High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy. Neurology 2001;57:1891–3.
[14] Gronlie SA, Myrvoll E, Hansen G, Gronning M, Mellgren SI. Multiple sclerosis in North Norway, and first appearance in an indigenous population. J Neurol 2000;247:129–1233.
[15] McDonnell GV, Hawkins SA. An epidemiologic study of multiple sclerosis in Northern Ireland. Neurology 1998;50:423–8.
[16] Pugliatti M, Sotgiu S, Solinas G, Castiglia P, Pirastru MI, Murgia B, et al. Multiple sclerosis epidemiology in Sardinia: evidence for a true increasing risk. Acta Neurol Scand 2001;103:20–6.
[17] Sumelahti ML, Tienari PJ, Wikstrom J, Palo J, Hakama M. Increasing prevalence of multiple sclerosis in Finland. Acta Neurol Scand 2001; 103:153–8.
[18] Wynn DR, Rodriguez M, O'Fallon WM, Kurland LT. A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. Neurology 1990;40:780–6.
[19] Rice-Oxley M, Williams ES, Rees JE. A prevalence survey of multiple sclerosis in Sussex. J Neurol Neurosurg Psychiatry 1995;58: 27–30.
[20] Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. Neurology 2002;58:136–8.
[21] Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84:223–43.
[22] Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes—the analysis of the data on published incidence trends. Diabetologia 1999;42:1395–403.