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High Prevalence and Fast Rising Incidence of Multiple Sclerosis in Caltanissetta, Sicily, Southern Italy

Luigi M.E. Grimaldi[a] Barbara Palmeri[b] Giuseppe Salemi[b] Giuseppe Giglia[b] Marco D'Amelio[b] Roberto Grimaldi[a] Gaetano Vitello[a] Paolo Ragonese[b] Giovanni Savettieri[b]

[a]Unità Operativa di Neurologia, Fondazione Istituto San Raffaele G. Giglio, Cefalù, e
[b]Dipartimento di Neuroscienze Cliniche, Palermo, Italia

Key Words
Multiple sclerosis incidence · Prevalence, Sicily

Abstract
Background: Epidemiological studies conducted in Sicily and Sardinia, the two major Mediterranean islands, showed elevated incidence and prevalence of multiple sclerosis (MS) and a recent increase in disease frequency. ***Objective:*** To confirm the central highlands of Sicily as areas of increasing MS prevalence and elevated incidence, we performed a follow-up study based on the town of Caltanissetta (Sicily), southern Italy. ***Methods:*** We made a formal diagnostic reappraisal of all living patients found in the previous study performed in 1981. All possible information sources were used to search for patients affected by MS diagnosed according to the Poser criteria. We calculated prevalence ratios, for patients affected by MS who were living and resident in the study area on December 31, 2002. Crude and age- and sex-specific incidence ratios were computed for the period from January 1, 1993, to December 31, 2002. ***Results:*** The prevalence of definite MS rose in 20 years from 69.2 (retrospective prevalence rate) to 165.8/100,000 population. We calculated the incidence of definite MS for the period 1970–2000. These rates calculated for 5-year periods increased from 2.3 to 9.2/100,000/year. ***Conclusion:*** This survey shows the highest prevalence and incidence figures of MS in the Mediterranean area and confirms central Sicily as a very-high-risk area for MS.

Introduction

Epidemiological studies conducted in Sicily and Sardinia, the two major Mediterranean islands, have consistently shown elevated incidence and prevalence of multiple sclerosis (MS) and a recent increase in disease frequency [1–3]. The prevalence of MS reaches 151.9/100,000 in rural areas of central Sardinia [4], and 120.2/100,000 in the central and hilly Sicilian town of Enna [1]. The most recent incidence rates range from 5.7 (Sicily) to 6.4/100,000/year (Sardinia) [1, 3].

The first survey of MS prevalence performed 21 years ago in Caltanissetta, a town located 35 km east of Enna, unexpectedly demonstrated a high prevalence [5]. To confirm the central highlands of Sicily as areas of elevated MS prevalence and in which the incidence may be increasing, we performed a follow-up study in Caltanissetta.

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Giovanni Savettieri, MD
Department of Clinical Neurosciences, University of Palermo
Via G. La Loggia, 1
IT–90129 Palermo (Italy)
Tel. +39 091 655 5146, Fax +39 091 655 5147, E-Mail gsavetti@tin.it

Materials and Methods

Area of Investigation

The city of Caltanissetta is located in central Sicily, at approximately 567 m above sea level. The population size on December 31, 2002, was 60,919 inhabitants compared to 60,713 inhabitants on December 31, 1981 (prevalence day of the previous study), indicating a stability of the population of this community in the last 20 years.

The level of public medical care is relatively high in Caltanissetta where a community-based department of neuroscience and a general hospital with a neurology unit have worked in conjunction until recently.

Case Collection and Ascertainment

We used the previous prevalence study as the foundation for the present survey. We made a formal diagnostic reappraisal of all surviving patients from the 1981 prevalence study and of all patients traced during the present survey. Personal contacts were undertaken with all general practitioners and neurologists working in the study area. The local branch of the Italian MS Association (AISM) was also involved in the study. Archives of the Department of Neuroscience of the 'Azienda Unità Sanitaria Locale' No. 2, of the Neurological Unit of the Caltanissetta Hospital, of the Department of Neurology of the University of Palermo and of two major Italian MS centers (Gallarate and Milano San Raffaele) were searched. The retrospective prevalence for the 1981 series was estimated including patients who had had onset of MS before the prevalence day but were diagnosed subsequently (onset-adjusted prevalence rate) [6]. Patients were classified according to the criteria of Poser et al. [7].

As onset of the disease was considered the year of appearance of the first symptom or symptoms attributable to MS.

Data Analysis

To calculate prevalence rates, we searched for patients affected by MS resident in the study area on December 31, 2002. Crude as well as age- and sex-specific prevalence ratios were calculated. Clinical features were also recorded. Crude and age- and sex-specific incidence ratios, based on the reported first symptom of MS, were computed for the period from January 1, 1993, to December 31, 2002.

Results

On December 31, 2002, 101 clinically definite MS patients (31 men, 70 women) were resident in the study area. Thirteen of them were the survivors of the 31 subjects with definite MS identified in the 1981 survey. Fifteen of the 31 were deceased and 3 were untraceable.

Eleven patients identified during the current survey had MS onset before January 1, 1981, but, at that time, they were not found and, as a consequence, had not been included in the previous study.

The mean age at onset was 30.75 years (range 12–55), 28.74 for men and 31.64 for women. The mean age on the prevalence day was 43.22 years (range 15–74), 39.03 for men and 45.07 for women. The mean interval between onset of the disease and diagnosis was 4.63 years (range 1–31) for the whole cohort; it was higher in women (5.34 years) than in men (2.96 years). The average duration of MS from onset to prevalence day was 12.13 years (range 1–38), 10.03 for men and 13.08 for women. Indeed the longest intervals between onset and diagnosis have influenced these data. This is true for those patients whose onset happened before 1981, but who were diagnosed after the first survey. The mean age at onset of patients whose disease started after 1981 was 32.9 years (30.2 in men, 34.2 in women). In this cohort the mean age at diagnosis was 35.8 years (32.6 in men, 37.3 in women) and the mean interval between onset and diagnosis was 2.6 years (2.3 in men, 2.8 in women).

The overall prevalence was 165.8/100,000 population (95% confidence interval = 158.5–173.1), 107.6 for men and 218.0 for women. The age-specific prevalence was found to increase up to the age group of 35–44 years and to decrease thereafter (table 1). Seventy-seven (74.7%) patients had a relapsing-remitting form of MS; 16 (15.5%) were affected by a secondary progressive form, 9 by a primary progressive form (8.8%), and 1 (1%) was affected by a primary progressive form with relapses. As shown in table 2, the retrospective prevalence rate for the 1981 survey was 69.2/100,000 population.

Between January 1, 1993, and December 31, 2002, 56 subjects (19 men and 37 women) had their first symptoms of MS. The average annual incidence was 9.2/100,000 population (95% confidence interval = 8.4–10.0), 6.6 for men and 11.5 for women. Age- and sex-specific incidence rates of MS in Caltanissetta are shown in table 3.

The highest age-specific incidence rate was observed in the age group of 25–34 years for men and 35–44 years for women. The mean interval between the onset and the diagnosis of the disease among incident patients was 1.8 years.

Discussion

In this survey we found a prevalence of 165.8/100,000 and an incidence rate of 9.2/100,000 population. These figures (a 2.4-fold increase in prevalence and an almost 2-fold increase in incidence across 2 decades) are the highest found in the Mediterranean area including Sardinia and confirm the extremely high frequency of MS in Sicily especially in the innermost part of the island. The

Table 1. Age- and sex-specific prevalence of MS in Caltanissetta as of December 31, 2002

Age years	Men			Women			Both sexes		
	cases	population	prevalence (per 100,000)	cases	population	prevalence (per 100,000)	cases	population	prevalence (per 100,000)
0–14	0	5,170	–	0	5,014	–	0	10,184	–
15–24	3	3,948	76.0	3	3,945	76.0	6	7,893	76.0
25–34	9	4,133	217.8	7	4,380	159.8	16	8,513	187.9
35–44	9	4,311	208.8	24	4,732	507.2	33	9,043	364.9
45–54	6	3,757	159.7	22	4,220	521.3	28	7,977	351.0
55–64	3	3,041	98.6	11	3,467	317.3	14	6,508	215.1
65–74	1	2,650	37.7	3	3,365	89.2	4	6,015	66.5
≥75	0	1,805	–	0	2,981	–	0	4,786	–
Total	31	28,815	107.6	70	32,104	218.0	101	60,919	165.8

Table 2. Age-specific, onset-adjusted prevalence of MS in Caltanissetta on January 1, 1981

Age, years	Cases	Population	Prevalence (per 100,000)
0–14	1	14,873	6.7
15–34	24	18,663	128.6
35–54	14	14,406	97.2
55–74	3	10,505	28.6
≥75	0	2,266	–
Total	42	60,713	69.2

fast rising incidence rate suggests that these figures might further increase in the near future.

Increases in the frequency of MS have often been described in follow-up studies [1–4]. The reasons for such increases may include changes in the population's structure, improvement in diagnostic tools, greater awareness of the disease and longer patient survival.

During the interval between the two surveys carried out in Caltanissetta, the population structure did not change. The gender and the age distribution did not change over the three population censuses performed in 1981, 1991 and 2001. The rates of migration were also modest and the population survival has not changed during the follow-up period. Although new diagnostic modalities have become available and the physicians' awareness of MS has increased over time, we consider it unlikely that a greater than 2-fold increase in prevalence and the high and increasing incidence rate observed might be explained by these epiphenomena. Table 4 summarizes MS figures from surveys performed in Sicily. We compared prevalences reported in the first surveys with rates recalculated at the follow-up. The increase in previous prevalence rates, corrected with new patients diagnosed in the follow-up period but who had onset before the first prevalence day, is not sufficient to justify alone the observed increase in MS at the follow-up survey.

The rates found in Caltanissetta are among the highest in Europe, but recently increasing prevalence and incidence rates have also been observed in a follow-up study conducted in Enna, a nearby Sicilian community [1]. A recent follow-up survey conducted in Catania, a coastal municipality of eastern Sicily, also reported an increased prevalence and incidence [2]. By reviewing the thorough MS epidemiological investigation some of us conducted in Monreale (northern coast of the island), an increasing prevalence was recorded between 1981 and 1991 [8], although of a lower magnitude compared to Caltanissetta and Enna. A second follow-up conducted in 2000 failed to show an additional increase in the prevalence rate, suggesting that in Sicily the increasing frequency of MS is not a homogeneous phenomenon [9].

The heterogeneous distribution of MS throughout Sicily and its main features (e.g. coastal vs. central and hilly) might not have a simple explanation. Poser's hypothesis [10] concerning the relationship between Viking invasions and MS dissemination throughout the world may be considered for the municipalities of Caltanissetta, Enna and Monreale whose population experienced an extended period of Viking domination. The high prevalence rates observed in other Sicilian communities characterized by different historical and genetic backgrounds [2, 11] are, however, not consistent with this theory.

Table 3. Age- and sex-specific average annual incidence rates of MS in Caltanissetta (January 1, 1993 to December 31, 2002)

Age years	Men				Women				Both sexes			
	cases	person-years	incidence (per 100,000)	95% CI	cases	person-years	incidence (per 100,000)	95% CI	cases	person-years	incidence (per 100,000)	95% CI
0–24	5	91,180	5.5	2.2–8.8	6	89,590	6.7	4.1–9.3	11	180,770	6.1	4.1–8.1
25–44	11	84,440	13.0	7.9–18.10	25	91,120	27.4	22.1–32.7	36	175,560	20.5	16.8–24.2
45–64	3	67,980	4.4	1.4–7.4	6	76,870	7.8	5.0–10.6	9	144,850	6.2	4.1–8.3
≥65	0	44,550	–	–	0	63,460	–		0	108,010	–	
Total	19	288,150	6.6	4.0–10.3	37	321,040	11.5	8.1–15.9	56	609,190	9.2	6.9–11.9

Person-year counts were obtained by multiplying the corresponding population figures as of the prevalence day (December 31, 2002) by 10. CI = Confidence interval.

Table 4. Comparison of prevalence rates between previous and follow-up surveys performed in Sicily

Municipality	Study year	Prevalence at first survey	Year of follow-up	Prevalence recalculated at follow-up survey (OAPR)	Prevalence at follow-up survey
Monreale	1981	43.3 (31.3–55-3)	1991	47.2 (35.2–59.2)	72.4 (43.6–113.1)
			2000	72.4 (43.6–113.1)	71.2 (60.2–82.2)
Enna	1975	53.2 (41.8–64.6)	1995	67.4 (56.0–78.8)	120.2 (83.8–63.2)
Catania	1995	58.5 (50.7–67.5)	1999	62.1 (59.8–65.4)	92.0 (81.8–103.2)
Caltanissetta	1981	51.1 (43.4–58.8)	2002	69.2 (61.5–76.9)	165.8 (158.5–173.1)

Figures in parentheses indicate confidence intervals. OAPR = Onset-adjusted prevalence rate defined according to Poser's definition.

Moreover, even in Sicily, the rates registered in Caltanissetta and Enna represent a unique occurrence. Both towns are located in the relatively isolated inner Sicily and have a stable population with a minimal immigration for many centuries, a setting where genetic influences may have been greater. These conditions and contingencies may, in fact, have permitted a higher rate of inbreeding and consequently a more homogeneous genetic background in the inner island. A similar phenomenon had already been described in Sardinia where clusters of particularly high prevalence and incidence rates have been reported [12]. The case for MS parallels that of other complex diseases with known immunopathogenesis and definite genetic component like type I diabetes [13]. In Italy, a south-to-north increasing gradient for young-onset diabetes had been previously described [14], but unexpectedly, a high frequency of type I diabetes has recently been reported in Sicily [15]. In these semi-isolated populations, recent environmental events may have interacted with a particular genetic background, modifying the risk for autoimmune diseases. This effect is more evident in genetically homogeneous populations with a higher probability of intracommunity inbreeding, like those located in inner Sicily and Sardinia. By contrast in coastal communities the more frequent interactions with other populations may have, over the centuries, buffered the effects of genetic influences. The evolution of MS epidemiology in central Sicily should be closely monitored in the coming years.

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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*

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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).

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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.

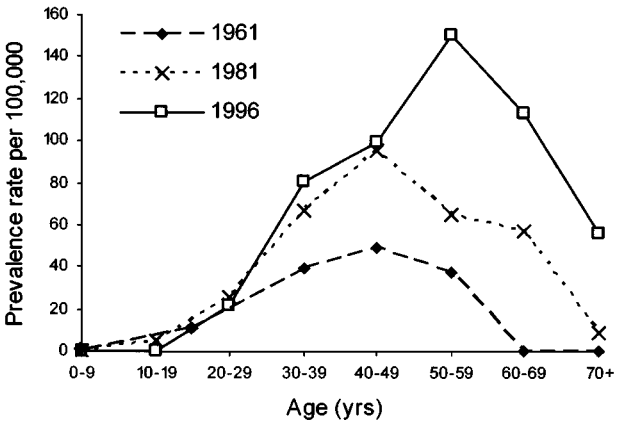

Fig. 1. Comparison between age-specific prevalence rates (all persons) 1961–1996.

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.

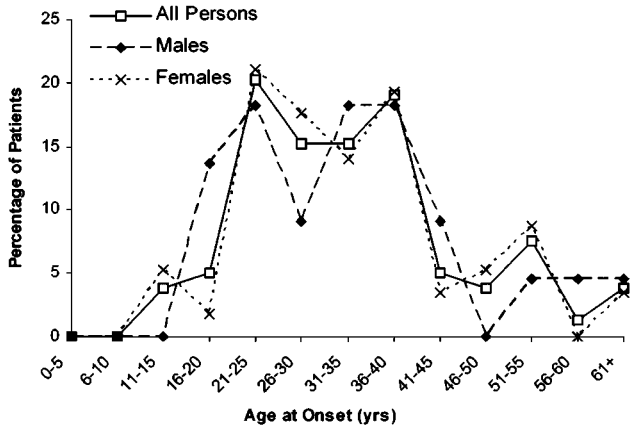

Fig. 2. Distribution of ages at disease onset by half-decades for male, female and all patients in 1996.

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.

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The increasing incidence and prevalence of MS in a Sardinian province

E. Granieri, MD; I. Casetta, MD; V. Govoni, MD; M.R. Tola, MD; D. Marchi, MD; S.B. Murgia, MD; A. Ticca, MD; M. Pugliatti, MD; B. Murgia, MD; and G. Rosati, MD

Article abstract—*Objective:* To verify incidence rates and their temporal trend in a homogeneous, ethnically, and genetically distinct population of central Sardinia (the Nuoro province). *Background:* Intensive epidemiologic studies carried out in Sardinia since the 1970s have suggested that the prevalence and incidence of MS are much higher in this Mediterranean island compared with those found on mainland Italy. *Methods:* The study area had a population of approximately 274,000 people in the 1991 census. The authors adopted a complete enumerative approach by reviewing all possible sources of case collection available in the investigative area. *Results:* Based on 469 MS patients, the mean annual incidence for 1955 to 1995 was 4.18 per 100,000 (or 4.3 per 100,000 if age- and sex-adjusted to the European population). The incidence, averaging 1.95 per 100,000 during 1955 to 1959, rose progressively over time, reaching rates of 6.6 in the quinquiennium 1985 to 1989 and 6.4 per 100,000 in 1990 to 1995. On December 31, 1994, the crude prevalence, based on 415 MS patients alive in the study area, was 151.9 per 100,000 (156.6 if adjusted to the European population). *Conclusion:* These incidence and prevalence rates are the highest to date that have been estimated for a large community in southern Europe, and they constitute some of the highest rates in the world. Based on other surveys, these results reinforce the position of Sardinia as a higher and rising prevalence area for MS compared with other Mediterranean populations. Genetic and social–historic data strengthen the hypothesis of the environmental role and genetic factors among Sardinians in determining the notable difference in MS frequency between Sardinians and other Mediterraneans.

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The epidemiologic studies of the last two decades indicate that the distribution of MS in southern Europe, particularly in Italy and Spain, is more complex than was supposed in the past, when a latitude-related model was commonly accepted.[1-3] In fact, the MS frequency in Europe seems uneven, with substantial variations between areas at the same latitude, and also within countries.[4-7] With regard to the Mediterranean areas, all descriptive studies conducted in Sardinia during the last two decades by our research groups indicate that this Italian island has twice the prevalence and incidence of MS compared with continental Italy.[8-11] The most recent survey performed in northwestern Sardinia indicated a prevalence of 102.6 cases per 100,000 population (in 1991) and a notable increase in MS incidence over time. Although averaging 2 per 100,000 from 1962 to 1971, MS incidence rose to 5 per 100,000 from 1977 to 1991.[12] These results represent striking exceptions to the north–south gradient in Europe and suggest that this island may be considered an area of high and increased risk for MS. We sought to verify the morbidity estimates of MS and its temporal trend in the well-defined areas of central Sardinia in the province of Nuoro, where studies in the 1980s indicated a high risk for the disease. The living population of approximately 270,000 persons is a self-contained and genetically characterized community that was isolated for centuries and excluded from any contact with other ethnically distinct populations occupying the island.

Methods. *Area of investigation.* The province of Nuoro includes 102 towns and villages. In the southern interior part of the province lies Barbagia, an area where MS epidemiologic studies were performed by our research group in the 1970s.[8,9] The mean population during 1955 through 1995 was 273,248 people (135,950 men, 137,298 women). The mean population density was 39 inhabitants/km^2 (range, 8 to 228 inhabitants/km^2). Only 37,527 people inhabit the town of Nuoro, whereas the rest of the population lives in two smaller towns (with a total population of approximately 10,000 people), and rural or sparsely populated areas.

The population is ethnically homogeneous, originating from an early split in the Caucasoid group, and is different from other European populations, Italians included. The origins of the Sardinian people in prehistory are not well known; however, historic, anthropologic, and genetic studies indicate that they are an ethnically distinct, homogeneous group. The original inhabitants of the island,

From the Multiple Sclerosis Center (Drs. Granieri, Casetta, Govoni, and Tola) Department of Neurology, University of Ferrara; the Section of Neurology and Neurorehabilitation (Drs. Marchi, S.B. Murgia, and Ticca), Nuoro Hospital; and the Department of Neurology, University of Sassari (Drs. Pugliatti, B. Murgia, and Rosati), Italy.

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Address correspondence and reprint requests to Dr. Enrico Granieri, Clinica Neurologica, Università di Ferrara, Corso della Giovecca 203, I-44100 Ferrara, Italy; e-mail: gnr@dns.unife.it

particularly those who settled in the mountainous and hilly areas of the interior part of central Sardinia, given the inaccessibility of the territory, had been excluded from any contact with other ethnically different populations who occupied the coastal and flat parts of Sardinia in subsequent centuries. Successive waves of invasions by Phoenicians, Carthaginians, Romans, Vandals, Byzantines, Arabians, Ligurians, Tuscans, Spaniards, and Piedmontese failed to penetrate the wild and barbarous inland, which is represented mostly by the province of Nuoro and particularly by Barbagia. Barbagia, the region of the barbarians, according to the name assigned by the Romans, has preserved an ethnic and genetic peculiarity among aboriginal Sardinians that differs from the remainder of continental Italy.[13] The particular ethnic structure of Sardinians has also been emphasized in a review on MS genetic epidemiology in the world.[14] Comparative studies on human leukocyte antigen (HLA) allelic frequencies have clearly demonstrated the genetic isolation of Sardinians from other Italian and European populations.[15,16] The permanence of certain linguistic relics in the Nuorese languages and the singularity of the family names, which are completely different from those of the rest of Italy, give further support to the previous assumption.[17]

From the end of World War II until 1980, there was mass emigration from the province of Nuoro to the industrialized regions of northern Italy and central northern Europe (based on the official data, the average annual emigration from the province during this period was 520 subjects per 100,000 population). Afterward, the migration flux was unremarkable and did not change substantially over time. Almost all the migrants from and to the province of Nuoro are Sardinians, and the ethnic composition of the population has remained primarily stable over time.

The study area was rural by tradition, most workers having been employed in agriculture and sheep breeding, the latter having been the most important activity in the province in the past. After the last war, the standard of living was low compared with the rest of Italy, where processes of modernization and industrialization were in progress. During the last few decades, the structure of the economy has undergone a slight change and is now also based on the service and construction industries associated with urban development. There is only one minor industrial sector, whereas tourism has more recently been reevaluated, mainly in the coastal zones. According to the data of the 1991 General Census, the active working population is employed as follows: agriculture and breeding, 19%; industry, 26.4%; and tertiary activities, 54.6%.

The health care system has been present in the area for many decades, and the level of medical organization is relatively high. There is a general hospital with a neurologic ward and service, and a motor rehabilitation unit located in the town of Nuoro. Other neurologic outpatient services and rehabilitation facilities are also available in the study area. Some patients are cared for in other hospitals of the bordering provinces of Sardinia, mostly in the university neurologic departments of Sassari and Cagliari, where MS centers have been operative for many years. The level of medical organization has improved during the study period in parallel with the general improvement achieved throughout the rest of Italy as far as diagnostic tools, medical facilities, and neurologic services are concerned. As in other parts of Italy, detailed CSF studies and MRI became available routinely for patients referring to the neurologic services of the Nuoro province in the middle 1980s.

Case collection and ascertainment. Our research group has previously investigated MS scattered in Sardinia and, in particular, some areas of the province of Nuoro, Barbagia, and Macomer. Therefore, MS patients traced during previous studies constituted the starting point for this survey. Other MS patients were drawn from the following sources: archives of discharge diagnoses from the hospital of Nuoro, other hospitals on the island (Lanusei, Olbia, Oristano, Ozieri), the Sassari and Cagliari university hospitals, the neurologic practices serving the community, files from motor rehabilitation and chronic care services, membership rolls of the local branch of the Italian MS Association (AISM), and archives of the National Pension Institute and National Health Insurance scheme. We reviewed the sources from 1950 to the present by manual screening of in- and outpatient records, and patient lists. Cooperation from general practitioners, chemists, and social workers employed in the region was also obtained. Other sources included the archives of national centers where several patients from various parts of Italy go for clinical consultation. The active collaboration of some members of AISM and of other service organizations allowed us to recruit some MS patients who were not identified from other sources.

All patients with diagnoses of MS, demyelinating disease, encephalomyelitis, myelitis, myelopathy, optic neuritis, and ataxia were reviewed by trained neurologists of our team. The inquiry included a detailed interview, clinical and neurologic examination, and further analysis of all clinical documents. For the deceased patients, close relatives were interviewed and available clinical files were examined. The senior neurologists of our team reviewed all data collected for each patient to verify the validity of the diagnosis and to establish the date of clinical onset of the disease, defined as the time of the first symptom referable to MS. Because criteria involving imaging procedures, laboratory, or other diagnostic tests were not applicable to every patient in this survey setting, case definition was based on both the criteria of Poser et al.[18] and on clinical diagnostic criteria.[19,20] Information regarding whether patients were alive and residing in the study area at prevalence day was obtained from register offices of the communes.

From the provisional list of 565 putative cases eligible from the incidence estimate, we excluded 29 patients with onset outside the study area, 41 patients with onset before 1955 or after 1995, 16 patients whose diagnosis of MS was excluded, and 10 patients whose clinical records did not allow us to make a probable or definitive diagnosis and who were not available for further evaluation. From the original list of 564 patients potentially eligible for a prevalence estimate, we excluded 48 patients living outside the province of Nuoro, 72 patients who died before the prevalence point, 16 patients whose final diagnosis was other than MS, 6 patients with disease onset after 1994, and 7 patients with suspected or possible MS. Thus, the final study consisted of 469 patients with MS onset occurring from 1955 through 1995 while they were residing in the study area, and 415 MS patients living in the study area on December 31, 1994.

Table 1 *Age- and sex-specific mean annual incidence rates of MS in the province of Nuoro, 1955 to 1995*

	Mean annual incidence rate per 100,000		
Age group, y	Total	Men	Women
10–14	1.13	0.5	1.8
15–19	8.5	6.1	11
20–24	14.35	8.3	20.6
25–29	13.4	11.5	15.2
30–34	10	6	13.8
35–39	9.2	6.45	11.8
40–44	7.86	5.6	10
45–49	3.8	3	4.5
50–54	1.5	1.1	2
55+	0.5	0	0.98

Table 2 *Incidence trend of MS in the province of Nuoro, 1955 to 1995*

Period	No. of patients	Incidence rate per 100,000	Mean age at onset, y; ± SD
1955–1959	26	1.95	28.6 ± 11
1960–1964	26	1.85	28.3 ± 10
1965–1969	33	2.3	30.8 ± 11
1970–1974	42	3	27.6 ± 9.4
1975–1979	67	4.8	28.4 ± 9.2
1980–1984	80	5.8	28.6 ± 9.8
1985–1989	91	6.6	28.0 ± 8.7
1990–1995	104	6.4	28.4 ± 9
Total	469	4.18	28.5 ± 9.7

Ninety-seven percent of patients included in this study were born within the study area (90%) or elsewhere in Sardinia. Most patients born in mainland Italy or abroad have typical Sardinian surnames.

Statistical analysis. Ninety-five percent CIs were calculated assuming a Poisson's distribution.[21] Crude rates were directly adjusted to the Italian (1981 General Census) and European populations.[22] Student's *t*-test was used to compare two averages, and the z test was used to compare two rates. The comparison between two adjusted rates was performed by calculating the variance of the difference between two directly standardized rates and the z value. The statistical significance of temporal variation in incidence rates was evaluated with the Armitage test for linear trends.[23]

Results. *Incidence.* From 1955 through 1995, 469 subjects (158 men and 311 women) living in the province of Nuoro first showed symptoms that were later determined to represent the clinical onset of MS. They were considered to be incidence cases in the year in which they showed onset of symptoms. The crude mean annual incidence rate was 4.18 per 100,000 people (95% CI, 3.8 to 4.62). The two sexes differed (men: incidence rate, 2.83 per 100,000; 95% CI, 2.41 to 3.3; women: incidence rate, 5.52 per 100,000; 95% CI, 4.9 to 6.18; $z = 6.99$, $p < 0.01$). The female-to-male ratio was 1.95.

The sex- and age-adjusted rate for the Italian population was 4.3 per 100,000 (2.98 for men, and 5.42 for women). The directly adjusted rate for the European population was 4.3 per 100,000 people.

The age at onset (mean ± SD) was 28.5 ± 9.7 years for the total population, 28.5 ± 9.7 years for men, and 27.9 ± 9.5 years for women (a nonsignificant difference). Table 1 shows the age- and sex-specific incidence rates. The highest annual incidence rates were observed between ages 20 and 24 for the total population (12.3 per 100,000) and for women (17.6 per 100,000), and between ages 25 and 29 for men (9.5 per 100,000). The difference in incidence between the two genders was significant for the age groups 15 to 24 years and 30 to 39 years ($p < 0.05$).

Table 2 shows the average annual incidence rates by year of onset for 5-year intervals from 1955 to 1995. The observed incidences increased from 1.95 per 100,000 (95% CI, 1.27 to 2.86) from 1955 through 1959 to 6.6 per 100,000 from 1985 to 1989 (95% CI, 5.3 to 8.1), to 6.4 per 100,000 (95% CI, 5.25 to 7.8) during the last 6-year study period ($\chi^2 = 91.48$, $df = 7$, $p < 0.001$). The increasing trend was confirmed for both sexes ($\chi^2 = 25.75$ for men; $\chi^2 = 66.28$ for women; $df = 7$, $p < 0.001$). During the study period, the mean age at onset of the disease did not change over time (see table 2). The incidence rate did not change significantly (4.1 per 100,000 per year) if the patients were classified according to widely used clinical diagnostic criteria.[19,20]

Prevalence. On the day selected, December 31, 1994, 415 MS patients (128 men and 287 women) were living in the study area. Their mean age was 40.6 ± 12.6 years: 41.6 ± 12.6 for men and 40.2 ± 12.5 for women, a nonsignificant difference. The total population was 273,146 persons (134,905 men and 138,241 women), and the crude prevalence rate was 151.9 cases per 100,000 population (95% CI, 137.6 to 167.7). The crude prevalence rate for men was 94.9 per 100,000 (95% CI, 79.5 to 113,2) and for women was 207.6 per 100,000 (95% CI, 184.7 to 234.4), a significant difference ($z = 7.6$). The directly adjusted rate for the Italian population was 148.8 per 100,000: 93.04 per 100,000 for men and 250.5 per 100,000 for women. The adjusted rate for the European population was 156.64 per 100,000.

The mean duration of the disease from onset to prevalence day was 16.3 ± 9.7 years: 16.1 ± 8.9 years for men and 16.5 ± 6 years for women (not significant).

Table 3 shows age- and sex-specific prevalence rates. They reached a maximum for the age groups 35 to 44 years for the total population (323.7 per 100,000) and for men and women considered separately (219.3 per 100,000 for men and 434 per 100,000 for women). The significant difference in prevalence rates between men and women was confirmed in the age range 15 to 64 years.

The adjusted prevalence in 1994 was significantly higher than in 1985 (102 per 100,000 for men, 94 per 100,000 for women; $z = 4.56$).

The prevalence rate was higher in the urban population of the town of Nuoro than in the other communities and rural areas of the province (200 per 100,000 for Nuoro versus 144.4 per 100,000 for other communities and rural areas; $z = 2.28$, $p < 0.05$).

Table 3 *Prevalence rates (per 100,000) of MS in the Nuoro province (December 31, 1994)*

	Total		Men		Women	
Age group, y	N	Rate	N	Rate	N	Rate
0–14	1	1.96	0	0	1	4
15–24	28	59.1	7	29	21	90.43
25–34	121	284.1	34	157.8	87	413.5
35–44	115	323.7	40	219.3	75	434
45–54	87	284.3	29	194.4	58	370
55–64	48	167.4	11	80.9	37	245.4
65–74	11	53.1	5	53.5	6	52.9
75+	4	23.2	2	27.2	2	20.2

Other features. Disease course at onset was primary progressive in 12.9% of patients and relapsing–remitting in the remaining patients. According to Kurtzke's Expanded Disability Status Scale (EDSS),[24] 56% of prevalence patients showed either no disability or minimal disability (EDSS score, 0 to 3.5 points), 17.5% exhibited relatively severe disability (EDSS score, 4 to 5.5 points) and 26.5% required partial or complete assistance (EDSS score, >5.5 points).

The mean interval between symptom onset and diagnosis was 4.61 years. The average lag time between symptomatic onset and diagnosis shortened over time from 6.3 years for patients with onset before 1974 to 1.9 years for patients with onset after 1984. The average lag time between onset and diagnosis was less than 1 year for patients with onset after 1990.

Pyramidal motor (40.1%) and sensory (42.9%) disorders were the most common presenting symptoms.

The overall MS population included 19 sibling pairs and 8 parent–children pairs.

Discussion. We found a prevalence of 152 per 100,000 and an incidence rate of 4.2 per 100,000 per year in the province of Nuoro. These are the highest rates estimated for a large community in southern Europe, and some of the highest in the world.[3,25] We adopted a complete enumerative approach by reviewing all possible sources of case collection throughout the study area and took advantage of a long-term epidemiologic surveillance in this region implemented by neurologists operating in Sardinia since the 1960s, most of whom belong to this research group.[8,9,26-29] The population size of this study can be considered suitable for accurate case finding because it was manageable within the resources of our research team, and for adequate precision. Conversely, the well-defined community residing in the province of Nuoro is not so small as to be subject to the quirks of clustering. Given the intensive methodological approach of case ascertainment and the repeated surveys in the same area, which usually led to a more careful case collection as a result of greater interest in the disease,[7,30] any underascertainment was expected to be minimal. Moreover, it is unlikely that newly diagnosed patients would go outside the island for hospitalization, because Sardinia is quite far from the mainland and, at the same time, it offers a widespread network of well-equipped public general hospitals, including two departments of neurology at the universities of Sassari and Cagliari, and rehabilitation facilities, providing national services to which general practitioners refer their patients.

On the basis of the previous surveys, our research group cited evidence indicating that the risk for MS is higher in Sardinia than in other parts of Italy,[8-11] disproving the hypothesis that MS distribution follows a latitude-related gradient, at least in Italy and in southern Europe,[2] and prompting the assumption that the frequency of MS in Sardinia is one of the highest in the world.[3] An increasingly high MS incidence was reported from northwestern Sardinia by some researchers of our team using the same methodology.[12] The incidence estimates from our study did not seem to reflect a steady pattern that was also present in previous years and was unrecognized because of different case collection completeness, but rather because of an increasing incidence during the last three decades. Some indications would confirm the latter explanation: The study area has already been investigated intensively by our own research group using the same methodology, giving morbidity figures higher than that of the rest of Italy, but considerably lower than the current estimates.[8,9] Analogous findings have emerged from the other study carried out in the bordering northern area of Sardinia, where an epidemiologic long-term surveillance study has also been implemented.

The possibility that improvement in diagnostic techniques and medical facilities during the past decades could have led to an apparent excess of cases in the last few years, by allowing more complete ascertainment even for mild and benign forms of MS, may be an alternative explanation. However, the percentage of patients showing no disability or minimal disability in our prevalence patients (56%) was close to that (50%) reported in a previous prevalence study in the same area[28] in 1971, suggesting that increased recognition of mild forms could not have played a crucial role in the morbidity estimates over time.

Moreover, substantial stability of incidence rates was demonstrated in an analogous study,[31] which we performed using the same methodology in the province of Ferrara—in northeastern mainland Italy—where, on par with the current study area and in the rest of Italy, new diagnostic tools have become available during the last 15 years (figure). However, differences in case ascertainment as a result of new diagnostic technology were reduced by using clinical inclusion criteria,[19,20] which are strictly clinical and not influenced significantly by time-dependent use of modern laboratory and imaging investigations. It is now accepted that the overall epidemiologic figures remain essentially unchanged when using either clinical criteria or the diagnostic criteria of Poser et al.[32]

Thus, a real change in disease frequency seems to be a more likely explanation for the upward trend

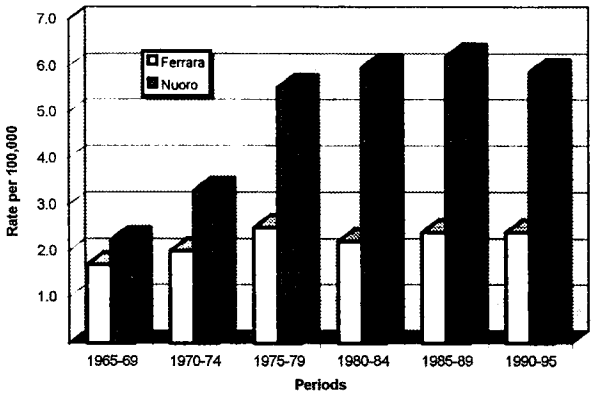

Figure. Incidence trend of MS in the provinces of Ferrara and Nuoro.

rather than methodological issues, which is based on an improvement in medical background because geographic areas where incidence rates of MS exhibit a stable, increasing, or decreasing pattern have been affected by these improvements.

The advances in diagnostic tools, medical facilities, public awareness, and so forth, have certainly led to a significant shortening of diagnostic latency. The lag time between onset and diagnosis, in fact, has been considerably reduced over time in the current population. Some changes in ascertainment factors must be acknowledged. However, our concurrent study with similar ascertainment in Ferrara showed no change in incidence.[31]

Therefore, taken together, the current figures from an ethnically homogeneous community that has not been influenced by substantial migratory flux in the last three decades, leave little doubt that Sardinia is an extremely high risk area for MS in southern Europe. Moreover, this study suggests that the risk is increasing with time.

It is well known that Sardinians are an ethnically homogeneous population, with a genetic structure somewhat different from that of the rest of continental Italian and European people.[13,15] Thus, the differences in MS frequency could reflect differences in genetic patterns, which could determine different susceptibility to the disease in Sardinians compared with other whites.[33-36] In this context, it has been suggested that the higher frequency of MS among Sardinians may depend on the higher frequency of DQB1*0201 and *0302 alleles.[37] The same alleles are related to disease susceptibility in other autoimmune diseases such as juvenile diabetes.[38,39] The distribution of juvenile diabetes in the world is similar to that of MS.[40,41] It is of interest that, among Sardinians, the incidence of insulin-dependent diabetes mellitus shows a temporal pattern that resembles the MS incidence trend: The incidence rates are now at least five times higher than those reported from mainland Italy, and they are the second highest in Europe, after Finland.[42] Sardinians may be genetically prone to insulin-dependent diabetes mellitus because of a particular HLA genotype with a scarcity of protective alleles and a high frequency of susceptible alleles compared with other white populations.[43] A similar hypothesis may be claimed for MS.

Even in populations with a high prevalence of susceptibility haplotypes, in which the supremacy of genetics over the environment seems to be emphasized, nongenetic factors must have a role if a steep increase in incidence is recorded. For insulin-dependent diabetes mellitus and MS, an increasing temporal trend has been detected in Sardinia during the past 20 to 30 years, which is too short a period for substantial changes in the genetic pool. Environmental factors must, therefore, be suspected. In other words, the increase in MS frequency may be related to environmental and socioeconomic changes as a result of the progressive modernization occurring in Sardinia after World War II. Having lost the protection of geographical isolation, the Sardinians were increasingly prone to a growing bulk of new environmental factors, such as increased contact with continental people; improvement in economy and general sanitary conditions with a postponement of childhood infection acquisition; changes in dietary habits, in overall lifestyle, and in industrial development; and growing exposure to toxicants and possibly other exogenous risk factors that, according to the epidemiologic literature, could play a causal role in the etiology of MS.[4,44,45] However, the putative role of unknown environmental factors still remains elusive.[6,46]

The majority of the incidence studies on MS among whites indicate that the distribution of incidence of the disease according to age has a peak in age groups between 25 and 40 years.[31,47,48] In the current study, the highest annual incidence rates are expressed in the age group between 20 and 24 years for both the total population and for female patients, and in the age group between 25 and 29 years for male patients. The mean age of clinical onset did not change during our study period. These findings are in agreement with the fact that, among Sardinians, the proportion of early MS onset is particularly high, perhaps in relation to their peculiar genetic characteristics.[49] These genetic characteristics could exert some influence on the age of clinical onset of the disease.

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High incidence and increasing prevalence of MS in Enna (Sicily), southern Italy

Article abstract—Twenty years after a first survey, a follow-up study was performed on the prevalence of MS in Enna (Sicily), southern Italy. The prevalence of definite MS rose from 53 to 120.2 per 100,000 population. The incidence of definite MS for the period 1986 to 1995 was 5.7 per 100,000 per year. The innermost part of Sicily shows an elevated prevalence of MS, second only to Sardinia in the Mediterranean area.

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L.M.E. Grimaldi, MD; G. Salemi, MD; G. Grimaldi, MD; A. Rizzo, MD; R. Marziolo, MD; C. Lo Presti, MD; D. Maimone, MD; and G. Savettieri, MD

Epidemiologic studies performed in the past decades indicate that the latitude-related model proposed to interpret the distribution of MS[1] does not apply to many regions of the Mediterranean area. Sicily and Sardinia, the two major Mediterranean islands, show an elevated frequency of MS and a recent increase in disease frequency.[2-8] The prevalence of MS in rural areas of Sardinia reaches the rate of 151.9 per 100,000 population.[2] The highest prevalence reported in Sicily so far has been in the town of Monreale (72.4 per 100,000 population).[7] The most recent incidence rates range from 3.3 (Sicily) to 4.2 (Sardinia).[2,7]

The first survey demonstrating an unexpectedly high prevalence of MS in Sicily was performed in Enna 25 years ago.[3] To confirm the rise of MS prevalence in the Mediterranean area we assessed the prevalence and incidence of MS in a follow-up study based on the town of Enna.

Materials and methods. *Area of investigation.* The city of Enna is located in central Sicily, at the top of a mountain (mean altitude, 931 m above the sea). The population, on prevalence day December 31, 1995, was 28,273 inhabitants. The population on December 31, 1975 (i.e., prevalence day of the previous study) was 28,189 inhabitants, indicating a substantial stability of this community. The size and the structure of the population did not change over 20 years. We asked the Regional Epidemiologic Office for particular events occurring in Enna during the past 25 years (epidemics, changes in daily living, migrational flows, diet).

The national health care system was established in this area in 1946. The level of public medical care is relatively high: Enna hosts a general hospital with a neurology unit; other neurologic outpatient services and rehabilitation facilities are available in the area.

Case collection and ascertainment. We employed various strategies to identify people suspected of having MS in the town of Enna. The prevalence survey performed in 1975 constituted the basis for the present survey. We made a formal diagnostic reappraisal of all living patients considered in the original study. Personal contacts were undertaken with all general practitioners and neurologists practicing in Enna. The population was also informed through local TV. The local chapter of the Italian MS Association was involved in the study and contributed to the identification of patients. Archives of the Neurologic Unit of the Enna Hospital, of all major MS centers of Italy, and of all centers of rehabilitation located in Enna were searched. Patients were classified according to the criteria of Poser et al.[9]

Data analysis. To calculate prevalence ratios, we searched for patients with MS who were living and resident in the study area on December 31, 1995. Crude as well as age- and sex-specific prevalence ratios were calculated. Clinical features were also recorded.

Crude as well as age- and sex-specific incidence ratios were computed for the period January 1, 1986 to December 31, 1995.

Results. On December 31, 1995, 34 patients with clinically definite MS (15 men, 19 women) were resident in the study area. Five of them were the survivors of the 15 subjects with definite MS identified during the 1975 survey. In four subjects, MS began before January 1, 1975, but at that time they were not found and, as a consequence, not included in the previous study.

The mean age at onset was 24.3 years (range, 9 to 41 years), 25.3 years for men and 23.5 years for women. The mean age on prevalence day was 37.6 years (range, 19 to 67 years), 38.1 years for men and 35.4 years for women. The mean interval between onset of the disease and diagnosis was 4.2 years (range, 1 to 15 years); it was higher in men (5.7 years) than in women (3.0 years). The average duration of MS from onset to prevalence day was 12.7 years (range, 1 to 32 years), 13.0 years for men and 12.4 years for women.

The overall prevalence was 120.2 per 100,000 population (95% CI, 83.8 to 167.2), 110.5 for men and 129.2 for women. Age-specific prevalence was higher between 25 and 54 years and decreased thereafter (table 1).

Twenty-three patients have a relapsing-remitting course of disease; 10 patients were affected by a secondary progressive form, and one patient had a primary disease progressive course.

Onset-adjusted prevalence calculated for the 1975 study

From the Department of Neuroscience (Dr. L. Grimaldi), Azienda Unita Sanitaria Locale 2, Caltanissetta; Institute of Neuropsychiatry (Drs. Salemi and Savettieri), University of Palermo; Neurology Unit (Drs. G. Grimaldi and Rizzo), Umberto I Hospital, Enna; Neurology Unit (Dr. Marziolo), Sant'Elia Hospital, Caltanissetta; Sicilian Rehabilitation Consortium (Dr. Lo Presti), Enna; and Neurology Unit (Dr. Maimone), Garibaldi Hospital, Catania, Italy.

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Address correspondence and reprint request to Dr. G. Savettieri, Institute of Neuropsychiatry, University of Palermo, Via Gaetano La Loggia 1-90129 Palermo, Italy; e-mail: gsavetti@tin.it

Table 1 *Age- and sex-specific prevalence of MS in Enna as of December 31, 1995*

	Men			Women			Both sexes		
Age, y	Cases, n	Population	Prevalence (per 100,000)	Cases, n	Population	Prevalence (per 100,000)	Cases, n	Population	Prevalence (per 100,000)
0–14	0	2,757	—	0	2,604	—	0	5,361	—
15–24	2	2,230	89.7	3	2,202	136.2	5	4,432	112.8
25–34	5	1,985	251.9	6	2,149	279.2	11	4,134	266.1
35–44	3	1,947	154.1	5	2,103	237.8	8	4,050	197.5
45–54	3	1,558	192.5	5	1,741	287.2	8	3,299	242.5
55–64	1	1,412	70.8	0	1,722	—	1	3,134	31.9
65–74	1	1,013	98.8	0	1,264	—	1	2,277	43.9
75+	0	667	—	0	919	—	0	1,586	—
Total	15	13,569	110.5	19	14,704	129.2	34	28,273	120.2

was 67.4 per 100,000 population. Table 2 shows the age-specific, onset-adjusted prevalence on January 1, 1975.

Between January 1, 1986 and December 31, 1995, 16 subjects (seven men and nine women) living in the study area had their first symptoms of MS. The average annual incidence was 5.7 per 100,000 population (95% CI, 2.0 to 10.5), 5.1 for men and 6.1 for women. Sex- and age-specific incidence ratios of MS in Enna are shown in table 3. The highest ratio was observed in the age group 15 to 24 years.

The mean period between the onset and the diagnosis of the disease among incident patients was 3.0 years; it was higher in women (4.0 years) than in men (1.7 years). No HLA characterization of the population of Enna is available at present. No epidemics, changes of daily living, or variation of migrational flows or diet have been recorded.

Table 2 *Age-specific, onset-adjusted prevalence of MS in Enna at January 1, 1975*

Age, y	Cases, n	Population	Prevalence (per 100,000)
0–14	0	7,403	—
15–34	12	8,266	145.2
35–54	5	6,630	75.4
55–74	2	4,869	41.1
75+	0	1,021	—
Total	19	28,189	67.4

Discussion. We found a prevalence of 120.2 per 100,000 and an incidence ratio of 5.7 per 100,000 population in Enna City. These are among the highest ratios found in the Mediterranean area (second only to Sardinia and at the level of northern European countries) and confirm the high frequency of MS in Sicily. Nonetheless, we might have even underestimated the ratios of MS in this area: assuming the common male:female ratio of about 1:2, the expected number of women with MS should have been higher than the observed. This discrepancy could be related to a selective underreporting.

As in Sardinia[2] and in Monreale,[7] the city of Enna shows an increase in MS prevalence. It is unknown whether this increase depends on a true change in MS frequency, related to environmental or socioeconomic changes, or reflects an improved case ascertainment depending on greater awareness and on new and more sophisticated diagnostic procedures. Incidence remained stable along the incidence period studied (1986 to 1995). Although the interval between the onset and the diagnosis of MS was 3.9

Table 3 *Age- and sex-specific average annual incidence rates of MS in Enna (January 1, 1986–December 31, 1995)*

	Men			Women			Both sexes		
Age, y	Cases, n	Person-years*	Incidence (100,000)	Cases, n	Person-years*	Incidence (100,000)	Cases, n	Person-years*	Incidence (100,000)
0–14	0	27,570	—	1	26,040	3.8	1	53,610	1.9
15–24	4	22,300	17.9	5	22,020	22.7	9	44,320	20.3
25–34	3	19,850	15.1	2	21,490	9.3	5	41,340	12.1
35–44	0	19,470	—	1	21,030	4.7	1	40,500	2.5
45+	0	46,500	—	0	56,460	—	0	102,960	—
Total	7	135,690	5.1	9	147,040	6.1	16	282,730	5.7

* Person-year counts were obtained by multiplying the corresponding population figures as of the prevalence day (December 31, 1995) by 10.

years in the period 1986 to 1990 and 2.1 years in the period 1991 to 1995 (indicating an improvement in diagnostic efficiency), the twofold increase in prevalence observed over 20 years strongly suggests a real increase in the disease frequency. Unfortunately, the lack of previous data on the incidence of MS in Enna or the changes in lag time between the onset and the diagnosis, precludes comparison with the previous study.

The incidence found in Enna, together with that reported in two other Sicilian cities (Monreale[7] and Bagheria[8]), is comparable to that reported either in Sardinia[2] or in Northern European countries; this further supports the high frequency of MS in this Mediterranean island. The Regional Epidemiologic Office has not detected particular events occurring in Enna during the past 20 years. Genetic predisposition might, indeed, play a role in the recorded elevated frequency of MS. Because Enna was one of the major centers of the Viking domination in Sicily, our data support Poser's[10] hypothesis on the contribution of Viking migrations to the dissemination of MS.

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Polymorphisms in the vicinity of the hypocretin/orexin are not associated with human narcolepsy

Article abstract—Human narcolepsy/cataplexy is associated with reduced hypocretin (orexin) transmission. A common preprophypocretin (HCRT) polymorphism (−909C/T) was identified and tested in 502 subjects (105 trio families, 80 Caucasian narcolepsy cases, and 107 Caucasian control subjects). This polymorphism was not associated with the disease. The promoter and 5' untranslated (5'URT) regions of the HCRT gene (−320 to +21 from ATG) were also sequenced in 281 subjects. None of the subjects carried −22T, a rare 5'UTR polymorphism previously reported to be associated with narcolepsy. The HCRT locus is not a major narcolepsy susceptibility locus.

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Marcel Hungs, MD, PhD; Ling Lin, MD, PhD; Michele Okun, MA; and Emmanuel Mignot, MD, PhD

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy (a pathognomonic symptom), hypnagogic hallucinations, and sleep paralysis. Narcolepsy/cataplexy affects 1/2,000 and usually begins during adolescence.[4] The disorder is tightly associated with HLA, suggesting an autoimmune mediation.[5] Most human cases have no family history, and monozygotic twins are frequently discordant, suggesting complex genetic inheritance and environmental effects.[4]

Recent studies have demonstrated a major role for hypocretins in the pathophysiology of narcolepsy.[2] A genetically determined canine model is associated with hypocretin receptor-2 mutations.[3] In humans, hypocretin-1 is undetectable in the CSF of most cases.[2] Most strikingly, recent neuropathologic studies indicate an almost complete loss of hypocretin (HCRT) mRNA and peptides in human narcoleptic brains.[6]

In humans, hypocretin abnormalities are rarely due to HCRT gene alterations.[6] An extensive mutation screening study in 74 selected cases identified a single mutation in the signal sequence of the HCRT

From the Stanford Center for Narcolepsy, Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, CA.

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Address correspondence and reprint requests to Dr. E. Mignot, Stanford Center for Narcolepsy, Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, 1201 Welch Road, Rm. P-114, Stanford, CA 94305-5485; e-mail: mignot@stanford.edu

