

# Multiple sclerosis epidemiology in Sardinia: evidence for a true increasing risk

Pugliatti M, Sotgiu S, Solinas G, Castiglia P, Pirastru MI, Murgia B, Mannu L, Sanna G, Rosati G. Multiple sclerosis epidemiology in Sardinia: evidence for a true increasing risk. *Acta Neurol Scand* 2001; 103: 20–26. © Munksgaard 2001.

**Objectives** – To update prevalence and incidence rates of MS among Sardinians. **Materials and methods** – The present work is a “spider” kind of population based survey, conducted over the interval 1968–97, on patients with MS (Poser criteria) living in the province of Sassari, Northern Sardinia (454,904 population). **Results** – A crude total prevalence rate of 144.4 per 100,000, an onset-adjusted prevalence rate of 149.7 per 100,000 and an average annual incidence rate of 8.2 for the period 1993–7 were found. **Conclusion** – Repeated epidemiological assessments of MS in Sardinia over decades have shown that the island is at high risk for MS. The present work highlights that MS incidence in Sardinia has been increasing over time. Although a substantial and widely spread improvement in MS case ascertainment can be postulated as the reason for such observations, a comparison between our data and those recently reported from a more industrialized province in Northern Italy seems to prove an at least partially real increase in MS risk among Sardinians and favours the hypothesis of a MS “Sardinian focus” as related to its latitude.

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Key words: multiple sclerosis; prevalence; incidence; Sardinia

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Accepted for publication September 12, 2000

Small population-based studies conducted by our research group in Northern Sardinia, insular Italy, since 1980 (1–4) indicated that multiple sclerosis (MS) prevalence rates have increased more than two or three times what has been observed in the rest of continental and insular Italy in the same time interval (5).

Because these small population-based rates cannot properly be compared with those from the rest of Europe, that are usually based on larger population samples (6, 7), another descriptive study (8) on MS epidemiology was conducted by the same researchers on a larger population of about 270,000 inhabitants in Northwestern Sardinia, which showed (prevalence day, December 31, 1991) a total prevalence rate of 103 per 100,000 and an average annual incidence rate of 5.7 per 100,000 in the period 1987–91.

The aim of the present work was to extend our investigations on MS frequency to the whole province of Sassari, Sardinia, which represents

about one-third of the overall Sardinian population in order to update the temporal trend. This area represents an ideal population for this type of investigation and guarantees a sufficiently powerful epidemiological MS study.

## Material and methods

### Area of investigation

The study area included the whole province of Sassari (Fig. 1), an area of 7,520 km<sup>2</sup>, Northern Sardinia that lies between latitudes 40°30'N and 41°N and encompasses 89 administrative communities. In the 1991 census, the total population was 454,904 (224,984 men and 229,920 women) (9). Based on census data, during the past 30 years the population of the province increased from 381,191 to 454,904. The populations which were used as denominators were calculated using log incremental rate between intercensus data (10). Migration flow was moderate:

in 1995, 1.7% of the total population registered as resident from other Italian provinces and from foreign countries, whereas 1.6% moved away from the study area (11). In our study, the population consisted almost completely of native individuals since the proportion of residents born outside the province of Sassari was negligible. In addition, immigration to the study area is still mostly from other Sardinian provinces so that it has not modified the ethnic composition of the study population. For the same reason, generalizations can be made from our data to the population of the whole island. The Sardinian population is ethnically and culturally homogeneous and distinct, as indicated by genetic, linguistic and historical studies. In particular, the genetic distances between Sardinia and the rest of Italy and Europe are 10-fold higher than between other Italians and Europeans, although Sardinians are also of Caucasoid origin (12).

#### Case collection and ascertainment

In 1995, a register of MS cases was created at the Neurologic Clinic, University of Sassari, representing the primary referral center for MS patients in the province. Information included in the database was also obtained from the other regional neurological departments (Ozieri, Olbia, Nuoro, the Neurological Clinic of the University of Cagliari, the Cagliari MS Center); the Neurosurgical and Ophthalmological Clinics of the University of Sassari; the provincial Centers for Motor Rehabilitation; the files of the National MS Society (AISM) centers; provincial general practitioners and all private neurologists; some extraregional centers (MRI Section of Gallarate General Hospital, Don Gnocchi's Foundation in Milan). Government death certificates were also reviewed for all over 50-year-old patients who were not being followed-up at the Clinic at the time of the study, so as to assess possible date of death.

Patients included in the register were diagnosed as suffering from MS according to the Poser criteria (13) for clinical or laboratory supported definite MS (CDMS, LSDMS) and clinical or laboratory supported probable MS (CPMS, LSPMS). For 92% of patients diagnosed after 1986, MRI was performed which supported the diagnosis of MS, whereas, prior to that date, diagnosis was based on clinical and paraclinical evidences and immunological study of the cerebrospinal fluid, which was performed in 78% of the cases. Other autoimmune and/or immunomediated and infectious diseases such as primary and secondary central nervous system vasculitides, post-infectious leukoencephalopathies and other demyelinating disorders have been ruled out by means of laboratory tests and

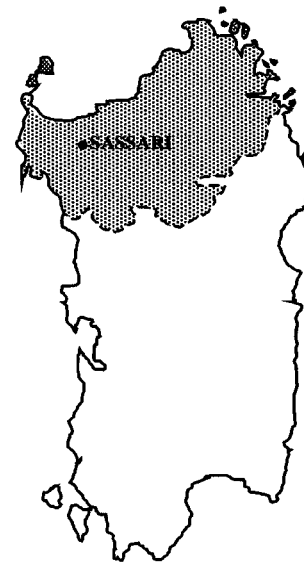


Fig. 1. The province of Sassari, Sardinia.

neuroimaging, besides neurological history and examination. By so doing, 45 cases out of the total individuals with suspected MS failed to meet the Poser criteria and were discarded.

On March 1, 1999, the database included 828 records of patients identified in the previous 60 years. Information on patients' birth date and place, residence between 5 and 15 years (the putative critical exposure age period (14)), residence at clinical onset of disease, possible exposure to risk factors, symptoms and date of clinical onset, date of diagnosis, classification and course of the disease and current Expanded Disability Status Scale (EDSS) (15) evaluation has been recorded. MS patients who had been identified outside of our Clinic underwent examination by trained neurologists from our team and their medical history collected with the contribution of their closest relatives.

A prevalent case was defined as any living individual, residing in the province of Sassari on prevalence day (December 31, 1997), who had been diagnosed as suffering from MS by the same date. Crude prevalence rates were calculated using as denominators both the 1997 population which was obtained through the log incremental rate and the 1991 census population. Standardized prevalence rates were carried out referring to the 1996 European population (16) and to the 1991 census Italian population (9). For this study, onset-adjusted prevalence was also assessed by reviewing all information about each patient according to Poser's method (17).

An incident case was defined as any individual who first experienced symptoms later related to MS (18) while residing in the province of Sassari. Incidence

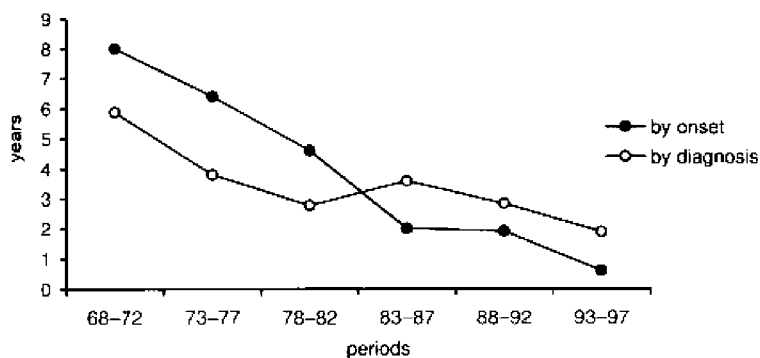


Fig. 2. Temporal trends of time lag median values between clinical onset and diagnosis, tabulated by year of clinical onset and by year of diagnosis (backward recurrence time).

was studied from January 1, 1968 to December 31, 1997 based on the number of incident cases in the mean population residing in the study area.

According to the binomial distribution for prevalence rates and the Poisson distribution for both onset-adjusted prevalence rates and incidence rates, 95% confidence intervals (CI 95%) were calculated. Differences of the time lag elapsing between onset and diagnosis among the 5-year periods 1968–97 were tested by year of clinical onset, using Kruskal–Wallis one-way analysis of variance by ranks. In order to avoid possible time lag truncation in recent onset cohorts, time lag was also calculated from diagnosis backward to clinical onset in the same time interval (backward recurrence time).

**Results**

Prevalence

On prevalence day (December 31, 1997), 686 MS cases (492 women and 194 men) were living in the

province of Sassari. Using as denominator the 1997 population, the crude overall prevalence rate was 144.4 per 100,000 (CI 95%, 134.0–155.6), 205.1 (CI 95%, 187.8–224.0) and 82.5 (CI 95%, 71.7–94.9) for women and men, respectively, and the standardized rate was 140.9 (16). The highest rates were observed in the age groups 30 to 49, ranging from 300.0 to 326.5; for women, in particular, the highest rates were assessed in the age group 30–34 (456.7 per 100,000). Age- and sex-specific prevalence rates are reported in Table 1. In order to compare our results with other studies (8), the 1991 census general population was used as denominator to calculate the prevalence; the total crude prevalence rate was 150.8 per 100,000 (standardized rate of 153.3 (9)).

The latency between clinical onset and diagnosis suggests that prevalence data based on the latter may underestimate the actual number of persons suffering from MS on prevalence day. In our study, the mean time elapsing between clinical onset and diagnosis significantly shortened from  $10.1 \pm 7.4$  years in the period 1968–72 to  $1.1 \pm 1.2$  in the period 1993–7 ( $P < 0.0001$ ). In order to correct for possible truncation in the more recent onset cohorts, backward recurrence time, i.e. the backward time from diagnosis to clinical onset has also been tabulated. Median values of both time lag distributions, i.e. by clinical onset and diagnosis, have been plotted in Fig. 2. In particular, the median values decreased from 8.0 to 0.6 years and from 5.9 to 1.9 in the quinquennia 1968–72 and 1993–7, when calculated by year of clinical onset and by year of clinical diagnosis, respectively; deviations from the trends pattern can be ascribed to different levels of diagnostic sensitivity in different time periods, e.g. secondary to the introduction of new diagnostic procedures such as MRI. On the basis of the trend observed in time elapsing between clinical onset and diagnosis, since all register records were reviewed on March 1, 1999, December 31, 1997 appeared to be a sufficiently remote date for calculating the prevalence. In fact, on March 1, 1999, we found that on

Table 1. Age- and sex-specific prevalence rates of MS (per 100,000) in the province of Sassari, on December 31, 1997. 1997 population was used as denominator

Age groups (years)	Women		Men		Total	
	Cases	Rate	Cases	Rate	Cases	Rate
0–9	0	0	0	0	0	0
10–14	0	0	0	0	0	0
15–19	7	35.8	1	4.8	8	19.8
20–24	26	125.5	9	41.3	35	82.4
25–29	44	200.8	12	56.1	56	129.3
30–34	84	456.7	26	142.3	110	300.0
35–39	75	435.1	27	150.0	102	289.5
40–44	70	426.4	39	223.7	109	322.0
45–49	66	446.8	31	207.6	97	326.5
50–54	53	358.9	21	150.7	74	257.9
55–59	26	206.4	9	73.4	35	140.8
60–64	22	152.7	2	15.0	24	86.4
65–69	15	123.2	11	111.6	26	118.0
> 70	4	16.5	6	35.0	10	24.2
Total	492	205.1	194	82.5	686	144.4
Standardized rate (16)		196		82		141

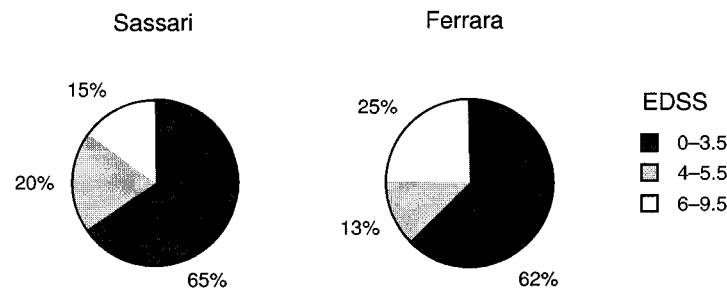


Fig. 3. Proportion of prevalent MS cases according to Kurtzke's Expanded Disability Status Scale (EDSS) in the provinces of Sassari and Ferrara, in 1996 and 1993, respectively.

December 31, 1997, 25 patients were already symptomatic but not diagnosed yet and could retrospectively be considered as prevalent cases. Therefore, on December 31, 1997, the actual number of symptomatic MS patients was 711 (686 diagnosed plus 25 non diagnosed cases), yielding to an onset-adjusted total prevalence rate of 149.7 (CI 95%, 139.1–161.1), 231.0 (CI 95%, 195.3–232.3) and 85.0 (CI 95%, 74.0–97.7) for women and men, respectively.

The mean age on prevalence day was  $42.4 \pm 12.2$  years, ranging from 16.3 to 88.1 (median age, 41.1 years); for women, mean age was  $41.8 \pm 12.1$  years, median age 40.5, ranging from 16.3 to 88.1 years; for men, mean age was  $43.6 \pm 11.9$ , median age 41.8, ranging from 16.9 to 74 years.

On March 1, 1999, 775 patients (93.6% of the total registered cases) were residing in the study area, of whom 87.6%, 8.4%, 2.7% and 1.2% were classified as having CDMS, CPMS, LSDMS and LSPMS, respectively, according to the Poser criteria (13).

According to Kurtzke's EDSS (15), 65.3% of patients showed no or minimal to moderate disability (EDSS 0–3.5), 19.7% suffered from a

severe disability, which did not however interfere with normal living activities (EDSS 4–5.5), and 15.0% required partial or complete assistance (EDSS 6–9.5).

#### Incidence

Incidence was studied in the period January 1, 1968 to December 31, 1997 and was based on the number of individuals residing in the province of Sassari at their clinical MS onset out of the mean population residing in the study area in the same time interval.

From 1968 to 1997, 637 patients (455 women and 182 men) had their MS clinical onset while living in the study area. The mean age at onset was  $28.0 \pm 9.0$  years ( $27.5 \pm 8.9$  for women and  $29.5 \pm 8.8$  for men), ranging from 8.4 to 63.3 years (median age, 27.3 years).

The mean total population of the province of Sassari during the incidence 5-year periods 1968 to 1997 varied from 394,016 to 467,845 with a mean of 431,670 for the whole period. The average annual incidence for the whole period was 4.9 per 100,000: 7.0 for women and 2.8 for men. The highest rates were noted in the age groups between 20 and 34 years for both sexes (Table 2).

The average incidence rates for the 5-year intervals from 1968 to 1997 is shown in Fig. 3. The total incidence rates increased over time from values of 2.0 per 100,000 in the period 1968–72 to 6.8 in the interval 1993–7 (from 2.4 to 9.2 for

Table 2. Age- and sex-specific average MS incidence rates (per 100,000) in the province of Sassari in the period 1968–97

Age groups (years)	Women		Men		Total	
	Cases	Rate	Cases	Rate	Cases	Rate
0–9	2	0.2	1	0.1	3	0.2
10–14	24	4.7	3	0.6	27	2.6
15–19	72	13.0	22	3.8	94	8.3
20–24	92	17.4	39	7.3	131	12.3
25–29	100	20.1	38	7.8	138	14.0
30–34	83	17.8	35	7.6	118	12.8
35–39	38	8.9	19	4.4	57	6.7
40–44	28	6.7	15	3.6	43	5.2
45–49	8	2.1	9	2.4	17	2.2
50–54	5	1.4	1	0.3	6	0.9
55–59	2	0.6	0	0.0	2	0.3
60–64	1	0.3	0	0.0	1	0.2
>65	0	0.0	0	0.0	0	0.0
Total	455	7.0	182	2.8	637	4.9

Table 3. MS sex-specific incidence rates (per 100,000) in the province of Sassari in the 5-year periods 1968 to 1997

Periods	Women			Men			Both sexes		
	Cases	Rate	95%CI	Cases	Rate	95%CI	Cases	Rate	95%CI
1968–1972	24	2.4	1.6–3.6	15	1.5	0.9–2.6	39	2.0	1.4–2.7
1973–1977	58	5.6	4.3–7.2	19	1.9	1.2–2.9	77	3.8	3.0–4.7
1978–1982	71	6.6	5.2–8.3	35	3.3	2.4–4.6	106	5.0	4.1–6.0
1983–1987	87	7.8	6.3–9.7	30	2.8	1.9–3.9	117	5.3	4.4–6.4
1988–1992	106	9.3	7.7–11.3	34	3.0	2.2–4.3	140	6.2	5.3–7.3
1993–1997	109	9.2	7.6–11.1	49	4.2	3.2–5.6	158	6.8	5.8–7.9
1968–1997	455	7.0	6.3–7.6	182	2.8	2.5–3.3	637	4.9	4.6–5.3

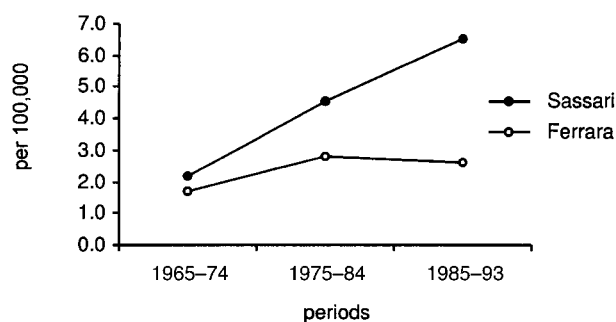


Fig. 4. Temporal trends of MS incidence rates in the province of Sassari and Ferrara, in the period 1965 to 1993.

women and from 1.6 to 4.2 for men, respectively, Table 3).

The commonest onset, in about 90% of the patients, was with a transient bout, whereas the remainder had a steady progressive course from the onset. Although patients frequently presented with more than one symptom, sensory, weakness and visual disturbances were the most frequent among the definite ones (18), accounting for 32.3%, 22.9% and 18.1% of all symptoms at presentation, respectively. While might occur in isolation, incoordination (11.0%) was usually concomitant with vertigo, oculomotor (11.4%), motor and sensory compromise; 1.6%, 1.1% and 1.6% of patients presented with genito-urinary deficits, seizures and other symptoms.

## Discussion

The first attempts to estimate MS prevalence in Sardinia date back to the early 1960s (19–21) supporting, the often cited relationship between disease prevalence and latitude. Further investigations demonstrated that Sardinia is a high risk area for MS (Table 4). In particular, a recent study of MS prevalence and incidence carried out in a large population of Northwestern Sardinia showed that, in 1991, the prevalence rate was 2- to 4-fold higher than in the rest of Italy (8).

The present research represents a “spider” kind of population based survey (22), wherein MS patients from a defined territory (i.e., the province of Sassari) come to one sole referral neurological center where updating has been accurate and medical record consulting easy over time, thus contributing to strengthen the study power. An update of MS prevalence to December 31, 1997 and a study of the temporal trend of MS incidence between 1968 and 1997 in the province of Sassari is reported.

## Prevalence

Out of the 686 prevalent cases on December 31, 1997, complete information on the residence during

Table 4. MS prevalence rates (per 100,000) recorded in Sardinia, since 1980

Study area	Population	Year	Rate	CI 95%	Reference
Alghero	77,981	1980	59.0	43–78	2
Barbagia	49,022	1981	65.3	44–93	21
Macomer	11,083	1981	90.2	43–166	1
Sassari	124,588	1985	69.0	55–86	3
Tempio	35,128	1987	102.5	72–141	4
Northwestern Sardinia	268,926	1991	102.6	92–115	8

the putative critical period of acquisition was available for 524 subjects born in the study area. However, due to the low rate of emigration, it can be assumed that the great majority of these patients still lived in the study area during the putative period of MS acquisition (5 to 15 years). Previous investigations conducted in different European countries have shown similar high rates. The highest prevalence rates in the world were recorded in the Orkney and the Shetland Islands in the early 1970s but began to fall in the 1980s (23–25).

Although it is difficult to estimate the significance of increasing MS prevalence in the absence of comparable onset-adjusted prevalence rates (26), such high rates observed in Sardinia not only confirm that Sardinia is a high-risk area for MS, but also appear to be in contrast with the theory of the north-to-south gradient in the northern hemisphere (26) and the hypothesis of a European Fennoscandian focus of MS (22).

Besides a real biological cause, an increase of prevalence over time can be the result of one or more of the following factors: 1) increase in disease duration due to longer survival; 2) increase in the number of benign and/or mild cases due to greater diagnostic accuracy and awareness for the disease, and the number of neurologists in practice; 3) improvement in epidemiological procedures; 4) influx of people in the high risk age groups; 5) immigration of individuals from a population genetically at higher risk for developing MS.

As the duration of the disease in the 53 registered patients who died during the 30-year interval considered did not significantly differ over time, increased MS prevalence secondary to a longer survival was thus ruled out. In Sardinia there has been a substantial improvement in MS case ascertainment over the last 15 years concomitantly with the introduction of new diagnostic procedures, with a larger number of neurologists trained to recognize MS and with public information on a wider scale. These factors have brought about a progressive increase of diagnosed mild and benign cases. It must be noted, however, that improvement in diagnostic accuracy has involved other Italian and European regions as well.

A comparison with a survey in the province of Ferrara, northern Italy in 1993 (27), using a similar methodology, reveals that prevalence rates in our study area are nearly 3-fold higher. In particular, there does not appear to exist a significant difference in the number of mild and/or benign cases expressed as the proportion of patients with no or mild disability at the EDSS (Fig. 3). Better diagnostic accuracy and improvement of epidemiological methodology cannot therefore fully account for the observed increased prevalence. Furthermore, a possible change in age structure was controlled for by standardization, and substantial differential migration flows in the population under investigation were ruled out.

#### Incidence

The temporal trend of MS incidence in the province of Sassari was analysed over the period 1968 to 1997. A significant increase of new MS cases per year was observed in the 3 decades considered. Several authors have reported similar increases of MS incidence rates over time: the incidence in the Orkney Islands had been the highest ever reported (10.5 per 100,000/year) between 1941 and 1961 but it fell to 3.7 in the following two decades (23); a similar declining trend was observed in Denmark between 1948 and 1964 (28), and in Iceland (29), where, in particular, increased incidence rates were demonstrated to coincide with the improved recognition of MS patients due to an increased number of neurologists in practice. This was also hypothesized for the Faroese data (30), in which a progressive declining of incidence trend across epidemics beginning in 1943 (31) was described.

We wondered if improvement of diagnostic accuracy could have been responsible for the greater number of mild cases due to the shortening of the time lag between symptomatic onset and diagnosis in Sardinia. However, when comparing the trend of the time lag between clinical onset and diagnosis in our study versus Ferrara (27), no differences were detected, but a clear difference in the two areas incidence trend over time was observed (Fig. 4). Similar considerations can be drawn by comparing our results with another Iceland study (32) in which, despite the shortening of time lag between clinical onset and diagnosis and a comparable proportion of diagnosed mild cases, no increase of incidence was observed.

Our results are consistent with what was previously observed in Sardinia by the same group of researchers confirming that Sardinia is among the areas at highest frequency of MS in the world (22). We demonstrated that better diagnostic accuracy cannot fully account for the steady increase of MS

frequency observed over a long period of time by means of repeated assessments, therefore supporting the evidence of a "Sardinian focus" and favouring the hypothesis that the rise of MS risk among Sardinians is at least partially due to biological etiological factors which are under investigation.

#### Acknowledgements

This study was supported by FISM (Fondazione Italiana Sclerosi Multipla) Grant no. 97/R/69 and ISS (Istituto Superiore di Sanità). Preliminary results were accepted for poster presentation at 122nd Annual Neurological Association meeting in San Diego, CA, USA, Sept 28–Oct 2, 1997.

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