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Epidemiology of multiple sclerosis in south-western Sardinia

Eleonora Cocco[1], Claudia Sardu[2], Rita Massa[1], Elena Mamusa[1], Luigina Musu[1], Paola Ferrigno[3], Maurizio Melis[3], Cristina Montomoli[4], Virginia Ferretti[4], Giancarlo Coghe[1], Giuseppe Fenu[1], Jessica Frau[1], Lorena Lorefice[1], Nicola Carboni[1], Paolo Contu[2] and Maria G Marrosu[1]

Abstract

Background: Sardinia is a known high-risk area for multiple sclerosis (MS), but no data for south-western Sardinia (SWS) are available. SWS has a genetically homogeneous population, apart from St Peter Island, and represents a peculiar environment related to the industrial, mineralogical and military economy.

Objective: To estimate prevalence and incidence and to evaluate temporal trends and geographical distribution of MS in SWS.

Methods: MS prevalence was evaluated on 31 December 2007 and crude mean annual incidence rate was defined between 2003 and 2007. Temporal trend in MS incidence was assessed using the Armitage test. To identify MS clusters, Standard Morbidity Ratio (SMR) was calculated for each village and geographical distribution prevalence by means of a Bayesian hierarchical model.

Results: Total crude prevalence rate was 210.4 (95% CI 186.3–234.5): 280.3 (95% CI 241.4–319.3) for females, 138 (95% CI 110.1–165.8) for males. The crude mean annual incidence rate was 9.7/100,000 (95% CI 3.4–13.2): 4.7/100,000 (95% CI 2.4–17.0) and 14.6/100,000 (95% CI 11.8–34.8) for males and females respectively. MS incidence has increased over the last 50 years. Cluster analysis showed an SMR of 0.2 (95% CI 0.05–0.68, $p = 0.002$) on the island of *San Pietro*, and 2.0 (95% CI 1.35–2.95, $p = 0.001$) in *Domusnovas*. Spatial distribution of MS was confirmed by Bayesian geographical analysis.

Conclusions: Our data confirm Sardinia as a high-risk area for MS and support the relevance of genetic factors in MS, as evidenced in St Peter Island. However, we found an unexpectedly high MS prevalence in one village, in particular in males, suggesting an environmental influence on MS occurrence.

Keywords

epidemiology, geographic cluster, multiple sclerosis, Sardinia, temporal trend

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, which can cause permanent disability in young adults. Disease aetiology is still unknown; however, interaction between genetics and environmental factors is involved in its pathogenesis.

Geographical distribution of MS is heterogeneous, but it is well known that the disease is more prevalent in temperate zones than in tropical areas. MS has a high

[1]Multiple Sclerosis Centre, Department of Cardiovascular and Neurological Science, University of Cagliari, Italy.
[2]Department of Public Health, University of Cagliari, Italy.
[3]Neurology Division, Brotzu Hospital, Cagliari, Italy.
[4]Department of Health Sciences, Section of Medical Statistics and Epidemiology, University of Pavia, Italy.

Corresponding author:
Eleonora Cocco, Centro Sclerosi Multipla, Ospedale Binaghi, Via Is Guadazzonis, 2, 09126, Cagliari, Italy
Email: ecocco@unica.it

prevalence in populations residing at high latitudes;[1] however, Sardinia is an exception to this and represents a high-risk area for MS.[2] Most available epidemiological data relevant to the island were obtained in central[2] and northern Sardinia,[1] while, to date, no data exist concerning the southern part.

We carried out an epidemiological study in south-western Sardinia (SWS) to estimate the prevalence and incidence of MS and to evaluate the presence of spatial clustering in the area. SWS is an ideal region for such a study, as it is characterized by a genetically homogeneous population,[3] apart from the island of *San Pietro*, which is genetically different.[4] On the other hand, this area has been affected by environmental pollution due to industrial and mineralogical activities for the last few centuries.[5]

Methods

Settings

This epidemiological study was conducted in the south-western part of Sardinia, which is located between latitudes 39° 26′ and 39° 0′ and longitudes 8° 42′ and 8° 18′. On 31 December 2007 the area numbered 138,765 inhabitants (70,627 females and 68,138 males).[6] Within the area there are two major cities (Iglesias and Carbonia) and 23 villages.

Data source

Patients were initially identified through clinical records at the two MS referral centres (the MS Centre at the University of Cagliari and the Neurology Division of the Brotzu Hospital) in southern Sardinia. No neurological clinic is available in SWS. In order not to miss patients with severe disabilities who had not been referred to a neurologist, all the rehabilitation centres located in SWS were contacted and patients were identified.

The data were confirmed and integrated by checking the territorial centralized sanitary archive. In Italy, all patients diagnosed with MS are identified by code 340 of the ICD-9 and recorded in an electronic archive.

The majority of patients were clinically evaluated and interviewed by an expert MS neurologist (RM, EM, LM, PF). A standard personal and clinical questionnaire was used to obtain homogeneous information. Data collected from MS patients were: origin, date of birth, gender, date of illness onset, date of diagnosis, MS course, onset symptoms, presence of other autoimmune disorders, MS familiarity. The patients' life status was checked through the communal register.

Only patients with MS diagnosis according to the McDonald Criteria were considered.[7,8]

Statistical analysis

Incidence and temporal trend. The crude mean annual MS incidence rate was defined by the ratio between the mean annual number of new cases diagnosed in the period between 1 January 2003 and 31 December 2007 and the general population at the mid-period. Incidence was expressed as the number of new cases per 100,000 inhabitants. The mean annual age and gender-specific incidence rates were also calculated. In order to take into account population structure variations, the temporal trend in incidence rates from 1955 to 2005 was analysed using the Armitage test adapted for the analysis of standardized ratio comparing the directly standardized mean annual incidence rates, calculated for 5 decades.

Prevalence and spatial clustering. The prevalence day was 31 December 2007. The prevalence rate was defined by counting the number of patients who had been diagnosed and were alive on that day. The age and gender-specific prevalence rates were expressed as the number of cases per 100,000 using the global population of the SWS region as the denominator.[6]

To explore the geographical pattern of MS in the considered area, standardized ratios were calculated for each of the 25 cities/villages. This standardization process eliminates the effects of age and gender differences when comparing many populations. Through the indirect method, the expected number of cases for each city/village is calculated using the total population of SWS region as the standard population. The Standardized Morbidity Ratio (SMR) is the ratio between the number of cases observed in a city/village and the number of expected cases if the population of the city/village has the same specific rates as the standard population.

The SMR indicates how the number of cases observed deviates from the number expected: if the SMR is 1, the number of cases observed is equal to the number expected; if it is higher than 1 the number of cases observed is higher than expected, while if it is lower the number of cases observed is lower than expected. Ninety-five per cent confidence intervals (CI) of SMR and significance tests were calculated according to Byar's approximation of the Poisson test.[9]

Bayesian analysis. The geographical variations of MS prevalence within the finest geographical grid for which data were available, that is, 25 cities/villages, were analysed and MS prevalence maps were drawn using a frequentist approach (crude prevalence rate) and a Bayesian approach in which the main underlying idea is that each area-specific prevalence is based on pooling

information from neighbouring areas (prior distribution). Methodological aspects of the Bayesian analysis applied to geographical mapping have been extensively described elsewhere.[10–13]

The Bayesian prevalence maps were accompanied by a posterior probability (PP) map that indicated whether the prevalence rate for each area was significantly lower or greater than a given reference value. The PP is the Bayesian equivalent of the *p*-value[14] and enables the testing of specific hypotheses. In our analysis, for example, we chose the median age-standardized MS prevalence rate of SWS as a reference value in order to ascertain whether each area-specific prevalence was different from the provincial values. We subdivided the PP range (0–1) into five intervals (<0.05, 0.05–0.25, 0.25–0.75, 0.75–0.95, >0.95). A PP value higher than or equal to 0.95 strongly indicated that the area-specific risk was higher than the reference value, while a PP value lower than or equal to 0.05 strongly indicated that the prevalence was lower than the reference value. In those areas where the PP value fell within the fourth interval (0.75–0.95), there was only an indication that the risk was higher than the reference value. Similarly, in those areas where the PP value fell within the second interval (0.05–0.25), there was an indication that the prevalence was lower than the reference value. When the PP value fell within the middle interval (0.25–0.75), evidence was insufficient to judge. In conclusion, the PP map can be used to evaluate how confident we should be when analysing a prevalence value that is much higher or lower than a reference value. The WINBUGS software package was used for the Bayesian analysis.[15]

Results

A total of 371 MS patients who lived or had lived in the SWS area were identified. Of these, 80% (298) were Sardinian going back at least three generations. Prevalence was calculated considering 292 MS patients (274 who live in SWS and in whom onset occurred in the region and 18 who live in SWS but in whom onset occurred outside the region). Seventy-nine patients were excluded because seven (1.9%) had died before the prevalence day and the other 72 were not living in SWS on the prevalence day.

Incidence and temporal trend

The crude mean annual incidence rate between 1 January 2003 and 31 December 2007 was 9.7/100,000 (95% CI 3.4–13.2): 4.7/100,000 (95% CI 2.4–17.0) and 14.6/100,000 (95% CI 11.8–34.8) for males and females respectively. The mean annual age and gender-specific incidence rates are reported in Table 1.

The temporal trend in incidence rate from 1955 to 2005 was analysed using the Armitage test and is summarized in Table 2.

Table 1. Mean annual gender and age-specific incidence rates per 100,000 people between 2003 and 2007

Age classes	Male Incidence (95% CI)	Female Incidence (95% CI)	Total Incidence (95% CI)
0–14	0 (0.0–41.9)	0 (0.0–45.7)	0 (0.0–21.9)
15–24	6.9 (0.3–63.8)	36.4 (7.5–106.4)	21.2 (6.4–60.3)
25–34	17 (2.3–68.3)	37.6 (10.8–101.4)	27.1 (10.6–63.1)
35–44	3.8 (0.0–35.4)	14.8 (2.2–66.7)	9.4 (1.1–34.0)
45–54	3.6 (0.0–33.5)	14.7 (2.2–66.5)	9.1 (1.1–33.0)
55–64	0 (0.0–42.7)	4.6 (0.0–42.3)	2.3 (0.0–21.3)
65 and over	0 (0.0–35.3)	0 (0.0–26.0)	0 (0.0–15.0)

CI: confidence interval

Table 2. Temporal trend of MS incidence in SWS over the last 50 years (1958–2007)

	Standardized incidence yearly rate for each decade					
	1958–1967	1968–1977	1978–1987	1988–1997	1998–2007	*p* value
Female	0.28	1.81	3.80	7.98	11.88	**0.0000**
Male	0.41	1.04	1.93	3.93	4.32	**0.026**
Total	0.34	1.42	2.86	5.94	8.07	**0.001**

MS: multiple sclerosis, SWS: south-western Sardinia

Table 3. Gender-specific crude prevalence of MS in south-western Sardinia on 31 December 2007

	Male		Female		Total	
Age Range (years)	*N*	Prevalence (95% CI)	*N*	Prevalence (95% CI)	*N*	Prevalence (95% CI)
0–14	0	0.0 (0.0–45.8)	0	0.0 (0.0–49.9)	0	0.0 (0.0–23.9)
15–24	3	37.7 (7.8–110.1)	11	144.2 (72.0–258.0)	14	89.8 (49.1–150.7)
25–34	20	197.6 (120.7–305.1)	48	508.4 (374.7–674.4)	68	347.5 (269.8–440.8)
35–44	22	215.0 (134.8–325.6)	48	463.9 (341.9–615.4)	70	340.2 (265.1–430.0)
45–54	32	294.0 (201.1–415.0)	55	495.9 (373.5–645.8)	87	395.9 (317.1–488.5)
55–64	12	124.4 (64.3–217.3)	27	282.2 (186.0–410.7)	39	203.0 (144.3–277.7)
≥65	5	44.5 (14.4–103.8)	9	59.3 (27.1–112.7)	14	53.0 (29.0–89.0)

CI: confidence interval, MS: multiple sclerosis; NC: not calcolable

This statistical analysis showed a significant increase in the incidence trend, in both males and females.

Prevalence and spatial cluster analysis

Using the population resident in this area as a denominator (on prevalence day, 138,765 individuals were living in SWS), the total crude prevalence rate was 210.4 (95% CI 186.3–234.5): 280.3 (95% CI 241.4–319.3) for females, 138 (95% CI 110.1–165.8) for males. The age and gender-specific prevalence rates are summarized in Table 3.

Table 4 shows SMR for each considered village. Only two villages show a significant difference between observed and expected cases. A lower prevalence was observed on the island of San Pietro (the town of Carloforte), with three observed vs. 13 expected cases and SMR = 0.23 (95% CI 0.05–0.68, $p = 0.002$). An excess was observed in Domusnovas, with 28 observed cases compared with the 14 expected, and SMR = 2.04 (95% CI 1.35–2.95, $p = 0.001$). When the two genders are considered separately, a significant excess is observed in Domusnovas only for males, with 15 patients instead of the 4.4 expected and SMR = 3.4 (95% CI 1.89–5.59, $p = 0.001$).

The Bayesian analysis

Crude prevalence rates, the Bayesian prevalence and the PP were calculated for each village and for gender (data not shown). We drew the map of the geographical variation of MS across the 25 villages in SWS with both the frequentist (Figure 1A) and the Bayesian (Figure 1B) approaches. Different scales of grey were proportional to the magnitude of values: the darker the shade of grey, the higher the prevalence; the lighter the shade, the lower the prevalence. The frequentist map showed a non-homogeneous map being influenced by random variability. This could be due to the strong effect of extreme prevalence values in sparsely populated villages. In contrast, the Bayesian map was smoother. Bayesian area-specific prevalence ranged from 84 to 195/100,000 inhabitants.

The PP map (Figure 1C) showed one MS prevalence cluster in the upper part of the region, and we were able to identify a village (Domusnovas) with a PP > 0.95, indicating that for this village the prevalence was greater than the median regional rate. When the region was analysed and patients were categorized on the basis of gender, the cluster was confirmed in males (data not shown). The PP of the island of San Pietro was below 0.05, indicating that the area was at a lower risk than the rest of the region (Figure 1C).

Discussion

This paper contributes to the epidemiology of MS in Sardinia by studying the area of SWS not yet considered in epidemiological reports. In fact, to date, studies have only been performed in the northern and central parts, showing a prevalence rate of 157/100,000 inhabitants in central Sardinia[10] and 102/100,000 in north-western Sardinia.[16] In SWS the prevalence of MS is 210.4/100,000, confirming the island as being one of the highest-risk areas for the disease in the world.

It is important to note that, when compared with narrowing Mediterranean population, Sardinia remains an MS hot spot. High frequency of the diseases, in any case lower than in Sardinia, had also been detected in the Mediterranean population of Sicily, ranging from 120.2/100,000 to 168.8/100,000 in the Sicilian provinces of Enna and Caltanisetta respectively.[17,18] Other studies performed in Malta (an island close to Sicily) and in Turkey and Greece showed lower prevalence rates[19–21] if compared with Sardinia. It is interesting to note that one hypothesis claims that MS originated in Northern Europe and was spread around by Vikings.[22] In accordance with this

Table 4. Spatial clustering in south-western Sardinia evaluated by the Standard Morbidity Ratio (SMR)

	Total					Male					Female				
Village	obs	exp	SMR	95% CI	*p*	obs	exp	SMR	95% CI	*p*	obs	exp	SMR	95% CI	*p*
Buggerru	0	2.3	NC	NC–NC	0.20	0	0.7	NC	NC–NC	0.96	0	1.6	NC	NC	0.42
Calasetta	3	5.9	0.5	0.10–1.49	0.32	1	1.9	0.5	0.01–2.92	0.87	2	4.0	0.5	0.06–1.83	0.49
Carbonia	65	64.2	1.0	0.78–1.29	0.95	17	20.2	0.8	0.49–1.35	0.57	48	44.4	1.1	0.80–1.43	0.63
Carloforte	3	13	0.2	0.05–0.68	0.002	1	4.2	0.2	0.00–1.32	0.15	2	8.6	0.2	0.03–0.84	0.02
Domusnovas	28	14	2.0	1.35–2.95	0.001	15.0	4.4	3.4	1.89–5.59	0.0001	13	9.3	1.4	0.74–2.39	0.30
Fluminimaggiore	4	6.2	0.6	0.17–1.65	0.52	2	2.0	1.0	0.11–3.55	0.66	2	4.2	0.5	0.05–1.74	0.43
Giba	7	4.4	1.6	0.63–3.24	0.32	3	1.4	2.1	0.42–6.05	0.35	4	3.0	1.3	0.36–3.42	0.70
Gonnesa	9	11.2	0.8	0.37–1.52	0.63	4	3.7	1.1	0.29–2.80	0.99	5	7.5	0.7	0.21–1.56	0.48
Iglesias	71	59.0	1.2	0.94–1.52	0.14	21	18.6	1.1	0.70–1.72	0.64	50	40.7	1.2	0.91–1.62	0.17
Masainas	3	3.0	1.0	0.20–2.94	0.86	1	1.0	1.0	0.01–5.78	0.77	2	2.0	1.0	0.11–3.55	0.66
Musei	1	3.2	0.3	0.00–1.72	0.33	0	1.1	NC	NC–NC	0.68	1	2.1	0.5	0.01–2.62	0.75
Narcao	5	7.0	0.7	0.23–1.66	0.59	2	2.3	0.9	0.10–3.10	0.82	3	4.7	0.6	0.13–1.88	0.63
Nuxis	3	3.5	0.9	0.17–2.52	0.91	1	1.2	0.9	0.01–4.82	0.64	2	2.3	0.9	0.10–3.17	0.79
Perdaxius	3	3.1	1.0	0.20–2.87	0.73	1	1.0	1.0	0.01–5.41	0.54	2	2.0	1.0	0.11–3.64	0.82
Piscinas	4	1.7	2.4	0.64–6.11	0.18	1	0.5	1.9	0.03–10.77	0.80	3	1.2	2.5	0.51–7.37	0.24
Portoscuso	13	11.6	1.1	0.60–1.92	0.75	4	3.7	1.1	0.29–2.75	0.98	9	7.8	1.2	0.53–2.19	0.76
San Giovanni Suergiu	10	12.8	0.8	0.37–1.44	0.54	3	4.2	0.7	0.14–2.10	0.80	7	8.6	0.8	0.33–1.68	0.75
Santadi	9	7.6	1.2	0.54–2.26	0.69	3	2.5	1.2	0.24–3.55	0.89	6	5.1	1.2	0.43–2.58	0.79
Sant'Anna Arresi	1	5.7	0.2	0.0–1.0	0.04	1	1.9	0.5	0.01–2.97	0.88	0	3.8	0.0	NC–NC	0.04
Sant'Antioco	16	24.1	0.7	0.38–1.08	0.11	6	7.9	0.8	0.28–1.66	0.66	10	16.2	0.6	0.30–1.13	0.14
Tratalias	2	2.3	0.9	0.10–3.14	0.80	0	0.7	NC	NC–NC	0.95	2	1.5	1.3	0.15–4.70	0.90
Villamassargia	8	7.8	1.0	0.44–2.01	0.95	2	2.5	0.8	0.09–2.88	0.91	6	5.4	1.1	0.41–2.44	0.89
Villaperuccio	3	2.3	1.3	0.26–3.84	0.80	0	0.7	NC	NC–NC	0.97	3	1.6	1.9	0.39–5.65	0.40
Siliqua	13	8.5	1.5	0.82–2.63	0.18	4	2.8	1.4	0.39–3.69	0.60	9	5.6	1.6	0.73–3.04	0.23
Teulada	8	8.1	1.0	0.43–1.96	0.83	1	2.8	0.4	0.00–1.99	0.46	7	5.1	1.4	0.55–2.85	0.49
Total	292	292				94	94				198	198			

CI: confidence interval, exp: expected, obs: observed

idea, Sicily in particular was dominated by the Normans for a long period of time; however, this was not the case with the Sardinians. The Sardinian population has been subjected to isolation over the centuries, and this, with founder effect, determined the selection of a very homogeneous genetic background, which differs from the narrowing population and could explain, at least in part, the high frequency of the disease in the island.[3]

In this study, we also analysed the possible existence of geographical clustering, exploiting the genetic and environmental particularities of SWS. The use of a conventional statistical approach does not appear to be reliable enough for this kind of analysis. Problems include the large random component that may confound disease rates across small areas. To deal with this, a Bayesian analysis was used to study MS geographical distribution in the region. This approach provides smooth estimates of disease risk and avoids the confounding effect of small numbers and consequently of random variation.[23]

In this way we were able to highlight two contrasting situations, in one part an area of very low MS presence and in another a hot spot for MS. A reduced occurrence of MS was seen in the island of San Pietro compared with what was expected (SMR = 0.2). The island of San Pietro (Italian: *Isola di San Pietro*) is an island lying approximately 7 km off the SW Coast of Sardinia, Italy, facing the Sulcis peninsula. Its 6000 inhabitants are mostly concentrated in the town of Carloforte. The island remained uninhabited for centuries until it was colonized by the Ligurian-speaking people from the Tunisian town of Tabarka in the 18th century, and today most of its population has retained a variant of the Genoese dialect, called *Tabarchino*. Many researchers have focused their attention on the population of San Pietro, because of its peculiar linguistic, genetic and demographic features.[4,24] Studies into surnames,

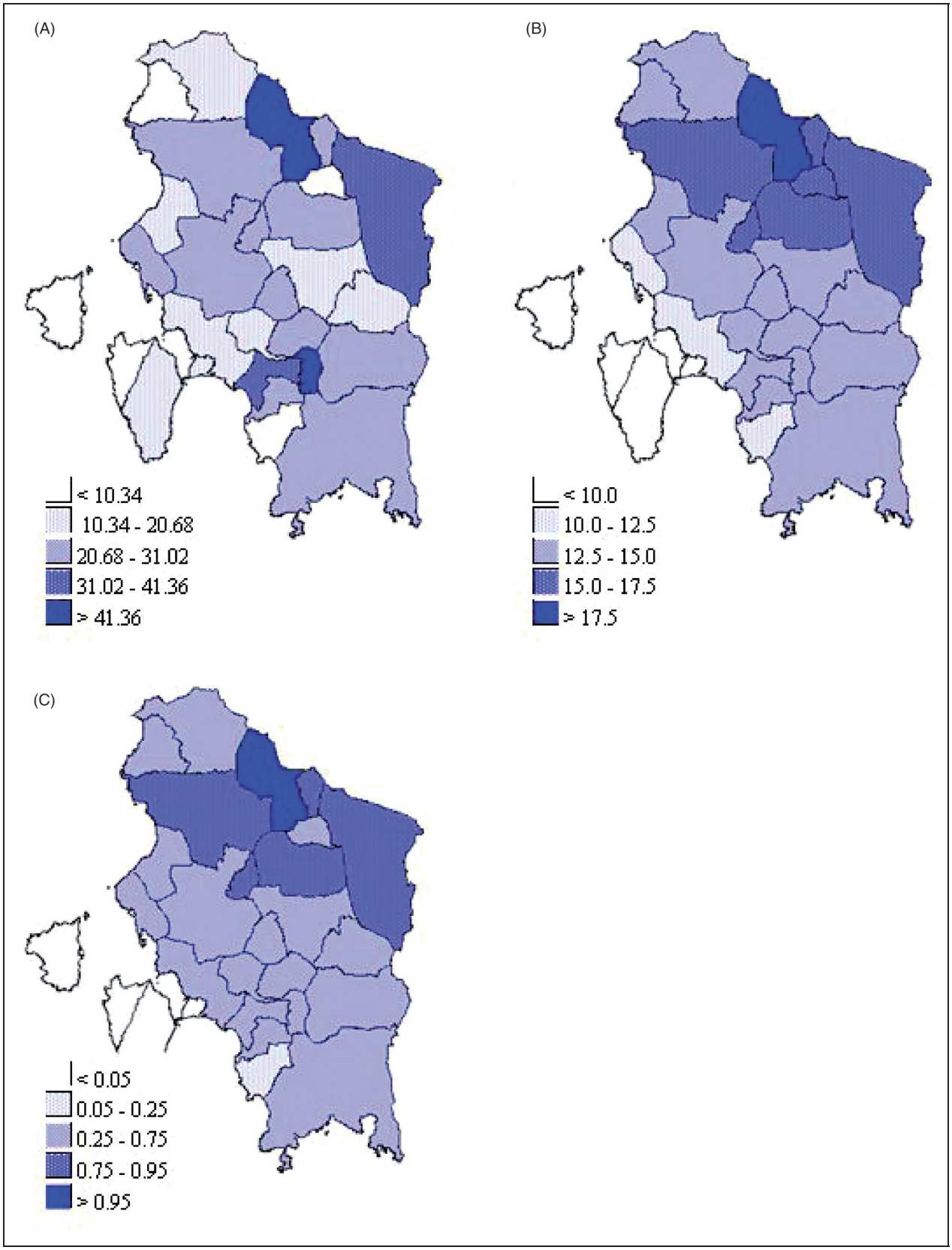

Figure 1. Map of the geographical variation of MS across the 25 villages in SWS. A, crude prevalence map; B, Bayesian prevalence map; C, PP map. MS: multiple sclerosis, PP: posterior probability.

matrimonial structure and genetic polymorphisms demonstrated a strong differentiation of the population of San Pietro from other Sardinian or Italian populations.[4,24] This differentiation is probably due to the isolation that for centuries characterized the island.[4,24] We can hypothesize that the genetic structure of the inhabitants of San Pietro could be protective against MS, determining in this way a very low disease prevalence in contrast to the surrounding areas. Furthermore, the environment could also play a role in MS occurrence in Sardinia: we found, using Bayesian analysis, an unexpectedly high MS prevalence in a band located in the upper part of SWS, particularly in the village of Domusnovas. No definitive data are available to understand the MS cluster in Domusnovas; however, considering that no reasons for genetic difference from other Sardinians are present, we could hypothesize that a role is played by the environment. Moreover, the elevated number of cases in the village was predominantly determined by an increased prevalence in male subjects, suggesting a possible occupational role. It is interesting to note that the economy of SWS in recent centuries was based on extraction and mining of different metals such as iron, lead, zinc and silver.[5] In particular, in Domusnovas, the mining activity was focused on the extraction of lead and there was also a steel industry.[5] The mines and foundry were closed a few decades ago; however, a power plant is still open in the town.[5]

We also observed a temporal trend, with an increase of MS incidence in SWS in recent decades. Although we cannot exclude the possibility that this could be due to ascertainment bias determined by improvements in diagnostic tools, our data are in line with what can be seen in other countries[25] and also in other parts of Sardinia.[2,26] It has been suggested that the increase in MS incidence is caused by environmental factors, and some authors have proposed the role of the 'hygiene hypothesis'.[27]

In conclusion, our data confirm the high frequency of MS in the southern part of the island and support the interaction of genetics with environmental factors in MS risk.

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Conflict of interest statement

Dr. Cocco serves on scientific advisory boards for Biogen Idec, and receives speaker honoraria from Biogen Idec, Merck Serono, Bayer Schering Pharma, and Sanofi-Aventis. Dr Sardu receives research support from Merck Serono. Dr Carboni receives research support from Bayer. Dr. Marrosu serves on scientific advisory boards for Biogen Idec, Bayer Schering Pharma, and Merck Serono and receives speaker honoraria and research support from Biogen Idec, Merck Serono, Bayer Schering Pharma, Novartis, and Sanofi-Aventis.

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