Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 57, No. 1, February 15, 2007, pp 171–178
DOI 10.1002/art.22500

ORIGINAL ARTICLE

Epidemiology and Clinical Course of Behçet's Disease in the Reggio Emilia Area of Northern Italy: A Seventeen-Year Population-Based Study

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Objective. **To investigate the epidemiology and clinical course of Behçet's disease (BD) over a 17-year period in a defined area of northern Italy.**

Methods. **All patients with incident BD diagnosed over a 17-year period (from January 1, 1988 to December 31, 2004) living in the Reggio Emilia area were identified through the following sources: physicians at Reggio Emilia Hospital, medical practitioners, and community-based specialists. We identified all patients registered in a centralized index and in the Reggio Emilia district database for rare diseases. Patients were followed up from the time of diagnosis until either their death or April 1, 2005.**

Results. **Eighteen patients (9 men and 9 women) had complete BD. Mean ± SD age at diagnosis was 33 ± 7 years. The incidence rate of BD was 0.24 per 100,000. The prevalence of BD on January 1, 2005 was 3.8 per 100,000. No patients died during the followup period. Although all patients developed oral ulceration during the disease course, 22.2% had no oral lesions at disease onset. Eye disease occurred in 55.6%. Ocular disease was more common in men and appeared at disease onset or within the first few years of disease onset (median 3 years). Only 1 patient had loss of useful vision in at least 1 eye at the end of followup. In all affected patients, visual acuity improved once treatment was started.**

Conclusion. **This population-based study is the first to report the prevalence and incidence of BD in Italy. In Italian patients, BD is nonfatal and the prognosis of eye disease is good.**

KEY WORDS. Behçet's disease; Population-based study; Epidemiology; Morbidity.

INTRODUCTION

Behçet's disease (BD) is a vasculitis of unknown etiology characterized predominantly by recurrent oral and genital aphthae, uveitis, and a variety of skin lesions (1,2). BD has a distinct geographic distribution, its prevalence being much higher in countries along the ancient Silk Road, extending from Japan to the Mediterranean and Middle Eastern countries, than in northern Europe (3).

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Submitted for publication December 8, 2005; accepted in revised form June 1, 2006.

A close correlation exists between the geographic distribution of HLA–B51 and the prevalence of BD, which is higher in countries with the highest frequency of HLA–B51 (3). Italy's general population has an HLA–B51 prevalence >10% (4–6). It is one of the countries with the highest prevalence of this allele in Europe. However, there are no population-based data on the epidemiology of BD in Italy.

Kural-Seyahi et al reported the long-term mortality and morbidity of patients with BD in Turkey over a 20-year period (7). Mortality and severity of most clinical manifestations tended to decrease with the passage of time. This finding suggests that the disease burden of BD is usually confined to the early years of its course, and that in many patients the disease burns out.

The aim of the present study was to investigate the incidence, prevalence, mortality, and clinical spectrum of BD in a defined area of northern Italy during a 17-year period. In particular, we examined the clinical manifestations at onset and throughout the disease course, treatment, followup, and outcome of patients with BD.

PATIENTS AND METHODS

Study design and population. In a retrospective cohort study, all patients with incident BD diagnosed over a 17-year period (from January 1, 1988 to December 31, 2004) living in the Reggio Emilia area (provincia di Reggio Emilia) were identified through the following sources: physicians based at the Reggio Emilia Hospital (Arcispedale Santa Maria Nuova), medical practitioners, and community-based specialists. All patients referred by medical practitioners and community-based specialists for suspected BD were reassessed by rheumatologists of Arcispedale Santa Maria Nuova, who periodically also provide consultations to general practitioners and community specialists outside the hospital in the 6 districts of the Reggio Emilia area. To ensure a virtually complete ascertainment of the cases, we identified all patients with BD in the Reggio Emilia area registered in a centralized index and in the Reggio Emilia district database for rare diseases. The centralized index comprises all diagnoses made by hospital- and community-based specialists in the Emilia Romagna region, which includes the Reggio Emilia area. Furthermore, the index permitted us to evaluate if patients living in the Reggio Emilia area were followed up within or outside of this area. Finally, we checked the Reggio Emilia district database for rare diseases, which was created to identify all patients with rare diseases, including BD, in order to exempt patients from payment of disease-related medical costs.

The lists of patients with BD obtained using these different methods were compared to ensure a complete ascertainment of patients with BD in the Reggio Emilia area. No new cases were found using either the centralized index or the district database for rare diseases.

Hospital Santa Maria Nuova is the only referral center for the population of 486,961 individuals living in the Reggio Emilia area. All patients were required to have been living in the Reggio Emilia area for at least 12 months prior to diagnosis. All identified patients were contacted by telephone and were called back to the outpatient clinic for reevaluation. Information on clinical manifestations, laboratory findings, disease course, and treatments was obtained through interviews and by reviewing the medical records of the patients. A standard form was used to collect clinical findings related to BD with special emphasis on mucocutaneous, ocular, articular, neurologic, vascular, and gastrointestinal manifestations. Results of pathergy tests and HLA–B51 typing were recorded when available. All patients with and without eye disease were examined by the same ophthalmologist (LC) when called back for a reevaluation at the end of followup. Visual acuity was measured using a Snellen chart and fundoscopy was performed. Patients were followed up from the time of diagnosis until either their death or April 1, 2005. Outcome information was available for all patients at the end of followup. A manifestation was considered to be currently present if it had occurred at least once during the previous 6 months of the final reevaluation visit.

Patients were classified as having complete BD if they fulfilled the International Study Group (ISG) criteria for BD (8). Serologic HLA class I typing was performed by the standard microlymphocytotoxicity technique using peripheral blood lymphocytes.

Statistical analysis. The population distribution was provided by the Ufficio di Statistica Generale della regione Emilia Romagna (9). In Italy the censuses are taken every 10 years when the last figure of the year is 1. In addition, municipalities in Regione Emilia Romagna assess the population every year (9). The target population comprised the entire population of the Reggio Emilia area during the 17-year study period. The Reggio Emilia population is predominantly white, with a steady increase of ~1% yearly from 414,264 inhabitants in 1988 to 486,961 in 2004 (9). The percentage of immigrants increased progressively from 1.5% in 1993 to 7.5% in 2004. The immigrant composition in 2004 was as follows: 20.4% Moroccan, 11.4% Albanian, 9.1% Indian, 8.6% Chinese, 6.5% Pakistani, 6.1% Tunisian, 5.0% Ghanian, 4.5% Ukrainian, 3.3% Romanian, 3.1% Egyptian, and 21.9% from other countries. Age- and sex-specific incidence rates were calculated using the number of new cases observed as the numerator and the mean of the Reggio Emilia population from 1988 to 2004 as the denominator. Rates were reported as cases per 100,000 in the population. Using the annual estimates of the Reggio Emilia population, sex-specific incidence rates were calculated for each year from 1988 to 2004. Single-year incidence rates were adjusted for age and sex to the 1991 Italian census population (10). We calculated 95% confidence intervals (95% CIs). Prevalence was estimated on January 1, 2005. The prevalence rate was obtained by dividing the number of patients who had the disease (active plus remitted) on January 1, 2005 by the number of individuals in the population (Reggio Emilia Provincia 2003 population). Comparisons were made using Student's *t*-test and Mann-Whitney U test. To analyze categorical data, we performed the chi-square test or Fisher's exact test when the minimum expected value was <5. Data were not analyzed for multiple variable testing and *P* values were not adjusted. Statistical analysis was conducted using the SPSS statistical package (SPSS, Chicago, IL).

RESULTS

Epidemiology. Eighteen patients (9 men and 9 women) satisfied the ISG criteria for BD (complete BD). All patients were white, were of Italian descent, and had been living in Italy for at least several generations. Mean ± SD age at diagnosis was 33 ± 7 years. Age- and sex-specific incidence rates are shown in Table 1. Differences by sex were not statistically significant. The yearly incidence rates by sex from 1988 to 2004 are shown in Table 2. As of January 1, 2005, the prevalence of active or resolved cases of complete BD was 3.8 per 100,000 (95% CI 2.0–5.8). No patients died during the followup period (median duration 7.5 years, range 1–17 years).

Clinical features. The initial clinical features and those present at the end of followup are shown in Table 3. The

Table 1. Average annual incidence of Behçet's disease among residents of Reggio Emilia provincia, northern Italy, 1988–2004, by sex and age group per 100,000 populations*

Age group, years	Men			Women			Total		
	No.	Rate	95% CI	No.	Rate	95% CI	No.	Rate	95% CI
0–4	0	—	—	0	—	—	0	—	—
5–9	0	—	—	0	—	—	0	—	—
10–14	0	—	—	0	—	—	0	—	—
15–19	1	0.506	0.013–2.818	0	—	—	1	0.260	0.007–1.451
20–24	1	0.415	0.010–2.311	0	—	—	1	0.211	0.005–1.178
25–29	1	0.339	0.009–1.888	2	0.709	0.086–2.561	3	0.520	0.107–1.512
30–34	4	1.288	0.351–3.297	1	0.343	0.009–1.914	5	0.831	0.270–1.940
35–39	2	0.684	0.083–2.472	3	1.089	0.225–3.182	5	0.881	0.286–2.055
40–44	0	—	—	2	0.769	0.093–2.778	2	0.377	0.046–1.363
45–49	0	—	—	1	0.408	0.010–2.274	1	0.202	0.005–1.126
>49	0	—	—	0	—	—	0	—	—
Total	9	0.245	0.112–0.466	9	0.235	0.107–0.446	18	0.240	0.142–0.379

* 95% CI = 95% confidence interval.

total clinical manifestations that occurred at any time throughout the disease course are shown in Table 4. Oral ulcerations were the most frequent initial manifestation of the disease. However, although oral ulcerations were observed in all patients during the disease course, 22.2% of patients had no oral lesions at disease onset. Cutaneous lesions were the second most common initial manifestations and occurred in all patients during the disease course. Ocular manifestations were present in 27.8% patients at disease onset and in 55.6% patients later in the disease course.

Ocular disease, in particular posterior uveitis/retinal vasculitis, was more common in men. There was a trend for increased prevalence of erythema nodosum in women, which, however, did not reach statistical significance.

Ten patients had ocular involvement. Ocular involvement was bilateral in 7 patients and unilateral in 3 patients. Panuveitis was observed in 4 patients, posterior uveitis in 4 patients, and anterior uveitis in 2 patients. One patient had posterior uveitis on the right eye and anterior uveitis on the left eye. In 5 patients, inflammatory eye disease was the presenting feature. In 2 patients it was the only initial manifestation, which preceded the second manifestation by 3 and 8 months, respectively, whereas in 3 other patients it appeared at the same time. In 5 patients eye involvement occurred a median of 36 months (range 6–60 months) after disease onset.

Two patients had neurologic involvement 1 year and 14 years after the initial manifestation of BD, respectively. One patient had right hemiparesis, and the other patient

Table 2. Yearly incidence of Behçet's disease in residents of Reggio Emilia provincia, northern Italy, by sex from 1988 to 2004 per 100,000 populations

Year	Men			Women		
	No.	Rate	Adjusted rate*	No.	Rate	Adjusted rate*
1988	1	0.495	0.519	—	—	—
1989	1	0.493	0.558	—	—	—
1990	—	—	—	1	0.464	0.500
1991	—	—	—	—	—	—
1992	—	—	—	1	0.460	0.462
1993	—	—	—	2	0.917	0.896
1994	—	—	—	1	0.456	0.445
1995	1	0.477	0.500	—	—	—
1996	—	—	—	—	—	—
1997	1	0.467	0.574	—	—	—
1998	1	0.461	0.391	—	—	—
1999	1	0.454	0.374	—	—	—
2000	—	—	—	1	0.431	0.433
2001	1	0.439	0.337	—	—	—
2002	2	0.868	0.710	—	—	—
2003	—	—	—	2	0.824	0.838
2004	—	—	—	1	0.405	0.320
1988–2004	9	0.245	0.247	9	0.235	0.227

* Age- and sex-adjusted to the 1991 Italian population.

Table 3. Frequency of clinical features in 18 patients with Behçet's disease at the time of disease onset and final visit*

Clinical feature	Disease onset	Final visit
Oral aphthae	14 (77.8)	7 (38.9)
Genital aphthae	3 (16.7)	2 (11.1)
Cutaneous lesions	6 (33.3)	4 (22.2)
Papulopustular lesions, acne, follicular lesions	3 (16.7)	3 (16.7)
Erythema nodosum	4 (22.2)	2 (11.2)
Inflammatory ocular involvement	5 (27.8)	0 (0)
Anterior uveitis	2 (11.1)	0 (0)
Posterior uveitis and retinal vasculitis	4 (22.2)	0 (0)
Arthritis	3 (16.7)	2 (11.1)
Central nervous system involvement	0 (0)	0 (0)
Venous thrombosis	0 (0)	0 (0)

* Values are the number (percentage). Manifestation was considered to be currently present if it occurred at least once during the previous 6-month period of the final reevaluation visit.

had bilateral internuclear ophthalmoplegia, peripheral palsy of the left VII cranial nerve, right hemiparesis, pyramidocerebellar syndrome, and behavioral changes. Cerebral magnetic resonance imaging scans were abnormal in both patients, showing bilateral lesions mainly located in the basal ganglion region and in the brainstem.

Genital ulcers, arthritis, and a positive pathergy test were observed during the disease course in 77.8%, 50%, and 11.1% of patients, respectively. One patient had superficial venous thrombosis.

Treatment, followup, and outcome. Corticosteroids (72.2%) were the most frequently used drug during the disease course, followed by colchicine (44.4%), cyclosporin (33.3%), and azathioprine (22.2%). Two patients were treated with methotrexate, whereas thalidomide, cyclophosphamide, chlorambucil, sulfasalazine, and interferon-α were used in 1 patient each.

The 2 patients with neuro-Behçet's disease were treated with chlorambucil (0.2 mg/kg/day) and cyclophosphamide (1 gm intravenously once a month) 10 days and 7 days, respectively, after the appearance of the initial neurologic manifestation, in both cases in combination with prednisone (1 mg/kg/day). The first patient was successfully treated with chlorambucil for 6 months, then the drug was progressively tapered over 2 months. This patient did not experience any neurologic relapse after discontinuation of treatment during a 14-year followup period. At the patient's last visit the disease was in complete remission without any therapy having been administered for the last 6 years. The second patient had a 6-month followup period. At the last visit cyclophosphamide was administered intravenously for the sixth time. Prednisone dosage was 10 mg/day. The patient was in complete remission with minimal neurologic sequelae.

Seven patients with ocular disease were treated with immunosuppressive agents: 5 patients were treated with cyclosporin (3–5 mg/kg/day), 3 with azathioprine (100–

Table 4. Comparison of clinical features between male and female patients occurring throughout the course of Behçet's disease in our patient population*

	Males (n = 9)	Females (n = 9)	*P* Males vs. females
Oral ulcers	9 (100)	9 (100)	NS
Genital ulcers	6 (66.7)	8 (88.9)	NS
Cutaneous lesions	9 (100)	9 (100)	NS
Papulopustular lesions	6 (66.7)	6 (66.7)	NS
Follicular lesions	1 (11.1)	2 (22.2)	NS
Acne	1 (11.1)	0 (0)	NS
Erythema nodosum	3 (33.3)	7 (77.8)	NS
Epididymitis	0 (0)	NA	—
Inflammatory ocular involvement	8 (88.9)	2 (22.2)	0.01
Anterior uveitis	5 (55.6)	1 (11.1)	NS
Posterior uveitis and retinal vasculitis	7 (77.8)	2 (22.2)	0.06
Arthritis†	3 (33.3)	6 (66.7)	NS
CNS involvement	0 (0)	2 (22.2)	NS
Venous thrombosis	1 (11.1)	0 (0)	NS
Deep venous thrombosis	0 (0)	0 (0)	—
Superficial venous thrombosis	1 (11.1)	0 (0)	NS
Positive pathergy test‡	1 (20.0)	0 (0)	NS
HLA–B51 positivity§	6 (85.7)	3 (60.0)	NS

* Values are the number (percentage) unless otherwise indicated. NS = not significant; NA = not applicable; CNS = central nervous system.
† Mainly oligoarthritis involving the knee and/or ankles.
‡ Performed in 9 patients (5 males and 4 females).
§ Determined in 12 patients (7 males and 5 females).

Table 5. Association between Behçet's disease prevalence and frequency of HLA–B51 in different countries*

Country (reference)	Prevalence per 100,000 population	HLA–B51 frequency in controls, %
Great Britain		
Scotland (3,12)	0.27	3.6
Yorkshire (3,13)	0.64	8.3
US		
Olmsted county, MN (14)	0.33	NR
Sweden (15)	1.18	3
Portugal (16)	1.53	17
Germany (17)	2.26	14
Italy		
Entire country (11)	2.50	17.4
Reggio Emilia area (present study) (5)	3.80	19.2
Spain (18,19)	7.50	15.5
Japan (20)	13.5	22
Iran (21,22)	16.7	33
Saudi Arabia (23,24)	20.0	26
Turkey (25–28)		24
Northeastern	370	
Ankara region	110	
Istanbul	420	

* NR = not reported.

150 mg/kg/day), 1 with methotrexate (20 mg/week), and 1 with interferon-α (initial dose 6 million units daily). Immunosuppressive agents were started in combination with oral corticosteroids at the beginning of eye involvement in 5 patients. Oral corticosteroids (initial dose: prednisone 1 mg/kg/day) were administered in 9 patients, while topical steroids were used in 4 patients. Outcome information on visual acuity was obtained by the same ophthalmologist (LC) at the last visit in all patients.

Initial visual acuity was reduced in 11 of 20 eyes (55%). In 10 eyes there was a significant improvement of visual acuity once treatment was started, which was maintained at the last visit: from 1/10 to 10/10 in 2 eyes, from 1/10 to 8/10 in 1 eye, from 2/10 to 10/10 in 1 eye, from 2/10 to 9/10 in 1 eye, from 3/10 to 10/10 in 1 eye, from 4/10 to 10/10 in 1 eye, from 7/10 to 10/10 in 2 eyes, and from 9/10 to 10/10 in 1 eye. Only 1 patient had loss of useful vision (finger counting) in 1 eye at the end of followup. In the other 9 eyes, initial visual acuity was 10/10 and did not worsen during the disease course.

Inflammatory ocular disease was in remission in all patients at the last visit. The median interval between the last episode of ocular inflammation and the last visit was 4.5 years (range 2–17 years). At the last visit, only 2 patients were still receiving therapy: 1 was receiving azathioprine (150 mg/day) and oral prednisone (10 mg/day), and the other patient was receiving interferon-α (3 million units 3 times weekly).

The frequency of clinical features at the time of the last visit is shown in Table 3. At the end of followup, all patients were alive and 8 patients (44.4%) were not receiving therapy because their condition was in remission or was only minimally active.

DISCUSSION

Most epidemiologic studies of BD are hospital based and have only been aimed at determining the prevalence of the disease. Very few studies are population based, and most do not use a case-finding design. The data have generally been obtained using cases referred to tertiary referral centers of ophthalmology, dermatology, or rheumatology. Therefore, the incidence/prevalence of BD have probably been underestimated, because hospital-based studies tend to select cases with more severe disease.

Our study is one of the few population-based studies that has ascertained both the prevalence and the incidence of BD in a specific area of Italy. We used a system that ensured a virtually complete ascertainment of all clinically recognized cases of BD among the Reggio Emilia area residents. We found a prevalence of 3.80 cases per 100,000, which is higher than that previously reported by Pivetti-Pezzi in a hospital (ophthalmologic) setting in Italy (11).

In Italy, as in virtually every population studied, the most closely associated risk factor for BD is the HLA–B51 allele, which confers a relative risk of 5.7 (5). The prevalence of the HLA–B51 allele in the Italian population has been estimated as being >10% (4–6), which is one of the highest prevalences in Europe. For the sake of comparison, the prevalence of BD and of the HLA–B51 allele in different populations is shown in Table 5 (12–28). As Table 5 exemplifies, there is a close correlation between the geographic distribution of the HLA–B51 allele and the prevalence of BD. In fact, the lowest prevalence has been found in Scotland (0.27 per 100,000), where the HLA–B51 frequency in the general population is 3.6% (3,12); by contrast, in Turkey the prevalence has been variably reported

as being in the range of 110–420 per 100,000 and the frequency of HLA–B51 is 24% (25–28). Portugal, Italy, and Spain are 3 southern European countries with a similar frequency of HLA–B51 in the general population; however, the prevalence of the disease is different, being 5 times higher in Spain than in Portugal. In Italy the prevalence is 2–3 times lower than in Spain, but is ~2 times higher than in Portugal (5,11,16,18,19). Therefore, the contributory influence of some other genes and/or environmental factors is likely. We also calculated the incidence rate of BD in the Reggio Emilia area. Consistent with previous data, we found an annual incidence rate of 0.24 per 100,000, which is lower than that observed in Iran (29), Spain (30), and Greece (31), where the annual incidence rates are 0.58 per 100,000, 0.66 per 100,000, and 4 per 100,000, respectively.

With regard to the clinical features of BD, in our population the age at diagnosis and the frequency of the specific clinical manifestations were similar to those observed in other European countries and in a previous hospital-based multicenter Italian study (6,32). In particular, we did not observe a significant preponderance of men, and the onset of BD at <16 years of age was exceptional. We observed an 11% frequency of positive pathergy tests, which is similar to that reported in Spanish patients (30), but is much lower than that reported in Middle Eastern countries and Japan (21,33–35). The frequencies of ocular lesions and neuro-Behçet's (55.6% and 11.1%, respectively) were similar to those reported in other European countries (32). Male patients had posterior eye disease (77.8%) more often than female patients (22.2%). Anterior uveitis was also more common in men than in women, but the difference was not significant. Male predominance in terms of BD eye involvement was observed in a previous multicenter Italian study and is well documented in the medical literature (6,36,37). There was a trend for increased prevalence of erythema nodosum in women, which, however, did not reach statistical significance. The other clinical features were equally represented in men and women.

All of our patients developed oral ulcers during the disease course, but in 22.2% oral lesions were absent at disease onset, which is in line with the results of previous hospital-based studies that reported absence of oral ulcers in 19–27% of patients with BD at disease onset (38,39). Because the ISG criteria for BD consider oral ulcers a prerequisite for a diagnosis of BD (8), our data suggest that such criteria are not entirely suitable for the early diagnosis of BD.

Our study provided us with the unique opportunity to evaluate the long-term mortality and morbidity of patients with BD in a population-based setting. Generally speaking, large-vessel disease and neurologic involvement are the main causes of mortality in BD (40,41). In our population, no patients had large-vessel disease. There were 2 patients with neuro-Behçet's, who were diagnosed at an early stage and were treated aggressively. These patients were in complete remission with minimal neurologic sequelae at the end of followup. In fact, none of our patients died during the followup period. In a hospital-based series, Kural-Seyahi et al (7) observed an increased mortality in patients with BD, in particular among young males, which tended to decrease with the passage of time. However, in agreement with our data, 2 other studies reported no increase in mortality in patients with BD (42,43). Turning to morbidity, we looked specifically at inflammatory ocular disease, because this is both a frequent and a potentially serious complication of BD with a significant risk of visual loss (1,2). At the end of followup, all patients with and without eye disease were reevaluated by an ophthalmologist. In keeping with previous studies (7,44–47), most of our patients developed eye disease at onset or within the first few years from disease onset. Contrary to the poor prognosis for eye involvement reported by older studies (44,45,47–49), we observed an overall favorable prognosis, in agreement with more recent studies (46,50–52). Only 1 (11%) of 9 patients with posterior eye involvement had loss of useful vision in at least 1 eye at the end of the followup, whereas almost all patients had improvement of visual acuity once treatment was started. The improved prognosis may be attributed to the early aggressive treatment with immunosuppressive agents and oral corticosteroids (7,53) and possibly to the long-term use of cyclosporin in most patients (50,52). In agreement with Kural-Seyahi et al (7), we demonstrated that the frequency and severity of eye involvement decreased over time. At the end of the followup, eye disease was in remission in all patients. Furthermore, only 2 patients remained in treatment. Mucocutaneous and articular manifestations also tended to decrease with the passage of time. Our data therefore confirm the impression that the disease burden of BD is usually confined to the early years of its course, and in many patients the disease eventually burns out (7).

In this study, we used several sources for case ascertainment to reduce a potential underestimation of BD cases and thus avoid incurring potential bias. However, it is possible that a small number of patients with BD may have escaped the recording system. This might apply to milder cases, in particular to patients with mild oral and genital ulcers and skin lesions. In contrast, all specialized medical care for the Reggio Emilia area is provided at the Santa Maria Nuova Hospital, there are no private hospitals or rheumatologists in private practice in this area, and rheumatologists of Santa Maria Nuova Hospital periodically also provide consultations outside the hospital in the 6 districts of the Reggio Emilia area. Finally, no patients with BD living in the Reggio Emilia area appeared to have been followed up outside of this area. Therefore, we do not expect any significant underestimation of BD cases in the area studied.

ACKNOWLEDGMENTS

The authors thank Drs. Silvia Candela and Nando Luberto (Unità Operativa di Reggio Emilia, Dipartimento di Sanità Pubblica, Azienda USL di Reggio Emilia) for assistance in the statistical analysis.

AUTHOR CONTRIBUTIONS

Dr. Salvarani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Drs. Salvarani, Macchioni, Olivieri, and Boiardi.

Acquisition of data. Drs. Cimino, Tumiati, Macchioni, and Bajocchi.
Analysis and interpretation of data. Drs. Pipitone, Catanoso, Cimino, Tumiati, Bajocchi, and Boiardi.
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