

# The Sardinian IDDM Study: 1. Epidemiology and geographical distribution of IDDM in Sardinia during 1989 to 1994

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**Summary** Analysis of the geographical variation of risk for a disease is a key issue in descriptive epidemiology and may provide useful suggestions for planning further studies to identify the underlying causes. We adopted a Bayesian approach to investigate the geographical distribution of insulin-dependent diabetes mellitus (IDDM) incidence rate across Sardinia. Data on incidence of IDDM in children aged under 15 years (619 IDDM cases) in Sardinia was obtained by the Sardinian Eurodiab ACE register. The overall completeness of ascertainment was: 91.3%. The average yearly standardized incidence rate for the years 1989–1994 was 33.24 per 100 000 (95% C.I. 30.60, 35.88), which is the second highest in Europe after Finland. Sex and age-specific risks were higher in males than in females. Considering the variation of IDDM risk according to the age at diagnosis, the risk profile increased up to the 13th year of age for both sexes, being steeper in males. The degree of geo-

graphical variation in IDDM risk was small with a slight difference between the highest and the lowest standardized rate across the map. Indeed, even the municipalities at lowest risk in Sardinia showed a risk higher than most European countries. The Sardinian population is genetically atypical, characterized by genetic homogeneity and marked susceptibility to autoimmune diseases. Our finding of a small geographical variation within the island coupled with a marked temporal trend previously observed in data on military conscripts could be interpreted as evidence of a relatively recent environmental aetiological factor that was uniformly distributed across the island and had its effect in a genetically predisposed population. [Diabetologia (1998) 41: 221–227]

**Keywords** Sardinia, childhood IDDM, incidence, statistics, epidemiology, Bayesian analysis, geographical distribution.

The study of the variation in space and time of disease risk may provide important clues about its aetiology [1–3] and also useful suggestions for planning further studies aimed at investigating the underlying causes. The high incidence of insulin-dependent diabetes mel-

litus (IDDM) observed in Sardinia and its peculiar genetic characteristics make Sardinia an interesting place to investigate the epidemiology of IDDM.

Previous studies showed that Sardinia has the second highest IDDM incidence (30.2/100 000 person-years [4]) after Finland (35.7/100 000 person-years [5]). A recent analysis of the Sardinian conscripts' register indicated that, like in Finland [5, 6], IDDM risk has been progressively increasing in Sardinia since the 1960s [3, 7, 8].

The Sardinian population is genetically distinct from all other Mediterranean and European populations because of a pre-historical and historical isolation from continental Italy and more generally from other Mediterranean areas because of the long history of its settlements. This population

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*Abbreviations:* SR, Standardized rate; CI, confidence interval; PP, posterior probability; IR, incidence rate; CB, credible band.

**Table 1** Sex and age incidence rate, standardized rates and number of IDDM cases in Sardinia, 1989–1994

	Males				Females				All <sup>a</sup>
	Age (years)				Age (years)				Total SR <sup>a</sup>
	0–4	5–9	10–14	SR <sup>a</sup>	0–4	5–9	10–14	SR	
Incidence rate (IR)	28.09	43.43	44.69	38.74 (34.77, 42.70)	23.29	32.31	27.62	27.74 (24.24, 31.24)	33.24 (30.60, 35.88)
Cases	75	132	166	373	58	92	96	246	619

<sup>a</sup> Age-standardized incidence rate (95 % CI)

originated from an early split in the Caucasoid group [9–11].

The main aim of this paper is to study the geographical variation of IDDM incidence rate in children aged under 15 years across the 366 municipalities of Sardinia, using the Eurodiab ACE population-based register in Sardinia for the period 1989–1994. We adopted a Bayesian approach to filter out the random variation of the estimates due to the small number of events in each geographical (municipality)/temporal (1-year age) unit. Furthermore, we report the sex and age distribution of incidence for the study period.

## Subjects and methods

**Study population:** The estimate of the population at the 1991 census provided by the Italian Istituto Centrale di Statistica (ISTAT) was of 1 648 248 residents [12]. The 0–14 year-old population consisted of 303 958 children, 157 068 males and 146 890 females.

**Case definition and ascertainment:** IDDM cases were defined according to the diagnosis of idiopathic IDDM as stated by a physician, as in most diabetic registries [13]. Other inclusion criteria for this study were: 1) date of the first insulin injection before 15th birthday and between 1 January 1989 and 31 December 1994; 2) place of residence within the study region at the date of the first insulin injection. Primary case ascertainment was based on hospital records, notification from family practitioners and paediatricians. A secondary independent source of data was the local IDDM patients' association (ADIG Sardegna). The estimated completeness of ascertainment was 91.3 %, calculated by the 'capture-recapture' method [14].

**Data collection:** A standard case record form was used to collect the data. The local investigator of the Eurodiab ACE study provided local collaborators with a case record form, which was sent back to the local investigator whenever a case arose. The recorded variables included case and centre identification, initials, date and place of birth, actual and past residences, gender, date of clinical diagnosis and date of first insulin injection.

**Statistical analysis:** Incidence rates were calculated as the number of newly diagnosed diabetic cases per 100 000 person-years for the age groups 0–4, 5–9 and 10–14 years. We also calculated the male and female age-specific incidence rates and the directly standardized rates (SR) using a reference population comprising equal numbers in each of the age- and sex-specific categories. The 95 % confidence intervals (CI) for these SRs

were calculated using the Gaussian approximation to the Poisson log-likelihood [15].

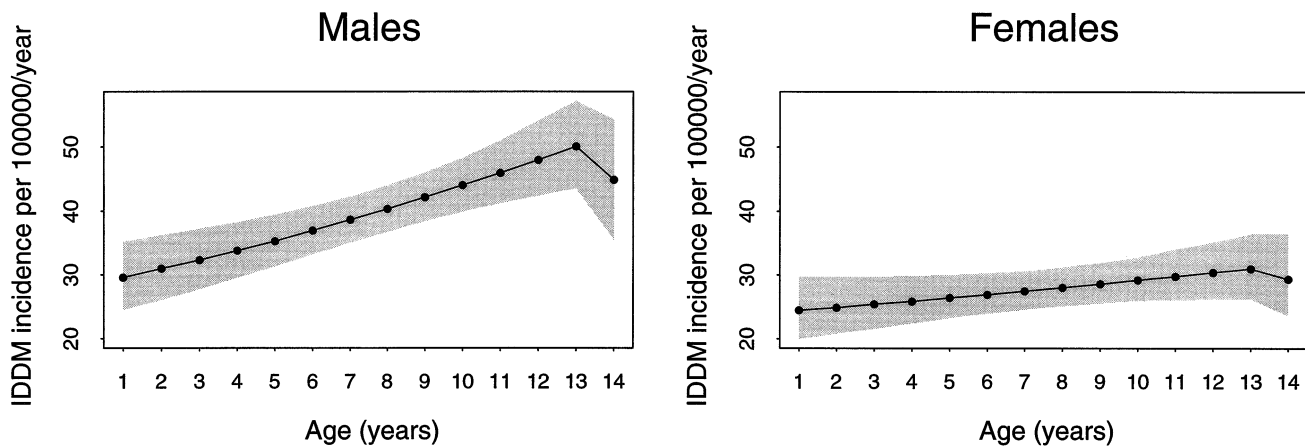
In order to study the geographical variation of IDDM risk, we filtered out the random variation and mapped the smoothed estimates of SRs at the smallest administrative area in the region, i.e. the municipality. We estimated the area-specific smoothed SRs using a Bayesian approach fully described previously [3, 16, 17]. The map of SRs was accompanied by two maps of the posterior probability (PP) that each area has an SR greater than a given reference value. The PP is the Bayesian equivalent of the *p*-value as defined by Meng and Dempster [18]. In our analysis, we chose the following reference values: (a) the SR in Finland and (b) the median SR over all Sardinian municipalities. The two corresponding PP maps allowed us to identify those areas in which (a) risk is greater than or equal to the highest rate in Europe and (b) risk is particularly high or low by comparison with the median risk in the region. We subdivided the range of PP (0–1) into five intervals (< 0.10, 0.10–0.25, 0.25–0.75, 0.75–0.90, > 0.90). A map of PP can be interpreted as follows. A value of PP higher than 0.90 strongly indicates that the SR is higher than the reference value, while a PP smaller than 0.10 indicates that the SR is lower than the reference value. In those areas where PP falls in the fourth interval (0.75–0.90) there is an indication that the SR is higher than the reference value. Similarly, in those areas where PP belongs to the second interval (0.10–0.25) there is an indication that the SR is lower than the reference value. Finally, when the value of PP falls in the central interval (0.25–0.75) there is no evidence of whether the area-specific SR is higher or lower than the reference value.

In order to filter out the random variation of the age-sex-specific incidence rates (IR), we estimated the age-specific IRs by sex using a Bayesian method [19]. The resulting age-specific IR profile is smoothed and hence more interpretable from an epidemiological point of view. For each IR profile the corresponding 95 % credible band (CB), which is the Bayesian equivalent of a 95 % confidence band, was calculated.

**Computational details:** We fitted the Bayesian model for mapping the area-specific SRs using the software package BUGS [20] and analysed the age-specific profile of IDDM risk using BEAM [21]. We performed the computing on the SUN system SPARC center 2000 owned by the Italian National Research Council (C.N.R.) – Istituto di Analisi Numerica, Pavia.

## Results

In each sex and age-group, the maximum likelihood estimates of IR and the number of IDDM cases observed in Sardinia during the study period are shown in Table 1. The sex-specific and the overall age standardized incidence rates (SR) with their correspond-



**Fig. 1.** Sex-specific incidence rates by 1-year age-group with corresponding 95 % credible bands

ing 95 % CI are also reported. During the period 1989–1994, the overall SR in Sardinian children aged under 15 years was 33.24/100000 person-years and it turns out to be higher in males than in females (38.74 and 27.74, respectively). There was a male excess in incidence and the male to female ratio was 1.4. About 21 % of the newly diagnosed children was under 5 years of age at the time of diagnosis. In both sexes the largest proportion of childhood IDDM cases (44.5 % in males and 39 % in females) was diagnosed among 10–14-year-olds. The highest age group incidence rate was in males 44.69/100000 person-years among 10–14-year-olds, and in females 32.31/100000 person-years among 5–9-year-olds.

The profile of the sex-specific incidence rates by 1-year age group is reported in Figure 1 together with their corresponding 95 % CB. Since the number of children diagnosed before their first birthday was very small (8 cases, 1.3 %) the IR estimate for this age group was omitted. The difference in steepness between the profiles of the two sexes is striking. In both profiles the highest incidence was around 13 years of age.

Figure 2a shows the map of SR by municipalities, while Figure 2b and c shows the PP calculated using the Finnish SR and the median SR over all the municipalities as reference values, respectively. The area-specific SRs range from 24/100000 person-years to 42/100000 person-years among the municipalities. The quartiles of the area-specific SRs distribution are: P5 = 28.75, P25 = 31.95, P50 = 35.21, P75 = 36.76, P95 = 38.67.

From Figure 2a it emerges that all the municipalities at higher risk are situated in the central-western part of Sardinia, while most of the lower risk areas lie in the north-western part of the island. Nevertheless, there is no great difference between the highest and the lowest SR throughout the map.

If we compare the area-specific SRs with the Finnish SR on the basis of Figure 2b, it emerges that all the municipalities at high risk highlighted in Figure 2a have their corresponding PP falling in the fourth interval; this means that for these areas there is an indication that the SRs are actually higher than the Finnish rate. No municipalities showed a PP higher than 0.9. If we compare Figures 2a and 2c, it emerges that most of the areas at high risk, i. e. those falling in the fifth interval in Figure 2a, do have a PP greater than 0.9. This means that these areas have a SR significantly higher than the median regional risk. The same applies to the areas at low risk: for all areas with an SR falling into the first category, the PP in Figure 2c is lower than 0.1. Two areas from central-western Sardinia showed a risk greater than that of Finland and than the median risk of the island.

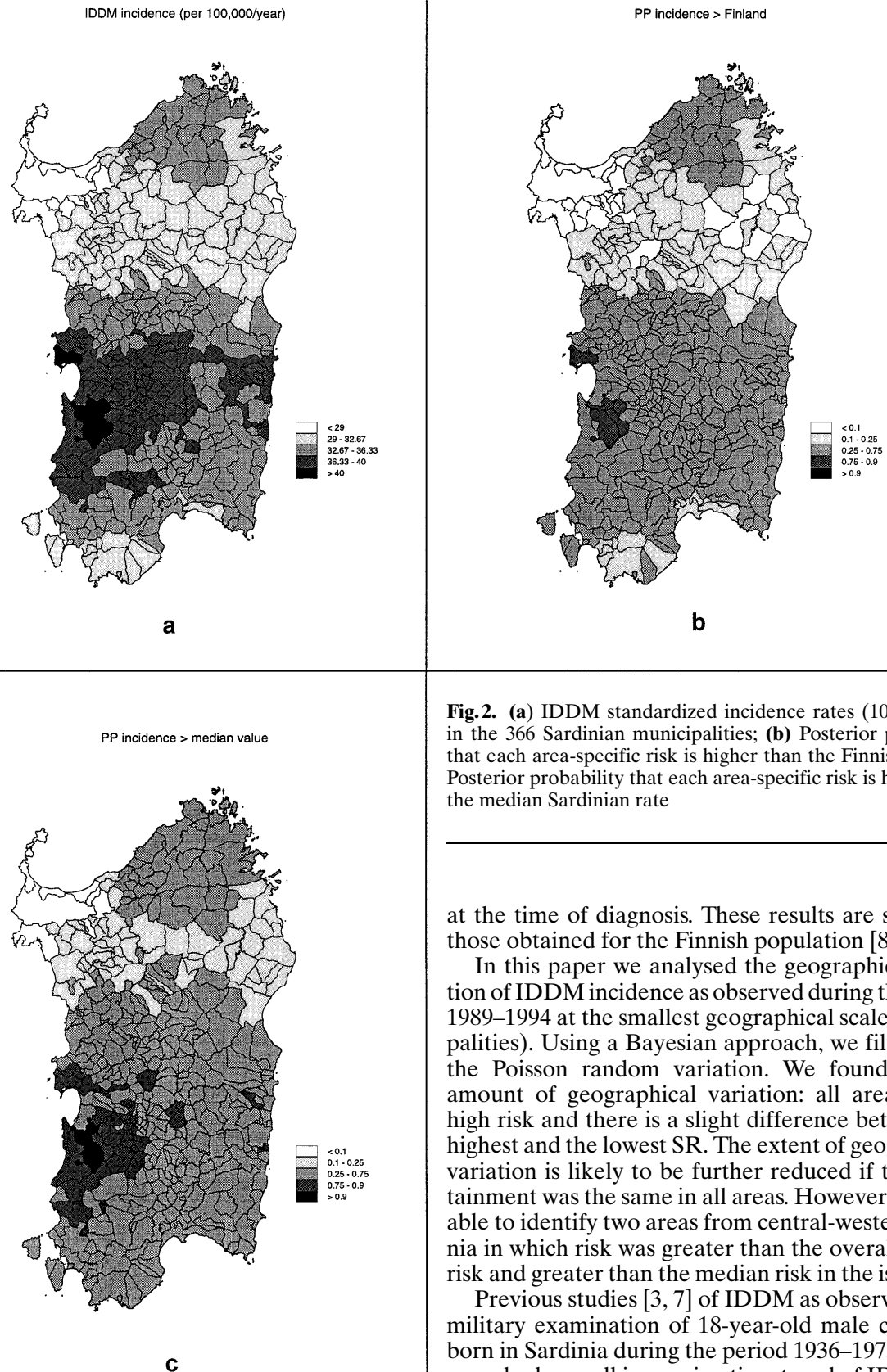
Figure 3 shows a map of the four Sardinian provinces, with the corresponding estimated completeness of ascertainment. By comparison with the SRs map in Figure 2a, IDDM risk seems to be higher in areas with higher completeness.

## Discussion

IDDM is one of the most frequent chronic diseases in children and young adults and it represents a major public health problem because of its associated risk of long-term complications and premature death.

Sardinia has a very high incidence of IDDM. The overall SR ranks second in Europe after Finland and is much higher than in any other Italian region for which IDDM incidence data are available [22–26].

IDDM risk is higher in males than in females, as already reported [8, 27]. Considering the variation of IDDM risk according to the age at diagnosis, the risk profile increases up to 13th year of age both for males and females, but the profile is steeper in males. In general, the lowest incidence rates are observed in the 0–4 age-group and the highest in the 5–9 for females and 10–14 age-groups for males. Of the newly diagnosed children 21 % were under 5 years of age

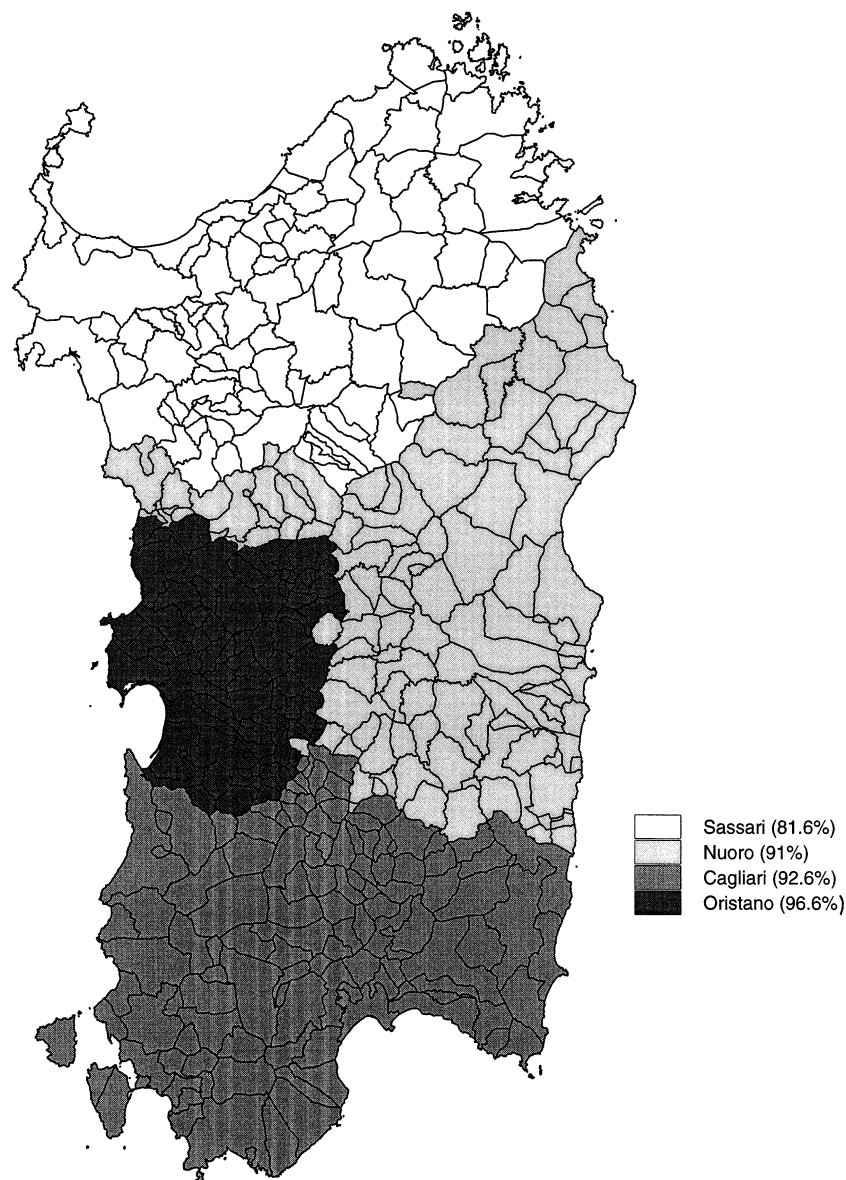


**Fig. 2.** (a) IDDM standardized incidence rates (100000/year) in the 366 Sardinian municipalities; (b) Posterior probability that each area-specific risk is higher than the Finnish rate; (c) Posterior probability that each area-specific risk is higher than the median Sardinian rate

at the time of diagnosis. These results are similar to those obtained for the Finnish population [8, 28].

In this paper we analysed the geographical variation of IDDM incidence as observed during the period 1989–1994 at the smallest geographical scale (municipalities). Using a Bayesian approach, we filtered out the Poisson random variation. We found a small amount of geographical variation: all areas are at high risk and there is a slight difference between the highest and the lowest SR. The extent of geographical variation is likely to be further reduced if the ascertainment was the same in all areas. However, we were able to identify two areas from central-western Sardinia in which risk was greater than the overall Finnish risk and greater than the median risk in the island.

Previous studies [3, 7] of IDDM as observed at the military examination of 18-year-old male conscripts born in Sardinia during the period 1936–1973 showed a marked overall increasing time trend of IDDM risk (sharp increase from the early 1960s) that cannot be explained in terms of variation in genetic susceptibili-



**Fig.3** Completeness of ascertainment in the four Sardinian provinces

ty to IDDM of Sardinians, which are a genetically distinct and stable population.

The lack of geographical variation in IDDM risk across Sardinia coupled with the marked temporal trend observed in the military conscript data may suggest that a relatively recent environmental factor uniformly distributed in the territory exerted its action in a population that is genetically predisposed to autoimmune diseases.

A possible indication emerging from these results is that it would be very difficult to identify the implicated factors in Sardinia because of its geographical uniform distribution. On the other hand the Sardinian population is particularly suitable for studying

the genetic susceptibility to IDDM because of its peculiar genetic characteristics.

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