High Incidence Rate of IDDM in Sardinia

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OBJECTIVE — To provide reliable data on the incidence of IDDM in Sardinia and contribute to a better understanding of its geographical variability throughout Europe.

RESEARCH DESIGN AND METHODS — All newly diagnosed cases of IDDM with onset <30 yr of age between 1 January 1989 and 31 December 1990 among residents in Sardinia were recorded. Primary ascertainment was based on notification by all Sardinian hospitals, outpatient clinics, family doctors, and pediatricians. The local IDDM patient association served as the secondary and independent source.

RESULTS — The completeness of ascertainment was 92.8%. The annual incidence rate of IDDM (per 100,000) over the 2-yr period was 30.7 in the 0–14-yr-old age-group and 24.1 in the entire 0–29-yr-old range, respectively, with no significant differences between the two groups. Male/female ratios were 1.25 and 1.55, respectively. No significant seasonal variation in incidence was observed.

CONCLUSIONS — Sardinia appears to have the second-highest IDDM incidence rate in Europe after Finland, and the island contradicts the generally accepted rule of a south-to-north incidence gradient.

During the past decade, considerable progress has been made in mapping the differences between countries in the incidence of IDDM, and wide geographical variability in its rate has been found. An apparent south-to-north gradient in IDDM incidence—the rates increasing with latitude—exists in both North America and Europe (1). However, reliable information on the incidence of IDDM in southern Europe is still scant.

Sardinia, as a large Mediterranean island with a geographically well-defined and ethnically homogeneous population of 1.6 million people, is suited particularly well to epidemiological surveys. One aim of this study was to gather up-to-date, reliable incidence data on IDDM. Another was to verify, on a region-wide basis, the results of a previous study. That study lacked a secondary validation source and circumscribed only to the province of Cagliari (<50% of the Sardinian population) and reported an unusually high incidence rate of IDDM—24/100,000—for individuals 0–18 yr old for 1983–86 (2). To contribute to a better understanding of geographical variability of IDDM incidence throughout Europe, we participated in the EURODIAB Subarea A Study (because we met the demands of its standard protocol). EURODIAB is a collaborative research action that forms part of the Fourth Medical Research Programme of the European Economic Community (3).

In this study, we measured the incidence of IDDM among residents in Sardinia who were 0–29 yr old during 1989–90. To compare our incidence data with those from several studies on childhood IDDM, we also considered the 0–14-yr-old age-group.

RESEARCH DESIGN AND METHODS

— Sardinians are a homogeneous, genetically distinct population, originated from an early split in the Caucasoid group (4). The 1987 population estimate by the Italian Istituto Centrale di Statistica was 1,643,789 residents (5). The 0–29-yr-old age-group consisted of 406,958 males and 390,978 females, totaling 797,936. In the 0–14-yr-old age-group, 183,435 were boys and 172,723 were girls, totaling 356,158.

The criteria for diagnosing IDDM in children were those generally recognized for diabetes registries (6), which also are those of the EURODIAB protocol: diagnosis of idiopathic diabetes stated by a physician, with insulin therapy started before the 15th birthday in the belief that long-term treatment with insulin will be necessary. The criteria for the diagnosis of IDDM among the adult population (15–29 yr old) were the same, apart from the age limit of starting insulin therapy, obviously <30 yr of age.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; CI, CONFIDENCE INTERVAL.

Individuals who met the criteria for diagnosis of IDDM were included if insulin treatment was started between 1 January 1989 and 31 December 1990 and if the patient had a permanent address on Sardinia at time of diagnosis. The date of diagnosis has been equated with the date of first insulin injection, according to international recommendations (6). In some cases, the clinical diagnosis preceeded the commencement of insulin treatment, but in general the delay was only a few days and had no practical consequence for this analysis. Mandatory data for each patient included personal identification, date and place of birth, sex, ethnic origin, address, date of diagnosis, age at diagnosis, date of first insulin injection, duration of symptoms, hospitalization at diagnosis, height and weight at diagnosis, reported weight loss prior to diagnosis, ketosis (urinanalysis), and blood glucose concentration at diagnosis.

Age- and sex-specific incidence rates have been calculated from the numbers of new cases observed, divided by the estimated number of person-years at-risk in each of the age-groups 0–4, 5–9, 10–14, 15–19, 20–24, and 25–29 yr, for each sex. The denominator was provided by the 1987 population estimate for the relevant age-groups (5).

Assessing the completeness of ascertainment was based on the capture-recapture model, which assumes independent ascertainment of the same catchment population by two alternative sources (7). The primary data source was based on notification to our center of new cases by all Sardinian hospitals, outpatient clinics, family doctors, and pediatricians. Personal identification of each new case (initials, date and place of birth, residence) enabled us to avoid multiple reports of the same case. As the secondary, independent source, we availed ourselves of the local IDDM patient association, ADIG Sardegna, which keeps up-to-date, computerized IDDM member files.

Validation analysis has been performed through calculation of the combined ascertainment probability (%) by the two independent sources, using the formula $a\,(a + b + c) / (a + c)(b + a)$ where a is the number of cases found by either sources, b by the secondary source only, and c by the primary source only (8).

To ensure mutual comparability with similar studies, direct age standardization has been calculated for the sexes separately and for males and females combined, assuming equal numbers in each of the 5-yr age classes (9). This criterion also has been adopted in the EURODIAB protocol.

The 95% CIs have been estimated assuming a Poisson distribution (10). Significance of differences between frequency data has been determined with χ^2 statistics (10).

Table 1—*Number of newly diagnosed cases of IDDM during 1989 and 1990*

	Age-group (yr)		
	0–14	15–29	1–29
Source A			
+	86	21	107
−	10	2	12
Total	96	23	119
Source B			
+	86	21	107
−	123	143	266
Total	209	164	373
Ascertainment probability (%)	93.9	92.4	92.8

Cases ascertained (+) or not (−) from hospital and clinical records (Source A) and from the Sardinian IDDM patient association, ADIG, (Source B). Ascertaiment probability was calculated according to the formula $a(a + b + c)/(a + c)(b + a)$ where a is the number of cases found by either sources, b by the Source B only, and c by the source A only (ref. 8). Example of formula applied to 0–14–yr-old age-group: $86(86 + 10 + 123)/(86 + 123)(10 + 86) = 0.939 = 93.9\%$.

RESULTS — The number of IDDM incident cases ascertained in the primary and secondary data sources and the calculated completeness of ascertainment in the age-groups 0–14, 15–29, and 0–29 yr old during 1989 and 1990 are reported in Table 1.

Over the 2-yr period 1989–90, 385 incident cases of IDDM, each of whom met all eligibility criteria, were identified. Of these, 373 were identified through the primary data source, and 12 through the secondary source only, providing a degree of ascertainment of 92.8%. In the primary source, 325 cases (87%) were notified from hospital departments where the patients had been admitted at diagnosis, and 48 cases (13%) were from outpatient clinics, none having been notified directly by family doctors or pediatricians.

Considering the two years separately, 202 incident cases were identified in 1989 (194 from the primary source) and 183 in 1990 (179 from primary source). The completeness of ascertainment exceeded 92% in both years, with insignificant differences (by χ^2 test) between the two years (data not shown).

Age-specific crude incidence rates in 1989 and 1990 were pooled together. In males and females, separate and pooled incidence rates are reported in Table 2. Age-standardized incidence rates in the 0–14, 15–29, and 0–29–yr-old age-groups for the two sexes pooled together also are reported in Table 2.

In both sexes, the incidence rate reached a plateau at 5–14 yr; the difference between rates (per 100,000) for 5–9 yr and 10–14 yr was not significant (40.1 and 36.9 in males, 32.0 and 28.4 in females, respectively). The overall incidence rates (per 100,000) for the two sexes pooled together were as high as 30.7 for 0–14 yr and 24.1 in the entire 0–29–yr-old age range. The direct standardization for age yielded negligible differences from the crude incidence rates (Table 2).

Males showed higher incidence rates than females in all age subgroups. At the χ^2 analysis, the sex differences were significant in the entire 0–29–yr-

Table 2—*Incidence rates (per 100,000/yr) of IDDM in Sardinia during 1989–1990*

	Population size	Observed cases (*n*)	Incidence rate	CI
Males				
Age-groups				
0–4	49,062	22	22.4	13.1–31.8
5–9	59,909	48	40.1	28.7–51.4
10–14	74,464	55	36.9	27.2–46.7
15–19	77,014	49	31.8	22.9–40.7
20–24	79,308	30	18.9	12.2–25.7
25–29	67,201	34	25.3	16.8–33.9
Age ranges				
0–14	183,435	125	34.1	28.1–40.1
15–29	223,523	113	25.3	20.6–29.9
0–29	406,958	238	29.2	25.5–32.3
Females				
Age-groups				
0–4	45,885	18	19.6	10.6–28.7
5–9	56,335	36	32.0	21.6–42.4
10–14	70,503	40	28.4	19.6–37.2
15–19	74,430	20	13.5	7.6–19.3
20–24	77,079	23	14.9	8.8–21.0
25–29	66,746	10	7.5	2.8–12.1
Age ranges				
0–14	172,723	94	27.2	21.7–32.7
15–29	218,255	53	12.1	8.9–15.4
0–29	390,978	147	18.8	15.8–21.8
Both sexes				
Age-groups				
0–4	94,947	40	21.1	14.5–27.6
5–9	116,244	84	36.1	28.4–43.9
10–14	144,967	95	32.8	26.2–39.3
15–19	151,444	69	22.8	17.4–28.2
20–24	156,387	53	17.0	12.4–21.6
25–29	133,947	44	16.4	11.6–21.3
Age ranges				
0–14	356,158	219	30.7	26.7–34.8
15–29	441,778	166	18.8	15.9–21.7
0–29	797,936	385	24.1	21.7–26.6
Age-standardized rate*				
0–14			30.0	26.0–34.0
15–29			18.7	15.9–21.6
0–29			24.3	21.9–26.8

*Both sexes pooled together.

old age range (29.2 vs. 18.8, $P < 0.02$) and in the 15–19–yr-old (31.8 vs. 13.5, $P < 0.001$) and 25–29–yr-old (25.3 vs. 7.5, $P < 0.001$) age-groups. The male/female ratios in the 0–29 and 0–14–yr-old age ranges were 1.55 and 1.25, respectively, with the highest ratio, 3.38, in the 25–29–yr-old group and the lowest, 1.14, in the 0–4 yr olds.

The distribution of cases by month of diagnosis showed no significant variation in incidence. Moreover, in comparing the two years, two different patterns were observed. In 1989, the highest incidence rate was recorded in March and the lowest in July; in 1990, the peak was in October (a month still warm in Sardinia), and the lowest point was in November. However, none of these variations within and between the two years were statistically significant.

CONCLUSIONS— This study has demonstrated a crude annual incidence rate (per 100,000) of IDDM in Sardinia of 30.7 for those <15 yr of age, and of 24.1 for those <30 yr, with age-standardized rates of 30.0 and 24.3 yr, respectively, during 1989–90, with only minor or no significant differences between the two years.

Completeness of ascertainment was 92.8%, mainly because of the high quality of primary data source, from which 96.9% of incident cases were notified. All such cases had been referred to the public medical care system (87% to hospitals, 13% to outpatient clinics), because in our region, as in all of Italy, diabetic patients receive every kind of health care, including the relevant diagnostic and therapeutic devices, free only when their disease has been diagnosed either in general or pediatric hospitals or in public outpatient clinics. This is the reason no patients were notified by private general practitioner or pediatrician, although some IDDM patients are treated by private doctors once diagnosis has been stated by the public system. Therefore, any underascertainment from our primary data source was expected to be minimal.

Moreover, it is unlikely that even one newly diagnosed patient who is a resident of Sardinia is sent outside for hospitalization for two main reasons. First, Sardinia is quite far from the mainland; and second, the island has a widespread network of public general and pediatric hospitals and diabetic outpatient clinics, which provide excellent diabetes care and to which all general practitioners and pediatricians refer their patients.

Our secondary, independent source of ascertainment was the Sardinian IDDM patient association, ADIG, which with most patients register, al-

Table 3—*Decreasing IDDM incidence rates from north to south in Europe and Israel—and the exceptions—Sardinia and Malta*

Country	Age range (yr)	Rate	Reference
Finland (eastern)	0–14	36.6	11
Sweden	0–14	25.1†	12
Norway	0–14	20.6†	12
Scotland	0–14	19.8†	14
Estonia	0–19	16.7	13
Denmark	0–29	14.0†	1
British Isles	0–14	13.5†	14
The Netherlands	0–14	10.3†	15
Luxembourg	0–19	10.2†	16
Hungary	0–14	8.2†	17
France	0–14	7.2†	18
Poland	0–17	6.6†	19
Italy (northern)	0–14	5.9	20
Israel	0–20	3.8†	12
Sardinia	0–14	30.0†	This study
Malta	0–14	13.6†	21

*Per 100,000 population.
†Age standardized.

though often with some delay from the date of diagnosis. Of the 385 IDDM patients identified through the primary source, 106 (27.5%) also were identified by ADIG, among whose files 12 more patients not identified in the primary source were found. For all of these reasons, the calculated ascertainment completeness of 92.8% likely estimates correctly the degree of underascertainment. Indeed, any degree of overascertainment as a consequence of notification of some cases from more than one source can be ruled out definitively, because identification of each new case entailed specification of initials of first and family name, date and place of birth, and residence. Thus, any multiple entering of the same case into our computerized files was avoided.

The average annual incidence of IDDM in Sardinia for 1989–90 places this island among those areas of Europe with the highest rates. In fact, a comparison with available rates in the <15-yr-old age-group in other European countries (Table 3) shows that Sardinia has the second highest IDDM incidence rate, approaching the 36.6% that has been reported in Finland (11).

Incidence rates in the 0–14-yr-old age-group reported most recently from other European and neighboring countries confirm the existence of a north-to-south negative gradient. But Sardinia represents a striking exception, in comparison with which the other exception—Malta, with 13.6/100,000—pales (Table 3). Comparison with other Italian and Italian-heritage populations (2) shows that in the early 1980s, the incidence of IDDM (per 100,000, 0–14 yr old) ranged from 4.2 in Lombardy to 10.9 in Vicenza, with the inclusion of 10.7 among Italians living in Montreal; yet, the annual incidence in Cagliari, Sardinia, was 24.0/100,000 in the 0–18-yr-old age-group for the 4-yr period 1983–86.

Taken together, these figures leave little doubt that Sardinia is a unique hot spot of IDDM incidence in southern Europe. As far as incidence by age is concerned, in both sexes the highest rates are reached at 5–9 yr old—somewhat earlier than in other European countries (14,18,20)—and persist steadily at 10–14 yr old. This age range of highest incidence is still earlier than in Estonia (13), where the peak is reached at 15–19 yr old in spite of an early mean age of onset of puberty—10 yr for girls and 12 yr for boys (13).

The male/female ratios of 1.55 and 1.25 in our 0–29- and 0–14-yr-old age-groups, respectively, are consistent with those reported for other countries (14,16,18,23,24). The reasons for this and for the contradictory female excess observed in Estonia (13), Hungary (17), and Malta (21), are unknown. In contrast with several countries, where a seasonal pattern of IDDM incidence has been found (25), variations in the number of cases diagnosed each month in Sardinia were not significantly different from a uniform seasonal incidence. Moreover, in comparing the two years observed, the highest and lowest incidence rates occurred during different seasons. The reasons for the lack of a clear seasonal pattern in Sardinia, and in Turin, Italy (22), are not likely to be the result of the Mediterranean climate, because seasonal variation of IDDM incidence through an 8-yr period also has been described in Malta (21).

Finally, the extraordinarily high rates of IDDM incidence we recorded in Sardinia during 1989–90 make us wonder whether they reflect a steady pattern that also was present in previous (unobserved) years; or, as in many northern European countries (12), whether they are the last figures of a rising incidence over the last decades. Some indications point to the latter. In fact, during the period 1983–86, an incidence of 24/100,000 for individuals 0–18 yr old, living in Cagliari was reported (2). This rate is somewhat lower than the 28.4 for 0–19 yr olds in this study. Moreover, a retrospective incidence study in Sardinia (26) describes a steady increase in incidence among children 0–14 yr old over the past 30 yr, with a doubling time even

shorter than the 20–30 yr in northern European countries (12). Although the two Sardinian studies cited lack a secondary validation source, we believe that the widespread increase in IDDM incidence recorded in Europe over the past 30 yr also is taking place in Sardinia.

Although the phenomenon of rising IDDM incidence points to environmental factors in the etiology of the disease, the high rate in Sardinia with respect to other Italian populations can be attributed to both genetic and environmental influence, as in other high-incidence countries. For example, a susceptibility haplotype has been described in the Finnish population (27), but it does not account for more than a small proportion of the excess in that country. Studies of an alternative susceptibility haplotype specifically occurring among Sardinians, a genetically distinct population (4), are underway in our laboratories (28).

In conclusion, from our present data, Sardinia appears to have the second highest IDDM incidence rate in Europe, approaching that of Finland, and one that contradicts the general rule of a south-to-north incidence gradient. Uncovering the reasons for such a high—and possibly rising—incidence could contribute to a better understanding of the etiology and pathogenesis of IDDM. Therefore, further research in this island population is warranted.

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