Type 1 Diabetes Among Sardinian Children Is Increasing

The Sardinian diabetes register for children aged 0–14 years (1989–1999)

OBJECTIVE — The Sardinian type 1 diabetes register represented the basis to determine the most recent trends and the age distribution of type 1 diabetes incidence among Sardinians <15 years of age during 1989–1999. Part of the data (1989–1998) has been already published by the EURODIAB Group with a lower completeness of ascertainment (87%). The geographical distribution of type 1 diabetes risk was also investigated.

RESEARCH DESIGN AND METHODS — The new cases of type 1 diabetes in children aged 0–14 years in Sardinia were prospectively registered from 1989 to 1999 according to the EURODIAB ACE criteria. The completeness of ascertainment calculated applying the capture-recapture method was 91%. Standardized incidence rates and 95% CI were calculated assuming the Poisson distribution. Trend of type 1 diabetes incidence was analyzed using the Poisson regression model. Maps of the geographical distribution of type 1 diabetes risk for the whole time period and separately for 1989–1994 and 1995–1999 were produced applying a Bayesian method.

RESULTS — A total of 1,214 type 1 diabetic patients were registered yielding to an overall age- and sex-standardized incidence rate of 38.8/100,000 (95% CI 36.7–41.1). There was a male excess with an overall male-to-female ratio of 1.4 (1.3–1.8). The increase of incidence during the 11 years analyzed was statistically significant ($P = 0.002$) with a yearly increasing rate of 2.8% (1.0–4.7). No evidence of an effect of age and sex on this trend has been found. The geographical distribution of type 1 diabetes relative risk (RR) showed that the highest risk areas are located in the southern and central-eastern part of the island and the lowest risk in the northeastern part, even if most of these differences were not statistically significant. This geographical distribution seemed to remain mainly the same between 1989–1994 and 1995–1999.

CONCLUSIONS — The homogeneity of diabetes risk and the increase of incidence over the age-groups in the Sardinian population stress the role of an environmental factor uniformly distributed among the genetically high-risk Sardinians.

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Type 1 diabetes among Sardinian children

Table 1—Type 1 diabetes incidences by age and sex among Sardinia children <15 years of age (1989–1999)

<table>
<thead>
<tr>
<th></th>
<th>SIR 0–14 years (95% CI)*</th>
<th>0–4 years*</th>
<th>5–9 years*</th>
<th>10–14 years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>38.8 (36.7–41.1)†</td>
<td>29.1</td>
<td>42.4</td>
<td>44.4</td>
</tr>
<tr>
<td>Boys</td>
<td>46.8 (43.4–50.2)†</td>
<td>34.1</td>
<td>47.4</td>
<td>55.7</td>
</tr>
<tr>
<td>Girls</td>
<td>32.3 (20.4–35.2)†</td>
<td>24.6</td>
<td>38.0</td>
<td>33.2</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>1.4 (1.3–1.8)</td>
<td>1.5</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Cases (%)</td>
<td>1,214 (100)</td>
<td>256 (21)</td>
<td>430 (35)</td>
<td>528 (44)</td>
</tr>
</tbody>
</table>

*Incidences per 100,000 person-years; †age and sex SIR; ‡age SIR

RESULTS—During the 11-year period from 1989 to 1999, a total of 1,214 patients (736 boys, 478 girls) with newly diagnosed type 1 diabetes <15 years of age were recorded. The overall age and sex SIRs in Sardinian children were 38.8/100,000 person-years (95% CI 36.7–41.1).

The incidence rates in the three age-groups (0–4, 5–9, and 10–14 years) by sex are shown in Table 1. The incidence was higher among boys than among girls, yielding an overall male-to-female ratio of 1.4 (95% CI 1.3–1.8). The highest male-to-female ratio was registered in the 10- to 14-year age-group (1.8). The highest incidence rate was registered among boys aged 10–14 years (55.7/100,000). Among girls, the highest incidence was registered in the 5- to 9-year age-group (38.0/100,000). The median age at onset was 9 years for both sexes. The peak of incidence was at 9 years of age for girls, whereas it was at a slightly older age among boys (12 years of age). For both sexes, incidence was quite high at the age of 3 years (41.0/100,000). The incidence rates tend to be higher among boys before the age of 3 years and after the age of 6 years (data not shown).

We observed a rising trend of incidence from 37.7/100,000 at the beginning of the study in 1989 up to 49.3/100,000 at the end in 1999. According to the Poisson regression analysis for a linear time trend adjusted by age and sex, the increasing trend of incidence during the 11 years analyzed was statistically significant (P = 0.002) with an estimated average yearly increase of 2.8% (95% CI 1.0–4.7) (Fig. 1). Results by age and sex are presented in Table 2.

To better understand the putative effect of an earlier presentation of the onset, the incidence between 0 and 2 years of age has been analyzed, yielding a lower incidence if the age of onset considered was <1 year (10.3/100,000 [95% CI 6.4–16.4]) and much higher if we considered
the age 1 (29.5/100,000 [22.4–38.9]) and 2 (19.9/100,000 [15.5–25.5]) years.

When the temporal trend 0–2 years was analyzed, no significant increase was found for both sexes as well as for girls, whereas an increase was found among boys (7.5% per year [0.3–15.1]). The temporal trend seems to have two peaks: in 1993 and in 1998. This is different from the Finnish data, in which the increase found in the younger ages over the last decade was higher among girls than among boys (16).

The geographical distribution of type 1 diabetes risk within the island was studied by mapping the relative risk at the municipality level. The standardized morbidity ratio observed in each small area varied largely from 0 to 1 and thus it gave no useful information. A Bayesian approach to the estimation of area-specific RR (Fig. 2A) showed that the highest risk areas were located in the southern and eastern parts of the island, whereas the lowest risk areas were in the northeastern part. However, the map of PP (Fig. 2B) shows that the RR was homogeneously distributed over the island with the exception of the Sassari municipality, where the RR is <0.95. A value of PP within the range of 0.25–0.75 indicates that the data do not provide any evidence of an RR being higher or lower than 1.

Furthermore, by comparing the maps of RR in 1989–1994 and in 1995–1999, the geographical distribution of type 1 diabetes risk seemed almost unchanged and it remained homogeneously distributed (data not shown). However, the RR tended to be higher in the Campidano plain (the largest plain in Sardinia, located

### Table 2—Time trend of type 1 diabetes incidence in children <15 years of age in Sardinia 1989–1999

<table>
<thead>
<tr>
<th>Sex and age-group</th>
<th>Incidence rate ratio</th>
<th>95% CI</th>
<th>Percent increase</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>1.043</td>
<td>0.991–1.097</td>
<td>4.3</td>
<td>0.104</td>
</tr>
<tr>
<td>5–9 years</td>
<td>1.006</td>
<td>0.967–1.047</td>
<td>0.6</td>
<td>0.755</td>
</tr>
<tr>
<td>10–14 years</td>
<td>1.036</td>
<td>1.001–1.071</td>
<td>3.6</td>
<td>0.041</td>
</tr>
<tr>
<td>0–14 years*</td>
<td>1.027</td>
<td>1.004–1.051</td>
<td>2.7</td>
<td>0.021</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>1.038</td>
<td>0.976–1.104</td>
<td>3.8</td>
<td>0.234</td>
</tr>
<tr>
<td>5–9 years</td>
<td>1.018</td>
<td>0.973–1.065</td>
<td>1.8</td>
<td>0.445</td>
</tr>
<tr>
<td>10–14 years</td>
<td>1.036</td>
<td>0.991–1.084</td>
<td>3.6</td>
<td>0.120</td>
</tr>
<tr>
<td>0–14 years*</td>
<td>1.029</td>
<td>1.001–1.059</td>
<td>2.9</td>
<td>0.045</td>
</tr>
<tr>
<td>Boys and Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 years†</td>
<td>1.041</td>
<td>1.001–1.082</td>
<td>4.1</td>
<td>0.044</td>
</tr>
<tr>
<td>5–9 years†</td>
<td>1.011</td>
<td>0.982–1.042</td>
<td>1.1</td>
<td>0.462</td>
</tr>
<tr>
<td>10–14 years†</td>
<td>1.036</td>
<td>1.008–1.064</td>
<td>3.6</td>
<td>0.010</td>
</tr>
<tr>
<td>0–14 years‡</td>
<td>1.028</td>
<td>1.010–1.047</td>
<td>2.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Results of the Poisson regression analysis. *Age-standardized incidence rate; †sex-standardized incidence rate.
CONCLUSIONS — Sardinia is known to have a very high incidence of type 1 diabetes (second after Finland [8] and five to seven times higher than continental Italy [17]). The present work confirms once again the high incidence of type 1 diabetes in the island.

We found one of the highest male-to-female incidence ratios ever reported in the 0- to 14-year age-group (1.4). The highest male-to-female ratio was found in the oldest age-group, even if a trend of male-to-female ratio with increasing age was not identified. Some authors describe a weak association between high incidence and high male-to-female ratio (18,19). Sardinia seems to confirm this observation. A possible explanation of this phenomenon could be found in a recent survey on type 1 diabetic patients from the U.S., the U.K., and Sardinia in which a male sex bias was described in patients carrying neither DR3 nor DR4 haplotypes, and this effect was more pronounced among Sardinian patients (20), 87% of whom are DR3 positive (21).

The results of the present study, characterized by a prospective registration of cases, confirmed that in Sardinia there is an increasing risk of type 1 diabetes, as already shown by the Sardinian military conscript data among boys over the last decades (4), and this increase is even higher in recent years. Similar increasing rates have been reported elsewhere, in several countries (2–6,22) and in Europe as a whole (8).

In the latter study (EURODIAB study), no increase of incidence was reported for Sardinia. The different results we obtained are attributable to the different time intervals considered (1989–1998 in the EURODIAB study and 1989–1999 in the present study) and mostly to a different completeness of ascertainment between the two studies. In fact, the completeness of the Sardinian data was 87% in the EURODIAB study and 91% in the present study. The difference was even higher if we consider the last years. This might be due to the fact that the new cases added to the present analysis were diagnosed in 1997–1998, which led to a higher incidence in the last years compared with the EURODIAB study and contributed toward a statistically significant temporal trend.

The increase of incidence observed in our analysis could be due to a higher degree of ascertainment over the last years compared with the previous ones, but even this seems not to be the case. In fact, the completeness of ascertainment varies
from 91 to 97% between 1989 and 1993 down to 82–92% between 1994 and 1999. Thus, if we would have calculated the incidence rates using the number of cases corrected for the completeness of ascertainment, then we would have obtained an even higher increase than the one we actually reported.

The increase was the same for both sexes. It is of notice that in the Finnish study, with a longer period of observation, the increase was more pronounced among boys in the past whereas among girls only recently (16). The observation period of our study might be too short to lead to any significant difference in increase between sexes even if this could explain the high male-to-female ratio.

This increase is apparent also in the youngest age-group, even if this is not statistically different from the other age-groups. It is, however, to be noticed that the highest increase was found in this age-group (4.1%). This could be explained by too few cases in this age-group to reach statistical significance.

On the basis of this trend, we can extrapolate the incidence for the future years. The predicted incidence based on the linear trend obtained with the Poisson regression analysis will be 52.7/100,000 (95% CI 43.3–94.0) in 2010 and 69.5/100,000 (47.8–100.1) in 2020. If this trend would remain the same, type 1 diabetes will represent one of the heaviest burdens for the Sardinian health authorities.

Apparently, the geographical distribution of type 1 diabetes risk exhibited only a slight heterogeneity. The highest risk areas were located in the southern and eastern part of the island, and the lowest risk areas were in the northwestern part. These findings confirm our previous study even if the risk seems to have leveled off in the whole island, with only the Sassari area at significant lower risk. A similar picture was obtained also from the data on military conscript for the birth cohorts 1974–1979 (23). Thus, the risk seems to be uniform within the island, and the comparison between the maps obtained for the first 5 years (1989–1994) and for the last 6 years (1995–1999) confirmed this impression. However, the RR tended to be higher in the Campidano plain (the largest plain in Sardinia located in the southwestern part of the island) over the period 1995–1999. A similar approach applied to Finland showed that the high-risk areas remained mainly the same between 1987 and 1996 (24).

The described geographical and temporal homogeneity of diabetes risk and the rapid increase of incidence in a genetically stable and homogeneous population such as Sardinians suggest the role of an environmental factor uniformly distributed in the island. This makes it almost impossible to point out any possible etiological factors by applying ecological analysis to the Sardinian population. Examples for that could be no effect toward type 1 diabetes risk of temperature, rainfall, nitrate content of drinking water, milk, and casein intakes and a weak association with malaria (25–27). Comparison with other populations is then recommended, although this kind of comparative study has been unable so far to pinpoint any possible factor that may explain the high incidence of type 1 diabetes in Sardinia. In the recent analysis published by the EURODIAB Group (28), type 1 diabetes incidence was strongly associated in Europe with indicators of national prosperity, even though Sardinia lies far from the regression line between type 1 diabetes incidence and gross domestic product, coffee consumption, latitude, or milk intake, suggesting that the high incidence of type 1 diabetes on the island could be only partially explained by these factors.

The increase of incidence described here seems to be due to a widespread environmental agent operating in a genetically susceptible Sardinian population. However, these data are not able to explain the high incidence of the disease in Sardinia or its increase. We could speculate that some of the changes that occurred in the environment and lifestyle in Sardinia after World War II might have played a significant role. Transportation and connection within the island and to mainland Italy improved gradually after the 1950s as the social, economic, and hygiene standards improved. The environment also changed, particularly after the Rockefeller campaign that took place in the 1950s and was aimed at the eradication of malaria on the island. During that campaign, large amounts of DDT were spread all over the island, and its metabolites continue to be detected in the food chain. According to the studies by our group, the areas with past high malaria morbidity seem to be currently at lower risk of type 1 diabetes (27), leading us to hypothesize that the Plasmodium falciparum might have had a protective role on type 1 diabetes, that it operated by selecting high-risk genes, or that it can be considered as an indicator of other parasitic infection that could be protective against type 1 diabetes. The disappearance of malaria might be then an epiphenomena of some radical changes occurring in the Sardinian environment during and after the 1950s. This is in accordance with the so-called “hygiene hypothesis” (29,30), according to which the slow but continuous decline of infestation by intestinal helminthes and by many other ectoparasites and the reduction of morbidity and mortality of infectious diseases brought about by changing lifestyles has resulted in disorders of the immune control and increases of immunemediated diseases. Animal data and epidemiological deductions are in accordance with this hypothesis. The high reduction of microbial exposure in infancy occurred in the last decade also in Sardinia, and the improved social standards might be responsible for the increase of several diseases in a genetically susceptible population. In fact, in Sardinia the almost complete disappearance of parasitic diseases and the eradication of polio, malaria, and tuberculosis have coincided with an increase of atopic and immunemediated diseases (type 1 diabetes, multiple sclerosis, Crohn’s disease, celiac disease). Unfortunately, very few data, if any, are available to support this hypothesis in Sardinia.

Furthermore, other changes occurred in the last 50 years in Sardinia (for example, there is better access to health care, high-caloric foods, fat, and meat proteins); the weight and height of the population also increased. Several reports linked linear growth and weight gain to the increased incidence of type 1 diabetes (31,32). Unfortunately, once again, no data are available on the growth velocity or the increase of obesity among Sardinian children in the past decades, even though it seems that the prevalence of overweight in Sardinian schoolchildren (12–24%) is comparable with the prevalence from mainland Italy (10–32%) (33).

In conclusion, the high incidence of type 1 diabetes is still increasing in Sardinia, confirming the increasing trend of prevalence among young boys shown by the analysis on the conscript registry (23).
In fact, our group already studied the temporal trend of type 1 diabetes point prevalence among young men aged 18 years at the moment of the conscript examination. This survey gave an increasing trend with the highest point prevalence of 4.92/1,000 registered in the last birth cohort of 1979. The Sardinian type 1 diabetes registry gave a cumulative incidence for young men aged 18 years of 6/1,000, which was higher than the point prevalence estimated from the military registry (23). This figure leads us to hypothesize a continuous, still ongoing increase of type 1 diabetes risk in Sardinian children and adolescents, at least among boys. Further investigations are needed to clarify whether this increase is mainly due to a peculiarity of the background environment, or both. Given the homogeneous distribution of type 1 diabetes risk within the island, these studies should compare the Sardinian population with populations at different levels of risk.

APPENDIX

Members of the Sardinian Type 1 Diabetes Epidemiology Study Group

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References
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