

## Epidemiology of childhood diabetes

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Monitoring diseases is critical for understanding their etiology and natural history and for the allocation of limited health-care resources. Thus, it is impossible to prevent and control diabetes and its complication unless we know the incidence and prevalence at which they occur. Near perfect numeration is the basis for monitoring the events and disease registries are based on this assumption. Good monitoring not necessarily ensures right decisions making, but it reduces the risk of wrong ones.

Diabetes registries currently use capture-recapture method. Diabetes is ideally suited for being captured because it is not too severe, it is not too frequent, has a classic set of symptoms and a simple test rapidly diagnoses the disease, so there are few misdiagnosed cases. Diabetes register needs definition of cases (for example diagnosed with diabetes and placed on insulin, and member of the defined population) and the description of the population at risk (for example people aged under 15 living in the defined area in a defined time period). Very simple data are needed to be collected for a diabetes register: name, sex, date of birth, date of diagnosis, place of residence, ascertainment status. Several sources of ascertainment are available to monitor diabetes. The choice of data sources is important in determining the accuracy of the estimated prevalence. Thus far many T1D registries have been established worldwide as EURODIAB (EUROpe and DIABetes; 0-14, Europe); DIAMOND (DIABetes MONDiale; 0-14, Worldwide); DiMe (Childhood Diabetes in Finland Study; 0-14, Finland); IDA [Insulin dependent T1D in young Adults, 15-29 (39), Europe]; RIDI (Re-

gistry for Insulin-dependent Diabetes in Italy; 0-14, Italy); DISS (Diabetes Incidence Study in Sweden; 15-34, any type of diabetes, Sweden); GLED (Grupo Latinoamericano Estudio del Diabete 1; 0-14, South America); Allegheny Country Registry (0-19, US); Swendic (South West Newly-diagnosed Diabetes Collection; 16-40, UK); BOX Study (Barth-Oxford Studies; 0-21, UK); Belgian registry; Yorkshire registry; The Sardinia T1D Register (0-29, Sardinia); The Sardinian Conscript IDDM Register (18 yrs, Sardinia), to remember just few of them.

Sardinia represents a model to study Type 1 Diabetes. It is the second largest island in the middle of the Mediterranean sea characterised by several genetic, demographic and linguistic peculiarities. The long isolation with a small number of founders, the long history of its settlements and the pressure of selecting factors (as malaria) have made the Sardinian population a genetic isolate with a unique distribution of alleles. This is probably one of the reasons for having high prevalence of many genetic diseases as thalassemia, G6PD deficiency, Wilson's disease and APECED, as well as autoimmune disorders such as multiple sclerosis, celiac disease, autoimmune thyroid diseases and Type 1 diabetes (T1D).

### The "IDDM-Sardinia" Project: state-of-the-art and future perspectives

The project (1) began in 1990 with two main objectives, 1) to map the geographical distribution of

the incidence of Type 1 Diabetes (T1D) in the Island and 2) to investigate the pre-T1D period in a large children cohort. This should lead to design models of prediction and safe preventive measurements in a general population living in areas at high risk of developing the disease. In order to reach the two objectives, several studies were organised and others have branched out from the initial project, in particular:

1. the continuation of the Sardinian T1D registry;
2. the Sardinian Migrants Study;
3. the ecological/environmental/veterinarian variables-T1D Study;
4. the Sardinian Schoolchildren-T1D Study;
5. the Diabfin Study;
6. the Subclinical Coeliac Disease Study;
7. the study on circulating antithyroid antibodies (ATA) in Sardinian schoolchildren
8. the Post-partum Thyroiditis and the Neonatal Hypothyroidism Studies;
9. Type 1 Diabetes and Multiple Sclerosis
10. the HHV-8 infection and Kaposi Sarcoma Study.

### 1. The continuation of the Sardinian T1D registry

*State of the art.* The data collected so far have shown that, in Sardinia, the average yearly standardised incidence rate of overt T1D for the years 1989-1999 is 38.8 per 100,000 (age range 0-14 years), which is about five times higher than the incidence of mainland Italy. The high incidence is also evident from the first year of life. The male to female ratio is 1.5 again higher than the Italian ratio. A clear seasonality of onset, with a peak of incidence in autumn, and of birth, with a peak in spring-summer, has been shown (2).

These results confirm that the incidence of the disease in the Island is one of the highest in the world (only Finland has a higher incidence) (3) and that it has progressively increased in the last decade with an average yearly increase of 2.8%, similar to the one registered elsewhere and to the mean increase in Europe (Figs. 1, 2). These results confirm the significant increase in prevalence which has been pointed out for

males aged 18 years with an apparent maximum for the birth cohorts of the late 60s (4, 5).

This picture strongly substantiates the existence of one or more environmental contributors to the aetiology of T1D. The most common environmental factors have been investigated: no association with T1D incidence was found for precipitation, average temperature, altitude, population density, G6PD deficiency, nitrate levels in drinking waters, milk and casein A1-B consumption. A negative association between T1D and past malaria or breast feeding has been shown.

The highest incidence has been found in the Middle-Western part of the island (Oristano province) and the lowest in the North-Western part (Sassari province), however these differences are not statistically significant. This distribution seems to be stable in the last decade (2, 6).

*Future perspectives.* It is planned to continue the registration extending and improving the ascertainment to the age range 0-29 years.

### 2. The Sardinian Migrant Study

*State-of-the-art.* The results of the Sardinian migrant studies appear to be in contrast with the environmental hypothesis: in fact, offsprings of both Sardinian parents migrated to mainland Italy (Turin, Lazio and Lombardy) (7-9), seem to have the same diabetes risk as the Sardinian population living in the island, while offspring of only one Sardinian parent have only half risk.

In order to understand the potential role of environmental factors in the IDDM onset, a prevalence study of the disease has been carried out in a Sardinian population, which migrated from the Island to Pavia (an Italian town in Lombardy) (10). A postal questionnaire has been sent to all the 2,252 Sardinian people living in the town, and a telephone call has been made in the non-responder cases. Through the survey, we have identified 10 patients with IDDM (prevalence = 4.4/1000). Three of them (mean age 14±2 SD years), became diabetic while still living in Sardinia and the remaining 7 (mean age 32.8±8.2 DS years) developed the disease after the time of the emi-

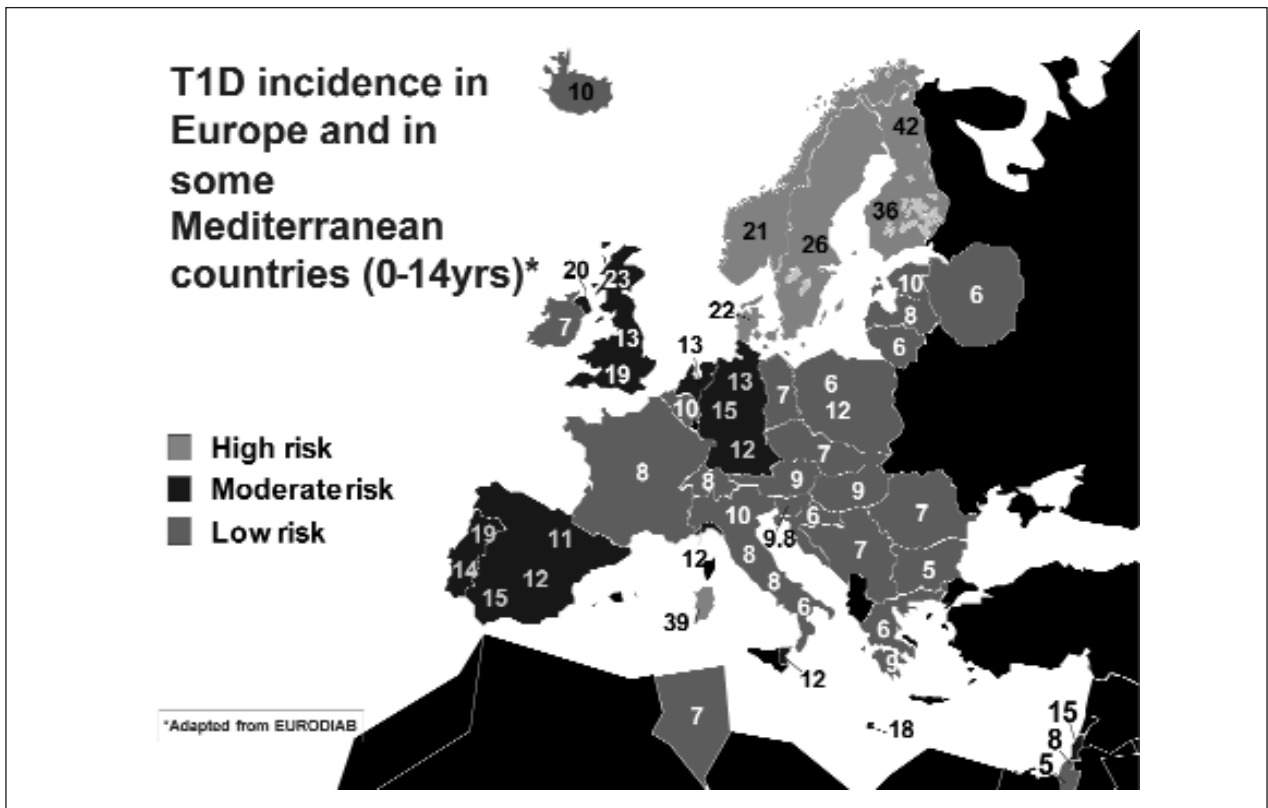


Figure 1. T1D incidence in Europe and in some Mediterranean countries

Sardinian Registry				
T1D incidence (per 100,000) in Sardinia (1989 -1999)				
Age Group 0 -14 yrs (N = 1,214)				
	SIR 0-14	0-4	5-9	10-14
Total	<u>38.8</u>	29.1	42.4	44.4
Males	46.7	35.0	51.2	51.4
Females	32.1	23.1	33.5	37.4
M/F	1.4	1.5	1.3	<u>1.8</u>
Cases (%)		22	35	<u>44</u>
Completeness= <u>91%</u>				

Figure 2. T1D incidence in Sardinia

gration to the mainland. These preliminary data show that prevalence of T1D in the Sardinian emigrants is still higher compared to the general population of the same geographical area, and, interestingly, that the age of the disease onset seems to be delayed in the indi-

viduals who became diabetic after the emigration compared with the ones who live in the Island.

*Future perspectives.* A ‘wet’ phase is ongoing where the entire cohort will be tested for immunological e genetic markers of T1D.

### 3. The study of the ecological/environmental/veterinarian variables in Sardinia

*State-of-the-art.* Several environmental factors and their relation to T1D have been investigated in Sardinia:

- 1) the seasonal pattern. As already reported in other Countries, the peaks of incidence of the disease occur in the autumn-winter seasons and the prevalence of the disease higher in males;
- 2) the impact of the temperature, precipitations and nitric content in the drinking-water. The

Sassari province, which has the lowest incidence of T1D in the Island, has also the lowest temperature, with the highest rainfall, but, unexpectedly, the highest nitric content in the drinking-water (11);

- 3) in the Island, there is no overlap between areas with high prevalence of T1D and areas of both past and present endemic disorders, such as thalassaemia, malaria and G-6-P-D deficiency;
- 4) a positive correlation between the occurrence of T1D in cow's milk rather than breast fed children has not been confirmed, although a study was carried out in the province of Sassari in this respect (12);
- 5) no correlation has been found between T1D incidence in Sardinia and nitrate intake with drinking water (11);
- 6) no correlation has been found also between T1D incidence and intake of Casein A1 and B supposed to be diabetogenic (13). Conflicting data are reported regarding the association between cow milk intake and incidence of T1D in the island, being the Italian region with both the highest diabetes incidence and the highest cow milk intake. However Sardinia lies far from the regression line between cow milk intake and T1D incidence drawn from the European data (14, 15).

*Future perspectives.* The impact of environmental factors will be extended by comparing "hot" and "cold" areas for incidence of the disease. A possible relationship between T1D and diseases affecting domestic animals (dogs, cats, cattle, equine and swine) will also be investigated.

#### 4. The Sardinian School Children IDDM Study

*State-of-the-art.* To better understand the natural history of T1D in Sardinia, a prediction study in the general population has been settled and prevention trials for the disease are ongoing.

In order to quantify the prevalence of islet-related autoantibodies (i.e. ICA, GADA and IA-2icA)

and to define their sensitivity, specificity and positive predictive value in relation to future onset of T1D, a large cohort of around 10,000 apparently healthy school children, recruited from the primary and middle schools of 36 towns scattered in the 4 Sardinian provinces, have been enrolled in a prospective study. Around 8,500 children have been tested for all the 3 autoantibody specificities and 28 (10M/18F) of them became diabetic, with a latency from 2 to 84 months after the initial test. Two main conclusions emerge from this study: a) the combination of 2 or 3 islet-related autoantibodies shows the best predictivity of the disease (PPV=32%) and b) the prevalence of this combination is higher in the 2 provinces of the Island, Oristano and Cagliari, which also have the highest incidence of T1D (16).

*Future perspectives.* A longitudinal study in the approximately 500 children initially found positive for any islet-related autoantibodies is already running. In the next future we shall be in a position to evaluate the persistence or disappearance of these serological markers and, together with the HLA typing pattern, further assess the predictive value of both serological and genetic markers. At the same time, a similar serological and genetic evaluation will also be extended to their first degree relatives (about 2,000). As a control group, a cohort of 1,000 children, initially found negative for the presence of islet-related autoantibodies and their first degree relatives (around 4,000), will be investigated for the same serological and genetic parameters.

#### 5. The Diabfin Study

*State-of-the-art.* To study the frequency of high risk genetic markers for T1D in the general Italian population and to follow them up with immune markers to understand the natural history of T1D, a large cohort study has been established in mainland Italy and Sardinia. In continental Italy the genetic screening started in 2000 and has been completed in 2001: a total of 5,000 newborn from the general population have been included. Among them, 650 high-moderate risk were identified and are nowadays under regular follow up with islet related autoantibodies and meta-

bolic tests. In Sardinia the screening is still ongoing since 2002 aimed to recruit 2,500 newborn from the general Sardinian population.

Preliminary results from continental Italy showed a lower prevalence of high risk (0.9%) haplotypes in the Italian population compared to the expected one of 1.5-2.0%

Recently the TEDDY collaborative project has been launched to study the environmental determinants of T1D in the young (>7,000 newborns from US and Europe will be clinically and serologically followed up to 15 yrs), and the Diabfin Study will join the group.

## 6. The subclinical coeliac disease study

*State-of-the-art.* Around 1,600 school children, living in 7 towns/villages in northern Sardinia, have been tested for coeliac disease (CD)-related autoantibodies (AGA-IgG, AGA-IgA and EMA) and in the positive ones an intestinal biopsic assessment has been performed. As for islet-related autoantibodies and T1D, a high prevalence of CD autoantibodies has been detected in the examined cohort as well as a very high prevalence of the subclinical form of CD, (10.5/1000 people aged 6-14 years), confirmed by a flat intestinal mucosa at biopsy (17).

*Future perspectives.* It is planned to extend the study to all the school children already enrolled in the "T1D-Sardinia" project and to their relatives, as well as to the newborn cohort.

## 7. Study on circulating antithyroid antibodies (ATA) in Sardinian schoolchildren

For more than a decade an extensive investigation on the prevalence of goiter and of antithyroid antibodies (ATA) has been carried out in more than 8,000 Sardinian schoolchildren, living in areas with different iodine intake. The initial objective of this survey was to detect the early preclinical phase of both endemic goiter and thyroid autoimmune disease. The same cohort has been used to investigate the preclinical

phase of Type 1 Diabetes (Sardinian School Children IDDM Study).

The study provided the following conclusions: 1) the prevalence of serum ATA displays geographical heterogeneity, unrelated to goiter prevalence and/or iodine supply; 2) the frequency of ATA is higher in females only after the age of 11 years suggesting that puberty has a role in determining the female predominance of thyroid autoimmunity; 3) the prevalence of ATA is slightly increased in goitrous children; 4) the presence of ATA appears to be associated with increased prevalence of subclinical hypothyroidism (18).

## 8. The post-partum thyroiditis and the post-natal hypothyroidism studies

We carried out a preliminary study with the aim of determining the prevalence of serological markers of anti-thyroperoxidase antibodies and ICA in 2,249 sera obtained from Cord-blood of Sardinian pregnant women at delivery. The prevalence of AbTPO was 11.9% and 2.6% that of ICA, with higher prevalence of AbTPO in sera with ICA positivity >20 JDFu. These preliminary data indicate that ATA are frequently observed in the general population of Sardinian pregnant women and the frequency of post-partum thyroiditis is expected to be high (19).

## 9. Type 1 Diabetes and Multiple Sclerosis

Recently, Marrosu et al. (20) reported an increased prevalence of Type 1 diabetes among Sardinian individuals with multiple sclerosis and their first degree relatives. The study showed that these autoimmune diseases were an "unlike alliance" because the HLA haplotype that increases the risk for multiple sclerosis, protects against type 1 diabetes. This is the first study which describes such an association. Similar results have been produced by JS Dorman et al. by the analysis of a cohort of type 1 diabetic subjects diagnosed before 17 years of age in Pittsburgh, PA, US. They conclude that adult women with T1D are at an enormously increased risk of multiple sclerosis (21).

## 10. The HHV-8 infection and Kaposi sarcoma study

*State of the art.* Sardinia has high occurrence of Kaposi sarcoma (KS), not related to HIV infection. Recently, an association between HHV-8 and this type of KS has been described. We have investigated the prevalence of antibodies to HHV-8 in the cord blood of 100 pregnant women, participating in the Sardinia Newborn T1D study. The preliminary data have shown that antibodies to HHV-8 were significantly higher in the mothers from Nuoro and Sassari provinces, compared to those living in the Cagliari province. Intriguingly, it is in these two provinces that the occurrence of KS is also higher (22).

*Future perspectives.* It is planned to expand the same investigation to a greater number of mothers and to investigate the possible vertical transmission (i.e. mother to child) of HHV-8 infection, by measuring levels of antibodies in the child at one year of age.

This later study shows that the original 'Sardinia-IDDM' project possesses an unpredicted potential, offering the possibility to branch out and investigate other pathological conditions which also have a high frequency in the Island.

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