Diabetes Incidence in 0- to 14-Year Age-Group in Italy

A 10-year prospective study

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OBJECTIVE — The Registry for Type 1 Diabetes Mellitus in Italy (RIDI) Study Group was established to coordinate the registries of type 1 diabetes in Italy. This report is based on 3,606 children younger than 15 years diagnosed with type 1 diabetes and prospectively registered during 1990–1999 by nine centers, covering >35% of the Italian population.

RESEARCH DESIGN AND METHODS — Registries were pooled in four geographic macro-areas: north, central, south, and insular. The completeness of registration was assessed by the capture-recapture method. Poisson regression analysis was used to evaluate temporal trend in incidence.

RESULTS — Large variations in incidence were confirmed not only between Sardegna and the mainland but also among peninsular areas. In Sardegna, there was an excess of boys (the boy-to-girl incidence ratio was 1.4). The overall incidence showed average increases of 3.6% ($P < 0.001$) and 3.7% ($P < 0.001$) per year in peninsular Italy and in Sardegna, respectively. Significant increases in incidence rates were found in boys aged 10–14 years (6.7%, 95% CI 0.5–13.3) and in girls aged 5–9 years (6.6%, 0.5–13.1) living in the southern area. The incidence rate also increased in boys aged 10–14 years (5.0%, 0.3–10) and in girls aged 0–4 years (4.9%, 0.8–9.1) living in Sardegna.

CONCLUSIONS — Italy is a country with large geographical variations in incidence rates of type 1 diabetes. However, the rates are evenly increasing both in the mainland and Sardegna, suggesting that similar environmental factors are operating over populations that have different genetic backgrounds.

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Abbreviations: RIDI, Registry for Type 1 Diabetes Mellitus in Italy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The incidence of childhood type 1 diabetes has increased in Europe and in many other countries of the world over the past 30 years (1,2). In Finland and in Oxford (U.K.), the maximum increase has been evident in children aged <5 years (3,4). Other studies reporting a changing pattern of age distribution of type 1 diabetes (5) suggest a movement of the disease onset toward the younger ages.

Most epidemiological studies, however, are based on relatively small numbers of registered cases over a relatively short period of time; therefore, the pattern of sex and age distribution of the incidence is not completely focused.

Large differences in incidence rates within Italy are well known; Sardegna, a region with a very high incidence rate of type 1 diabetes, coexists with regions in which the incidence is three to four times lower (6–22). We also reported a large incidence variation among different areas of the continental peninsula of Italy (23), whereas few data concerning temporal trends in the incidence rates are available (24–26).

This study, based on 10 years of prospective registration by the Registry for Type 1 Diabetes Mellitus in Italy (RIDI) Study Group, updates the knowledge on the epidemiology of type 1 diabetes in children living in Italy with respect to the incidence of disease.

RESEARCH DESIGN AND METHODS

RIDI Study Group

RIDI was set up in 1997 aiming to coordinate preexisting registries for the incidence of type 1 diabetes in Italy and to promote the establishment of new registries in uncovered areas.

All registries report newly diagnosed insulin-treated children using a special form that includes patients' personal identification number, date of birth, sex, date of diagnosis (defined as the date when the first insulin injection was

Registries		Average Completeness of ascertainment
North Italy		
1	#Trento province	99.0%
2	Torino province	99.0%
3	Pavia province	99.0%
4	#Modena province	99.0%
5	Liguria region	98.1%
Central Italy		
6	Firenze-Prato province	98.0%
7	Marche region	98.5%
8	Umbria region	99.0%
9	Lazio region	97.8%
South Italy		
10	#Abruzzo region	98.1%
11	Campania region	96.3%
12	**Sardegna** region	90.7%

 # Registries not included in this survey

Figure 1—*Geographical distribution of RIDI registries.*

given), and municipality of residence. Cases diagnosed as type 2 diabetes or other specific types were excluded.

Each registry used at least two independent data sources for case ascertainment, including hospital discharges, prescription registries, personal national health system cards needed by each patient to obtain syringes and strips free of charge, summer camp rosters for diabetic children, membership lists of patient associations, and records of diabetes centers. The completeness of ascertainment of each registry has been estimated by using the capture-recapture method (27). Italy consist of 23 regions; each region encompasses two or more provinces. RIDI includes a total of 12 local registries (Fig. 1): seven regional registries (Liguria, Marche, Umbria, Lazio, Abruzzo, Campania, Sardegna) and five province registries (Trento, Torino, Pavia, Modena, Firenze-Prato). To date, no other registry is operating, apart from Catania province's registry, the data from which we hope to include in our database in the near future.

Cases and population

The RIDI registries began their activities in different years, and therefore, different temporal series of data were available: Trento, Modena, and Abruzzo registries had a shorter period of surveillance; they were not included in this analysis. This report was based on 3,602 incident cases aged 0–14 years, prospectively registered during 1990–1999 by nine registries, covering an at-risk Italian population of 15,718,296 (35% of the whole population). Data came from eight registries in peninsular Italy (Torino, Pavia, and Firenze-Prato provinces and Liguria, Marche, Umbria, Lazio, and Campania regions) and the Sardegna region (Fig. 1).

Because registries are located in four geographic macro-areas, data were stratified according to the geographical definition used by the National Institute for Statistics (28): north (Torino and Pavia provinces and the Liguria region), central (Marche, Umbria, and Lazio regions and the Firenze-Prato province), south (Campania region), and insular (Sardegna region).

Data on at-risk residents in the geographical area covered by each registry for each year of the study period were obtained from the National Institute for Statistics.

Statistical analyses

Age-specific and age-standardized incidence rates on the world standard population per 100,000 person-years for the period 1990–1999 were calculated for each registry, for sex, and for the four geographic macro-areas. The 95% CI of rates were estimated assuming the Poisson distribution of the cases. Homogeneity testing among registries belonging to the same macro-area was performed to detect differences in age-standardized incidence rates (29). The change in incidence rates during the study period was analyzed by fitting the Poisson regression models to the number of cases; resident population was the normalizing constant. Statistical analysis was performed using SAS statistical software, version 8.2 (SAS Institute, Cary, NC). A level of 5% was used to assess statistical significance.

RESULTS — Figure 1 shows the geographical distribution of the regional and provincial registries. The degree of case ascertainment was estimated for each registry separately and ranged from an average value of the study period from 90.7% in Sardegna to 99.0% in the Umbria region. The completeness of ascertainment of registries varied across the study period, but no significant temporal trend was observed.

The homogeneity test showed no evidence of heterogeneity among age-standardized incidence rates of registries belonging to the same geographical macro-area mentioned above, with the exception of boys in the central area (P = 0.005), where the incidence rate of the Lazio region was significantly lower than that of the Firenze-Prato province (8.8 [95% CI 7.9–9.8] vs. 13.0 [10.6–16.0], respectively) (Table 1). However, to obtain more stable estimates of trend analysis, we decided to consider data from registries aggregated in the geographical macro-areas.

Incidence rates

The incidence rates per 100,000 person-years in the age-group 0–14 years in peninsular Italy were 8.4 (95% CI 7.9–8.9). There were few differences in incidence rate between sexes: 8.8 (8.3–9.4) in boys and 8.0 (7.5–8.5) in girls. Overall incidence rates were 11.2 (10.3–12.2) in North Italy, 9.3 (8.8–9.9) in Central Italy, 6.2 (5.8–6.7) in South Italy, and 36.9 (34.7–39.3) in Sardegna.

Significant differences were found among age-standardized incidence rates of the macro-areas; rates in the south were significantly lower than those in the north and central areas for both the sexes (Table 1). Moreover, in peninsular Italy, the age-standardized incidence rates in boys showed a significant decreasing trend from the north to the south. As expected, the highest incidence rates were observed in Sardegna, with fivefold and fourfold higher rates in boys and girls, respectively, than in the peninsular area. A significantly higher incidence rate was observed in Sardinian boys than in Sardinian girls, whereas no differences between sexes were found in the other areas. Because significant differences between sexes were observed, subsequent analyses were performed separately for boys and girls.

Table 2 shows that South Italy has the lowest incidence of type 1 diabetes in all age-groups, except for girls aged 5–9 years. Incidence rates in girls aged 0–4 years from Central Italy, South Italy, and Sardegna were significantly lower than in girls aged 5–9 years. In the girls from South Italy, the age-group of 5–9 years had an incidence rate significantly higher than both the age-groups of 0–4 and 10–14 years.

A significant difference in incidence between sexes was found only in Sardegna in the age-group of 10–14

Table 1—*Incidence rates of type 1 diabetes in Italy and homogeneity test according to registry, geographic area, and sex (age 0–14 years, period 1990–1999)*

	Boys					Girls				
Registries and areas	Cases (n)	Person-years	Incidence rates*	95% CI	Homogeneity test (P)	Cases (n)	Person-years	Incidence rates*	95% CI	Homogeneity test (P)
Torino	167	1,444,818	11.1	9.5–12.9	0.253	139	1,367,388	10.0	8.4–11.8	0.491
Pavia	36	287,218	12.1	8.5–16.8		34	270,965	12.0	8.3–16.7	
Liguria	124	893,677	13.5	11.3–16.2		89	845,828	10.5	8.5–13.0	
North Italy	327	2625713	12.0	10.8–13.4		262	2,484,180	10.4	9.2–11.7	
Firenze-Prato	96	709,218	13.0	10.6–16.0	0.005	53	679,220	7.7	5.8–10.2	0.231
Umbria	67	552,863	12.4	9.7–15.9		56	521,612	11.1	8.5–14.6	
Marche	104	1,010,665	10.1	8.3–12.3		93	956,318	9.6	7.8–11.8	
Lazio	359	4,006,647	8.8	7.9–9.8		333	3,803,133	8.6	7.7–9.6	
Central Italy	626	6,279,392	9.8	9.0–10.6		535	5,960,282	8.9	8.1–9.6	
Campania/South Italy	403	6,164,187	6.4	5.8–7.0		362	5,897,456	6.0	5.4–6.7	
Peninsular Italy	1,356	15,069,292	8.8	8.3–9.4		1,159	14,341,918	8.0	7.5–8.5	
Sardegna	660	1,461,924	43.3	40.1–46.8		427	1,376,378	30.1	27.4–33.2	

*Standardized on the world standard population per 100,000 person-years.

Table 2—*Age-specific incidence rates of type 1 diabetes in Italy according to sex and geographical area (age 0–14 years, period 1990–1999)*

	Boys				Girls			
Age-group	Cases (*n*)	Person-years	Incidence rates*	95% CI	Cases (*n*)	Person-years	Incidence rates*	95% CI
0–4 years								
North	72	831,008	8.7	6.8–11.0	69	782,022	8.8	6.9–11.2
Central	161	1,965,620	8.2	7.0–9.6	136	1,861,656	7.3	6.2–8.7
South	100	1,949,131	5.1	4.2–6.3	81	1,855,831	4.4	3.5–5.5
Sardegna	143	418,477	34.2	28.9–40.4	93	392,069	23.7	19.3–29.2
5–9 years								
North	116	849,561	13.7	11.3–16.4	92	802,262	11.5	9.3–14.1
Central	230	2,049,681	11.2	9.8–12.8	207	1,945,589	10.6	9.3–12.2
South	140	2,047,506	6.8	5.8–8.1	162	1,959,088	8.3	7.1–9.7
Sardegna	220	481,170	45.7	40–52.3	163	453,459	36.0	30.7–42
10–14 years								
North	139	945,145	14.7	12.4–17.4	101	899,896	11.2	9.2–13.7
Central	235	2,264,092	10.4	9.1–11.8	192	2,153,037	8.9	7.7–10.3
South	163	2,167,550	7.5	6.4–8.8	119	2,082,537	5.7	4.8–6.9
Sardegna	297	562,278	52.8	47.1–59.3	171	530,851	32.2	27.6–37.5

*Per 100,000 person-years.

years; the incidence was higher in boys than in girls.

The age-specific incidence rates were estimated for each year of age according to sex and geographical area. In peninsular areas, no significant peaks, neither strong irregularities nor differences, between sexes were found. In Sardegna, the pattern of rates was much more irregular in both sexes; there was a significantly higher risk in boys than in girls aged 12 years (63.6 per 100,000 person-years [95% CI 50.1–80.6], 23.4 per 100,000 person-years [15.1–34.6], respectively).

Trend analysis

The overall incidence of type 1 diabetes throughout the 10-year study period showed average increases of 3.6% ($P < 0.001$) and 3.7% ($P < 0.001$) per year in peninsular Italy (adjusted for geographical area, sex, and age-group) and in Sardegna (adjusted for sex and age-group), respectively. Because geographical area (for peninsular Italy), sex, and age showed a significant effect on incidence rates for both peninsular Italy and Sardegna, a stratified trend analysis was performed. A significant trend was found in Central Italy (3.6% [95% CI 1.2–6.0]) and South Italy (4.7% [2.1–7.4]), but not in North Italy (2.1% [−0.5–4.8]) (Table 3). Significant increases were found in southern boys aged 10–14 years (6.7% [0.5–13.3]), in southern girls aged 5–9 years (6.6% [0.5–13.1]), in Sardinian boys aged 10–14 years (5.4% [0.3–10.8]), and in Sardinian girls aged 0–4 years (4.9% [0.8–9.1]) (Table 3).

CONCLUSIONS — This is the first study reporting a wide picture of Italian incidence data during a 10-year period. We used high-quality data coming from prospective, coordinated incidence registries with a good level of ascertainment. Time trends and geographical variation in children with different genetic backgrounds were analyzed. Our results will be helpful in investigating the etiology of type 1 diabetes through analytical epidemiological studies.

It is generally accepted that the etiology of childhood type 1 diabetes involves both genetics and environment. The rise in incidence during a relatively short period of time could be an indicator of the effect of environmental factors. During the past decade, the increase in temporal trends of type 1 diabetes was not significant in all examined European countries (2). Incidence of type 1 diabetes in Italy is characterized by large variability because we observed geographical areas with very high levels of incidence (Sardegna) and areas with intermediate level of incidence (Peninsular areas), according to the classification proposed by the DiaMond Study Group (30). This group defined five levels of incidence rate: *1*) very low, <1/100,000 per year; *2*) low, 1–4.99/100,000 per year; *3*) intermediate, 5–9.99/100,000 per year; high, *4*) 10–19.99/100,000 per year; and *5*) very high, ≥20/100,000 per year.

It is interesting to underline that the incidence of type 1 diabetes showed wide variations not only between Sardegna and mainland Italy, but also among the peninsular regions, as we formerly observed (6,23). The lowest incidence rate was noted in South Italy, which was sixfold lower than in Sardegna. This report refers to only one southern region; however, the total population at risk in Campania is 33% of the total children living in South Italy.

Recently, a different incidence rate of type 1 diabetes (12.3 per 100 000 person-years [95% CI 10.9–13.9]) has been reported in children younger than 15 years living in the province of Catania (Sicily region, South Italy), including only 6% of the total southern children (25). More investigation is needed for a better understanding of the occurrence of type 1 diabetes in South Italy.

It remains to be clarified whether differences in incidence of type 1 diabetes in mainland Italy could be attributed to the genetic differences (31) or to a different distribution of environmental determinants of the disease.

Compared with other studies (32,33), we found a higher incidence rate of type 1 diabetes in boys than in girls in Sardegna, which was significant in the age-group 10–14 years, reaching a boy-

Table 3—*Trend coefficients and 95% CIs according to sex, age-groups, and geographical areas (1990–1999)*

	Trend	95% CI	*P*	Goodness of fit		
				χ^2	df	*P*
North Italy	1.021*	0.995–1.048	0.111	57.10	55	0.397
Boys						
0–4 years	1.019	0.950–1.093	0.591	7.23	8	0.512
5–9 years	1.046	0.973–1.124	0.228	8.70	8	0.369
10–14 years	1.023	0.962–1.088	0.468	8.49	8	0.387
Girls						
0–4 years	1.020	0.947–1.100	0.599	8.12	8	0.422
5–9 years	1.040	0.964–1.123	0.312	8.04	8	0.429
10–14 years	0.978	0.950–1.006	0.126	8.04	8	0.429
Central Italy	1.036*	1.012–1.060	0.003	53.29	55	0.540
Boys						
0–4 years	1.047	0.994–1.103	0.083	7.91	8	0.442
5–9 years	1.033	0.983–1.085	0.199	7.23	8	0.512
10–14 years	1.051	0.996–1.109	0.072	7.65	8	0.469
Girls						
0–4 years	0.985	0.907–1.070	0.724	8.22	8	0.413
5–9 years	1.049	0.982–1.121	0.156	8.00	8	0.433
10–14 years	1.034	0.989–1.081	0.143	7.71	8	0.462
South Italy	1.047*	1.021–1.074	<0.001	54.05	55	0.511
Boys						
0–4 years	1.043	0.984–1.105	0.158	7.66	8	0.467
5–9 years	1.021	0.966–1.078	0.464	7.90	8	0.443
10–14 years	1.067	1.005–1.133	0.034	7.88	8	0.445
Girls						
0–4 years	1.036	0.959–1.120	0.370	8.09	8	0.425
5–9 years	1.066	1.005–1.131	0.033	7.52	8	0.481
10–14 years	1.040	0.984–1.099	0.165	8.22	8	0.412
Sardegna	1.037*	1.018–1.057	<0.001	53.94	55	0.515
Boys						
0–4 years	1.031	0.981–1.083	0.233	7.70	8	0.464
5–9 years	1.009	0.979–1.039	0.558	7.51	8	0.483
10–14 years	1.054	1.003–1.108	0.039	7.97	8	0.436
Girls						
0–4 years	1.049	1.008–1.091	0.019	7.84	8	0.450
5–9 years	1.035	0.994–1.078	0.098	7.81	8	0.452
10–14 years	1.047	0.992–1.105	0.093	7.64	8	0.470

*Adjusted for sex and age-group.

to-girl ratio of 1.6. Conversely, in mainland Italy, the observed higher incidence in boys was not statistically significant. Some authors showed an association between sex and levels of type 1 diabetes incidence. They identified incidence thresholds by which an incidence rate >23/100,000 (like that of Sardegna) is associated with an excess of boys, whereas an incidence rate <4.5/100,000 (lower than that we observed in mainland Italy) is associated with an excess of girls (33). Because the reasons for these differences are still unknown, there is currently a great amount of interest regarding the sex influence in the pathogenesis of type 1 diabetes (32). Among populations of Caucasian origin, including Sardegna, it was reported that the higher incidence in boys is largely restricted to the patients carrying HLA-DR3 (34). In Sardinian type 1 diabetic patients, the DR3/X category (with X = not DR4) showed a boy-to-girl ratio of 2.1, whereas in the DR3/DR3 homozygous group, the rate was 2.3. Moreover, a linkage to Xp chromosome in HLA-DR3–positive patients has been shown. This evidence suggests that a gene localized in the X chromosome may play a role in the disease pathway (35,36). Recently, the association between type 1 diabetes and neonatal infections was observed in boys but not in girls (37). It is interesting to note that this association was not evident when the interaction with sex and neonatal infection was not considered. On the basis of these considerations, both analytical and descriptive studies on type 1 diabetes should be performed stratified according to sex.

Regarding the age effect, our main finding is the significantly lower incidence of the youngest age-group in both boys and girls. Nevertheless, the analysis of incidence according to year of age showed no peak of incidence rate to a specific age. Some authors observed a peak of incidence (25), but the statistical significance was not always considered.

Our survey shows an increasing incidence of type 1 diabetes in children younger than 15 years both in mainland Italy and in Sardegna of 3.6 and 3.7% per year, respectively. Because similar increasing trends were found in two populations characterized by different genetic susceptibility, the role of shared environmental risk factors on these geographical area could be hypothesized (21).

Other European studies have reported significant incidence trends, suggesting changes in environmental factors over time (2,24–26). In fact, an increase observed in a relatively short period is not readily explained by shifts in the frequencies of susceptibility genes (38); therefore, the inhomogeneous pattern of incidence across geographical areas, sex, and age-group found within Italy could suggest the hypothesis that different environmental exposures act in each group.

Our data showed significant differences of temporal trends between geographical areas, ages, and sex, as described in other European studies (2,25,39–42).

Our study underlines the importance of performing epidemiological descriptive studies on type 1 diabetes, taking into account not only the geographical, age, sex, and period effects, but also estimating incidence rates and trends in subgroups of populations stratified according to geographical area, age, and sex.

Due to the relatively short period of this survey (10 years) and the lack of incidence data for patients older than 14 years, it was not possible to perform an analysis of the age-specific incidence by birth cohorts in our dataset. Therefore, we cannot speculate on the shift to younger age at diagnosis observed in other large surveys from northern European countries (3,5). Thus, it is important to continue the registration of newly diabetic cases by population-based registries.

In conclusion, from 1990 to 1999, epidemiology of type 1 diabetes in Italy, with respect to incidence data, is characterized by *1*) geographical differences between Sardegna and mainland Italy and within peninsular Italy; *2*) excess of incidence rate in boys in Sardegna only; *3*) lower incidence in the 0- to 4-year age-group; *4*) a temporal trend in some geographical-age-sex groups; *5*) an even increasing temporal trend both in mainland and in Sardegna, suggesting the hypothesis that similar environmental factors may be operating in populations with different genetic backgrounds.

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APPENDIX

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