Age-Period-Cohort Analysis of 1990–2003 Incidence Time Trends of Childhood Diabetes in Italy

The RIDI Study

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OBJECTIVE—To investigate age-period-cohort effects on the temporal trend of type 1 diabetes in children age 0–14 years in Italian registries.

RESEARCH DESIGN AND METHODS—This report is based on 5,180 incident cases in the period 1990–2003 from the Registry for Type 1 Diabetes Mellitus in Italy (RIDI). Multilevel (random intercept) Poisson regression models were used to model the effects of sex, age, calendar time, and birth cohorts on temporal trends, taking into account the registry-level variance component.

RESULTS—The incidence rate was 12.26 per 100,000 person-years and significantly higher in boys (13.13 [95% CI 12.66–13.62]) than in girls (11.35 [10.90–11.82]). Large geographical variations in incidence within Italy were evident; incidence was highest in Sardinia, intermediate in Central-Southern Italy, and high in Northern Italy, particularly in the Trento Province, where the incidence rate was 18.67 per 100,000 person-years. An increasing temporal trend was evident (2.94% per year [95% CI 2.22–3.67]). With respect to the calendar period 1990–1992, the incidence rates increased linearly by 15, 27, 35, and 40% in the following time periods (P for trend < 0.001). With respect to the 1987–1993 birth cohort, the incidence rate ratio increased approximately linearly from 0.63 (95% CI 0.54–0.73) in the 1975–1981 cohort to 1.38 (1.06–1.80) in the 1999–2003 cohort. The best model, however, included sex, age, and a linear time trend (drift).

CONCLUSIONS—Large geographical variations and an increasing temporal trend in diabetes incidence are evident among type 1 diabetic children in Italy. Age-period-cohort analysis shows that the variation over time has a linear component that cannot be ascribed to either the calendar period or the birth cohort. ***Diabetes* 59:2281–2287, 2010**

The incidence of type 1 diabetes among children is increasing worldwide with great geographical heterogeneity (1–6). Recently, the EURODIAB Study showed that within Europe the most striking changes during the 1989–2003 period were observed in central and eastern European countries (7). The etiology of the disease is unclear, although a genetic component is evident, and other nongenetic factors, such as infections, nutritional components, and toxins, have been suggested (8). Investigating the spatial and temporal variations of diabetes incidence might provide insights into the etiology of the disease (9–15). Moreover, if associations between environmental factors and the disease exist, it is relevant to establish whether increasing temporal trends are occurring cross-sectionally, affecting all age-groups at the same point in time (period effects), or longitudinally, affecting all age-groups from the same birth cohort (cohort effects) (16). Whereas a nonlinear period increase would suggest an abrupt exposure to an environmental determinant, a nonlinear cohort increase would be consistent with the effect of an epidemic of congenital infections. The linear dependence among age, period, and cohort makes it necessary to apply specific modeling strategies for this task (16). Whereas national diabetes temporal trends (17) and regional age-period-cohort modeling have been published previously (15,18), the age-period-cohort analysis of the Registry of Type 1 Diabetes Mellitus in Italy (RIDI) for the combined national data has never been conducted. The aim of this report is to describe the incidence time trends of childhood-onset type 1 diabetes in Italy in the 1990–2003 period using an age-period-cohort approach.

RESEARCH DESIGN AND METHODS

RIDI was set up in 1997 to coordinate registries for the incidence of type 1 diabetes in Italy (17). All registries reported newly diagnosed cases of childhood type 1 diabetes using a special form, which includes each patient's personal identification number, date of birth, sex, date of diagnosis (defined as the date when the first insulin injection was given), and municipality of residence. A diagnosis of type 1 diabetes was based on permanent insulin treatment within 6 months of diagnosis, fasting C-peptide levels ≤0.20 nmol/l, or positivity for insulinoma-associated protein 2, islet cell antibody, or GAD antibody. Case subjects diagnosed as having type 2 diabetes or other specific

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TABLE 1
Incidence rates of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003 by sex, age-group, calendar period, and geographical area of residence

	Incident cases (*n*)	Person-years at risk (*n*)	Incidence rates per 100,000 person-years (95% CI)	% Estimated completeness of ascertainment (range)
All	5,180	42,246,144	12.26 (11.93–12.60)	
Boys	2,840	21,629,264	13.13 (12.66–13.62)	
Girls	2,340	20,616,878	11.35 (10.90–11.82)	
Age-group (years)				
0–2	479	7,984,265	6.00 (5.49–6.56)	
3–5	961	8,002,496	12.01 (11.27–12.79)	
6–8	1,118	8,259,614	13.54 (12.77–14.35)	
9–11	1,366	8,672,116	15.75 (14.94–16.61)	
12–14	1,256	9,327,652	13.47 (12.74–14.23)	
Calendar period				
1990–1992	1,089	10,659,853	10.22 (9.63–10.84)	
1993–1995	1,139	9,871,152	11.54 (10.89–12.23)	
1996–1998	1,184	9,297,165	12.74 (12.03–13.48)	
1999–2001	1,091	7,836,490	13.92 (13.12–14.77)	
2002–2003	677	4,581,483	14.78 (13.7–15.93)	
Birth cohort				
1975–1981	273	2,536,714	10.76 (9.56–12.12)	
1978–1984	560	4,440,171	12.61 (11.61–13.70)	
1981–1987	819	6,100,235	13.43 (12.54–14.38)	
1984–1990	1,012	7,278,051	13.90 (13.07–14.79)	
1987–1993	1,047	8,137,636	12.87 (12.11–13.67)	
1990–1996	715	6,285,553	11.38 (10.57–12.24)	
1993–1999	457	4,186,785	10.92 (9.96–11.96)	
1996–2002	226	2,385,021	9.48 (8.32–10.80)	
1999–2003	71	895,977	7.92 (6.28–10.00)	
Northern Italy	945	8,006,808	11.80 (11.07–12.58)	
Turin	419	3,823,910	10.96 (9.96–12.06)	99.0 (98.2–99.4)
Liguria	280	2,377,687	11.78 (10.47–13.24)	98.2 (96.7–99.0)
Pavia	93	768,584	12.10 (9.87–14.83)	99.0 (97.8–99.8)
Modena	74	613,452	12.06 (9.61–15.15)	99.3 (98.1–100)
Trento	79	423,175	18.67 (14.97–23.27)	99.4 (98.7–100)
Central-Southern Italy	2,728	30,550,760	8.93 (8.6–9.27)	
Firenze-Prato	214	1,923,090	11.13 (9.73–12.72)	98.8 (98.0–100)
Marche	284	2,696,075	10.53 (9.38–11.83)	99.0 (97.8–99.9)
Lazio	678	7,522,247	9.01 (8.36–9.72)	97.0 (95.3–98.8)
Umbria	145	1,255,832	11.55 (9.81–13.59)	99.0 (98.0–100)
Abruzzo	115	1,196,101	9.61 (8.01–11.54)	98.1 (97.2–100)
Campania	1,292	15,957,414	8.10 (7.67–8.55)	96.2 (94.2–98.5)
Island				
Sardinia	1,507	3,688,576	40.86 (38.84–42.97)	91.0 (89.0–96.0)

types were excluded. Each registry used at least two independent data sources for case ascertainment (17), and the completeness of ascertainment was estimated by the capture-recapture method. In a previous report (17), we presented incidence rates based on 3,602 incident case subjects aged 0–14 years, who had been registered during 1990–1999 by nine registries. To date, 12 registries regularly update incidence rates as part of RIDI: seven regional registries (Liguria, Marche, Umbria, Lazio, Abruzzo, Campania, and Sardinia) and five province registries (Trento, Torino, Pavia, Modena, and Firenze-Prato), covering an at-risk population of 3,321,459 children (39.7% of the whole Italian population aged 0–14 years (a geographical distrubution map is available in an online appendix at http://diabetes.diabetesjournals.org/cgi/content/full/db10-0151/DC1).

This report is based on 5,180 incident cases registered in the 1990–2003 period. Most registries contributed data over the whole study period. The registries of Modena and Trento contributed cases in periods 1996–2003 and 1998–2003, respectively, whereas registries of Abruzzo, Lazio, and Umbria contributed data in periods 1990–1995, 1990–1999, and 1990–2001, respectively. 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 analysis. The presence of extra-Poisson variability has been evaluated assuming a γ distribution of the true incidence rates through the likelihood ratio test. Multilevel random intercept Poisson regression models have been used to estimate the effects of sex, age (five 3-year age-groups: 0–2, 3–5, 6–8, 9–11, and 12–14 years), calendar time (four 3-year periods: 1990–1992, 1993–1995, 1996–1998, 1999–2001; and one 2-year period: 2002–2003), and birth cohorts (nine 6-year birth cohorts: 1978, 1981, 1984, 1987, 1990, 1993, 1996, 1999, 2001 mid-years), taking into account the registry-level variance component. The models assume a γ distribution of the registry-level random intercept, accounting also for within-registry dependence. Six models were fitted to data: sex; sex, age; sex, age, linear time trend (drift); sex, age, cohort; sex, age, period; and sex, age, period, cohort. The term "drift" denotes a temporal variation of rates that does not distinguish between the influences of two of the three temporal variables involved in the analysis. The hierarchically ordered models were compared by likelihood ratio test. The χ^2 test for trend in incidence rates used is the Mantel extension of the Armitage-Cochran trend test (19). The trend test is adjusted by sex. Poisson regression analyses were performed using xtpoisson in STATA, version 9.0. Age-period-cohort models were fitted using apc.fit in R (http://www.R-project.org) (16).

RESULTS

In the 1990–2003 period, 5,180 incident cases of type 1 diabetes were identified among children aged 0–14 years. All registries provided high estimated completeness of ascertainment (Table 1). Incidence rates by sex, age-group, calendar period, birth cohort, Italian macro-area

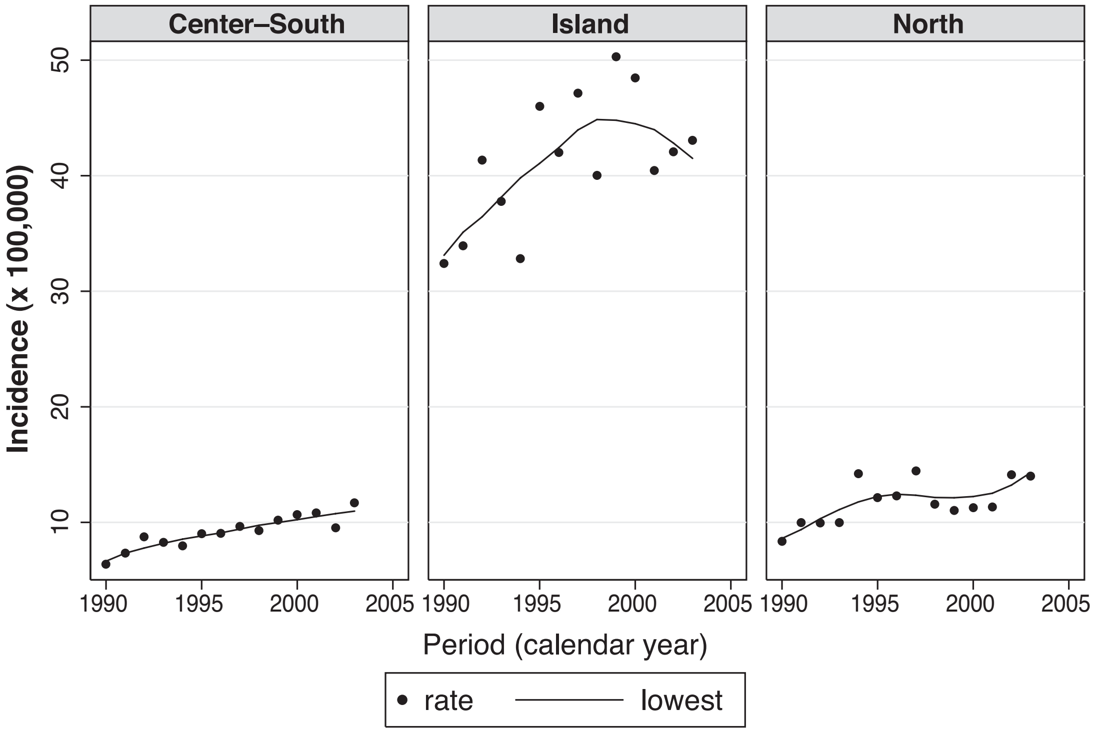

FIG. 1. Incidence rates of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003 in the three Italian macro-areas (Center-South, Island [Sardinia], and North).

(North, Center-South, Island [Sardinia]), and registry are shown in Table 1. The incidence rate was 12.26 per 100,000 person-years (95% CI 11.93–12.60), with significantly lower risk in girls (11.35 [95% CI 10.90–11.82]) than in boys (13.13 [12.66–13.62]). In peninsular Italy, the incidence rates were 9.53 (95% CI 9.22–9.84) overall, 9.97 (9.54–10.42) in boys, and 9.06 (8.64–9.50) in girls.

The likelihood ratio test showed substantial and statistically significant presence of overdispersion ($P < 0.001$). To account for this heterogeneity, multilevel random-intercept Poisson regression models were fitted to data accounting for the registry-level variance component. In the regression analysis, after controlling for age, the rate ratio (RR) for girls with respect to boys was 0.87 (95% CI 0.82–0.92); corresponding values in peninsular Italy and in Sardinia were 0.91 (0.85–0.97) and 0.77 (0.70–0.85), respectively. The incidence steeply increased from the age-group 0–2 to the age-group 3–5 years (Table 1), was quite similar in age-groups 6–8 and 12–14, and peaked at 9–11 years.

Large geographical variations in type 1 diabetes incidence were evident (Table 1), with the highest rate in Sardinia, an intermediate rate in Central-Southern Italy, and a high rate in Northern Italy, particularly in the Trento Province (18.67 per 100,000 person-years [95% CI 14.97–23.27]). The lowest incidence rate was recorded in the Campania Region (8.10 [7.67–8.55]).

An increasing temporal trend was evident both examining the whole Italian area and the three Italian macro-areas separately; in Sardinia we found a tendency toward lower risk in more recent years (Fig. 1). Overall, the rates increased from 10.22 per 100,000 person-years in 1990–1992 to 14.78 per 100,000 in 2002–2003 (Table 1). Controlling for age and sex, the annual increase was 2.94% (95% CI 2.22–3.67).

Table 2 shows age-specific incidence rates by calendar period (diagonals) and birth cohorts. An increasing temporal trend across calendar period was evident ($P < 0.0001$): with respect to the calendar period 1990–1992, the RR was 1.15 (95% CI 1.06–1.25) in the period 1993–1995, 1.27 (1.17–1.39) in the period 1996–1998, 1.35 (1.24–1.47) in the period 1999–2001, and 1.40 (1.27–1.55) in the period 2002–2003. In all periods (diagonals), the highest incidence rates were found in the age-group 9–11 years; in the last period (2002–2003) only, after a rapid increase from the first to the second age-group, rates remained similarly high from 6 years old onwards.

With respect to birth cohort 1987–1993 (1990 mid-year), the incidence rates increased approximately linearly. As shown in Table 2, the RR increased from 0.63 (95% CI 0.54–0.73) in birth cohort 1975–1981 (1978 mid-year) to 1.38 (1.06–1.80) in birth cohort 1999–2003 (2001 mid-year).

Multilevel Poisson regression analysis was also used to assess whether the observed temporal increase in incidence rates could be due to period or cohort effects. Table 3 shows the main results of fitting different models to the data. The best model (model 3) included sex, age, and a linear time trend (drift). Therefore, the variation over time has a linear component that cannot be ascribed to either the calendar period or the cohort. Indeed, the sex, age, and cohort model (model 4) and the sex, age, and period model (model 6) were not significantly better than the sex, age, and drift model (model 3). The estimated variance of the registry-level random intercept showed statistically significant heterogeneity between registries (P value of the likelihood ratio test <0.001 in all models, Table 3).

Figure 2 shows incidence rates (on a logarithmic scale) over age-groups by birth cohorts, over calendar period by age-groups, and over birth cohorts by age-groups. Results were similar when data were analyzed by geographical macro-areas (data not shown).

TABLE 2
Age-specific incidence rates (per 100,000 person-years) of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003, by birth cohorts 1978–2001, and by calendar periods (diagonals) 1990–1992, . . ., 2002–2003

	Birth cohorts											
Age-group (years)	1978	1981	1984	1987	1990	1993	1996	1999	2001	Yearly increase (%)	P	α*
0–2					5.0 (95)	4.9 (92)	6.4 (114)	7.1 (107)	7.9 (71)	3.9	0.001	0.3
3–5				10.3 (199)	12.4 (229)	12.1 (223)	12.6 (191)	13.5 (119)		1.6	0.056	0.2
6–8			10.9 (225)	13.1 (246)	14.4 (263)	14.6 (232)	17.0 (152)			3.3	<0.001	0.2
9–11		13.4 (297)	15.2 (309)	16.2 (299)	18.2 (293)	17.6 (168)				2.4	0.001	0.2
12–14	10.8 (273)	11.9 (263)	14.3 (285)	16.5 (268)	17.4 (167)					4.0	<0.001	0.3
RR (95% CI)	0.63 (0.54–0.73)	0.72 (0.64–0.80)	0.82 (0.74–0.90)	0.91 (0.83–0.99)	Ref.	0.99 (0.89–1.09)	1.12 (1.00–1.26)	1.18 (1.01–1.38)	1.38 (1.06–1.80)			

Number of cases are in parentheses. Percent yearly increases, test for age-specific trends adjusted by sex over calendar periods, and estimated variance of the registry-level random intercept (α) are shown in the last column. *Likelihood ratio test of $\alpha = 0$; $P < 0.001$ in all age-groups. RR, rate ratio for each birth cohort taking as reference those born in 1987–1993 (1990 mid-year).

TABLE 3
Comparison of different age-period-cohort models fitted to incidence rates of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003

Covariates included in the model	DF	Likelihood ratio χ^2	P	α*
1. Sex				
2. Sex + age	4	385.00	<0.0001	0.21
3. Sex + age + drift	1	65.33	<0.0001	0.20
4. Sex + age + cohort	7	8.51	0.29	0.20
5. Sex + age + period + cohort	3	2.23	0.53	0.20
6. Sex + age + period	−7	−6.51	0.48	0.20
3. Sex + age + drift	−3	−4.24	0.24	0.20

Each model is compared with the one above through the likelihood ratio test. *Likelihood-ratio test of $\alpha = 0$; $P < 0.001$ in all models. DF, difference in the number of degrees of freedom.

DISCUSSION

Results of the present analyses of the RIDI study provide evidence of *1*) large geographical variations in risk of childhood type 1 diabetes within Italy, with high-risk areas in both Sardinia and Trento, in the North-East of Italy; *2*) a significantly lower risk in girls than in boys, which is more pronounced in Sardinia (−23%) than in peninsular Italy (−9%); and *3*) a linear increasing temporal trend, with an annual increment of 2.94%, affecting all age-groups and both sexes. In our dataset, however, it was impossible to ascribe this increase definitively to either a birth cohort or a calendar period effect.

Our findings are based on a national registry using standardized methods of ascertainment of incident cases, covering 40% of the Italian population at risk; moreover, the long time period on which this report is based allows us to add to current knowledge on epidemiology of type 1 diabetes. Heterogeneity of type 1 diabetes risk has been reported worldwide, but Italy is one of the countries with greater variation within it. Indeed, incidence in peninsular Italy is fourfold lower than in Sardinia. In the latter, rates appeared to decline in more recent years, suggesting the possibility that an upper limit has been reached. The novel finding of the updated report of the RIDI Study is that a new high-risk area has been identified in the North-East of Italy, in Trento. The lower boundary of the CI of the incidence rate for Trento is higher than the upper value of the CI of all other peninsular areas (with the exception of Modena), and is similar to risk of children living in neighboring European areas, Germany, and Austria (4–5). Whether this heterogeneity is due to either genetic or environmental factors is difficult to establish on the basis of available data and advocates further studies. Moreover, the extension of the RIDI project to other Italian areas not covered by registries would provide a more accurate estimate of risk at national level.

Sex differences in risk of both type 1 and type 2 diabetes, with an almost two-fold higher risk in males than in females, have been previously reported in young Italian adults (20–21). The large number of cases on which this report is based allows us to provide evidence that the male excess in risk of type 1 diabetes is evident even in Italian children, consistent with studies performed in high-risk areas (22). This finding could suggest a role for sex-linked differences in β-cell function or in insulin sensitivity, with a higher rate of β-cell exhaustion in male than in female subjects.

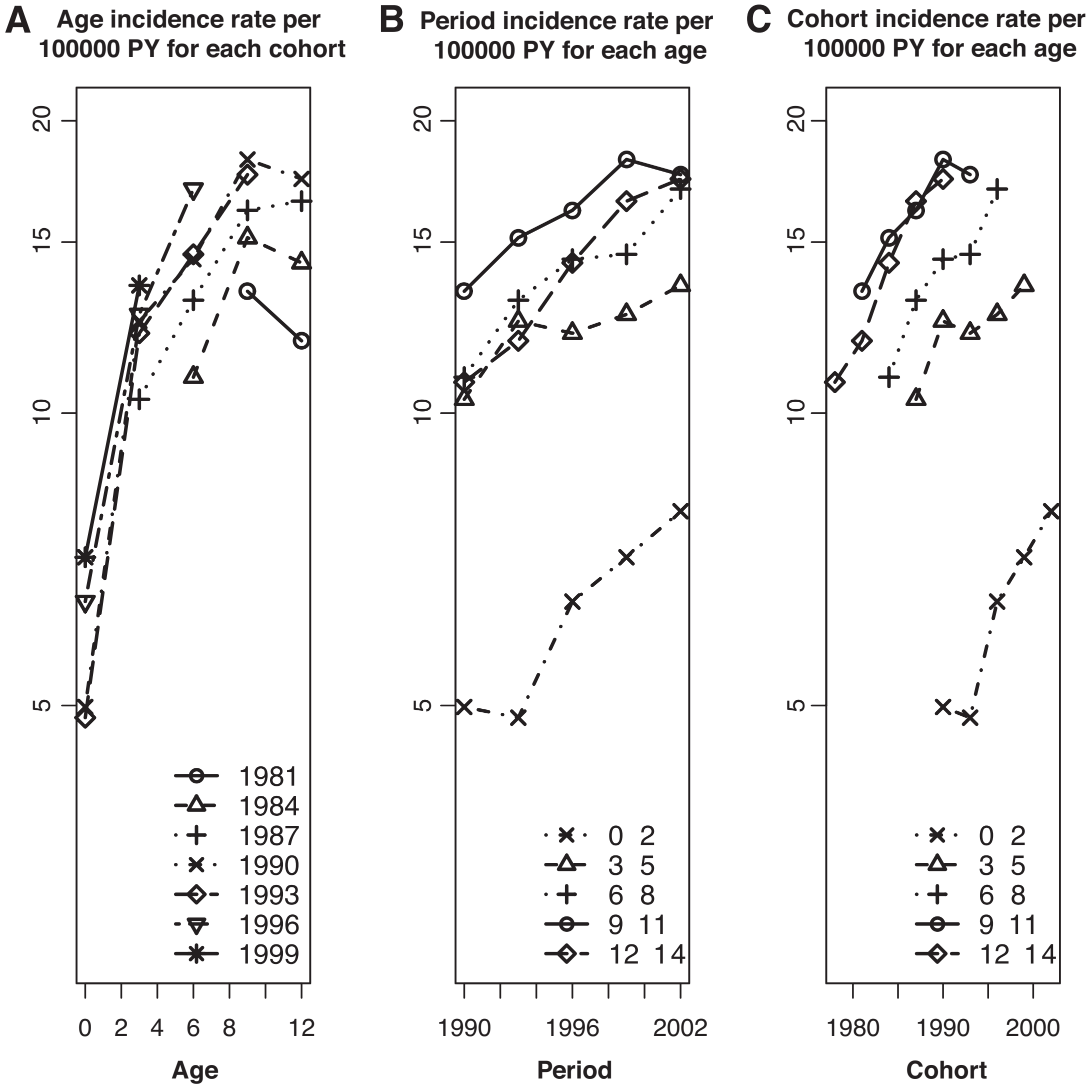

FIG. 2. Incidence rates of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003 over age-groups by birth cohorts (mid-year of birth cohorts) (*A*), over calendar period by age-groups (*B*), and over birth cohorts by age-groups (*C*).

Our analyses show that the increasing temporal trend involved all age-groups similarly. This finding is consistent with a recent report from the registry of Turin, showing a similar increase in incidence of childhood and adulthood diabetes since 1984, suggesting that widespread environmental determinants are involved in this phenomenon (18). This finding, however, is in contrast with studies suggesting that the incidence increase could be explained by a shift to a younger age at onset (7,11–12,14,23–24). In our study, we carried out an age-period-cohort analysis that included evaluation of both the drift (the linear variation of the incidence in time due to either a calendar period or a cohort effect) and the nonlinear components of the effects of the two temporal variables. We did not find evidence of nonlinear effects because there were no improvements in the models when the nonlinear components of calendar period or birth cohort were introduced. Because the incidence increase was linear, it was not possible to distinguish between the effects of calendar period and birth cohort, and our data do not support the hypothesis of a shift to a younger age at onset.

Previously published age-period-cohort models in childhood diabetes temporal trend have shown inconclusive results. A period effect was found in Poland but not in a U.S. county in the years 1970–1985 (25). In 1978–1987 in Sweden (13), in 1965–1984 in Finland (14), and in 1973–2000 in Norway (9) linear and nonlinear effects of the calendar period were evident, but no statistically significant cohort effect was found; the Finnish study (14) found only some evidence of younger age at diabetes onset. A later Swedish study (24) found no evidence of an increase in incidence rates, whereas it strongly supported a cohort effect because of a steeper increase in younger age-groups. In 1970–2000 in Denmark, a modest drift effect and a significant cohort effect were found, with increased risk for children born after 1985 (12). Similarly, in 1978–2000 in Yorkshire, U.K., increased incidence rates were associated with late birth cohorts (in particular 1985 and 1995) and with calendar periods (12). Finally, the most recent EURODIAB study (7) showed a statistically significant yearly increase in all age-groups (+5.4% in 0–4, +4.3% in 5–9, and +2.9% in 10–14 years old) and a statistically significant interaction between calendar year and age-group, with the highest increase in the youngest age-groups. An analysis of the Registry of Turin in the period 1984–2003 for the age-group 0–29 years found a linear effect that could not be ascribed to either the calendar period or the birth cohort (18). The RIDI study does not support the interpretation of the observed steady increase as a cohort or a calendar period effect, and reasoning on causal and biological plausibility of different hypotheses becomes crucial. Because prevalence of childhood obesity is increasing over time, the "accelerated hypothesis" has been suggested as a possible explanation of the increasing temporal trend of type 1 diabetes (26). Other studies have proposed that the decreasing early life exposure to infectious diseases, which typically occurred over the past three decades in developed countries, could be involved in this trend (27). Evidence supporting both hypotheses, however, is still inconclusive.

In conclusion, the incidence of type 1 diabetes among Italian children increased during the study period. Such an increase cannot be ascribed to either the calendar period or the birth cohort.

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G.B. researched data and wrote the manuscript. M.M. researched data and wrote the manuscript. F.M. researched data and reviewed and edited the manuscript. G.N. researched data. A.F., A.I., L.I., E.A., G.d'A., S.P., P.P., D.I., M.S., F.R., and S.T. researched data and contributed to the discussion. F.C. and V.C. researched data and reviewed and edited the manuscript.

APPENDIX

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