Increasing trend of Type I diabetes in children and young adults in the province of Turin (Italy). Analysis of age, period and birth cohort effects from 1984 to 1996

G. Bruno¹, F. Merletti², A. Biggeri³, F. Cerutti⁴, N. Grosso¹, A. De Salvia¹, E. Vitali¹, G. Pagano¹,
Piedmont Study Group for Diabetes Epidemiology

¹ Department of Internal Medicine, University of Turin, Italy

² Unit of Cancer Epidemiology, Department of Human Oncology and Centre for Oncologic Prevention, University of Turin, Italy

³ Department of Statistics G. Parenti, University of Florence, Italy

⁴ Department of Paediatrics, University of Turin, Italy

Abstract

Aims/hypothesis. This study aimed to determine if the incidence of Type I (insulin-dependent) diabetes mellitus increased over time and if the time trend is attributable to linear trend, calendar period or birth cohort effects.

Methods. This study was based on a cohort of subjects aged 0–29 years from 1984 to 1996, who resided in the province of Turin, Italy. Poisson regression models were used to estimate the effect of sex, age, calendar time and cohorts on incidence rates.

Results. The mean incidence rate in the age group of 0 to 29 years was 7.78 of 100,000 person-years (95 % confidence interval: 7.26–8.32), with a lower risk in women than in men [rate ratio (RR): 0.76 (0.67–0.88)]. We found a trend of incidence increasing over time (annual increase of risk 2.25 % a year, 95 % CI 0.44–4.10). In Poisson regression analysis we found that the best model was the one with sex, age and a lin-

ear term attributable to either calendar period or cohort effects. The linear term corresponds to a RR of 1.12 (1.02–1.22, $p = 0.015$) for each 5-year age span.

Conclusion/interpretation. We found that the time trend in this Mediterranean area was similar in magnitude to that reported in northern European countries. The increase was linear in pattern, each birth cohort and each calendar period showing a higher risk than the preceding one with some evidence of two steep increases in the incidence of Type I diabetes centered on the years 1964 and 1984. We found that the incidence of diabetes increased in the 0 to 14 age group and also in the older age group of 15 to 29 years and that the age-period models were not statistically significantly better than the age-cohort models. [Diabetologia (2001) 44: 22–25]

Keywords Age-period-cohort models, time trend, incidence, Italy, Type I diabetes, epidemiology, temporal variation.

The increase in incidence rates of Type I (insulin-dependent) diabetes mellitus have been reported and are consistent with the hypothesis that increasing prevalence results from exposure to environmental factors. In Europe, time trends have been detected in northern Europe (Sweden, Finland, Norway, United Kingdom) and in central European countries (Austria, Netherlands, Poland, Hungary) [1–8]. The most striking increase has been observed in Finland, the country with the highest risk of Type I diabetes

in the world, where the incidence rate in the age group of 0 to 14 years has increased from 12 of 100 000 in the year 1953 up to 45 of 100 000 in 1996 [9].

A worldwide increase of 3 % in incidence rates of Type I diabetes was reported recently, pooling published rates from studies lasting 8 or more years. A weighted log-linear regression on the incidence rates as a function of calendar years was fitted [10].

Few studies have analysed time trends using modelling procedures, which disentangle the effects of age, period or cohort on the incidence of the disease [1, 2, 7]. These analyses could have implications for aetiological hypotheses. A linear trend (either by calendar period or birth cohort) would suggest the causal role of environmental factors diffusing over time

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Corresponding author: Dr G. Bruno, Dipartimento di Medicina Interna, Corso Dogliotti 14, I-10126 Torino, Italy

Table 1. Age-specific incidence rates (per 100 000 person-years) of Type I diabetes for ages 0–29 years in the Province of Turin, Italy, by birth cohorts 1955–1996 and by calendar periods (diagonals) 1984–1988, 1989–1993, 1994–1996

	BIRTH COHORTS										
AGE(years)	1959	1964	1969	1974	1979	1984	1989	1994	χ^2 trend	<i>p</i>	% yearly increase
0–4						5.17 (24)	7.50 (33)	8.05 (21)	2.4	0.11	4.7 %
5–9					7.82 (44)	10.74 (50)	11.98 (32)		3.8	0.05	4.6 %
10–14				11.10 (84)	13.10 (75)	11.26 (32)			0.14	0.70	0.7 %
15–19			7.40 (64)	7.67 (58)	7.39 (26)				0.003	0.95	0.1 %
20–24		6.00 (54)	6.35 (55)	7.30 (35)					0.76	0.38	1.9 %
25–29	4.70 (38)	6.50 (57)	6.54 (35)						2.2	0.14	3.4 %
RR	0.62	0.85	0.90	0.96	1	1.09	1.44	1.6			
95 % CI	0.38–1.04	0.58–1.25	0.65–1.24	0.75–1.23		0.83–1.43	1.00–2.07	0.90–2.86			
Ratios*		1.37	1.06	1.07	1.04	1.09	1.32	1.12			

Number of cases on which rates are based are in parentheses. Test for age specific trends adjusted by sex, over calendar periods and per cent yearly increases are shown in the last col-

umns. Bottom line reports rate ratios for each birth cohort taking as reference those born in 1979

^a Ratios of successive rate ratios (second order effects)

(e.g., increased protein intake or pollution) [11–12]. Non-linear period effects would suggest, for instance, the role that viral infections have in causing epidemics. Non-linear birth cohort effects would be consistent with the hypothesis that factors such as rubella virus infection operate in the perinatal phase. Birth cohort effects could produce time trends, which vary across age groups, such as an increasing incidence in childhood and a decreasing incidence in young adults. This pattern could be interpreted erroneously as a shift in the age of disease onset [13–14]. Data for these analyses are often not available because most registries recruit children with Type I diabetes who are younger than 15 years and have a short time series of recording.

This study was based on the registry data of Turin from 1984 to 1996 which recruited Type I diabetic subjects who were to 29 years old, as part of the World Health Organization (WHO) Diamond Project. We aimed to determine if the incidence of Type I diabetes increased over time and if the time trend is attributable to linear trend, calendar period or birth cohort effects.

Materials and methods

This population based study comprised residents from the Province of Turin who were 0 to 29 years of age from 1 January 1984 to 31 December 1996. Incidences of Type I diabetes during the study period were ascertained by the following sources: diabetes clinics where diabetic patients are referred after diagnosis; files of hospital discharges from the public and private hospitals; files of all subjects who were exempt from paying for medicine, syringes, and glucose monitoring strips because they were diagnosed with diabetes. Completeness of ascertainment by using capture-recapture methods was estimated (98.3 %) [15, 16].

We used Poisson regression models to estimate the effects of sex, age (six age groups: 0–4, ..., 25–29), calendar time (three periods: 1984–88, 1989–93, 1994–96) and birth cohorts (eight cohorts: 1959, 1964, ..., 1994 mid-years). Five models

were fitted: sex, age; sex, age, linear time trend; sex, age, period; sex, age, cohort; sex, age, period, cohort. The models were ordered hierarchically and therefore we compared them using likelihood ratios [17]. The chi-squared test for trends in incidence rates that we used was the Mantel extension of the Armitage-Cochran trend test [17]. The trend test was adjusted for sex. Analysis was done using Stata [18]. A *p* value of less than 0.05 was considered significant.

Results

We identified in the period 1984 to 1996, 817 residents of Turin (age 0–29) with new onset of Type I diabetes. The incidence rate was 7.78 of 100,000 [95 % confidence interval (CI) 7.26–8.32], with a lower risk observed in women than in men [6.72 (6.05–7.47) vs 8.78 (8.02–9.60)]. In the Poisson regression analysis, after controlling for age, the rate ratio (RR) for women was 0.76 (0.67–0.88) (model 1 in Table 2). In the first and second time periods (diagonals) the highest incidence rates were found in the age group of 10 to 14 years, whereas in the third period (1994–1996) the peak was in the age group of 5 to 9 years (Table 1).

When controlling for age and sex, incidence rates increased across time. The annual increase was 2.25 % (0.44–4.10) (model 2 in Table 2). With respect to the calendar period 1984–88, the incidence rates were, respectively, 20 and 23 % higher in the second and in the third time period [RRs 1.20 (1.03–1.41) and 1.23 (1.02–1.48)], (model 4 in Table 2). With respect to birth cohorts 1959–1994, the incidence rates increased approximately linearly (RRs from 0.62 to 1.61, as shown at the bottom of Table 1; model 3 in Table 2).

We also used Poisson regression analysis to assess if the temporal increase over time in incidence rates could be due to period or cohort effects. Table 2 shows the main results of fitting different models. The best model found was on sex, age and drift term. The drift term denotes a linear trend of time which

Table 2. Fitting of the different age-period-cohort models

Model	Deviance	df	<i>p</i> value	L R	df	<i>p</i> value	LR	(df)	<i>p</i> value
1. sex, age	145.48	149	0.57						
2. sex, age, drift	139.60	148	0.68	5.88 (1 vs 2)	1	0.015			
3. sex, age, cohort	136.87	142	0.61	2.71 (4 vs 5)	6	0.844	2.73 (2 vs 3)	6	0.842
4. sex, age, period	138.33	147	0.68	1.25 (3 vs 5)	1	0.264	1.27 (2 vs 4)	1	0.264
5. sex, age, period, cohort	135.62	141	0.61						

(df: degrees of freedom, LR: likelihood ratios)

cannot be interpreted on a statistical basis as calendar or cohort effects. The linear term corresponds to a RR of 1.12 (1.02–1.22; $p = 0.015$) for each age span of five years. The sex, age, cohort model and the sex, age, period model were not statistically significantly better than the sex, age, drift model.

Discussion

To identify the factors responsible for temporal changes in rates of disease, it is necessary to establish if they are cross-sectional, affecting all age groups at the same point in time (period effects) or longitudinal, affecting all age groups from the same birth cohort (cohort effects). When a constant increase (or decrease) in rates over time is found (temporal linear trends), from a statistical point of view it is not possible to interpret the increase (or decrease) as cohort or calendar period and therefore it becomes crucial to hypothesize according to reasoning causal and biological plausibilities [19]. Age-period-cohort models involving rates from probability modelling have been rarely used in diabetes research, showing increasing temporal trends, which have been interpreted as calendar period effects [1, 2, 7].

Our results partially confirm these previous findings. Because our data is based on a cohort aged 0 to 29 years rather than 0 to 14 years we show that increasing temporal trends of Type I diabetes affect both children and young adults (Table 1). In the age group of 0 to 14 years the pattern is consistent with recent results from Finland [20].

Our data cover the period from 1984 to 1996 whereas the three previous age-period-cohort analyses covered periods from the late 1960s to mid 1980s. We found only a strong linear effect, whereas previous results showed non-linear calendar periods which were attributed to environmental factors [1] or epidemic peaks [2, 7].

Our data based on subjects aged to 29 years allowed us to study birth cohorts from 1957 to 1996. We used 5-year groupings for age, period and cohort classification to ensure a more ready interpretation

and more stable rates [19, 21]. A consequence of this grouping (instead of analysing data based on a finer categorization) could be spurious cohort effects resulting from sudden changes in birth rates within cohort groups. We can exclude this in the cohort from Turin in the time span considered. Furthermore, the age-specific rates for the third calendar period are less stable because they are based on fewer observed events collected only over three years. The increasing trend over cohorts is clearly seen at the bottom of Table 1 and goes from 0.6 to 1.6 taking cohorts centered on 1979 as reference. This trend can be interpreted more easily as linear than the variable pattern of period trends by age seen in the right column of Table 1.

Although the non-linear trend by birth cohort is not statistically significant (Table 2), it suggests two steep increases in incidence rates affecting those cohorts those cohorts centered in 1964 and 1989; this can be seen in the second order effects at the bottom line of Table 1.

Contrary to one previous study, which spanned longer time windows (1970–1985) but with fewer age groups (0–14) [7], in our study it is possible to look at a wider age span over a shorter period of time. This allows us to detect cohort effect more easily, rather than calendar period effects. Birth cohorts are only partially observed over age (Table 1).

Our results show an average pattern of increase of 2.25 % a year. This is consistent with a recent analysis of pooled data from 37 published studies mainly from northern Europe and the United States (3 % annual increase in 1960–1996) [10]. The time trend of increasing incidence in our Mediterranean area is similar in magnitude to that reported in northern European countries. This suggests that in countries with a high and medium risk for disease, a change in prevalence due to exposure to environmental factors is likely to have occurred. A greater increase in incidence has been recently shown in low incidence countries [10].

Our results have implications for aetiologic hypotheses and for the differential relative weight of genetic susceptibility and environmental factors. We have suggested recently in two case-control studies

based on the same cohort of this report that younger age at the onset of Type I diabetes is related to a higher genetic susceptibility both in Sardinian migrants to Turin and in the population as a whole where prevalence of HLA-DQ $\alpha\beta$ heterodimers is associated with early onset of disease [22–23]. The interaction of this genetic susceptibility with a new environmental determinant could explain the increase seen in younger age groups. Epidemic peaks observed in the past could explain the higher risk for cohorts born in 1962 to 1966 and in 1987 to 1991.

By using age-period-cohort models, we found that temporal trend in this Mediterranean area is similar in magnitude to that reported in northern European countries. The increase had a linear pattern, each birth cohort and each calendar period showing a higher risk than the preceeding one, with some evidence of two steep increases of incidence in 1964 and 1984. Our main findings are that there was an increase in incidence of diabetes in the age group of 0 to 14 years and also in the older age group of 15 to 29 years and that age-period models were not significantly better than age-cohort models.

Members of Piedmont Study Group for Diabetes Epidemiology

Autino R (Osp. Civile di Ivrea); Davì S, Ambrosca C (Div. Medicina, Osp. Susa); Bertello P, Gurioli L (Servizio di Diabetologia, sede Rivarolo, ASL9-Ivrea); Bendinelli G, Bogazzi A (Osp. Venaria); Trinelli V, Caraffa F (Osp. Ciriè); Sivieri R, Ozzello A (Osp. Civile, Pinerolo); Gamba S, Blatto A (Div. Endocrinologia, Osp. Maria Vittoria, Torino); G. Macchia (INRCA, Torino); Imperiale G, Griseri P (Osp. Martini, Torino); Cerutti F, Sacchetti (Osp. Infantile Regina Margherita), Giorda C, Imperiale E (Osp. Chieri); Grassi G, Dani F (Osp. Molinette, Torino); Clerico A (Osp. Valdesse, Torino); dott. Perrino R (Osp. S. Lorenzo, Carmagnola); Melò F (Osp. Civile, Avigliana); Chiambretti A, Appendino S (UONA di Diabetologia, ASL 7, Chivasso); Veglio M, Grassi A (Osp. Mauriziano, Torino); Marengo C, Comoglio M (Osp. Moncalieri); Martelli S (Osp. Giovanni Bosco, Torino); Condo C (Osp. Valdesse, Torre Pellice); Ballestrero G, Patanè (Amb. di Diabetologia, ASL 4); Corgiat-Mansin L (Osp. Oftalmico, Torino); Quadri R, Zanone M (Div. Universitaria, Medicina Generale IV, Osp. Molinette, Torino); Porta M, Passera P (Div. Universitaria, Medicina Gen II, Osp. Molinette, Torino); Pisu E, Bruno A (Div. Universitaria, Medicina Gen III, Osp. Molinette Torino); Martina V, Tagliabue M (Div. Universitaria, Endocrinologia, Osp. Molinette, Torino); Trovati M, Cavalot F (Div. Universitaria, Diabetologia, Osp. S. Luigi, Orbassano).

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