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More than twenty years of registration of type 1 diabetes in Sardinian children: temporal variations of incidence with age, period of diagnosis and year of birth

Running title: incidence time trend of type 1 diabetes in Sardinia

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ABSTRACT

We analysed Sardinian Registry data to assess time trends in incidence rates of Type 1 diabetes, period 1989-2009 (2371 cases aged 0-14 years). Poisson regression models were used to estimate the effects of sex, age, period of diagnosis and birth cohorts. Incidence rate was 44.8 cases per 100,000 person-years (95% CI 43.1-46.7). The annual increase was 2.12% (1.45-2.80, test for linear trend: $p<0.001$). For boys, the increasing trend was evident up to 5 years of age, and for girls up to 8 years. Compared with the 1989-94 birth cohort, the relative risk increased from 0.78 (0.61-1.10) in 1974-79 to 1.62 (1.18-2.23) in 2004-09. The increase over period was less striking, with a tendency to regress in more recent years. The best fitting model for boys included age and a linear time trend, for girls age and non-linear effects of calendar period and birth cohort. In conclusion, incidence increased over time, the increase tended to level off in more recent years by calendar period but not by birth cohort, with some evidence of a stronger increase among girls than boys. Should the increase be attributable to the effects of some perinatal environmental factor, this would mean that such a factor has started affecting females before males.

The most striking feature of type 1 diabetes epidemiology is the evidence of large geographical variation in disease risk (1-3). Sardinia has the second highest incidence rates in the world after Finland, and this excess likely started around 1950, as shown by the analysis of incidence in males conscript cohorts in the period 1936-1979 (4).

An increasing trend of type 1 diabetes, ranging around 2-3% has been shown in almost all areas covered by population-based registries (3). The increase involved both children and young adults in Turin, Northern Italy (5), whereas it was limited to children in Sweden, and interpreted as the anticipation of age at disease onset (6). Updated incidence data of registries included in the EURODIAB study have provided the interesting finding that the lowest risk areas of Eastern Europe underwent the highest yearly increase up to year 2004 while, in the highest risk areas of Northern Europe, the increasing trend was lower (7).

Aims of this report from the high risk Sardinia Region were 1) to update the analysis of incidence rates of type 1 diabetes up to 2009 in children aged 0-14 years; 2) to assess temporal trends over the twenty-one-year period 1989-2009; 3) to assess whether it was possible to disentangle the effects of age, calendar period of diagnosis and birth cohort and if such effects were heterogeneous by age and sex.

RESEARCH DESIGN AND METHODS

The study base of this report were all children aged 0 to 14 years resident in Sardinia in the period 1989-2009. As previously described (8), the registration of incident cases was performed according to the EURODIAB criteria. Type 1 diabetes was defined on the basis of clinical diagnosis of insulin-dependent diabetes by a doctor, excluding cases occurring secondary to other conditions. The date of onset was taken as the date of first insulin injection. Diabetes clinics for children and adults and departments of internal medicine and endocrinology were the first source of ascertainment. The second independent data source

was a membership of the local patient associations and the personal National Health System identification cards needed by each patient to obtain medications and devices free of charge. The estimated completeness of ascertainment was 92% in period 1989-97, 90% in period 1998-2003 and 91% in period 2004-09, with no differences among genders and age-groups over the study period .

Population data by sex and year of birth were provided by the Italian National Institute of Statistics (ISTAT, URL: http://www.demo.istat.it/). Age- and sex- specific incidence rates/100,000 person-years were calculated for calendar year of diagnosis and birth cohort (9). The chi-square test for trend in incidence rates used is the Mantel extension of the Armitage-Cochran trend test. The trend test is either stratified by sex or calculated separately for the two genders. Poisson regression models were used to estimate the effects of sex, age (five three-year age-groups: 0-2, 3-5, 6-8, 9-11, 12-14), calendar time (seven three-year periods: 1989-91, 1992-94, 1995-97, 1998-2000, 2001-03, 2004-06, 2007-09) and birth cohorts (eleven six-year birth cohorts: 1974-79, 1977-82, 1980-85, 1983-88, 1986-91, 1989-94, 1992-97, 1995-2000, 1998-2003, 2001-06, 2004-09). Six models were fitted to data: sex; sex, age; sex, age, linear time trend (drift); sex, age, cohort; sex, age, period; sex, age, period, cohort (online Figure 1). The latter five models were then fitted to data separately for the two genders. The term drift denotes a linear temporal variation of rates which does not distinguish between the influences of two of the three temporal variables involved in the analysis. The hierarchically ordered models were compared through the likelihood ratio test. Further Poisson regression models were fitted to data including sex (or separate models were fitted to the two genders), age, linear time trend (drift) and quadratic terms for period and cohort, after centering the 2 variables, in order to check if temporal variation was non linear. Statistical analyses were performed using STATA/SE, release 11.0.

RESULTS

In the period 1989-2009, 2371 incident cases of type 1 diabetes were identified among children aged 0-14 years resident in Sardinia. Incidence rates (IR) by sex, age group and calendar period are shown in Table 1. The IR over the study period was 44.8 cases per 100,000 person-years (95% confidence interval [CI] 43.1-46.7), with significantly higher risk in boys (50.6, 48.0-53.4) than in girls (38.7, 36.4-41.2). In the regression analysis, after controlling for age, the rate ratio (RR) for boys with respect to girls was 1.31 (1.21-1.42). IRs in the age groups 0-4, 5-9, 10-14 years were 37.8 (34.9-41.0), 47.0 (43.9-50.3) and 48.4 (45.4-51.5), respectively; corresponding RRs (boys *vs*. girls) were 1.22 (1.04-1.44), 1.18 (1.03-1.36) and 1.49 (1.31-1.69).

The IR steadily increased over the study period, from 35.8 (32.2-39.7) in 1989-91 to 51.0 (45.7-56.9) in 2007-09 (Table 1). Controlling for age and sex, the annual increase in the period 1989-2009 was 2.12% (1.45-2.80; test for linear trend: $p<0.001$). Controlling for age, such an increase was higher in girls (2.67%, 1.63-3.73) than in boys (1.73%, 0.85-2.62), although not significantly.

Table 2 shows age-specific IRs by birth cohort and calendar period (diagonals), for all children and for boys and girls separately. The table shows how IRs increased with each subsequent birth cohort in each age group. The yearly increase, adjusted for age and sex, was highest in the age group 0-2 years (4.3%, $p<0.001$). Time trends were heterogeneous between sexes: in boys, large statistically significant increasing linear trends were evident in the age group 0-2 years (4.4%, $p<0.001$) and, to a smaller extent, in 3-5 years old (2.4%, $p=0.034$), whereas in girls, a yearly increase of similar magnitude was evident not only in the age groups 0-2 years (4.2%, $p=0.006$) and 3-5 (3.0%, $p=0.013$) but also in the age group 6-8 (4.3%, $p<0.001$).

A different pattern of increase in time by birth cohorts and by calendar periods of diagnosis is evident analyzing age-adjusted RRs, which are shown in Table 3. With respect to the 1989-94 birth cohort, the RR increased from 0.78 (0.61-1.10) for children born in 1974-79 to 1.62 (1.18-2.23) for those born in 2004-09. In contrast, the pattern of increase of RRs by calendar period of diagnosis was less striking. Indeed, with respect to children diagnosed in period 1998-2000, the RR increased from 0.73 (0.63-0.85) for children diagnosed in 1989-91 to 1.06 (0.91-1.23) for those diagnosed in 2007-09.

In order to try to disentangle the effect of age, calendar period and birth cohort on the overall temporal trend of the disease in period 1989-2009, we fitted hierarchically ordered Poisson regression models to the data, for all incident cases, and separately by gender, since there was evidence of interaction (sex*cohort, p=0.018; sex*period, p=0.143) (Table 4). For both boys and girls, using the Akaike information criteria, the best model (model 2) was the one with age and a linear time trend (drift). This finding means that the variation over time has a linear component which cannot be ascribed to either the calendar period or the cohort. However, for girls as well as for all children analyzed together, nonlinear effects of both birth cohort (model 4) and period of diagnosis (model 5) are apparent. Fitting models including quadratic terms for period and cohort showed that the temporal variation was non linear. Indeed, this model fitted to the total (boys+girls) data resulted in a slightly improvement of the Akaike information criteria vs model 2. Opposite signs for the coefficients of the quadratic period and cohort terms indicated that, whereas there was a steady increase with birth cohort, in the most recent periods incidence started to show a tendency to decrease. This result was already apparent in Table 2, showing that incidence rates in children diagnosed in 2007-09 (last diagonal from top right to bottom left, incidence rates: 43.6 in 0-2 years, 48.6 in 3-5 years, …) were lower than those diagnosed in 2004-06 in almost all age groups (next diagonal on the left: 51.2 in 0-2 years, 54.0 in 3-5 years, …).

CONCLUSIONS

Our analysis of incidence data from the Sardinia Registry of Type 1 diabetes in the twenty-one years period 1989-2009 provides evidence of a strong increase of incidence rates among Sardinian children. Results of our age-period-cohort analysis of time trends are intriguing. Indeed, we provide evidence that the incidence of type 1 diabetes has increased non linearly with the birth cohort. Such a birth cohort effect seems to have started some 5-10 years earlier among girls, starting from those born in 1980-85, than among boys, starting from those born in 1986-91. This finding allows us to explain why annual percent increases are higher and statistically significant in girls up to 8 years of age but affect boys to a lesser extent and up to 5 years of age only. Should the increase be attributable to the effects of some perinatal environmental factor, this would mean that such a factor has started affecting females before males. In Sardinia, both a period and a cohort effect were evident, with heterogeneities among sexes. Indeed, the nonlinear temporal effects were more evident among girls, with larger increases with time than among boys. In more recent years a tendency of time trends to level off was also evident, particularly in the youngest age groups, which could merely reflect year-to-year variability in incidence rates and need to be confirmed over a longer time period.

Recently Patterson and colleagues (10) have pointed out that the potential of age-period-cohort analysis in disentangling the effects of time trends on different age groups at different times is often hampered by the paucity of age classes and the limited length of time series. Indeed, incidence rates up to 14 years of age do not allow us to capture the total effect of time variations in the whole population. However, despite the small number of age groups and the limited sample size, our analysis, taking advantage of more than 20 years of registration,

shows that incidence has increased more than linearly with birth cohort, whereas the increase with calendar period has shown signs of regression in the most recent periods. Previous age-period-cohort analyses have found different and discordant results, including linear and nonlinear period effects (5, 11-13) as well as cohort effects (14-15), often interpreted as a shift towards earlier age at onset (7, 16-18).

Studies have proposed that the decreasing early life exposure to infectious diseases could be involved in the increasing temporal trends of immune-mediate disorders (19). Lower socioeconomic level and higher crowding in early life, proxy measures of early childhood infection, increase the risk of type 1 diabetes up to 3 years and decrease the risk in the following age groups (20). Experimental models have shown a relationship between intestinal microbioma and type 1 diabetes (21). As regards Sardinia, the frequencies of elmintiasis, which was endemic up to the 1980s, has now almost completely disappeared. The role of mycobacterium avium paratuberculosis infection has also been suggested to play a role, and an homology between its epitopes and beta cell antigen ZnT8 has been identified in Sardinian patients with type 1 diabetes (22).

Another intriguing and still unsolved issue in the epidemiology of type 1 diabetes is the heterogeneity of risk among sexes. Whereas in most of countries incidence is higher in males than in females among young adults only, Sardinian boys have a statistically significant 31% higher risk than girls of the same age, which is not chromosoma Y-linked (24), but until now no other hypothesis has been tested. Moreover, our data show heterogeneities among sexes in time trend patterns, with girls appearing to show the potential effects of hypothetical environmental factor exposures at least 5-10 years before boys. This finding is intriguing and further experimental and epidemiological studies should explore sex differences in the interaction between environment and genetic in the pathogenesis of type 1 diabetes.

In conclusion, our study showed a strong increase of incidence rates of type I diabetes among Sardinian children in the period 1989-2009, which was non linear with the birth cohort, whereas the increase with calendar period showed signs of regression in the most recent periods. The birth cohort effect seems to have started earlier among girls than among boys. Should the increase be attributable to the effects of some perinatal environmental factor, this would mean that such a factor has started affecting females before males.

Authors contribution: GB researched data and wrote the manuscript, MM researched data and wrote the manuscript, AB researched data and contributed to the discussion, AL researched data, CM researched data, FM contributed to the discussion and reviewed/edited manuscript, MS researched data, contributed to the discussion and reviewed/edited manuscript.

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Guarantors of the data: Graziella Bruno and Marco Songini are the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis."

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Table 1: Incidence rates of type 1 diabetes among Sardinian children 0 to 14 years old in the years 1989-2009 by sex, age group, calendar period.

		Cases N.	Person-years	incidence rate (per 100,000 person-years)	95% CI	
total		2371	5,286,212	44.8	43.1	46.7
sex	boys	1380	2,725,601	50.6	48.0	53.4
	girls	991	2,560,611	38.7	36.4	41.2
age	0-2	320	910,143	35.2	31.5	39.2
	3-5	396	961,497	41.2	37.3	45.5
	6-8	482	1,034,124	46.6	42.6	51.0
	9-11	613	1,127,595	54.4	50.2	58.8
	12-14	560	1,252,853	44.7	41.2	48.6
period	1989-91	346	967,116	35.8	32.2	39.8
	1992-94	334	857,969	38.9	35.0	43.3
	1995-97	362	785,852	46.1	41.6	51.1
	1998-00	351	723,217	48.5	43.7	53.9
	2001-03	311	678,325	45.8	41.0	51.2
	2004-06	348	648,162	53.7	48.3	59.6
	2007-09	319	625,571	51.0	46.0	56.9

Table 2 Age-specific incidence rates (per 100,000 person-years) of type 1 diabetes among Sardinian children 0 to 14 years old in the years 1989-2009, by birth cohorts (1974-79, …, 2004-09) and by calendar periods (diagonals: 1989-91, …, 2007-09). Number of cases are in parentheses. Percent yearly increases and test for age specific time trends are shown in the last columns (adjusted by sex, or separately for the 2 genders).

		Birth cohort												
	Age	**1974-79**	**1977-82**	**1980-85**	**1983-88**	**1986-91**	**1989-94**	**1992-97**	**1995-00**	**1998-03**	**2001-06**	**2004-09**	**% yearly increase**	**p**
total	**0-2**					22.8 (35)	24.5 (35)	32.4 (43)	36.8 (45)	40.8 (49)	51.2 (61)	43.6 (52)	4.3	<0.001
	3-5				30.9 (52)	34.8 (53)	40.2 (58)	44.0 (58)	41.2 (50)	54.0 (66)	48.6 (59)		2.7	0.001
	6-8			33.8 (64)	45.3 (75)	49.5 (76)	45.1 (66)	42.6 (56)	63.2 (78)	53.9 (67)			2.3	0.002
	9-11		50.6 (107)	44.8 (84)	54.0 (90)	65.9 (102)	48.5 (72)	60.0 (80)	62.3 (78)				1.3	0.052
	12-14	36.1 (88)	41.4 (87)	50.4 (95)	47.6 (80)	53.6 (84)	42.0 (63)	46.6 (63)					1.2	0.093
boys	**0-2**					25.3 (20)	28.5 (21)	42.2 (29)	47.1 (30)	38.8 (24)	60.1 (37)	55.1 (34)	4.4	<0.001
	3-5				31.2 (27)	42.1 (33)	44.4 (33)	33.7 (23)	34.8 (22)	60.3 (38)	51.1 (32)		2.4	0.034
	6-8			43.0 (42)	54.0 (46)	53.2 (42)	46.6 (35)	51.4 (35)	55.8 (36)	53.1 (34)			0.8	0.423
	9-11		51.5 (56)	50.7 (49)	59.4 (51)	69.2 (55)	49.9 (38)	70.9 (49)	58.1 (38)				1.1	0.214
	12-14	47.9 (60)	54.6 (59)	69.0 (67)	56.7 (49)	55.9 (45)	54.6 (42)	70.0 (49)					1.2	0.180
girls	**0-2**					20.1 (15)	20.2 (14)	21.9 (14)	25.6 (15)	42.9 (25)	41.6 (24)	31.2 (18)	4.2	0.006
	3-5				30.7 (25)	27.1 (20)	35.7 (25)	55.1 (35)	48.1 (28)	47.3 (28)	45.9 (27)		3.0	0.013
	6-8			23.9 (22)	36.2 (29)	45.6 (34)	43.5 (31)	33.1 (21)	71.2 (42)	54.8 (33)			4.3	<0.001
	9-11		49.7 (51)	38.5 (35)	48.2 (39)	62.4 (47)	47.1 (34)	48.2 (31)	66.9 (40)				1.5	0.127
	12-14	23.6 (28)	27.4 (28)	30.6 (28)	37.9 (31)	51.1 (39)	28.8 (21)	21.5 (14)					1.2	0.314

Table 3: Rate ratios (RR) for each birth cohort taking those born on 1989-1994 as a reference and each calendar period of diagnosis taking those diagnosed in 1998-2000 as a reference. RRs are adjusted for age and for sex when both genders are analysed together (total). RRs for birth cohort do not incorporate period effect and RRs for period do not incorporate birth cohort period effect

Birth cohort	total		boys		Girls	
	RR	95% CI	RR	95% CI	RR	95% CI
1974-79	0.78	0.61-1.01	0.84	0.61-1.14	0.70	0.45-1.08
1977-82	0.94	0.78-1.13	0.95	0.74-1.21	0.93	0.69-1.24
1980-85	0.92	0.78-1.10	1.04	0.83-1.29	0.77	0.58-1.02
1983-88	1.03	0.87-1.21	1.05	0.85-1.30	1	0.78-1.28
1986-91	1.13	0.97-1.32	1.10	0.89-1.35	1.18	0.93-1.49
1989-94	1	-	1	-	1	-
1992-97	1.12	0.96-1.32	1.2	0.97-1.48	1.02	0.80-1.32
1995-00	1.32	1.11-1.56	1.18	0.93-1.48	1.50	1.17-1.93
1998-03	1.45	1.20-1.76	1.36	1.05-1.76	1.57	1.18-2.09
2001-06	1.64	1.31-2.06	1.66	1.23-2.24	1.62	1.15-2.28
2004-09	1.62	1.18-2.23	1.72	1.16-2.57	1.45	0.85-2.45
Period of diagnosis						
1989-91	0.73	0.63-0.85	0.79	0.65-0.97	0.66	0.53-0.83
1992-94	0.80	0.69-0.93	0.91	0.75-1.11	0.67	0.53-0.84
1995-97	0.95	0.82-1.10	1.06	0.88-1.29	0.81	0.65-1.02
1998-00	1	-	1	-	1	-
2001-03	0.95	0.81-1.10	0.91	0.74-1.12	0.99	0.79-1.24
2004-06	1.11	0.96-1.29	1.18	0.97-1.43	1.04	0.83-1.30
2007-09	1.06	0.91-1.23	1.13	0.93-1.38	0.97	0.77-1.22

Table 4: Summary of testing different age-period-cohort effects to incidence rates of type 1 diabetes among Sardinian children 0 to 14 years old in the years 1989-2009. See online supplemental Figure for notation referring to hierarchical models tested. For convention we also use the Variable | Model notation, i.e. the notation Cohort|Age+Drift denotes the effect of Cohort added to the Age+Drift model.

	Residual deviance (df; p)		**d.f.**	**LR χ^2**	**p**
TOTAL					
0. Sex	181.51 (68; <0.001)	**A. Sex**			
1. Sex+Age	135.88 (64; <0.001)	**B. Age|Sex**	4	45.63	<0.0001
2. Sex+Age+Drift	97.46 (63; 0.004)	**C. Drift|Sex+Age**	1	38.41	<0.0001
3. Sex+Age+Cohort	86.34 (54; 0.003)	**D. Cohort|Sex+Age+Drift**	9	11.12	0.268
4. Sex+Age+Period+Cohort	71.08 (49; 0.021)	**E. Period|Sex+Age+Cohort**	5	15.27	0.009
5. Sex+Age+Period	89.52 (58; 0.005)	**F. Cohort|Sex+Age+Period**	9	18.44	0.030
		G. Period|Sex+Age+Drift	5	7.95	0.159
BOYS					
1. Age	41.72 (30) (0.088)	**B.Age**			
2. Age+Drift	26.80 (29) (0.649)	**C. Drift|+Age**	1	14.92	0.0001
3. Age+Cohort	19.76 (20) (0.557)	**D. Cohort|Age+Drift**	9	7.03	0.634
4. Age+Period+Cohort	9.98 (15) (0.869)	**E. Period|Age+Cohort**	5	9.78	0.082
5. Age+Period	18.42 (24) (0.828)	**F. Cohort|Age+Period**	9	8.45	0.490
		G. Period|Age+Drift	5	8.37	0.137
GIRLS					
1. Age	68.31 (30) (<0.001)	**B. Age**			
2. Age+Drift	42.98 (29) (0.051)	**C. Drift|+Age**	1	25.33	<0.0001
3. Age+Cohort	28.79 (20) (0.113)	**D. Cohort|Age+Drift**	9	14.19	0.116
4. Age+Period+Cohort	17.53 (15) (0.369)	**E. Period|Age+Cohort**	5	11.26	0.047
5. Age+Period	35.85 (24) (0.065)	**F. Cohort|Age+Period**	9	18.32	0.032
		G. Period|Age+Drift	5	7.13	0.211