Type 1 (insulin-dependent) diabetes mellitus is an autoimmune disease characterized by the selective destruction of insulin-producing β cells in the pancreatic Islet of Langerhans. Despite decades of intensive investigation, the trigger for this self-attack is still unknown. Geographical and temporal variation in incidence suggest that environmental factors, such as infections, dietary components or toxins, could precipitate the disease in susceptible individuals.

Effect of Sardinian heritage on risk and age at onset of type 1 diabetes: a demographic case-control study of Sardinian migrants

Graziella Bruno, Gianfranco Pagano, Fabrizio Faggiano, Alberto De Salvia and Franco Merletti

Background
Children of Sardinian heritage are at high risk of type 1 diabetes, whereas no data are available in young adults. Age at onset of type 1 diabetes could be associated with different relative weight of genetic susceptibility and environmental determinants in the pathogenesis of the disease. We test this hypothesis in subjects with Sardinian heritage 0–29 years of age living in the city of Turin, a highly industrialized area in Northern Italy.

Methods
In all, 202 cases with onset of type 1 diabetes aged 0–29 years during 1984–1991 and 1010 controls randomly selected from residents of the city of Turin, frequency-matched by sex and year of birth to cases, were included in this study. Name and place of birth of parents were ascertained by postal inquiry and linkage with city population and census files. Social class was based on the highest educational level of parents abstracted from 1991 and 1981 census files.

Results
Differential effects on risk of type 1 diabetes of Sardinian heritage and social class in the age groups 0–14 and 15–29 years were found. In children with one and both Sardinian parents the odds ratios (OR) were 2.09 (95% CI : 0.85–5.15) and 3.20 (95% CI : 0.75–13.64); in young adults 0.81 (95% CI : 0.18–3.64) and 1.95 (95% CI : 0.51–7.40), respectively. In subjects with low social class the OR were 1.16 (95% CI : 0.68–1.97) in children and 0.66 (95% CI : 0.41–1.05) in young adults.

Conclusions
This study shows higher risk of type 1 diabetes in subjects of Sardinian heritage; higher risk in children than in young adults and a protective effect of low social class in young adults. These findings are consistent with the hypothesis of heterogeneity of type 1 diabetes by age at onset, with prevailing genetic effect in childhood and environmental determinants in adulthood.

Keywords
Migrants, insulin-dependent diabetes mellitus, Sardinia

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Most registries have been limited to childhood-onset diabetes. However, a persisting high risk of the disease at least until age 30 has been found by the few surveys that expanded registration up to this age. Factors associated with variability in the age at onset of the disease are not known. With respect to childhood-onset, in adult-onset type 1 diabetes lower frequencies of HLA DQA1-DQB1 susceptibility alleles and diabetogenic heterodimers have been found, together with better preservation of β cells function. Therefore, the relative weight of genetic susceptibility and environmental determinants may have a bearing on age at clinical onset and rate of progression of the disease. A differential effect of Sardinian heritage by age at onset of type 1 diabetes could suggest that the importance of genetic susceptibility may vary by age at onset.

Whereas previous studies on type 1 diabetes among subjects of Sardinian heritage living in other Italian areas were limited to age 0–14 years, the population-based registry of the city of Turin, Northern Italy, allows for estimates of incidence up to age 29. Therefore, on the basis of the above hypothesis, we have analysed risks for type 1 diabetes among residents in the city of Turin separately for those aged 0–14 and 15–29 years. Our analysis has been designed as a demographic case-control study, testing also the hypothesis of an aetiological role of social class, as suggested by others.

**Methods**

The population base of the case-control study was the inhabitants 0–29 years of age (325,882 at 1991 general census) of the city of Turin, a highly industrialized area in the northwest part of Italy. In 1984, a population-based registry was established in the Province of Turin (789,882 inhabitants 0–29 years of age) which has collected all incident cases of type 1 diabetes in the age group 0–29 years. Three independent sources of ascertainment have been employed to ensure that case ascertainment was as complete as possible. The primary data source was the list of all patients with type 1 diabetes who attended one of the diabetes clinics where most diabetic patients are referred after the diagnosis. The secondary data sources were: (1) the file of hospital discharges from public and private hospitals in the city of Turin in the period 1984–1988; (2) the computerized file of all subjects who obtained, in the study period, exemption from payment for medicine, syringes, and glucose monitoring strips because of a diagnosis of diabetes mellitus. The estimated completeness of ascertainment, according to the capture-recapture method was high (99% in the age group 0–14 years and 95% in the age group 15–29 years).

Age-specific incidence rates in the period 1984–1991 were 8.4/100,000 (95% CI: 7.2–9.7) and 6.7/100,000 (95% CI: 6.0–7.6), respectively, in the age groups 0–14 and 15–29.

Cases in this report were 202 residents of the city of Turin with onset of type 1 diabetes from 1 January 1984 to 31 December 1991. Controls were 1010 subjects randomly selected from Turin residents frequency matched by sex and year of birth to cases in a 5 to 1 ratio. Information on exposures of interest (Sardinian heritage and social class) were obtained mainly by linkage with demographic files.

Name and place of birth of parents of cases were ascertained through clinical records (150 parents), the population file of the city of Turin residents (108) or postal inquiry to the place of birth of cases for parents no longer residents of Turin (146). One father was unidentified. Demographic data of 1878 parents of controls were ascertained through the files of the city of Turin, whereas 142 required a postal inquiry. Six fathers were unidentified.

Social class of cases and controls was based on the highest educational level of either parents abstracted from 1991 and 1981 census files. Eight cases and eight controls could not be classified. Social class was defined dichotomously as either <6 or 6+ years of schooling based on previous studies on social inequalities.

Univariate analysis was carried out estimating odds ratios (OR) and their 95% CI using the exact method. Multivariate analysis applied unconditional logistic models (Sardinian heritage and social class as independent variables; diabetic status as dependent one). Since univariate results did not differ substantially from results of multivariate analysis, only the latter are presented.

**Results**

Mean age (standard deviation) of cases and controls was 15.4 (7.0) and 15.4 (7.05), respectively. Sixty per cent were male. No sex differences were found in the frequency of subjects with either one or both Sardinian parents. Parents of controls of low versus high social class were 7/1010 (0.69%) and 7/1010 (0.69%) versus 25/1010 (2.38%) and 7/1010 (0.69%) (one or both Sardinian parents). Corresponding figures for parents of cases were 3/102 (1.49%) and 2/202 (0.99%) versus 6/202 (2.97%) and 4/202 (1.98%).

As shown in Table 1, subjects with both Sardinian parents have more than a twofold higher risk of type 1 diabetes relative to those without Sardinian parents, with intermediate value in subjects with only one Sardinian parent. The effect of Sardinian heritage was higher in children than in young adults. Indeed, in the latter no effect was evident for those having only one Sardinian parent.

An effect of social class by age at onset of type 1 diabetes was evident, with a slightly higher risk in the low social class in children and a marked increase in the higher social class in young adults.

**Conclusions**

This population-based case-control study, based on demographic data, shows that children of Sardinian heritage living in Northern Italy remain, for at least one generation, at increased risk of the disease, particularly when both parents are Sardinians. This finding, which is consistent with results of previous studies conducted in Lazio and in Lombardia provides further evidence of a strong genetic effect on the pathogenesis of the disease in this population. In both previous studies, census data on children with Sardinian heritage allowed the estimation of incidence rates based on a reasonably large number of cases limited to this subgroup of patients. In the present study we assessed the effect of being of Sardinian heritage on the risk of type 1 diabetes not only in children but also in young adults. To test the hypothesis that this effect may vary with the age at onset, we employed data provided by the
registry of Turin, which is among the few extending the registration up to 29 years of age. A case-control study was designed, since census data on Sardinian heritage are not available after childhood.

An original feature of our findings is the suggestion that the association with Sardinian heritage is stronger for those with clinical onset of the disease early in life and relatively low for those with disease onset after age 15, leading to the hypothesis of a dependence of age at onset on the weight of genetic susceptibility. Given the low incidence of the disease, limited Sardinian migration and the low birth rate in Italy, numbers cannot be large, even if 46 subjects of Sardinian heritage in a population of one million over a period of 8 years is sound information from a sound study base. We are aware that results in the specific sub-analyses are based on very few cases, as shown by the large and overlapping confidence intervals, and that they should be interpreted as suggestive of a working hypothesis. Nevertheless, our finding is consistent with the few studies comparing childhood-onset with adult-onset type 1 diabetes,14–16 including one of ours,17 which show higher frequencies of HLA-DQA1 and DQB1 susceptibility alleles and heterodimers in children than in adults in populations at medium risk. In addition, with respect to most geographical areas, where the peak of incidence is found at age 10–14 years, in Sardinia the age group at highest risk is younger (5–9 years).24

At present, the complexity of gene-environment interaction in the pathogenesis of type 1 diabetes has not been adequately addressed. It is likely that the disease is caused by environmental determinants in genetically susceptible individuals. However, as pointed out in cancer epidemiological studies,25 an effect modification by weight of genetic susceptibility might also operate in type 1 diabetes. That is, children with high genetic susceptibility to type 1 diabetes, such as those with Sardinian heritage, might develop the disease early in life irrespective of environmental exposure, whereas the occurrence of diabetes in those who are less genetically susceptible could be the expression of a relatively long-lasting exposure to environ-

mental agents. For the time being, we present this as a working hypothesis for the design of further epidemiological studies on type 1 diabetes.

The second finding of this study was the suggestion of a protective effect (with borderline statistical significance) of low social class (<6 years of schooling) with regard to onset of disease at age 15–29 years. Results of population-based studies examining socioeconomic status in type 1 diabetes have been conflicting.19–21,26 In Northern Ireland, children with higher social class had higher risk, whereas no effect was evident in Scotland.20 Higher rates have been reported in children living in areas with higher average income in Montreal19 and in Denmark,21 but not in Pittsburgh in the age group 0–19.26 However, no previous study examined the effect of social class on risk of type 1 diabetes separately in children and young adults.

In conclusion, this case-control study shows: (1) higher risk of type 1 diabetes in subjects of Sardinian heritage; (2) a greater effect of Sardinian heritage in children than in young adults; (3) a protective effect of low social class in young adults. These findings are consistent with the hypothesis of heterogeneity of type 1 diabetes by age at onset, with prevailing genetic effect in childhood and environmental determinants in adulthood.

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References


Table 1 Effect of Sardinian heritage and social class on risk of type 1 diabetes in the city of Turin, Northern Italy

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Sardinian parentb</th>
<th>Social classc</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
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<td>0–14 years</td>
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</tbody>
</table>

^a Odds ratio.

^b Odds ratios were adjusted for social class.

^c Odds ratios were adjusted for Sardinian heritage; social class was defined by educational level (6+ versus <6 years of schooling).


Vandewalle CL, Decraene T, Shuit FC et al. The Belgian Diabetics Registry. Insulin autoantibodies and high titre islet cell antibodies are preferentially associated with HLA DQA1*0301-DQB1*0302 haplotype at clinical onset of type 1 diabetes before age 10, but not at onset between age 10 and 40 years. Diabetologia 1993;36:1155–62.


