

A 5-Year (1989–1993) Prospective Study of the Incidence of IDDM in Rome and the Lazio Region in the Age-Group 0–14 Years

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OBJECTIVE — To provide data on the incidence of IDDM in Rome and the Lazio region evaluated prospectively from 1989 to 1993 for a total of >5 million subjects younger than 15 years.

RESEARCH DESIGN AND METHODS — All patients with newly discovered IDDM diagnosed between 1 January 1989 and 31 December 1993 among residents in Rome and its region were recorded. Primary ascertainment was based in diabetes clinics and specialized hospitals in the region, whereas the secondary independent source was taken from the archives of the region where patients are registered to obtain exemption from paying for medications.

RESULTS — We identified 330 new patients with a degree of ascertainment of 85%. Overall the incidence rate of the disease was 7.9 per 100,000 per year (95% CI 7.1–8.8). The incidence was higher in the 5- to 9-year-old age-group (10.4 per 100,000) and in winter (36.2%). The cumulative risk for the disease is on the order of 1.18 per 1,000 subjects <15 years of age. No significant differences in incidence were observed between boys and girls. There were 14 instances of coma at diagnosis (4.3%), but hyperglycemia without ketonuria was diagnosed in 35% of patients, suggesting an early diagnosis.

DISCUSSION — Compared with the other continental Italian regions for which data are available for a single year, the IDDM incidence rate in Rome is similar. We conclude that the IDDM incidence rate in Rome and its region is comparable to that in other Southern European countries and remained stable over the 5-year observation period.

IDDM is a chronic disease found all over the world, although its prevalence varies greatly according to both surroundings and race (1,2). Several IDDM incidence studies have been carried out (3); in Europe, IDDM incidence varies considerably between the North and the South with some areas considered at higher risk (i.e., Finland and Sardinia) (4).

The incidence of IDDM in Italy ranges from between 7 and 30 cases per 100,000 for those younger than 15 years

old (5–8). However, no prospective figures during 2 years are available, except for the province of Turin in the northern part of the country (1984–1988) (9).

As part of the EURODIAB Subarea A study (4), which is a prospective investigation of IDDM incidence in Europe, we have carried out a survey over a period of 5 years (1989–1993) of IDDM incidence in Rome and its region. Evaluation of the incidence rate of IDDM in Italy for EURODIAB ACE is presently being carried out

in four regions (Lombardy, Lazio, Sardinia, and eastern Sicily) that are located in the northern (Lombardy), central (Lazio), and southern regions of the country, including the islands Sicily and Sardinia. Rome is the capital of the Lazio region with nearly three-quarters of the total inhabitants of the region. The incidence of IDDM was analyzed according to age-group (0–14 years old), seasonality, and year of diagnosis. We have also taken into account the mode of presentation of the disease since it has been suggested that IDDM may be diagnosed earlier today compared with some years ago (10).

RESEARCH DESIGN AND METHODS

Description of the area of the study

The survey was conducted in Rome and its region (Lazio), which is situated in the central part of Italy on the western coast. This region has a temperate and rather uniform climate with an average temperature ranging between 5 and 22°C. Average annual rainfall is generally of medium intensity, ranging from 800 to 1,000 mm (January: 75–100 mm; July: 10–20 mm).

The total population of Lazio is 5,170,672 inhabitants with a slight predominance of the female sex (2,667,605 female vs. 2,503,067 male [*Italian Statistical Year Book* for 1991]). The distribution of the population in each of the five provinces of the Lazio region reveals a distinct difference between the Rome province (73% inhabitants) and the other four provinces, indicating the high urbanization typical of this region. Regarding the distribution of the population by age-group, the age-group 0–14 years includes 838,745 subjects (408,707 girls and 430,038 boys).

Case definition

According to EURODIAB criteria (4), all patients in whom IDDM was diagnosed between 1 January 1989 and 31 December 1993, who were younger than 15

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Received for publication 15 March 1995 and accepted in revised form 16 August 1995.

Table 1—Standardized incidence rate (per 100,000) by year and sex in Rome and the Lazio region

Year	Boys		Girls		Total	
	Cases	Incidence rate	Cases	Incidence rate	Cases	Incidence rate
1989	41	9.5 (6.8–12.9)	31	7.6 (5.11–10.83)	72	8.6 (6.73–10.89)
1990	39	9.1 (6.5–12.33)	24	5.9 (3.76–8.74)	63	7.5 (5.89–9.53)
1991	30	7 (4.71–9.98)	32	7.8 (5.28–11.19)	62	7.4 (5.69–9.60)
1992	34	7.9 (5.50–10.98)	43	10.5 (7.67–14.09)	77	9.2 (7.32–11.47)
1993	26	6.1 (3.95–8.89)	30	7.3 (4.95–10.49)	56	6.7 (5.13–8.67)
1989–1993	170	7.9 (6.8–9.2)	160	7.8 (6.7–9.1)	330	7.9 (7.1–8.8)

Data are n (95% CI) or case number.

years of age, were included in the study. In reported cases, the clinical diagnosis of diabetes was made by a physician, and patients needed insulin permanently with the date of diagnosis being that of the first insulin injection. In addition, patients had to be living permanently in the Lazio region before diagnosis.

Primary ascertainment

The primary ascertainment was carried out at the region's diabetes clinics, where patients are usually first seen, and at specialized departments of the three Roman universities where patients are admitted. Questionnaires were presented to patients and their relatives and comprised two sections: the first with personal data to be filled in by one of them and the second describing the clinical characteristics at the time of presentation to be

filled in by the physician in charge. For every recruited patient, the following data were collected: date and place of birth, sex, address, age, date of clinical diagnosis (first insulin injection), duration of symptoms, hospitalization record, blood glucose, and presence of ketones in the urine at the time of first presentation. Patients in a coma were defined as unconscious or with an impaired level of consciousness at presentation.

Secondary ascertainment

This was conducted in the archives of the Lazio region where age and date of diagnosis of IDDM patients are recorded. Thus, to obtain medicine, syringes, and glucose monitoring strips free of charge, patients need to register with their recognized regional health office. This office issues the patient a document to be pre-

sented to the pharmacist (which allows exemption from payment) and reports all these diabetic patients to the regional archives.

Statistical analysis

For the incidence of IDDM, the 95% CI was estimated assuming a Poisson distribution. The completeness of ascertainment was based on the model that assumes independent ascertainment of the same population by two alternative sources (11).

RESULTS— In the 5 years of the survey, 330 new IDDM patients were identified (170 boys and 160 girls), with an average annual incidence of 7.86 per 100,000 (95% CI 7.1–8.8) (7.91 per 100,000 for boys and 7.81 per 100,000 for girls) (Table 1). The standardized incidence rate for different years based on data from the *Italian Statistical Year Book* (1991) was 8.58 in 1989 for 100,000 children <15 years of age, 7.51 in 1990, 7.39 in 1991, 9.18 in 1992, and 6.67 in 1993. Year differences in incidence were not significant either in the whole group or in different age-groups (χ^2 test).

Incidence by age-group is shown in Table 2. In the various age-groups, the highest IDDM incidence (although not significant) was observed in the 5- to 9-year-old age-group, while the lowest was detected in the 0- to 4-year-old age-group. The cumulative risk of the disease was 0.3 per 1,000 in the age-group 0–4 years old, 0.81 per 1,000 in the age-group 5–9 years old, and 1.18 per 1,000 in the age-group 10–14 years old. Peak age for disease development was 9 years: 11.8% of all cases (11.9% for boys and 14.1% for girls, respectively).

Table 2—Annual incidence rate (per 100,000) by age-group and sex

	Age-group			Total 0–14 years
	0–4 years	5–9 years	10–14 years	
Total (n)	78	130	122	330
Annual incidence rate (95% CI)	6.3 (5.0–7.9)	9.8 (8.3–11.6)	7.5 (6.2–9.0)	7.9 (7.1–8.8)
Cumulative risk per 1,000	0.32	0.81	1.18	
Boys (n)	36	71	63	170
Annual incidence rate (95% CI)	5.7 (4.0–7.9)	10.4 (8.1–13.2)	7.5 (5.8–9.8)	7.9 (6.8–9.2)
Cumulative risk per 1,000	0.28	0.80	1.18	
Girls (n)	42	59	59	160
Annual incidence rate (95% CI)	7.0 (5.0–9.5)	9.8 (7.5–12.7)	7.4 (5.7–9.6)	7.8 (6.6–13.3)
Cumulative risk per 1,000	0.35	0.8	1.18	

Analysis of seasonal trend confirmed previous findings that the disease occurs significantly more often during winter (36.2%) and spring (25.8%) but less in summer and autumn (20.1% and 17.9%, respectively) ($P < 0.02$). In the summer of 1992 (June and July), an unexpected rise of new cases of IDDM was recorded ($n = 15$ vs. average of 8.7 in other years). The rainfall in the 5 years of observation was within expected values for the season (15 mm). However, average rainfall in May/June 1992 was 10 times higher (118 mm) than that in the previous 43 years with only a modest reduction in air temperature.

The place of residence of patients varied within the region, but the majority (66%) of them live in the main towns of the Lazio region, 24% in smaller towns, and 10% in rural areas, thus reflecting the distribution of the population in this region.

Completeness of ascertainment

Through secondary ascertainment, we identified patients who were seen initially by private physicians but later were registered at the regional office to obtain exemption from paying for diagnostic devices. Overall, the completeness of ascertainment was 85% due to the high quality of the primary data source and to the analysis conducted for the years 1989–1991 (84%) and 1993 (87%).

Clinical characteristics of patients at presentation

Blood glucose levels at the time of first presentation were highly variable with the highest blood glucose values observed in the youngest age-group (0–4 years old), but differences between sex and age-groups were not significant.

Regarding disease severity at diagnosis, the majority of patients (60.9%) had hyperglycemia and ketonuria, 34.8% showed hyperglycemia only, and 14 patients (4.2%) were in a state of coma at diagnosis (5 boys and 9 girls). No significant differences were found between the two sexes with respect to the occurrence of hyperglycemia and ketonuria; however, the highest percentage of patients with ketonuria (although not significant) were in the younger age-group (0–4 years old, 63.2%). A total of 270 (81.8%) patients required hospitalization.

DISCUSSION— This is the first 5-year prospective study of IDDM inci-

dence in children 0–14 years of age in Italy involving the Lazio region with its capital Rome. It reveals a crude incidence rate of 7.9 per 100,000 per year (95% CI 7.1–8.8) for children <15 years of age during the period 1989–1993. The age-standardized incidence rate of Lazio did not differ significantly from that in other areas within the Italian peninsula. It is similar to that in other northern (Piemonte: 8.0 per 100,000) and central (Marche: 7.9 per 100,000) Italian regions. However, it is slightly higher compared with Lombardy (6.8 per 100,000) but less than Sardinia (30.2 per 100,000), the region with the second highest IDDM incidence in the world.

In our region, the 5- to 9-year-old age-group, regardless of sex, showed the highest (although not significant) incidence rate. Other Italian regions have reported similar patterns, but throughout Europe, the peak incidence was found in the 10- to 14-year-old age-group (4). This earlier age of onset of IDDM may be due to the genetic characteristics of IDDM patients in the Lazio region (indeed, some human leukocyte antigen genotypes occur more frequently in this population than others) (12).

No sex difference was found in any age-group of IDDM patients. This finding is of interest because a slight male preponderance was reported in IDDM patients from Northern Europe and from the Piemonte region (9) located in Northwest Italy. We have no clear explanation for this finding; however, the results seem to exclude an effect of sex hormones in the development of this disease, as suggested by these authors.

Overall, data indicate that in the Lazio region, the incidence of IDDM in the age-group 0–14 years old is similar to the rate of other Southern European countries and remained stable over the 5-year observation period except for 1992 when the incidence of the disease increased to 9.2 per 100,000. We speculate that the unexpected rise in the incidence of IDDM in this year in the Lazio region may be attributable to changes in environmental factors, in this case increased rainfall (13), which might have in turn favored the development of intercurrent disease in a period (June/July) when colds and flu are less frequent. Infections of this kind are indeed well-known precipitating factors for the clinical onset of IDDM in susceptible subjects. Finally, presentation

of IDDM indicates that although the majority of patients, as expected, showed ketonuria, in more than one-third of them, the diagnosis was made on the basis of hyperglycemia only. Coma was observed in 4.2% of patients with the youngest age-group (0–4 years old) showing the highest percentage (9.2%). These results are encouraging when compared with previous studies, which reported a much higher number of patients presenting with severe ketoacidosis and coma (14,15). Improved information, availability of glucose meters with general practitioners, and the awareness of predictive programs for IDDM by the public have made possible an earlier diagnosis in our region.

Acknowledgments— We are grateful to EURODIAB ACE for providing assistance in our survey and to the physicians of the IMDIAB Study Group in Rome for collecting incidence cases: N. Visalli, M.L. Bocconi, M.G. Baroni, R. Buzzetti, E. Fioriti, C. Mesturino, A. Signore, M.G. Cavallo, L. Lucentini, M.C. Matteoli, A. Crinò, C.A. Cicconetti, C. Teodonio, R. Amoretti, F. Paci, M. Ruggeri, L. Pisano, M.G. Penafina, G. Santopadre, C. Suraci, B. Boscherini, S. Stoduto, M.T. Fonte, F. Batelli, G. Multari, L. Campea, M.A. Suppa, G.C. De Mattia, M. Cassone Faldetta, G. Marozzi, A. Mancini, G. Testa, G. Marietti, E. Ponte, F. Perrone, A.V. Greco, and G. Ghirlanda. We thank Professor D. Andreani for useful comments and advice.

References

1. Diabetes Epidemiology Research International Group: Geographic patterns of childhood insulin-dependent diabetes mellitus. *Diabetes* 37:1113–1119, 1988
2. WHO Diamond Project: WHO multinational project for childhood diabetes. *Diabetes Care* 13:1062–1068, 1990
3. Karvonen M, Tuomilehto J, Libman I, La Porte R, for the World Health Organization DIAMOND Project Group: A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 36:883–892, 1993
4. Green A, Gale EAM, Patterson CC, for the EURODIAB ACE Study: Incidence of childhood onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 339:905–909, 1992
5. Cherubini V, Cantarini M, Ravaglia E, Bartolotta E: Incidence of IDDM in the Marche region, Italy. *Diabetes Care* 17: 432–433, 1994

6. Mazzella M, Cotellessa M, Bonassi S, Mulas R, Caratozzolo A, Gaber S, Romano C: Incidence of type I diabetes mellitus in the Liguria region, Italy: results of a prospective study in a 0–14 year age-group. *Diabetes Care* 17:1193–1196, 1994
7. Prisco F, Iafusco D, Palumbo F: Incidenza in Campania del diabete mellito tipo 1 in soggetti di età < 14 anni nel triennio (1989–1991) (Abstract). *Diabete* (Suppl. 1):190, 1992
8. Verrotti A, Chiarelli F, Tumini S: WHO Diamond Study: epidemiologia del diabete tipo 1 in età pediatrica in Abruzzo negli anni 1990, 91, 92 (Abstract). *Atti IX Congresso Società Italiana Endocrinologia e Diabetologia Pediatrica, Bari, 1993*. p. 128
9. Bruno G, Merletti F, Vuolo A, Pisu E, Giorgio M, Pagano G: Sex differences in incidence of IDDM in age-group 15–29 years: higher risk in males in Province of Turin, Italy. *Diabetes Care* 16:133–136, 1993
10. Pozzilli P, Andreani D: Type 1 diabetes at presentation: the scene changes. *Diabetic Med* 7:762–762, 1990
11. Hamman RF, Gay EC, Cruickshanks KJ, Cook M, Lezotte DC, Klingensmith GJ, Chase HP: Colorado IDDM registry: incidence and validation of IDDM in children aged 0–17 yr. *Diabetes Care* 13:499–506, 1990
12. Buzzetti R, Nisticò L, Osborn JF, Giovannini C, Chersi A, Sorrentino R: HLA-DQA1 and DQB1 gene polymorphisms in type 1 (insulin dependent) diabetic patients from Central Italy and their use for risk prediction. *Diabetes* 42:1173–1178, 1993
13. Pozzilli P, Visalli N, Suppa A, Buzzetti R: IDDM and rainfall. *Lancet* 342:1496, 1993
14. Drash AL: In *Clinical Care of the Diabetic Child*. Chicago, Year Book, 1947, p. 35–47
15. Pickney JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EAM: The Barts Oxford Study Group: presentation and progress of childhood diabetes mellitus: a prospective-based study. *Diabetologia* 37:70–74, 1994
16. Istat Istituto Nazionale Di Statistica: *Annuario Statistico Italiano*. Rome, Italy, 1991, p. 55