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Research: Epidemiology

Incidence of childhood Type 1 diabetes mellitus in Crete

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Abstract

Aim To investigate the epidemiology of childhood Type 1 diabetes mellitus in Crete over the last 25 years and to evaluate incidence trends over time.

Methods The study included all children aged 0–14 years who live in Crete and were diagnosed during the 25-year period from 1 January 1992 to 31 December 2016.

Results A total of 271 children were diagnosed with Type 1 diabetes during the 25-year period: 148 boys and 123 girls (boy:girl ratio 1.2). The median (interquartile range) age at diagnosis was 8.3 (5.0–12.0) years for boys and 8.0 (5.3–11.3) years for girls. The standardized annual incidence rate was 10.5 per 100 000 children (95% CI 9.2 to 11.8). Incidence rates were higher in children aged 5–9 years. During the 25-year study period an average 4.4% annual increase in incidence was documented and was most prominent in the age group 5–14 years. Incidence seemed to remain relatively stable for the age group 0–4 years in the last decade. No seasonality of the clinical onset of Type 1 diabetes was observed.

Conclusions The recent increase in Type 1 diabetes incidence places Crete among regions with high incidence as per the World Health Organization DiaMond project classification. The rising trends in incidence confirmed by this study are in accordance with the reported global trends in Type 1 diabetes incidence.

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Introduction

Type 1 diabetes mellitus is one of the most common endocrine disorders among children worldwide [1]. Its incidence varies significantly among as well as within countries [2]. Incidence is considered as very low, low, intermediate, high or very high at rates of <1, 1–4.99, 5–9.99, 10–19.99 and ≥20 per 100 000 per year, respectively [3]. Greece is listed among the countries with high rates, with 10.4 new cases per 100 000 per year according to the International Diabetes Federation (IDF) estimates for 2013 [4]. A 7-year study, conducted from 1989 to 1995 in the greater Athens area, reported an average incidence rate of 9.7 per 100 000 person-years-at-risk [5].

Europe has the highest number of children with Type 1 diabetes, with northern European countries having some of the highest incidence rates worldwide. No uniform incidence pattern exists for Mediterranean countries; incidence is low in several countries, but Italy's autonomous region of Sardinia has one of the highest rates in Europe (37 new cases per 100 000 per year) [6]. The incidence in countries neighbouring Greece varies, with the Former Yugoslavian Republic of Macedonia and Bulgaria having intermediate incidence rates of 5.8 new cases per 100 000 per year and 9.4 cases per 100 000 per year, respectively, while Cyprus has a higher incidence rate, estimated to 14.4 cases per 100 000 per year, according to the 2013 IDF estimates.

The incidence of Type 1 diabetes is increasing worldwide. The overall annual increase was 3.9% in Europe [7], with a left shift in age at onset [8,9]. It is predicted that, with present trends, the number of new cases in children aged <5 years may double in some regions between 2005 and 2020, with cases in children aged <15 years rising to 70% of the total Type 1 diabetes population [7].

Patterns of seasonality with regard to diagnosis have been extensively studied, with most cases documented during late autumn, winter and early spring; however, evidence of seasonality patterns has often been conflicting and patterns seem to be more obvious among populations with higher incidence and further from the equator [10].

The aim of the present study was to document the epidemiological data over the last 25 years in Crete, to define incidence and to evaluate incidence change over time,

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What's new?

- Childhood-onset Type 1 diabetes mellitus seems to be increasing in Crete, an area with very low rates in the past, but recent reports on incidence rates are lacking.
- Incidence rates now place Crete among regions with a high incidence of Type 1 diabetes.
- The average annual incidence increase of 4.4% during the 25-year period studied is considerable and in accordance with global trends in Type 1 diabetes incidence.
- Incidence rates among the 0–4 years age group have remained relatively stable in the last decade.

as well as to investigate possible seasonality. A previous report on the epidemiology of childhood-onset Type 1 diabetes in Crete published data from the 12-year period 1990–2001. During that period the standardized annual incidence rate reported was 6.1 per 100 000 person-years-at-risk [11], which was lower than that reported by Bartsocas [5] in a 7-year survey in the greater Athens area, conducted around the same period [5].

Materials and methods

Population and research design

Crete is the largest and most populous of the Greek islands and the fifth-largest island in the Mediterranean Sea. The population is quite stable and homogenous and numbers 623 065 inhabitants, according to the 2011 census. Crete is divided into four prefectures, Chania, Rethymno, Heraklion and Lasithi (west to east), with half the child population residing in Heraklion. There are no considerable differences between the four prefectures of Crete concerning climate and population. Crete's climate is temperate Mediterranean, characterized by mild winters and warm summers, with only slight variations.

The study included all children aged 0–14 years with new-onset Type 1 diabetes, according to the WHO definition [12], who were diagnosed during the 25-year period from 1 January 1992 to 31 December 2016. Data were collected from the Paediatric Diabetes Clinic at the University Hospital of Heraklion, which is the only one in the island. The clinic cares for all children (aged <18 years) with Type 1 diabetes; children diagnosed in other public hospitals in Crete are always referred to this clinic for further evaluation, treatment and follow-up. There are no private clinics with a paediatric department on the island. A second independent source of private endocrinologists and paediatricians was used but they did not report any newly diagnosed children during this period that were not referred to the University Hospital of Heraklion. Changes made in healthcare over the study period during the 25-year period were mostly with regard to awareness campaigns about early Type 1 diabetes symptom recognition. No changes were noted concerning the methods of diagnosis used during the study period.

Children who had resided in Crete for <12 months at diagnosis were excluded from the study, as well as all children diagnosed with Type 2 diabetes mellitus, monogenic diabetes or who developed diabetes secondary to other medical conditions. The study collected data on age at onset, gender, family history of diabetes, month and year of diagnosis.

Statistical methods

Children were grouped, according to their gender, into three age groups in 5-year intervals (0–4 years, 5–9 years and 10–14 years) according to their age at diagnosis, and by the month and season of diagnosis. Incidence rates were calculated as the incidence per calendar year and 100 000 individuals at risk, using the number of cases as the numerator and population estimates of children aged ≤14 years, based on the 1991, 2001 and 2011 census counts, from the data provided by the Hellenic Statistical Authority, as the denominator, with linear interpolation between census years. Age- and gender-specific incidence rates were also calculated accordingly. We estimated 95% CIs for the incidence rates using the assumption that the number of cases per year followed a Poisson distribution [13]. To calculate the average annual increase in incidence during the studied period a linear regression was used to test temporal trends. The regression coefficient is approximately the average annual increase in incidence per year expressed as a percentage [14]. To smooth data on incidence rates per year, a 5-year moving average was used to help identify trends over time [15]. The IBM statistics package SPSS V17.0 was used for statistical analysis of the data. To study seasonality, the Pearson chi-squared goodness-of-fit test was used to assess statistical significance. *P* values <0.05 were taken to indicate statistical significance.

Results

Incidence

Type 1 diabetes was diagnosed in a total of 271 children aged 0–14 years during the 25-year studied period. All study participants were identified through the capture enrolment. Of the 271 children, 148 (54.6%) were boys and 123 (45.4%) girls; the boy:girl ratio was 1.2 (the boy:girl ratio in the general population is 1.0), with male predominance in all age groups. The standardized overall incidence rate was 10.5 per 100 000 children at risk (95% CI 9.2 to 11.8). The annual new cases and incidence rates with 95% CIs are presented in Table 1. The annual incidence rate is also represented in Fig. 1 where a 5-year moving average was

Table 1 Incidence rate (new cases per 100 000 per year) of Type 1 diabetes mellitus in children aged 0–14 years in Crete, 1992–2016

	New cases	Person-years at risk	Incidence per 100 000 person years	95% CI
All children	271	2 592 139	10.5	9.2 to 11.8
Boys	148	1 322 081	11.2	9.5 to13.2
Girls	123	1 270 058	9.7	8.0 to 11.6
0–4 years	58	831 573	7.0	5.3 to 9.0
5–9 years	105	853 159	12.3	10.1 to 14.9
10–14 years	108	907 407	11.9	9.9 to 14.4

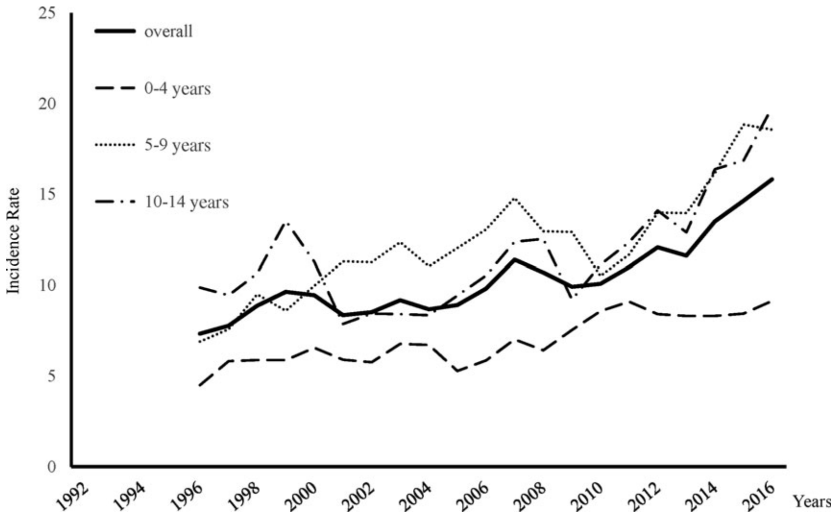

FIGURE 1 Five-year moving average for overall annual incidence of Type 1 diabetes mellitus and for each age group separately, 1992–2016.

used to smooth the data and help identify time trends. To better study time trends over the 25-year period and avoid stochasticity, incidence rates were also calculated for the 5-year periods 1992–1996, 1997–2001, 2002–2006, 2006–2010 and 2011–2016 (Table 2). The lowest incidence increase was noted for the age group 0–4 years, which was almost twice as low as that for the 5–9-year age group. The average annual increase in incidence during the studied period was calculated as 4.4% per year (95% CI 3.2 to 5.6; P=0.001). This increase was most prominent in the last 5 years and in the age groups 5–9 and 10–14 years. The incidence seemed to be fairly stable for the age group 0–4 years in the last decade.

Age of onset

The median age at diagnosis was 8 years [median (interquartile range) 8.3 (5.0–12.0) years for boys and 8.0 (5.3–11.3) years for girls], and did not differ significantly among girls and boys in any age group. Incidence rates among the different age groups were calculated per year and for 5-year periods (Table 2). In the 25-year study period, the highest incidence rates (12.3 per 100 000 person-years, 95% CI 10.1 to 14.9) were present in the age group 5–9 years, followed by the age group 10–14 years (incidence rate 11.9 per 100 000 person-years, 95% CI 9.9 to 14.4), whereas the lowest incidence rates were documented for the youngest age group, 0–4 years (incidence rate 7.0 per 100 000 person-years, 95% CI 5.3 to 9.0). In the last decade the incidence in the age group 0–4 years remained relatively low and stable (incidence rate 9.1 per 100 000 person-years, 95% CI 5.2 to 14.9). Although the overall annual incidence was higher in the age group 5–9 years, in the last decade a shift towards the oldest age group was seen. Figure 1 shows incidence rates per year per age group.

Seasonal variation

Figure 2 represents the distribution of children by month of diagnosis. April was the month with the highest rate of new diagnosis without significant difference compared with other months. Children were also divided into three groups according to their diagnosis in cold months (December, January, February, March), warm months (June, July, August, September) and intermediate months (April, May, October, November). This grouping was based on the average island temperatures as per the Hellenic National Meteorological Service. Analysis of seasonality did not reveal

Table 2 Incidence rates in 5-year periods, overall, for each gender, and for each age group, 1992–2016

Year	1992–1996		1997–2001		2002–2006		2007–2011		2012–2016		*P* for trend
	N	Incidence	N	Incidence	N	Incidence	N	Incidence	N	Incidence	
Total	39	7.2 (5.1 to 9.9)	41	8.3 (5.3 to 12.5)	51	9.8 (7.3 to 12.5)	57	11.0 (8.3 to 14.2)	83	15.8 (7.7 to 18.9)	0.016
Boys	23	8.3 (5.3 to 12.5)	24	9.7 (6.2 to 14.4)	27	10.1 (6.7 to 14.7)	30	11.4 (8.3 to 14.2)	44	16.5 (12.0 to 22.1)	0.035
Girls	16	6.1 (3.5 to 9.8)	17	7.0 (4.1 to 11.3)	24	9.5 (6.1 to 14.1)	27	10.6 (7.2 to 15.3)	39	15.1 (10.9 to 20.5)	0.008
0-4 years	7	4.5 (1.8 to 9.2)	9	5.9 (2.7 to 11.2)	10	5.9 (2.8 to 10.8)	16	9.1 (5.2 to 14.8)	16	9.1 (5.2 to 14.9)	0.018
5-9 years	12	6.8 (3.5 to 11.9)	18	11.3 (6.7 to 17.8)	22	13.0 (8.2 to 19.7)	20	11.7 (7.1 to 18.0)	33	18.6 (12.8 to 26.1)	0.040
10-14 years	20	9.6 (5.8 to 14.9)	14	7.9 (4.3 to 13.2)	19	10.5 (6.3 to 16.4)	21	12.4 (7.7 to 18.9)	34	19.8 (13.7 to 27.7)	0.068

A linear regression model was used to evaluate incidence increase over time for each group.

significant differences. Fewer children in the age group 0–4 years were diagnosed during the cold months (25.9%), while in the older age group, 5–14 years, a cold month predominance (38.0%) was observed, although the difference was not significant (*P*= 0.39 and *P*= 0.07, respectively for each group).

Discussion

Data from large epidemiological studies indicate that the incidence of Type 1 diabetes has been increasing by 2–5% worldwide, with the largest increase seen in the youngest age group [16]. Data from our 25-year study reveal a standardized overall annual incidence of 10.5/100 000 person-years at risk, which now places Crete among the regions with high incidence rates. In a previous study during the 1990–2001 period, Crete was placed among regions with intermediate incidence rates (incidence rate 6.1/100 000 person-years at risk). The incidence rate peaked in the 5–9-year age group, followed by the age group 10–14 years. During our 25-year study a growing incidence trend was observed, with an overall average annual incidence increase of 4.4%, while the youngest children had a stable and relatively low incidence rate. This is in contrast to global trends reporting the highest incidence rise in the youngest age group.

Wide variation in incidence has been described among different countries, with a 350-fold difference in incidence documented worldwide [17]. These variations could be explained by differences in the genetic makeup of specific ethnic groups and diverse environmental factors [18–20]. Studies have also shown significant difference between neighbouring countries [21], but even between regions of the same country [22,23]. This could be attributed to the presence of ethnic minorities [24], but has also been observed in more homogenous populations, pointing to an influence of environmental factors. The Cretan population is considered to be relatively homogeneous because Crete is an island and no considerable population movements have taken place in the last century.

Reported findings on seasonality in Type 1 diabetes diagnosis are inconsistent [25], with some studies, including studies in Greece and in Cyprus [26–28], having reported evidence of seasonality with regard to diagnosis and others not finding significant differences in seasonality [29]. In the present study we did not observe statistical significance regarding seasonality, but a seasonal pattern was observed in the age group 0–4 years, with more children being diagnosed during the warm months. This finding has been previously reported [26].

A major strength of the present study is that it recorded all cases of Type 1 diabetes in the study area and for a prolonged period of 25 years. To our knowledge this is the longest-duration epidemiological study in the Greek region concerning the incidence of Type 1 diabetes as well as the most recent one.

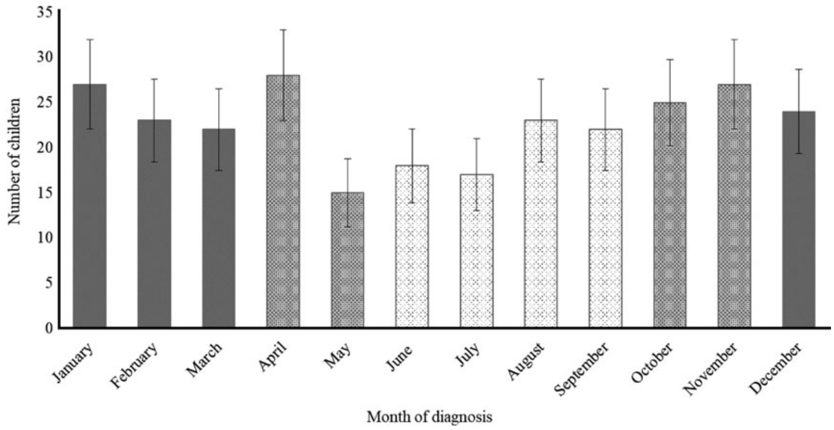

FIGURE 2 Number of children diagnosed for each month in the 1992–2016 period.

A limitation of the study is that nutritional, environmental and genetic factors were not included. Another limitation is that the epidemiological data presented did not include documentation and incidence of Type 2 diabetes in Cretan children.

In conclusion, over the 25 years studied, childhood-onset Type 1 diabetes significantly increased compared with previous findings in Crete, with a rapid incidence increase of 4.4% per year. With this rate, a doubling in incidence could be expected in <20 years. The incidence has remained low among the youngest children.

More studies need to be conducted with other socio-economic and environmental factors included. Epidemiological studies can play an important role in the investigation of causes and triggers of Type 1 diabetes, elucidate its nature and possibly help us devise preventive strategies.

Funding sources

None.

Competing interests

None declared.

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