The epidemiology of Type 1 diabetes mellitus is not the same in young adults as in children

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Abstract

Aims/hypothesis. This prospective study examined the epidemiology of Type 1 diabetes in young adults in Europe.

Methods. We ascertained incident cases of Type 1 diabetes in the 15 to 29 years (both inclusive) age group throughout Europe over a period of 2 years. Diabetes registries in nine countries, in which incidence rates for Type 1 diabetes in the 0 to 14 age group were available, took part. Incidence rates were estimated per 100000 person years and standardised for sex and age. Cumulative incidences per 1000 from birth to age 30 were estimated. Heterogeneity between centres was tested with a Poisson regression model.

Results. A total of 2112 diabetes cases were ascertained in 1996 and 1997, of which 61.4% were considered to be Type 1 diabetes. Completeness of ascertainment varied from 70 to 90%. Standardised inci-

dence varied from 4.8 per 100000 person years to 13.4 per 100000 person years. The male–female ratio was estimated to be one or more, and in the 25 to 29 age group 1.5 or more in all countries. Cumulative incidences for males and females indicate that the former exceeds the latter from age 24. In the two centres with highest childhood incidence, this applied already from 14 years of age.

Conclusions/interpretation. The incidence of Type 1 diabetes in adults is lower than in children and the range of incidence is also reduced, with a less than threefold variation in adults, against an eightfold variation in children. There is a male excess in incidence, especially in the age group 25 to 29 years. [Diabetologia (2004) 47:377–384]

Keywords Type 1 diabetes · Incidence · Cumulative incidence · Epidemiology · Adults

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Abbreviations: EURODIAB TIGER, European Diabetes: Type I Genetic Epidemiology Resource

Type 1 (insulin-dependent) diabetes mellitus is a common chronic disease of childhood, and presents with acute, sometimes life-threatening, symptomatic hyperglycaemia. Children with diabetes present to paediatric services and are highly visible within the health system. This is not the case in patients who are 15 to 29 years of age; symptoms are typically less acute, and both gestational and Type 2 diabetes are increasingly prevalent in this age group, compared with children [1, 2]. Adolescent and young adult patients are

treated in diabetes units, general medical or obstetrical units, or by general practitioners. Consequently ascertainment and classification of Type 1 diabetes are more difficult than in children, and standardised comparisons between age groups and between areas with differing incidences of Type 1 diabetes in childhood have not been carried out.

Type 1 diabetes is a multifactorial disease in which environmental risk factors trigger an immune-mediated destruction of the pancreatic beta cells in genetically susceptible individuals [3]. Studies of the epidemiology of Type 1 diabetes in different populations can provide important clues about putative environmental risk factors. The incidence of the disease in children up to 15 years of age is well documented by two multi-centre studies [4, 5, 6, 7], with incidence varying from less than 1 per 100000 person years in Venezuela and China to more than 35 per 100000 person years in Finland and Sardinia. Furthermore, recent studies suggest a higher rate of increase in disease among children younger than 5 years than in children between 5 and 15 years of age [8, 9, 10, 11], although other studies have not observed a differential rise in incidence [12, 13, 14].

Although Type 1 diabetes has traditionally been considered a disease of childhood, the majority of cases present in adult life [15]. Adult cases are characterised by a reduced frequency of HLA susceptibility haplotypes, as compared with children [1, 16, 17], and overall have less acute symptoms than children [1]. Male predominance is a further, unexplained feature of Type 1 diabetes in young adults [18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. This is in marked contrast to most other common immune-mediated conditions, which are typified by female preponderance [28].

The epidemiology of Type 1 diabetes in adults is less well characterised than in children of 0 to 14 years of age, especially with regard to international comparisons of incidence rates and to differences in incidence between the sexes. Here we report on a collaborative research project, which has studied the incidence of Type 1 diabetes mellitus in the 15- to 29-year age group in European regions known to represent high, intermediate and low childhood incidence areas to investigate the geographical distribution by sex and age of Type 1 diabetes mellitus with onset in young adulthood.

Subjects and methods

Centres participating in the study. European centres were eligible for participation on the basis of the following requirements: first, they had to be able to identify all new cases of diabetes mellitus or all new cases of Type 1 diabetes mellitus in the 15- to 29-year age group, as reported by treating physicians in a geographically well-defined population with reliable demographic data. Second, they had to be able to validate the completeness of registration by means of one or more independent secondary source of ascertainment [29].

A total of nine centres are taking part in the concerted action and results are complete for 1996 and 1997. The participating centres represent geographical areas known from European Diabetes: Type I Genetic Epidemiology Resource (EURODIAB TIGER) to be areas with high (Sardinia and Sweden), intermediate (England, Antwerp in Belgium and Catalonia in Spain) and low (Lithuania, Bucharest in Romania and Slovakia) Type 1 diabetes incidence in children. In Sweden only childhood incidence data from Stockholm were used for the EURODIAB studies of childhood Type 1 diabetes, and in Yorkshire, England only the western part of the area (West Yorkshire) took part in the study of young adults. Thus our comparison is also based on this.

Data sources and classification of disease. In all centres, direct notification from hospitals, diabetologists and/or general practitioners constituted the primary data source. Prescriptions, diabetes associations, summer camps, registries of social benefits and general practitioners were used as secondary sources.

Classification of diabetes was based on the diagnosis made by the diabetologist and the date of the first insulin injection was used as date of diagnosis of Type 1 diabetes.

Statistical analysis. Population data from each local study centre's geographically defined area were used to calculate age- and sex-specific incidences. Incidence rates per 100000 person years at risk and 95% CI were calculated. The incidence rates were standardised for sex and age, with the pooled data used as the standard. The 95% CI were estimated using an approximated Poisson distribution as described previously [30]. Incidence data from 1996 and 1997 in children of 0 to 14 years of age were provided by EURODIAB TIGER, details of which have been previously published [4, 6].

Incidence rates within centres, e.g. children versus adults, males versus females and males versus females in the two age categories, were compared with chi square and Mantel-Haenszel chi square tests and 95% CI for the incidence rate ratios calculated. Differences between centres were tested using a Poisson regression model. Cumulative incidence per 1000 was calculated and sex-specific cumulative incidence was analysed in groups based on childhood incidence in areas with low, intermediate and high childhood incidence. Trends in cumulative incidences were assessed by linear and log-linear regression models. The curves were compared using multivariate general linear regression models. We considered *p* values below 0.05 to be statistically significant. The software packages Excel, SPSS (SPSS, Chicago, Ill., USA) and Stata version 7 (StataCorp, College Station, Tex., USA) were used.

Ethics. The study was carried out in accordance with the Helsinki Declaration as revised in 2000. All local study centres fulfilled the ethical requirements of their national legislation, and had permission from their local scientific and ethics commission, as well as from their national data protection agencies where applicable. Only anonymous data were submitted to the central co-ordinating office in Denmark and this was approved by The Danish Data Protection Board.

Results

Of the 2112 cases of diabetes that were ascertained in 1996 and 1997 in the 15 to 29 age group, 1296 (61.4%) were classified as Type 1 diabetes cases by referring doctors (Table 1). Completeness of ascertainment within the local study centres varied from 70 to 90%.

Table 1. Ascertainment of Type 1 diabetes cases in young adults (men and women) by study centre for 1996 and 1997

Centre	Completeness of ascertainment (95% CI)	Number of cases, men	Number of cases, women
Belgium (Antwerp region)	90% (86–93%)	17	16
Italy (Sardinia)	70% (58–84%)	71	33
Lithuania	90% (79–100%)	81	51
Romania (Bucharest area)	100% ^a	45	32
Spain (Catalonia)	90% (87–93%)	200	116
UK (Leicestershire)	90% (84–98%)	29	22
UK (West Yorkshire)	98% (96–99%)	67	35
Sweden	85% ^b	238	127
Slovakia	80% (71–89%)	77	49

^a According to the Bucharest centralised medical system for diabetes care, all diabetic patients from Bucharest are registered in the Diabetes Centre and thus in the registry. Free in-

sulin is distributed only by the pharmacy belonging to this Centre.

^b Average of several studies of level of ascertainment

Fig. 1. Standardised incidences with 95% CI of Type 1 diabetes in children and young adults by study area. Results are arranged according to childhood incidence. *Black bars:* 0–14 years (children); *shaded bars:* 15–29 years (young adults). R1, Romania (Bucharest area); K4, Lithuania; Z1, Slovakia; B1, Belgium (Antwerp area); S1, Spain (Catalonia); U3, UK (Leicestershire); U4, UK (West Yorkshire); X1, Sweden; I3, Italy (Sardinia)

The total incidence for 1996 to 1997 in young adults varied from 4.8 per 100000 person years in Slovakia to 13.4 per 100000 in Leicestershire, England. Age- and sex-specific rates are shown in Table 2 and standardised rates are illustrated in Fig. 1. In Bucharest, Romania the incidence rates in adults was higher than in children, although this was not statistically significant ($p=0.9$). In all the other centres incidence was lower in young adults than in children. This was only statistically significant in Catalonia, Spain ($p=0.05$), Yorkshire, England ($p<0.001$), Sardinia, Italy ($p<0.001$) and Sweden ($p<0.005$). In the centres with a high incidence in children the incidence in young adults was approximately one-third of that value or less, the incidence rate ratios for Sardinia and Sweden being 3.3 and 2.6. Heterogeneity among centres was established (Poisson regression LR chi square, 6 $df=111.33$; H_0 : no difference among centres: $p<0.001$).

The cumulative incidence of Type 1 diabetes mellitus before age 30 (Fig. 2) fitted a linear curve in all centres, except Sweden and Sardinia which had a logarithmic curve. The curves from all centres showed

Fig. 2. Cumulative incidence of Type 1 diabetes from 0 to 30 years

significant trends, but multivariate analysis did not result in significant differences between the slopes of the centres ($p>0.05$). The cumulative incidence in males and females (Fig. 3a–c) when centres were grouped according to low, intermediate and high levels of incidence of childhood diabetes shows a tendency for cumulative incidence in males to exceed that in females from the age of 25 years. For the two centres with the highest childhood incidence, this applied already from age 15.

With the exception of Slovakia, where there was a higher incidence in male children than in female children ($p<0.005$), incidence rates in children younger than 15 years of age did not vary according to sex. In all centres the point estimates of the male to female incidence rate ratio were greater than one in young adults. The sex-specific incidence rates in the total age group (15–29 years) were statistically different in all centres apart from Antwerp (Belgium) and Leicestershire (England). In the 25 to 29 age group all ratios exceeded 1.5 (Fig. 4) and differed significantly from one in all centres except Antwerp and Leicestershire (Table 2). The stratified analysis of incidence rates in

Table 2. Incidence (per 100 000 with 95% CI) of Type 1 diabetes for the 15 to 29 age group by 5-year age groups, sex and study centre

Age group (years)	Sex	Study centre		Lithuania	Bucharest Romania	Catalonia Spain	Leicestershire UK	West Yorkshire UK	Sweden	Slovakia
		Antwerp Belgium	Sardinia Italy							
15–19	No. of cases	2	27	22	10	60	7	17	82	31
		6	15	22	10	37	3	13	46	28
	Population	54 912	132 228	266 393	198 462	469 466	58 280	138 793	517 570	477 822
	Incidence	52 860	126 304	257 848	189 204	451 474	56 766	129 020	492 652	464 422
20–24		3.6	20.4	8.3	5.0	12.8*	12.0	12.3	15.8*	6.5
		0.3–13.4	13.4–29.7	5.2–12.5	2.4–9.3	9.7–16.5	4.8–24.8	7.1–19.7	12.6–17.6	4.4–9.2
		11.4	11.9	8.5	5.3	8.2*	5.3	10.1	9.3*	6.0
		4.1–24.9	6.6–19.6	5.3–12.9	2.6–9.8	5.6–11.2	1.0–15.6	5.4–17.2	6.8–12.4	4.0–8.8
25–29	No. of cases	6	23	20	10	76	6	16	79	27
		5	13	12	8	42	9	9	41	14
	Population	55 357	147 940	270 050	174 890	518 716	65 512	145 760	583 936	459 071
	Incidence	54 646	142 850	268 420	183 266	502 088	66 112	139 750	561 884	430 154
15–29		10.8	15.6	7.3	5.7	14.7*	9.2	11.0	13.5*	5.9
		3.9–23.8	11.8–23.2	4.4–11.3	2.7–10.6	11.5–18.3	3.3–20.1	6.3–17.9	11.0–16.8	3.8–8.6
		9.2	9.1	4.5	4.4	8.8*	13.6	6.4	7.3*	3.3
		2.9–21.5	4.8–15.6	2.3–7.8	1.8–8.6	6.1–11.3	6.2–26.0	3.0–12.2	5.2–10.0	1.8–5.4
15–29	No. of cases	9	21	39	25	64	16	34	77	19
		5	5	17	14	37	10	13	40	7
	Population	67 298	142 134	289 658	198 906	489 730	66 170	166 989	628 080	381 718
	Incidence	65 205	140 826	274 912	217 588	477 504	68 650	159 238	601 842	362 530
15–29		13.4	14.7*	13.5*	12.6*	13.0*	24.2	20.4*	12.3*	5.0*
		6.1–25.5	9.1–22.6	9.6–18.4	7.1–18.6	10.1–16.7	14.0–38.8	14.1–28.4	9.6–15.4	3.0–7.8
		7.7	3.6*	6.2*	6.4*	7.8*	14.6	8.2*	6.7*	1.9*
		2.4–18.0	1.1–8.4	3.6–9.9	3.5–10.8	5.5–10.7	7.0–27.0	4.4–14.0	4.8–9.0	0.8–4.0
15–29	No. of cases	17	71	81	45	200	29	67	238	77
		16	33	51	32	116	22	35	127	49
	Population	177 567	422 302	826 101	572 258	1 477 912	189 962	451 542	1 729 586	1 318 611
	Incidence	172 711	409 980	801 180	590 058	1 431 066	191 528	428 008	1 656 378	1 257 106
TOTAL		9.6	16.8*	9.7*	7.9*	13.5*	15.3	14.8*	13.8*	5.8*
		5.6–15.4	13.1–21.2	7.7–12.0	5.7–10.6	11.7–15.6	10.2–22.0	11.6–18.8	12.1–15.9	4.6–7.4
		9.3	8.1*	6.4*	5.4*	8.1*	11.5	8.2*	7.7*	3.9*
		5.3–15.1	5.5–11.3	4.7–8.4	3.7–7.6	6.7–9.7	7.2–17.4	5.8–11.4	6.4–9.2	3.0–5.2
TOTAL	No. of cases	33	104	132	77	316	51	102	365	126
		350 278	832 282	1 627 281	1 162 316	2 908 978	381 490	879 550	3 385 964	2 575 317
	Population	9.4	12.5	8.1	6.6	10.9	13.4	11.6	10.8	4.8
	Incidence	6.6–13.4	10.3–15.2	6.8–9.6	5.3–8.3	9.7–12.3	10.1–17.7	9.5–14.1	9.7–12.0	4.1–5.8

Results are for 1996 and 1997. * Significantly different incidence rates in men and women $p < 0.05$. M, men; W, women

Fig. 3a–c. Sex-specific cumulative incidence of Type 1 diabetes for study areas with low (a), intermediate (b) and high (c) childhood incidence

Fig. 4. Male to female ratio of Type 1 diabetes incidence by age groups and study areas. Dark grey bars: 0–14 years; light grey bars: 15–19 years; open bars: 20–24 years; black bars: 25–29 years. R1, Romania (Bucharest area); K4, Lithuania; Z1, Slovakia; B1, Belgium (Antwerp area); S1, Spain (Catalonia); U3, UK (Leicestershire); U4, UK (West Yorkshire); X1, Sweden; I3, Italy (Sardinia)

male children and female children (0–14 years of age) compared with young adults (15–29 years of age) showed significant differences between the two groups in Slovakia ($p < 0.0001$), Catalonia ($p < 0.0001$) and in both centres with high incidence of Type 1 diabetes in children, i.e. Sweden ($p < 0.0001$) and Sardinia ($p < 0.0001$).

Discussion

The incidence of Type 1 diabetes in children varies more than tenfold across Europe and 350-fold between Finland and China [4, 7]. We selected study areas with a childhood incidence ranging from 5.3 per 100000 person years (Bucharest) to 41.6 per 100000 person years (Sardinia), and showed that there is far less variation in incidence in young adults from the same regions. In all centres but Bucharest the incidence in young adults was lower than in children, and the incidence rate ratios in Sardinia and Sweden, the countries with the highest childhood incidence, were over 2.5.

In all nine centres the estimated male to female ratio of Type 1 diabetes incidence was greater than one in the 15 to 29 age group and greater than in children. In the age group 25 to 29 years the male to female incidence rate ratio was equal to or greater than 1.5 in all centres, although this was not statistically significant in Antwerp and Leicestershire, the two centres with the smallest study populations [21, 31]. However, the Belgian Diabetes Registry has shown a significant difference between incidence rates in men and women ($p < 0.001$) in the age range 15 to 39 years [21, 32].

A potential problem with this study is the completeness of ascertainment, which was lower than in the childhood studies [4, 6, 7]. This is a reflection of the difficulties encountered when trying to ascertain young adults, who are less visible in the health care system, while diabetes in this age group is more heterogeneous and classification more complex. Patients in this age group are treated in diverse settings, making capture from multiple-ascertainment sources necessary for completeness. They are also much more mobile. Under these circumstances the completeness of ascertainment obtained in our study can be regarded as satisfactory, as it was comparable to previous findings [7].

Some of the centres participating in this EU-project ascertain few cases from limited geographical areas, and this can result in loss of power to detect differences. In Belgium a national diabetes registry exists, but achieves only 40% ascertainment. A comparison between the Antwerp registry with 92% ascertainment and the national Belgian registry with 40% ascertainment showed that demographic, clinical and biological data did not differ in the two registries, indicating

that the registry with 40% ascertainment was nevertheless representative [21]. However, we chose to use the smaller Antwerp registry for this EU project because high ascertainment is more important than representability of cases, when it comes to ensuring maximum reliability of incidence rate estimates. A longer observation period will thus be necessary to obtain better estimates.

Another potential problem in this study is the difficulties involved in classifying type of diabetes in patients older than 14 years of age. HLA-types and immunological markers have not been used for classification, but the treating physicians did of course have clinical information. The same information is in the data sheets used for report at diagnosis. An earlier study on the difficulties of classifying type of diabetes showed that more cases are initially classified as Type 1 diabetes and later changed to Type 2 diabetes than the other way around [33]. The estimates of incidence rates in this study could therefore be regarded as conservative.

The strength of our study is that incidence data were ascertained in the same standardised way in centres throughout Europe for which well-validated incidence rates of childhood diabetes were available.

The difference in incidence between populations was much less marked in the 15 to 29 than in the 0 to 14 age groups. There was, however, heterogeneity between countries. Regional European differences with regard to socio-economic standards and maternal and child health could possibly contribute to these differences. A comparison of the cumulative rate of Type 1 diabetes up to age 30 within the countries studied shows that the two countries with the highest childhood incidence both had a slow-down of the rate of increase after age 15, whereas the remaining countries had a continued linear trend. Our results indicate that caution should be exercised when extrapolating regional differences in incidence of childhood onset Type 1 diabetes to differences in lifelong risk for the disease. To decide whether the higher and increasing incidence rates of childhood Type 1 diabetes in certain countries are due to earlier disease presentation [1, 8, 9, 10] or to an overall increased lifelong risk when compared to countries with lower incidence rates of childhood Type 1 diabetes, it would be necessary to compare incidence rates across countries over even larger age-ranges and longer observation periods.

A number of studies have reported a strong male preponderance in the incidence of Type 1 diabetes in adults [18, 19, 20, 21, 22, 23, 24, 25, 26, 27]. In this respect young adults differ from children, for overall sex-specific differences in children are slight, although high-incidence populations tend to show male preponderance, and low-incidence populations (mostly non-European) show female preponderance [34]. We therefore considered sex in relation to childhood incidence of Type 1 diabetes in our populations. In

fact, all participating centres had a male excess in incidence rates, although this was not statistically significant in Antwerp and Leicestershire. From the centres with the highest childhood incidence Sweden had a clear male incidence excess as early as the age of 14 years. In the areas with intermediate childhood-onset diabetes incidence Catalonia had the same male excess pattern, whereas data from Sardinia, the English centres and the low-incidence areas Romania, Slovakia and Lithuania only showed a male excess from the age of 25 years. Studies from Belgium with a longer follow-up period have also found a male excess as described here [21, 34].

The difference in incidence rates between the sexes could be due to factors operating in males, in females, or in both. One possible explanation of the sex-difference in incidences is under-ascertainment of women with Type 1 diabetes who are diagnosed with gestational diabetes, because these were excluded from the Insulin-dependent Diabetes in young Adults study, although primary ascertainment sources in each locality would be expected to register those with Type 1 diabetes after a delay. Most other autoimmune diseases, e.g. autoimmune thyroid diseases, rheumatoid arthritis and multiple sclerosis, have a high female to male ratio, and it is not clear why Type 1 diabetes mellitus shows the opposite picture [28]. The reasons for the difference are not clear, but possibly related to oestrogen secretion in women or to a higher metabolic burden due to android fat distribution. Obesity and insulin resistance could precipitate post-pubertal clinical onset of a slowly progressive immune-mediated diabetes [31].

A study of English, American and Sardinian patients with Type 1 diabetes showed that the male to female excess was restricted to *HLA-DR3* positive subjects lacking *DR4*, thus providing evidence of a linkage between chromosome Xp and diabetes [35]. A Belgian study failed to confirm the finding of HLA restriction with regard to the male to female excess in young adulthood, but did not completely rule out the suggestion of an interaction between an X-linked genetic factor and high-risk HLA types as a route to diabetes [31].

Although Type 1 diabetes is commonly considered a disease of children, only a minority of cases actually present in childhood [1, 2, 17]. We still know remarkably little about the "silent majority" that develop the condition in adult life. Our study, an international comparison of incidence in children and young adults, has shown that the incidence of Type 1 diabetes in young adults in Europe is lower than in children in most areas, and that the range of incidence is also reduced. We have also confirmed a consistent male excess of cases in this age group, which is most marked over the age of 25 and which remains unexplained, standing in marked contrast to the female excess characteristic of most common immune-mediated condi-

tions. Our understanding of Type 1 diabetes is likely to remain biased and incomplete as long as we focus upon its childhood variant, which is only the tip of the iceberg.

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