

The age at diagnosis of type 1 diabetes continues to decrease in Belgian boys but not in girls: a 15-year survey

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Abstract

Background The age at clinical onset of type 1 diabetes is decreasing. Preliminary Belgian data suggested that this anticipation occurred preferentially in boys. We investigated whether this gender-specific anticipation could be confirmed over a 15-year observation period.

Methods In Antwerp, we studied incidence trends between 1989 and 2003 in 746 type 1 diabetic patients under age 40. For 2928 antibody-positive patients diagnosed nationwide during the same period, age at diagnosis was analysed according to gender and calendar year.

Results In Antwerp, the incidence of type 1 diabetes under age 15 increased significantly with time from 10.9/100 000/year in 1989–1993 to 15.8/100 000/year in 1999–2003 ($p = 0.008$). The rising incidence in children was largely restricted to boys under age 10 where the incidence more than doubled during the 15-year period (6.8/100 000/year in 1989–1993 vs 17.2/100 000/year in 1999–2003; $p < 0.001$). Such an increase was not found in girls under age 10 ($p = 0.54$). This selective trend toward younger age at diagnosis in boys was confirmed in the larger group of Belgian patients where the median age at diagnosis decreased in boys – but not in girls – from 20 years in 1989–1993 to 15 years in 1999–2003 ($p < 0.001$).

Conclusions Over a 15-year observation period, a selective anticipation of clinical onset of type 1 diabetes was found in boys but not in girls. This suggests that an environmental factor may preferentially accelerate the sub-clinical disease process in young boys. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords type 1 diabetes; epidemiology; age; gender; incidence; trend

Introduction

Most diabetes registries have studied disease incidence under age 15 [1–3]. In the rare instances where older age groups were studied in parallel, it was found that in spite of an incidence peak around puberty the majority of new type 1 diabetic patients are diagnosed in adulthood with a marked male preponderance [4–7].

Several reports have indicated a rapid increase in the incidence of childhood type 1 diabetes worldwide, especially under age 5 [1,2]. The most striking increase has been observed in Finland, which has the highest incidence of

type 1 diabetes in the world [1]. At least in Sweden and Belgium, this rise was not ascribed to a global increase in disease incidence, but rather to an earlier clinical manifestation [8,9].

Preliminary data from Belgium over a 12-year period ($n = 571$) suggested that this anticipation may preferentially occur in boys [8], consistent with the positive correlation between male-to-female (M/F) ratio and incidence levels in childhood diabetes noted throughout the world [3]. If confirmed, this may suggest that a gender-related environmental factor is preferentially driving male subjects to earlier diabetes onset.

Therefore, we investigated whether this gender-specific anticipation could be further substantiated in the Belgian population of type 1 patients by extending our monitoring of incidence trends according to age and gender to a 15-year observation period.

Subjects and methods

During the 15-year study period (1 January 1989 till 31 December 2003), 746 type 1 diabetic patients (429 males and 317 females) residing in the Antwerp district and diagnosed before age 40 were prospectively registered [5,8]. In line with EURODIAB (EUROpe and DIABetes) and DIAMOND (DIABetes MONDiale) studies, diabetic patients were diagnosed as type 1 according to the 1985 WHO classification of diabetes criteria [10], and resided in Antwerp for at least 6 months prior to clinical onset of diabetes [5,8]. Data on diabetes autoantibodies were available for 68% of the included type 1 patients. In line with the previous studies [8], completeness of registration was assessed by the capture-recapture method, which assumes the availability of independent primary and (a combination of) secondary sources [11]. By cross-classifying cases according to their presence or absence in the primary and at least one of the secondary sources, the degree of completeness was estimated according to Bishop *et al.* [12]. Paediatricians and endocrinologists participating in the Belgian Diabetes Registry (BDR) constituted the primary source of ascertainment. As independent secondary source of ascertainment, a combination of reporting by general practitioners, diabetes nurses, the Antwerp branch of the Flemish Diabetes Association (VDV), participation in diabetes summer camps and the patients themselves (through voluntary participation in a nationwide family study on 'Early Diagnosis and Prevention of Diabetes') was used. The ascertainment rates averaged 97% (95% confidence interval, CI 95–99) in the age group 0–14 years and 92% (95% CI 89–94) in the age group 15–39 years and did not change significantly during the observation period (for more details, see Table 1). The epidemiological survey in Antwerp was conducted within the framework of the EURODIAB ACE and TIGER studies (0–14 years; coordinators: A. Green, Univ. of Aarhus,

Table 1. Case ascertainment according to age and gender in three consecutive 5-year periods

Age (years)	Ascertainment rate [% (95% confidence interval)]		
	1989–1993	1994–1998	1999–2003
0–39	95 (92–97)	96 (93–98)	94 (91–97)
0–14	99 (94–100)	98 (93–100)	95 (90–98)
15–39	90 (85–94)	93 (88–97)	95 (90–98)
0–4	100 (81–100)	96 (80–100)	100 (90–100)
5–9	100 (90–100)	97 (85–100)	96 (87–100)
10–14	100 (93–100)	98 (89–100)	91 (80–97)
15–19	97 (85–100)	100 (88–100)	100 (91–100)
20–24	86 (71–95)	100 (88–100)	91 (76–98)
25–29	94 (82–99)	78 (62–89)	100 (89–100)
30–34	95 (82–99)	100 (89–100)	83 (64–94)
35–39	76 (59–89)	100 (87–100)	100 (83–100)
0–9			
Male	95 (75–100)	100 (91–100)	98 (89–100)
Female	100 (88–100)	90 (73–98)	94 (80–99)
10–39			
Male	93 (88–97)	94 (88–98)	89 (82–94)
Female	95 (88–98)	97 (91–100)	100 (96–100)

Denmark and G. Soltész, Univ. of Pécs, Hungary) and of the Insulin-dependent Diabetes in young Adults (IDA) study (15–39 years; coordinator: K. O. Kyvik, Univ. of Odense, Denmark).

In the same 15-year period, 2928 antibody-positive diabetic patients were prospectively recruited nationwide by the BDR [13]. All the patients fulfilled the following criteria: (1) Belgian residency for at least 6 months prior to diagnosis, (2) primary diabetes (no gestational, secondary or unknown type of diabetes), (3) Caucasian ethnicity, (4) demographic data and blood samples within 18 months after diagnosis, and (5) positivity for at least one type of autoantibody [autoantibodies against islet cell cytoplasm (ICA) as determined by indirect immunofluorescence, and antibodies against insulin (IAA), insulinoma-associated protein 2 (IA-2A) and glutamate decarboxylase (GADA) as determined by radiobinding assay] [14]. Comparison with the Antwerp district with near-complete case ascertainment has demonstrated that the Belgian group, with incomplete ascertainment (52% over the entire study period), is representative for the Belgian diabetic patients with diagnosis before age 40 years in terms of demographic, clinical and biological characteristics [5,8].

Data on the background population (1989–2003) were obtained from the National Institute for Statistics [15]. The study was approved by the ethical committees of the universities participating in the scientific projects of the BDR and informed consent was obtained from each subject and/or its parents in accordance with the Helsinki Declaration.

Statistical analysis

Differences between groups were assessed by Mann–Whitney U test for continuous variables and by χ^2 test with Yates' correction or Fisher's exact test,

when appropriate, for discontinuous variables. Poisson regression models were used to investigate trends in incidence rate according to age group, sex and calendar year and interactions among these variables. Two-tailed statistical tests were performed by SPSS for Windows 13.0 (SPSS Inc., Chicago, IL, USA) for personal computers, by STATA (STATA corporation, College Station, Texas, USA) for Poisson regression analysis and were considered significant at $p < 0.05$.

Results

Incidence rate according to age and gender – Antwerp

Between 1989 and 2003, the age- and sex-standardized incidence rate (95% CI) of the disease averaged 10.5 per 100 000 per year (9.8–11.3) in the age category 0–39 years. To facilitate comparison of our results with other epidemiological studies such as EURODIAB [2], IDA (Insulin-dependent Diabetes in young Adults) [7] (both European Union-sponsored), and DIAMOND (DIabetes MONDiale) (World Health Organisation-sponsored), patients were classified into two age categories: 0–14 years and 15–39 years at diagnosis. The incidence rate under 15-years age was significantly higher than that in the older group [$n/100\,000/\text{year}$ (95% CI); 0–14 years: 13.1 (11.7–14.6) vs 15–39 years: 9.0 (8.1–9.9); $p < 0.001$]. The majority of the patients (427 of 746 or 57%) were diagnosed after age 15. In this adult-onset group, the M/F ratio was strikingly increased [n/n (ratio) = 263/164 (1.60); $p < 0.001$] compared to the M/F ratio in the background population [n/n (ratio) = 2 452 774/2 370 916 (1.03)] in the age group 15–39 years and to the value in patients diagnosed under age 15 [n/n (ratio) = 166/153 (1.08)] [15]. Altogether, there was a male excess for diagnosis under age 40 [n/n (ratio) = 429/317 (1.35); $p < 0.001$ vs background population; n/n (ratio) = 3 696 391/3 563 319 (1.04)] [15].

Time trend in incidence according to age – Antwerp

The overall incidence of type 1 diabetes under age 40 did not increase according to calendar year in the period 1989–2003 ($p = 0.104$; Figure 1). However, comparison of the incidence in the age groups 0–14 and 15–39 years (Figure 1) showed a significant increase with time in the younger age group ($p = 0.008$) but not in the older ($p = 0.145$). This trend could not be explained by temporal changes in ascertainment levels over the study period (for more details, see Table 1). The age group 0–39 years was further stratified into 5-year age categories. It was found that the rising incidence was limited to the age groups under age 10 (Figure 2) in which the incidence almost doubled between the first and

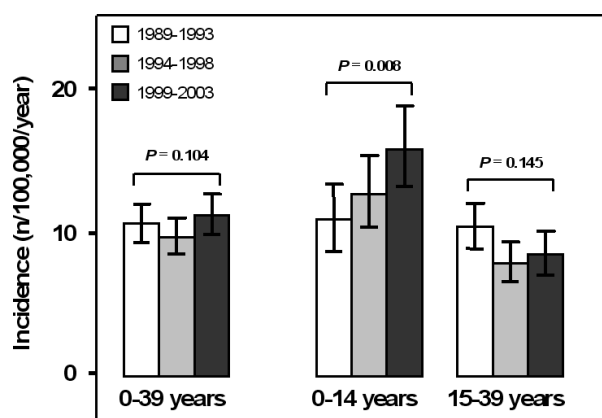


Figure 1. Incidence of type 1 diabetes in the Antwerp district according to calendar years (1989–2003) and age. Whiskers indicate 95% confidence interval (CI)

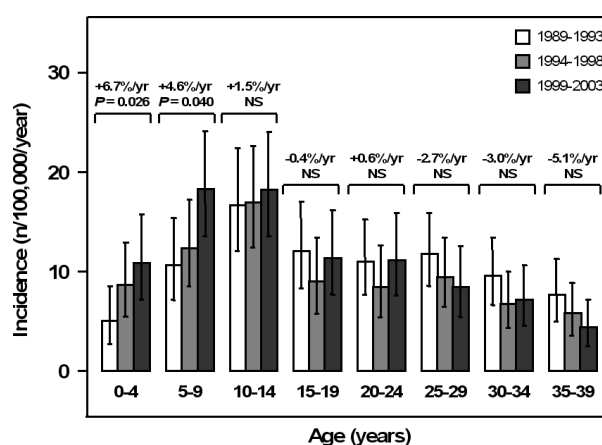


Figure 2. Incidence of type 1 diabetes in the Antwerp district according to calendar years (1989–2003) and age. Whiskers indicate 95% confidence interval (CI). Figures above bars represent the annual increase in incidence and significance by Poisson regression analysis between 1989 and 2003

last observation period of 5 calendar years [0–9 years: 7.9 (5.7–10.7) in 1989–1993 vs 14.5 (11.5–18.2) in 1999–2003; $p = 0.001$]. No such change was seen in the age group 10–14 years [16.7 (12.1–22.4) in 1989–1993 vs 18.3 (13.6–24.1) in 1999–2003; $p = 0.311$] or above age 15 (Figure 2).

To further analyse secular trends in incidence according to age, we performed Poisson regression analysis, which showed a significant difference in trend according to age at diagnosis ($p = 0.001$). There was an overall annual increase of 3.7% (95% CI: 1.0%, 6.4%) under age 15 paralleled by an annual decrease of 1.9% (95% CI: -4.1%, 0.2%) above that age. Annual rate of increase and significance for each 5-year age category are given in Figure 2.

Time trend in incidence according to age and gender – Antwerp

Stratification according to gender in the age group under age 10 showed that the standardized incidence rate significantly and gradually increased from

6.8/100 000/year (4.1–10.7) in 1989–1993 to 17.2 (12.7–22.9) in 1999–2003 in boys ($p < 0.001$; Figure 3). In contrast, the incidence in girls did not rise significantly ($n/100\ 000$ /year; $p = 0.536$: 9.0 (5.8–13.4) in 1989–1993 vs 11.9 (8.1–16.9) in 1999–2003; Figure 3]. Furthermore, no significant trend in incidence was found above age 10, both in males and females. The presence or absence of trends could not be explained by temporal changes in ascertainment levels between males and females (for more details, see Table 1). Poisson regression analysis confirmed the significant difference in trend according to gender in the youngest age groups. In boys under age 10, there was an annual increase in the incidence of 8.2% (95% CI: 3.2%, 13.5%; $p < 0.001$) while in girls the trend was not significant ($p = 0.362$).

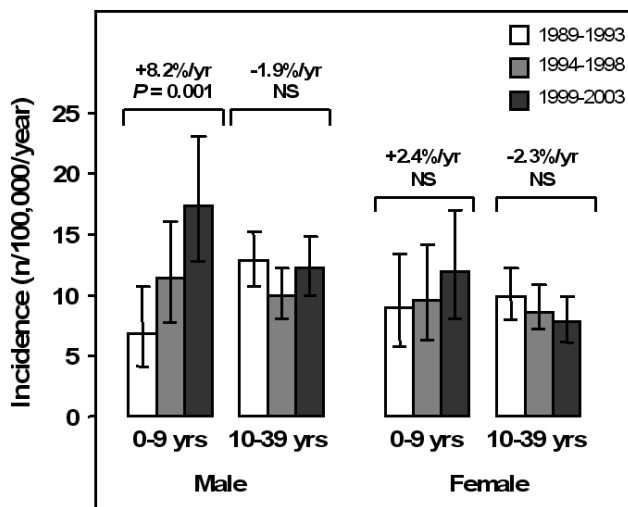


Figure 3. Incidence of type 1 diabetes in the Antwerp district diagnosed under age 10 according to calendar years (1989–2003) and gender. Whiskers indicate 95% confidence interval (CI). Figures above bars represent the annual increase in incidence and significance by Poisson regression analysis between 1989 and 2003

Age distribution according to gender – Belgium

Overall, median age (interquartile range, IQR) at diagnosis decreased from 18 years (11–27) in 1989–1993 to 14 years (8–25) in 1999–2003 ($p < 0.001$). The fraction of boys – but not of girls – diagnosed nationwide under age 15, and in particular under age 10, significantly increased at the expense of the fraction of subjects diagnosed after age 15 between 1989 and 2003 (Table 2). There were no changes in age distribution of the background population during the same period (not shown) [15]. In boys, we found a significant shift in median age at diagnosis (interquartile range) from 20 years in 1989–1993 to 15 years in 1999–2003 ($p < 0.001$), which was not observed in girls ($p = 0.311$; Table 2).

Discussion

In line with earlier reports from Belgium and Sweden [8,9], the present 15-year epidemiological survey shows that the incidence of type 1 diabetes arising before age 40 has overall remained stable in the Antwerp district between 1989 and 2003. However, during that period the incidence rate of type 1 diabetes diagnosed under age 10 progressively increased and almost doubled at the expense of a decreasing incidence in older age groups. Consequently, the age at diagnosis continues to decrease in Belgium. These observations further support the view that the worldwide rise in incidence of childhood diabetes [1,2,16,17] may be due to an anticipation of clinical manifestation rather than to a global increase in lifelong disease risk [8,9,18,19]. Our results also confirm the striking M/F excess in adult-onset diabetes [5,7,8], which contrasts with the strong female preponderance in other autoimmune diseases [20].

In addition, the present study indicates that the secular trend toward earlier clinical manifestation was largely restricted to boys under age 10, both in the Antwerp

Table 2. Age distribution expressed as percentage of all patients registered in the indicated observation period and the age at diagnosis of male and female antibody-positive type 1 diabetic patients recruited by the Belgian Diabetes Registry during 3 consecutive 5-year periods throughout Belgium

Age (years)	Male			P^a	Female			P^b
	1989–1993	1994–1998	1999–2003		1989–1993	1994–1998	1999–2003	
	$n = 432$	$n = 618$	$n = 645$	–	$n = 330$	$n = 482$	$n = 421$	–
0–4% ^c	6.0	8.7	12.1	0.003	9.7	8.9	11.9	0.325
5–9% ^c	9.5	15.5	17.2	0.002	16.4	16.4	18.3	0.699
10–14% ^c	19.4	18.1	20.3	0.613	20.9	22.8	22.6	0.795
15–39% ^c	65.0	57.6	50.4	<0.001	53.0	51.9	47.3	0.228
Age, median (IQR) ^d	20 (12–28)	17 (10–27)	15 (8–25)	<0.001	15 (9–26)	15 (9–26)	13 (9–25)	0.311

^aOverall chi-square test in male subjects: $p < 0.001$.

^bOverall chi-square test in female subjects: $p = 0.621$.

^cData are % of all patients registered in indicated observation period.

^dData are median (interquartile range); age distribution in the background population for male and female subjects remained constant in all periods: 0–4 years = 11%, 5–9 years = 11%, 10–14 years = 11%, 15–39 years = 67% [15].

district with near-complete case ascertainment [2,5,8] and nationwide as demonstrated in a group of almost 3000 antibody-positive recent-onset type 1 diabetic patients with incomplete (>50%) case ascertainment. Under age 10, the incidence rate more than doubled progressively in boys over the 15-year observation period, with a similar increment in the age groups 0–4 and 5–9 years in absolute terms but a larger relative increase under age 5.

Our study has several strengths: inclusion of subjects over a broad age range (diagnosis under age 40 and not only under age 15 as most other diabetes registries), a 15 year survey, and comparison with a large and representative group of patients. The small number of cases in Antwerp and the fact that nationwide a selection bias cannot be completely ruled out limits the study. However, a selective underregistration of female patients is highly improbable.

Gender-specific differences in time trends of diabetes incidence have, so far, mostly been investigated in patients diagnosed under age 15 [1–3,17], with conflicting results depending on the region and observation period [2,17,21–27]. Several studies reported different patterns of change between boys and girls [21–25]. Two small studies (Malta, 1980–1996; Devon and Cornwall, UK, 1975–2001) concluded to a more pronounced decrease in age at diagnosis and a faster increase in diabetes incidence in boys as compared with girls [24,25]. Other studies between 1965 and 2000 reported a rising incidence of type 1 diabetes in both sexes but noticed that the increase in boys preceded that in girls by years to decades (Finland and Sweden) [22,23] or was more pronounced in males, especially in an urban setting (Lithuania) [21]. Moreover, a positive correlation was found between incidence rates of childhood-onset diabetes worldwide and M/F ratio in patients [3]. In contrast, no differences in incidence time trends according to sex were found between 1989 and 2000 in other countries (e.g. Norway, Sardinia) or in the European EURODIAB ACE and TIGER studies [2,17,26,27]. However, large differences in patient numbers between centres, pooling of data and limited follow-up time might have blunted geographical variations in gender-specific incidence trends across Europe.

The observed gender-dependent differences in incidence of type 1 diabetes and its patterns of changes may reflect differences in lifestyle, hormonal status, metabolic demands or genetic susceptibility between males and females [28]. The observed rapid increases in the incidence are probably attributable to changes in external factors, rather than to shifts in the frequency of susceptibility genes [2,17,29]. Careful comparison of incidence trends with differences in environmental exposures according to age and gender over a long period and in different countries may provide further clues as to the nature of the external factors involved. Among the wide array of risk factors proposed so far, putative triggers of autoimmunity – such as viral infections or early introduction of cows' milk proteins – are less likely to drive the increasing

incidence of childhood diabetes [18,19,30]. However, it is noteworthy that males were found to be more prone to complications of enteroviral infections [31]. Furthermore, a Finnish study showed that boys are given infant formula and other supplementary foods at an earlier age than girls [32].

On the other hand, suspicion rests increasingly on factors that might accelerate pre-existing immune damage and beta cell destruction by overloading the insulin cells metabolically [18,19,33–35]. In any case, the proposed culprits should be able to explain the observed temporal, geographical and age- and sex-related differences in incidence. Factors acting early in life, even *in utero*, and preferentially in males should be considered in particular. Child growth, early weight gain, birth weight and maternal age at delivery have all increased over the past decades in many countries worldwide in parallel with other parameters of community wealth and risk of childhood type 1 diabetes [18,19,36–40]. In this respect, it is interesting to note that gender-dependent differences were found in the prevalence and secular trends of obesity, a well-known risk factor for type 2 diabetes, but also now for type 1 diabetes [18,34,38]. In several countries – including Belgium – but not in others, male subjects are more likely to be obese than females [41–44]. Furthermore, the increasing prevalence of childhood obesity has been related to television viewing, availability of computer games and early physical inactivity [45–47]. Regional and gender-dependent differences are likely to exist in this respect.

In conclusion, the present study has shown a selective and progressive anticipation of clinical onset of type 1 diabetes in boys, but not in girls, over a 15-year observation period in Belgium. This suggests that an environmental factor – or a combination of factors – may preferentially accelerate the sub-clinical disease process in diabetes-prone male individuals. This earlier presentation may further increase the burden of diabetes complications in future [48]. The possible implication of lifestyle habits associated with wealth and overfeeding may, however, create perspectives for prevention.

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Conflict of interest

None declared.

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