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Article

The incidence of Type I diabetes has not increased but shifted to a younger age at diagnosis in the 0–34 years group in Sweden 1983 to 1998

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Abstract

Aims/hypothesis. To analyse the incidence of Type I (insulin-dependent) diabetes mellitus in the 0–34 years age group in Sweden 1983–1998.
Methods. Incidence and cumulative incidence per 100 000 and Poisson regression analysis of age-period effects was carried out using 11 751 cases from two nation-wide prospective registers.
Results. Incidence (95%-CI) was 21.4 (20.8–21.9) in men and 17.1 (16.6–17.5) in women between 0 and 34 years of age. In boys aged 0–14 and girls aged 0–12 years the incidence increased over time, but it tended to decrease at older age groups, especially in men. Average cumulative incidence at 35 years was 748 in men and 598 in women. Cumulative incidence in men was rather stable during four 4-year periods (736, 732, 762, 756), while in women it varied more (592, 542, 617, 631). In males aged 0–34 years, the incidence did not vary between the 4-year periods (p=0.63), but time changes among the 3-year age groups differed (p<0.001). In females the incidence between the periods varied (p<0.001), being lower in 1987–1990 compared to 1983–1986, but time changes in the age groups did not differ (p=0.08). For both sexes median age at diagnosis was higher in 1983–1986 than in 1995–1998 (p<0.001) (15.0 and 12.5 years in males; 11.9 and 10.4 in females, respectively).
Conclusion/interpretation. During a 16-year period the incidence of Type I diabetes did not increase in the 0–34 years age group in Sweden, while median age at diagnosis decreased. A shift to younger age at diagnosis seems to explain the increasing incidence of childhood Type I diabetes. [Diabetologia (2002) 45:783–791]

Keywords Type I diabetes mellitus, incidence, secular trend, epidemiology.

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Abbreviations: DISS, Diabetes Incidence Study in Sweden; LADA, latent autoimmune diabetes in adults; ICA, islet cell auto-antibody; IA-2A, thyrosine phosphatase auto-antibody

The current theory is that Type I (insulin-dependent) diabetes mellitus develops in genetically susceptible individuals as a result of progressive autoimmune destruction of beta cells and environmental factors are believed to be involved both as triggers, modifiers and promoters of the disease occurrence [1, 2, 3, 4, 5]. Most epidemiological studies on the incidence of Type I diabetes have been performed in 0–14 years old children, due to ease of case ascertainment and straightforward classification. However, a large proportion of Type I diabetes cases are diagnosed later in life [6, 7, 8, 9].

During the last decades, an increase of childhood Type I diabetes incidence has occurred in many countries worldwide [10, 11], in Europe [12] and in Sweden [13]. However, little is known about the time trend in a broader age span [14, 15], as most of the registers covering diabetes incidence above the age of 14 years have been operating for a relatively short period of time.

Analysis of the variation of incidence over time could shed light on the causes of Type I diabetes, because changes in incidence, which can be described as age, calendar period or birth cohort effects, can be expected to reflect the temporal changes of the population exposure to environmental risk factors. In this report, we analysed a large data set containing 11 751 cases of Type I diabetes, prospectively registered over a period of sixteen years in two Swedish population-based diabetes registers, covering the age group 0 to 34 years. We studied the change of cumulative incidence by the age of 35 years over time, and used Poisson regression modelling to study the effects of age and time period. Age-specific incidence was also compared among people born during the 1990s, 1980s, 1970s, 1960s and 1950s.

Subjects and methods

Age group 0–14 years: Swedish Childhood Diabetes Study (SCDS). In the Swedish health care system all children aged 0–14 years with suspected diabetes are referred to paediatric departments. Since 1 July 1977, all 43 paediatric clinics in Sweden report newly diagnosed insulin-treated diabetes patients using a special form. This includes information about the patient's personal identification number, sex, county of residence, date of diagnosis (date when first insulin injection was given), date of reporting, reporting hospital and physician. Every 6 to 12 months the central register in Umeå requests the local contact person to verify and complete details about the recorded cases through the hospital medical records. The same methods of data collection and verification have been used since the start of the register. Comparisons with the registers of the Swedish Diabetes Association [16] and the Swedish Military Conscripts [17] showed that the Swedish Childhood Diabetes Register covered 96–99% of all cases 0–14 years old at diagnosis. During the sixteen-year period (1983 through 1998), 3664 boys and 3385 girls below the age of 15 years when diabetes was diagnosed were registered.

Age group 15–34 years: Diabetes Incidence Study in Sweden (DISS). Since 1 January 1983, all departments of internal medicine (n=96), paediatrics (n=43), endocrinology (n=3) and more than 700 primary health care units in Sweden report newly diagnosed patients with diabetes mellitus in the age group 15–34 years. Information about personal identification number, name, address, sex, date of diagnosis, physician's clinical classification of diabetes type (Type I, Type II, secondary, type unknown or not yet classified), date of reporting, reporting unit and physician and some clinical characteristics are filled in by the physician on a special form. Diabetes was diagnosed and classified according to clinical criteria as recommended by the World Health Organisation (WHO) [18, 19] as described in detail previously [20]. The actual classification into diabetes types was left to the physician's own judgement, based on the clinical impression at the time of diagnosis. According to common practice, severe hyperglycaemia, ketosis, low or normal body weight and an immediate need of insulin therapy are synonymous with Type I diabetes. Once a year the units who had reported at least one patient during the last year receive a list of reported patients, and every unit receives a list of patients reported since the start of the register in 1983.

During the first five years of the study (1983–1987), the completeness of ascertainment in the DISS was estimated in the two southernmost counties, covering 9.2% of the population aged 15–34 years by using a computer-based patient administrative register as a second source. The completeness of ascertainment was similar for males and females, being 86% for Type I diabetes [21]. A study in the county of Västerbotten in the Northern Sweden, covering 2.9% of the population and using a similar second source, found no obvious trend in the number of cases not reported to the DISS during 1986–1997. The completeness of ascertainment was 91% during the whole period, and during 1986–1991 and 1992–1997 it was 97% and 86%, respectively.

During the four 4-year periods of the study (1983–1986, 1987–1990, 1991–1994 and 1995–1998) 71.6%, 73.9%, 74.9% and 74.6% of all cases in the DISS were classified as Type I diabetes by the reporting physicians. The corresponding figures for cases which could not be classified as either Type I or Type II diabetes on clinical grounds at the time of diagnosis was 6.9%, 10.7%, 8.9% and 7.6%, respectively. The proportions of Type I, Type II and unclassified diabetes cases over time were similar in males and females. A total of 3052 male and 1650 female Type I diabetes cases were recorded 1983 through 1998 in the 15–34 years age group in Sweden.

Cases diagnosed with Type I diabetes between 1 January 1983 and 31 December 1998 were selected from both registers and merged into one data file, forming a large data-set of 6716 males and 5035 females below 35 years of age at diagnosis. To calculate the age-specific incidence rates according to the birth cohort, we have also included the 0–14 year old cases recorded in the Swedish Childhood Diabetes Study between 1 January 1978 and 31 December 1982 (n=1843). Population data were obtained from the Statistics Sweden.

Statistical methods. Age and sex specific incidence rates per 100 000 and year, and cumulative incidence per 100 000 were calculated. 95%-CI for the incidence rates were estimated assuming Poisson distribution of the cases. Direct age-standardisation of the incidence rates was performed assuming a standard population with equally sized five-year age groups. Poisson regression analysis of age-period effects was done using Egret for Windows (CYTEL, Cambridge, Mass., USA). For the Poisson regression analyses age was categorised into twelve 3-year age groups and calendar time into four 4-year periods (1983–1986, 1987–1990, 1991–1994, 1995–1998). Boys, 0–2 years age group and 1983–1986 years calendar period were used as reference categories. Median age at diagnosis during the 4-year calendar periods was compared using the Mann-Whitney test, as age at diagnosis was non-normally distributed.

In our material, the patients were born between 1948 and 1998 (0–14 years old between 1963 and 1998, 15–34 years old between 1948 and 1983). We calculated the age-specific incidence rates for 100 000 live births for five successive 10-year birth cohorts – people born in the 1950s, 1960s, 1970s, 1980s and 1990s. For people born during different time periods full data was available for varying age spans at diabetes diagnosis (1950–1959: 25–34 years; 1960–1969: 10–34 years; 1970–1979: 0–26 years; 1980–1989: 0–16 years; 1990–1997: 0–6 years). Every age category in the birth cohorts covered an interval from 2 to 10 calendar birth years.

Results

Incidence. Between 1983 and 1998, the average age standardized incidence in the 0–34 years group was significantly higher in Swedish males, 21.4 per 100 000 and year (95%-CI 20.8–21.9) than in females, 17.1 (95%-CI 16.6–17.5). The age distribution of the incidence for males and females 1983 through 1998 is presented in Figure 1. The incidence was low in children under one year of age (only 51 cases were diagnosed during the 16-year study period), but was already high in one to two year old children. The age-specific incidence pattern was similar for males and females. However, in females the incidence peak occurred about two years earlier and the incidence decreased and remained lower than in males afterwards. In children below the age of 15 years at diagnosis, the incidence of Type I diabetes did not differ between boys and girls, while in the older age groups it was significantly higher for the males (Table 1).

Figure 2 shows the age-specific incidence rates per 100 000 and year in 2-year age groups of males (A) and females (B) during four 4-year periods 1983 through 1998. A gradual increase over time occurred in boys aged up to 13–14 years and in girls aged up to 11–12 years at diabetes diagnosis, although the age of peak incidence appeared little changed. On the contrary, in the older age groups the incidence tended to decrease over time and was lower during the last 4-year period compared to the first one, especially in males (Fig. 2). Compared to 1983–1986 the age-adjusted incidence in the 0–14 years group in 1995–1998 was 23% ($p<0.001$) and 16% ($p=0.002$) higher in boys and girls, respectively (Table 1). In the 15–34 years group during the corresponding periods the age-adjusted incidence was 20% ($p<0.001$) lower in males, although in females the decrease was statistically not significant (12% ($p=0.07$)) (Table 1).

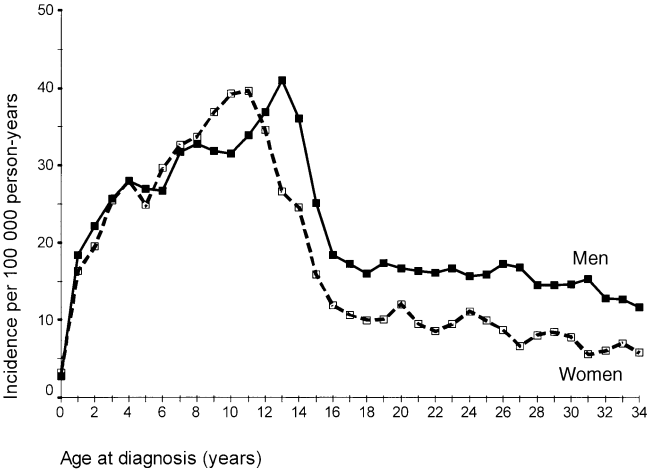


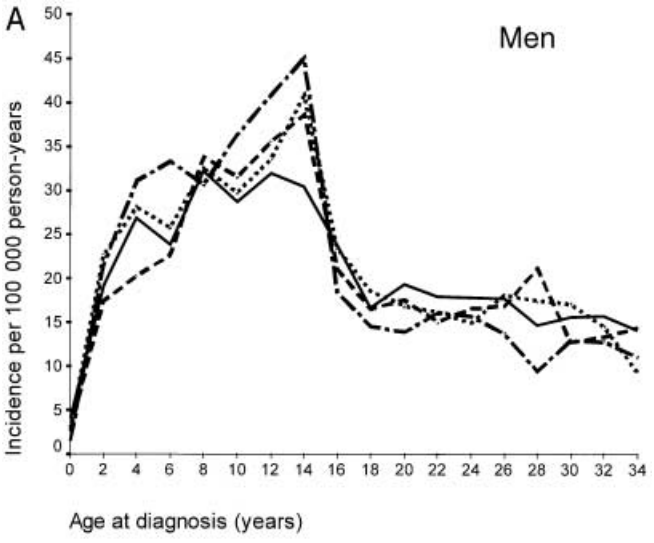
Fig. 1. Incidence of Type I diabetes per 100 000 and year in 0–34 years old Swedish males and females by age 1983–1998

Cumulative incidence. Figure 3 shows cumulative incidence curves up to the age of 35 years for males and females 1983 through 1998. By 15 years of age cumu-

Table 1. Number of Type I diabetes cases and mean incidence per 100 000 and year by age group and sex in the 0–34 years group in Sweden during four 4-year periods 1983–1998

	Age (years)	Cases (*n*) 1983–98	Incidence by period of diagnosis				Mean incidence (95%-CI) 1983–98
			1983–86	1987–90	1991–94	1995–98	
Male	0–4	853	19.2	15.3	20.8	22.1	19.4 (18.2–20.8)
	5–9	1284	28.1	29.6	29.0	32.7	30.0 (28.4–31.6)
	10–14	1527	30.9	35.4	35.9	41.8	35.9 (34.1–37.8)
	15–19	844	19.5	18.5	20.7	16.0	18.7 (17.5–20.1)
	20–24	778	18.5	16.1	15.2	15.4	16.3 (15.2–17.5)
	25–29	772	15.9	17.8	17.1	12.4	15.8 (14.7–16.9)
	30–34	658	15.2	13.6	13.5	11.6	13.4 (12.4–14.5)
	0–14[a]	3664	26.0	26.8	28.6	32.2	28.4 (27.5–29.4)
	15–34[a]	3052	17.3	16.5	16.6	13.8	16.1 (15.5–16.6)
	0–34[a]	6716	21.0	20.9	21.7	21.7	21.4 (20.8–21.9)
Female	0–4	772	18.6	13.2	18.8	23.2	18.5 (17.2–19.9)
	5–9	1282	28.7	26.0	34.0	36.2	31.5 (29.8–33.3)
	10–14	1331	32.5	32.0	33.4	33.7	32.9 (31.2–34.7)
	15–19	499	12.8	11.8	11.9	9.8	11.6 (10.6–12.7)
	20–24	462	9.0	10.4	10.3	10.7	10.1 (9.2–11.1)
	25–29	389	10.1	7.9	7.9	7.6	8.3 (7.5–9.2)
	30–34	300	6.8	6.6	6.7	5.8	6.4 (5.7–7.2)
	0–14[a]	3385	26.6	23.7	28.7	31.0	27.6 (26.7–28.6)
	15–34[a]	1650	9.7	9.2	9.2	8.5	9.1 (8.7–9.6)
	0–34[a]	5035	16.9	15.4	17.6	18.1	17.1 (16.6–17.5)

[a] Age standardized rates



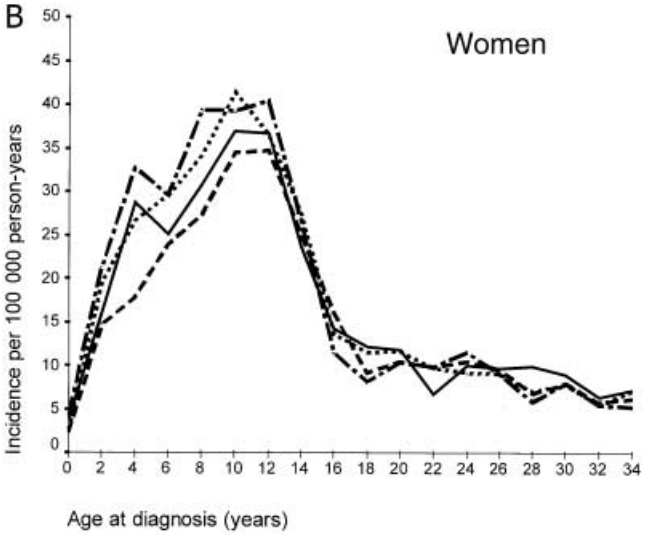


Fig. 2A, B. Incidence of Type I diabetes per 100 000 and year in 0–34 years old Swedish males (**A**) and females (**B**) by age (2-year groups) during four 4-years periods 1983–1998. 1983–86 (——); 1987–90 (- - - -); 1991–94 (·····); 1995–98 (-·-·-)

lative incidence was similar for males and females (426 and 415 per 100 000, respectively), while by 35 years of age, it was much higher for males (748 and 598 per 100 000 for males and females, respectively). Figure 4 shows the cumulative incidence curves up to the age of 35 years for males and females during four 4-year periods 1983 through 1998. In males the cumulative incidence per 100 000 by 15 years of age gradually increased (390, 402, 429 and 479), while it was rather stable by 35 years of age (736, 732, 762 and 756). During the last 4-year period (1995–1998), the increase in the cumulative incidence by 15 years of age coincided with a decrease of incidence in the older age groups, thus cumulative incidence did not increase further by 35 years of age. In

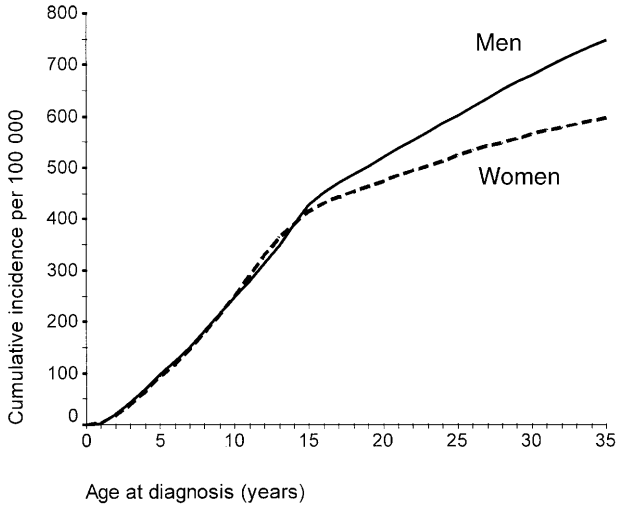
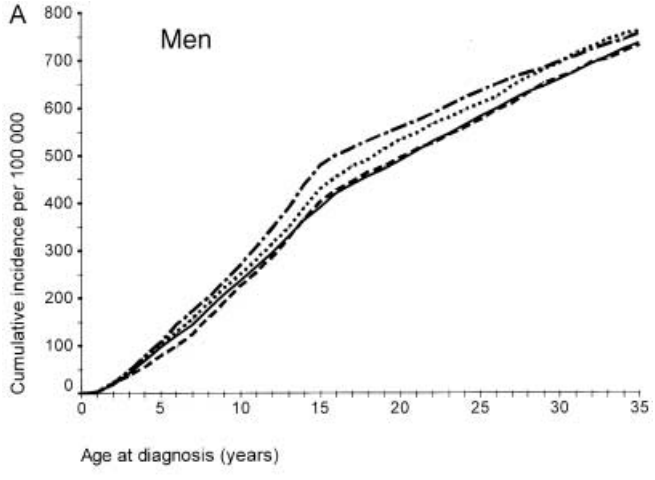


Fig. 3. Cumulative incidence of Type I diabetes per 100 000 in 0–34 years old Swedish males and females 1983–1998



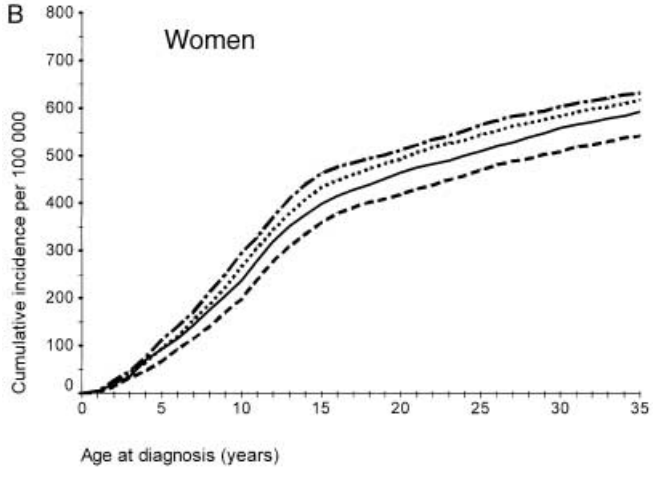


Fig. 4A, B. Cumulative incidence of Type I diabetes per 100 000 in 0–34 years old Swedish males (**A**) and females (**B**) during four 4-year periods 1983–1998. 1983–86 (——); 1987–90 (- - - -); 1991–94 (·····); 1995–98 (-·-·-)

Table 2. Poisson regression modelling of Type I diabetes incidence in 0–34 years age group in Sweden 1983–1998, with age (3-year groups) and calendar period (4-year periods) as categorical variables. Males, 0–2 years age group and 1983–1986 calendar period were used as reference

		Deviance	*df*	Likelihood ratio test Deviance		
				difference	*df*	*p* value
	1. constant (c)	4545.0	1119			
	2. c, age	1962.9	1108	2582.1	11	<0.001
	3. c, age, sex	1798.6	1107	164.3	1	<0.001
	4. c, age, sex, age*sex	1538.7	1096	259.9	11	<0.001
Female	5. constant	2673.6	559			
	6. c, age	748.5	548	1925.1	11	<0.001
	7. c, age, period	732.7	545	15.7	3	0.001
	8. c, age, period, age*period	687.9	512	44.9	33	0.08
Male	5. constant	1706.3	559			
	6. c, age	790.2	548	916.1	11	<0.001
	7. c, age, period	788.5	545	1.7	3	0.63
	8. c, age, period, age*period	704.1	512	84.4	33	<0.001

age*sex, age*period denote interaction terms between age and sex, and between age and period, respectively

females the cumulative incidence by 15 years of age was lower during 1987–1990, and rose above the value of 1983–1986 during 1991–1994 and 1995–1998, cumulative incidence during the four 4-year periods being 399, 358, 433 and 462, respectively. The same pattern was seen by the 35 years of age (592, 542, 617 and 631). During the last 4-year period (1995–1998), only a slight decrease of rates occurred in the older age groups in females, thus the cumulative incidence was increased both by 15 and 35 years of age.

Poisson regression modelling. Table 2 shows the results of the Poisson regression modelling of age, sex and calendar period effects in the 0–34 years age group. Incidence rates varied significantly depending on the age (model 2) and sex (model 3). The variation of the age-specific incidence rates differed between males and females (model 4), in agreement with Figure 1. Because of the age-sex interaction, the calendar period effect was modelled separately for the sexes. As shown in Table 1, the age-adjusted incidence in the 0–34 years age group did not vary between the 4-year periods in males (model 7). Compared to 1983–1986 the incidence was 2% (p=0.54) higher in 1995–1998. However, as can be seen in Figure 2A, the pattern of change by the time period differed between the 3-year age groups (model 8). In females the age-adjusted incidence in the 0–34 years group varied between the periods (Table 1, model 7). Compared to 1983–1986, the incidence was 8%

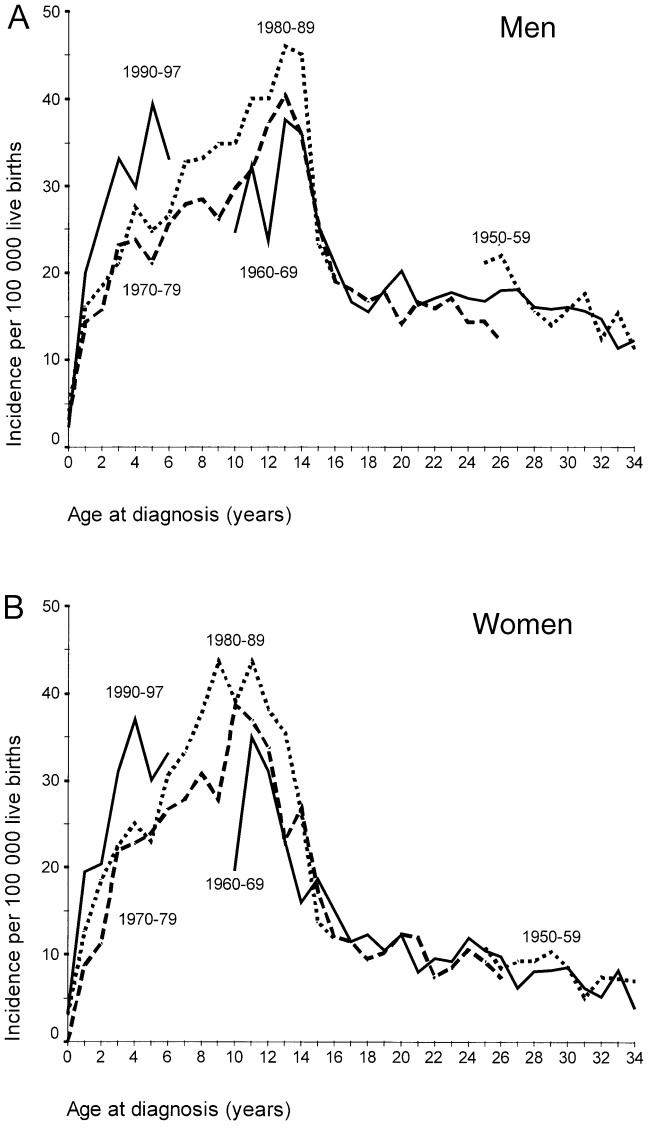


Fig. 5A, B. Age-specific incidence of Type I diabetes per 100 000 live births in 0–34 years old Swedish males (**A**) and females (**B**) born during the 1950s, 1960s, 1970s, 1980s and 1990s (separate line for every birth cohort)

(p=0.03) lower in 1987–1990, and tended to increase by 7% (p=0.10) in 1995–1998. The pattern of change by the time period tended to differ between the age groups in females as well, but did not reach statistical significance (p=0.08) (Figure 2B, model 8). Thus, no statistically significant increase in incidence has occurred in the 0–34 years group for either sex during the 16-year study period.

Age distribution during four 4-year periods. For both sexes median age at diagnosis in 1983–1986 was higher than in 1995–1998 (p<0.001) (15.0 and 12.5 years in males; 11.9 and 10.4 in females, respectively).

Birth cohort effects. Figure 5 shows incidence rates for 1-year age groups in five birth cohorts, each including 10-year birth intervals, except those born in the 1990s. There has been an increase of age-specific incidence in both boys and girls below 14 years of age at diabetes diagnosis in successive birth cohorts. Compared to children born during the 1970s and 1960s, age-specific incidence was higher for 7–14 years old children born during the 1980s, while for the youngest children, who were 0–6 years of age at diagnosis, incidence increased for the birth cohort of 1990s. However, no clear birth cohort effect could be seen in the older age groups, comparing the birth cohorts of 1950s, 1960s and 1970s.

Discussion

In this large study, using data from two prospective, population-based diabetes registers with good ascertainment, we found no increase of Type I diabetes incidence in the age group 0 to 34 years in Sweden during a 16-year period. However, median age at diagnosis had decreased. For both sexes, the change of the age-specific incidence over time had opposite directions below and above the age, where the highest age-specific incidence is reached.

Very few studies have analysed time trends of diabetes incidence in the age groups over 14 years at diabetes diagnosis. A tendency of an increase was found in both children (0–14 year) and young adults (15–29 year) in Turin (Italy) 1984 through 1996 [14]. In West Yorkshire, the incidence tended to increase in the 0–14, and was stable in the 15–29 years age group 1991 through 1997 [15]. However, both of these studies were rather small (817 cases in Turin and 885 in Yorkshire), and thus had a lower power to detect small changes, compared to our study.

There are some methodological issues, important for the interpretation of our results. The completeness of ascertainment of the two diabetes registers differs: it is higher in the SCDS than in the DISS (96–99% and 86–91%, respectively). There was no clear evidence of a decrease in the completeness of ascertainment for Type I diabetes over time in the DISS (see Methods). The completeness of ascertainment during 1992–1997 in the Northern Sweden was the same as during 1983–1987 in the Southern Sweden. However, it was about 10% lower during 1992–1997 compared to 1986–1991 in the Northern Sweden. Thus, although it is not likely that the tendency of a decrease in incidence seen in the age groups above 14 years of age should be the result of the differences in the case ascertainment only, our results should be interpreted with some caution.

Classification, based on the clinical impression at the time of diagnosis probably underestimates the true number of the Type I diabetes cases, especially in the older age groups, as it is difficult to distinguish the cases with Type II diabetes and LADA from their clinical characteristics [22, 23, 24]. Among the cases, not classified as Type I diabetes at the time of diagnosis in the DISS, about 30% are ICA-positive [25] and about 50% are positive for at least one auto-antibody (either ICA, GAD or IA-2A) [24]. Most of these cases probably have Type I diabetes, as 98% of the ICA-positive and 93% of those positive for any auto-antibody are treated with insulin six [26] and three [24] years after the diagnosis, respectively. Of the cases registered in the DISS, about 75% have clear clinical characteristics of Type I diabetes, thus 30–50% of the remaining cases could be wrongly classified, which would give a 7.5–12.5% higher incidence of Type I diabetes in the 15–34 years age group. The impact of the misclassification would, however, differ between the age groups, as the proportion of cases, not classified as Type I diabetes increases with age, being 8%, 20%, 29% and 42% in the 15–19, 20–24, 25–29 and 30–34 years age groups, respectively [25]. A similar classification based on clinical characteristics was used during the whole study period, and the proportion of cases classified as Type I, as well as the proportion of cases that could not be classified at the time of diagnosis, were stable over time (see Methods). Thus it seems that there has been no major shift in the classification of the type of diabetes over time. However, it should be kept in mind that the completeness of ascertainment for Type II diabetes in the DISS is low (estimated 53% during 1983–1987) [21], which makes it difficult to assess the true proportion of cases with LADA in the 15–34 years age group.

Our study indicates that Type I diabetes is not becoming more common, at least not by the age of 35 years in Sweden, but more patients are being diagnosed at an early age. However, it is difficult to estimate how much the results of the current study would be influenced by the inclusion of all cases with LADA in the 15–34 years group, or if the incidence of Type I diabetes was registered even after the age of 34 years. It is not possible to know whether, and to what extent, the observed increase in the incidence of Type I diabetes in childhood is due to a shift towards an earlier age

at diagnosis, or due to additional cases diagnosed during childhood, or both. If environmental risk factors promoting the disease process, or precipitating the diagnosis by increased insulin demand, have become more prevalent over the years, or the timing of the exposure to such factors has become earlier, this could have led to a clinical presentation of diabetes at an earlier age without increasing the total risk of the disease, a hypothesis which is in agreement with the results of the current study. Adverse changes in insulin sensitivity during the pre-diabetic period are thought to accelerate the rates of progression to frank hyperglycaemia and be important in determining the time of the clinical presentation [27, 28]. Indeed the highest age-specific incidence for both boys and girls in most countries coincides with the timing of puberty and age at peak height velocity, when insulin resistance physiologically increases [29, 30]. This also explains why the age at peak incidence has changed little over the years although median age at diabetes diagnosis has decreased. However, growth is associated with insulin demand even earlier in childhood. Already in the beginning of 1990's two Swedish case-control studies found that high linear growth rate [31] and weight gain [32] were associated with increased risk of childhood Type I diabetes. More recently higher BMI or relative weight in addition to increased linear growth throughout childhood, but especially during the first three years of life, were shown to be risk factors for the development of Type I diabetes [33, 34, 35]. Thus, increasing height, BMI and prevalence of overweight and obesity in the childhood population over time could have contributed to the observed changes in diabetes incidence. Mean BMI at the age of seven years has increased for both sexes in Stockholm schoolchildren born between 1963 and 1983, without changes in the mean height for the girls, but with an increase in height for the boys [36]. In a large population-based study in Sweden, a higher BMI gain between the age of 2 and 8 years was related to an increased gain in height during the same period, an earlier onset of puberty and less height gain in adolescence [37]. We therefore speculate, that over-nutrition of children could be a part of the explanation of the younger age at diagnosis of Type I diabetes, as it leads to increased growth in height, increased weight gain and BMI during the childhood, as well as an earlier onset of puberty, all associated with increased insulin resistance. Still it cannot be excluded that the activation of the autoimmune process by more, or new triggers has taken place in Sweden.

Our conclusions are based on cumulative incidence, calculated from cross-sectional data during four 4-year periods, and apply to the age span up to 35 years, although Type I diabetes can occur even later in life [6, 7, 8, 9]. However, mean BMI and the prevalence of overweight and obesity has increased in the older age groups of both sexes as well [38, 39, 40, 41]. Thus Type I diabetes cases that would have been diagnosed after 34 years age might be presenting earlier as well, masking the decrease of the incidence in the 15–34 years group. Interestingly, during the 1980s, mean BMI increased most in the 25–34 years age group in Sweden and more for women [38] than for men [39], which could, perhaps, partly explain why the decrease of Type I diabetes incidence was more pronounced in the 15–34 years old males than in females.

Analysis of age-specific incidence rates by birth cohort shows, that childhood Type I diabetes incidence has increased in successive birth cohorts. The most marked increases in incidence seems to have occurred for the 7–14 year-old children born during the 1980s and for the 0–6 year-old children born during the 1990s. However, no birth cohort extends over the whole age span yet, and the cohort born during the 1980s could only be followed until the age of 16 years. Thus, it is important to continue the follow-up of these birth cohorts for the confirmation of the results of the present study in a birth cohort material.

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