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Incidence trends in childhood onset IDDM in four countries around the Baltic sea during 1983–1992

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Summary We present secular trends of childhood onset insulin-dependent diabetes mellitus (IDDM) in Finland, Estonia, Latvia and Lithuania during the period of 1983–1992. Incidence data were obtained from the national IDDM registries. The average age-standardized incidence per 100 000/year was 35.0 in Finland, followed by 10.2 in Estonia, 7.1 in Lithuania and 6.5 in Latvia. A male excess in incidence was recorded in Finland (1.15) and Latvia (1.01). In all countries, the highest age-specific risk of IDDM was observed in the 11–13 year age range. The large difference in incidence between Finland and other Baltic countries was seen even in 1–2-year-old children. During the 10-year study period overall changes in incidence of IDDM were relatively small in these four countries. The incidence increased in Finland and Lithuania on average by 1 % and 1.4 % per year, respectively. A statistically significant increase was recorded only in 0–4 year old children in Finland, at 5.6 % per year. In Estonia, an 8.3 % increase in this age group, however, was not statistically significant. The different trends in the age-group specific incidence rates were confirmed in Finland. In conclusion, from 1983 to 1992 the incidence of childhood onset IDDM was increasing in Finland and Lithuania, while in Latvia and Estonia it was stable. There are still great differences in IDDM incidence between the countries around the Baltic Sea. [Diabetologia (1997) 40: 187–192]

Keywords Insulin-dependent diabetes mellitus, incidence, secular trends.

Incidence of childhood insulin-dependent diabetes mellitus (IDDM) is rising in many areas of the world [1, 2]. Despite the role of HLA genetics in the aetiology of IDDM being well known [3, 4] the role of putative environmental factors is not yet understood [5–7]. Epidemiologically based standardized surveillance systems provide information on the pattern of IDDM incidence which make comparison of IDDM incidence between countries within close geographical areas possible, thus offering an "indirect" way to trace potential environmental factors in the aetiology of IDDM. A collaborative study on the childhood IDDM incidence in countries around the Baltic Sea was started in 1989 named "DIABALT". Short-term data have demonstrated a wide variation in the incidence of IDDM between countries around the Baltic Sea [8, 9], from the highest incidence in the world in Finland to one of the lowest within Europe in Poland. In order to obtain more standardized rates for comparison of secular trends in incidence of IDDM in Finland, Estonia, Latvia and Lithuania the analyses of the data were carried out for the period 1983 to 1992.

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus.

Subjects and methods

Geographically the Baltic States of Estonia, Latvia and Lithuania are located on the south-east coast, while Finland is on the northern coast of the Baltic Sea. Genetically and culturally, the population of Finland is homogeneous [10], while Estonia

and Latvia have a considerable admixture of immigrant groups, mainly Russian in origin. In 1989, 61 % of the Estonian population were Estonian and 30 %, Russian [11]. Other ethnic groups in Estonia consisted of Ukrainians (3 %), Byelorussians (1 %), Jews, Polish and Latvians. In Latvia the proportion of native Latvians was 52 %, while Russians constituted 34 % [12]. The rest of the population consisted of 4.5 % Byelorussians, 3.5 % Ukrainians, Polish and Lithuanians. The admixture of Russian population in Lithuania was less than 10 % in 1989 [13], and is still decreasing. Other ethnic groups were Polish (7 %), Byelorussians (2 %), Ukrainians, Jews, Latvians and Germans.

The following standard case-definition criteria for childhood IDDM were used in all countries: 1) diagnosed as diabetic patient; 2) placed on insulin therapy before the 15th birthday; 3) resident of the country at the time of the first insulin administration.

Case ascertainment

Finland. The Central Drug Register of the Social Insurance Institution was used for the period 1983 to 1986. Since 1987, data from a prospective nationwide register for childhood diabetes were used. Hospital records of incident cases were used as the main data source (all newly diagnosed diabetic children are hospitalized for 1–2 weeks). Data from the Social Insurance Institution served as an independent data source for case ascertainment [14].

Estonia. The childhood diabetes register was compiled retrospectively in 1988–1989, starting from 1989 it has been done prospectively. Reports from district paediatricians were used as the main data source. Medical records from the Republic Endocrinology Center served as an independent source for case ascertainment [8, 9].

Lithuania. Data were collected prospectively using annual reports from regional paediatricians and endocrinologists. As a secondary data source (however not fully independent), annual statistics from the Ministry of Health were used. Since 1989, medical records of in-patient childhood endocrinology departments (which were established in 1989 and where all newly diagnosed diabetic children are hospitalized) were used as the main data source. Annual reports from regional paediatricians and endocrinologists remained as an independent source for case ascertainment [9, 15].

Latvia. Data were obtained from the prospective childhood diabetes register. Medical records from the department of endocrinology of the Children's Hospital were used as the main data source. Annual reports from regional paediatricians were used as an independent data source for case ascertainment [9].

Currently, all countries continue the prospective collection of incidence data within the framework of the World Health Organization (WHO) DIAMOND Project [16]. The degree of case-ascertainment was estimated according to the capture-recapture method [17]. Ascertainment ranged from 95 to 100 % in all the countries except Latvia where it was between 80 and 100 %.

Statistical analysis

The average annual incidence rates were calculated per 100 000 population per year. The mid-year populations aged 14 years and under were used as the denominator. The 95 % confidence interval was estimated assuming the Poisson distribution of the cases. Age adjustment of the rates was done using 5-year intervals (0–4, 5–9 and 10–14 years) with the proportions 1/3, 1/3 and 1/3, respectively as the standard according to the previous approach by the Diabetes Epidemiology Research International Study Group [18].

The change in IDDM incidence from 1983 to 1992 was estimated by fitting the linear regression with the annual incidence data. The change per unit in regression coefficient (regression slope) demonstrates the absolute change in incidence per year. The secular trend in IDDM incidence (relative change) was also calculated from logarithms of incidence using linear regression, where the regression coefficient is approximately the change per year as a percentage unit. The differences in incidence between the sexes, difference between the three age groups (0–4, 5–9, 10–14 years) and between two periods (1983–1985, 1990–1992) were tested with ANOVA procedure.

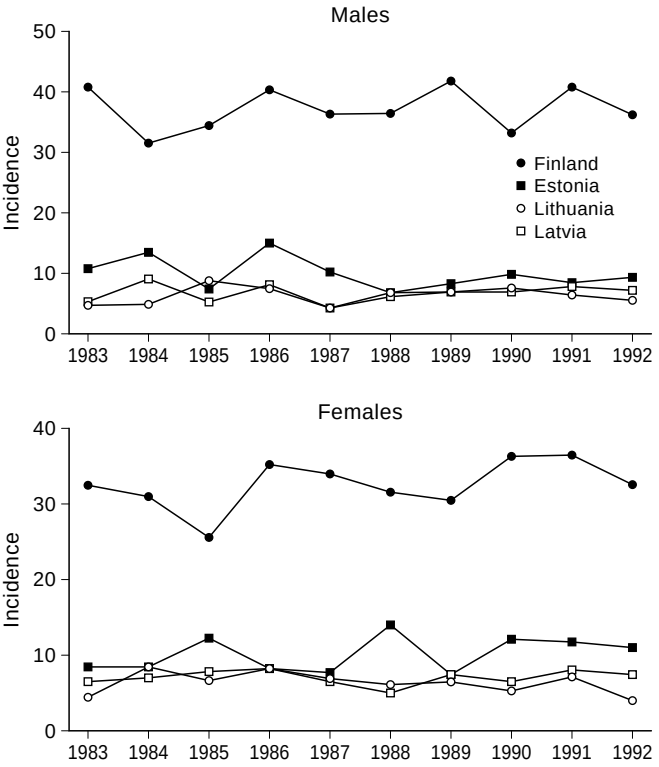

Fig. 1. Age-standardized incidence of IDDM in children aged 14 years or under in countries (Finland, Estonia, Latvia and Lithuania) around the Baltic Sea, 1983 to 1992

Results

The age-standardized incidence of IDDM in four populations during the 10-year study period is presented in Figure 1. The highest incidence (35 per 100 000/year) was found in Finland whereas in Estonia, Latvia and Lithuania the incidence was markedly lower (Table 1). The age distribution of IDDM incidence presented in Figure 2 showed that in all countries, the highest age-specific risk of IDDM was observed around 11–13 years of age. In males the highest IDDM incidence was recorded in the 10–14 year

Table 1. Incidence of IDDM (per 100000/year) in children aged 14 years or under in four countries around the Baltic Sea from 1983 to 1992

Country	Males				Females				All	
	Age (years)				Age (years)					
	0–4	5–9	10–14	All[a]	0–4	5–9	10–14	All[a]	All[a]	Male/female ratio[b]
Finland	25.5	40.4	46.3	37.4 (35.7; 39.1)	23.3	37.9	36.6	32.6 (31.0; 34.3)	35.0 (33.9; 36.2)	1.15
Estonia	4.3	9.7	16.5	10.2 (8.7; 11.8)	5.0	11.9	14.0	10.3 (8.8; 12.0)	10.2 (9.2; 11.4)	0.99
Lithuania	4.4	7.5	9.0	7.0 (6.2; 7.8)	3.3	8.7	9.8	7.2 (6.4; 8.1)	7.1 (6.5; 7.7)	0.97
Latvia	3.3	5.5	11.0	6.6 (5.7; 7.6)	3.4	6.7	9.3	6.5 (5.6; 7.5)	6.5 (5.9; 7.2)	1.01

[a] Age-standardized incidence and 95 % confidence intervals for children aged 14 years or under; [b] male to female ratio in age-standardized incidence

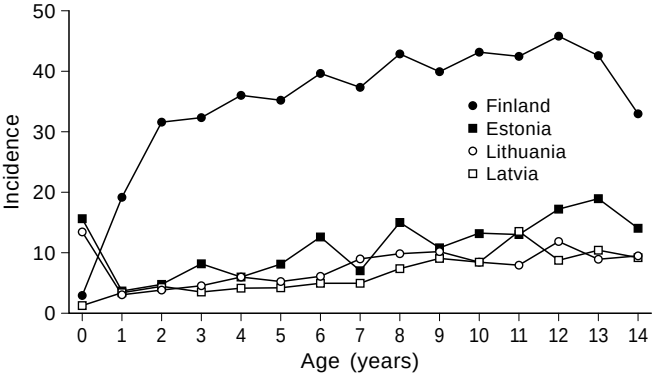

Fig. 2. Age distribution of IDDM incidence in children aged 14 years or under in countries (Finland, Estonia, Latvia and Lithuania) around the Baltic Sea 1983 to 1992

age group in all populations. Similar patterns existed for females in all countries except Finland, where the highest incidence was in 5–9-year-olds. The large difference in incidence between Finland and the three Baltic republics of Estonia, Latvia and Lithuania was seen also among 1–2-year-old children. A male excess in incidence was recorded in Finland (1.15), whereas in other countries no clear difference in incidence between sexes was seen.

Regression-based linear trends in IDDM incidence during 1983–1992 for each country is shown in Figure 3. Results of the regression models (Table 2) showed an increasing incidence of IDDM in Finland and Lithuania. The average increase in incidence, estimated from the regression coefficients, was 0.32 and 0.09 per 100000/year, respectively, and the increase in incidence per year during 1983–1992 was 1 % in Finland and 1.4 % in Lithuania, but these slopes did not reach statistical significance. There was no change in the incidence in Estonia and Latvia.

The age-group specific analyses showed a statistically significant increase in IDDM incidence in 0–4-year-olds in Finland ($p < 0.005$, Table 2), but not in children aged 5–14 years. On the contrary, the incidence in Lithuania increased in 5–14-year-olds. In Estonia, IDDM incidence slightly increased in 0–4-year-olds with a regression slope of 0.4 and 8.3 % change in incidence per year. However, due to the relatively small number of cases the results should be interpreted with caution.

Analysis of variance showed a significant age-group variation in incidence in all countries ($p = 0.0001$). Only in Finland was the incidence significantly higher in males than in females ($p = 0.004$). When comparing the first 3 years (1983–1985) with the last 3 years (1990–1992) of the study period, a significant variation was observed in Finland ($p = 0.047$). The statistically significant interaction between period and age group in Finland ($p = 0.015$) confirmed the observation of different incidence trends among the three age groups. When separately analysing the 0–4 and 5–14-year-age groups, the period effect ($p = 0.005$) and the interaction between the age group and period in Finland became more pronounced ($p = 0.005$). In Finland, the incidence rate ratio between 10–14-year-olds and 0–4-year-olds changed from 2.1 during 1983–1985 to 1.4 during 1990–1992.

Discussion

The variation in IDDM incidence among the countries around the Baltic Sea during 1983 to 1992 remained almost the same as reported earlier in the 1980s [9]. The incidence in Finland was 3–5 times higher than in the Baltic republics of Estonia, Latvia and Lithuania. The reason for such a large difference in incidence within relatively small geographic area is unknown. One theory is that the pool of individuals genetically susceptible to IDDM has been increasing more in some countries than in others [19]. This may be partly associated with different survival rates of young onset IDDM patients. Data from Estonia show a lower survival of childhood onset IDDM patients compared with Finland.

In Finland and in many other industrialized countries, perinatal mortality rates for diabetic pregnancies have decreased since the 1970s and now they are approaching those of the general population [20, 21]. Results from the Joslin Diabetes Center, Boston,

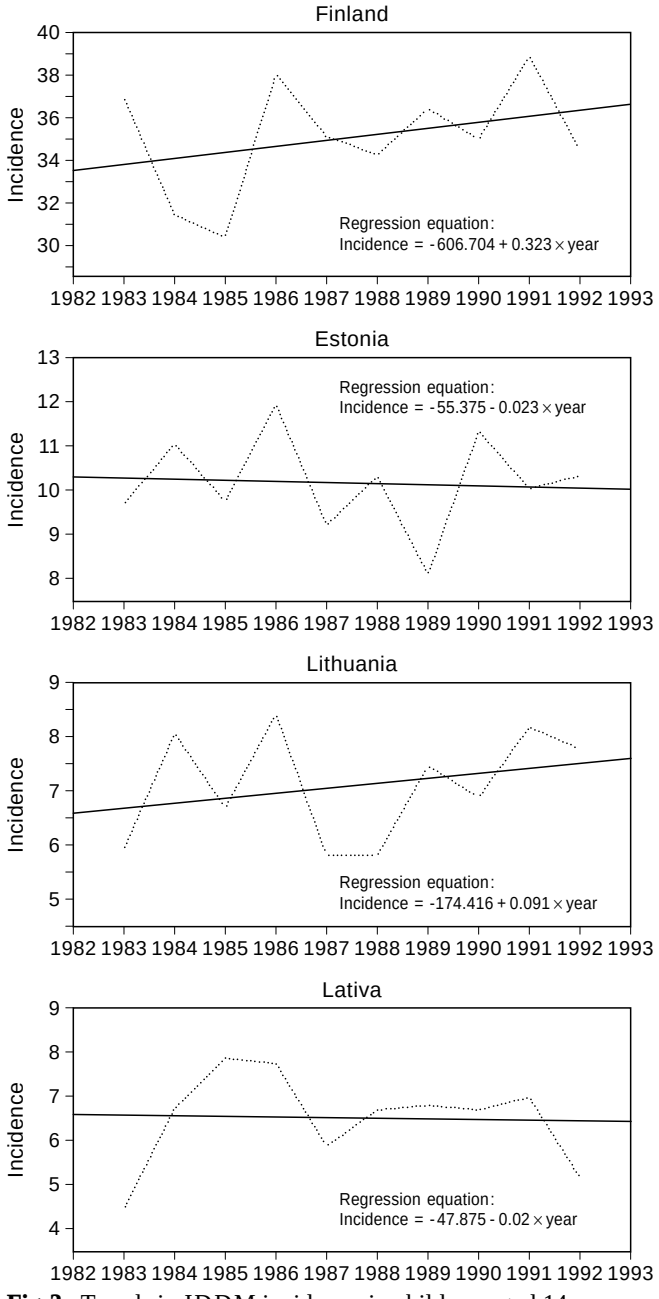

Fig. 3. Trends in IDDM incidence in children aged 14 years or under in countries (Finland, Estonia, Latvia and Lithuania) around the Baltic Sea 1983 to 1992

Mass., USA show that perinatal mortality of diabetic pregnancies was 23 % before 1961. After a dramatic drop in 1961 it stabilized around 14 % until 1975, and since then it has decreased to 4 % [22]. It has been shown that half of the fetal deaths occur due to poor metabolic control of mothers with IDDM or gestational diabetes, HbA_{1c} (assessed by chromatographic methods with ranges of 5–8 % representing healthy metabolism) also has a significant and independent effect on severe neonatal morbidity [23, 24]. The review of existing data on the determinants of perinatal outcome in diabetic pregnancies concluded that metabolic control during gestation is more important than duration of diabetes [25]. Maternal mortality of diabetic pregnancies followed the same pattern as perinatal mortality [20, 21, 24, 26].

Marked differences in specific health indicators exist between Finland and the Baltic republics. Perinatal mortality in Estonia, Latvia and Lithuania – 16.0; 18.7; 15.6 per 1000 births, respectively [27] – is extremely high compared with 4.4 in Finland [28]. Also, overall maternal mortality rates differ greatly, with an average rate of 31 per 100 000 live births in the Baltic republics compared to 4.7 in Finland [29]. No comparable data on perinatal and maternal mortality rates in diabetic pregnancies exist in Estonia, Latvia and Lithuania. However, higher mortality rates in the general population, as well as overall deterioration in the public health situation over the last few years, cannot suggest selective stabilization or even improvement in health of diabetic patients. Although we do not have data for comparison of metabolic control between countries, the recent findings from Lithuania show that the mean HbA_1 of diabetic children was 12–14 % during 1992–1994 [30], which is extremely high compared with internationally accepted levels of metabolic control, which according to Diabetes Control and Complications trial (DCCT) criteria should be less than 8.4 % [31].

The reasons for the high and increasing IDDM incidence in Finland are unknown and can only be speculated. It is possible that a pool of genetically susceptible individuals has increased in Finland during the past decades more rapidly than in Estonia, Latvia and Lithuania; although at present we do not have sufficient data, this possibility cannot be excluded.

The incidence of IDDM varies markedly within Europe, even within relatively small areas. In the former eastern European countries incidence is lower than that on average in the rest of Europe. However, there seems to be marked similarity in incidence among these countries, despite the wide variation both in their genetic background and physical environment, due to the great geographical distance (about 3300 km) in south-north direction between countries. The identical socio-economic systems and uniform health care systems associated with poor control of IDDM, high morbidity and mortality in IDDM and high infant mortality suggest that these factors may have prevented the increase in the genetic pool predisposing to IDDM.

In Estonia, non-Estonians have a significantly lower risk of IDDM compared to native Estonians [11]. It is very likely that similar differences in IDDM risk exist in Latvia. Thus, part of the incidence variability between the Baltic republics may be due to ethnic differences. Simultaneously, non-Estonians (mainly Russians) living in Estonia had significantly higher risk of IDDM compared to the population of

Table 2. Regression slopes and the regression-based change in IDDM incidence in children aged 14 years or under in four countries around the Baltic Sea from 1983 to 1992

Country	Age group						Males		Females	
	0–4 years		5–9 years		10–14 years					
	Regression slope	Change per year (%)	Regression slope	Change per year (%)	Regression slope	Change per year (%)	Regression slope	Change per year (%)	Regression slope	Change per year (%)
Finland	1.31[a]	5.56[a]	–0.24	–0.57	–0.19	–0.50	0.16	0.48	0.49	1.54
Estonia	0.45	8.34	–0.45	–4.79	–0.05	–0.42	–0.32	–2.84	0.29	2.85
Lithuania	–0.02	–0.93	0.08	1.17	0.23	2.31	0.13	2.27	0.05	0.72
Latvia	–0.05	–2.78	0.05	0.96	–0.03	–0.24	0.08	1.78	–0.13	–1.83

[a] $p < 0.01$

Novosibirsk, Russia. Therefore, the observed difference in IDDM risk in Russians might be due to higher prevalence or intensity of some environmental causal agents in Estonia [32].

Population-based case-control studies have shown an association between a short duration of breast-feeding, early introduction of cow's milk, and an increased risk of IDDM [33–35]. Although the frequency and duration of breast feeding has increased in Finland [35] during the last decade, IDDM incidence has increased significantly in children aged 4 years or under. In comparison, the duration of breast feeding in the Baltic republics, which have markedly lower IDDM incidence, has been and still is very short. In Lithuania [13] less than 30 % of children are breast-fed until the age of 2 months, and cow's milk is introduced very early in life. In Estonia only 21 % of infants were breast-fed for more than 3 months in 1994 (T. Podar, personal communication). It is very likely that the duration of breast feeding in Latvia is similar to that of Lithuania and Estonia. From the epidemiological and immunological point of view it seems that the duration of breast feeding and early introduction of cow's milk do not explain the difference in IDDM incidence between countries around the Baltic Sea.

During the 10-year period studied IDDM incidence significantly increased only in Finland in the 0–4 year age group. It has been proposed, that about 25 % of IDDM cases could be explained by existence of two specific high-risk HLA haplotypes [36]. Although Finland and Estonia are ethnically quite similar, the incidence of IDDM in Estonia is closer to the level seen in Lithuania and Latvia than that in Finland. In order to explain the existing differences in incidence by genetic means HLA genotyping of multiplex diabetic families (with an IDDM child diagnosed under 15 years of age) from Finland and Estonia has been performed. No Estonian diabetic patient possessed the A2,C1,B56,DR4,DQ8 haplotype which is the third most common transmitted "diabetic" haplotype in Finland with the highest absolute risk of IDDM [37]. Most probably, Finns and Estonians have quite different genetic susceptibility for IDDM. Whether the higher incidence in Estonians than in Russians is somehow related to their genetic similarity with the Finns needs to be addressed in comparative genetic studies.

Although a period of 10 years is obviously too short to describe time trends in IDDM incidence adequately the results show that large difference in incidence between Finland and the Baltic republics has not markedly changed during the last decade. Major political and economical changes in the Baltic republics have since 1990 influenced lifestyles and environment which may induce changes in IDDM incidence trends. Therefore, longer periods are needed to draw conclusions about variability of IDDM incidence in time in countries around the Baltic Sea.

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