Comparison of Incidence of IDDM in Childhood Between Estonia and Finland, 1980–1988

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Objective: To compare nationwide incidence of childhood insulin-dependent diabetes mellitus (IDDM) in children aged 0–14 yr between Estonia and Finland during 1980–1988. For Estonia, which has a population genetically and linguistically related to Finland, only limited information was available. Finland has the highest incidence of IDDM in the world.
Research Design and Methods: The registration of all new cases of IDDM in Estonia was conducted by the local district pediatricians who reported every newly diagnosed diabetic patient to the Republic Endocrinology Centre. Registration of all new cases of IDDM in Finland was based on the statistics of the Social Insurance Institution, which approves free-of-charge insulin treatment for diabetes. These data were validated with one or more additional data sources. The case ascertainment rate approached 100% in both countries.
Results: The average yearly incidence of IDDM standardized for age for the years 1980–1988 in Estonia was ~33% of that in Finland. Among males it was 11.3 (95% confidence interval [CI] 10.3–12.3) per 100,000 in Estonia and 35.1 (95% CI 33.4–36.9) per 100,000 in Finland, and among females 10.1 (95% CI 9.2–11.1) per 100,000 in Estonia and 30.4 (95% CI 28.8–32.1) per 100,000 in Finland. When the two periods 1980–1982 and 1986–1988 were compared, the age-standardized incidence in Estonia remained unchanged, whereas in Finland it increased ~20%. Conclusions: The data between two populations who are ethnically and linguistically similar and live geographically close but in a different environment, provides further evidence that both genetic and environmental factors are contributing to the risk of IDDM. *Diabetes Care* 14:982–88, 1991

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Insulin-dependent diabetes mellitus (IDDM) shows a wide geographic variation. This has been interpreted as evidence for both environmental and genetic etiological factors in IDDM (1). To produce the disease, environmental factors have to operate in genetically predisposed subjects (2). Epidemiological investigations of IDDM are important to determine the environmental risk factors, which are the main steps needed to develop measures for prevention (3).

Incidence data are available for most countries around the Baltic Sea including Norway, Sweden, Finland, Poland, East Germany, and Denmark but not for West Germany and the Baltic republics of Latvia and Lithuania. The highest incidence of IDDM has been registered in Finland (4). In Sweden and Norway, the incidence is also high (5). In Poland, on the other hand, the incidence of IDDM is one of the lowest in Europe, about five to six times lower than in Finland (5).

The main purpose of this report is to compare the incidence of IDDM in children in Estonia and Finland with standardized procedures in the estimation of the incidence between these two populations that share some, although not all, ethnic and linguistic background and who live close to each other.

RESEARCH DESIGN AND METHODS

Estonia lies on the southern coast of the Gulf of Finland (Fig. 1). The area of Estonia is ~45,000 sq km, and the

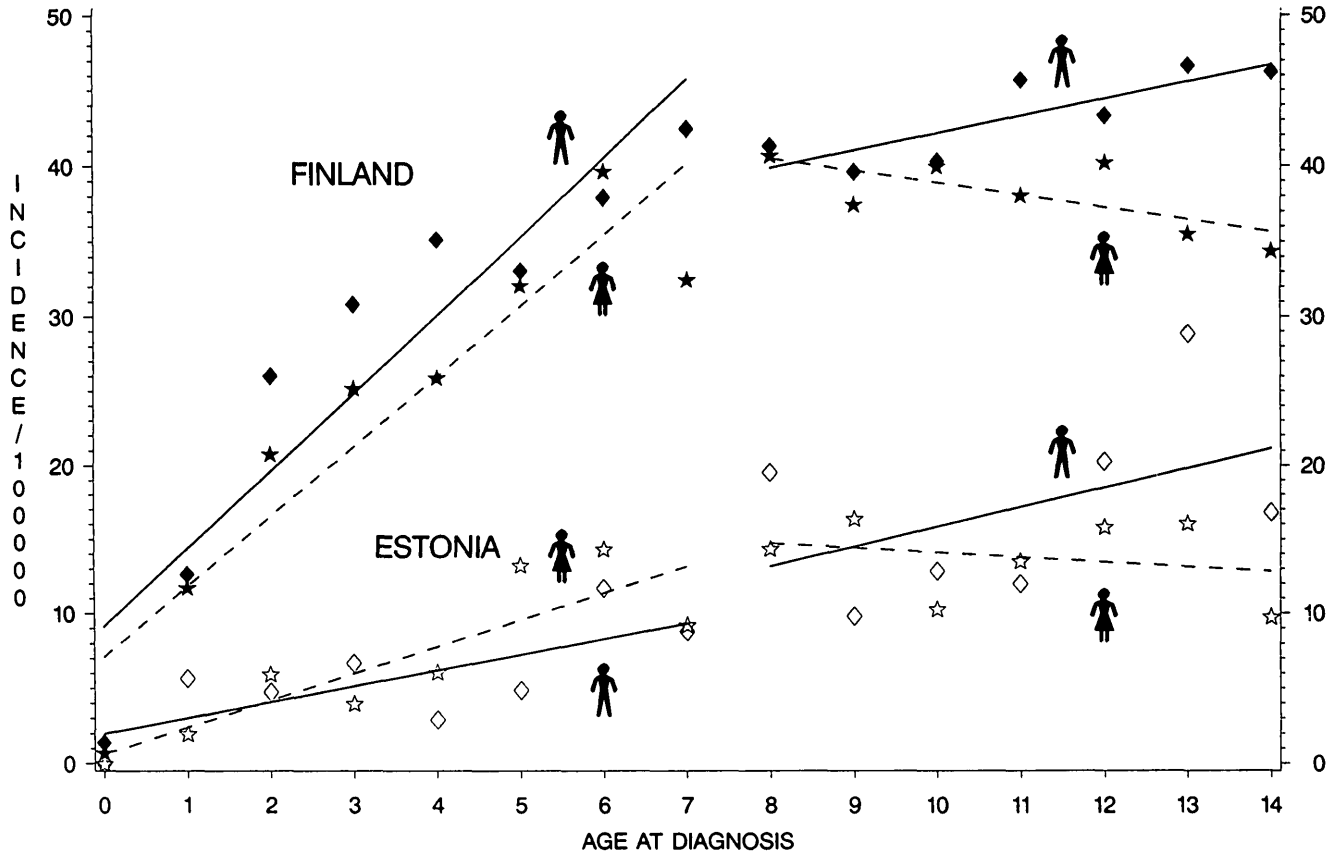

FIG. 1. Incidence of childhood insulin-dependent diabetes mellitus (IDDM) in Estonia and Finland by age and sex in 1980–1988. Linear regression lines have been estimated for 2 age-groups (≤7 or ≥7 yr) separately. ♦, Finnish males; ◇, Estonian males; ★, Finnish women; ☆, Estonian women.

population of Estonia was ~1.6 million in 1988. Estonia has been ruled by Danes, Swedes, Germans, and Russians for >700 yr. Since 1940, Estonia has been 1 of 15 constituent republics of the Soviet Union. Approximately 60% of the population of Estonia consists of Estonians and the rest are mainly Russians. The Estonian language belongs, like the Finnish and the Hungarian, to the Finno-Ugrian language group in contrast to most European languages that belong to the Indo-European language group.

The Estonian Childhood IDDM Registry for the years 1980–1988 was compiled retrospectively in 1988–1989 with procedures that met the criteria cited in the Diabetes Epidemiology Research International study (3). The criteria for the diagnosis of IDDM were *1*) diagnosis of diabetes by a physician, *2*) daily insulin injections from the time of diagnosis, *3*) age at time of first insulin administration <15 yr, and *4*) residence of the patient in the area of registration at the time of the first insulin administration.

For each patient, name, sex, ethnic background (Estonian or non-Estonian), date of birth, date of first insulin injection, and region of residence at the time of diagnosis were reported. Various sources of information were used to compile the registry. The main source was the reports from the district pediatricians. The health services in Estonia are divided into 15 districts. Because the number of IDDM cases is not very large and most of the district pediatricians have served for a relatively long time at their clinics, most childhood IDDM patients are well known to them. Death certificates of children who died in the main hospital in Tallinn, which treats children with IDDM, were reviewed. Subjects who migrated from Estonia after the diagnosis of IDDM were included in the registry if their main residence was in Estonia at the time of diagnosis. Additional data were obtained from district endocrinologists. For Tallinn, the capital of Estonia, reports from the follow-up clinic for adolescents (15- to 17-yr-old patients) were also used. Another data source that was used was the medical records of the Republic Endocrinology Centre in Tartu, Estonia, which receives referral consultations for the entire republic. Data collection methods of the recent registration of subjects with IDDM during 1988 are described elsewhere (6).

To estimate the completeness of the registry, the number of cases reported by all other sources was compared with the number of cases known to the Republic En-

TABLE 1
Results of case verification of Estonian Childhood Insulin-Dependent Diabetes Mellitus (IDDM) Registry

IDDM onset (yr)	Cases known to Republic Endocrinology Centre (*n*)	Confirmed by other sources (*n*)	Percentage of completeness
1980	6	5	83
1981	9	9	100
1982	18	17	94
1983	9	8	89
1984	9	9	100
1985	17	16	94
1986	16	15	94
1987	9	9	100
1988	5	5	100
Total	98	93	95

docrinology Centre. The results of the case validation procedure, which included 98 cases (31% of all registered cases) known to the Republic Endocrinology Centre, are given in Table 1. Ninety-three of 98 (95%) cases could be verified from all sources combined. For different years, this procedure gave an estimate of completeness from 83 to 100%.

Finland, a comparatively sparsely populated country (15.6 inhabitants/sq km) in the north of the Gulf of Finland, covers an area of 338,000 sq km. It has a population of ~4.9 million, of which 93.5% are Finnish speaking and 6.3% Swedish speaking. All IDDM patients or their parents receive reimbursement for the cost of insulin in Finland, which is approved by the Social Insurance Institution, and these patients are included in the Central Drug Registry. Rarely do the parents of a diabetic child or adolescent not seek reimbursement for the cost of insulin and thus not be included in the registry. Therefore, the ascertainment rate of childhood IDDM is ~100% in Finland. Comparison of the drug registry data and hospital discharge data conducted for northern Finland during 1970–1978 showed a good agreement between these two sources (7). Data from the nationwide prospective IDDM registry kept by the National Public Health Institute demonstrated that during 1987–1989 the Central Drug Registry missed only two newly diagnosed children with IDDM, both of whom died soon after diagnosis (J.T., unpublished observations). Although the purpose of the Central Drug Registry is to provide a basis for social security and health insurance, it is useful for epidemiological surveillance of IDDM. The data source of the Central Drug Registry has often been used to estimate the incidence and prevalence of IDDM in Finnish children and adolescents (1,4,5,7–12). Earlier reports from Finland covered data to 1984.

Statistical analysis. The incidence of IDDM was estimated for each calendar year and 1-yr age-group separately. For calculating the age-standardized incidence for the entire age-group 0–14 yr, the population distribution of Finland in 1980 by 1-yr intervals was used as the standard. The 95% confidence intervals for the incidence were computed assuming the Poisson distribution. The change in incidence during 1980–1988 was estimated by a linear regression model. In addition, we compared the two periods 1980–1982 and 1986–1988, because the trend in Finland obviously followed a nonlinear rather than linear pattern.

The heterogeneity of regression slopes between the two countries were tested separately for two age-groups: 0–7 and 8–14 yr. Variance analysis was used, i.e., SAS general linear models assuming a constant regression relationship among groups (13). The linear trend in the change in the incidence in both countries was tested with a regression model with the GLIM statistical package.

RESULTS

Between 1980 and 1988, 313 newly diagnosed cases of childhood IDDM were registered in Estonia (Table 2); 166 were male (119 Estonians and 47 non-Estonians) and 147 female (109 Estonians and 38 non-Estonians). In Finland, 2803 newly diagnosed cases were registered (1530 males and 1273 females).

The age-standardized incidence of IDDM among 0- to 14-yr-old children in Estonia was ~33% of that in

TABLE 2
Number of newly diagnosed insulin-dependent diabetes mellitus cases per year in Estonia and Finland by sex

	1980	1981	1982	1983	1984	1985	1986	1987	1988	Total 1980–1988
Males										
Estonia	18	11	26	20	22	13	26	18	12	166
Finland	137	159	161	199	153	168	197	175	181	1530
Females										
Estonia	11	20	19	14	13	20	14	13	23	147
Finland	127	141	126	151	143	119	163	153	150	1273
Total										
Estonia	29	31	45	34	35	33	40	31	35	313
Finland	264	300	287	350	296	287	360	328	331	2803

Finland (Table 3). In both countries, the overall incidence during 1980–1988 was ~10% higher in males than females. In Estonia, the highest incidence was recorded in 1982 and 1986, but the yearly average incidence did not change significantly during the study. In Finland, the highest incidence was recorded in 1983 and 1986. There was a 23% increase in the average incidence among Finnish males between the two periods 1980–1982 and 1986–1988 (31.1 vs. 38.1/100,000) and a 18% increase in Finnish females (28.1 vs. 33.3/100,000). The linear regression–based increase in the incidence was 2.5%/yr in Finnish children during 1980–1988. In males in both countries the highest incidence was observed around 12–13 yr of age (Table 4). In females, the incidence rose evenly in both countries up to the age of 5–6 yr to a level where it remained also during older age-groups. The GLIM regression models also showed a linear increasing trend in the incidence in Finland ($P = 0.001$) but no trend in Estonia ($P = 0.9$).

The rate of change in the incidence by age was analyzed for two truncated age-groups, 0–7 and 8–14 yr separately. In 0- to 7-yr-old children, the linear regression slopes for Estonia were significantly less steep than those for Finland ($P = 0.001$ for males, $P = 0.007$ for females; Fig. 1). The increment in the risk of diabetes per 1-yr increase in age was 1.98 for Estonian males, 1.79 for Estonian females, 5.23 for Finnish males, and 4.72 for Finnish females in the age-group <7 yr. There was no difference in the regression slopes between males and females in this younger age-group. Among 8- to 14-yr-old children, there was no statistically significant difference in the regression slopes between Finland and Estonia but the actual incidence rate was higher in Finland. A small and statistically significant difference in the regression slopes between males and females in both Estonia and Finland was observed among this older age-group. The slope was positive for the males in both countries and the increment in the risk of diabetes was ~1 per 1-yr increase in age. In females the increment was zero.

CONCLUSIONS

Data on the incidence of IDDM are available for most countries around the Baltic Sea. These data suggest a steep gradient in the incidence of IDDM (Fig. 2). An increase in incidence has been reported in several countries around the Baltic Sea (5,10–12,14,15). These epidemiological features make diabetes research particularly interesting in these countries.

A comparison of two populations, who share much of their ethnic and linguistic background and live geographically close, but in different environments, and

TABLE 3
Incidence of insulin-dependent diabetes mellitus (per 100,000 population) in children aged 0–14 yr standardized for age in Estonia and Finland during 1980–1988

	Males		Females		Both sexes	
	Incidence	95% Confidence interval	Incidence	95% Confidence interval	Incidence	95% Confidence interval
Estonia						
1980	11.5	8.7–14.9	7.3	5.1–10.2	9.4	7.6–11.6
1981	6.7	4.6–9.4	12.5	9.5–16.1	9.5	7.7–11.7
1982	16.4	13.1–20.4	11.1	8.3–14.5	13.8	11.6–16.4
1983	12.5	9.6–16.0	8.6	6.2–11.7	10.6	8.6–12.8
1984	13.5	10.4–17.1	8.1	5.7–11.1	10.9	8.9–13.1
1985	7.6	5.4–10.4	12.5	9.5–16.1	10.0	8.1–12.2
1986	15.3	12.0–19.1	8.8	6.3–11.9	12.1	10.0–14.5
1987	10.8	8.1–14.2	8.0	5.7–11.0	9.5	7.6–11.6
1988	7.3	5.1–10.1	14.4	11.2–18.2	10.8	8.8–13.0
1980–1988	11.3	10.3–12.3	10.1	9.2–11.1	10.7	10.0–11.4
Finland						
1980	27.6	23.2–32.7	26.8	22.3–31.8	27.2	24.0–30.7
1981	32.6	27.8–38.0	30.0	25.2–35.3	31.3	27.9–35.0
1982	33.1	28.3–38.6	27.5	22.9–32.6	30.4	27.0–34.0
1983	41.0	35.6–47.1	32.6	27.7–38.1	36.9	33.2–40.9
1984	32.2	27.4–37.6	31.2	26.4–36.7	31.7	28.3–35.5
1985	35.1	30.1–40.8	25.9	21.6–31.0	30.6	27.3–34.3
1986	41.0	35.5–47.0	35.6	30.4–41.4	38.3	34.6–42.4
1987	36.4	31.3–42.1	32.6	27.7–38.2	34.6	31.0–38.5
1988	37.0	31.8–42.7	31.5	26.7–37.0	34.3	30.7–38.2
1980–1988	35.1	33.4–36.9	30.4	28.8–32.1	32.8	31.6–34.0

TABLE 4
Number of new insulin-dependent diabetes mellitus cases per year in Finland and Estonia by age at diagnosis and sex (the years 1980–1988 are together)

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males															
Estonia	0	6	5	7	3	5	12	9	20	10	13	12	20	28	16
Finland	4	37	77	92	105	98	111	123	119	114	116	132	126	137	139
Females															
Estonia	0	2	6	4	6	13	14	9	14	16	10	14	15	15	9
Finland	2	33	59	72	74	91	111	90	112	103	110	105	112	100	99
Total															
Estonia	0	8	11	11	9	18	26	18	34	26	23	26	35	43	25
Finland	6	70	136	164	179	189	222	213	231	217	226	237	238	237	238

who differ with respect to cultural, behavioral, and environmental characteristics can be most informative to the assessment of potentially avoidable etiological factors. The results of this Estonian-Finnish comparison form the essential data base for more specific and extensive comparative studies of genetic and environmental risk factors for IDDM.

There are many anthropological and genetic studies that have addressed the issue of the origin of the Finns and Estonians and the relationship between these two populations. These include paleoanthropology (16), physical anthropology (17,18), and seroanthropology (19,20). It has been suggested, based on archeological grounds, that a large migration from Estonia to Finland took place ~2000 yr ago (20). Both in Finland and Estonia a significant East-West difference has been documented, reflecting the admixture with the nearby populations (17). Finns and Estonians display "eastern dental traits" with a peculiar combination of "western dental markers" (18). The immigration from Estonia stopped around A.D.1100. There are Finnish blood group features (called "eastern type") not found in any other European population except Finland and Estonia (20), but those in Estonia are diluted by ~50%. These characteristics occur among several Siberian tribes and increase toward Asia. Eastern influences are indicated by high A1 and B frequencies, and the additional high M frequency can be used to separate East Baltic elements from other eastern elements. The high A2 frequency in the Finns is probably due to the Lappish influence, which is rather low in Estonia. Overall, the M frequency in Finland is higher than that found in any other European population apart from the Estonians and Sardinians. This is interesting because the incidence of IDDM in Sardinia was recently reported to be almost as high as that in Finland (21). In the 1980s, a specific Baltic blood group, LWb, was described with a frequency of 6% in Finland, 8% in Estonia, and 12.5% in Lithuania (22). Thus, there are distinct and strong similarities among the Finns and Estonians that confirm they share a common origin. Many differences are due to the higher genetic admixture of Lappish genes in the Finns. The Lapps have relatively strong Mongoloid influences. Because IDDM is relatively rare among the Mongoloid populations, we can assume that this genetic difference between the Finns and Estonians does not contribute to the higher incidence of IDDM in Finland compared with Estonia.

The Estonian Childhood IDDM Registry, which meets the standard criteria of the Diabetes Epidemiology Research International group (1,5), provides reliable data for comparison with other populations. The yearly incidence of childhood diabetes in Estonia was approximately equal to that of many other European countries, about three times less than in Finland. The incidence of IDDM in Estonia remained on the same level between 1980 and 1988.

There is substantial evidence that the incidence of IDDM in Finland has been increasing during the past

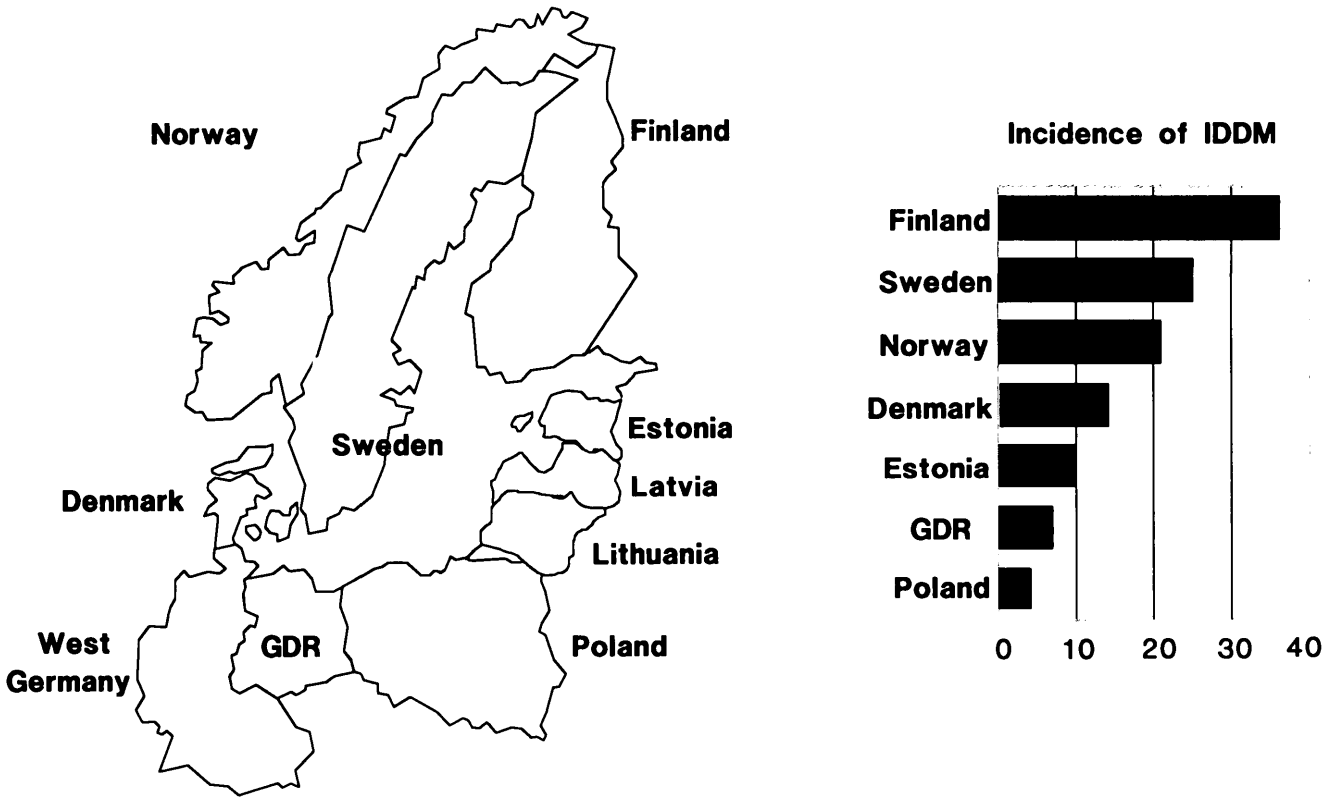

FIG. 2. Incidence of insulin-dependent diabetes mellitus in children aged 0–14 yr in different countries around Baltic Sea. *Bars* indicate average yearly incidence per 100,000. Data for Estonia and Finland are from this study and data for other countries are from Diabetes Epidemiology Research International Group. From the Diabetes Epidemiology Research International Group (1). © by the American Diabetes Association.

decades (10,11). The reason for the high risk of IDDM in Finland is not known. There might be some specific HLA haplotypes in the Finnish population that have not been found in other populations (23). The rapid increase in the incidence of IDDM in Finland strongly suggests the influence of environmental factors (3). A 20% increase was seen during 1980–1988 among Finnish children.

The incidence rose with age during the first 7 yr of life, less steeply in Estonia than in Finland. In 8- to 14-yr-olds the age relationship of the incidence of IDDM between the two populations did not differ. This could also be interpreted as evidence that suggests the importance of environmental factors in the etiology of IDDM. This indicates that etiological factors might operate early in life. These factors are still unidentified and will be the subject for in-depth studies.

We may speculate about the role of viral infections and diet that may possibly lead to the greater incidence of IDDM in Finland. According to this view, viruses may act as a triggering event unmasking the disease process that has already advanced to a preclinical stage (24,25). The vaccination programs are somewhat different between Estonia and Finland. For instance measles-mumps-rubella immunization was launched in Finland nationwide in 1982. However, there is no evidence that viral factors would account for the difference in the incidence between these two countries. This would mean that the penetration of viral infections would be increased in Finland. Dietary habits differ between Estonia and Finland markedly. Finland has a high consumption of milk products and coffee, which have been mentioned as possible initiators of the diabetogenic process early in life (26–28).

Part of the increase in IDDM incidence in several countries, including Finland, is due to the fact that children who develop IDDM survive and reach the age of reproduction. Before the discovery of insulin and still long after, a large proportion of diabetic children died early and the fertility rate was low in those who survived. Thus, the reduction in mortality increased the survival poulation attributable fraction of susceptibility genotypes to IDDM. Mortality in childhood IDDM in Finland is relatively low (29). Comparative data for Estonia are not available. However, we may speculate that the survival and fertility rate among IDDM patients has been lower in Estonia than Finland. If this is the case, a lesser frequency of susceptibility genotypes may be found in Estonia today.

In Estonia, further studies are needed to estimate the risk of IDDM in Estonia separately for Estonian and non-Estonian children; such a study is in process and preliminary information suggests that the incidence among the Estonians is somewhat higher than among non-Estonians

(T. Podar, unpublished observations). Now that the incidence data are established in a standardized way for Estonia and Finland, it is possible to start detailed studies into the differences in genetic and environmental risk factors for IDDM between the two countries.

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