

Articles

Worldwide increase in incidence of Type I diabetes – the analysis of the data on published incidence trends

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Abstract

Aims/hypothesis. Several reports on the incidence of Type I (insulin-dependent) diabetes mellitus have suggested that the incidence is increasing. The aim of this study was to find out whether the incidence is increasing globally or restricted to a selected populations only and to estimate the magnitude of the change in incidence.

Methods. During 1960 to 1996 37 studies in 27 countries were carried out. To fulfil the inclusion criteria the study periods ranged from 8–32 years. The temporal trend was fitted by linear regression, with the logarithm of the age-standardized incidence as the dependent variable and the calendar year as the independent variable. Then, the regression coefficient ($\times 100\%$) is approximately the average relative increase in incidence per year (as percentage).

Results. Results from the pooled data from all 37 populations showed that the overall increase in incidence

was 3.0% per year (95% CI 2.6; 3.3, $p = 0.0001$). The statistically significant increase was found in 24 of 37 populations including all high incidence (> 14.6 per 100 000 a year) populations. The relative increase was, however, steeper in the populations with a lower incidence. The correlation between logarithm of the incidence and the increase in incidence was $r = -0.56$, $p = 0.0004$.

Conclusion/interpretation. The incidence of Type I diabetes is increasing worldwide both in low and high incidence populations. By the year 2010 the incidence will be 50 per 100 000 a year in Finland and also in many other populations it will exceed 30 per 100 000 a year. [Diabetologia (1999) 42: 1395–1403]

Keywords Epidemiology, geographical variation, incidence, increase, modelling, prediction, trend, Type I diabetes.

The aetiology and natural history of Type I (insulin-dependent) diabetes mellitus are still not known but both genetics and environmental factors contribute to the development of the disease [1–3]. Although HLA genetics have a major role in the aetiology of Type I diabetes, other genes also contribute to the genetic effect, but the mode of inheritance of the disease is not clear [4]. The genetic effect contributes

70–75% of the susceptibility to Type I diabetes [5, 6]. Environmental factors possibly initiate or trigger the process which leads to the destruction of the beta cells and the onset of diabetes [3, 7, 8].

In the late 1970s epidemiological reports of diabetic children for the first time showed a wide geographical variation in the incidence of Type I diabetes. During the 1960s to the early 1980s the data on incidence of Type I diabetes were available for a few populations only, mostly from regions with a high or intermediate risk for this disease. A large number of registries had been established since the mid 1980s worldwide. The lack of standardized data made it difficult to determine the true magnitude of the worldwide variation in incidence or time trends [9]. The Di-

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abetes Epidemiology Research International Group (DERI) started the collection of the aggregate data on incidence of Type I diabetes in the late 1970s and the early 1980s [10]. The efforts of the DERI group led to an increase in the number of registries on diabetic children and to the establishment of the World Health Organization Project of Childhood Diabetes (DIAbetes MONdiale) in 1990 [11]. The collaborative research project EURODIAB ACE was established also in the late 1980s [12] to gather information of Type I diabetes in Europe. The latest reviews on the incidence of Type I diabetes among populations have indicated that differences in the incidence are 60-fold between the highest and the lowest rates [10, 12–14]. The highest incidence is found in Caucasoid populations, particularly in northern Europe, and the lowest rates are found in Asia and South America [13, 14].

Thus far only one trend analysis of the incidence of Type I diabetes comparing simultaneously several but yet a limited number of populations has been carried out by the DERI group [15]. The standardized procedures agreed upon for the incidence data collected around the world now permit a comparative assessment of temporal trends among several populations. We estimated the temporal trends in the incidence of Type I diabetes from incidence data collected through a systematic literature review. A statistical analysis of the data was done in order to find out whether the incidence is increasing globally. Another objective was to evaluate quantitatively the extent to which the change in incidence of Type I diabetes differs among populations.

Materials and methods

Literature search. The literature was searched using MEDLINE, direct examination of reference lists of the articles, hand searches of selected journals and published conference abstracts. By the closing date, 28th February 1999, more than 160 original publications reporting time series of the incidence of Type I diabetes were found.

Inclusion criteria. The publications were further evaluated with the strict inclusion criteria in order to choose appropriate studies for the quantitative analysis. The inclusion criteria were: 1) the study period was 8 years or more, 2) the incidence rates were presented for each year separately, 3) the number of cases per year was five or more, 4) in the papers in which the age standardization had been reported, the incidences had been estimated with age standardization according to the world population and, 5) Type I diabetes was diagnosed according to the WHO definition. Studies comparing incidence rates estimated with different methods during different periods were excluded. No requirement for a minimum case-ascertainment level of the data source was made as reliable case ascertainment estimation had usually not been done until the 1990s. The articles were evaluated by two independent reviewers according to the above-mentioned inclusion criteria.

Description of the data. Incidence data were obtained either from the tables or from the figures in the published articles. In approximately half of the original articles the annual incidence rates were presented in the tables and in another half in the figures only. The numbers derived from the figures were reconfirmed by the second reviewer. For Montreal (Canada), Allegheny County (USA), Scotland, Auckland (New Zealand), Prince Edward Island (Canada), Leicestershire (UK) and Wielkopolska (Poland) we used the original database of the DERI Study [15].

Altogether 37 studies from 27 countries met the inclusion criteria and were included in the analysis (Table 1). The registration of diabetic children was prospective in most of the studies. In 30 studies the age of children ranged from 0 to 14 years and in 7 studies from 0 to 15, 16, 17 and 19 years. The time period of the studies ranged from 8 to 32 years. The average length of the study period was 14.9 years (median 14 years). The estimates of the degree of case-ascertainment were high, ranging from 85 to 100%. The degree of ascertainment remained unspecified only in five studies. The studies included in the analysis were from the period 1960 to 1996.

Statistical methods. The incidence of Type I diabetes for our analysis was taken from the individual studies as it was reported in these publications. The incidence for the data obtained from the DERI Study [15] was calculated per 100 000 people a year. Age standardization of the rates was done using 5-year intervals with the proportions 33/100, 33/100 and 34/100 (for the age groups 0–4 years, 5–9 years, and 10–14 years respectively) as the standard according to the approach by the DERI Study Group [16], which is the same as the world population standard.

The temporal trend for each population was fitted by a simple linear regression under the assumption of normally distributed errors, with the age-standardized incidence as dependent variable expressed on a logarithmic scale and the calendar year as independent variable: $\ln \lambda_i(t) = \alpha_i + \beta_i t$, where $\lambda_i(t)$ denote the age-standardized incidence predicted at year t for population i ; the intercept α_i is different for each population, and β_i is the population specific regression coefficient (the trend), respectively. In such a multiplicative model the regression coefficient ($\times 100\%$) is a percentage, approximately being the average relative increase in incidence per year. The multiplicative regression model was used because it fitted the data well. It is commonly used in estimating time trends in incidence and allows a simple interpretation of the regression coefficient.

The overall estimate of the relative annual increase was obtained by using a pooled, centralized data set: to start, for each population the logarithms of the age-standardized incidence rates and the time points were centralized to make the different lengths of the studies and incidence levels more comparable. Then, using the method of least squares, a straight line constrained to cross the origin of the centralized coordinate system was fitted to the pooled data set. The regression coefficient has the same interpretation as in the population-wise analysis. The analysis was subsequently repeated as weighted regression, where the residual sum of squares was weighted with the number of cases in individual studies, to give more weight for observations with a higher number of cases.

The association between the level of incidence and increase in incidence was assessed by calculating the correlation coefficient between the logarithms of incidences in 1983 predicted by the model and the incidence increases estimated by the multiplicative model. The year 1983 was chosen because almost all studies covered it.

Table 1. The studies included in the analysis

Country: area	Study period	Length of study period (years)	Age-group (years)	Number of cases	Mean incidence (100,000/year)	Study design ^{a)}	Degree of ascertainment	Rates obtained from ^{b)}	Reference
Algeria: Oran	1979–1988	10	0–14	173 ^{c)}	4.7	P, R	?	F	36
Australia: West	1985–1992	8	0–14	350	14.9	P	99.6%	T	37
Austria	1979–1993	15	0–14	1551	7.8	P, R	> 90%	T	15, 38
Bulgaria, East	1974–1995	22	0–14	818	6.3	R, P	98.8%	T	39
Canada: Montreal	1971–1985	15	0–14	839	9.3	R	94%	T	40
Canada: Prince Edward Island	1975–1986 1990–1993	19	0–14	115	23.5	P	99%	T	41, 42
China: Shanghai	1980–1993	14	0–14	67	0.7	R	85.2%	F	43, 44
East-Germany	1960–1989	30	0–19	9581	6.7	P	99%	F	45
Estonia	1983–1996	14	0–14	523	10.2	P	92% ^{d)} 96% ^{e)}	T	42, 46
Finland	1965–1996	32	0–14	9047	30.3	P, R	100%	T	14, 47
France	1988–1995	8	0–19	1439	8.0	P	96%	T	48
Hungary	1978–1987	10	0–14	1060	6.1	P	96.2%	T	49
Iceland	1970–1988	19	0–14	120	9.0	P, R	100%	F	50
Israel: Yemenite Jews	1965–1993	29	0–17	1665	5.0	P	?	F	51
Italy: Turin	1984–1991	8	0–14	227	8.4	R, P	99%	F	52
Japan: Hokkaido	1973–1992	20	0–14	396	1.7	P	100%	F	53
Latvia	1983–1996	10	0–14	652	7.2	P	80–100%	F, T	54, 55
Libya	1981–1990	10	0–14	251	8.7	P	?	T	56
Lithuania	1983–1992	10	0–14	215	6.4	P	95–100%	F	54
Malta	1980–1996	17	0–14	90	14.7	P	?	F	57
New Zealand: Auckland	1977–1987	11	0–15	206	10.1	P	100%	T	58
New Zealand: Canterbury	1982–1990	9	0–19	123	12.7	P	100%	F	59
Norway	1973–1982	10	0–14	1914	20.8	R	99.4%	F	60
Peru: Lima	1985–1994	10	0–14	111	0.5	P	85%	T	61
Poland: Krakow	1987–1994	8	0–14	396	5.9	P	100%	T	62
Poland: Rzeszów	1980–1992	13	0–14	122	5.1	P, R	99%	F	63
Poland: Wielkopolska	1970–1985	15	0–16	451	4.4	P	> 95%	T	15, 64
Slovakia	1985–1995	11	0–14	1127	7.5	P	95%	T, F	65, 66
Sweden	1978–1992	15	0–14	5831	24.9	P, R	100%	F	3
UK: Leicestershire	1965–1981	17	0–14	248	7.8	P, R	97.6%	F	15
UK: Oxford	1985–1995	11	0–14	1037	18.5	P	?	T	67
UK: Plymouth	1975–1996	22	0–14	488	14.9	P	95.3%	F	68
UK: Scotland	1976–1993	18	0–14	4182	21.6	R	> 95%	T	15
UK: Yorkshire	1978–1992	15	0–14	1721	14.3	P	97.6%	F	69, 70
USA: Allegheny County	1965–1985	21	0–14	1041	14.7	P, R	100%	T	71
USA: Colorado	1978–1988	11	0–17	1376	7.8	P, R	93.3%	F	72
USA: Hawaii	1980–1990	11	0–14	113	12.3	P	97%	F	73

^{a)} P = prospective, R = retrospective ^{b)} F = figure, T = table ^{c)} families ^{d)} non Estonian ^{e)} Estonian

Predictions until the year 2010 have been made with both multiplicative and additive regression models, meaning that the curve produced by fitting the model to the data is simply extrapolated to the year 2010. In essence, the multiplicative model fits an exponential curve to the incidence, whereas the additive model fits a straight line. The additive regression model is used here to point out the differences between predictions when using alternative models.

Results

Incidence. The mean incidence of Type I diabetes among the study populations varied from 0.5 to 30.3 per 100 000 a year during the observation period (Table 1). The mean incidences were divided into quartiles: low incidence, less than 6.4 per 100 000 a year (the lowest 25% of the mean incidences), intermediate 6.4–14.6 per 100 000 a year (50% of the mean in-

cidences, thus the two intermediate groups combined), and high, more than 14.6 per 100 000 a year (highest 25% of the mean incidences).

Increase in the incidence of Type I diabetes. The relative change (% per year) in incidence among individual populations ranged from –0.2% in Colorado (USA) to 9.5% in Leicestershire (UK) (Table 2). A statistically significant increase in incidence was found in 65% (24/37) of the populations. An upward tendency in incidence not reaching statistical significance was observed in another 12 populations. Only in one population, Colorado (USA), the trend was slightly, but not significantly, negative (–0.2% per year) and the upper limit of the 95% confidence interval show that an increase of 2.2% per year was possible.

The global trend and the annual increase in the incidence of Type I diabetes were estimated from the

Table 2. Relative increase in incidence of Type I diabetes in children aged 14 years or less in 37 populations. The populations are arranged in descending order according to the rela-tive increase per year. The 95 % confidence interval is given in the parentheses. *P* value stands for the two-sided test for a non-zero regression coefficient

Country: area	Mean incidence	Increase in incidence % per year (95 % CI)	<i>p</i> value
UK: Leicestershire	7.8	9.5 (6.51; 12.53)	0.0001
Hungary	6.1	8.5 (6.50; 10.42)	0.0001
Algeria: Oran	4.7	7.9 (1.85; 14.00)	0.0338
USA: Hawaii	7.8	7.8 (1.80; 14.87)	0.0315
Peru: Lima	0.5	7.7 (-0.97; 16.40)	0.1197
China: Shanghai	0.7	7.4 (2.30; 12.51)	0.0148
Poland: Krakow	5.9	6.8 (2.27; 11.41)	0.0262
New Zealand: Auckland	10.1	6.4 (4.20; 8.52)	0.0003
Australia: West	14.9	6.3 (2.11; 10.50)	0.0259
Libya	8.7	6.3 (0.69; 11.8)	0.0589
Japan: Hokkaido	1.7	5.9 (4.14; 7.63)	0.0001
Slovakia	7.5	5.5 (3.64; 7.41)	0.0003
Poland: Wielkopolska	4.4	4.8 (1.94; 7.66)	0.0054
France	8.0	3.9 (2.85; 4.94)	0.0003
UK: Oxford	18.5	3.7 (1.82; 5.50)	0.0037
Canada: Prince Edward Island	23.5	3.2 (-0.33; 6.38)	0.0728
Israel: Yemenite Jews	5.0	3.2 (2.51; 3.88)	0.0001
Norway	20.8	3.2 (1.19; 5.22)	0.0143
Austria	7.8	2.7 (1.58; 3.76)	0.0003
UK: Plymouth	14.6	2.7 (0.91; 4.50)	0.0079
New Zealand: Canterbury	12.7	2.7 (-0.05; 10.50)	0.5262
UK: Scotland	21.6	2.5 (1.85; 3.08)	0.0001
East-Germany	6.7	2.4 (1.96; 2.90)	0.0001
Finland	30.3	2.3 (1.98; 2.57)	0.0001
Iceland	9.0	2.3 (-2.38; 6.96)	0.3498
Italy: Turin	8.4	2.2 (-3.99; 8.35)	0.5150
Bulgaria: East	6.3	2.1 (1.03; 3.15)	0.0010
UK: Yorkshire	14.3	1.9 (0.30; 3.53)	0.0372
Canada: Montreal	9.3	1.6 (-0.67; 3.82)	0.1937
USA: Allegheny County	14.7	1.5 (0.21; 2.83)	0.0348
Sweden	24.9	1.2 (0.42; 2.02)	0.0103
Poland: Rzeszów	5.1	1.1 (-3.25; 5.40)	0.6339
Lithuania	6.4	1.1 (-4.25; 6.41)	0.7023
Latvia	7.2	0.9 (-1.90; 3.75)	0.5350
Malta	14.7	0.5 (-2.15; 3.19)	0.7078
Estonia	10.2	0.4 (-0.96; 1.76)	0.5741
USA: Colorado	12.3	-0.2 (-2.52; 2.19)	0.8938
Change globally		3.0 (2.59; 3.33)	0.0001
Change globally (weighted by number of cases)		2.5 (2.32; 2.66)	0.0001

age-standardized incidence rates using the log-linear regression (Table 2). The *p* value of less than 0.05 for the two-sided test for a non-zero regression coefficient was regarded as evidence for the trend. The global annual increase was 3.0% (95% CI 2.59; 3.33, *p* = 0.0001) during 1960 to 1996, showing a highly significant increasing trend. When the annual incidence rates were weighted with the number of cases in each individual study, the increase in incidence was 2.5% (95% CI 2.32; 2.66; *p* = 0.0001). The estimated population-wise regression lines illustrate well the increasing trends (Fig. 1, 2).

Comparison of increase rates. The relation between the increase in incidence of Type I diabetes and the average level of incidence expressed as the incidence in 1983 estimated from the regression model is shown

in Figure 3. There was a significant inverse association between the increase and the logarithm of the level of incidence ($r = -0.56$, $p = 0.0004$). The association indicates that the relative increase was more pronounced in the populations with a low incidence. Nevertheless, in the five populations with the highest incidence the increase was also statistically significant, varying from 1.2 to 3.2% per year.

The incidence level of Type I diabetes and its increase seemed to be similar in some geographically adjacent populations. For example in the northern European countries; Finland, Sweden and Norway where the incidence of Type I diabetes has been high for a long time, the increase was 1 to 3% per year. Adjacent countries around the Baltic Sea, Estonia, Latvia, Lithuania and Poland with an intermediate or low incidence (4–10 per 100 000 a year) showed

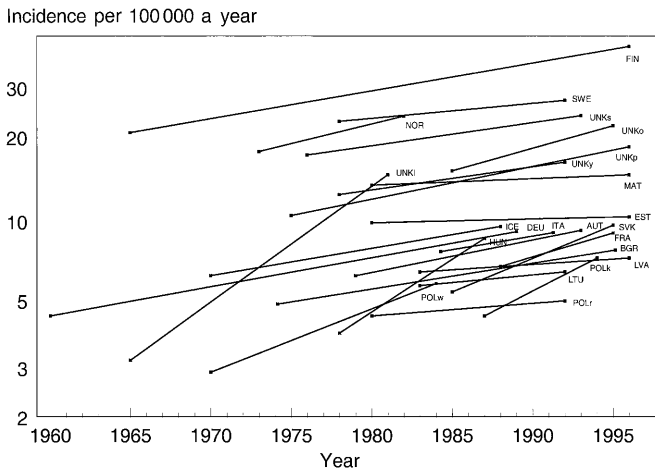


Fig. 1. Trends in incidence of Type I diabetes in European populations. AUT: Austria; BGR: Bulgaria; DEU: East-Germany; EST: Estonia; FIN: Finland; FRA: France; HUN: Hungary; ICE: Iceland; ITA: Italy (Turin); LVA: Latvia; LTU: Lithuania; MAT: Malta; NOR: Norway; POLk: Poland (Krakow); POLr: Poland (Rzeszów); POLw: Poland (Wielkopolska); SVK: Slovakia; SWE: Sweden; UNKI (UK, Leicestershire); UNKo (Oxford); UNKp (Plymouth); UNKS (Scotland); UNKy (Yorkshire). The model fitted to the incidence data was a multiplicative regression model with logarithm of the age standardized incidence as dependent variable, thus the scale of the incidence is logarithmic when straight lines were used in drawing the regression lines

an upward course but not a statistically significant trend in incidence. The increase in incidence in eastern Europe varied from 2.1 % per year in East Bulgaria to 8.5 % per year in Hungary. In the United Kingdom the mean incidence ranged from 14.3 to 21.6 and the increase in incidence ranged between 1.9 and 3.7% except for Leicestershire where the mean incidence was 7.8 with an increase of 9.5%. The data for Leicestershire, however, were considerably older (from 1965 to 1981) than from other UK study populations.

Predictions until the year 2010. Since no effective prevention has thus far been invented or is foreseen in the near future, we used the observed trends to predict the incidence of Type I diabetes at least until the year 2010 (Table 3). For the prediction we applied both linear and exponential models, since the model of the increase in incidence is not known. The exponential predictions were only calculated for populations with a study period of at least 14 years. In general, the linear model produces more conservative predictions than the exponential model, however, in those populations where an increase had started during the very last years of the observation period, the exponential model gave more conservative predictions than the linear.

The predictions based on the linear model show that Finland will still have the highest incidence in

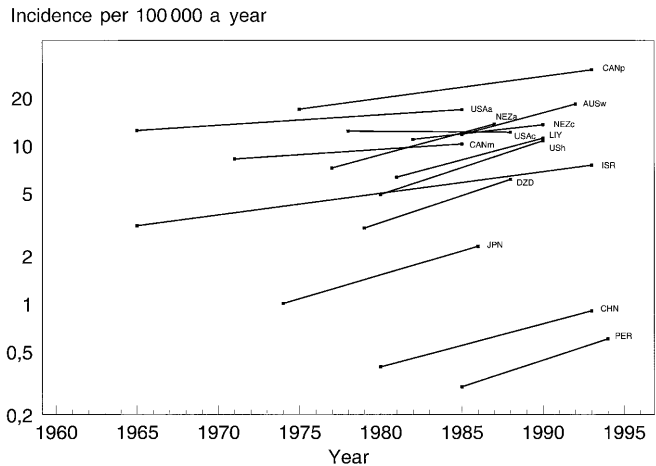


Fig. 2. Trends in the incidence of Type I diabetes mellitus in Non-European populations. DZD: Algeria (Oran); AUSw: Australia (West); CANm: Canada (Montreal); CANp: Canada (Prince Edward Island); CHN: China (Shanghai); ISR: Israel (Yemenite Jews); JPN: Japan (Hokkaido); LIY: Libya; NEZa: New Zealand (Auckland); NEZc: New Zealand (Canterbury); PER: Peru (Lima); USAa: USA (Allegheny County); USAc: USA (Colorado); USAh: USA (Hawaii)

the world (50 per 100 000 a year) in the year 2010, followed by Norway, Prince Edward Island (Canada), western Australia, Scotland (UK), Oxford (UK), and Sweden. Despite the large relative increases in the incidence observed in China and Peru, the absolute incidence rates in these countries would still remain low, less than 2 per 100 000 a year. Based on these predictions, in Japan the incidence will be lower than 5 per 100 000 a year and in Poland, Latvia and Lithuania the incidence will be under 10 per 100 000 a year.

Discussion

There are also other populations in which an increase in the incidence of Type I diabetes has been recently reported such as Croatia, Denmark, Kuwait, the Netherlands, Russia and Switzerland [17–23]. These studies, however, did not meet the inclusion criteria of this study and were not included in our analysis. To find out whether the rising incidence is really a global phenomenon, we carried out an analysis of incidence trends among 37 populations worldwide for which the data had been collected for 8 years or more. The incidence of Type I diabetes is globally increasing by 3.0 % per year (or by 2.5 %, when the incidences were weighted by the number of diabetic children included in the individual studies). Confidence intervals for these estimates were fairly narrow indicating that these estimates are reliable. According to this estimate, the incidence of Type I diabetes will be 40 % higher in 2010 than in 1998. This is a realistic, although a rather frightening, scenario.

is small and the study period short. The analysis of the pooled data was repeated excluding populations for which the case ascertainment level was not reported (Algeria, Israel, Libya, Malta and Oxford, UK). The results were essentially the same as in the analysis using all data: 2.95% per year vs 2.96% per year, respectively, and for the weighted regression, 2.40% vs 2.49%, respectively.

There is presently no way to know whether the observed trend in incidence might reflect a change in the age at onset of diabetes instead of a true rise in prevalence. The increase in incidence in 0–14-year-olds might just be a transition of the age at onset from the age group 15 years or older. Data on incidence trends in older age groups exist from just a few populations; thus, reliable information a possible decrease in incidence in young adults is not available. Our main result is that the incidence is globally increasing in the age group of 0–14-year-olds.

The genetic factors have been shown to be important in the susceptibility to Type I diabetes [5, 6]. Although it is possible that the part of the population genetically predisposed for Type I diabetes is increasing, this increase may have been modest during the last decades and not alone a sufficient cause for the observed increase in incidence. The changes in the genetic code of the human populations are usually slow. In this analysis even the longest study period covered only 30 years, which is approximately the time span of one generation. It is very unlikely that a three to tenfold increase in the proportion of subjects with genetic susceptibility to Type I diabetes has taken place in any population during such a short time. Instead, the penetrance of the susceptibility genes might be changing. The penetrance is likely to be determined by an interaction between several susceptibility genes and unknown environmental factors [4, 24].

During the recent years much attention has been paid to the identification and possible control of environmental factors which possibly initiate or trigger the process leading to Type I diabetes. Although some studies suggest associations between environmental factors such as diet and viral infections with the risk of Type I diabetes [25–35], their causative role has not been shown. It is also difficult to show that any of these environmental factors has changed in such a way that a continuous global increase in the incidence of Type I diabetes would be easily explained.

The incidence of Type I diabetes is increasing worldwide. Thus far no population has been identified in which the incidence has significantly decreased. The population-based WHO DIAMOND Project and the EURODIAB study started at the beginning of the 1990s but have not yet reported results from the long-term progress in the incidence of Type I diabetes. It seems obvious that in both of these studies the 10-year monitoring period planned thus far is

too short to produce reliable trend estimations and predictions for the change of the incidence of Type I diabetes, especially in countries where incidence is low. There is a need to continue with the community-based registries on Type I diabetes worldwide. Efforts are also needed to identify effective primary prevention measures for Type I diabetes to stop the global increase in the incidence of this disease.

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