Secular Trends in Incidence of Childhood IDDM in 10 Countries

DIABETES EPIDEMIOLOGY RESEARCH INTERNATIONAL GROUP

Standardized childhood insulin-dependent diabetes mellitus (IDDM) incidence data were collected from 21 ethnic groups in 10 countries to evaluate temporal trends in the disease between 1966 and 1986. Population-based registries contributed information concerning periods from 6 to 21 yr. The incidence rates were modeled with Poisson regression. For the past 2 decades, a linear increase in IDDM risk for people <15 yr of age has been observed in most of Europe and the Western Pacific but not in North America. The temporal variation did not appear to differ significantly by age or sex in most locations. The observed pattern of temporal variation suggests that a proportion of diabetes in childhood may be caused by a potentially preventable environmental factor. ***Diabetes*** **39:858–64, 1990**

The assessment of geographic and temporal variation in the incidence of insulin-dependent diabetes mellitus (IDDM) can provide important clues concerning its unresolved etiology (1). Recently, a standardized global approach demonstrated extremely large geographic differences in IDDM risk (2,3). A similar collaborative analysis has not been reported for temporal trends in IDDM. However, limited data suggest that the disease can exhibit epidemic outbreaks (4) and that in some areas both prevalence (5) and incidence (6–8) appear to be rising.

The objective of this study was to formally evaluate the global time trends in the incidence of childhood IDDM for the past 21 yr (1966–1986). Standardized incidence data were available for different periods of observation (range 6–21 yr) from 17 collaborating population-based registries on four continents. Statistical models of temporal variation corresponding to five specific etiologic hypotheses were formally compared. *1*) In the null model, IDDM incidence is determined by factors that do not vary rapidly in time (e.g., population gene pool); therefore, incidence would be stable during the observation period. *2*) In model A, IDDM is caused by a ubiquitous environmental factor for which prevalence is increasing, e.g., a food additive or chemical pollutant; this would affect age-groups 0–4, 5–9, and 10–14 yr proportionately, leading to parallel linear increases in incidence for the three age-groups. *3*) In model B, the causative environmental factor, e.g., a virus, affects the three age-groups about equally, creating parallel nonlinear (epidemic) patterns of incidence in the three age-groups. *4*) In model C, the causative factor is being introduced or removed preferentially into the environment of children at certain ages (e.g., cow's milk in infant feeding); the resulting time variability in IDDM incidence would be a linear trend with a steeper slope for the youngest age-group. *5*) In model D, IDDM is caused by different factors at different ages or is preceded by an incubation period that varies with age; therefore, the time variability in incidence would be nonparallel in the three age-groups and could be nonlinear if the factor occurs in periodic outbreaks.

Finally, it was of interest to determine whether IDDM incidence is increasing uniformly worldwide or is changing with time in dissimilar patterns in diverse regions.

RESEARCH DESIGN AND METHODS

Cases were selected for inclusion into the registries if they fulfilled the following case definition of childhood IDDM: *1*) diagnosed as diabetic, *2*) placed on insulin before the 15th birthday, and *3*) resident in the area of registration at the time of the first insulin administration.

The design and standardization protocol of the Diabetes Epidemiology Research International Group have been reported elsewhere (2,3). To participate in this study, the collaborating IDDM registries were expected to meet the following criteria. *1*) The registry is a population-based registry of incident IDDM cases. *2*) The population at risk includes age-group 0–14 yr. *3*) Individual patient records are

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available. 4) The completeness of ascertainment is verified. 5) Incidence data are available for at least 6 consecutive years between 1966 and 1986.

Eighteen eligible registries were identified worldwide. Data were available from 16 of these registries. In addition, the nationwide Austrian registry was included, which covers age-group 0–13 yr. Descriptive data are given in Table 1 for the 17 participating registries.

An advantage of studying the epidemiology of childhood IDDM is that the clinical onset is relatively dramatic and characteristic. Although the pattern of hospitalization of children at diagnosis of IDDM may vary by place (3,9), most patients are admitted to a hospital. Estimates of the completeness of the primary source of ascertainment were obtained from each registry through cross-validation with additional sources of data. These ascertainment rates are given in Table 1. The minimum rate was 88%, and for all but three of the registries, the completeness of the primary data source was >95%. Moreover, previously unregistered cases found through validation procedures were included in the analyses, so the final ascertainment rates were even higher. For example, in Norway, the completeness of hospital records was 91.5% during 1973–1982; when cases found only through a validation source (insurance institutions) were added, the final ascertainment was estimated to be 98.8% (18). Neither methods of ascertainment nor completeness changed discernibly in any of the participating registries over time.

The numbers of incident IDDM patients were reported by race, sex, calendar year, and annual age. The numerators reported from each registry are given in Table 1. A total of 18,418 IDDM patients were included in the analyses.

The combined population of the registries at risk in 1979, a year for which all the registries provided incidence data, was 10 million in the age-group 0–14 yr. Most of the registries submitted population-at-risk denominators as detailed as the numerators. Otherwise, estimated denominators were obtained through a cohortwide margin-adjusted interpolation (23). Population data available for 5-yr age-groups were used for interpolation in Allegheny County, Pennsylvania,

TABLE 1
Basic information concerning insulin-dependent diabetes mellitus (IDDM) registries participating in Diabetes Epidemiology Research International Group study of temporal trends in IDDM

Registry	Registration period	Completeness of primary source of ascertainment		*n*	Population at risk (person-yr × 10^3)	Ref.
		%	Period			
North America						
United States						
Allegheny County, PA	1966–1985	100	1965–1976			10
White				1002	5852	
Black				92	848	
Rochester, MN	1966–1986	100	1966–1986	54	296	11
Jefferson County, AL	1979–1985	96	1979–1985			
White				104	606	
Black				25	430	
Colorado	1978–1983	95–100	1978–1983			12
Non-Hispanic				542	3367	
Hispanic				62	673	
North Dakota	1979–1986	95–100	1979–1986	231	1268	
Canada						
Montreal	1971–1985	94	1979–1985	920	9264	13
Prince Edward Island	1975–1986	99	1975–1981	92	378	14
Europe						
Scandinavia						
Finland	1966–1979	95–100	1966–1979	4014	15,184	15
Vasterbötten, Sweden	1966–1986	98	1966–1970	167	682	16
		100	1971–1986			
Sweden	1978–1986	95–100	1978–1986	3471	14,137	17
Norway	1973–1982	96	1973–1977	1929	9334	18
		88	1978–1982			
United Kingdom						
Leicestershire	1966–1981	95–100	1966–1981	268	2990	9
Scotland	1976–1983	>95	1980–1983	1856	9154	19
Central Europe						
Wielkopolska, Poland	1970–1985	95	1970–1981	473	10,097	4
		99	1982–1985			
Austria*	1979–1986	>90	1979–1984	810	10,663	20
Asia						
Hokkaido, Japan	1974–1986	95–100	1974–1986	283	16,663	21
Western Pacific						
Auckland, NZ	1977–1986	100	1988			22
White				187	1520	
Maori and Polynesian				19	522	
Total				18,418	113,928	

*Age-group 0–13 yr.

(1966–1979) and Rochester, Minnesota (1966–1986). Census data, provided by annual age-groups, were used for interpolation in Jefferson County, Alabama, and North Dakota (1970 and 1980 census); Leicestershire, United Kingdom (1966, 1971, and 1981 census); Hokkaido, Japan (1970, 1975, 1980, and 1985 census); and Auckland, New Zealand (1976, 1981, and 1986 census). In Montreal, the 1971 and 1981 census data were available by 5-yr age-groups. For descriptive purposes, the annual incidence rates were directly age standardized for each population as previously described (3) and then plotted.

Poisson regression models were fit to each series to determine if there was temporal variation in the IDDM rates and to investigate the nature of such variation (24). The rates were modeled on a logarithmic scale, and likelihood-ratio statistics were used for significance testing. Adjustments were made for the effects of age, sex, and interaction between age and sex by entering these terms into the regression models. The models were fit with the GLIM (Royal Stat. Soc.; 25) computer program.

Five forms of temporal variation were considered for the data from each population, corresponding directly to the five etiologic hypotheses listed previously. Under the null model, the yearly variation in rates reflects only random variability. The four alternative models are presented schematically in Fig. 1. The first alternative allowed a common linear time trend for the entire 0- to 14-yr age-group (model A). Generalizations of this model allowed a common nonlinear time variability (model B) or different linear trends (model C). The least-restrictive model allowed different nonlinear time variability in each of the three age-groups (model D).

The most parsimonious of models A–D that did not exhibit lack of fit was compared with the null model. To adjust for multiple comparisons, significance testing was done at a type I error rate of 1%.

For those populations where a linear trend was an adequate representation of temporal variation (model A), the annual percent change in incidence was computed. The rates of change in IDDM incidence in these populations were formally compared to determine whether the slopes were different among these registries and among the corresponding regions of the world. This was done by comparing models that allowed a single slope, separate slopes for each region of the world, and separate slopes for each registry.

RESULTS

Figures 2 and 3 present a descriptive summary of IDDM incidence data for the 21 populations studied. Age-standardized annual incidence is plotted by geographic region.

In the United States, there is little evidence of significant temporal change, although data are available for a long period in only two areas. The rates from Rochester and each of the three non-White populations are based on a few cases. In Canada, incidence was stable in Montreal until the early 1980s, when the rates appear to rise. The rates in Prince

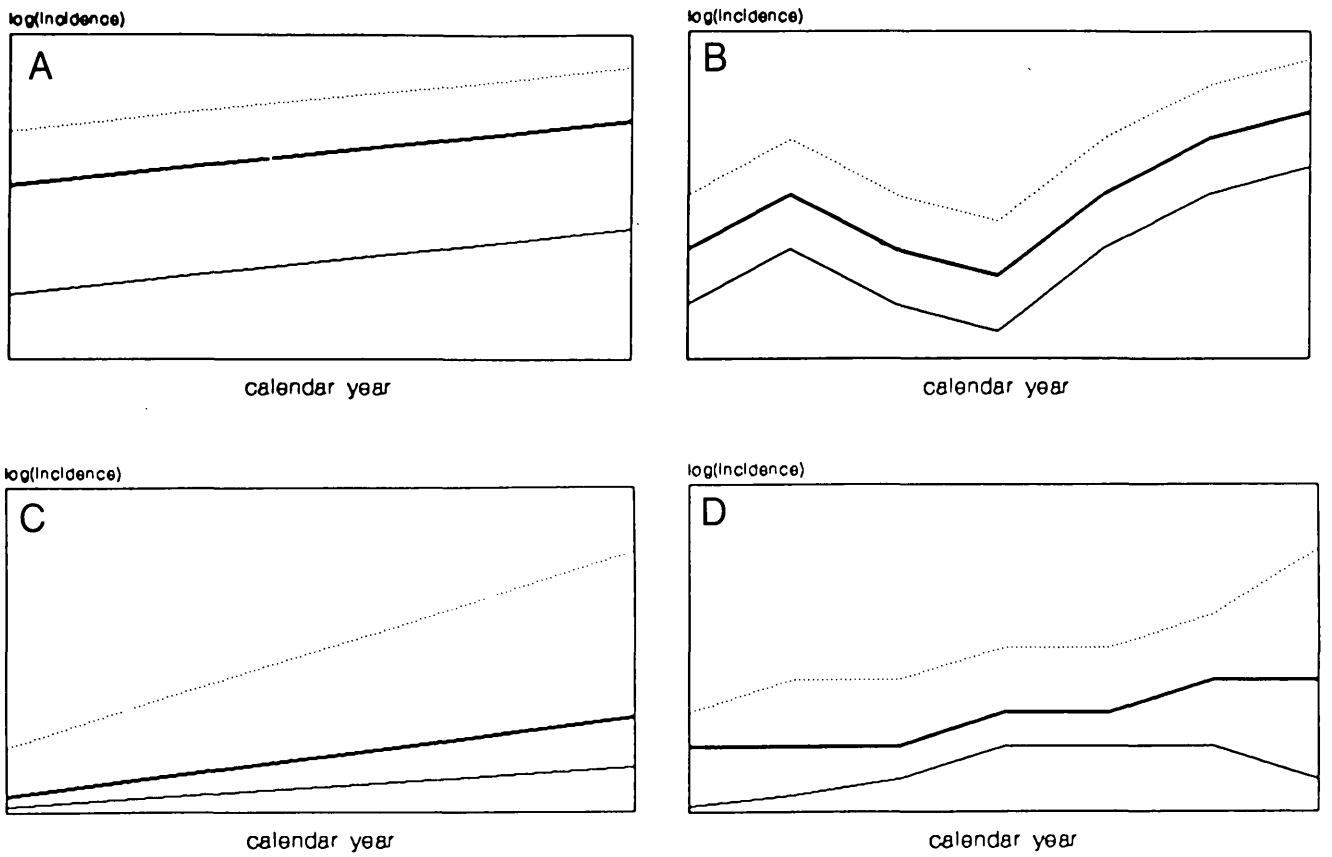

FIG. 1. Four alternative models of temporal variation considered for registries participating in Diabetes Epidemiology Research International Group for age-groups 0–4 (*thin lines*), 5–9 (*bold lines*), and 10–14 (*dashed lines*) yr. *A*: parallel linear temporal trends. *B*: parallel nonlinear temporal variation. *C*: different linear temporal trends. *D*: different nonlinear temporal variation.

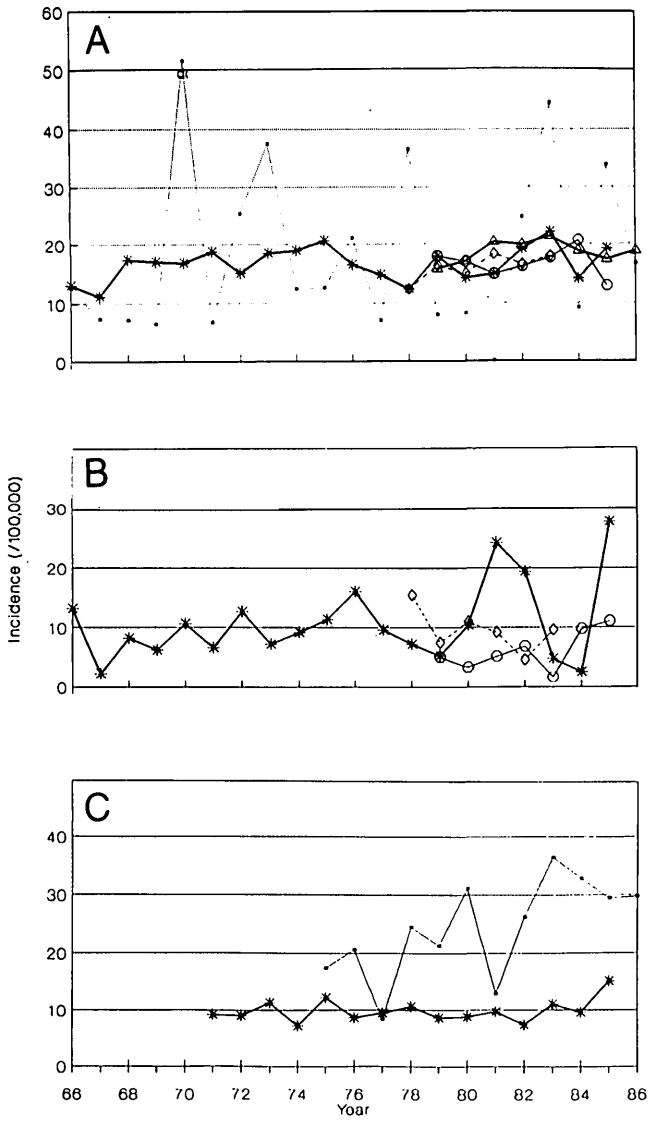

FIG. 2. Time trends in childhood insulin-dependent diabetes mellitus incidence among North American registries participating in Diabetes Epidemiology Research International Group. *A*: non-Hispanic Whites in United States. ✻, Allegheny County; ■, Rochester, MN; ○, Jefferson County; ◇, Colorado; △, North Dakota. *B*: Blacks and Hispanics in United States. ✻, Allegheny County Blacks; ○, Jefferson County Blacks; ◇, Colorado Hispanics. *C*: Canadians. ✻, Montreal; ■, Prince Edward Island. For locations, see RESEARCH DESIGN AND METHODS and RESULTS.

Edward Island, based on a limited number of cases, suggest a rapid increase in incidence.

In Europe (Fig. 3), incidence appears to be increasing in Finland, Sweden, Leicestershire, Austria, Wielkopolska (Poland), and perhaps Norway. The data from Vasterbötten, Sweden, display an irregular pattern based on an average of 7 cases/yr. In Hokkaido and in White children in Auckland, incidence appears to be increasing, although incidence in Hokkaido remains extremely low.

Table 2 summarizes the results of model selection for temporal variation in IDDM risk. Among the North American registries, significant year-to-year variability in IDDM incidence was found only in Montreal. There was some evidence of variability in IDDM rates over time in Allegheny County White children (P = 0.041 for model B). The power to detect time effects in the remaining North American series may be low because of their small sample sizes or short observation periods. Overall, there was no strong evidence of a major increase in IDDM in North America.

In contrast, significant temporal changes were found in all European populations studied except Scotland. In Scotland, there was some evidence of temporal heterogeneity in the rates (P = 0.029 for model B). In Finland, Sweden, Norway, Wielkopolska, and Austria, linear increases of risk were observed that were not statistically different for the age-groups 0–4, 5–9, and 10–14 yr. In Leicestershire, the linear increase in IDDM risk was different for the three age-groups, with the steepest rise in the youngest children. In Vasterbötten, significant nonlinear temporal variability in IDDM risk differed for the three age-groups.

Since the mid-1970s, the incidence of childhood IDDM also has been linearly increasing in Hokkaido and in White children in Auckland. There was no evidence for heterogeneity of the time trends among the Scandinavian countries

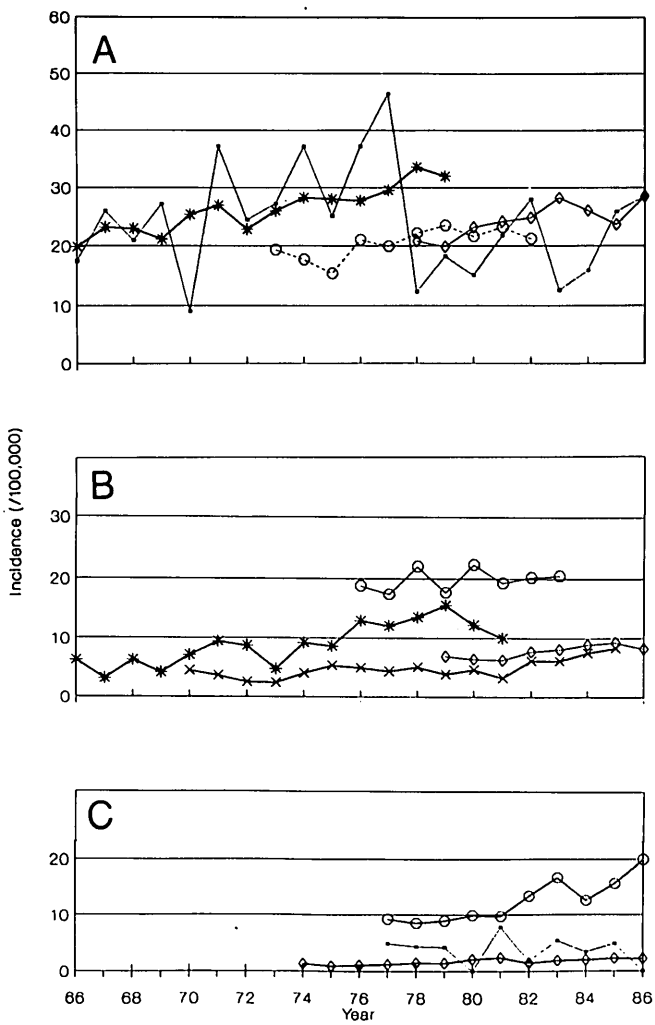

FIG. 3. Time trends in childhood insulin-dependent diabetes mellitus incidence among European and Western Pacific registries participating in Diabetes Epidemiology Research International Group. *A*: Scandinavia. ✻, Finland; ■, Vasterbötten; ◇, Sweden; ○, Norway. *B*: United Kingdom and Central Europe. ✻, Leicestershire; ○, Scotland; x, Wielkopolska; ◇, Austria. *C*: Western Pacific. ◇, Hokkaido; ○, Auckland Whites; ■, Auckland non-Whites. For locations, see RESEARCH DESIGN AND METHODS and RESULTS.

TABLE 2
Best-fitting models for temporal variation in age- and sex-adjusted incidence of insulin-dependent diabetes mellitus for registries participating in Diabetes Epidemiology Research International Group

Registry	Best model	Annual change (%)
North America		
United States		
Allegheny County, PA		
White	No temporal variation	
Black	No temporal variation	
Rochester, MN	No temporal variation	
Jefferson County, AL		
White	No temporal variation	
Black	No temporal variation	
Colorado		
Non-Hispanic	No temporal variation	
Hispanic	No temporal variation	
North Dakota	No temporal variation	
Canada		
Montreal	Common nonlinear variation	
Prince Edward Island	No temporal variation	
Europe		
Scandinavia		
Finland	Common linear trend	+3.4
Vasterbötten, Sweden	Different nonlinear variation in age-groups 0–4, 5–9, and 10–14 yr	
Sweden	Common linear trend	+3.7
Norway	Common linear trend	+2.8
United Kingdom		
Leicestershire	Different linear trends	
	0–4 yr	+11.5
	5–9 yr	+12.2
	10–14 yr	+2.6
Scotland	No temporal variation	
Central Europe		
Wielkopolska, Poland	Common linear trend	+5.6
Austria	Common linear trend	+5.1
Asia		
Hokkaido, Japan	Common linear trend	+6.3
Western Pacific		
Auckland, NZ		
White	Common linear trend	+10.1
Maori and Polynesian	No temporal variation	

(Finland, Sweden, and Norway) or between the two Central European registries (Poland and Austria). However, when the time trends for Scandinavia, Central Europe, Hokkaido, and Auckland were compared, they were found to be significantly different from one another ($P < 0.01$). The absolute rate of rise in incidence was highest in Finland (0.7/100,000 annually), and the relative increase was steepest in New Zealand White children (annual change 10.1%).

Significant sex differences in incidence were found only in Finland (male excess) and Japan (female excess). Borderline significant male excesses were noted in Norway and Sweden, and a borderline female preponderance was seen for the Allegheny County Black population. In none of the 21 ethnic groups studied did the temporal trends differ by sex.

DISCUSSION

In some population-based studies of cancer or cardiovascular diseases, rising incidence trends have been attributed to improvements in diagnosis or registration or to changes in case definition. We do not think that these factors play a significant role in this study, because the diagnosis of IDDM in childhood is straightforward, the ascertainment does not appear to change over time, and the case definition is unambiguous. Underdetection of IDDM due to the death of a substantial number of undiagnosed incident patients is unlikely in any of the populations studied. Underregistration can be measured and corrected with multiple sources of data. All of the registries have validated the completeness of the primary data source with at least one secondary source. Misclassification of non-insulin-dependent patients as having IDDM is negligible for all White populations in the age-group studied. It is possible that some Japanese or Black children with an atypical form of IDDM (26,27) are now more likely to be diagnosed and placed on insulin at diagnosis of diabetes than they were in the 1960s or 1970s. We think it is unlikely that the major increase in IDDM incidence in Europe and the Western Pacific is an artifact of data collection.

Some earlier reports have suggested that IDDM risk has markedly increased in the United States (6), Norway (28), Finland (8), and Denmark (29) over the last 60 yr. Those reports compiled data from studies that may have used progressively improving ascertainment procedures and are impossible to validate.

Our findings provide little evidence of a major increase in IDDM incidence in North America, which corroborates previous observations (10,11,13,30). On the other hand, the results confirm reports of significant increase in IDDM incidence in Europe (4,8,17,31). Although IDDM risk appears to rise more steeply in Central Europe than in Scandinavia, this rise is relative to a three- to five-fold lower baseline in Central Europe. The incidence of IDDM is highest in Scandinavia, but so is the absolute increase in risk measured by the number of additional cases per year.

In contrast, the risk of childhood diabetes has not changed markedly in the past 2 decades in the German Democratic Republic (D. Michaelis, E. Jutzi, unpublished observations); data from this registry were not available in a format compatible with our study. We were unable to detect a significant increase of IDDM incidence in Scotland during the period studied (1976–1983), although a year-to-year variation in the rates was present. Thus, IDDM risk previously reported as increasing in Scotland during 1968–1976 apparently leveled off in the late 1970s (7).

Jarrett (32) suggested that the higher incidence in younger age-groups in some ethnic groups may be compensated by differences in the reverse direction at older ages. An extension of this hypothesis is that the lifetime incidence of diabetes is not increasing but that the disease is being manifested at an earlier age in susceptible individuals (5). Some evidence has been presented for the latter hypothesis (8,33). Our results provide little support for the hypothesis because dissimilar time trends for the three age-subgroups were observed only in Leicestershire and Vasterbötten.

Sparse data and short observation periods correspond to low power. For this reason, the results consistent with no significant temporal variation in the series with short observation periods and/or sparse data should be interpreted with caution.

This report is limited to analysis of variation in IDDM incidence rates by calendar time of diagnosis. Another temporal factor in disease occurrence is the year of birth of the patient (birth cohort), which was not studied. Our previous analyses of data from Allegheny County, Wielkopolska, Finland, and Hokkaido (34,35) indicated that temporal variation in IDDM incidence was better explained by calendar-time effects. We are currently evaluating the alternative age-cohort pattern of IDDM in selected populations. However, the data reported in this article represent periods of observation that vary too much to be useful in disentangling period versus cohort effects on the global scale.

The existence of a temporal trend in disease occurrence provides considerable evidence for environmental determinants of the disease. In most populations studied, the observed temporal pattern of IDDM incidence was a linear increase in incidence, parallel in the three age-groups 0–14 yr (model A). This cannot be explained on a population basis by an increase in the number of susceptible individuals. This pattern is consistent with the existence of a causal environmental factor whose prevalence is increasing. Among putative risk factors, a viral infection is the most plausible etiologic agent responsible for the temporal variation. However, attempts to prove that a virus is a major cause of IDDM have been inconclusive, perhaps due to a long incubation period (36,37). Moreover, it would be difficult to explain why a virus is causing increased IDDM incidence in some parts of the world but not in the others and why Scandinavia is most affected despite having the highest baseline IDDM incidence. Unexplored or barely explored avenues of etiologic research include reproductive and perinatal factors and early childhood diet.

In summary, our data suggest that for the past 2 decades a linear increase in IDDM risk for people <15 yr of age has been observed in most of Europe and in the Western Pacific but not in North America. Except for two registries, the temporal variation did not appear to differ significantly by age. Our data from Europe and the Western Pacific are consistent with the hypothesis that an etiologic factor that affects all ages 0–14 yr proportionately is being introduced into or removed from the environment.

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APPENDIX: DIABETES EPIDEMIOLOGY RESEARCH INTERNATIONAL GROUP

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