Geographic Differences in the Risk of Insulin-dependent Diabetes Mellitus: The Importance of Registries

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There are marked geographic differences in the incidence of insulin-dependent diabetes mellitus (IDDM); for example, children in countries such as Finland are over 35 times more likely to develop IDDM than children in Japan. An understanding of the reasons for the geographic differences is likely to be important for understanding and, hopefully, preventing IDDM. There are problems, however, because of the lack of registries with adequate standardization. The major needs for the future studies include (1) to clarify the definition of IDDM for epidemiologic study, (2) to establish a standardized approach for IDDM registries, (3) to use registries to evaluate viral, immunologic, and genetic differences in order to explain differential risks across populations, and (4) to encourage the development of new population-based registries worldwide. DIABETES CARE 1985; 8 (SUPPL. 1):101–107.

The analysis of the distribution of illness across populations has provided important insight into the etiology of disease including heart disease,[1] cancer,[2] polio,[3] and multiple sclerosis.[4] Cross-cultural studies have generated hypotheses concerning environmental and genetic causes of disease. These types of geographic comparisons have been a first step for identification of factors, such as diet, that are associated with heart attack[1] and cancer,[2] and the viral etiology of cancer such as Burkitt's lymphoma.[5] Surprisingly, the approach of contrasting populations that differ in disease risk has been little used in insulin-dependent diabetes mellitus (IDDM) research.

To evaluate population differences in risk of disease, it is essential to develop a case registry. For example, in diabetes research, all new cases (incident) of IDDM are registered during a specified time period in a defined geographic area. Registries of prevalent cases (existing cases) are subject to more potential biases, such as differential mortality, migration, and incomplete ascertainment, than incidence registries. Typically, for evaluating factors associated with the occurrence of a disease, incidence registries are considerably more valuable than prevalence registries. However, when only limited incidence data are available, which is the case with IDDM, the determination of the prevalence rates can provide crude information concerning the distribution of cases in a given population, which may be compared with similar data from other populations.

The paucity of incidence registries for IDDM is illustrated in Figure 1, where the names of the areas where incidence rates have been reported are identified. As presented, there are very few IDDM incidence registries. The registries that are in existence are clustered in northern Europe and the northeastern United States. Overall, there are currently 19 published reports of incidence representing only 13 countries.[6–27] New registries are being developed in Colorado,[20] Tasmania,[28] and Poland.[29] There are no registries for the continents of Africa, South America, and Asia. The risk of developing IDDM is unknown for more than 94% of the world's population. The small number of IDDM registries in existence is in stark contrast to the epidemiologic research in cancer, where there are over 60 registries worldwide, representing all continents except Antarctica.[2]

It will be important to develop new incidence IDDM registries in the unrepresented areas. From the registries, we will be able to determine the risk of developing IDDM; moreover, by using the registries as a population source for viral, immunologic, and genetic markers, it will be possible to accurately determine how these factors are associated with risk of IDDM and whether these factors can explain the different patterns of incidence between and within populations.

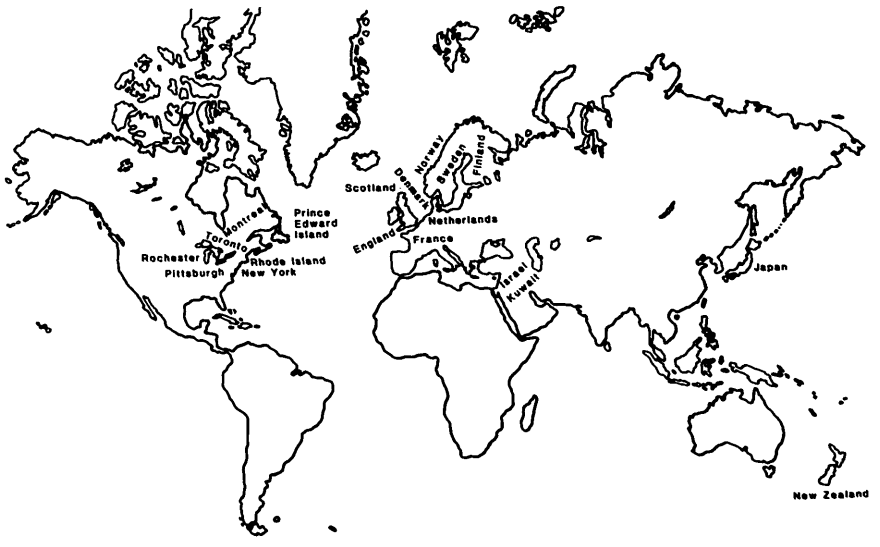

FIG. 1. Complete IDDM incidence registries across countries.

Table 1 presents an overview of several of the existing population-based incidence registries. A critical problem with existing registries is the lack of standardization. As illustrated, different information has been obtained (Table 2). Cases included in the registries vary by age, definition of cases, and degree of ascertainment. Therefore, comparison of incidence across registries has been extremely difficult. It will therefore be important to develop a standardized approach to data collection, data storage, and data reporting for current and future registries.

GEOGRAPHIC COMPARISON OF INCIDENCE

To illustrate the potential importance of geographic comparisons, initial analyses of cross-country differences in IDDM incidence and prevalence are presented. Figure 2 presents the risk per year per 100,000 children for developing IDDM in various countries of the world. This risk is generally for children and adolescents under the age of 20. However, certain registries, as indicated in Table 1, have presented their results for somewhat different age groups. The striking feature is the remarkable variation in risk of developing IDDM. There appears to be more than a 35-fold difference in risk between countries having the highest incidence of disease compared with countries having the lowest incidence. The magnitude of this difference appears to be greater than the geographic variation in overall cancer and heart disease incidence.[1,2]

It is useful to illustrate these incidence differences by calculating the actual number of children developing diabetes and potential implications for risk and prevention. A child

TABLE 1
Population-based IDDM incidence registries

	Allegheny county (U.S.)[16]	England[12]	Colorado (U.S.)[20]	Finland[6]	Japan (central registry)	Midwest Poland[29]	Rhode Island (U.S.)[17]	Toronto (Canada)[22]	Montreal (Canada)[21]	Prince Edward Island (Canada)[26]	Rochester, Minnesota (U.S.)[19]	The Netherlands[27]
Population base (million)	1.5	59	2.8	4.5	117	2.3	1	2.5	0.8	0.12	0.05	4.5
Time period	1965 to present	1972 to present	1978 to present	1970 to present	1974 to present	1970 to present	1979 to present	1976–78	1971 to present	1964 to present	1945 to present	1978–80
Age criteria	<20	<16	<18	<20	<18	<17	<30	<18	<17	<20	None (all ages)	<20
Diabetes criteria												
Insulin use	x		x	x (Drug)		?	x	x	x	x	x (plus other factors)	x
Case ascertainment	Hospitals	Hospitals and physicians	Physicians	Drug usage	Medical certificate for payment	Hospitals	Hospitals	Hospitals	Hospitals	Physicians	Any contact with medical care system	Physicians
No. of cases in registry	1300	12,500	300	3475	2200	374	>1000	132	1000	2400 (IDDM and NIDDM)	200	1271
Estimate of completeness	90–95%	65%	Unknown at this time	95%	90% (?)	?	95–99%	100%	?	99%	100%	75–94%

TABLE 2
Information on registries

Information collected from hospital/ physician	Allegheny county (U.S.)[16]	England[12]	Colorado (U.S.)[20]	Finland[6]	Japan (central registry)	Midwest Poland[29]	Rhode Island (U.S.)[17]	Toronto (Canada)[22]	Montreal (Canada)[21]	Prince Edward Island (Canada)[26]	Rochester, Minnesota (U.S.)[19]	The Netherlands[27]
Name	x	x	x	x	x	?	x	x	x	x	x	x
Address	x	x	x	x	x	?	x	x	x	x	x	x
Rate	x	x	x	x	x	?	x	x	x		x	
Sex	x	x	x	x	x	x	x	x	x	x	x	x
Hospital at diagnosis	x	x	x		x		x	x	x		x	x
Birth date	x	x	x	x	x	x	x	x	x	x	x	x
Insulin use	x		x	?	x	?	x	x	x	x	x	x
Date of diagnosis	x	x	x	x	x	x	x	x	x	x	x	x
Symptoms at onset	x	x			x	?	x	x	x		x	
Duration of symptoms	x	x				?	x	x				
Family history	x					?	x		x		x	
Onset mortality	x			x	x	?	x			x	x	
Information obtained directly from the families at onset	x	x	x			?	x		x			
Current mortality status	x			x	x	?					x	
Current morbidity status	x				x	?					x	

in Finland is 36 times more likely to develop diabetes than a child in Japan.[6,23,24] About 390 children and adolescents under the age of 20 develop IDDM per year in Finland. If it were possible, through preventive action, to make the children in Finland at the same risk as children in Japan, then 97% of the new cases of IDDM in Finland would be prevented and only about 10 children, instead of 390, would develop IDDM. Similarly, in the United States, over 12,000 children per year under the age of 20 develop IDDM. Remarkably, only 650 children would develop diabetes if the incidence in the United States were the same as that in Japan. Thus, the identification of cross-cultural factors that could be modified, hopefully, could make preventive actions feasible and thus lower the likelihood of children developing diabetes.

The magnitude of the geographic differences in diabetes incidence must also be viewed in the context with other risk factors for IDDM. A family history of IDDM among siblings is associated with a 15-fold increase in risk.[30] In addition, having the HLA DR_3 or DR_4 antigen is associated with a 4–8-fold increased risk, and having both DR_3 and DR_4 is associated with a 30–40-fold increased risk. In comparison, being born and living in Finland, rather than in Japan, is associated with more than a 35-fold increased risk. Thus, the country of birth and place of residence appear to be major factors associated with IDDM risk. An understanding of these geographic differences will therefore be important for identifying factors related to the etiology of IDDM.

Rank ordering populations by their incidence rates leads to the generation of several important testable hypotheses, as presented in Figure 2. Somewhat different age groups were employed in reporting the incidence results (Table 1); how-

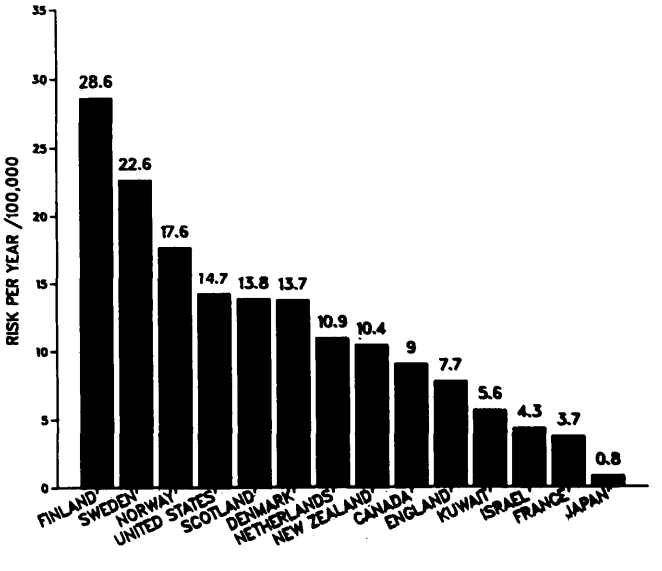

FIG. 2. The risk per year of developing IDDM in various countries across the world.

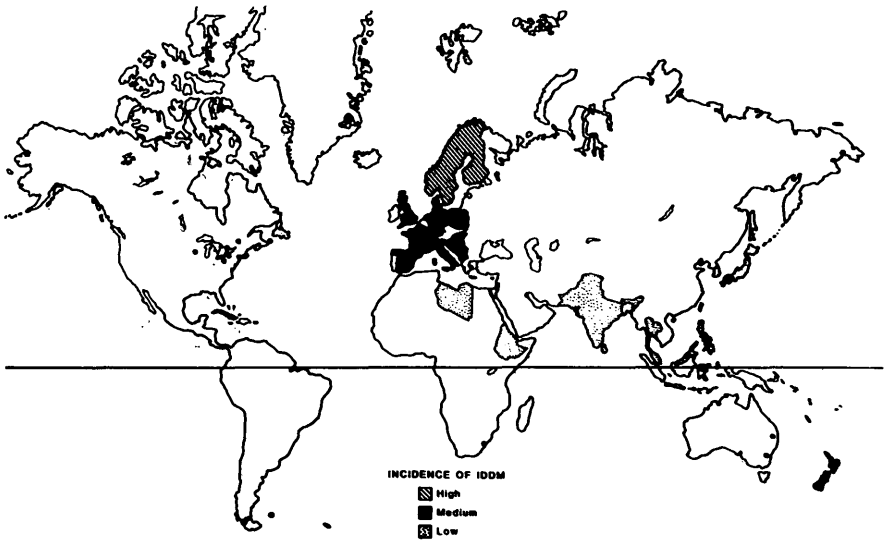

FIG. 3. High-, medium-, and low-risk countries.

ever, these are unlikely to affect the rank ordering. Evaluation of the incidence rates in relation to distance from the equator reveals a positive association (Figure 3) between latitude and the incidence of IDDM. To further determine the geographic patterns of risk of developing IDDM, incidence and prevalence studies were roughly categorized into high-, medium-, and low-risk populations. For countries where there were both incidence and prevalence data, the incidence data were employed. The high-risk countries represent populations whose IDDM incidence is at least 15/100,000 under the age of 20. The medium-risk countries are associated with a risk between 1 and <15/100,000, and the low-risk countries have a risk that is <1/100,000. We recognize the inadequacy of some of the data. It is believed, however, that this crude classification is sufficient for identifying the over 10-fold difference in risk across populations for the three classifications.

These countries are graphed in Figure 4. As with the representation in Figure 3, there appears to be a strong gradient in risk; countries closest to the equator have over a 10-fold lower risk compared to populations farther away from the equator. It is interesting that within the Netherlands, a similar north-south gradient has been found.[27] Clearly, hypotheses concerning genetic or environmental factors could be generated and tested to explain the gradient. There are certain unpublished reports, however, that do not completely fit into the latitude hypothesis, e.g., Cubans appear to have a similar rate of IDDM as inhabitants of more northern countries.[31]

One might speculate as to whether this gradient is a function of genetic migration or environmental factors. Genetic variation is likely to play an important role in the incidence differences. However, this does not exclude important environmental factors such as viral infection or other diabetogenic factors. Recent reports from Israel reveal that the incidence of IDDM among Askenzai Jews (Jews who migrated from northern Europe) was 6.8/100,000 compared with 4.3/100,000 for non-Askenzai Jews in Israel.[32] This may be due to a genetic difference because of the somewhat different genetic background of the two groups. However, the results may also imply an environmental influence. The remarkably low rate of 6.8/100,000 for the European Jews in Israel is approximately one-half that for Europeans (both Jewish and non-Jewish). Therefore, the results from Israel may suggest both genetic and environmental factors are associated with the risk of IDDM.[33] Clearly, the development of registries to evaluate immigrants would be important for an understanding of the degree to which environmental and genetic factors influence the risk of developing IDDM.

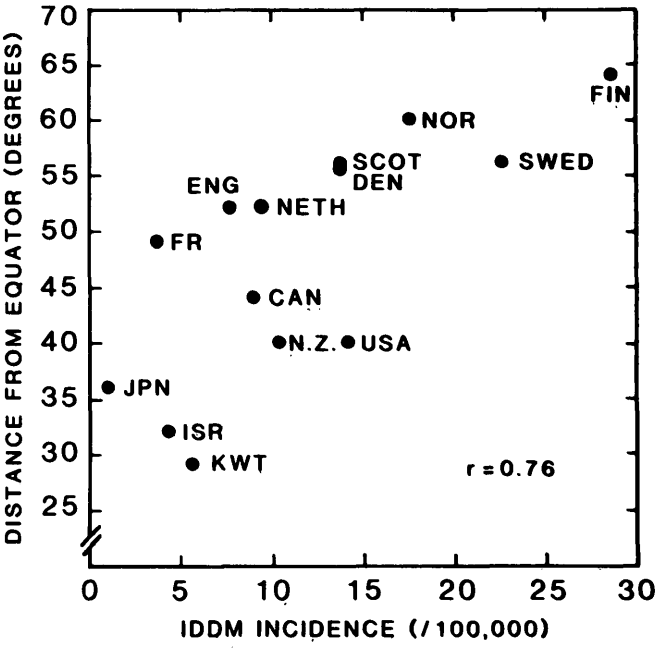

FIG. 4. Relationship between the incidence rates and the distance from the equator. KWT: Kuwait; other abbreviations as in Figure 5.

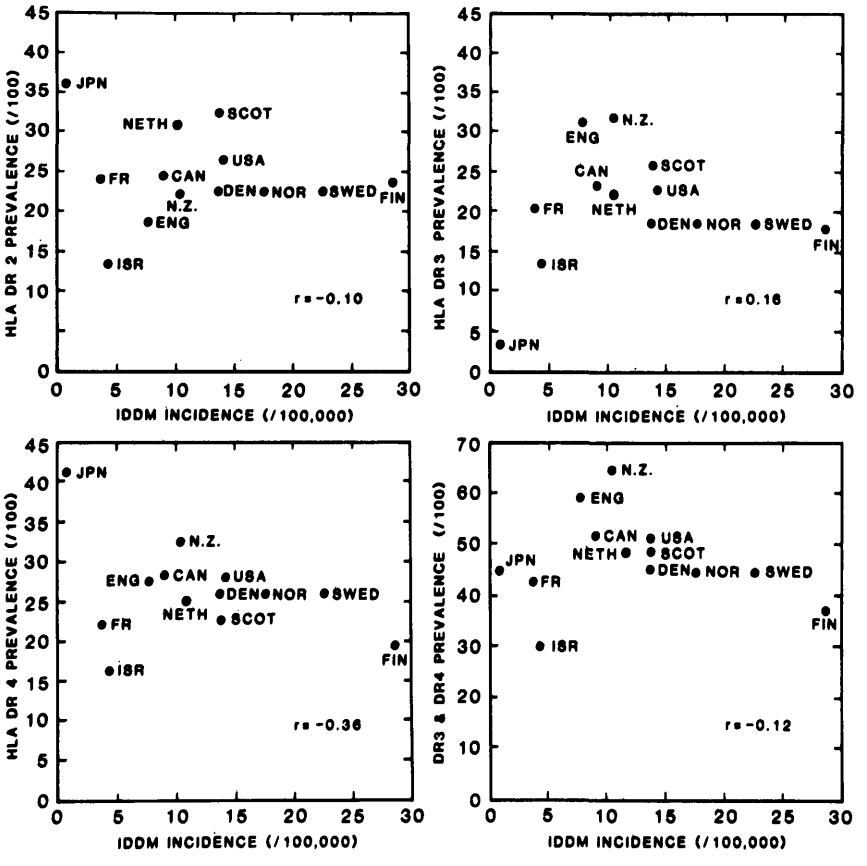

FIG. 5. Associations between the frequency of specific HLA DR locus in a general population and IDDM incidence in 13 countries. Abbreviations are as follows: FIN: Finland; SWED: Sweden; NOR: Norway; USA: The United States of America; SCOT: Scotland; DEN: Denmark; NETH: The Netherlands; N.Z.: New Zealand; CAN: Canada; ENG: England; ISR: Israel; FR: France; JPN: Japan.

One approach to explain the incidence differences is that the populations differ in the prevalence of high-risk DR types.[33,34] Figure 5 presents the proportion of the population that has at least one high-risk DR antigen. The combined DR_3 and DR_4 measures represent the proportion of people having either a DR_3 or DR_4 within the populations. If the HLA DR types were the primary factors associated with the incidence differences, then one might expect a high positive correlation between the proportion of the population with the high-risk DR types and IDDM incidence. As illustrated in the figure, there was little association between the DR frequencies and the incidence of IDDM. Clearly, it will not be until more incidence data as well as HLA frequencies from representative populations are available that the relationship will be accurately determined between population differences in incidence and the prevalence of genetic markers.

RECOMMENDATIONS FROM THE PHILADELPHIA INTERNATIONAL MEETING ON IDDM EPIDEMIOLOGY

There is little question that the country of birth and place of residence of a child are highly associated with IDDM risk, with a relative risk over 35 comparing high and low risk populations. Many potential variables need to be explored to explain the cross-country and cross-continent differences in IDDM risk, such as diet, temperature, cultural practices, viral associations, and genetic factors. However, we are hampered by considerable gaps concerning the risk of developing IDDM across the world.

A primary recommendation therefore is that new incidence registries need to be developed. These registries should be in definable populations with a high degree of ascertainment.

The minimum criteria for entry into the registry are that individuals should be diagnosed as being diabetic and placed on insulin. The date of diagnosis would be the date of first insulin administration. Moreover, the registries should include as a minimum the ages of onset of 0–14 yr of age in order to capture the period of highest incidence. It was recognized that ideally it would be important to have an in-depth classification scheme, which would include measures such as HLA typing, islet cell antibody, and serum and/or urine C-peptide levels. These measures, although optimal, are not currently practical for research across the world because of the lack of standardized methods and the cost of doing these tests. The proposed inclusion criteria of insulin use and a young age at onset can be broadly applied across populations. It is recommended, however, that other information such as the biochemical assays mentioned above, plus height and weight at onset, be collected for future, more in-depth classifications. It is important to point out that a classification based on insulin usage and age at onset is likely to be more accurate for IDDM than classifications for other diseases such as certain cancers, coronary heart disease, or autoimmune disorders. Although there may be some mis-

Table 3
Minimum criteria for IDDM registries

Registries should be population based
Registries should use a standard definition of a case
Diagnosis of diabetes
Insulin treatment
Age at onset of diabetes is at least 0–14 yr
Registries should include as the minimum core of information
Name
Birth date
Sex
Race
Address at onset
Date when insulin treatment started
Registries should have an external source of validation
Registries should standardize results by reporting incidence rates by
Sex
Race
Age (0–4, 5–9, 10–14, . . .)

classification of cases using this approach, it is unlikely to markedly affect the 36-fold incidence rate differences across countries.

It is also recommended that a common core of information be collected for all registries. This would include as a minimum the individual's address at diagnosis, birth date, race, sex, and date of first insulin administration (diagnosis date). With this information, it will be possible to directly examine geographic differences in IDDM incidence by age, race, and sex.

The critical problem of many registries is underascertainment. Therefore, it is recommended that registries have some form of external validation. For example, if IDDM cases are identified from hospital records, then an external check could be a second independent source of IDDM patients, such as schools, physicians, insulin prescriptions, or health insurance. The secondary source would be used to sample only a proportion of the cases. This would yield an estimate of the completeness of the primary source of cases. It is only through relatively complete case listings across countries that the incidence of diabetes can be directly compared. An in-depth discussion of validation difficulties in other epidemiologic studies has been recently presented.[35] Additionally, a standardized approach for reporting incidence is important. Since census figures are typically in 5-yr increments (0–4, 5–9, 10–14, . . .), this age grouping provides the most logical method for reporting results. In the current report, for example, there was difficulty in directly comparing incidence rates because some studies reported data as incidence rates under age 15, 16, 20, or for school-aged children. The results should also be stratified by race and sex. In Table 3, we have summarized the minimum requirements for IDDM registries.

Additionally, future viral, immunologic, and genetic studies should strive to be population-based through the use of registries or at least attempt to determine the representativeness of the IDDM population under investigation. This is likely to reduce the major inconsistencies that have appeared in IDDM research, which may reflect biases in patient selection. By having a population-based cohort, blood samples can easily be obtained for analysis, which can be directly related to the risk of developing IDDM. Without a population-based cohort where the incidence of IDDM can be determined, it is difficult, if not impossible, to directly relate the various parameters, such as islet cell antibodies, viral titers, or HLA type, to the risk of developing IDDM.

The final and perhaps most important recommendation is that communication and collaboration be developed for researchers who have IDDM registries or who are planning to develop registries. It is only through collaborative efforts that it will be possible to identify the reasons for the major incidence and, perhaps, complication differences in IDDM across the world. Future areas of investigation might be to evaluate presenting characteristics of IDDM across populations,[36] developing population-based cross-cultural HLA, islet cell antibody, and virology studies, and evaluating complication and mortality risk between and within representative IDDM populations. One important step would be to develop guidelines, perhaps through the World Health Organization, for standardization of data collection forms, procedures for data collection, ascertainment assessment, programs for data analysis, and data reporting, which could be applicable to current and future IDDM registries.

We are currently compiling the types of forms and procedures for developing IDDM registries. Individuals interested in obtaining copies of existing forms or assistance in developing IDDM registries should contact the senior author of this article.

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