Pediatric Diabetes 2007: 8 (Suppl. 6): 6–14

Pediatric Diabetes

Review Article

Worldwide childhood type 1 diabetes incidence – what can we learn from epidemiology?

Soltesz G, Patterson CC, Dahlquist G on behalf of EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence – what can we learn from epidemiology?
Pediatric Diabetes 2007: 8 (Suppl. 6): 6–14.

Abstract: Type 1 diabetes is the most common form of diabetes in most part of the world, although reliable data are still unavailable in several countries. Wide variations exist between the incidence rates of different populations, incidence is lowest in China and Venezuela (0.1 per 100 000 per year) and highest in Finland and Sardinia (37 per 100 000 per year). In most populations girls and boys are equally affected. In general, the incidence increases with age, the incidence peak is at puberty. After the pubertal years, the incidence rate significantly drops in young women, but remains relatively high in young adult males up to the age 29–35 years. Prospective national and large international registries (DIAMOND and EURODIAB) demonstrated an increasing trend in incidence in most regions of the world over the last few decades and increases seem to be the highest in the youngest age group. Analytical epidemiological studies have identified environmental risk factors operating early in life which might have contributed to the increasing trend in incidence. These include enteroviral infections in pregnant women, older maternal age (39–42 years), preeclampsia, cesarean section delivery, increased birthweight, early introduction of cow's milk proteins and an increased rate of postnatal growth (weight and height). Optimal vitamin D supplementation during early life has been shown to be protective. Some of these environmental risk factors such as viruses may initiate autoimmunity toward the beta cell, other exposures may put on overload on the already affected beta cell and thus accelerate the disease process.

G Soltesz[a], CC Patterson[b] and G Dahlquist[c] on behalf of EURODIAB Study Group

[a]Department of Pediatrics, University of Pécs, Hungary; [b]Department of Epidemiology and Public Health, The Queen's University of Belfast, United Kingdom; and [c]Department of Clinical Sciences, Pediatrics, Umea University, Sweden

Key words: epidemiology – global incidence – international registries – type 1 diabetes – type 2 diabetes

Corresponding author:
G Soltesz
Department of Pediatrics
University of Pécs
7623 Pécs József A. u. 7
Hungary.
Tel: 0036 72 535973;
fax: 0036 72 535971;
e-mail: gyula.soltesz@aok.pte.hu

Submitted 6 June 2007. Accepted for publication 20 June 2007

Epidemiology was developed as a tool to understand the cause of epidemic disease, but over the past 50 yr, epidemiological approaches have been rewarding also in the search for the etiology of non-communicable disease not least of complex diseases such as cancer, cardiovascular diseases and diabetes. Indeed, it is now well accepted that the population perspective is necessary to understand the complex interaction between genes and environment and for the identification of risk determinants, which may be further assessed in experimental studies to disclose the mechanism of action. Thus, epidemiology has become an important method for the ultimate aim of either primary prevention or secondary intervention.

Population-based disease registers are organized for different purposes such as health-care planning, quality assessment and epidemiological research. For the latter purpose, incidence registers looking at the dynamics of disease occurrence in the populations would be the most efficient.

International childhood diabetes registries

Two major international type 1 childhood diabetes registries (EURODIAB and DIAMOND) were established in the 1980s.

The primary goal of both projects was to establish a network for the prospective registration of newly

diagnosed children with type 1 diabetes in geographically well-defined regions using a standardized protocol.

By the end of the last millennium, 44 European centers have contributed to the incidence registration in EURODIAB. The corresponding population coverage represents about 30 million children and most European regions. At present, the registry comprises 47 000 children, 14 yr of age or younger, diagnosed between 1989 and 2006.

The DIAMOND network includes 112 centers from 57 countries from around the world, representing about 84 million children with the data set of 43 000 children diagnosed between the years 1990 and 1999 (1). Most European countries included in the DIAMOND study are members of EURODIAB.

Methods

The national and regional registries participating in the *EURODIAB and DIAMOND network* are using a standardized protocol for data collection. The registries have to be able, first, to identify all new cases of type 1 diabetes in which insulin treatment has started before the 15 yr of age within a geographically defined population for which reliable demographic data are available and second, to validate the completeness of ascertainment by at least one independent, secondary source.

Primary ascertainment was in most registries based on hospital records together with notification by family doctors and pediatricians.

Assessment of the completeness of ascertainment varies according to local conditions and is based on independent notification from other sources such as social insurance schemes, patient associations, summer camps for diabetic children, and prescription data.

In the EURODIAB network, study centers were visited by a 'site visitor', who reviewed the local study protocol and ascertainment procedures.

The incidence data center for DIAMOND is located at the Diabetes and Genetic Epidemiology Unit, National Public Health Institute, Helsinki, Finland (Jaakoo Tuomilehto and Marietta Karvonen), and for EURODIAB, the coordinating office was based at the Odense University Hospital, Odense, Denmark until 1999 (Anders Green), and since then it has been located at the Department of Pediatrics, University of Pécs, Pécs, Hungary (G. S. and Eva Gyürüs). Co-coordinators are G. D. (Umea Sweden) and C. P. (Belfast, UK).

Type 1 diabetes was defined on the basis of a clinical diagnosis of idiopathic diabetes by a doctor. Cases meeting this criterion were included if insulin treatment was started before the 15th birthday.

Age-specific and sex-specific incidence rates were calculated from the numbers of new cases divided by the estimated numbers of person-years 'at risk' in 5-yr age groups for each sex, the denominators being provided by the available demographic information from each center. To adjust for differences in age and sex between the study populations and to ensure mutual comparability, directly standardized rates were calculated; the common standard population assumes equal numbers in each of the age groups 0–4, 5–9, and 10–14 yr for each sex.

Results from descriptive epidemiological studies

Global variation in incidence

The first important result of the establishment of the international (and national/regional) registries was

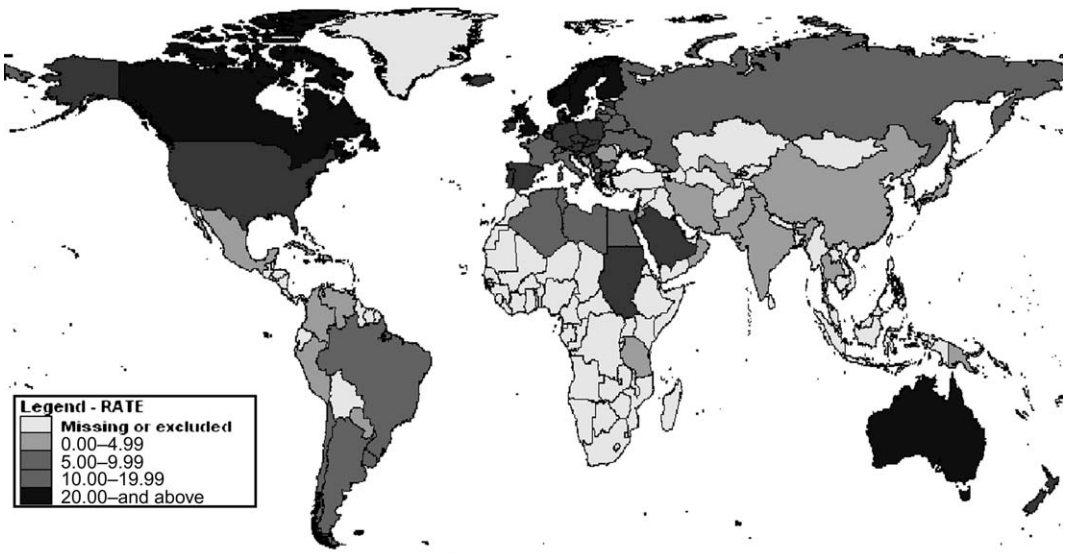

Fig. 1. Map of published incidence rates (per 100 000) of type 1 diabetes in children. Source: Soltész et al. (2).

the recognition of the extremely wide global variation in the incidence of childhood type 1 diabetes. The overall standardized incidence varies from 0.1/100 000 per year in the Zunyi region within China to more than 40/100 000 per year in Finland (1). This represents an approximately 400-fold variation in incidence in the over 100 populations/countries studied (Fig. 1) (2).

The brief account of the incidence in the various regions of the globe will follow the International Diabetes Federation (IDF) regions.

Europe. Europe has by far the most complete and reliable data. Many countries have registries that either are nationwide or cover several different parts of the country (Fig. 2). European countries show the broadest range of incidence rates.

The incidence rate is highest in populations in Europe or in populations of European origin (e.g., USA, Canada, Australia, and New Zealand) (1).

In Europe, a north–south gradient has been described (3, 4), with Sardinia as an outlier being 3000 km south of Finland and having a similarly high incidence rate.

A marked variation in incidence (from 6.0/100 000 per year to 36.9 per 100 000 per year) was found among the five populations of the relatively small area around the Baltic Sea (5).

Africa (sub-Saharan). Published rates are available in very few countries in this region. Some of the studies were of prevalence rather than incidence, of poor quality, and based on small numbers. Therefore, the validity of estimates in many parts of this region is questionable. Furthermore, tropical and malnutrition diabetes may account for a proportion of cases. The incidence in this region is generally low.

Eastern Mediterranean and Middle East. Reliable data are available in a number of African Countries bordering the Mediterranean Sea and in the Middle East Region. The incidence varies between 1/100 000 per year (Pakistan) and 8/100 000 per year (Egypt) (2).

North America. Rates for only a few countries are available, but these at least provide estimates for the three largest countries. USA (16.1/100 000 per year) and Canada (21 7/100 000 per year) have incidence rates similar to Northern Europe, but the incidence in Mexico is low (1.5/100 000 per year) (2).

South and Central America. The incidence in this region is generally low except for some South American countries, e.g., Argentina (6.8/100 000 per year) and Uruguay (8.3/100 000 per year) (2).

Southeast Asia. Only two countries, India and Mauritius, have published rates. Two sources for India are available, both from Urban Madras, and

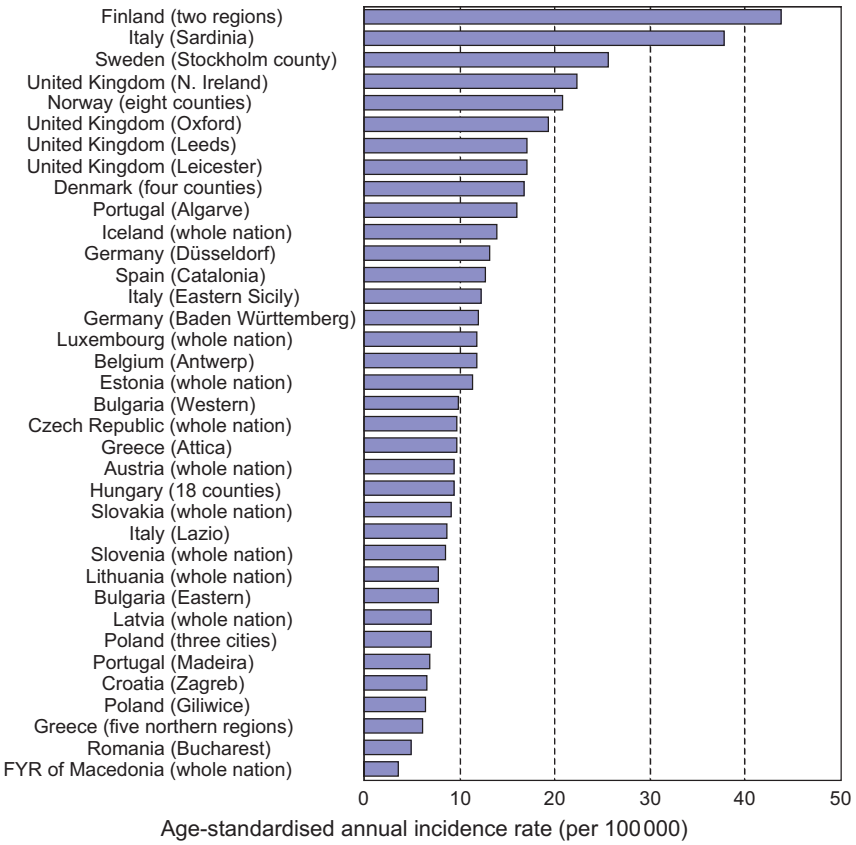

Fig. 2. Standardized incidence rates in 1989–1998 for 36 EURODIAB centers.

therefore not representative of the country as a whole. The first study showed an incidence rate of 4.2/100 000 per year, and the rate in the second study was more than double as compared with that in the first (2). The incidence in Mauritius was low (1.4/100 000 per year) (2).

Western Pacific. With the exception of Australia and New Zealand, the incidence in this region appears uniformly low. China, the world's most populous country, has one of the lowest incidence rates in the world (1).

Detailed tabulation of the worldwide incidence rates can be found in the recently published IDF ATLAS (2) and DIAMOND Report (1).

The explanation for the wide disparities in incidence between populations and ethnic groups could be the differences in the distribution of genetic susceptibility markers, differences in the distribution of environmental disease determinants, or the combination of both.

In Europe, the level of incidence was correlated with the prevalence in the general population of genetic susceptibility and protective markers encoded by the human leukocyte antigen-DQ loci. A positive association was found, suggesting that a substantial part of the transnational variation in incidence is explained by variation between populations in the distribution of DQ genotypes conferring a high risk for diabetes (6).

On the other hand, ecological correlation between incidence and various environmental, health, and economic indicators suggested that differences in environmental risk factors such as nutrition and lifestyle may be important in determining a country's incidence rate (7).

Within-country variation in incidence

In many countries having data from more than two registries, a marked within-country variation in incidence has been reported. The variation in incidence in the four Italian regions participating in EURODIAB was more than fivefold (4). This large difference was mainly because of the very high incidence in the Mediterranean island of Sardinia as opposed to other mainland Italian regions. The question is that – like in the case of the extremely wide global variation in incidence – to what extent this variation in incidence reflects variation in genetic susceptibility or environmental influences. Muntoni et al. have tried to answer this question by studying the incidence among children of Sardinian heritage, born and living in Lazio, a region of mainland Italy opposite to Sardinia across the Tyrrhenian Sea (8). The incidence in children born in Lazio to parents of Sardinian origin was fourfold higher than the incidence in children born to parents from mainland Italy. Children with one parent of Sardinian origin had intermediate risk. The finding supports genetic factors being more important than environmental factors in determining the high incidence in Sardinia, but the numbers of children in the study are very small, so the confidence limits are wide.

Important within-country differences in incidence have been reported for other countries as well. These may reflect ethnic differences (both genetic and lifestyle factors) (9), differences in body mass index (BMI) (10), area characteristics that are likely to be associated with exposure to infections such as deprivation, child population density, urban–rural status and remoteness (11).

Age-specific incidence

In most registries, the age-specific incidence rates are calculated and presented using 5 yr age groups (0–4, 5–9 and 10–14 yr) separately for boys and girls.

In general, the incidence increases with age, the incidence peak is at puberty with the associated gender effect (12). The pooled data of the DIAMOND group have demonstrated that the 5 to 9-yr olds had 1.62 (95% confidence intervals 1.57–1.66) times higher risk, and the 10 to 14-yr olds had 1.94 (1.89–1.98) times higher risk as compared with the 0 to 4-yr olds (1).

The age-specific incidence rates did not differ between the genders in most studies. However, if data are tabulated in 1-yr classes, then a difference in the age-specific incidence rates becomes apparent between boys and girls at the oldest ages (Svensson et al., submitted).

After the pubertal years, the incidence rate significantly drops in young women but remains relatively high in young adult males up to the 29–35 yr of age (12, 13).

Sex-specific incidence

Unlike the other common autoimmune diseases of childhood such as thyrotoxicosis and Hashimoto's thyroiditis, which affect mainly girls, type 1 childhood diabetes does not show a female bias. The overall sex ratio is roughly equal in children. A minor male excess in incidence have been reported in Europe and in populations of European origin and a slight female excess in populations of African or Asian origin (3, 14). There is a weak association between male sex and high incidence: populations with an incidence higher than 23/100 000 year have a male excess and populations with an incidence lower than 4.5/100 000 per year have a female excess.

In contrast to children, however, male excess is a constant finding in type 1 diabetes populations of European origin 15–40 yr of age (12, 13, 15, 16).

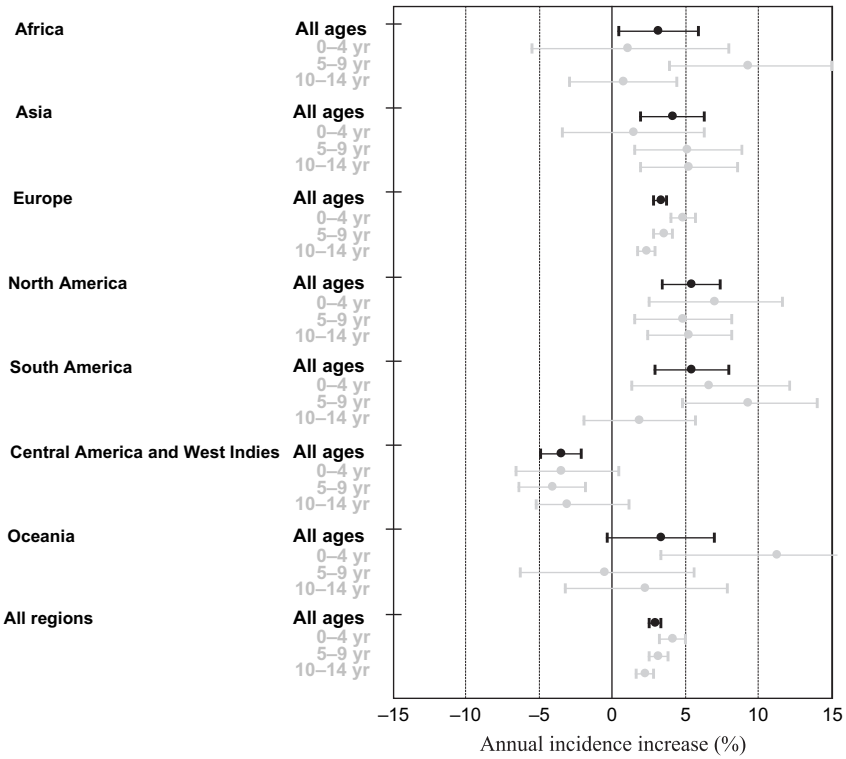

Fig. 3. Incidence rate changes (95% confidence intervals) by continent and age group. DIAMOND centers 1990–1999.

Temporal trends in incidence

Incidence trends in the 1990s have been summarized in two publications (1, 17). The DIAMOND analysis of trends by continent in 1990–1999 showed that increases were observed in every region with the exception of Central America and West Indies (Fig. 3). Only in Europe were numbers sufficient to enable a useful comparison of incidence rates in the three age groups, and here, there was clear evidence that increases were highest in the youngest age groups. Analysis of EURODIAB registration data for 1989–1998 in regions within Europe indicated that rates of increase were significantly different ($p < 0.001$) and that the highest rates of increase were occurring in Central Eastern European countries represented by the Hungarian, Romanian, Polish, and Slovakian centers.

Seasonality of onset

A seasonality of onset has been reported in many Northern Hemisphere studies (18) and in some Southern Hemisphere studies as well (19). Seasonality of diagnosis conformed well to a cyclic, sinusoidal model with a peak occurring in winter, a feature usually observed in both sexes and in all age groups. It is more pronounced in countries with marked differences between summer and winter temperatures, the greater the variation in temperature, the greater the variability of incidence in different seasons. In the analysis of the Swedish registry, a significant independent effect of monthly temperature on the incidence was found (20).

The seasonal variation of onset can be interpreted as an expression of the precipitating factors of the disease, such as infections and cold climate.

Seasonality of birth

It has been suggested that children who subsequently develop type 1 diabetes have a different seasonality of birth as compared with the background population supporting the hypothesis that perinatal viral infection is a trigger for the autoimmune process leading to type 1 diabetes. The literature is controversial. The analysis of data from 19 EURODIAB regions provided no consistent evidence that environmental factors, which vary from season to season, have any influence on the fetal and neonatal life to determine the onset of type 1 diabetes. Significant seasonality was confirmed only in two of five regions of Great Britain (21).

The issue of clustering of birth date in space and time remains to be resolved (22, 23).

Geographical variation of clinical presentation

Clinical and laboratory data of consecutive cases over one full calendar year were analyzed in the EURODIAB

network to study the possible geographical variation of clinical presentation. It was found that the frequency of presentation (onset) ketoacidosis defined as a pH of $\leq$7.3 varied from 26 to 67%, and there was an inverse correlation between the frequency of diabetic ketoacidosis and the background incidence rate (24). This suggests that the higher level of medical awareness in countries with higher incidence increases the chances of earlier diagnosis and reduces the risk of 'onset ketoacidosis'.

Results from analytical epidemiological studies

From descriptive epidemiological studies, we may formulate hypotheses about environmental triggers of disease in a population perspective. Based on patterns of disease occurrence as described above, such hypotheses have been addressed in analytical epidemiological studies, many of them directly connected to the registers. Over the past 20 yr, an increasing number of mainly case–control studies have thus been conducted in childhood-onset diabetes and a number of environmental risk factors have been associated with the disease, some of them with a potential for primary prevention.

From numerous animal experiments (see 25), seasonality of diabetes incidence as well as time space clustering and birth dates (21, 22) indicate infectious diseases to be involved. Conflicting results have been shown in retrospective studies, suggesting that unspecified infections before disease onset (26–28) may be associated with an increased risk whereas preschool day-care attendance, a proxy for early infection load, has been indicated to be protective (27, 29, 30). Population-based collection of maternal sera during pregnancy or at the time of delivery, however, clearly indicated association with viruses from the enterovirus group (31–33), and a large Finnish prospective cohort on high-risk individuals indicated an association with enteroviral exposure and diabetes onset (32, 34). Thus, epidemics of certain viruses such as enteroviruses may explain both some of the year to year temporal variation of incidence and also part of the seasonality of disease occurrence. The so-called polio hypothesis expands the hygiene hypothesis arguing that diabetes is increasing rapidly in countries like Finland and Sweden where the frequency of enterovirus infections has tended to decrease over the last decades (35). Thus, because of efficient vaccination programs, poliovirus, which is an enterovirus type, would increase the susceptibility of young children to the diabetogenic effect of different enteroviruses. Still, no clear associations have yet been found with any vaccination programs (26, 29, 36).

The findings of an association between fetal rubella infection and diabetes (37) as well as the findings of increased enteroviral antibodies among pregnant mothers whose children later became diabetics stimulated the search for environmental risk factors operating in the early period of life. A number of population-based studies has identified associations with maternal age (38–41), preeclampsia (38, 41), cesarean section delivery (38, 40, 41), increased birth weight (42), gestational age and birth order (38, 39, 40). Moreover, an intriguing association was found with blood group incompatibility not clearly separated from treatment effects (38). Many of these associations, i.e. old maternal age, maternal preeclampsia, neonatal respiratory disease, and blood group incompatibility, were confirmed in the large EURODIAB multicenter study, where blood group incompatibility was the strongest risk factor (43).

Early exposure through feeding patterns was highlighted by the epidemiological notion that diabetic children had been breastfed for a shorter time than controls, and this has been confirmed in a number of studies including a meta-analysis (44). From this observation, a large number of epidemiological and experimental studies started to analyze whether early introduction of cow's milk protein or cereal products could be the explanation rather than a protective effect from breast milk. It was early thought that different protein residues that could mimic antigens on the beta-cell surface were explaining this association (review in 45), but more recently, a new intriguing hypothesis was proposed by a Finnish group, arguing that an early exposure to cow's milk formula results in an immune response to bovine insulin present in minute amounts in such formulas and that this could trigger an immune response to insulin, a key beta-cell antigen (46). The cow's milk theory would also be compatible with the high diabetes incidence in milk-consuming countries such as Finland, Sweden, and Norway. A prospective intervention study is ongoing (TRIGR), to give an answer to the question of what harm early formula feeding may do (47).

Other interesting hypothesis that have been explored based on the north–south gradient and seasonality pattern of diabetes incidence is that of sunshine and vitamin D as a protector. In agreement with a series of experimental animal studies, a large European population-based case–control study clearly indicated vitamin D to be protective also in children (48).

Not only birth weight but also early child growth, defined either as height, weight, and BMI, has been associated with increasing risk for type 1 diabetes in a number of population-based studies based on prospectively recorded growth data (49–51). The largest study was based on five EURODIAB centers and involved almost 500 diabetic children and 1350 control

subjects. Height and weight standard deviation score (SDS) were significantly increased among patients from 1 month after birth, and the maximum risk difference occurred between 1 and 2 yr of age. The increased risk could be seen already with small increases in SDS when adjusted for several potential confounders (52). The increases in height and weight recorded in many western countries during the last decades correlates well with the linear increase in childhood diabetes incidence over time, seen in most countries. Because child growth is strongly associated with national GNP estimates, it was interesting that an ecological study covering 44 EURODIAB centers, showed correlations between GNP and childhood diabetes incidence (7).

Thus, descriptive, analytical, and to some extent ecological epidemiological studies have contributed to the puzzle of the complex etiopathogenesis of childhood-onset type 1 diabetes and to possible explanations of the increasing trends in incidence with time. Population-based studies have suggested that some environmental risk factors such as viruses may associate with the initiation of autoimmunity toward the beta cell. Whereas not all children who show signs of autoimmunity will develop diabetes (53), other exposures associated with lifestyle habits that may put an overload on the already attacked beta-cell accelerate the disease process (54, 55, 56), offering a comprehensive potential explanation for the descriptive findings of both the increasing trend seen in most westernized countries and an earlier age at onset.

Type 2 diabetes in children

Compared with type 1 diabetes, there is little information available on the epidemiology of type 2 diabetes in children. This is, at least in part, because of the fact that the symptoms and diagnosis of type 2 diabetes are less straightforward than those of type 1 diabetes. Only a few population-based studies have examined the epidemiology on type 2 diabetes in children. The currently available information comes mainly from clinic-based studies, case data, and the screening of groups of obese children and adolescents.

Type 2 diabetes affects mainly obese children and children who belong to certain ethnic populations; most children with type 2 diabetes are above 10 yr of age. Ethnicity appears to be an important factor. In USA, less than 5% of children of European origin in diabetes clinics have type 2 diabetes, and this percentage is even lower in Europe. But as many as 80% of children with diabetes of African, Hispanic, Asian, and Native American origin have type 2 disease. (57). These observations, in addition to the rising incidence of childhood obesity observed in many countries worldwide, call for population-based screening programs to monitor also the incidence of type 2 diabetes in childhood.

Conflicts of interest

The authors have declared no conflicts of interest.

References

1. The DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006: 23: 857–866.
2. Soltész G, Patterson C, Dahlquist G. Global trends in childhood type 1 diabetes. In Diabetes Atlas. chapter 2.1, 3rd edn. International Diabetes Federation, 2006: 153–190.
3. Green A, Gale EAM, Patterson CC; for the EURODIAB ACE Study Group. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE study. Lancet 1992: 339: 905–909.
4. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Lancet 2000: 355: 873–876.
5. Tuomilehto J, Podar T, Brigis G, et al. Comparison of the incidence of insulin-dependent diabetes mellitus in childhood among five Baltic populations during 1983-1988. Int J Epidemiol 1992: 21: 518–527.
6. Rønningen KS, Keiding N, Green A; on behalf of Genomic Marker Contributors and the EURODIAB ACE Study Group. Correlations between the incidence of childhood-onset type 1 diabetes in Europe and HLA genotypes. Diabetologia 2001: 44 (Suppl. 3): B51–B59.
7. Patterson CC, Dahlquist G, Soltész G, Green A; on behalf of the EURODIAB ACE Study Group. Is childhood-onset type 1 diabetes a wealth-related disease? An ecological analysis of European incidence rates. Diabetologia 2001: 44 (Suppl. 3): B9–B16.
8. Muntoni S, Fonte MT, Stoduto S, et al. Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. Lancet 1997: 349: 160–162.
9. Neu A, Willasch A, Ehehalt S, Kehrer M, Hub R, Ranke MB. Diabetes incidence in children of different nationalities: an epidemiological approach to the pathogenesis of diabetes. Diabetologia 2001: 44 (Suppl. 3): B21–B26.
10. Waldhör T, Schober E, Rami B; the Austrian Diabetes Incidence Study Group. Regional distribution of risk for childhood diabetes in Austria and possible association with body mass index. Eur J Pediatr 2003: 162: 380–384.
11. Cardwell CR, Carson DJ, Patterson CC. Higher incidence of childhood-onset type 1 diabetes mellitus in remote areas: a UK regional small-area analysis. Diabetologia 2006: 49: 2074–2077.
12. Pundziute-Lyckå A, Dahlquist G, Nyström L, et al. The incidence of insulin dependent diabetes has not increased in the 0-34 years group in Sweden 1983-1998. Diabetologia 2002: 45: 783–791.
13. Kyvik KO, Nystrom L, Gorus F, et al. The epidemiology of type 1 diabetes mellitus is not the same in young adults as in children. Diabetologia 2004: 47: 377–384.
14. Karvonen M, Pitkaniemi M, Pitkaniemi J, Kohtamaki K, Tajima N, Tuomilehto J. Sex differences in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. Diabetes Metab Rev 1997: 13: 275–291.

15. Weets I, De Leeuw IH, Du Caju MVL, et al. The incidence of type 1 diabetes in the age group 0-39 years has not increased in Antwerp (Belgium) between 1989 and 2000. Diabetes Care 2002: 25: 840–846.
16. Gale EAM, Gillespie KM. Diabetes and gender. Diabetologia 2001: 44: 3–15.
17. Green A, Patterson CC; on behalf of the EURODIAB TIGER Study Group. Trends in the incidence of childhood-onset diabetes in Europe 1989-1998. Diabetologia 2001: 44 (Suppl. 3): B3–B8.
18. Lévy-Marchal C, Patterson C, Green A; on behalf of the EURODIAB ACE Study Group. Variation by age group and seasonality at diagnosis of childhood IDDM in Europe. Diabetologia 1995: 38: 823–830.
19. Glatthaar C, Whittall DE, Welborn TA, et al. Diabetes in Western Australian children: descriptive epidemiology. Med J Aust 1988: 148: 117–123.
20. Dahlquist G, Mustonen L. Childhood onset diabetes – time trends and climatological factors. Int J Epidemiol 1994: 23: 1234–1241.
21. McKinney PA, EURODIAB Seasonality of Birth Group, Europe and Diabetes. Seasonality of birth in patients with childhood type 1 diabetes in 19 European regions. Diabetologia 2001: 44 (Suppl. 3): B67–B74.
22. Dahlquist G, Kallen BA. Time-space clustering of date at birth in childhood-onset diabetes. Diabetes Care 1996: 19: 328–332.
23. Patterson CC, Carson DJ, Hadden DR. Epidemiology of childhood IDDM in Northern Ireland 1989-1994: Low incidence in areas with highest population density and most household crowing. Diabetologia 1996: 39: 1063–1069.
24. Lévy-Marchal C, Patterson CC, Green A; on behalf of the EURODIAB ACE Study Group. Geographical variation of presentation an diagnosis of type 1 diabetes in children: the EURDIAB Study. Diabetologia 2001: 44 (Suppl 3): B75–B80.
25. Jun HS, Yoon JW. A new look at viruses in type 1 diabetes. Diabetes Metab Res Rev 2003: 19: 8–31.
26. Blom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study. Vaccinations and infections as risk determinants for diabetes in childhood. Diabetologia 1991: 34: 176–181.
27. Pundziute-Lycka A, Urbonaite B, Dahlquist G. Infections and risk of type I (insulin-dependent) diabetes mellitus in Lithuanian children. Diabetologia 2000: 43: 1229–1234.
28. Soltész G, Jeges S, Dahlquist G. Non-genetic risk determinants for type 1 (insulin-dependent) diabetes mellitus in childhood. Hungarian Childhood Diabetes Epidemiology Study Group. Acta Paediatr 1994: 83: 730–735.
29. EURODIAB Substudy 2 Study Group. Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. Diabetologia 2000: 43: 47–53.
30. Verge CF, Howard NJ, Irwig L, Simpson JM, Mackerras D, Silink M. Environmental factors in childhood IDDM. A population-based, case-control study. Diabetes Care 1994: 17: 1381–1389.
31. Dahlquist G, Ivarsson SA, Lindström B, Forsgren M. Maternal enteroviral infection during pregnancy as a risk factor for childhood insulin dependent diabetes mellitus – a population based case-control study. Diabetes 1995: 44: 408–413.
32. Hyoty H, Hiltunen M, Knip M, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study Group. Diabetes 1995: 44: 652–657.
33. Dahlquist GG, Boman JE, Juto P. Enteroviral RNA and IgM antibodies in early pregnancy and risk for childhood-onset IDDM in offspring. Diabetes Care 1999: 22: 364–365.
34. Hiltunen M, Hyoty H, Knip M, et al. Islet cell antibody seroconversion in children is temporally associated with enterovirus infections. Childhood Diabetes in Finland (DiMe) Study Group. J Infect Dis 1997: 175: 554–560.
35. Viskari HR, Koskela P, Lonnrot M, et al. Can enterovirus infections explain the increasing incidence of type 1 diabetes? Diabetes Care 2000: 23: 414–416.
36. Dahlquist G, Gothefors L. The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG-vaccination. Diabetologia 1995: 38: 873–874.
37. Menser MA, Forrest JM, Bransby RD. Rubella infection and diabetes mellitus. Lancet 1978: 1: 57–60.
38. Dahlquist G, Källén B. Maternal-child blood group incompatibility and other perinatal events increase the risk for early-onset type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1992: 35: 671–675.
39. Wagener DK, Laporte RE, Orchard TJ, Cavender D, Kuller LH, Drash AL. The Pittsburgh diabetes mellitus study. 3: An increased prevalence with older maternal age. Diabetologia 1983: 25: 82–85.
40. Patterson CC, Carson DJ, Hadden DR, Waugh NR, Cole SK. A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. Diabetes Care 1994: 17: 376–381.
41. McKinney PA, Parslow R, Gurney K, Law G, Bodansky HJ, Williams DR. Antenatal risk factors for childhood diabetes mellitus; a case-control study of medical record data in Yorkshire, UK. Diabetologia 1997: 40: 933–939.
42. Dahlquist G, Bennich SS, Kallen B. Intrauterine growth pattern and risk of childhood onset insulin dependent (type I) diabetes: population based case-control study. BMJ 1996: 313: 1174–1177.
43. Dahlquist GG, Patterson C, Soltesz G; for the EURODIAB Substudy 2 Study Group. Perinatal risk factors for childhood type 1 diabetes in Europe. Diabetes Care 1999: 22: 1698–1702.
44. Gerstein HC. Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. Diabetes Care 1994: 17: 13–19.
45. Dahlquist G. Nutritional factors. In: Leslie RDG, ed. Causes of Diabetes: Genetic and Environmental Factors. Chichester: Wiley, 1993: 125–132.
46. Vaarala O, Knip M, Paronen J, et al. Cow's milk formula feeding induces primary immunization to insulin in infants at genetic risk for type 1 diabetes. Diabetes 1999: 48: 1389–1394.
47. Akerblom HK, Virtanen SM, Ilonen J, et al. Dietary manipulation of beta cell autoimmunity in infants at increased risk of type 1 diabetes: a pilot study. Diabetologia 2005: 48: 829–837. Epub 2005 Apr 19.
48. The EURODIAB Substudy 2 Study Group. Vitamin D supplement in early childhood and risk for type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1999: 42: 51–54.
49. Blom L, Persson LA, Dahlquist G. A high linear growth is associated with an increased risk of childhood diabetes mellitus. Diabetologia 1992: 35: 528–533.
50. Johansson C, Samuelsson U, Ludvigsson J. A high weight gain early in life is associated with an increased risk of type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1994: 37: 91–94.

51. Hypponen E, Kenward MG, Virtanen SM, et al. Infant feeding, early weight gain, and risk of type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. Diabetes Care 1999: 22: 1961–1965.
52. The EURODIAB Substudy 2 Study Group. Rapid early growth is associated with increased risk of childhood type 1 diabetes in various European populations. Diabetes Care 2002: 25: 1755–1760.
53. Kulmala P, Savola K, Reijonen H, et al. Genetic markers, humoral autoimmunity, and prediction of type 1 diabetes in siblings of affected children. Childhood Diabetes in Finland Study Group. Diabetes 2000: 49: 48–58.
54. Dahlquist G. Environmental risk factors in human type 1 diabetes – an epidemiological perspective. Rev Diabetes Metab Rev 1995: 11: 37–46.
55. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. Diabetologia 2001: 44: 914–922.
56. Dahlquist G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. Diabetologia 2006: 49: 20–4. Epub 2005 Dec 14.
57. Singh R, Shaw J, Zimmet P. Type 2 diabetes in the young. Diabetes Atlas, chapter 2.2, 3rd edn. International Diabetes Federation, 2006: 193–207.