Geographical variation in the incidence of Type 1 diabetes in the Nordic countries: a study within NordicDiabKids

Short running title: Geographical incidence of Type 1 diabetes

Ulf Samuelsson[1], Lars Westerberg[2], Karin Aakesson[3], Niels Holtum Birkebæk[4], Ragnar Bjarnason[5], Ann Kristin Drivvoll[6], Torild Skrivarhaug[6], Jannet Svensson[8], Arni Thorsson[5], Lena Hanberger[7], Nordic Childhood Diabetes Registry Study Group, NordicDiabKids

[1]Department of Clinical and Experimental Medicine, Division of Paediatrics and Diabetes. Research Centre, Linköping University, Linköping, Sweden,

[2]IFM Biology, Linköping University, Linköping, Sweden

[3]Department of Pediatrics, County Hospital Ryhov, Jönköping, Sweden and Jönköping Academy for Improvement of Health and Welfare, Jönköping University, Jönköping, Sweden

[4]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark

[5]Landspitali University Hospital and Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[6]Norwegian Childhood Diabetes Registry, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway and Institute of clinical medicine, University of Oslo, Oslo, Norway

[7]Department of Medicine and Health Sciences, Div. of Nursing, Linköping University, Linköping, Sweden

[8]Herlev University Hospital, CPH-Direct, Pediatric Department, Herlev, Denmark and University of Copenhagen, Faculty of Health and Medical Science, Blegdamsvej 3B. 2200 Copenhagen

Author contributions: US took the initiative to the study. US and LW designed and conducted the statistical analysis. US, LH and KA wrote the first draft of the manuscript. All authors edited and reviewed the manuscript and approved the final version. US and LH are guarantors of this work.

Acknowledgements

We thank the Icelandic Thorvaldsens Foundation, The Danish Society for Diabetes in Childhood and Adolescence (DanDiabKids), the Norwegian Study group in Childhood and Adolescent Diabetes, and the Steering Committee of Swedish Paediatric Diabetes Quality Registry, SwedDiabKids. Our big thank to Professor Owe Löfman who started the project with us and did a great work at the beginning but unfortunately passed away.

Abstract

Background: The incidence of Type 1 diabetes (T1D) is high in the Nordic countries with geographic differences between as well as within countries.

Objective: To describe the geographical distribution of the incidence of T1D among children in four Nordic countries, an area where the population is considered genetically similar.

Methods: Data on children 0-14 years of age and diagnosed with T1D 2006 – 2011 was collected from four Nordic national pediatric quality diabetes registries. Data included year of diagnosis (2006 – 2011), sex, and age at diagnosis. Figures for number of children at risk during 2006 -2011 – as well as total population, proportion with foreign background and size of populated areas of geographic regions – were collected from official statistics.

Results: The total incidence during the study period for all four countries was 35.7/100 000 person years but differed between the countries (range 18.2 – 44.1; $p < 0.001$). The incidence difference between the countries was most obvious in the highest age group, 10-14 years of age, whereas there was no difference in the youngest age group 0-5 years of age. Iceland had similar incidence in the entire country, whereas the other countries had areas with different incidence. Densely populated areas, such as major cities, had the lowest incidence.

Conclusion: The incidence of T1D differed between the Nordic countries and also between the neighboring countries and generally decreased with population density. This indicates that environmental factors may contribute to the level of incidence of T1D.

Key words: Type 1 diabetes, incidence, children, geographical variation, environmental factors

Introduction

The incidence of Type 1 diabetes (T1D) is high in the Nordic countries, with the highest numbers in Finland and Sweden (1–3). Worldwide, T1D incidence has increased in recent decades (4–7), although there has been a leveling off in the Nordic countries over the past few years (8–12). The incidence of T1D differs between countries (4, 6), and regional differences have been observed in one country (12). Earlier, a north-south gradient was found in Europe, with the highest incidence rates in northern and north-western Europe and the lowest in southern and eastern Europe (13). In a German study, incidence was higher in the northern parts of the country than in the southern parts (14). However, no geographic gradient was found by Chong et al. in their Australian study (15). The reasons behind temporal trends and geographic differences within and between countries remain unresolved, but both genetic and environmental factors have been proposed.

Certain HLA types are associated with an increased risk of T1D (16) and may partly explain differences in incidence (17). As the proportion of newly diagnosed children with high-risk genotypes is decreasing, it has been suggested that environmental factors may trigger T1D in children with previously protective genes (16, 18).

A possible geographical covariation between incidence and geology has been found, and certain minerals in soil and drinking water have been associated with the risk of developing T1D (19). Moreover, a high level of 25-hydroxyvitamin D has been posited as a preventive or delaying factor in the progression to T1D (20, 21), although recent studies do not confirm any influence of vitamin D (22–24). The finding that seasonal variation exist, with higher incidence during autumn and winter (25, 26), may also suggest that environmental factors play a role for the risk of develop T1D. Also, being born in Sweden with parents originating from low-incidence countries increases the risk of T1D, further suggesting that environmental factors in fetal or early life are important for triggering T1D (27).

Different socio-economic factors have also been studied where incidence of T1D is correlated to higher wealth. On a small scale, families with few children, high education and income had higher incidence, while gross domestic product (GDP) correlated positively with incidence on a European scale. Also, increased population density has been found to correlate with lower incidence (28, 29, 30).

In this study we describe the geographical distribution of the incidence of T1D between 2006 and 2011 among children in four Nordic countries, an area where the population is considered

genetically similar (31). We specifically ask whether there are differences within and between countries and whether geographical gradients exist. We also explore the relationship with population density, GDP and foreign background as these are available for geographical mapping and can be considered being confounding factors when studying the mechanisms that may trigger T1D. The countries included in this study have population-based national pediatric diabetes quality registries with data on all children with diabetes, which makes this study possible. The registries in Denmark and Iceland were established, with the current organizations, in 1996, followed by Sweden in 2000 and Norway in 2006 (1).

Methods

Study population

Data on children diagnosed with T1D 2006–2011 was collected from the Nordic national childhood databases—the Danish Childhood Database (DanDiabKids), the Iceland Childhood Diabetes Register (ICDR), the Norwegian Childhood Diabetes Register (NCDR) and the Swedish Pediatric Diabetes Quality Register (SWEDIABKIDS)(1, 27, 32). The extracted data included year of diagnosis (2006–2011), sex, and age at diagnosis (0 to 4, 5 to 9 and 10–14 years, respectively) (Table 1). Geographic data on area of residence at diagnosis was available at various local administrative levels and was aggregated at regional administrative level (henceforth “regions”). For Iceland, data was recorded at local postcode level (n=131) and aggregated into two regions: either within or outside the Reykjavik region (n=2). For Denmark, the data was collected per municipality (n=98) and aggregated into regions (in Danish “landsdel”, n=11). The same was done for Norway, in which municipalities (n=428) were aggregated into regions (in Norwegian “fylke”, n=19) and Sweden, in which municipalities, (n=290) were aggregated into regions (in Swedish “län”, n=21). Figures for total population, population with foreign background and number of children at risk (21,191,716 person years in total) in the local administrative levels during 2006–2011 were collected from official statistics (33–36). The total population in the four countries in 2009 was about 20 million, with 9.4 million in Sweden, 5.6 million in Denmark, 4.9 million in Norway and 0.32 million in Iceland.

Data analysis

Incidence was calculated as the number of children diagnosed from 2006 to 2011 per 100,000 person years. Differences in incidence between countries were estimated for data at regional administrative level. A negative Binomial regression (without intercept and with log (population at risk) as offset) was used to estimate the effect of country (Denmark, Norway and Sweden), population density and the interaction, on the incidence. The interaction allows for estimating if the effect of population density is different between countries. The negative binomial was preferred over standard Poisson regression as the latter was over dispersed.

Standardised mortality ratio, i.e. the ratio between observed and expected number of diagnosed children, is used to illustrate the geographical variation in incidence. It is calculated as the observed diagnoses for a region divided by the expected number based on the rate in the general population.

Population density was estimated by dividing the total population of a region with the total area of urban texture in the European Corine Land Cover data set for 2006 (class: artificial land cover). ArcGIS 10.2 (ESRI 2015) was used for maps and analysis of geographical data (37). The package for all statistical analyses was R (38)

Results

The total incidence during 2006–2011 for all four countries combined was 35.6 (Table 1). The overall incidence was lowest in Iceland and highest in Sweden (Table 1). The regression analysis indicated that incidence differed significantly between the Nordic countries ($p<0.001$). It was especially Sweden that was high (coefficient, 95% confidence interval and p-value of partial regression coefficient was -7.34 [-7.52, -7.17], $p<0.001$), while confidence intervals for Denmark and Norway overlapped (Denmark -8.0 [-8.14, -7.84], $p<0.001$, and Norway -7.74 [-7.89, -7.58], $p<0.001$). During these six years, there was a yearly variation in incidence, which was about the same for girls and boys. In Denmark the incidence during this period was higher for girls (27.2) than for boys (26.3). In the other countries, the incidence was higher for boys than for girls. This was most obvious in Norway, which reported averages of 33.7 and 30.9 respectively. Some areas showed somewhat higher incidence for girls as well as areas of higher incidence for boys, but these were randomly distributed. For comparison, Table 2 also includes data on the proportion of foreign citizens and the gross domestic product (GDP) per capita in the Nordic and neighboring countries.

The youngest age group, 0–4 years, showed no obvious incidence difference between the countries (Figure 1). There were more obvious differences in the 5–9 years age group and in particular for 10–14 year-olds, where most regions in Sweden had an average incidence above 60/100 000, followed by Norway. For comparison, mean age at onset over the study period differed slightly between years and between Denmark (range: 9.0–9.7 years of age), Iceland (9.6–11.9), Norway (8.5–9.5) and Sweden (8.5–9.5). Iceland had the highest mean age range.

Standardised mortality ratio show that incidence is generally lower in regions with more children, and when neighbouring regions have many children (Figure 2). It is also clear that incidence is very different between countries and that geographic variation does not correlate clearly across borders. There is an overall greater geographic variation in Sweden and Norway, where the northern part of Sweden has the highest incidence. Densely populated areas, such as major cities and southern Sweden, had the lowest incidence, yet higher than most neighbouring countries (Table 2; Figure 2 & 3). Incidence generally decreased with population density for all countries (negative Binomial regression coefficient for density: -1.4e-4 95% CI: [-2.2e-4, -6.0e-5], $p<0.001$), and the effect of density did not differ between countries ($p>0.05$). The incidence converged at approx. 20 per 100,000 at densities >4000 per km^2 of urban area for all countries (Figure 3). Population density correlated positively with the number of citizens with foreign background (Denmark $r=0.85$, $p<0.001$; Iceland $r=0.73$; Norway $r=0.82$, $p<0.001$; Sweden $r=0.78$, $p<0.001$).

Discussion

This study showed that the incidence of T1D varied between and within the Nordic countries, with low transborder similarity. There was a geographical north-south gradient but that coincide with the concentration of larger cities in the south. The incidence was, as in other studies (29, 31, 44, 45), lowest in the major cities and densely population areas and highest in relatively sparsely populated areas and/or rural areas in Sweden, Denmark and Norway, but not Iceland. A suggested explanation for the rise in the incidence of T1D has been the hygiene hypothesis, as countries reporting low exposure to infectious agents in early childhood have an increased susceptibility to T1D (29,42,43). A plausible reason for the lower incidence in densely populated areas could therefore be that the childhood population is more exposed to infectious agents than children in rural areas. Studies have shown that living in a high-density area with a wider range of infections offers protection against getting T1D (29,31,44,45).

When comparing the national incidences, Sweden which is the most easterly of the Nordic countries, had the highest incidence, whereas in the other three countries further west, incidence was lower. Finland, although not included in this study, but even further to east, has the highest incidence of diabetes in the world (41). This indicates that an east-west gradient may be plausible. On the other hand, this hypothesis might be contradicted by the lower incidence of T1D in the Baltic states and Poland. This unclear pattern could be due to the influence of historical migration between the countries (46, 47). Furthermore, during almost 700 years up to 1809 Finland and Sweden was considered as one country and the most southern part of Sweden was considered as one country with Denmark up to 1658 when that part become Swedish. Further studies are needed to elucidate if there is a common genetic background between Finland and northern Sweden that cause high incidence.

Socioeconomic factors may also contribute to incidence differences. Some found higher incidence in areas with a high proportion of families with high income (30, 48) contrary to another study in adults that showed a higher incidence in more deprived areas (49). Socioeconomic data is not included in the present study. Instead, the official GDP from 2011 was used as a proxy marker for socioeconomic status (40). Most of the countries with high incidence also had high GDP, whereas most of the countries with low incidence around the Baltic Sea had low GDP. However, the pattern is unambiguous.

The major cities in Denmark, Norway and Sweden had a low incidence and a high proportion of foreign citizens. However, it is difficult to separate the effect of population density and the proportion of population with a foreign background as they are greatly correlated. Future, preferably individual-based studies of incidence of T1D, socio-economic and population density factors need to carefully separate, or control for, these intertwined and potentially confounding factors.

In the lowest age group (0–4 years of age at diagnosis), the incidence figures in the four countries were rather similar. The difference began to appear among children aged 5–9 years at diagnosis and was most obvious in the oldest age group. Could this be due to immunological, genetic or environmental factors or are some factors still unknown to us? As the mean age at onset in these four countries is rather similar, this could neither explain the incidence differences nor could any conclusion be drawn by the random distribution of area differences in incidence between boys and girls. Another explanation is purely numerical: that diagnosis is cumulative and differences are not visible early in the process.

The strengths of the study were that the population consisted of data on the absolute majority of children with T1D in the four Nordic countries in a six-year period and data completeness was high. All four countries have comparable health care systems and free access to health care.

The study is limited in that information on immunological and genetic variables, and ethnicity was not included, although it was assumed that the population in these four neighboring was genetically similar (31). This limitation may, as mentioned above, be solved by individual based studies.

To summarize, this study showed that there are differences in incidence of T1D between the Nordic countries and also between neighboring countries. There is a T1D incidence gradient, with lower incidence in highly populated areas and high incidence in sparsely populated areas. Assuming that the populations are genetically similar, the difference between countries and the notably lower incidence in areas of high density suggest that environmental factors may contribute to the level of incidence of T1D. How socioeconomic factors and immunological aspects are associated with incidence of T1D must be further explored.

Funding

This project was supported by the Health Research Fund of Central Denmark Region, and the Swedish Board of Health and Welfare and the Swedish Association of Local Authorities and Regions. The Norwegian Childhood Diabetes Registry is financed by the South-Eastern Norway Regional Health Authority. The Danish registry is funded by the Danish Regions' Clinical Quality Development Programme. The funding source has no role in data collection or analysis

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Table 1. Number of children with Type 1 diabetes in total, and for different ages, in the Nordic countries during 2006-2011.

	Denmark	Iceland	Norway	Sweden	*Total*
Diagnose	1612	72	1764	4112	7560
Person years	6033701	396469	5429153	9332393	21191716
Incidence	26.7	18.2	32.4	44.1	35.6
Range (min-max)	19.1-32.1	17.0-19.8	22.4-46.8	35.0-62.3	17.0-62.3
N regions	11	2	19	21	53
Age 0 to 4					
Diagnose (%)[1]	281 (17%)	10 (14%)	326 (18%)	905 (22%)	1522 (20%)
Person years	1949214	134365	1769359	3252249	7105187
Incidence	14.4	7.44	18.4	27.8	21.4
Age 5 to 9					
Diagnose (%)[1]	546 (34%)	25 (35%)	616 (35%)	1475 (36%)	2662 (35%)
Person years	1996225	128028	1788362	2983522	6896137
Incidence	27.4	19.5	34.4	49.4	38.6
Age 10 to 14					
Diagnose (%)[1]	785 (49%)	37 (51%)	822 (47%)	1732 (42%)	3376 (45%)
Person years	2088262	134076	1871432	3096622	7190392
Incidence	37.6	27.6	43.9	55.9	46.9

1) percent diagnosed per age group and country.

Table 2. The mean incidence per 100,000 children 0–14 years of age during 2006–2011. GDP and proportion of foreign citizens in the studied area and surrounding countries from 2011

	Incidence/100 000[b]	GDP per capita (USD)[c]	Foreign citizens (%)[c]
Sweden	44.1 (SD 3.7)	59. 593	15.1
Stockholm[a]	33.8		21.7
Gothenburg[a]	39.3		17.0
Norway	32.4 (SD 5.4)	100.574	12.4
Oslo[a]	22.4		28.3
Denmark	26.7 (SD 3.5)	61.904	7.9
Copenhagen[a]	17.5		16.1
Iceland	18.2	45.971	10.9
Reykjavik[a]	19.2		
Finland	57.6	50.788	4.9
Germany	18.0	45.936	12
Estonia	17.1	17.454	15.8
Lithuania	7.8	14.367	1.2
Latvia	7.5	13.781	17.9
Poland	17.3	13.891	1.8
Russia	12.8	14.212	

a) Municipality; b) this study and the IDF-atlas (41); c) OECD-data (39,40);

Figure legends

Figure 1. The proportion of children with T1D between 0–4, 5-9 and 10-14 years of age, 2006–2011. The size is proportional to the number of diagnosed children. Some pie charts have been moved to reduce overlap.

Figure 2. The Standardized Mortality Ratio (the ratio between observed and expected number of children with T1D, assuming an expected rate of 35.7 per 100,000 person years) for regional administrative units in Denmark, Iceland, Norway and Sweden. The size of circles indicates the person years for that region. The location of some circles has been moved to reduce overlap. The incidence for T1D per 100,000 person years is indicated for neighboring countries.

Figure 3. The relationship between incidence of T1D in 2006–2011 in regional administrative units in Sweden (N=21), Norway (N=19), Denmark (N=11) and Iceland (N=2), and population density based on total urban area (km^2). Size of symbols is proportional to total population. Labels indicate the regions that contain the ten largest cities: AARhus, BERgen, COPenhagen, GOThenburg, MALmö, OSLo, REYkjavik, STAvanger, STOckholm and TROndheim.