Spatiotemporal Trends and Age-Period-Cohort Modeling of the Incidence of Type 1 Diabetes Among Children Aged <15 Years in Norway 1973–1982 and 1989–2003

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OBJECTIVE — We have investigated age-period-cohort effects and spatial and temporal trends for the incidence of type 1 diabetes among 0- to 14-year-old children in Norway.

RESEARCH DESIGN AND METHODS — We included children with the diagnosis of type 1 diabetes in Norway during 1973–1982 and 1989–2003. We studied age, calendar period, and birth cohort effects using Poisson regression, including Holford's method of parameterization, to model the dependencies between age, period, and cohort effects. To study spatiotemporal clustering of cases, we used spatial scan statistics.

RESULTS — The overall incidence rate for the study population <15 years of age was 22.7 cases per 100,000 (95% CI 22.1–23.4), showing an average annual increase of 1.2% (95% CI 0.7–1.5%) during the study period. One specific area with 30% increased incidence rates was identified in the southern part of Norway during 1976–1980 ($P = 0.001$). Also, children born during 1964–1966 in a specific region in the southern part of Norway as well as children born during 1987–1989 in a region in northern Norway showed 2.0 and 2.6 times, respectively, higher incidence rates compared with the rest of the country (both $P = 0.001$).

CONCLUSIONS — The incidence of type 1 diabetes among children increased during the study period. Birth cohort effects were identified using the spatiotemporal scan statistic but not using age, period, and birth cohort modeling. Such effects, within the relatively homogenous Norwegian population, suggest the influence of nongenetic etiological factors.

Diabetes Care 30:884–889, 2007

The incidence of type 1 diabetes among children is increasing worldwide (1,2). The incidence rate varies among countries and is highest in the Nordic countries (1). The etiology of the disease is not known. The presence of genetic components is evident, but nongenetic factors are also thought to be involved in the etiology. Different environmental factors are suggested, such as infections, nutritional factors, and toxins (3). Several of these show different spatial and temporal variability. Specific infections are often limited in space and time, and dietary factors reflect cultural differences and show both geographic and temporal variability. If associations among such exposure variables and the disease exist, it is likely that the distribution of the disease also depends on geographic location, time of birth (birth cohort), or calendar period. If the incidence rate increases steadily over time (linearly), the increase may be attributable to a steadily increasing exposure to one or more risk factors or steadily decreased exposure to protective factors, as opposed to nonlinear or epidemic-like patterns in incidence rates, which may point to potential etiological factors changing abruptly over time. For instance, nonlinear birth cohort effects could be consistent with epidemics of specific congenital infections. It is therefore of importance to depict the geographic and temporal distribution of the disease as precisely as possible to enable identification of potential etiological factors. The linear dependence among age, period, and cohort makes it necessary to apply specific modeling strategies for this task (4,5).

Calendar period, birth cohort, and age effects are described in different studies of type 1 diabetes (6–11), but few studies have been devoted to age-period-birth cohort modeling. Spatial variability has also been studied with different methodological approaches (8,12–14), but few studies have used a combined spatiotemporal approach to type 1 diabetes.

Temporal trends and regional variation in incidence of childhood-onset type 1 diabetes among counties in Norway have been published previously for the periods 1973–1982 (15) and 1989–1998 (16). In addition to presenting new data for the period 1999–2003, we aimed to study both temporal and spatial trends in the incidence for the combined nationwide data collected for 1973–1982 and 1989–2003, including age, period, and cohort modeling.

RESEARCH DESIGN AND METHODS

— All children <15 years of age with the diagnosis of type 1 diabetes are included in the Norwegian Child-

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Received for publication 26 July 2006 and accepted in revised form 20 December 2006.

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Abbreviations: APC, age-period-cohort.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-1568

hood Diabetes Registry. Children were included retrospectively during 1973–1982 and prospectively from 1989 to the present date, both with a high level of ascertainment (15,16). In this study, we included cases until December 31, 2003.

Norway is situated in the northwestern part of Europe and consists of 19 counties and 434 municipalities. The Norwegian population was 4,557,457 inhabitants in 2004: 467,046 were boys and 443,490 were girls <15 years of age. The size of the population aged <15 years varies considerably in the municipalities. The median, 25th, and 75th percentiles were 4,455, 2,210, and 9,470 inhabitants, respectively. Data on population size for each sex and the 3-year age-groups in each single calendar year were taken from Statistics Norway (http://www.ssb.no).

Age-period-cohort analysis

Age-period-cohort (APC) models were used to study different time trends. The APC model is associated with an intrinsic problem of dependencies among the variables age, calendar period, and birth cohort. To solve this problem, we used Holford's method (4,5). The calendar period and birth cohort effects are split into two parts: a linear part called the drift component, which is common to both calendar period and birth cohort and which represents a constant annual change in the incidence rate, and nonlinear parts that are attributed specifically to either the calendar periods or the birth cohorts. The incidence rate is thus modeled as a function of age, calendar period, and birth cohorts, according to the log-linear model:

$$\log(\lambda_{abc}) = A_a + D \cdot p + P_p + C_c,$$

where λ_{abc} is the incidence rate, A_a is the age effect for age-group a, D is the drift component described above, P_p is the calendar period effect for calendar period p, and C_c is the birth cohort effect for birth cohort c. In this application, the drift component was chosen to be dependent on calendar period p, as a continuous variable, and for the nonlinear part, the calendar period is included as a categorical variable. The calendar period and birth cohort effects are therefore independent of the linear drift component.

We used a likelihood ratio test to compare different models. The observations were categorized into 3-year intervals: The groups for age at onset were 0–2, 3–5, 6–8, 9–11, and 12–14 years of age. The calendar periods were 1973, 1974–1976, and 2001–2003. This resulted in 15 birth cohorts from 1958 to 2003 with corresponding middle years 1959 and 2001.

Spatial and spatiotemporal trend analysis

To investigate whether specific calendar years or specific birth cohorts showed any elevated incidence rate of the disease at some specific geographic locations, we used a spatial scan statistic (17). This method is based on a comparison of the number of expected and observed cases within different circles drawn from each municipality. The spatial scan method works as follows. Circles of different sizes (from 0 up to 50% of the total population size) are placed at every municipality in Norway. For each circle (C), a likelihood statistic $L(C)$ is computed on the basis of the number of observed and expected cases within and outside the circle and compared with the likelihood L_0 under the null hypothesis. The circles with the highest likelihood ratio values $[L(C)/l_0]$ are identified as potential clusters. The spatiotemporal extension of the scan method includes the temporal registrations, which are given on an annual basis. An associated P value, based on Monte Carlo simulations, is computed and used to evaluate whether the cases are randomly distributed in space. For each simulation the likelihood ratio statistic is computed, and the observed value is compared with the set of simulated values to find the significance probability. We used the SaTScan software, version 5, to identify the clusters (http://www.satscan.org). The P values were based on 999 Monte Carlo simulations. Because the onset of the disease is dependent on age, we used the covariate adjustment facility in SaTScan when identifying spatiotemporal clusters among the birth cohorts. We included a linear temporal trend to avoid an arbitrary trend in the last interval of the study interval.

Separate analyses were performed for *1*) pure spatial clusters, *2*) spatiotemporal clusters for calendar periods, and *3*) spatiotemporal clusters for birth cohorts. For the pure spatial analysis and spatiotemporal analysis for diagnostic periods, models were fitted for the two periods of registration (1973–1982 and 1989–2003). The spatial scan method has been shown to have satisfactory power in detecting clusters but difficulties in identifying the shape of the clusters for low magnitudes of incidence rate ratios (18,19).

RESULTS — Estimated incidence rates (with corresponding 95% CIs) for sex, age-groups, calendar periods, and county are shown in Table 1. The mean incidence rate for children aged 0–14 years was 22.7 (22.1–23.4) cases per 100,000 and was increasing during the study period.

APC study

Table 2 shows the results from the APC models, in which sex is also included. The model that best fit the data included sex, age, the drift component, and calendar period (model 6, Table 2). The drift component is common to both the calendar period and birth cohort. The calendar period included in the model is a nonlinear effect deviating from the linear drift component and showed that there were higher incidence rates during the last part of the study period. The birth cohort component was not statistically significant once age, period, the drift component, and cohort were included in the model ($P = 0.471$, compare models 6 and 9 in Table 2). The incidence rate was 1.12 (95% CI 1.06–1.17) times higher for boys than for girls. The age component showed a peak for children in the age-group between 9 and 11 years (see also Table 1). The drift component showed an annual increase of 1.2% (95% CI 0.7–1.5%). To study whether the age at onset changed during the study period, we included an interaction term between age and the drift component in the model (see Table 2, models 6 and 10). The interaction term was not significant ($P = 0.527$), showing that such a change was not present in our data.

Calendar period and geographic location

Incident cases during the period 1973–1982. The result from the spatial scan method for pure spatial clusters showed one cluster during 1973–1982, located in the southern part of Norway ($P = 0.001$). The incidence rate was 23.7 per 100,000 in the cluster, which is 1.2 times higher than expected. The result from the spatiotemporal analysis showed one cluster for this period of time. The cluster was located in the central part of southern Norway during the years 1976–1980 (Fig. 1*A*). The incidence rate was 25.0 per 100,000 in the cluster, which was 1.3 times higher than expected ($P = 0.001$).

Table 1—*Number of cases, person-years under observation, and incidence rates among Norwegian children aged <15 years in 1973–1982 and 1989–2003 by sex, age, calendar period, and county*

	Person-years at risk	Cases	Incidence rate (95% CI)
Total	22,151,884	5,035	22.7 (22.1–23.4)
Sex			
Boys	11,360,366	2,726	24.0 (23.1–24.9)
Girls	10,791,518	2,309	21.4 (20.5–22.3)
Age			
0–2 years	4,346,219	437	10.1 (9.1–11.0)
3–5 years	4,457,538	849	19.0 (17.8–20.3)
6–8 years	4,507,975	1,133	25.1 (23.7–26.6)
9–11 years	4,469,145	1,391	31.1 (29.5–32.8)
12–14 years	4,371,007	1,225	28.0 (26.5–29.6)
Calendar period			
1973	956,799	183	19.1 (16.4–21.9)
1974–1976	2,857,724	507	17.7 (16.2–19.3)
1977–1979	2,789,610	615	22.0 (20.3–23.8)
1980–1982	2,674,977	598	22.4 (20.6–24.1)
1989–1991	2,418,994	549	22.7 (20.8–24.6)
1992–1994	2,489,587	545	21.9 (20.1–23.7)
1995–1997	2,576,283	584	22.7 (20.8–24.5)
1998–2000	2,664,800	668	25.1 (23.2–27.0)
2001–2003	2,723,112	786	28.9 (26.8–30.9)
County			
Østfold	1,182,074	297	25.1 (22.3–28.0)
Akershus	2,269,578	502	22.1 (20.2–24.1)
Oslo	1,917,584	403	21.0 (19.0–23.1)
Hedemark	886,410	188	21.2 (18.2–24.2)
Oppland	881,861	210	23.8 (20.6–27.0)
Buskerud	1,108,320	276	24.9 (22.0–27.8)
Vestfold	1,008,710	244	24.2 (21.2–27.2)
Telemark	809,229	208	25.7 (22.2–29.2)
Aust-Agder	514,141	134	26.1 (21.6–30.5)
Vest-Agder	817,653	243	29.7 (26.0–33.5)
Rogaland	1,998,405	452	22.6 (20.5–24.7)
Hordaland	2,254,383	512	22.7 (20.7–24.7)
Sogn og Fjordane	584,236	144	24.6 (20.6–28.7)
Møre og Romsdal	1,307,326	275	21.0 (18.5–23.5)
Sør-Trøndelag	1,326,359	306	23.1 (20.5–25.7)
Nord-Trøndelag	698,165	144	20.6 (17.3–24.0)
Nordland	1,310,933	292	22.3 (19.7–24.8)
Troms	827,346	158	19.1 (16.1–22.1)
Finnmark	449,176	47	10.5 (7.5–13.5)

Incident cases during the period 1989–2003. The result from the pure spatial analysis showed two spatial clusters. The first cluster was situated in the southern part of south Norway and showed an incidence rate equal to 33.6 per 100,000, which is 1.5 times higher than expected ($P = 0.001$). The second cluster was situated in the middle part of southern Norway and showed an incidence rate equal to 25.9 per 100,000. This was only 1.1 times higher than expected ($P = 0.017$). During this registration period, one spatiotemporal cluster close to statistical significance and located in the southern part of Norway during the last 4 years (2000–2003) was identified (Fig. 1*B*). The incidence rate was 1.3 times higher than expected ($P = 0.076$).

Birth cohorts and geographic location

Two clusters of elevated risk of type 1 diabetes for birth cohorts and sites were identified. The first cluster consisted of children born during 1964–1966 in the southern part of Norway. The number of observed cases was 304 children, and the number of expected cases from the SaTScan method was 151.2 children. Thus, the incidence rate was 2.0 times higher than expected for children in this cluster ($P = 0.001$). The other cluster was found for children born during 1987–1988 in specific municipalities in the northern and middle parts of Norway. For this cluster, the number of cases was 173 children, and the expected number of cases using the SaTScan method was 67.7 children, leading to an incidence rate 2.6 times higher than expected ($P = 0.024$). Both clusters are shown in Fig. 1*C*.

CONCLUSIONS — Our studies show that despite a stable incidence period from 1989 to 1998 (16), the incidence of type 1 diabetes increased in a nonlinear way during the study period. We found no overall cohort effect for Norway, but there were indications that children born during specific intervals and living in specific regions experienced relatively high incidence rates. Children living in a region in southern Norway were also more likely to get the disease during some time intervals. The regions identified as hotspot clusters were relatively large, with modest increases in incidence, although the increases were up to 2.6-fold in models including spatiotemporal windows.

Strengths and limitations

A strength of our study is that the Norwegian Childhood Diabetes Registry includes all municipalities in Norway during two long periods of time. Our data lack registrations between 1983 and 1988. Still, we cover all birth cohorts from 1958 to 2003. The spatial scan method applied enabled us to identify not only the presence but also the locations and the temporal window of the clusters, in contrast to studies in which a global cluster detection method, such as Knox's method, is used to identify the presence, but not the location, of the clusters (14). Knox's method is also dependent on a relatively arbitrary limit of closeness both in space and time. In other studies (8,12,13), different disease mapping methods have been used, based on, for instance, Bayesian statistics (8,12). The spatial scan method we used has excellent properties to detect the presence of clusters, but for incidence rate ratios with magnitudes of 1.2–1.5, the identification of the areas with increased incidences is difficult and shows low sensitivity (18). The specificity is still good (>99%), and it is therefore likely that the "true" areas

Table 2—*Results from the APC modeling*

Model	Variables	Deviance	df
0	Null model	800.6	89
1	Sex	785.6	88
2	Age	192.6	85
3	Period + D	714.6	81
4	Cohort + D	639.7	75
5	Sex + age	177.7	84
6	Sex + age + period + D	89.3	76
7	Sex + age + cohort + D	93.9	70
8	Sex + period + cohort + D	464.2	67
9	Sex + age + period + cohort + D	76.6	63
10	Sex + age + period + D + age × period	88.9	63
11	Sex + age + period + D + sex × period	89.1	62

Model comparisons	Δ Deviance	Δdf	*P*
Models 2 and 5	14.9	1	<0.001
Models 5 and 6	88.4	8	<0.001
Models 5 and 7	83.8	14	<0.001
Models 6 and 9	12.7	13	0.471
Models 6 and 10	0.4	1	0.527
Models 6 and 11	0.2	1	0.654

D, drift.

with elevated incidences of type 1 diabetes are located near the identified clusters. The SaTScan method is also dependent on some specific choice of the geographic units. We used the municipalities as our unit, and some of the larger municipalities could potentially hide hot-spot clusters, although most municipalities have relatively low population sizes. Clusters intersecting parts of a set of municipalities are also difficult to detect.

Comparisons with previous studies

Age, period, and birth cohort effects are described in a few previous studies with some variation in results, probably in part because of differences in study size, length of calendar periods, and methods of analysis. An increased incidence of type 1 diabetes was shown for children born after 1985 in Denmark (6). An additional period effect was not significant in that study. In a Swedish investigation (7), the authors found a linear period effect and a shift of onset to younger children during the study period. No birth cohort effect was found. A report from Yorkshire, U.K. (20), concluded that the incidence rate increased during the study period and that there was a change to younger age at onset. In the same study these authors identified two cohorts (children born in 1985 and 1995) with sharp increases of incidence. Examinations in Italy (8,9) showed a general drift in the period and birth cohort, and in a Finish study (21), a period effect was shown, but a birth cohort effect was not found to be statistically significant. Rewers et al. (10) reported that the incidence of type 1 diabetes in a Polish county showed a significant period effect, but no similar period effect was found for a U.S. county. Thus, other studies have, in common with ours, found that calendar period effects seem to be stronger than pure cohort effects.

Regional variation has previously been described in Norway at the level of counties, with an increased incidence in the southern county called Vest-Agder, which includes 15 municipalities and a total of about 3.5% of the Norwegian population (16). Our study identified a cluster north of the previously identified county. Although different statistical methods have been used in different studies, several reports show significant spatial variability within countries. In accordance with our data, investigations from Finland (12) and Italy (8) have shown relatively large areas with increased incidence, whereas a Swedish study (13) identified smaller hot-spot regions the size of municipalities.

Possible explanations for the observations

The relative increase in incidence for pure spatial clusters was smaller in magnitude than the spatiotemporal clusters. Hence, we think it is more likely that the clusters are related to more temporary conditions in parts of Norway than to more permanent characteristics of the municipalities, such as population density and climatic differences. The clusters identified have both populated and less populated areas, including both urban and rural munici-

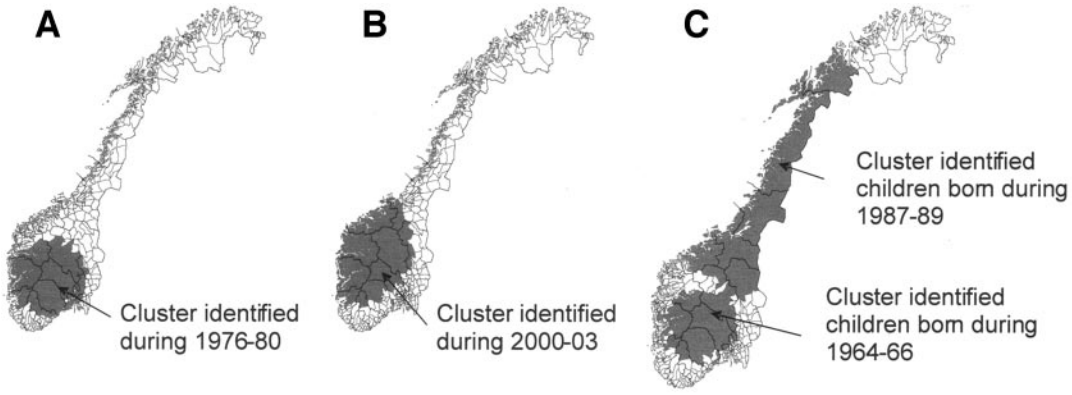

Figure 1—*Results from the spatiotemporal analysis.* A*: Cluster from the first study period (1973–1982).* B*: Cluster identified from the second study period (1989–2003).* C*: Two clusters identified for the birth cohorts and place of living.*

palities. Some Norwegian disease mapping studies of selected cancer diagnoses (22) and cardiovascular diseases (23) show considerable geographic variability. There is, however, no clear correspondence to the clusters that we identified.

Consistent with earlier studies showing acidic waters in southern Norway, we have previously demonstrated an association between lower tap water pH and a higher risk of type 1 diabetes (24), which potentially could explain part of the clustering in southern Norway. Future studies could include municipality level information on acidity and other measures of quality of drinking water in ecologic analyses. It is difficult to imagine that genetic factors can explain the increasing incidence of type 1 diabetes over time; although the Norwegian and other Nordic populations are commonly believed to be relatively homogeneous, we cannot exclude the possibility that some of the spatial variation is due to genetic factors. Previous studies have shown that the high-risk HLA genotype could explain some of the variations between European countries (25) and even between three areas in Finland (26). We have, however, previously reported that the prevalence of the high-risk HLA genotype in the general population in Vest-Agder county (27) is very similar to that identified in Norway as a whole (28). This is an important argument against the hypothesis that the most important genetic factors in type 1 diabetes contribute to the regional variation in incidence in Norway. More research on spatial variability of genetic markers within countries like Norway is needed to better understand the link between genetic predisposition and spatial variability of disease. Future studies could also benefit from inclusion of information on different ethnic groups.

Although data are not entirely consistent with a role of enterovirus in the etiology of type 1 diabetes, it might be speculated that aspects of enterovirus infections could be explained in part by the spatiotemporal patterns in type 1 diabetes incidence. Studies of spatiotemporal distribution of enterovirus in Norway are ongoing, but the correct identification of relevant enterovirus species and serotypes is difficult and laborious. Results obtained up to now demonstrate epidemic-like patterns specific for enterovirus species and perhaps serotypes (29). Future analysis of enterovirus in larger samples from the MIDIA study (29), a study of environmental causes of type 1 diabetes, may aid in the endeavor to explain our observed spatiotemporal patterns in type 1 diabetes incidence.

To conclude, the incidence of type 1 diabetes among children increased during the study period 1973–2003, and there were birth cohort effects only when regions were taken into account. Using methods simultaneously accommodating age, period, cohort, and geographic location, we found regional differences for both calendar period and birth cohorts. Such effects indicate complex interactions including environmental factors, lifestyle, and perhaps genetics in the etiology of type 1 diabetes.

Acknowledgments— We thank Bjørn Møller, PhD, at the Norwegian Cancer Registry for providing us source code and assistance for APC modeling.

APPENDIX

Members of the Norwegian Childhood Diabetes Study Group are the following: Henning Aabech and Sven Simonsen, Fredrikstad; Helge Vogt, Lørenskog; Kolbeinn Gudmundsson, Anne Grethe Myhre, Knut Dahl-Jørgensen, and Geir Joner, Oslo; Jon Grøtta, Elverum; Ola Tallerås and Dag Helge Frøisland, Lillehammer; Halvor Bævre, Gjøvik; Kjell Stensvold, Drammen; Bjørn Halvorsen, Tønsberg; Kristin Hodnekvam, Skien; Ole Kr. Danielsen, Arendal; Jorunn Ulriksen and Unni Mette Köpp, Kristiansand; Jon Bland, Stavanger; Dag Roness, Haugesund; Oddmund Søvik and Pål R. Njølstad, Bergen; Per Helge Kvistad, Førde; Steinar Spangen, Ålesund; Per Erik Hæreid, Trondheim; Sigurd Børsting, Levanger; Dag Veimo, Bodø; Harald Dramsdahl, Harstad; Bård Forsdahl, Tromsø; and Kersti Elisabeth Thodenius and Ane Kokkvoll, Hammerfest.

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