Nationwide, Prospective Registration of Type 1 Diabetes in Children Aged <15 Years in Norway 1989–1998

No increase but significant regional variation in incidence

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OBJECTIVE — An increasing incidence rate of childhood-onset type 1 diabetes has been described in several countries, particularly among the youngest children, and the Nordic countries have consistently been shown to have the highest incidence rates. An increasing incidence had previously been reported in Norway for 1973–1982, together with regional variation within the country. The aim of this study was to test whether there has been an increasing incidence of type 1 diabetes and a continued regional variation among children aged <15 years in Norway during 1989–1998.

RESEARCH DESIGN AND METHODS — As a part of the activities of the National Childhood Diabetes Registry of Norway and the EURODIAB study, a 10-year prospective, nationwide case registration of type 1 diabetes was done among children aged <15 years.

RESULTS — A total of 1,867 new case subjects (1,009 boys and 858 girls) were identified. The total incidence rate was 22.4 per 100,000 person-years (95% CI 21.5–23.5). The incidence was 13.1, 26.3, and 28.8 per 100,000 in the age-groups 0–4.9, 5–9.9, and 10–14.9 years, respectively. No increase or decrease over time was detected in any of the age-groups during the 10-year period. We found significant variation between the 19 counties, which only partly reflected the pattern previously described for 1973–1982.

CONCLUSIONS — We found a significant regional variation within Norway. After a previous period of increase, the incidence has been stable in all age-groups <15 years during 1989–1998.

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There is substantial variation in the incidence rates of type 1 diabetes between countries, and the Nordic countries have consistently been shown to have the highest incidence rates (1,2). Regional differences have also been demonstrated within countries regarded to have homogenous populations, such as Norway (3), Sweden (4), and Finland (5) and in other European countries (6–9). An increase in the incidence rate with time has been observed in Norway (3) and many countries (10). In some countries, a particularly strong relative increase in incidence over time has been noted among children aged <5 years (2).

In Norway, a nationwide, prospective registration of new cases of type 1 diabetes diagnosed in children <15 years of age started 1 January 1989. The objective was to describe the incidence patterns for childhood-onset type 1 diabetes in Norway in the period 1989–1998. We set out to test whether there was an increasing incidence among children <5 years of age and whether there was significant variation between counties that was similar to the pattern previously described for 1973–1982.

RESEARCH DESIGN AND METHODS

— All incident cases of type 1 diabetes diagnosed in children <15 years of age in Norway are referred to a hospital, and most of them are hospitalized in a pediatric ward. However, because of long traveling distances, some patients are referred to a department of internal medicine in a nearby hospital. The incidence of type 1 diabetes in Norway for the period 1973–1982 has been described previously, with an estimated ascertainment >98% (3). Since 1 January 1989, all new case subjects <15 years of age with type 1 diabetes have been reported prospectively, according to the EURODIAB criteria (2). Case subjects must be discharged from the hospital on insulin injections and be permanent residents of Norway. The date of diagnosis was defined as the date of the first insulin injection, and age at diagnosis was <15 years. Incidence trends for eight counties of Norway in the period 1989–1994 (2) and average incidence for the period 1989–1998 in eight counties (11) have previously been reported as part of the EURODIAB collaboration. The current report describes incidence trends and regional variation for all 19 counties of Norway in the period 1989–1998.

The membership registry of the Norwegian Diabetes Association was used as a secondary source for estimation of case ascertainment using capture-recapture methodology (12). All members born 1 January 1974 or later received a letter

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*A complete list of the Norwegian Childhood Diabetes Study Group can be found in the APPENDIX.

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

Table 1—*Incidence rate of type 1 diabetes in Norway during 1989–1998*

Sex	Age-group (years)	Cases diagnosed (*n*)	Person-years*	Incidence rate/100,000 person-years (95% CI)†
Boys and girls	0–4.9	385	2,935,370	13.1 (11.9–14.5)
	5–9.9	721	2,738,419	26.3 (24.5–28.3)
	10–14.9	761	2,645,756	28.8 (26.8–30.9)
Boys	0–14.9	1867	8,319,545	22.4 (21.4–23.5)
	0–4.9	213	1,506,544	14.1 (12.4–16.2)
	5–9.9	387	1,404,592	27.6 (24.9–30.4)
	10–14.9	409	1,356,072	30.2 (27.4–33.2)
Girls	0–14.9	1009	4,052,337	23.6 (22.2–25.2)
	0–4.9	172	1,428,826	12.0 (10.4–14.0)
	5–9.9	334	1,333,827	25.0 (22.5–27.9)
	10–14.9	352	1,289,684	27.3 (24.6–30.3)
	0–14.9	858	4,267,208	21.2 (19.8–22.6)

*Sum of the mean population in each single year during 1989–1998; †95% CI calculated using the formula $\hat{SE}(\ln IR) = 1/\sqrt{D}$, in which D is number of cases and IR is the incidence rate.

from the investigators in the spring of 1997 with three questions: the year of diabetes diagnosis, the county of residence at the time of diagnosis, and the hospital they were referred to initially.

The number of person-years at risk was calculated from the mean population size for each sex and 5-year age-group for each year of the study period, using high-quality official population data from Statistics Norway (www.ssb.no). The incidence rate was calculated as the number of case subjects divided by the number of person-years (for each specific combination of age, sex, and calendar year). Incidence rates are expressed as number of case subjects per 100,000 person-years. We calculated 95% CIs for incidence rates based on the Poisson assumption (13) and using a log transformation. The formula for the standard error of the log of the rate is $\hat{SE}(\ln IR)=1/\sqrt{D}$, in which IR is the incidence rate and D is the observed number of case subjects. The incidence rate was sex and age standardized, assuming equal proportions of boys and girls and equal proportions of children in each of the age-groups of 0–4, 5–9, and 10–14 years (2). Poisson regression was used for evaluating the impact of sex, age-group, time trends, and regional variation on the incidence rate (14), using the AMFIT program of the EPICURE package (15). We tested whether effects were similar over levels of other variables, e.g., whether the ratios between boys and girls were similar in different age-groups by testing two-way interaction terms in the regression models. The cumulative incidence was estimated using the formula $1 - e^{-\Sigma IR_j \Delta t_j}$, in which Δt_j is the number of years covered by the age-group (here 5 years) in each group (j) (16).

RESULTS — A total of 1,867 new cases were identified in the diabetes registry during the 10-year period. Of 912 children identified from the Norwegian Diabetes Association (secondary source), 870 were also found in the primary registry. The ascertainment of the primary registry was thus estimated to be 95.4%.

The total incidence rate of type 1 diabetes was 22.4 per 100,000 person-years (Table 1). The incidence in the 5- to 9.9-year age-group was approximately twice that of the 0- to 4.9-year age-group, with a further but moderate increase for the 10- to 14.9-year age-group. The incidence for boys was 11% higher than for girls, a result that was similar in the different age-groups and calendar years (data not shown). The sex- and age-standardized incidence rate was 22.7 per 100,000 person-years.

We observed a significant regional variation within Norway ($P < 0.001$). Vest-Agder, the southernmost county in Norway, had the highest incidence rate at 37 per 100,000 person-years (Table 2). Finnmark, the northernmost county, had the lowest incidence at 13.8 per 100,000 person-years.

Figure 1 shows the incidence rates for each calendar year in the period 1989–1998 for children in three age-groups. No significant time trend was found in any specific age-group. We also tested

Table 2—*Incidence rate of type 1 diabetes in 19 counties of Norway (1989–1998)*

County	Cases (*n*)	Person-years*	Incidence rate/10^5 (95% CI)†
Østfold‡	107	428,967	24.9 (20.6–30.1)
Akershus‡	187	863,613	21.7 (18.8–25.0)
Oslo‡	127	752,315	16.9 (14.2–20.1)
Hedmark	69	324,628	21.3 (16.8–26.9)
Oppland	68	319,073	21.3 (16.8–27.0)
Buskerud	74	416,428	17.8 (14.1–22.3)
Vestfold‡	91	381,670	23.8 (19.4–29.3)
Telemark	75	300,846	24.9 (19.9–31.3)
Aust-Agder	49	202,101	24.2 (18.3–32.1)
Vest-Agder‡	116	313,140	37.0 (30.9–44.4)
Rogaland	178	784,386	22.7 (19.6–26.3)
Hordaland‡	197	859,445	22.9 (19.9–26.4)
Sogn og Fjordane	53	220,440	24.0 (18.4–31.5)
Møre og Romsdal	108	485,636	22.2 (18.4–26.9)
Sør-Trøndelag	116	489,293	23.7 (19.8–28.4)
Nord-Trøndelag	58	256,602	22.6 (17.5–29.2)
Nordland	120	472,829	25.4 (21.2–30.4)
Troms‡	53	295,610	17.9 (13.7–23.5)
Finnmark‡	21	152,523	13.8 (9.0–21.1)
Total	1,867	8,319,545	22.4 (21.4–23.5)

*Sum of the mean population size in each single year during 1989–1998; †95% CI calculated using the formula $\hat{SE}(\ln IR)=1/\sqrt{D}$, in which D is number of cases and IR is the incidence rate; ‡counties included in the EURODIAB collaboration.

whether there was any variation in time trend between boys and girls and among different counties. There were no such significant differences (data not shown).

Because there was no indication of a time trend, we estimated the 15-year cumulative incidence based on the pooled data for the whole 10-year period. The cumulative incidence = $1 - e^{-[(13.1 \times 10^{-5} \times 5)+(26.3 \times 10^{-5} \times 5) + (28.8 \times 10^{-5} \times 5)]} = 0.0034 = 0.34\%$. In other words, for newborns in Norway, there is an expected 0.34% chance of developing type 1 diabetes by the age of 15 years or a 1 in 294 chance.

CONCLUSIONS — We have described the results of a nationwide childhood diabetes registry of Norway in the 10-year period of 1989–1998 using standard criteria and methods, including estimation of case ascertainment with an independent source. The Nordic countries keep high-quality population registries, which is an advantage for epidemiological studies. The standardized incidence rate was among the highest in the world, with a rate ranging between that in Denmark (2) and Sweden (17) but lower than that in Finland (2). Among the interesting findings was a significant regional variation within the country, but there was no indication of an increase in the incidence in any age-group during the current study period. The latter finding is in contrast to a previous Norwegian study covering the period 1973–1982 (3) and results from some other European countries (2). However, there had been a slight increase from 20.5 to 22.4 per 100,000 person-years in the overall mean incidence in the current 10-year period compared with the mean incidence in the previous 10-year period (3).

Although many studies have reported an increasing incidence in recent years (2), an interesting study from Sweden reported that an apparent increase among children was accompanied by a decreasing incidence among those aged 15–34 years (17). A similar downward shift in age at onset has also been reported from other countries but was not seen in the present study. Unfortunately, we have not been able to study the incidence in Norway in age-groups >15 years. Regional variation has previously been described in Norway (3), and we hypothesized that the pattern of regional variation would be similar in the current study. Although Finnmark was still the county with the lowest incidence, Vest-Agder had the highest incidence in the current study period but an average incidence during the time period 1973–1982 (3). The relatively small population sizes make it difficult to study potential causes in any one county. We are not aware of any serious attempt to explain the consistently low incidence rate in Finnmark county. This is an interesting question, but further study is complicated by the fact that only 21 new cases of type 1 diabetes arose during a 10-year period. We have made some effort to investigate potential factors explaining the high incidence in Vest-Agder (18,19), but the explanations remain elusive. In a study from Vest-Agder, we found that 2.6% of children aged 0–17 years, randomly selected from the official population registry, had the high-risk genotype DRB1*0401-DQA1*0301-DQB1*0302/DQA1*0501-DQB1*0201 (20), very similar to that found among newborns representative of Norway (21). This shows that the most important genetic risk marker for type 1 diabetes cannot explain the high incidence in Vest-Agder as compared with the rest of the country. Oslo had a relatively low incidence. The reason for this is also unknown, but it can be speculated that part of this is due to a relatively high proportion of ethnic groups with lower incidence of type 1 diabetes. The idea that increased infectious load in areas with high population density could explain a lower incidence of type 1 diabetes via the so-called hygiene hypothesis has been proposed and supported with ecological data (6). This is an interesting thought given the relatively high population density in Oslo compared with the rest of the country, but there is also conflicting evidence from other countries (9). Because our present data are based on county of residence at the time of diagnosis, the resulting geographical variation may be influenced by people moving between counties at relevant ages, if county-associated environmental factors have an impact on risk of type 1 diabetes. Although it is not uncommon to move to a different house during the first 15 years of life, most people move within the county, and previous results using county of residence at birth (rather than at diagnosis) shows essentially the same regional variation (22). The ascertainment in the current study was high but still slightly lower than in the previous study period (1973–1982). This may represent random variation, but one possible explanation is that we used different secondary sources in the two studies. The disability pension registry used previously is no longer available for our purpose.

A slight male excess is common but not consistently found in high-incidence populations in Europe (23). The slightly higher incidence for boys compared with girls was consistent across strata of age-groups and calendar period, and the male excess was similar to that found during 1973–1982 (3). Furthermore, we have previously found that the sex difference cannot be explained by perinatal factors (22).

In conclusion, this nationwide study from Norway showed a significant regional variation within the country. After a period of increasing incidence during the late 1970s and early 1980s, the incidence in all age-groups <15 years has been stable for the period 1989–1998. Continued efforts to investigate possible explanations for the time trends and geographical variation in type 1 diabetes incidence within and among countries are warranted.

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APPENDIX

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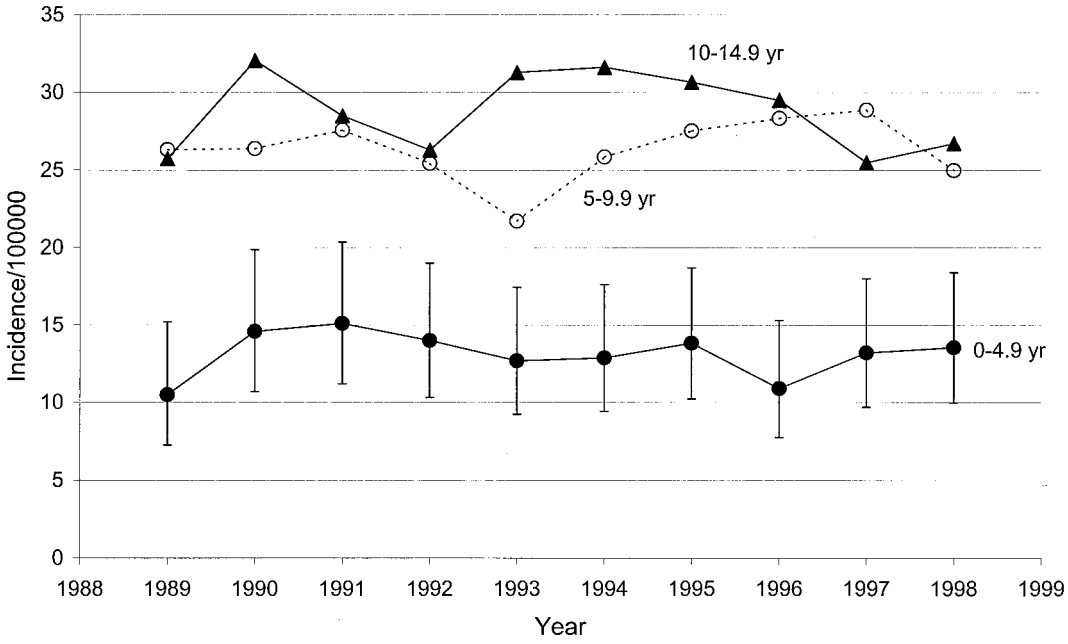

Figure 1—*Incidence trends for type 1 diabetes in Norway 1989–1998 in age-groups 0–4.9 (●), 5–9.9 (○), and 10–14.9 (▲) years (95% CIs are shown for the 0- to 4.9-year age-group).*

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