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SHORT COMMUNICATION

Higher incidence of childhood-onset type 1 diabetes mellitus in remote areas: a UK regional small-area analysis

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Abstract
Aims/hypothesis We investigated the association between the incidence of type 1 diabetes mellitus and remoteness (a proxy measure for exposure to infections) using recently developed techniques for statistical analysis of small-area data.
Subjects, materials and methods New cases in children aged 0 to 14 years in Northern Ireland were prospectively registered from 1989 to 2003. Ecological analysis was conducted using small geographical units (582 electoral wards) and area characteristics including remoteness, deprivation and child population density. Analysis was conducted using Poisson regression models and Bayesian hierarchical models to allow for spatially correlated risks that were potentially caused by unmeasured explanatory variables.
Results In Northern Ireland between 1989 and 2003, there were 1,433 new cases of type 1 diabetes, giving a directly standardised incidence rate of 24.7 per 100,000 person-years. Areas in the most remote fifth of all areas had a significantly (p=0.0006) higher incidence of type 1 diabetes mellitus (incidence rate ratio=1.27 [95% CI 1.07, 1.50]) than those in the most accessible fifth of all areas. There was also a higher incidence rate in areas that were less deprived (p<0.0001) and less densely populated (p=0.002). After adjustment for deprivation and additional adjustment for child population density the association between diabetes and remoteness remained significant (p=0.01 and p=0.03, respectively).
Conclusions/interpretation In Northern Ireland, there is evidence that remote areas experience higher rates of type 1 diabetes mellitus. This could reflect a reduced or delayed exposure to infections, particularly early in life, in these areas.

Keywords Epidemiology · Risk factors · Type 1 diabetes

Abbreviation
IRR incidence rate ratio

Electronic supplementary material Supplementary material is available for this article at http://www.dx.doi.org/10.1007/s00125-006-0342-0 and is accessible for authorized users.

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Introduction

Type 1 diabetes mellitus is a complex disorder caused by multiple genes, which interact with environmental factors. The geographical distribution of type 1 diabetes mellitus within countries affords an opportunity to investigate environmental risk factors. A theory, referred to as the hygiene hypothesis, suggests that reduced or delayed exposure to infections, particularly early in life, may increase the possibility of an abnormal immune response increasing the risk of type 1 diabetes mellitus [1]. Previous ecological analyses of type 1 diabetes mellitus have examined variations in incidence rates in relation to area characteristics which are likely to be associated with exposure to infections such as deprivation [2–4], child population density [3–5] and urban–rural status [2, 6–8]. Only one study [9] has investigated the association between type 1 diabetes and remoteness (another proxy measure for exposure to infections) but in that study remoteness was measured primarily using population density. To the best of our knowledge, our study is the first to investigate the association between type 1 diabetes and remoteness using a measure based solely upon accessibility.

The primary aim of this study was to investigate if children living in remote areas, who are likely to have a reduced or delayed exposure to infections in early life, have a higher incidence of type 1 diabetes mellitus.

Subjects, materials and methods

Study protocol

In Northern Ireland, the type 1 diabetes mellitus register has prospectively recorded newly diagnosed children under the age of 15 years since 1989. Register cases were included in the analysis if they were diagnosed between 1 January 1989 and 31 December 2003. The completeness of ascertainment of the register was assessed by capture–recapture methodology using hospital discharge records as an independent source of ascertainment. Further details of the register have been previously published [3].

Cases were allocated to an electoral ward (*n*=582) using their postcode at diagnosis. The Northern Ireland Statistics and Research Agency supplied childhood population figures for 2001 for electoral wards by 5-year age group [10]. Population density was calculated by dividing the population by the geographical area (in hectares). Remoteness of the ward [11] was based upon the road distance to a general practice doctor’s surgery, an accident and emergency hospital, a dentist, an optician, a pharmacist, a Job Centre (or Jobs and Benefits Office), a Post Office, a food shop and the centre of a settlement of 10,000 or more people. Income deprivation [11] was based upon the proportion of people in an area living in families reliant on out-of-work benefits and in-work support.

Statistical analysis

Poisson regression was used to compare the incidence rates of the electoral wards categorised by explanatory variables. The analysis was repeated using a Bayesian hierarchical model to allow for extra-Poisson variation. The regression coefficients for area characteristics in this model are adjusted to allow for spatially correlated rates, potentially caused by unmeasured explanatory variables. The use of this model for ecological analysis has been described in detail previously [12].

Bayesian modelling was conducted using WinBUGS version 1.4.1 (WinBUGS; Imperial College and Medical Research Council, UK). All other statistical analyses were performed using STATA release 8.0 (Stata Corporation, College Station, TX, USA).

Results

Cases and incidence rate

Between 1989 and 2003 the register was estimated using capture–recapture methodology to be 99.3% (95% CI 98.8, 99.8%) complete. In Northern Ireland there were 1,433 cases of type 1 diabetes mellitus in 5,762,775 person-years of follow-up during the period in question. The directly age-standardised incidence rate (using a standard population of six equal-sized age sex subgroups) was 24.7 (95% CI 23.4, 26.0) per 100,000 person-years.

Ecological analysis Table 1 shows the observed and expected number of cases for wards divided into groups by electoral ward characteristics. Also shown are incidence rate ratios (IRRs) before and after adjustment for deprivation and remoteness.

There was a significantly higher incidence of type 1 diabetes mellitus in more remote electoral wards (p=0.0003). The incidence rate for the most remote fifth of wards was 1.27 (95% CI 1.07, 1.50) times the rate of the most accessible fifth of wards. This IRR was slightly attenuated after adjustment for deprivation (IRR=1.19) but a significant association remained (p=0.01). Despite a strong inverse relationship between the remoteness and childhood population density indicators in the 582 wards (Spearman’s r=−0.87, p<0.001), after further adjustment for childhood population density the remoteness term remained significant (p=0.03). A goodness-of-fit test (p=0.48) indicated that the model containing deprivation and remoteness described the data adequately.

Wards which were deprived had a significantly lower incidence of diabetes (p for trend <0.0001). This association persisted after adjustment for remoteness and child population density. Wards which were more densely populated had a lower disease incidence (p=0.03) but this association was attenuated after adjustment for deprivation (p=0.17) or remoteness (p=0.66).

The corresponding IRRs from Bayesian analysis (adjusting for deprivation and remoteness) were only negligibly different from those presented, and are shown in Table 1 of the Electronic Supplementary Material (ESM).

Table 1 Observed cases, expected cases, and crude and adjusted incidence rate ratios (IRRs) for type 1 diabetes mellitus in 582 electoral wards divided by ward characteristics

	No. of wards	Observed cases	Expected cases	Crude		Adjusted (models include deprivation and remoteness)	
				IRR (95% CI)	*p*	IRR (95% CI)	*p*
Remoteness							
1st fifth (accessible)	116	268	304.9	1.00	0.0003	1.00	0.01
2nd fifth	117	292	293.6	1.13 (0.96, 1.34)		1.06 (0.89, 1.26)	
3rd fifth	115	292	330.0	1.01 (0.85, 1.19)		0.94 (0.79, 1.11)	
4th fifth	117	317	267.3	1.35 (1.15, 1.59)		1.20 (1.01, 1.43)	
5th fifth (remote)	117	264	237.2	1.27 (1.07, 1.50)		1.19 (0.99, 1.42)	
	Linear trend across categories			1.07 (1.03, 1.11)	0.0006	1.05 (1.01, 1.09)[a]	0.02
Income deprivation							
1st fifth (affluent)	116	332	295.8	1.00	0.0001	1.00	0.005
2nd fifth	116	306	266.1	1.02 (0.88, 1.20)		1.01 (0.86, 1.18)	
3rd fifth	121	255	259.5	0.88 (0.74, 1.03)		0.85 (0.72, 1.01)	
4th fifth	113	258	265.3	0.87 (0.74, 1.02)		0.86 (0.73, 1.02)	
5th fifth (deprived)	116	282	346.3	0.73 (0.62, 0.85)		0.76 (0.64, 0.90)	
	Linear trend across categories			0.92 (0.89, 0.96)	<0.0001	0.93 (0.90, 0.97)[a]	0.0003
Child population density (child/hectare)							
<0.2	103	228	194.4	1.00	0.03	1.00	0.36
0.2–2.4	126	325	301.9	0.92 (0.77, 1.09)		0.90 (0.74, 1.08)	
2.4–5.9	119	279	292.7	0.81 (0.68, 0.97)		1.09 (0.81, 1.45)	
5.9–11.3	118	285	300.6	0.81 (0.68, 0.96)		1.15 (0.84, 1.59)	
>11.3	116	316	343.5	0.78 (0.66, 0.93)		1.16 (0.83, 1.61)	
	Linear trend across categories			0.94 (0.91, 0.98)	0.002	1.03 (0.96, 1.11)[a]	0.42

[a]Estimates taken from model fitting all other model variables as categorical

Discussion

This study detected higher rates of type 1 diabetes mellitus in remote areas. This association was independent of deprivation. Our analysis also indicated that remoteness was more relevant than population density, but this observation should be interpreted cautiously as these area characteristics were strongly correlated. Secondary analyses revealed higher rates in affluent areas and sparsely populated areas.

A strength of this analysis was the use of 15 years of prospectively collected incidence data in small geographical units (electoral wards). Additionally, the measure of remoteness adopted was objective, based upon road distances, and thus has advantages over previously used measures such as urban–rural classifications, which are based upon more subjective judgements and do not necessarily reflect remoteness. Also our findings were little altered after adjustment for spatially correlated extra-Poisson variation, using Bayesian analysis [12], which if present could incorrectly exaggerate the significance of associations. Few previous ecological analyses of type 1 diabetes mellitus incidence rates have made such adjustments [5, 7].

This study also has weaknesses. Small-area analyses rely upon aggregated data and there is the possibility that inferences at area level do not directly transfer to individuals, often referred to as ecological bias. In an attempt to reduce this possibility, the main analysis was conducted using small areas (containing on average 2,900 people and 637 under the age of 15 years). Another weakness of the study was the use of address at the time of diagnosis, which may not be relevant for exposures occurring early in life, e.g. if a child has subsequently moved house. In addition, child population figures from 2001 were used to represent the period 1989 to 2003. Finally, it was not possible to directly adjust the analysis for various potential confounders related to diabetes risk, such as maternal age and breast-feeding, since area level data were not available.

Our finding of a higher incidence of type 1 diabetes in children from remote areas is not consistent with an analysis from Western Australia [9], which detected a lower incidence in remote areas, defined primarily by population density. Although the classification of remoteness differed in the two studies the difference is unlikely to explain the contrasting conclusions. The secondary analysis of deprivation and child population density are consistent with a previous analyses of a subset of these cases over the period 1989–1994 [3] and also with small-area analyses conducted in other countries which have investigated material deprivation [2, 4] and population density [4, 5]. In addition, a number of small-area studies have detected higher incidence rates in rural areas [2, 7], broadly in agreement with our results. In contrast to the Northern Ireland findings, two studies detected lower rates in rural areas in Italy [6] and Lithuania [8]. The contradictory associations noted in Italy and Lithuania may reflect a different rural lifestyle in these countries.

The hygiene hypothesis suggests that the developing immune system requires stimulation by exposure to infections and other immune challenges to achieve a mature and balanced repertoire of responses [1]. The novel association between remoteness and type 1 diabetes mellitus may provide support for this hypothesis, as intuitively it seems likely that children living in remote areas will have less social contact at an early age, and consequently a reduced or delayed exposure to infections. The increased incidence of type 1 diabetes mellitus may reflect the lack of stimulation of the developing immune system, by exposure to infections, in children living in remote areas. Also in support of the hygiene hypothesis, studies have demonstrated inverse associations between type 1 diabetes mellitus and increased exposure to infections in early life and other proxy measures for infection, including day-care attendance [13].

In conclusion, in Northern Ireland over the period 1989 to 2003, there was evidence that children in remote areas experienced higher rates of type 1 diabetes mellitus, an observation that could reflect the reduced or delayed exposure to infections, particularly early in life, in these areas.

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