Table 1. *SUR1* exon 16 variants in Dutch Type II diabetic patients

Genotype	Breda Study		't Hart et al. [1]		Rotterdam cohort[1]		Hoorn cohort[1]	
	Control subjects $n = 150$	Patients $n = 566$	Control subjects $n = 336$	Patients $n = 388$	Control subjects $n = 170$	Patients $n = 196$	Control subjects $n = 166$	Patients $n = 192$
–3 *c/c*	0.29	0.36	0.33	0.25	0.31	0.22	0.35	0.28
–3 *c/t*	0.50	0.47	0.51	0.54	0.53	0.57	0.49	0.51
–3 *t/t*	0.21	0.17	0.16	0.21	0.16	0.21	0.16	0.21
χ^2 c vs p[2]	2.36		6.81		3.48		3.42	
p-value	0.31		0.03		0.18		0.18	
Allele								
–3*c*	0.54	0.59	0.59	0.52	0.57	0.51	0.60	0.53
–3*t*	0.46	0.41	0.41	0.48	0.43	0.49	0.40	0.47
χ^2	2.30		6.24		2.90		3.36	
p-value	0.13		0.01		0.09		0.07	
OR *t*-allele	0.82		1.30		1.29		1.32	
95 % Cl-OR *t*-allele	0.63–1.06		1.06–1.61		0.96–1.73		0.98–1.78	

[1] The different cohorts from Rotterdam and Hoorn used by 't Hart et al. [1]
[2] Chi-square of control subjects vs patients; OR, odds ratio

problem has afflicted many association studies done in inhomogeneous populations, ranging from the population of metropolitan Los Angeles to Native American tribes [4, 5]. Since Rotterdam is the city with the largest harbour in the world, it shows a mixed population due to continuous migration and immigration.

A combination of all the above mentioned points may explain the difference between the study by 't Hart and our study in the Dutch Breda cohort.

In conclusion, it appears that the *SUR1* exon 16 *t*-allele is not a risk factor for developing Type II diabetes in the Breda cohort of 566 patients with an apparently low insulin use. It will be of great interest to see if this *t*-allele is associated with Type II diabetes mellitus and insulin use.

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Yours faithfully,
J.H.O. van Tilburg, L.B. Rozeman, H. van Someren, C.A.E. Rigters-Aris, J.P. Freriks, P.L. Pearson, L.A. Sandkuijl, T.W. van Haeften, C. Wijmenga

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Rising incidence of childhood diabetes is seen at all ages and in urban and rural settings in Yorkshire, United Kingdom

Dear Sir,
The incidence of childhood Type I (insulin-dependent) diabetes mellitus in those under 5 years of age is rising in the United Kingdom and Europe but there has been conflicting evidence in the United Kingdom as to whether the rise is occurring in all age groups. A study of 1037 children diagnosed between 1985 and 1996 from Oxford, United Kingdom [1] showed rising incidence was accounted for by children aged 0–4 years. A study of 2326 children diagnosed between 1984 and 1993 from Scotland, United Kingdom [2] has shown a rising incidence in all ages (0–14) and for each age-band (0–4, 5–9, 10–14). In Yorkshire, temporal trends between 1978 and 1993 showed the most statistically significant rise in 10–14 year olds [3].

In an extended data set we have investigated whether the incidence of childhood Type I diabetes in Yorkshire has continued to rise over the last 5 years, in which age groups and whether this is occurring differentially in urban and rural settings. Geographical variation in incidence is present in Yorkshire [4] and no previous studies have examined geographical differences in incidence over time.

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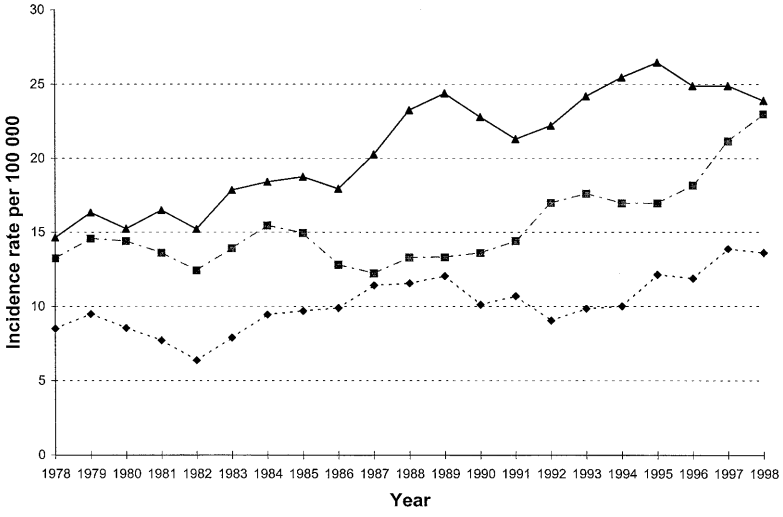

Fig. 1. Smoothed (3-year moving average) incidence rates of childhood diabetes in Yorkshire by age group (1978–1998). ◆ 0–4 ($n = 514$), 2.5% increase per year ($p = 0.01$), ■ 5.9 ($n = 775$), 2.2% increase per year ($p = 0.01$), ▲ 10–14 ($n = 1074$), 3.0% increase per year ($p = 0.01$)

The county of Yorkshire which had a childhood population (0–14) of approximately 700 000 at the 1991 census, has an age- and sex-standardised incidence rate (1978–1998) of childhood Type I diabetes of 15.5 per 100 000 per year (95% CI 14.9, 16.1). The age-standardised rate for boys was 15.7 (14.8, 16.6) and for girls 15.2 (14.4, 16.1). The sex-standardised rates by age group were 10.4 (9.5, 11.4) for 0–4 year olds, 15.4 (14.3, 16.4) for 5–9 year olds and 20.3 (19.1, 21.5) for 10–14 year olds.

Time trends from 1978 to 1998 were analysed for 2363 subjects diagnosed with Type I diabetes before their 15th birthday and recorded on the population-based Yorkshire Children's Diabetes Register [4]. The register's completeness, comparing 3 independent sources of ascertainment, was verified using log-linear modelling and shown to be 99% complete [5]. Sex-standardised incidence rates per 10^5/year by age group (0–4, 5–9, 10–14) were derived using annual mid-year population estimates, and tested by linear regression modelling ($p < 0.05$ was considered to be statistically significant). Yorkshire districts ($n = 22$) were classified as mainly urban or mainly rural by levels of person-based population density (< 7 per hectare = rural [$n = 11$], > 7 per hectare = urban [$n = 11$]) and incidence trends tested within each setting.

There was a statistically significant rise in incidence both overall and in each age group: 0–4: 2.5% per year ($p = 0.01$), 5–9: 2.2% per year ($p = 0.01$), 10–14: 3.0% per year ($p < 0.01$) and 0–14: 2.6% per year ($p < 0.01$) (Fig. 1). Urban incidence increased from 11.7 in 1978 to 18.7 in 1998 ($p < 0.01$) and rural incidence from 14.7 to 19.5 ($p = 0.06$). On average, incidence in rural areas was 4.5 per 10^5 year higher compared with urban areas ($p = 0.03$). These differences were reflected in each age group. We predict the incidence in Yorkshire will be approximately 26.6 and 30.2 in the years 2005 and 2010, respectively, if these trends continue.

In Yorkshire, we have shown that over the last 21 years the incidence of childhood diabetes has continued to rise on average by 2.5% per year and this statistically significant increase in incidence is occurring in all ages. This supports findings from a Finnish study [6], which reported annual increases of 2.6% for 1–4 year olds and 1.9% for 5–14 year olds and Scotland [2], which is north of Yorkshire, where incidence increased by 2% per year for 0–14 year olds. Although age group specific annual changes in incidence were not available in the Scottish study, there was no evidence of heterogeneity in time trends between age groups. Data from a more southerly part of the United Kingdom in Oxford [1] suggested, however, there was a much higher increase of 11% in the 0–4 age group, with the incidence in 5–9 and 10–14 year olds rising by 4% and 1%, respectively. Differences in completeness for each study could explain part of the differences observed in rates but other reasons are not obvious. Recent incidence in Europe is also rising and most prominently in the youngest age group but the patterns differ by country [7] and it remains to be seen whether the rise for the 0–4 age group is yet to appear in Yorkshire.

Rising trends over time were seen in both urban and rural populations. Children living in sparsely populated parts of Yorkshire had a significantly higher incidence than those from urban areas, supporting the results of a previous study in Yorkshire [8]. The increases in rates over this relatively short time indicate the influence of environmental factors on disease occurrence. The homogeneity of the temporal trends by age and by area of residence suggest a uniform widespread non-selective agent could be involved. Investigations of temporal trends in rare conditions should cover lengthy time periods, to avoid misinterpretation.

Yours sincerely,
R.G. Feltbower, P.A. McKinney, H.J. Bodansky

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Vaccinations as risk factors for Type I diabetes mellitus

Dear Sir,
With much interest I have read the study 'Infections and vaccinations as risk factors for childhood Type I (insulin-dependent) diabetes mellitus' from the EURODIAB Substudy 2 Study Group [1]. The study shows that pre-school day-care attendance reduces the risk of Type I diabetes whereas vaccination had no notable effect. The outcome for day-care attendance seems clear. The outcome for vaccinations is, however, less so in my opinion. Some information is lacking, on which the authors hopefully can comment.

Vaccination is a challenge for the immune system with the aim of protecting the recipient against wild-type infection. On a population base, vaccination will also modify the epidemiological pattern of wild-type infection. Mass-vaccination reduces circulation of wild-type infection, resulting in a change from endemic to sporadic infections with incidental outbreaks. This is observed in some regions of the Netherlands where a minority population lives that refuses vaccination for religious reasons [2]. Such a change in epidemiology can have paradoxical and unintended effects because it results in postponement of infection to a later mean age [3].The ultimate outcome of mass-vaccination will be the establishment of herd-immunity with disappearance of the pathogen from the community and protection also for the non-immune, e.g. those who are not vaccinated. The authors did not incorporate such non-stochastic effects in their analyses, which probably will confound the outcome, at least for some of the vaccinations included. Such effects will furthermore hamper a proper comparison between the participating centres, which have their own history of immunisations and because of that will vary for the incidence of wild-type infections.

Yours sincerely,
J.M.D. Galama

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Dear Sir,
J.M.D. Galama asks if we can incorporate into our analysis information about indirect effects of vaccination such as the establishment of herd-immunity, the postponement of infection to later ages and the eradication of pathogens from the community. Clearly it would be very difficult to collect data on such factors in dispersed populations over the lengthy periods during which the children in our study were at risk of these infections. Because the children in our control groups were drawn from the same populations as those with Type I diabetes any indirect effects of vaccination might be expected to affect both diabetic and control subjects equally. We therefore argue that the conclusions from our comparisons of the two relate to the direct effects of vaccination and that any modifications to the epidemiology of infectious diseases produced by mass vaccination are unlikely to confound our comparisons. Although we agree that such indirect effects could have a role in explaining the large variation in incidence within Europe, we would point out that the purpose of our study was not to make comparisons between participating centres.

Sincerely, C.C. Patterson, G. Dahlquist, G. Soltész (on behalf of the EURODIAB Substudy 2 Study Group)

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