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Relationship between the incidence of type 1 diabetes and maternal enterovirus antibodies: time trends and geographical variation

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Abstract *Aims/hypothesis:* We have previously observed an inverse correlation between the incidence of type 1 diabetes and enterovirus infections in the background population. The aim of this study was to analyse whether maternal enterovirus antibody status, which reflects both the frequency of enterovirus infections and the protection conferred by the mother on the offspring, also correlates with the incidence of type 1 diabetes. *Methods:* Maternal enterovirus antibodies were analysed from serum samples taken from pregnant women between 1983 and 2001 in Finland and Sweden using enzyme immunoassay and neutralisation assays. Comparable samples were also taken between 1999 and 2001 in countries with a lower incidence of diabetes (Estonia, Germany, Hungary, Israel, Lithuania, Russia). *Results:* A clear decrease was observed in maternal enterovirus antibody levels over the past 20 years ($p<0.0001$). The frequency of enterovirus antibodies was higher in countries with a low or intermediate incidence of type 1 diabetes compared with high-incidence countries ($p<0.0001$). *Conclusions/interpretation:* These findings are in line with our previous observations supporting the hypothesis that a low frequency of enterovirus infection in the background population increases the susceptibility of young children to the diabetogenic effect of enteroviruses.

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Keywords EIA · Enterovirus · Environment · Immunity · Maternal antibody · Neutralisation assay · Population · Type 1 diabetes

Abbreviations CAV9: coxsackievirus A9 · CBV4: coxsackievirus B4 · CBV5: coxsackievirus B5 · EIA: enzyme immunoassay · EIU: enzyme immunoassay unit · EV9: echovirus 9 · IgG: immunoglobulin G · OR: odds ratio · PV1: poliovirus type 1

Introduction

The incidence of type 1 diabetes has increased worldwide over recent decades, and the incidence varies remarkably even among geographically close countries, such as Finland compared with Estonia and Russia [1–3]. The reasons behind this epidemiological pattern have remained obscure, although it has been related to certain risk factors for type 1 diabetes, such as cow's milk consumption [4]. Enterovirus infections are one of the main candidates as environmental trigger of type 1 diabetes [5] but only a few studies have evaluated the epidemiological association between type 1 diabetes and enterovirus infections in the background population [6–8].

Enterovirus infections are common in all age groups. The group of enteroviruses comprises more than 60 serotypes and the infections are usually asymptomatic or mild flu-like diseases. Rarely, enteroviruses cause severe infection, such as meningitis or myocarditis. Protection against enterovirus infection depends mainly on neutralising antibodies. Passively acquired neutralising antibodies protect newborn infants for the first 6–9 months, during which time the child can develop his/her own specific immunity [9].

Enteroviruses are transmitted mainly via the faecal–oral or respiratory route, and the rate of transmission depends on socio-economic factors such as crowding and standards of hygiene [9, 10]. The endemic and epidemic viruses vary annually and also between different areas, and are often found in sewage, surface water and seawater [11–14]. Human enteroviruses are mostly restricted to humans but several of them have occasionally been detected also in animals [15–17]. Along with an increased standard of living, improved hygiene and diminished crowding may have decreased the transmission rate of enteroviruses in many countries.

We have previously shown that enterovirus infections are less frequent among children in Finland and Sweden, where the incidence of type 1 diabetes is high, than in countries with a lower incidence of type 1 diabetes [7]. In addition, in our preliminary study we found that the frequency of enterovirus infections decreased in Finland during the 1980s and 1990s, whereas the incidence of type 1 diabetes increased [6]. Based on these initial observations, we proposed a hypothesis, named the 'polio hypothesis', which links enterovirus infections to the increasing trend and geographical variation in the incidence of type 1 diabetes [6]. This hypothesis was based on experience with another enterovirus disease, poliomyelitis, in which the risk of paralytic complications was inversely related to the frequency of poliovirus infections in the background population at the beginning of the last century. In circumstances where the circulation of the virus was low (increased standard of hygiene), children experienced their first poliovirus infection after maternal antibodies had already disappeared, and the virus was therefore able to spread to the blood and cause paralytic complications in some individuals. According to the polio hypothesis, this same phenomenon may play a role in enterovirus-induced diabetes and contribute to the increase and geographical variation in the incidence of type 1 diabetes. Recently, it has been proposed that the same type of phenomenon plays a role in other infections and autoimmune diseases [18, 19].

In the present study we analysed the enterovirus antibody status in pregnant women at different time-points during the last 20 years in two countries with a high and increasing incidence of type 1 diabetes. In addition, maternal enterovirus antibody status at the end of the last decade was analysed in six other European countries with lower incidences of type 1 diabetes. The aim was to further assess whether the frequency and geographical location of enterovirus infections in the background population correlates with the incidence of type 1 diabetes in these countries, and whether the frequency of enterovirus infections has changed over the past 20 years. Importantly, this study evaluates the status of protective enterovirus antibodies in pregnant women, and thus relates to the early immune protection of the offspring.

Subjects, materials and methods

Time-trend series Stored serum samples were available from two countries, Finland and Sweden, for the analysis of possible changes in enterovirus epidemiology over the past 20 years. In Finland, a serum sample has been taken from practically all pregnant women (>98%) at the end of the third month of pregnancy for routine screening of infectious diseases since 1982. These samples have been stored at −20°C at the National Public Health Institute. A series of 1,000 samples, which were taken during July in each of the years 1983 (n=232, mean age 26.7±5.5 SD years), 1989 (n=240, mean age 28.1±5.1 SD years), 1995 (n=243, mean age 28.9±5.6 SD years) and 2001 (n=285, mean age 29.0±6.3 SD years), were randomly selected from this serum bank for the enterovirus antibody analyses. They represented different age groups of women living in various parts of Finland. Data from years 1983, 1989 and 1995 have also been presented in our earlier study [6]. In Sweden, stored serum samples have been collected from mothers at delivery in Linköping, covering approximately 95% of the mothers, and samples (n=999) were randomly selected from specimens obtained during June and July in the years 1985 (n=250, mean age 28.4±5.3 SD years), 1990 (n=250, mean age 27.1±5.0 SD years), 1995 (n=250, mean age 29.2±4.7 SD years) and 2000 (n=249, mean age 29.4±4.8 SD years). The mean age of preg-

nant women in Finland and Sweden increased during the study period from 27.6 to 29.2 years ($p< 0.0001$).

International comparison Eight countries in Europe with different incidences of type 1 diabetes were included in the study. The high-incidence countries comprised Finland (n=104, mean age 28.8±4.7 SD years) and Sweden (n=128, mean age 29.7±4.0 SD years), while the low- and intermediate-incidence countries (later referred to as low-incidence countries) included Estonia (n=100, mean age 28.1±8.1 SD years), Germany (n=110, mean age 32.9±4.6 SD years), Hungary (n=100, mean age 27.5±4.7 SD years), Israel (n=377, mean age 29.1±5.0 SD years), Lithuania (n=154, mean age 26.5±5.1 SD years) and Russian Karelia (n=103, mean age 25.9±5.5 SD years). Sera from pregnant women were collected at the end of the first trimester of pregnancy from randomly selected women during their regular visits to a prenatal clinic in all countries. The sera were collected throughout the year during the years 1999–2001 and the participation rate was 90% (range 86–98%). The time period of sampling was within the same range in high- and low-incidence countries. The mean age of the women was slightly higher in the high-incidence countries than in the low-incidence countries (mean±SD age, 29.3±4.4 vs 28.4±5.8 years, p=0.032).

The study protocols were approved by local ethics committees in each country and the study was carried out in accordance with the Declaration of Helsinki.

Antibody analyses The frequency of enterovirus infections in different countries was studied by analysing enterovirus antibodies in the study series using both an enzyme immunoassay (EIA) to measure group-specific antibodies and a neutralisation assay for serotype-specific antibodies. All samples were analysed under code in the Virus Laboratory, University of Tampere. Samples from each country and/or different years were included in the same run. The frequencies and levels of these antibodies were taken as indicators of past exposure to enteroviruses, since it has been reported that they reflect the frequency of enterovirus infections in a given population [20].

Enzyme immunoassay Immunoglobulin G (IgG) class antibodies were measured separately against a panel of antigens including highly purified coxsackievirus B4 (CBV4), poliovirus type 1 (PV1, strain Sabin) and a synthetic enterovirus peptide (sequence KEVPALTAVETGAT-C), which is a common epitope for enteroviruses [21], as described previously [22]. CBV4 was first heat-treated (30 min at +56°C) to expose antigenic epitopes, which are cross-reactive between various enterovirus serotypes. Microtitre plates (Nunc Immunoplate, Nunc, Glostrup, Roskilde, Denmark) were coated with the antigen at concentrations of 2.5 μg/ml (bovine serum albumin-conjugated peptide), 2.4 μg/ml (CBV4) and 0.8 μg/ml (polio 1) in carbonate buffer (pH 9.4). Serum samples were analysed at 1/2,000 dilution in phosphate-buffered saline supplemented with 1% bovine serum albumin and 0.05% Tween 20. Binding of specific antibodies was documented using peroxidase-conjugated anti-human IgG (P214; Dako, Copenhagen, Denmark) as the second layer. The results are given as enzyme immunoassay units (EIU) with reference to the same negative and positive control samples used in all analyses. The value of 15 EIU was used as the cut-off for seropositivity [6].

Antibodies against tetanus toxoid (National Public Health Institute, Helsinki, Finland) were measured from the samples taken in 1983 and 2001 in Finland, as described previously [23], to assess the possible effect of long storage on antibody levels, such as a higher concentration due to possible vaporisation (regular tetanus vaccinations for children started in 1957 in Finland and have not changed substantially during the study period).

Plaque neutralisation assay The presence of neutralising antibodies against CBV4, CBV5, echovirus 9 (EV9) and coxsackievirus A9 (CAV9) was analysed in a subset of the series using the classical plaque neutralisation assay [24]. Samples from Estonia and Russian Karelia (n=203) and 200 samples from Finland from each of the years 1983 and 2001 were analysed. Two serum dilutions were used to detect high (1/256) and low (1/4) levels of neutralising antibodies. The viruses (American Type Culture Collection reference strains) were first treated with four-fold or 1/256 dilutions of serum for 1 h at 36°C, followed by overnight incubation at room temperature. The virus was then added on monolayers of green monkey kidney cells on six-well plates (Nunclon, Nunc). The amount of infectious virus was measured by counting the plaques after 46 h of incubation at 36°C. The serum was taken as antibody-positive if it blocked more than 80% of the virus infectivity.

Incidence of type 1 diabetes The mean annual incidences of type 1 diabetes (per 100,000 children under the age of 15 years) were taken from publications covering approximately the same period in the 1990s [1, 3, 25]. The incidences were 12.3 in Estonia, 40.8 in Finland, 12.0 in Germany, 9.4 in Hungary, 7.3 in Israel, 7.8 in Lithuania, 7.3 in Russia and 25.7 in Sweden. Finland and Sweden were considered high-incidence countries and Estonia, Germany, Hungary, Lithuania, Russia and Israel low-incidence countries.

Statistical analyses Comparisons were done between high- and low-incidence countries in the cross-sectional series. Age differences between study groups were tested by ANOVA. The Mann–Whitney test was used in the analysis of levels of antibodies between high- and low-incidence countries. A logistic regression model was applied to explain seropositivity in the neutralisation assay with the geographical area (high/low incidence) or time point as covariate (binomial logistic regression). Multinomial logistic regression was used to test the dose effect of multiple positivity for neutralising antibody in terms of absolute titres separately and the dose effect of titre for each serotype separately (0, seronegative [reference category]; >4, low positive; >256, high positive). Age was considered a confounding factor, and accordingly the logistic regression

analyses were adjusted for maternal age. The differences in antibody levels between different years in the time-trend series were tested by the non-parametric test of Cuzick for linear trend [26]. The software packages used were Stata version 6.0 (Stata Corporation, College Station, TX, USA), SPSS version 10.1 (SPSS, Chicago, IL, USA) and CIA [27]. A p value of 0.05 or less was considered statistically significant.

Results

Time-trend series A significant decrease was observed in enterovirus antibody levels in pregnant women between 1983 and 2001 both in Finland and in Sweden (Fig. 1). This decrease was observed in antibodies against both the highly purified coxsackievirus B4 as well as the synthetic peptide epitope of the VP1 protein (p<0.0001 for both in Cuzick's test for linear trend). Maternal age did not affect the antibody levels in the EIA test (ANOVA). In the neutralisation antibody assay, seropositivity for multiple antigens (three or four of the four serotypes screened) did not differ between the years 1983 and 2001. When serotypes were tested separately, a significant decrease was observed in neutralising antibodies for CBV4 (titre 4) and CBV5 (titre 256) (p=0.023 and 0.024, respectively in the binomial logistic regression model; Table 1). No dose effects were observed. The prevalences of EV9 and CAV9 antibodies did not differ between these years. The wide age range of pregnant women (from 15 to 44 years) influenced the neutralising antibody result in the time-trend series. For example, the frequency of CBV4 seropositivity was higher among older women (odds ratio [OR] 1.06, 95% CI 1.02–1.10, p=0.001) per year increase in age.

The antibody levels against tetanus toxoid that are induced by vaccinations did not decrease during this period but rather showed a slight increasing trend (median IgG levels were 36 EIU in 1983 and 52 EIU in 2001 in Finland).

International comparison The neutralising antibodies were more frequent in the low-incidence countries (Estonia and Karelia) than in the high-incidence country (Finland). Multiple antibodies (three or four of the four viruses tested) were significantly more frequent in Estonia and Karelia than in Finland (Table 1). This was also reflected in a clear dose response in the multinomial logistic regression: when compared to seronegativity, the OR increased from 2.4 to 9.1, 31.5 and 66.9 according to the number of antibodies tested (one, two, three and four of the four tested viruses, respectively). When serotypes were tested separately, all four tested viruses showed a 20–45% difference in antibody prevalence at a titre greater than 4 (p<0.0001 for all comparisons in binomial logistic regression; Table 1, Fig. 2a).

In addition to the low-titre antibodies, the high-titre antibodies (256 or higher) were also more frequent in Estonia and Karelia than in Finland. However, this difference was not as strong as for the low-titre antibodies, being statistically significant only for EV9 antibodies and multiple antibodies (Table 1). This was due to the fact that seropositive women in Finland had stronger antibody responses than seropositive women in Estonia and Karelia. For example, the proportion of high positives among seropositives was 71.3% for CBV4 and 53.5% for EV9 in Finland compared with 55.7 and 39.7% in Estonia and Karelia respectively (p<0.05 for both in logistic regression). This was also seen when the dose effect of antibody

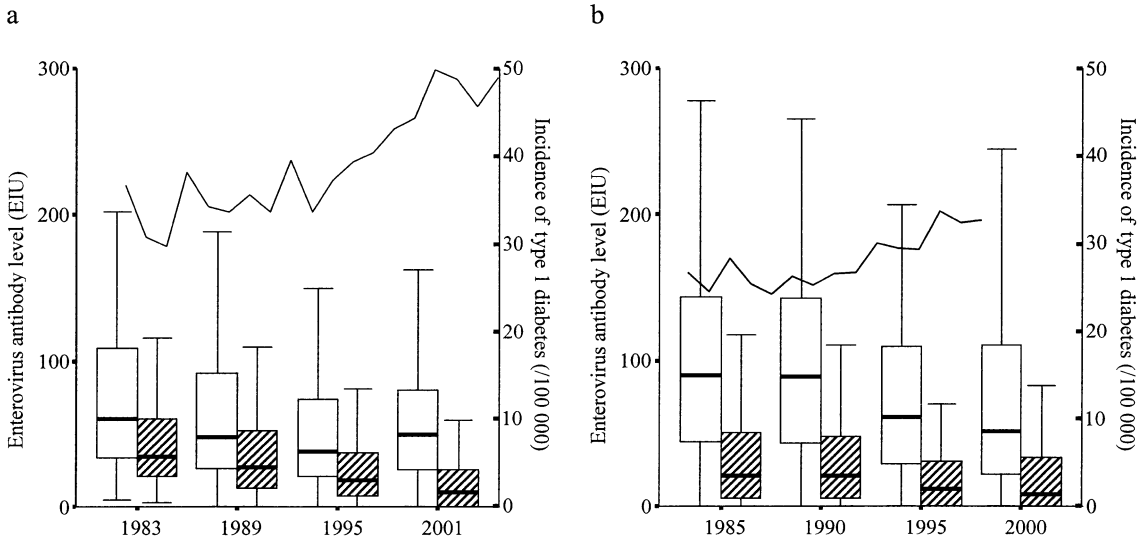

Fig. 1 Annual distribution of CBV4 IgG levels (*white box plots*) and synthetic enterovirus peptide-IgG (*hatched box plots*) among pregnant women in Finland and Sweden. The lines represent (**a**) the annual incidence of type 1 diabetes in Finland between 1983 and 2001 (incidence data from [3] and A. Reunanen, unpublished observation) and (**b**) the annual incidence in Sweden from 1983 to 1998 (incidence data from [46]). Each box plot represents the median (*black bar*) and the 25th and 75th percentiles in enterovirus antibodies. The *error bars* represent the lowest and highest values that are not outliers. Cuzick's test for linear trend: p<0.0001 for both antibodies in Finland as well as in Sweden

Table 1 Proportion of seropositive pregnant women (neutralising antibodies)

Antibody specificity	Finland year 1983 (*n*=200) Percent (%) (95% CI)	Finland year 2001 (*n*=200) Percent (%) (95% CI)	Estonia and Karelia year 2000 (*n*=203) Percent (%) (95% CI)
Titre 4			
CBV4	65.5[a] (58.7–71.7)	57.5 (50.6–64.5)	85.7[b] (80.2–89.9)
CBV5	58.0 (51.1–64.6)	53.0 (46.1–59.8)	71.9[b] (65.4–77.7)
CAV9	64.0 (57.1–70.3)	65.0 (58.2–71.3)	90.6[b] (85.8–93.9)
EV9	41.5 (34.9–48.4)	40.5 (33.9–47.4)	85.7[b] (80.2–89.9)
Multiple neutralising antibodies (three or four)	44.0 (37.3–50.9)	38.5 (32.0–45.4)	84.2[b] (78.6–88.6)
Titre 256			
CBV4	46.0 (39.2–52.9)	41.0 (34.4–47.9)	47.8 (41.0–54.6)
CBV5	24.5[a] (19.1–30.9)	16.0 (11.6–21.7)	17.2 (12.7–23.0)
CAV9	50.5 (43.6–57.4)	51.5 (44.6–58.3)	64.0 (57.2–70.3)
EV9	19.0 (14.2–25.0)	21.5 (16.4–27.7)	34.0[c] (27.8–40.7)
Multiple neutralising antibodies (three or four)	16.0 (11.6–21.7)	11.0 (7.4–16.1)	19.7[a] (14.8–25.7)

CBV4 Coxsackie virus B4; *CBV5* coxsackie virus B5; *CAV9* coxsackievirus A9; *EV9* echovirus 9
[a]$p<0.05$; [b]$p<0.0001$; [c]$p<0.01$ in binomial logistic regression when compared with corresponding samples from year 2001 in Finland

titre was analysed for each serotype: the low-titre (>4) antibodies showed a higher OR than the high-titre antibodies. For example, for CAV9, the OR for more frequent presence of neutralising antibodies in low-incidence countries was 8.3 at a titre greater than 4 and 5.5 at a titre greater than 256 when compared with seronegative samples ($p<0.001$ for both).

In contrast to neutralising antibodies, enterovirus antibodies measured against the synthetic enterovirus peptide and the PV1 and CBV4 antigens using EIA did not differ between Estonia and Karelia compared with Finland. When antibody results from all low-incidence countries (Estonia, Germany, Hungary, Israel, Lithuania and Russian Karelia) were compared with the two high-incidence countries (Finland and Sweden), no difference was found either, except that the levels of CBV4 antibodies were slightly higher in high-incidence countries than in low-incidence countries (median level 70 vs 59 EIU, $p=0.037$). The country-specific levels of enterovirus antibodies did not show any correlation with the incidence of type 1 diabetes (Fig. 2b).

The association between the two antibody detection methods was assessed by comparing CBV4 antibody results in the neutralisation and EIA assays. Sixty-one per cent of the samples were positive in both assays and 5% of the samples were negative in both assays. Twenty-five per cent of the samples that were negative in the neutralisation assay were positive in the EIA test, and 9% of the samples positive in the neutralisation test were negative in the EIA test.

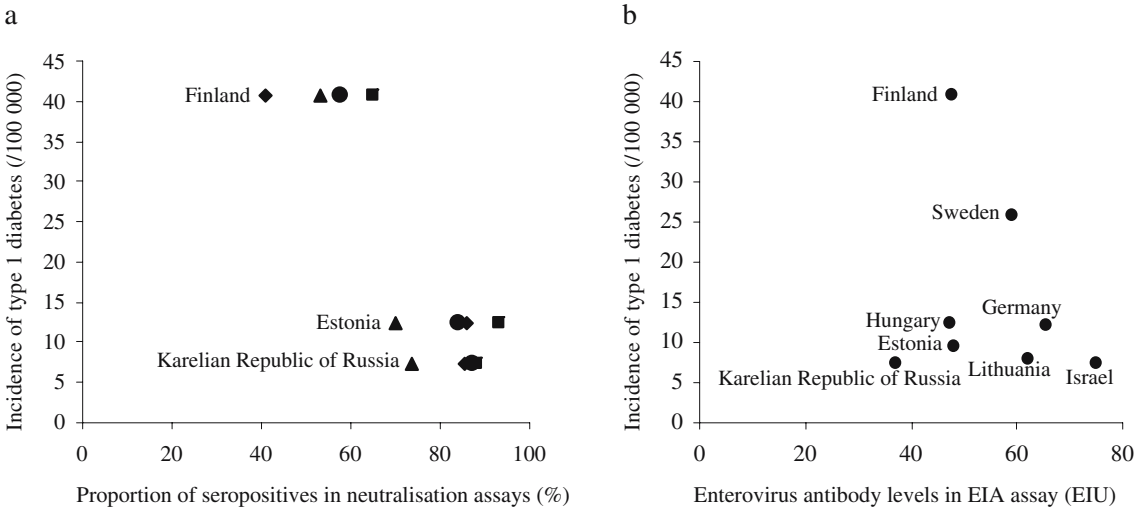

Fig. 2 Scatter plots of enterovirus antibodies and incidence of type 1 diabetes. **a** Proportion of seropositive pregnant women (%) in the neutralisation assay for CBV4 (*circles*), CBV5 (*triangles*), CAV9 (*squares*) and EV9 (*diamonds*) in Estonia, Finland and the Karelian Republic of Russia in relation to the annual incidence of type 1 diabetes (per 100,000 children). The differences between Finland and low-incidence countries (Estonia and Karelia) were significant in multinomial regression, as described in the Results section. **b** Median peptide enterovirus antibody levels (EIU) in EIA in different countries in relation to the incidence of type 1 diabetes (per 100,000 children). Incidence data for both figures are from [1, 3, 25]

Discussion

This study shows a decrease in enterovirus antibodies in the background population over the past 20 years in Finland and Sweden, while the incidence of type 1 diabetes has increased during the same time period. Furthermore, the populations with a high incidence of type 1 diabetes had a lower frequency of enterovirus antibodies than populations with a low diabetes incidence. These findings support our previous observations of an inverse relationship between the frequency of type 1 diabetes and enterovirus infections in the background population.

The enterovirus antibody status of pregnant women reflects their exposure to enterovirus infections (frequency of infections) as well as the protection of the offspring against enterovirus infections conferred by these maternal antibodies when transferred to the infant either transplacentally or in breast milk. The decrease in enterovirus antibody levels over the past 20 years suggests that the overall exposure rate to enteroviruses has decreased in both the Finnish and the Swedish population. The samples were taken between 1983 and 2001. However, the antibody status reflects not only recent infections but also the past infection history of a given individual. Therefore, the observed decrease in antibody levels probably reflects a change in enterovirus epidemiology during a longer period of time. In addition to the decrease in antibody levels seen in pregnant women, we have observed a parallel significant decrease in enterovirus antibody levels in a younger age group (10- to 14-year-old Finnish children) using serum samples collected during the years 1975, 1983 and 1998–2002. This finding further supports a decrease in enterovirus infections during recent decades (Viskari et al, data not shown). Increasing standards of living and hygiene and other factors that diminish the spread of the virus are probably the reasons for this decrease. For example, we have previously observed that children who had attended day-care experienced more enterovirus infections [7].

Several studies have reported an inverse relationship between the incidence of type 1 diabetes and population density, population mixing or the proportion of children in the population [28–32]. In Finland, a strong inverse correlation has been reported between population density and the incidence of type 1 diabetes [33, 34]. A number of reports have suggested that day-care protects against diabetes, but larger studies are needed to confirm this association [35]. Thus, these epidemiological findings support a possible protective role of such an environment where infections are readily transmissible. In fact, studies on common childhood infections suggest that one or more infections during the first 6–12 months of life may decrease the risk of type 1 diabetes [36–38]. Severe neonatal infections were, instead, a risk factor for diabetes [39, 40].

The differences in the prevalence of neutralising antibodies between Russian Karelia, Estonia and Finland were substantial, suggesting that Finnish women have experienced clearly fewer enterovirus infections. For example, in the year 2001, 42% of Finnish pregnant women lacked antibodies to CBV4 and were thus unable to protect their children against this particular serotype, which has most often been associated with type 1 diabetes. The corresponding figure in Estonia and Karelia was 14%. Multiple antibodies were observed in 39 and 84% of the mothers, respectively. This difference was observed also when samples from 1983 in Finland were compared with the samples from the year 2000 in Karelia and Estonia, even though a further decrease was observed in the CBV4 and CBV5 neutralising antibodies over the last 20 years in Finland. Enterovirus infections are, however, still frequent in young infants in Finland. We have previously shown that 30–50% of infants have had at least one enterovirus infection by the age of 6 months [41].

Ecological studies such as the present one may be biased by several confounding factors. The population selection bias is one possibility. In this study the sample collection was carried out in a regular prenatal clinic in each country where the participation rate is known to be high. In addition, the participation rate in our study was high in both the time-trend series and the cross-sectional series.

The long storage of the serum samples at −20°C may have influenced the quality of the sera. However, we observed no decrease in tetanus antibody levels during the same period, suggesting that this was not the case. IgG class antibodies are quite stable but we cannot exclude the possibility that some antibody degradation may have occurred during the 20 years of storage of sera. The degradation, however, should have been more prevalent in the oldest samples, thus rather diminishing than increasing the observed time-trend in antibody levels.

In the international comparisons, the distribution of HLA risk alleles for type 1 diabetes is one possible source of bias as HLA can modulate the immune response to enterovirus antigens [42–44]. These HLA allele combinations vary between countries, and high-risk combinations may be more prevalent in countries with a high diabetes incidence, thus contributing to the international variation in diabetes incidence [45]. However, the difference observed between high- and low-incidence countries is opposite to the expected one if HLA risk genes were involved, as a strong antibody response to enteroviruses is associated with HLA risk alleles for type 1 diabetes [44]. The present observation that Finnish women had a stronger antibody response when positive in the neutralisation assay may reflect the effect of HLA, even though other factors such as a low level of background enterovirus infection in the Finnish population may also play a role, leading to a higher response to the infection.

In the present study, enterovirus antibodies were measured using both EIA and neutralising antibody assays. The antibodies observed in the neutralisation assay represent the specific, lifelong-accumulated, ‘biological’ ability of antibodies to neutralise the infective virus. The difference in enterovirus antibodies between high- and low-incidence countries was not observed in the EIA but was apparent in the neutralising antibodies. These two methods are not directly comparable as they assess different aspects of enterovirus immunity. EIA measures antibodies binding to several different epitopes, whereas neutralising antibodies

target serotype-specific sites in the viral capsid proteins and are highly specific and sensitive markers of past infection. In contrast to the neutralising antibodies, the antibodies measured by EIA cross-react between serotypes, and are thus more group-specific than serotype-specific. This was also observed in our study, in which 25% of the CBV4 antibodies detected with the EIA were negative in the neutralisation assay. We measured neutralising antibodies against four enterovirus serotypes out of more than 60 serotypes, whereas the EIA assay included the group-specific CBV4 antibodies as well as the synthetic enterovirus antigen of the VP1 region that is common to all enteroviruses. Accordingly, the two methods complement each other and facilitate the generation of both specific and sensitive information on the epidemiology of enterovirus infections. The fact that the difference between the high- and low-incidence countries was seen in neutralising antibodies but not in EIA antibodies may reflect the masking effect of cross-reactive antibodies in the EIA test.

The mother plays a crucial role in the immunity of the newborn baby. The neutralising antibodies provided by the mother protect the offspring for the first 3–9 months after birth, during which time the child can be infected with enteroviruses and develop his or her own specific immunity. The observed decrease in levels of enterovirus antibodies among pregnant women in Finland and Sweden is in line with the polio hypothesis, which we proposed earlier [5–8]. Accordingly, we hypothesise that a low frequency of enterovirus infections in the background population will increase the susceptibility of young children to the diabetogenic effect of enteroviruses. The reason for this is that the proportion of mothers who lack enterovirus antibodies is increasing and children also experience their first infection later, when maternal antibodies have already disappeared.

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