Childhood Type 1 insulin dependent diabetes is an autoimmune pathogenesis which destroys insulin producing pancreatic beta cells. While genetic susceptibility is necessary, it is not sufficient to initiate the disease process suggesting that environmental factors are implicated. No single agent has been identified as causative for childhood diabetes but there are several pieces of evidence relating infections to disease incidence including animal models, where a pathogen-free neonatal environment is associated with increased incidence and early exposure to infections with decreased incidence.\(^2\)

The ‘hygiene hypothesis’ postulates that reduced exposure to common microbial infections in early life may increase the risk of Type 1 diabetes in childhood. The epidemiology of Type 1 diabetes implicates a role for infectious exposure which has been suggested as protective for atopy.\(^4\)

Studies at the population level show that living in overcrowded and deprived areas and areas with a high proportion of ethnic minority groups appears to reduce the risk of diabetes.\(^5\)–\(^8\) Case-control studies have shown that protection from diabetes is conferred on children who experience and are exposed to more infections in the first year of life.\(^2\)–\(^9\),\(^10\) The hygiene hypothesis is non-specific in terms of suggesting the type or ‘dose’ of exposure that might confer protection through modulation of the immune system. The identification of specific enteroviruses which may attack beta-cells directly\(^11\) is not necessarily inconsistent with this concept. Children whose immune system is not upregulated in the first year of life may be particularly susceptible to diabetogenic viruses at a later stage. This ‘late
exposure model’ where early immunity is not established was first described for polio.12

Areas with higher levels of population mixing, attributable to migration, are likely to represent communities where the prevalence and range of infections is high due to a larger proportion of infectives and susceptibles.13 Communities with low population density and low migration rates are less likely to maintain a wide range of endemic infections and hence immunity.13,14 The resultant susceptible population may be exposed to a novel suite of infections carried by infective incomers (i.e. those carrying a different suite of infections); a theory proposed by Kinlen in relation to childhood leukaemia.15 Acute lymphoblastic leukaemia and Type 1 diabetes in children have many epidemiological features in common16 and the requirement for a competent immune system appropriately stimulated in early life may be necessary to prevent the development of a wide range of chronic conditions including diabetes, leukaemia and atopy.4,17 The theoretical approach to analysing the association between childhood leukaemia and population mixing18 has been extended and refined and applied to childhood diabetes. We tested the hypothesis that low levels of population mixing in electoral wards are associated with increased incidence of Type 1 childhood diabetes.

Methods

Subjects were 994 children (<15 years) diagnosed with Type 1 diabetes between 1986–1994 in the former Yorkshire Regional Health Authority whose details are recorded on the 98% complete, population-based Yorkshire Register of Childhood Diabetes.19 Population totals by sex and 5-year age-band and data on ethnic origin, unemployment, household overcrowding, housing tenure and car ownership were obtained for the 532 electoral wards in the study area from the 1991 UK Census (The 1991 Census, Crown Copyright, ESRC purchase). The latter four variables were used to calculate the Townsend deprivation score.20 The population weighted average of the population density (persons per hectare) for each census enumeration district was aggregated to electoral ward to provide a person-based measure of population density which more accurately reflects the density at which the average person lives.21 Ethnicity was defined as the proportion of non-white children living in each electoral ward at the 1991 Census.

Using the 1991 Census Special Migration Statistics population migration and population mixing were calculated separately for ‘any age’ (≥1 year) and children (1–15 years)—those under 1 year of age would not have been born one year prior to the census). Population migration was the proportion of either the ‘any age’ or childhood population with a different address one year before the census, excluding those moving within wards. Population mixing was defined as the diversity of the origin of these incoming migrants. This was calculated using flows of all migrants i.e. ‘any age’ (≥1 year) and flows of children (1–15 years) from all other wards (England and Wales) and postcode sectors (Scotland) to calculate the Shannon index of diversity, $H_j$.22

$$H_j = \frac{1}{2} \sum_{i=1}^{S} \left[ \frac{p_i \ln p_i}{N_j} - \frac{1 - \sum p_i^{-1}}{12N_j^2} + \frac{\sum (p_i^{-1} - p_j^{-2})}{12N_j^3} \right]$$

Where for each area $j$, $p_i$ is the proportion of migrant individuals coming from the $i$th area as a proportion of all migrants moving from the total number of areas $S$, and $N$ is the total number of migrants. This formula incorporates a correction23 for wards with low numbers of originating areas which can result in an artificially inflated value of the index where there is possibility of under-ascertainment or error in the census data. In practice any correction beyond the second term is very small. Higher values indicate higher diversity of originating areas and higher levels of population mixing.

Negative binomial regression models were fitted to observed counts of cases in each ward using the log of the number of expected cases as the offset derived from age-sex specific incidence rates. Incidence rate ratios (IRR) with 95% CI are reported as a measure of association between diabetes incidence for 0–14-year-olds and by age (0–4, 5–9, 10–14) and the independent variables: deprivation, ethnicity, population density, population migration and population mixing (childhood and ‘any age’). Separate models were constructed for each age band. Initially, Poisson regression was used and model fit assessed comparing its residual deviance to a $\chi^2$ distribution with $n–1$ degrees of freedom. With sparse and potentially over-dispersed data however, the residual deviance in a Poisson model is not necessarily distributed as $\chi^2$ so the goodness-of-fit of the null and final models were checked by simulation.24 The results of 10 000 simulations confirmed the poor fit determined by $\chi^2$ goodness-of-fit tests from the Poisson models. In view of this, negative binomial regression was used to avoid overestimation of the significance of variables in the model.25 The negative binomial model is more conservative in that while the point estimates are not changed, confidence intervals are widened.

Each variable was analysed as a continuous variable and in five categories, each category containing approximately equal populations. For each age band the category cut points were recalculated to take account of their slightly different distribution between wards. Population mixing was also categorized into those wards below the 10th centile, between the 10th and 90th centile and those above the 90th centile. The proportion of individuals with an address different to that one year ago (children and ‘any age’) were highly skewed and were subject to a log transformation which gave a more random spread of deviance residuals when plotted against fitted values. The proportion of non-white children (ethnicity) also had a highly skewed distribution but log transformation correcting for zeroes by the addition of 0.01 produced a bimodal plot and did not improve the spread of deviance residuals. It was thus retained as a continuous variable.

Improvement in model fit was assessed using the likelihood ratio test between the saturated and unsaturated models, defined as minus twice the difference in log likelihoods, approximated to a $\chi^2$ distribution. Standardized deviance residual plots were examined for any sign of abnormal distribution of deviance residuals together with plots of fitted values. Two multivariate models were constructed, each containing person-based population density and ethnicity—one using ‘any age’ population mixing and ‘any age’ population migration, the other, childhood population mixing and childhood population migration. Deprivation was not included as it dropped out of the model when included with population density. Modelling was carried out for 0–14-year-olds and in separate 5-year age bands (0–4, 5–9 and 10–14 years).
Results

Summary data for the characteristics of the study area at electoral ward level are given in Table 1. The univariate results (data available on request) for 0–14 years showed significantly reduced IRR for higher levels of population density, ethnicity and Townsend score (i.e. more deprived), patterns which were generally reflected in each age group. For childhood population mixing (bottom decile), significantly raised IRR were observed for 0–14-year-olds (1.76, 95% CI: 1.25–2.48), 5–9-year-olds (2.22, 95% CI: 1.27–3.89) and 10–14 years (1.96, 95% CI: 1.23–3.13) whereas a non-significant reduction was present for 0–4-year-olds (0.72, 95% CI: 0.23–2.26).

Results from the multivariate analysis are summarized in Table 2. Two notable results are firstly that increasing childhood population density is negatively associated with diabetes incidence when modelled either with ‘any age’ or childhood population mixing. Secondly, there was a significant increase

Table 1 Demographic characteristics of 532 census wards in Yorkshire

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Minimum</th>
<th>Median</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (ha)</td>
<td>1.385 337</td>
<td>17</td>
<td>1132</td>
<td>21 751</td>
</tr>
<tr>
<td>Population</td>
<td>3 562 000</td>
<td>488</td>
<td>4193</td>
<td>25 291</td>
</tr>
<tr>
<td>Childhood population</td>
<td>708 912</td>
<td>71</td>
<td>760</td>
<td>6012</td>
</tr>
<tr>
<td>Townsend score</td>
<td>–</td>
<td>–</td>
<td>–4.78</td>
<td>17.86</td>
</tr>
<tr>
<td>Population density (persons ha⁻¹)</td>
<td>–</td>
<td>0.01</td>
<td>5.52</td>
<td>51.01</td>
</tr>
<tr>
<td>Migrants (‘any age’) as proportion of ward population</td>
<td>–</td>
<td>0.03</td>
<td>0.06</td>
<td>0.24</td>
</tr>
<tr>
<td>Population mixing (‘Any age’)</td>
<td>2.34</td>
<td>3.58</td>
<td>7.11</td>
<td></td>
</tr>
<tr>
<td>Childhood population mixing (1–15 years)</td>
<td>0.21</td>
<td>0.21</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

Population density was categorized separately for each age band (see text).

Table 2 Incidence rate ratios (IRR) and 95% CI for Type 1 childhood diabetes associated with childhood and all age population mixing, adjusting for ethnicity, childhood population density and proportion of migrants using negative binomial regression modelling

<table>
<thead>
<tr>
<th>Model/Variables</th>
<th>Rangea</th>
<th>Age group</th>
<th>0–4 years</th>
<th>5–9 years</th>
<th>10–14 years</th>
<th>0–14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood population mixing</td>
<td>1 (–)</td>
<td>IRR</td>
<td>95% CI</td>
<td>IRR</td>
<td>95% CI</td>
<td>IRR</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Continuous</td>
<td>1.34 (0.47–3.85)</td>
<td>0.99 (0.39–2.53)</td>
<td>0.49 (0.22–1.09)</td>
<td>0.83 (0.49–1.40)</td>
<td></td>
</tr>
<tr>
<td>Log₁₀ child migrants</td>
<td>Continuous</td>
<td>0.88 (0.56–1.38)</td>
<td>1.33 (0.92–1.92)</td>
<td>0.90 (0.67–1.22)</td>
<td>1.00 (0.82–1.24)</td>
<td></td>
</tr>
<tr>
<td>Population density</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>0.88 (0.57–1.35)</td>
<td>0.99 (0.69–1.42)</td>
<td>0.88 (0.66–1.18)</td>
<td>0.91 (0.75–1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.88 (0.58–1.34)</td>
<td>0.94 (0.65–1.35)</td>
<td>0.77 (0.57–1.03)</td>
<td>0.82 (0.67–1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.62a (0.40–0.98)</td>
<td>1.01 (0.71–1.44)</td>
<td>0.60c (0.43–0.82)</td>
<td>0.76c (0.61–0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.61 (0.36–1.04)</td>
<td>0.65 (0.41–1.02)</td>
<td>0.78 (0.56–1.11)</td>
<td>0.68c (0.52–0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood population mixing 10th–90th decile</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>1 (–)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10th decile</td>
<td>0.56 (0.17–1.82)</td>
<td>2.25c (1.20–4.11)</td>
<td>1.47 (0.89–2.42)</td>
<td>1.46c (1.01–2.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90th decile</td>
<td>0.87 (0.61–1.25)</td>
<td>1.18 (0.89–1.56)</td>
<td>1.06 (0.83–1.35)</td>
<td>1.04 (0.88–1.23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Any age population mixing | 1 (–) | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI |
| Ethnicity | Continuous | 1.38 (0.49–3.88) | 0.79 (0.32–1.97) | 0.52 (0.24–1.13) | 0.80 (0.48–1.33) |
| Log₁₀ ‘any age’ migrants | Continuous | 0.61 (0.36–1.02) | 1.29 (0.86–1.94) | 1.01 (0.72–1.42) | 0.97 (0.77–1.23) |
| Population density | 1 (–) | 1 (–) | 1 (–) | 1 (–) | – | – |
| 2 | 0.85 (0.57–1.28) | 0.90 (0.64–1.27) | 0.86 (0.65–1.12) | 0.87 (0.72–1.05) |
| 3 | 0.89 (0.59–1.33) | 0.87 (0.61–1.22) | 0.75c (0.57–0.99) | 0.79c (0.65–0.96) |
| 4 | 0.68 (0.43–1.07) | 0.93 (0.66–1.31) | 0.58d (0.42–0.78) | 0.74d (0.60–0.91) |
| 5 | 0.66 (0.38–1.13) | 0.60d (0.38–0.94) | 0.74 (0.53–1.04) | 0.66d (0.51–0.84) |
| ‘Any age’ population mixing 10th–90th decile | 1 (–) | 1 (–) | 1 (–) | 1 (–) | – | – |
| 10th decile | 1.21 (0.70–2.10) | 1.04 (0.62–1.77) | 1.14 (0.77–1.69) | 1.15 (0.87–1.51) |
| 90th decile | 1.05 (0.71–1.55) | 1.26 (0.93–1.71) | 1.12 (0.87–1.44) | 1.15 (0.96–1.37) |

a Child and ‘any age’ migrant variables were subject to a log transform but ethnicity remained un-transformed; population density was categorized separately for each age band (see text).
b Likelihood ratio test against null model χ² = 29.97, 8 d.f., P < 0.001.
c Significant at P < 0.05.
d Likelihood ratio test against null model χ² = 29.03, 8 d.f., P < 0.001.
in IRR for the bottom decile of childhood population mixing for 0–14-year-olds (1.46, 95% CI: 1.01–2.11) and in the 5–9 age group (2.23, 95% CI: 1.20–4.11) but no significant effect was present for ‘any age’ population mixing (IRR 1.15, 95% CI: 0.96–1.37 for 0–14-year-olds and 1.26, 95% CI: 0.93–1.71 for 5–9-year-olds).

The likelihood ratio χ² statistics for model fit for childhood and ‘any age’ population mixing were 29.97 and 29.03, respectively (8 d.f., P < 0.001 in both cases), indicating a significant improvement in fit over the base models. Standardized deviance residual plots revealed no gross outliers and were randomly distributed.

Discussion

‘Population mixing’, involving the migration of individuals between different geographical areas increases the range and levels of infections in the community through contacts between susceptible and infective individuals.14,26 Areas that have low levels of population mixing are therefore likely to experience a more limited number of infections circulating in the community. We have shown that childhood diabetes incidence is significantly raised in areas where childhood population mixing is low. This novel finding is not explained either by the ethnic composition of the population or by population density, both factors associated with Type 1 diabetes incidence at a small geographical scale.6,27,28 Population density, deprivation and ethnicity are highly correlated but it is important to identify whether they have independent effects as for example in the case of infectious tuberculosis.29,30 Both deprivation (the Townsend index) and population density were included as a priori factors related to the incidence of Type 1 diabetes but because of their high correlation the effect of removing each one when modelled with the other was investigated. There was a reduction in model fit on removal of population density (likelihood ratio χ² = 3.59, P = 0.0581) but not on removal of the Townsend index (likelihood ratio χ² = 0.38, P = 0.5355). The Townsend index is a composite score which uses three parameters (unemployment, car-ownership and housing tenure) which relate to adult activities, only the fourth parameter (household overcrowding) relates to children and adults. Thus we chose not to include deprivation (Townsend index) in the final model. In addition, population density was considered a proxy measure for the intensity of contacts with individuals in conjunction with migration which was designed to provide a proxy measure of the diversity of individuals moving to an area. The census data allowed us to restrict these two measures specifically to children.

High proportions of non-whites were significantly associated with reduced risk in the univariate analysis but this effect became non-significant in the multivariable model. Our data did not lead us towards thinking that ethnicity could be a proxy measure for population mixing but the possibility does exist.

Measures of population mixing

Our study measured population mixing using an index which accounted not only for the proportion of migrants but also the range of places from which they came. We assumed that increased diversity of incomers would increase the pool of community infections more substantially than movement within the same local area.14 The Shannon diversity index has been used by ecologists to describe the diversity of different habitats in relation to plant and animal species31 and has been applied to the investigation of population mixing and childhood leukaemia18,32 and sudden infant death syndrome13 but never previously to childhood diabetes. It calculates diversity on the basis of the number of origins and the proportion of individuals coming from those origins and could be considered a good representation of population mixing at the scale of electoral wards used in this study. The index does not take into account the distance between origin and destination wards as there are inherent problems with natural geographical barriers such as mountains, rivers and estuaries. However, it may not be the distance moved into a ward that is important but differences in the number and type of infections circulating in the originating communities. Other potential measures of population mixing such as commuting patterns or mode of commuter transport were not investigated as they were considered to be applicable to adult exposure rather than specific to childhood population mixing and parental occupational mixing with individuals does not appear to effect the risk of diabetes in their offspring.34

Separate measures of ‘any age’ and childhood population mixing were used to differentiate between the likely exposure or contact of children with other children in a community and their contact with adults. It was of considerable interest that no significant geographical differences in childhood diabetes incidence were associated with levels of ‘any age’ population mixing. Although children might be expected to move with adults the reverse is not the case: out of 1036 wards in England and Wales categorized as being in the bottom decile in terms of population mixing for 1–15-year-olds, for 425 of those wards ‘any age’ population mixing lies between the 10th and 90th percentiles. Increased social mixing of children particularly at an early age has been shown to reduce the risk of childhood diabetes in case-control studies9,10 whereas contacts with parents involved in occupations with high levels of social contact (as a proxy for infectious exposure) had no effect.34 This suggests that contacts with children rather than adults may be the key factor.

Categorization of the population mixing variables was used to investigate the possibility of a threshold effect in those areas subject to very high or low levels of population mixing. A UK study of childhood leukaemia used this methodology as they suggested little variation within normal ranges may exist in heterogeneous populations.18 Categorization also removes the assumption of linearity in the relationship between log incidence and population density and population mixing.

Age effects

The overall finding of increased risk of childhood diabetes in the most extreme areas of low childhood population mixing was not observed in all age groups. Those in the older age groups (5–9, 10–14) have an increased IRR whereas there was a decreased IRR in the 0–4-year-olds. These observations are consistent with a ‘late infectious exposure’ hypothesis. This scenario is well established for infections such as polio where the consequence of early isolation leads to an immune system unable to adequately challenge a later exposure.12 Our findings for childhood diabetes support the hygiene hypothesis, where
the absence of necessary stimulation to the developing immune system, experienced in areas of low diversity of migrant children, increases vulnerability to a later infectious exposure, which may itself be common, but uncommonly precipitates the autoimmune pathogenesis of diabetes. Higher risks in the 5–9-year-olds may reflect a broader range of infectious exposures occurring when starting school. Later measles infection in rural compared with urban areas has also been demonstrated in children.\textsuperscript{35} The migration data available do not give any information on the movement of those children under one year old. This reduces the overall numbers of migrants included in the calculation but there is no information on their probable origins thus it is not possible to quantify what effect this might have on the analysis.

Census data only provides information at a fixed point in time and in the case of the Special Migration Statistics our calculation of population mixing relied on the address of individuals one year prior to the census date. Large-scale population movements occurring between 1985 and 1995 but excluding those within one year of the 1991 Census date would not contribute to the calculation of population mixing in an area but no data were available to include such changes in the modelling. Such highly localized increases in population have been associated with increased risk of developing childhood leukaemia, another rare disease of childhood with possible links to an infectious aetiology.\textsuperscript{15,17,36,37} Stiller and Boyle\textsuperscript{18} show increased incidence of childhood leukaemia in areas of high inward migration in 0–4- and 5–9-year-olds whereas for childhood diabetes there is increased incidence in areas of low population mixing in 5–9-year-olds. These differing results lend themselves to different interpretations. For diabetes, children may become ‘susceptible’ as a result of living in an area of low population mixing/low infectious exposure followed by a ‘late exposure’ through increased social contact at school (4–5 years in the UK). Stiller and Boyle\textsuperscript{18} suggest that the risk of childhood leukaemia in areas of high and diverse population mixing is seen at a young age (0–9) as a result of early infection with a corresponding decrease in incidence in the 10–14-year-olds.

Ecological analyses which attempt to characterize an area from snapshot data and extrapolate to a period of time can always be criticized but although we might have missed localized migrations it is unlikely this misclassification would have strongly affected our overall results. Area-based measures are prone to the ‘ecological fallacy’ but some small area census variables may actually be better discriminators of circumstance than individual measures.\textsuperscript{38}

Our study describes a single method of approaching investigations of the relationship between diabetes and infections. It is unable to distinguish between risk associated with possible exposure (or lack of exposure) either to a single agent or to a broad spectrum of infections, which may be symptomatic or asymptomatic. However, this is the first investigation of population mixing and childhood diabetes and our findings support the hypothesis of a role for infections in disease aetiology. The potential lack of early exposure to a variety of incoming children of diverse origins with a potentially wider range of infections is shown to be an important component of increasing risk. Further investigations of population mixing around the time of birth may clarify the time at which exposure to infections, or lack of infectious contacts, may modify risk.

Acknowledgements

All the Paediatricians, Physicians and General Practitioners in Yorkshire are thanked for their continuing collaboration and we are grateful for the active support of all the Diabetes Specialist Nurses. We are indebted to Carolyn Stephenson and Sheila Jones for careful data collection and processing. Paul Boyle is thanked for his contribution to discussions on population mixing.

References

Commentary: Population mixing and childhood diabetes

Anthony Staines

There has been a suspicion that Type 1 (insulin-dependent) diabetes (IDDM) is due to an infection since the early years of the last century. This arose from the typical acute clinical presentation of the disease. The specific hypothesis was that IDDM was due to direct virally mediated immune destruction of the pancreatic islets. A number of case reports of IDDM as a consequence of overwhelming enteroviral infection, and the high risk of IDDM amongst children with congenital rubella infection, specifically that due to infection, increases the risk of developing IDDM. There is evidence from several lines of animal and epidemiological data that early life circumstances may affect later immune response, but the details and mechanisms involved remain frustratingly obscure. A shift in the balance between Th1 and Th2 responses, as has been suggested for asthma, is probably too simple an explanation for the complex changes seen in IDDM, and perhaps in atopy also.3–5

A more interesting role for infectious disease, the ‘hygiene hypothesis’ has been proposed. This is that early protection from antigenic challenge, specifically that due to infection, reduces the risk of developing IDDM and that early exposure to infection.

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Possible conflict of interest: This paper is written by colleagues of mine. Although I now live in another country, I worked with them on collecting the original data for the diabetes register on which this paper is based.
The major limitations of this work are those of any ecological study, namely an untestable assumption about personal exposure correlating with area-level measurements. However, several of the measures used in this group of studies have no obvious person-level counterpart. It is difficult to see how population density, and population mixing could be measured meaningfully at an individual level. It is now critically important that further attempts are made to replicate these results outside the UK. This would then address the concern that these studies have merely identified some quirk of British life, which itself leads to an increased risk of IDDM.

The results of several recent case-control studies are also broadly consistent with this hypothesis, but suggest that the full picture may be quite complicated. Pundziute-Lycka et al. found that infection in the first six months of life reduced the risk of developing IDDM after the age of 5 years. The EURODIAB Substudy 2 study group found that while perinatal infections increased the risk of IDDM, attendance at pre-school facilities, known as a major source for exposure to infections, decreased the risk. If, as these results suggest, the precise timing of childhood infection is of the essence, very sophisticated studies will be needed to resolve these questions.

Another crucial area for research is an understanding of the biology of immune system development. Recent work has shown that relatives of people with IDDM, who are at high risk of developing IDDM themselves, as defined by raised islet-cell antibody titres, have Th1-like responses, but these are not found in children newly diagnosed with IDDM. At present while it is possible to talk about immune system maturation, it does not seem to be possible to measure it in ways which are biologically relevant for understanding the aetiology of IDDM. It is also unclear precisely what should be measured to define ‘exposure to infection’ in childhood.

The picture emerging from this body of work is still unclear. Evidence from ecological studies and case-control studies suggest that infection is important in the aetiology of Type 1 diabetes. Evidence from immunological studies in rats and humans suggest that the immune response in Type 1 diabetes is influenced in important ways by infection, and that certain patterns of abnormal immune response may predispose to Type 1 diabetes. The respective roles of breastfeeding, dietary exposure, and other perinatal events remain to be explained. The interplay between genetic susceptibility and patterns of immune response, as influenced by immunological experience is a promising area for further study.

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