Acute lymphoblastic leukaemia (ALL) and type 1 diabetes have an environmental aetiology and common epidemiological features. Incidence rates and national characteristics of both conditions were investigated in 40 countries worldwide. There was a significant positive correlation between diseases. Markers of wealth and affluence were significantly associated with high incidence.

Acute lymphoblastic leukaemia (ALL) and type 1 diabetes in children appear to be biologically unconnected conditions, but there are common threads in both their epidemiology and possible aetiology. Over the past 20 years, the incidence of both diseases has been slowly rising in western countries, a phenomenon that cannot be explained by underlying genetic changes at the population level. Furthermore, rates of ALL and type 1 diabetes display geographical variation both internationally and within countries; in Yorkshire, UK the spatial distribution of both diseases is closely linked.

A common and recurring theme in the aetiology of ALL and type 1 diabetes has been the possible involvement of infections. One explanation involves a paradox of development in westernised societies: that common infections in infancy may protect from later disease by appropriate modulation of the naïve immune system. Contrarywise, in the absence of such early exposures, later infection, for example with social mixing of children, may precipitate abnormal immune reactions and disease. Inherited genetic factors may also influence susceptibility. This scenario has been referred to as the “hygiene hypothesis” in the context of both type 1 diabetes and allergy/asthma and the “delayed infection” hypothesis for childhood ALL. Although the underlying immunological pathology of childhood allergies and type 1 diabetes are dissimilar (T-helper 2 versus T-helper 1 T cell overactivity), their shared environmental associations are reflected in positive correlations between their respective international incidence rates. We therefore anticipated that type 1 diabetes and childhood ALL might show a similar association.

RESULTS
The analysis showed a significant positive correlation between the incidence rates of ALL and type 1 diabetes ($r = 0.53$, 95% CI 0.36 to 0.72) (fig 1). This pattern was similar across Europe ($n = 26$) and the rest of the world ($n = 14$) and the exclusion of Finland as the only outlier made no difference to the results.

Higher rates of diabetes are associated with wealth and affluence in European countries, so we tested for associations with diabetes worldwide and for the first time explored the relation between levels of national prosperity and ALL incidence. The explanatory variables were gross domestic product (GDP), infant mortality, and life expectancy. Additional factors previously linked to disease incidence were examined including population density (linked to diabetes and ALL), coffee consumption (diabetes), and cows’ milk consumption (diabetes). A recently suggested potential protective effect from vitamin D supplementation in early life for type 1 diabetes was indirectly measured by examining latitude and average hours of sunshine.

The logarithmic or reciprocal transformation was used for factors which were highly skewed (GDP, infant mortality and population density; table 1). The remaining explanatory variables and incidence rates themselves were all reasonably normally distributed. Correlations and separate linear regression models were applied to each disease, with each factor included as an independent variable. All statistical analyses were performed using Stata.

The correlation and regression analyses showed positive associations for GDP, infant mortality, and life expectancy with both ALL and type 1 diabetes (table 1).

Population density was associated (inversely) only with diabetes, while coffee and milk consumption were significantly associated with both conditions. Latitude and sunshine were both linked to diabetes alone. The $R^2$ statistic showed that GDP and infant mortality along with milk and coffee consumption were factors which best explained the variation in incidence for ALL and diabetes, although this goodness of fit test should be interpreted with caution.

DISCUSSION
Our analysis clearly shows for the first time that the international incidence of ALL and type 1 diabetes are positively associated. Countries with either high or low incidence of either disease are likely to have a corresponding rate of the other condition.

Markers of national prosperity appear to explain some of the worldwide variation between countries for both ALL and type 1 diabetes, which is consistent with observations in European populations. The same links with socioeconomic variables can also be seen within countries at a smaller geographical scale. Exactly what specific “affluent” lifestyle
Table 1 Correlation and parameter estimates from linear regression for standardised incidence rates of childhood acute lymphoblastic leukaemia and type 1 diabetes from 40 countries for specific national characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Acute lymphoblastic leukaemia</th>
<th>Type 1 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation* (95% CI)</td>
<td>Parameter estimate (95% CI)</td>
</tr>
<tr>
<td>Gross domestic product (1994, US$ per head)</td>
<td>0.47 (0.19 to 0.68)</td>
<td>0.69 (0.27 to 1.11)</td>
</tr>
<tr>
<td>Infant mortality (1995, per 1000 live births)</td>
<td>0.41 (0.12 to 0.64)</td>
<td>6.16 (1.72 to 10.61)</td>
</tr>
<tr>
<td>Life expectancy (1995)</td>
<td>0.42 (0.13 to 0.65)</td>
<td>0.12 (0.03 to 0.20)</td>
</tr>
<tr>
<td>Population density (ages 0–14 per km²)</td>
<td>-0.19 (-0.47 to 0.13)</td>
<td>0.14 (-0.39 to 0.11)</td>
</tr>
<tr>
<td>Coffee consumption (1999/01, 60 kg bags per 1000 head)</td>
<td>0.38 (0.03 to 0.65)</td>
<td>0.0061 (0.00046 to 0.01)</td>
</tr>
<tr>
<td>Milk consumption (liquid, 1990s, kg per head)</td>
<td>0.41 (0.05 to 0.67)</td>
<td>0.014 (0.0016 to 0.03)</td>
</tr>
<tr>
<td>Sunshine (average hours per day)</td>
<td>0.22 (-0.10 to 0.50)</td>
<td>0.016 (-0.079 to 0.04)</td>
</tr>
<tr>
<td>Latitude (degrees from equator, capital)</td>
<td>-0.20 (-0.48 to 0.12)</td>
<td>-0.13 (-0.35 to 0.09)</td>
</tr>
</tbody>
</table>

*Pearson’s product moment correlation coefficient.
†Logarithmic transformation used; ‡Inverse transformation used.

Figure 1 Standardised incidence rates for childhood acute lymphoblastic leukaemia. Data from the UK were separated into England, Wales, Scotland, and Northern Ireland (UK-EWS) and Northern Ireland (UK-NI). International incidence rates were based on the 54 registries of the EURODIAB ACE Study group.

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also in relation to temporal trends. The striking parallels in the descriptive epidemiology of type 1 diabetes and ALL in children suggest that an exploration of common causal pathways linked to the immune response in early life and underlying genetic susceptibility in individuals would be fruitful.

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Accepted 17 April 2003

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