

Is childhood-onset Type I diabetes a wealth-related disease? An ecological analysis of European incidence rates

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Abstract

Aims/hypothesis. To describe the epidemiology of childhood-onset Type I (insulin-dependent) diabetes mellitus in Europe, the EURODIAB collaborative group established prospective, geographically-defined registers of children diagnosed under 15 years of age. A total of 16362 cases were registered by 44 centres during the period 1989–1994. The registers cover a population of approximately 28 million children with most European countries represented.

Methods. In most centres a primary and a secondary source of ascertainment were used so that the completeness of registration could be assessed by the capture-recapture method. Ecological correlation and regression analyses were used to study the relationship between incidence and various environmental, health and economic indicators.

Results. The standardised average annual incidence rate during the period 1989–94 ranged from 3.2 cases per 100 000 person-years in the Former Yugoslavian

Republic of Macedonia to 40.2 cases per 100 000 person-years in Finland. Indicators of national prosperity such as infant mortality ($r = -0.64$) and gross domestic product ($r = 0.58$) were most strongly and significantly correlated with incidence rate and previously-reported associations with milk consumption ($r = 0.58$), coffee consumption ($r = 0.51$) and latitude ($r = 0.40$) were also observed.

Conclusion/interpretation. The wide variation in childhood Type I diabetes incidence rates within Europe could be partially explained by indicators of national prosperity. These indicators could reflect differences in environmental risk factors such as nutrition or lifestyle that are important in determining a country's incidence rate. [Diabetologia (2001) 44 [Suppl 3]: B9–B16]

Keywords Type I diabetes mellitus, epidemiology, geographical variation, incidence, risk factors, ecological analysis, gross domestic product.

The low concordance rates of Type I (insulin-dependent) diabetes in monozygotic twin pairs [1–3], and the continuing increase in the incidence of Type I diabetes in many European countries in recent years confirms the importance of environmental factors as causes of this disease [4–7]. Useful clues about these environmental factors can be obtained

by studying geographical variation in incidence rates in relation to the characteristics of the countries involved. Such ecological analyses should be undertaken with high-quality incidence data obtained from population-based registers adhering to a standard protocol. We have previously reported such data for the years 1989–90 from 26 registries in the EURODIAB Study Group and have established the existence of a wide range of incidence rates within Europe [8]. The network has since expanded to include 44 registries, with most European countries and Israel being represented. Incidence data in the 6-year period, 1989–94, are examined in this paper.

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We explored the wide geographic variation in incidence rates using ecological analysis. The strikingly higher incidence in Finland compared to ethnically-similar sub-populations in Estonia [9] as well as the apparent decrease in Type I diabetes in the war years in Germany [10] could reflect wealth-related risk factors. Therefore we studied geographical variability in relation to estimates of national prosperity. We also analysed a selection of indicators dictated mainly by existing environmental hypotheses. Coffee consumption, milk consumption and early breast-feeding have been the subject of previous ecological analyses and have also been studied at the individual level [11–15]. Climatological factors and population density have received rather less attention [16, 17]. A North-South gradient within Europe has long been hypothesised and prompted consideration of both latitude and longitude [18].

Subjects and methods

The establishment of the EURODIAB collaborative group of childhood diabetes registers has been described previously [8, 19]. In 1988 prospective registers of new subjects with Type I (insulin-dependent) diabetes mellitus among children under 15 years of age were established in 26 geographically-defined centres in Europe and Israel. Other centres, including many from the countries of Central and Eastern Europe, have since joined the group and the current membership of 44 centres includes most European countries.

In the majority of centres, both a primary and a secondary source of ascertainment were used to allow the completeness of registration be assessed. Primary sources were usually based on hospital records or on notifications by paediatricians and family doctors. Secondary sources varied depending on local circumstances but included social insurance schemes, diabetes associations and prescription data.

Subjects with Type I diabetes were identified on the basis of a clinician's diagnosis and the need for daily insulin injections. The date of onset was taken as the date of the first injection. Information on the date of birth, gender, sources of ascertainment (primary and/or secondary), date of clinical diagnosis and date of first insulin injection was submitted in anonymous form to a co-ordinating office in Odense, Denmark, for data processing.

Annual estimates of the resident population in each centre's area were obtained and were used as denominators in the calculation of incidence rates. Standardisation for age and gender was achieved using the direct method, the standard population comprising equal numbers in each of six subgroups defined by age-group (0–4, 5–9 and 10–14 years) and gender. All analyses were performed on the standardised rates.

For the ecological analysis, 34 geographical units were derived from the 44 centres by grouping together centres in the same country, unless they were situated in different land masses. Therefore Sardinia, Sicily, Madeira and Northern Ireland were each treated as separate centres distinct from their mainland counterparts.

For the ecological indicators the most appropriate figure for each centre (or group of centres) has been used but data for the nation as a whole has been substituted if no more specific information was available (e.g. Italian data have been

used for Sardinia and Sicily). For centres from the former Czechoslovakia and Yugoslavia, figures relating to the original countries have been used when necessary. Coffee consumption data for 1990/91 (bags per 1 000 head of population) were obtained from the International Coffee Organisation [20] and liquid milk consumption data for 1991 (or subsequent years if 1991 data were unavailable) from the International Dairy Federation [21]. Breast feeding rates were obtained by averaging the results of national surveys since 1980, which are recorded in the World Health Organisation Global Data Bank [22], unless there was a more relevant regional survey. When no national data was available regional surveys were substituted and if necessary the most recent pre-1980 survey was used. Lack of standardisation concerning the definition of breast-feeding duration meant that figures for breast-feeding only could be used. Cartographic data (latitude as °N and longitude as °E of the Greenwich meridian) and climatological data (rainfall, sunshine hours and temperature averages for up to 30 years) were also considered [23]. Population density figures (children under 15 years per km²) were derived from population data and estimates of study area provided by each centre. Health indicators (infant mortality and life expectancy) were estimates prepared in 1994 by the United Nations Population Division, obtained from the World Health Statistics Annual [24]. Gross domestic product per head of population for 1994, defined as the value of all goods and services produced within a country (measured on a purchasing power parity basis in US\$), was obtained from the World Health Organisation's Human Development Report [25]. The ecological data are presented in the Appendix.

Initial assessment of the ecological associations between the standardised incidence rates and characteristics of the various centres was obtained using simple (unweighted) Pearson's product-moment correlation coefficients. Both the standardised incidence rate and those indicators whose distribution was heavily skewed (infant mortality, gross domestic product, coffee consumption, milk consumption, population density and rainfall) were logarithmically transformed before analysis. Regression analyses were then performed with the logarithm of the rate as the dependent variable and indicators as independent variables. Only one independent variable was included at a time. Weights were defined by an iterative method to be intermediate between an unweighted analysis and an analysis with weights derived from the sampling variation of the standardised rates [26]. The analysis was performed using the GLIM package [27].

Results

Information summarizing all 44 of the participating centres, including the geographical coverage, the number of cases, the age-standardised and sex-standardised annual incidence rate and the estimated completeness of ascertainment, has already been published [19]. The standardised rates varied from 3.2 cases per 100 000 person-years in the Former Yugoslavian Republic of Macedonia to 40.2 cases per 100 000 in two regions of Finland. Incidence rates were highest in northern and north-western Europe and low in central, southern and eastern Europe, although Sardinia was a notable exception. In most centres, estimates of the completeness of ascertainment exceeded 95 %.

Table 1. Incidence rates during 1989–94 for 34 EURODIAB ACE centre groupings

Country	Number of cases in the period	Average population under 15 years (thousands)	Standardised incidence rate (95 %-Confidence limits) per 100 000 person-years
Austria	753	1373.2	9.1 (8.5, 9.8)
Belgium	112	162.6	11.6 (9.4, 13.7)
Bulgaria (two centres)	521	1034.9	8.2 (7.5, 8.9)
Croatia	83	209.0	6.8 (5.3, 8.3)
Czech Republic	1144	2095.2	8.9 (8.3, 9.4)
Denmark	221	228.3	16.0 (13.9, 18.1)
Estonia	206	334.0	10.3 (8.9, 11.7)
Finland	425	175.4	40.2 (36.4, 44.1)
France	837	1662.6	8.3 (7.8, 8.9)
Germany (two centres)	1212	2050.3	11.5 (10.8, 12.1)
Greece (two centres)	382	686.7	8.9 (8.0, 9.8)
Hungary	822	1511.1	8.9 (8.2, 9.5)
Iceland	52	64.5	13.5 (9.8, 17.2)
Israel	433	1502.1	5.9 (5.3, 6.4)
Italy (two mainland centres)	926	2058.0	7.4 (7.0, 7.9)
Italy – Sardinia	675	300.5	36.6 (33.9, 39.4)
Italy – Sicily	150	219.2	11.4 (9.5, 13.2)
Latvia	221	563.5	6.6 (5.8, 7.5)
Lithuania	368	834.3	7.4 (6.6, 8.1)
Luxembourg	49	68.2	12.1 (8.7, 15.5)
Macedonia, Former Yugoslav Republic of	93	486.9	3.2 (2.5, 3.8)
Netherlands	421	545.3	13.0 (11.8, 14.3)
Norway	491	393.0	21.2 (19.3, 23.1)
Poland (four centres)	1201	3618.4	6.1 (5.8, 6.5)
Portugal (two mainland centres)	76	82.6	15.0 (11.6, 18.4)
Portugal – Madeira	24	57.5	6.9 (4.1, 9.6)
Romania	138	449.5	5.0 (4.1, 5.8)
Slovakia	656	1290.4	8.4 (7.7, 9.0)
Slovenia	186	394.7	7.6 (6.5, 8.7)
Spain	839	1054.4	12.3 (11.4, 13.1)
Sweden	451	298.8	25.8 (23.4, 28.2)
Switzerland	353	1131.0	7.9 (7.1, 8.7)
United Kingdom (three mainland centres)	1379	1409.8	16.4 (15.6, 17.3)
United Kingdom – Northern Ireland	462	392.8	19.6 (17.8, 21.4)
Total	16362	28738.8	

For the ecological analyses, incidence results were pooled across centres from the same country (Bulgaria, Germany, Greece, mainland Italy, Poland, mainland Portugal and mainland United Kingdom) giving a total of 34 units for analysis (Table 1).

Preliminary analyses suggested that standardised incidence rate was most strongly associated with low infant mortality rate, high gross domestic product, high liquid milk and coffee consumption, long life expectancy and northern latitude (Table 2). The climatological variables showed very weak associations with incidence.

The iterative regression analysis identified the same group of six indicators as statistically significantly associated with incidence rate ($p < 0.05$). In general the results were much closer to those obtained by unweighted regression than by weighted regression, reflecting the fact that the greater part of the unexplained variation in rates between centres was not attributable to sampling variation in the rates. The fitted linear relationships between incidence (logarithmically transformed) and four of

these indicators are depicted in Figures 1–4. The other two indicators, infant mortality rate and life expectancy, have been omitted because of their very high correlations with gross domestic product ($r = -0.88$ and 0.89 , respectively).

Discussion

The indicators of national prosperity that we found to be associated with incidence are most likely surrogates for other, still not identified, risk factors. The relevance of environmental influences early in life has been stressed and although the exact nature of these exposures is not yet clear, increased perinatal infections or a rapid growth rate in early life could be contributory factors [28–33]. Improving standards of hygiene, low rates of infection in infancy and low exposure to peer social contact in early life could also be relevant because they could interfere with the normal development of the immune system thus increasing the risk of autoimmune diseases such as childhood di-

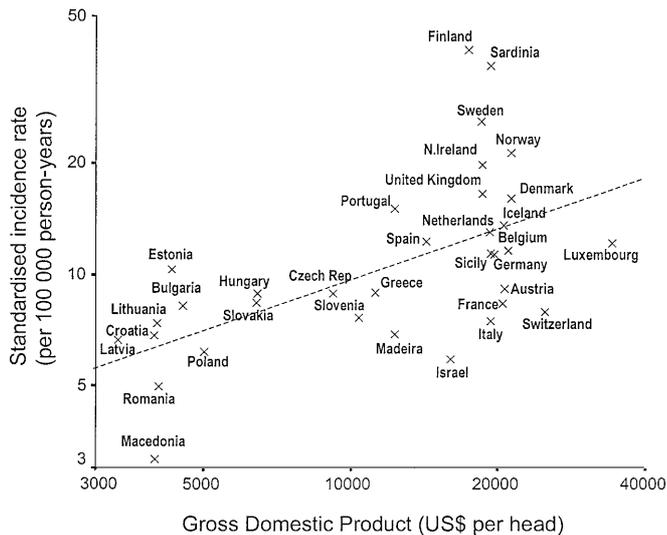


Fig. 1. Ecological association between childhood Type I diabetes incidence rates during 1989–94 and gross domestic product in 1994 measured on a purchasing power parity basis (US\$ per head)

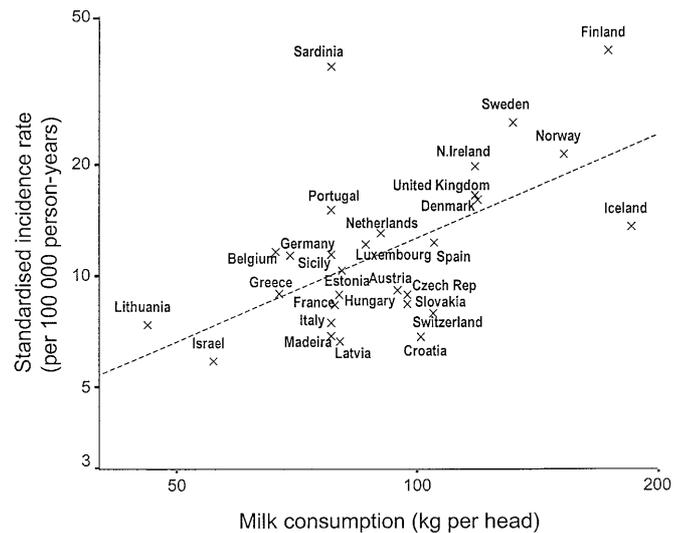


Fig. 2. Ecological association between childhood Type I diabetes incidence rates during 1989–94 and national liquid milk consumption (kg per head)

abetes [34–38]. It is interesting to note that the ecological association with national prosperity is consistent with three of four small-area analyses in the United Kingdom [17, 39–41] that reported lower childhood diabetes rates in more materially-deprived areas.

Our analysis confirms that a relationship between incidence and latitude is present within Europe but we found only weak associations between incidence and climatological variables suggesting that they are not responsible for the north-south incidence gradient. A possible alternative explanation is that this gradient reflects an important source of genetic variation within Europe possibly attributable to historic patterns of migration in a north-westerly direction across Europe of Neolithic farmers from the Middle East and their partial admixture with local hunter-gatherer populations [42].

Caution is recommended in interpreting ecological analyses as they can sometimes be misleading; associations observed at country level need not necessarily hold at individual level. Unfortunately the information required to explore this issue is not readily available. Our results raise the possibility that the previously reported associations between childhood incidence rate and population coffee and milk consumption could be attributable to confounding by other factors such as national prosperity or its correlates. It would have been easy to extend our regression model to include both coffee and milk consumption and indicators of national prosperity as predictor variables in order to investigate such confounding by using analyses similar to those employed to investigate confounding at the individual level. However, it has been shown that model misspecification and measurement error can have serious and unpredictable

Table 2. Correlation coefficients between indicators and standardised incidence rate^a in 34 EURODIAB ACE centre groupings

Indicator	<i>n</i>	Pearson correlation coefficient, <i>r</i>	<i>p</i>
Infant mortality rate per 1 000 ^a	34	−0.64	< 0.001
Gross domestic product (US\$ per head) ^a	34	0.58	< 0.001
Liquid milk consumption (kg per head) ^a	29	0.58	0.001
Coffee consumption (bags per 1 000 head) ^a	31	0.51	0.003
Life expectancy (years)	34	0.50	0.003
Latitude (°N)	34	0.40	0.02
Longitude (°E)	34	−0.29	0.09
Population density (children per km ²) ^a	34	−0.26	0.13
Any breast feeding (%)	29	−0.21	0.28
Sunshine (hr)	33	−0.18	0.32
Rainfall (mm) ^a	34	−0.16	0.36
Temperature (°C)	34	−0.03	0.89

^a logarithmic transformation used

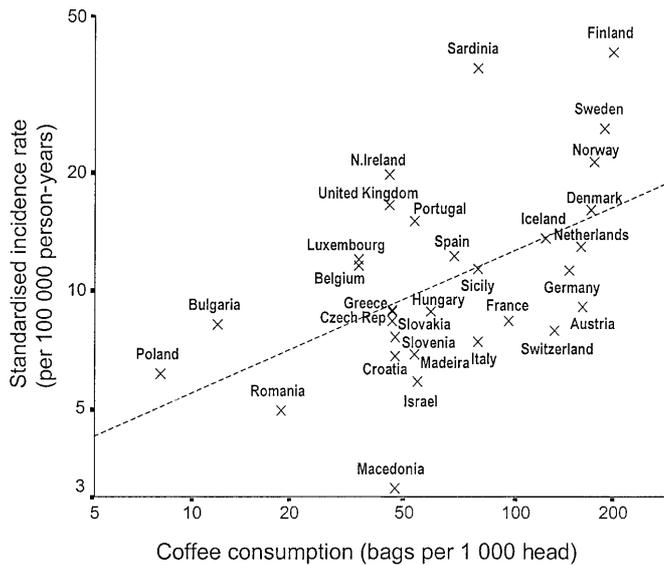


Fig. 3. Ecological association between childhood Type I diabetes incidence rates during 1989–94 and national coffee consumption (number of 60 kg bags per 1 000 head)

consequences for the investigation of confounding in ecological analyses and could easily introduce further bias into estimates [43]. We therefore choose not to pursue this approach.

In conclusion, indicators of national prosperity could explain a significant portion of the large variability in childhood diabetes incidence rates across Europe. A wealthier lifestyle could influence normal growth and development and so increase the risk of childhood diabetes.

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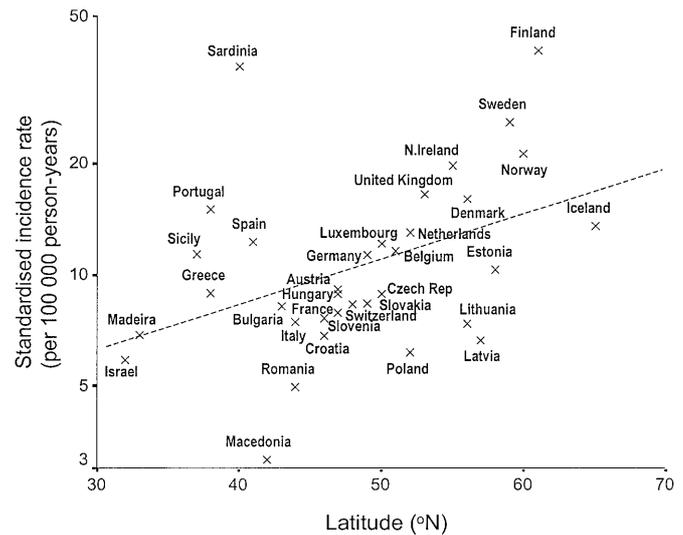


Fig. 4. Ecological association between childhood Type I diabetes incidence rates during 1989–94 and latitude

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Appendix. Ecological data in 34 EURODIAB ACE centre groupings

Country	Coffee	Milk	Bfed	Latit	Longit	Rain	Sun	Temp	Pdens	Infmor	Lifexp	GDP
Austria	161	94.4	82	47	14	660	5.1	9.8	16.8	6.0	77.1	20667
Belgium	33	66.5	32	51	4	855	4.3	10.0	165.5	5.6	77.4	20985
Bulgaria	12	–	–	43	25	661	5.6	10.7	14.2	13.9	71.3	4533
Croatia	43	101.0	72	46	16	865	5.3	11.7	122.6	8.5	72.3	3960
Czech Republic	42	97.1	87	50	15	411	5.2	7.9	24.7	9.4	71.3	9201
Denmark	172	119.0	96	56	11	603	4.4	8.5	22.9	6.9	75.8	21341
Estonia	–	80.5	–	58	26	585	4.8	4.7	6.8	15.6	69.3	4294
Finland	201	173.1	98	61	25	688	5.0	4.8	4.7	4.9	76.5	17417
France	96	78.7	55	48	3	619	5.0	11.6	17.3	6.6	77.6	20510
Germany	147	69.3	87	49	9	676	4.3	10.5	56.6	5.6	76.8	19675
Greece	42	67.2	65	38	24	402	7.7	18.3	38.7	9.0	78.1	11265
Hungary	55	79.8	97	47	19	614	5.7	11.2	16.4	15.4	69.0	6437
Iceland	125	185.2	–	65	–18	779	3.5	5.0	0.6	5.3	78.8	20556
Israel	50	55.5	83	32	35	529	9.3	17.6	17.9	7.5	77.4	16023
Italy	77	78.0	75	44	11	744	6.8	16.1	46.8	7.0	78.3	19363
Italy – Sardinia	77	78.0	45	40	9	451	6.8	17.6	11.5	7.0	78.3	19363
Italy – Sicily	77	78.0	75	37	15	512	6.9	18.3	61.5	7.0	78.3	19363
Latvia	–	80.0	–	57	25	567	5.1	5.4	8.5	13.7	69.1	3332
Lithuania	–	46.0	–	56	24	662	5.0	5.9	12.5	12.8	70.4	4011
Luxembourg	33	86.1	68	50	6	760	4.0	9.3	28.1	6.0	76.5	34155
Macedonia	43	–	90	42	22	510	–	12.1	18.7	23.9	72.7	3965
Netherlands	160	90.1	64	52	5	766	4.2	9.6	186.0	6.3	78.1	19238
Norway	176	152.2	76	60	10	730	4.5	6.2	3.8	7.4	77.3	21346
Poland	8	–	90	52	18	555	4.5	8.3	31.6	12.5	71.1	5002
Portugal	49	78.0	76	38	–8	453	6.6	18.7	7.0	8.5	75.5	12326
Portugal-Madeira	49	78.0	76	33	–17	614	8.7	17.8	74.3	8.5	75.5	12326
Romania	19	–	91	44	26	592	5.9	11.0	208.9	22.6	69.8	4037
Slovakia	42	97.1	90	49	19	649	5.7	10.7	24.7	12.4	70.9	6389
Slovenia	43	–	76	46	15	1383	4.3	10.0	18.2	7.4	73.4	10404
Spain	65	105.0	62	41	2	587	6.8	16.6	29.0	6.9	78.2	14324
Sweden	190	131.6	92	59	18	554	5.4	6.6	49.6	5.2	79.0	18540
Switzerland	133	104.8	55	47	8	1089	4.8	9.6	28.7	5.7	78.6	24967
United Kingdom	41	118.3	66	53	–1	593	4.0	10.6	59.0	6.3	77.0	18620
United Kingdom – Northern Ireland	41	118.3	35	55	–7	846	3.4	9.1	29.0	6.3	77.0	18620

Notes for Appendix

Indicator	Description	Source	Indicator	Description	Source
Coffee	Coffee consumption in 1990/91 (60 kg bags per 1000 head)	ICO	Pdens	Population density (under 15 year population per km ²)	ACE
Milk	Liquid milk consumption in 1991 or later (kg per head)	IDF	Infm or	Infant mortality in 1995 (per 1000 livebirths)	WHS
Bfed	Breast feeding ever (%) from surveys conducted since 1980	GDB	Lifexp	Life expectancy in 1995 (both sexes)	WHS
Latit	Latitude (degrees N) of major urban area	TAW	GDP	Gross Domestic Product in 1994 purchasing power parity basis (US\$ per head)	HDR
Longit	Longitude (degrees E) of major urban area (negative denotes degrees W)	TAW	Key to sources		
Rain	Annual rainfall (mm)	WWG	ICO, International Coffee Organisation; IDF, International Dairy Federation Bulletin; GDB, Global Data Bank on breast feeding, World Health Organisation Nutrition Program; TAW, Times Atlas of the World; WWG, World Weather Guide; ACE, EURODIAB ACE co-ordinating centre; WHS, World Health Statistics Annual, World Health Organisation; HDR, Human Development Report, World Health Organisation		
Sun	Average sunshine (hours per day)	WWG			
Temp	Average of monthly min. and max. average daily temperatures (°C)	WWG			

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References

1. Leslie RDG, Lo SSS, Hawa M et al. (1992) Lessons on the etiology of insulin-dependent diabetes from twin studies. In: Levy-Marchal C, Czernichow P (eds) *Epidemiology and Etiology of Insulin-dependent Diabetes in the Young*. Karger, Basle
2. Kaprio J, Tuomilehto J, Koskenvuo M et al. (1992) Concordance for Type I (insulin-dependent) and Type II (non-insulin dependent) diabetes mellitus in a population based cohort of twins in Finland. *Diabetologia* 35: 1060–1067
3. Kyvik KO, Green A, Beck-Neilsen H (1995) Concordance rates of insulin dependent diabetes mellitus: a population based study of young twins. *BMJ* 311: 913–917
4. Karvonen M, Tuomilehto J, Libman I, LaPorte R (1993) A review of the recent epidemiological data on the worldwide incidence of Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 36: 883–892
5. Green A, Sjolie AK, Eshoj O (1997) The epidemiology of diabetes mellitus. In: Pickup JC, Williams G (eds) *Textbook of Diabetes*. Blackwell Science, Oxford
6. Onkamo P, Väänänen S, Karvonen M, Tuomilehto J (1999) Worldwide increase in incidence of Type I diabetes – the analysis of the data on published incidence trends. *Diabetologia* 42: 1395–1403
7. Rosenbauer J, Herzig P, von Kries R, Neu A, Giani G (1999) Temporal, seasonal, and geographical incidence patterns of Type I diabetes mellitus in children under 5 years of age in Germany. *Diabetologia* 42: 1055–1059
8. Green A, Gale EAM, Patterson CC for the EURODIAB ACE Study (1992) Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 339: 905–909
9. Tuomilehto J, Podar T, Reunanen A et al. (1991) Comparison of incidence of IDDM in childhood between Estonia and Finland, 1980–1988. *Diabetes Care* 14: 982–988
10. Dorner G, Thoelke H, Mohnike A, Schneider H (1985) High food supply in perinatal life appears to favour the development of insulin-treated diabetes mellitus (ITDM) in later life. *Exp Clin Endocrinol Diabetes* 85: 1–6
11. Tuomilehto J, Tuomilehto-Wolf E, Virtala E, LaPorte R (1990) Coffee consumption as trigger for insulin dependent diabetes in childhood. *BMJ* 300: 642–643
12. Dahl-Jorgensen K, Joner G, Hanssen KF (1991) Relationship between cows' milk consumption and incidence of IDDM in childhood. *Diabetes Care* 14: 1081–1083
13. Scott FW (1990) Cow milk and insulin-dependent diabetes mellitus: is there a relationship? *Am J Clin Nutr* 51: 489–491
14. Virtanen SM, Rasanen L, Aro A et al. (1994) Is children's or parents' coffee or tea consumption associated with the risk for Type I diabetes mellitus in children? *Eur J Clin Nutr* 48: 279–285
15. Gerstein HC (1994) Cow's milk exposure and type I diabetes mellitus. A critical overview of the clinical literature. *Diabetes Care* 17: 1713–1719
16. Dahlquist G, Mustonen L (1994) Childhood onset diabetes – time trends and climatological factors. *Int J Epidemiol* 23: 1234–1241
17. Patterson CC, Waugh NR (1992) Urban/rural and deprivation differences in incidence and clustering of childhood diabetes in Scotland. *Int J Epidemiol* 21: 108–117
18. Vaandrager GJ, Bruining GJ, Veenhof FJ, Drayer NM (1984) Incidence of childhood diabetes in The Netherlands: a decrease from north to south over north-western Europe? *Diabetologia* 27: 203–206
19. EURODIAB ACE Study Group (2000) Variation and trends in the incidence of childhood diabetes in Europe. *Lancet* 355: 873–876
20. International Coffee Organisation (1996) *Coffee statistics no 4*. International Coffee Organisation, London
21. International Dairy Foundation (1993) *Consumption statistics for milk and milk products 1991 (Bulletin no 282)*. International Dairy Federation, Brussels
22. World Health Organisation Nutrition Unit (1990) *Breast-feeding: prevalence and duration, Europe*. World Health Organisation, Geneva
23. Pearce EA, Smith CG (1984) *World Weather Guide*. Hutchinson, London
24. World Health Organisation (1996) *World Health Statistics Annual 1995*. World Health Organisation, Geneva
25. World Health Organisation (1997) *Human Development Report 1997*. Oxford University Press, New York

26. Pocock SJ, Cook, DG, Beresford SAA (1981) Regression of area mortality rates on explanatory variables: What weighting is appropriate? *Appl Statist* 30: 286–295
27. Francis B, Green M, Payne C (1993) *The GLIM system release 4 manual*. Clarendon Press, Oxford
28. Leslie RD, Elliott RB (1994) Early environmental events as a cause of IDDM. Evidence and implications. *Diabetes* 43: 843–850
29. Dahlquist GG (1997) Viruses and other perinatal exposures as initiating events for beta-cell destruction. *Ann Med* 29: 413–417
30. Dahlquist GG, Ivarsson S, Lindberg B, Forsgren M (1995) Maternal enteroviral infection during pregnancy as a risk factor for childhood IDDM. A population-based case-control study. *Diabetes* 44: 408–413
31. Hyöty H, Hiltunen M, Knip M et al. (1995) A prospective study of the role of Coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 44: 652–657
32. Blom L, Persson LA, Dahlquist G (1992) A high linear growth is associated with an increased risk of childhood diabetes mellitus. *Diabetologia* 35: 528–533
33. Johansson C, Samuelsson U, Ludvigsson J (1994) A high weight gain early in life is associated with an increased risk of Type I (insulin-dependent) diabetes mellitus. *Diabetologia* 7: 91–94
34. Kolb H, Elliott RB (1994) Increasing incidence of IDDM a consequence of improved hygiene? *Diabetologia* 37: 729–731
35. Gibbon C, Smith T, Egger P, Betts P, Phillips D (1997) Early infection and subsequent insulin dependent diabetes. *Arch Dis Child* 77: 384–385
36. McKinney PA, Okasha M, Parslow RC et al. (2000) Early social mixing and childhood diabetes: a case-control study in Yorkshire, UK. *Diabet Med* 17: 236–242
37. The EURODIAB Substudy 2 Study Group (2000) Infections and vaccinations as risk factors for childhood Type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. *Diabetologia* 43: 47–53
38. Rook GAW, Stanford JL (1998) Give us this day our daily germs. *Immunol Today* 19: 113–116
39. Crow YJ, Alberti KG, Parkin JM (1991) Insulin dependent diabetes in childhood and material deprivation in northern England. *BMJ* 303: 156–160
40. Patterson CC, Carson DJ, Hadden DR (1996) Epidemiology of childhood IDDM in Northern Ireland 1989–1994: Low incidence in areas with highest population density and most household crowding. *Diabetologia* 39: 1063–1069
41. Staines A, Bodansky HJ, McKinney PA et al. (1997) Small area variation in the incidence of childhood insulin-dependent diabetes mellitus in Yorkshire, UK: Links with overcrowding and population density. *Int J Epidemiol* 26: 1307–1313
42. Cavalli-Sforza LL, Piazza A (1993) Human genomic diversity in Europe: A summary of recent research and prospects for the future. *Eur J Hum Genet* 1: 3–18
43. Greenland S, Robins J (1994) Ecological studies – biases, misconceptions, and counterexamples. *Am J Epidemiol* 139: 747–760