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Title: Seasonal variation in month of diagnosis in children with type 1 diabetes registered in 23 EURODIAB centres during 1989-2008: little short-term influence of sunshine hours or average temperature.

Running Title: Seasonality in type 1 diabetes diagnosis

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Abstract

Aims/hypothesis To investigate if meteorological and other factors influenced seasonal variation in month of diagnosis in children with Type 1 diabetes registered in EURODIAB centres during 1989-2008.

Methods Twenty-three population-based registers recorded date of diagnosis for new cases of type 1 diabetes among children under 15 years. Tests for seasonal variation in monthly counts aggregated over the 20 year period were conducted. Time series regression was used to investigate if sunshine hour and average temperature data were predictive of the 240 monthly diagnosis counts after taking account of seasonality and long term trends.

Results Significant sinusoidal pattern was evident in all but two small centres with peaks in December to February and relative amplitudes ranging from ±11% to ±39% (median ±18%). However, most centres showed significant departures from a sinusoidal pattern. Pooling results over centres, there was significant seasonal variation in each age-group at diagnosis, with least seasonal variation in those under 5 years. Boys showed greater seasonal variation than girls, particularly those aged 10-14 years. There were no differences in seasonal pattern between four five-year sub-periods. Departures from the sinusoidal trend in monthly diagnoses in the period were significantly associated with deviations from the norm in average temperature (0.8% reduction in diagnoses per 1°C excess) but not with sunshine hours.

Conclusions/interpretation Seasonality was consistently apparent throughout the period in all age-groups and both sexes, but girls and the under 5s showed less marked variation. Neither sunshine hour nor average temperature data contributed in any substantial way to explaining departures from the sinusoidal pattern.

Keywords Epidemiology, seasonality, temporal change, type 1 diabetes mellitus, sunshine, temperature

Introduction

Seasonal variation in the date of diagnosis of childhood type 1 diabetes has been described from many registers both in Europe [1] and worldwide [2] with most reports suggesting a winter peak. Although a sinusoidal (sine wave) pattern specifying a single peak and a single trough six months apart has often been assumed, it has been found not to supply an adequate description of the data with significant lack of fit being apparent in many instances. To address this lack of fit some have included higher-order harmonic terms to the sinusoidal pattern, but with little biological rationale for doing so. Possible reasons for lack of fit include the rising and possibly changing trends in incidence [3,4] and deficits in numbers of diagnoses during weekends or public holidays [5], but in this analysis we consider also the role of two possible meteorological factors, sunshine hours and temperature, which have previously been associated with incidence [6].

Seasonal fluctuation in sunshine hours is particularly relevant to vitamin D levels since most of the body’s vitamin D is synthesized through the action of sunlight on the skin. The evidence from animal experiments and observational studies in humans of a role for vitamin D in the etiology if type 1 diabetes has been extensively reviewed, and a number of stages in the pathogenic process leading to the destruction of the insulin-producing cells have been identified which could potentially be influenced by vitamin D [7–9]. Animal studies suggest that vitamin D may reduce the rate of progression to diabetes even after the autoimmune process has begun.

Ambient temperature has been linked with seasonality in some infections and is, for example, thought to be responsible for winter peaks in gastroenteritis through enhanced survival at low temperature of rotavirus and norovirus [10]. Hand, foot and mouth disease, which shows summer peaks in incidence in Asian countries and has been linked with short term effects of temperature [11], can be caused by enteroviruses which are implicated in type 1 diabetes with markedly increased enterovirus frequency having been reported in several studies within a month of diabetes diagnosis [12]. In addition studies show that blood glucose is increased in colder months [13] and may thus precipitate disease onset due to an increased insulin requirement. Non-specific viral infections may also curtail the `prediabetic' period by substantially increasing insulin requirements [14].

The purpose of this analysis is to characterize the patterns of seasonal variations in the 23 EURODIAB registers of childhood diabetes in 19 European countries during the 20 year period 1989 to 2008 and to assess if monthly departures from the sinusoidal pattern could be explained by deviations from the norm in monthly sunshine hours and average temperature. A simple correlation analysis of raw time series results over the 20 years between monthly meteorological variables and numbers of diagnoses is not likely to be useful since all three series show marked seasonal variation which will induce spurious associations. Instead we chose to assess if deviations from the monthly norms in the meteorological data were able to explain departures from the sinusoidal pattern in the diagnoses since we considered that associations over relatively short timescales, possibly incorporating a slight lag, would be more indicative of a causal relationship.

Methods

Case inclusion criteria were as previously described for the EURODIAB registers [15], new diagnoses of type 1 (insulin-dependent) diabetes mellitus among children aged under 15 years resident in the geographically defined region. Date of diagnosis was taken as the date of the first insulin injection. Incidence rates and trends with calendar year in the 23 centres during the 20 year period have previously been documented and completeness of ascertainment, assessed through capture-recapture methodology, was in excess of 90% in most centres [4].

Sunshine hour and average temperature data for the most appropriate observation station were obtained from national meteorological offices. The meteorological data used are summarized in Supplemental Table S1.

Both a general test for seasonal variation (11 degrees of freedom (df)) and Edward's test for sinusoidal (sine/cosine wave) variation (2df) were employed and a test for lack of fit of the sinusoidal variation (9df) was also obtained [16]. Monthly counts were adjusted for the number of days in the month. Associations between the amplitude of the seasonal component and the centre characteristics (latitude, incidence level and meteorological results) were examined using Spearman's rank correlation coefficient. Comparisons of the seasonal pattern in subgroups defined by gender, age-group and five-year sub-period were obtained by fitting interactions with the seasonal (sine and cosine) terms in Poisson regression analyses.

To investigate lack of fit of the sinusoidal pattern, a time series regression approach was employed [17] with Poisson regression used to assess if monthly deviations from the norm in meteorological variables (sunshine hours or average temperature) were predictive of monthly numbers of diagnoses. This methodology has been used frequently for investigating environmental risk factors on disease, for example asthma admissions in relation to atmospheric pollutants [18] and myocardial infarction in relation to temperature [19]. Separate analyses were conducted for each of the 23 centres. The 240 monthly counts arising from the 20 year period were used as the dependent variable in the Poisson regression model which contained terms to represent sinusoidal seasonality, long term trends, number of weekend days in the month as well as sunshine hour or average temperature effects expressed as deviations from the monthly norm. These deviations had previously been derived as residuals from a linear regression which included terms representing the 12 months of the year and with linear and quadratic terms in time fitted, if significant, to remove long term trends. The analyses were repeated with case counts lagged for up to 3 months after the meteorological data. To account for extra-Poisson variation a scale parameter obtained by dividing the Pearson chi-squared statistic for lack of fit by its residual degrees of freedom was used in the analysis. Poisson regression models were fitted using the poisson and glm commands in Stata Release 11 (College Station, Texas). The risk ratio estimates obtained for each centre were then combined by an inverse variance weighting approach in a random effects meta-analysis using the RevMan 5 program (Copenhagen, Denmark). In addition to testing the combined overall effect for significance, this program also provides a test for heterogeneity of effects between centres as well as an I^2 statistic representing the percentage of total variation across centres that is due to heterogeneity rather than chance. Tests of significance were performed at the 5% significance level.

Results

Table 1 shows that significant general seasonal variation was apparent in all but two of the smallest centres, with an excess of cases apparent in the winter quarter (December-February). Significant sinusoidal pattern was also evident in all but two of the smallest centres with peaks in November (2 centres) December (14 centres), January (5 centres) or February (2 centres). Relative amplitude varied from ±11% to ±39% (median ±18%). However, there was also clear evidence of a significant lack of fit in the sinusoidal pattern in the majority of centres.

Significant differences in the numbers of cases diagnosed by day of the week were seen in all centres with the percentage of cases diagnosed at the weekend varying from 10% to 20% (median 13%) in the 23 centres compared with the 29% (2 out of 7) expected if diagnoses were to occur uniformly throughout the week. Compensatory excesses early in the week were apparent in most centres.

Pooling results across centres (Figure 1), boys showed marginally greater seasonal variation than girls (amplitudes of ±18% and ±14%, respectively). There was also significant seasonal variation in each age-group at diagnosis, with larger amplitudes observed in the older age groups (±9%, ±17% and ±19% in the 0-4, 5-9 and 10-14 year age-groups, respectively). Further model fitting revealed a significant interaction between age, sex and the sinusoidal terms (χ^2=12.3, df=4: P=0.02) indicating that the difference in amplitude between the genders was not uniform in each age-group; although the amplitudes in boys in the three age-groups (±10%, ±18% and ±23%) were all greater than for girls (±8%, ±17% and ±15%) the oldest age-group showed a much larger gender difference. However the sinusoidal pattern showed significant lack of fit in both sexes and each age-group. There were no significant differences in seasonal pattern between four sub-periods of the 20 year period (amplitudes of ±20%, ±15%, ±15% and ±15% in 1989-1993, 1994-1998, 1999-2003 and 2004-2008, respectively). All peaks were in winter months.

There was no relationship across centres between relative amplitude of the seasonal variation in diagnoses shown in Table 1 and the centre's latitude (Spearman rank correlation coefficient r_s=-0.26, P=0.23), incidence level in 2004-08 (r_s=-0.25, P=0.26) or meteorological data (sunshine hours and average temperature) expressed either as means throughout the 20 year period (r_s=0.20, P=0.35 and r_s=0.27, P=0.40, respectively) or as ranges across the 12 months of the year (r_s=0.27, P=0.22 and r_s=0.29, P=0.19, respectively).

The extent to which departures in diagnoses from a sinusoidal pattern could be explained by deviations from the norm in monthly sunshine hours and mean temperature was examined in each of the 23 centres and the results were pooled in a random effects meta-analysis (Electronic Supplementary Material Figures 1 and 2). Risk ratios were scaled to represent the increase in the diagnosis rate for a 30 hour per month (or approximately 1 hour per day) excess in sunshine hours relative to the norm and a 1°C excess in average monthly temperature relative to the norm. Numbers of cases were lagged by up to three months after the meteorological data. The unlagged analyses provided some evidence that months with either sunshine hours or temperature above the monthly norm had lower diagnosis rates than expected when judged against the underlying seasonal pattern (Table 2). However, the risk ratios were both 0.992 indicating that the effects were small in magnitude (0.8% reduction in diagnoses for 30 hours per month extra sunshine or for a 1°C excess in temperature) and only the temperature result achieved significance. None of the lagged analyses suggested that sunshine hours or average temperature had an influence on rates of diagnosis in subsequent months.

Discussion

The EURODIAB collaboration, because of its population-based registers with broad geographic coverage and high levels of ascertainment, provides a unique dataset of approximately 50,000 cases spanning 20 years for the study of seasonal variation in the diagnosis of type 1 diabetes in Europe. Seasonality in monthly case counts of childhood type 1 diabetes is apparent in most centres, in all age-groups and both sexes, but is less marked in girls and under 5 year olds. Given the greater infection load in young children, their reduced seasonality may appear paradoxical, but the disjointed nature of school terms relative to the more uniform pattern of pre-school care may help to explain this finding although an increased genetic susceptibility in young cases could offer another explanation [20]. The seasonal pattern has changed little during the 20 year period indicating that the pattern of presentation throughout the year is not changing as incidence rates have increased. There was little evidence that deviations from the norm in monthly sunshine hours or average temperature played any important role in explaining departures from the underlying seasonal pattern in diagnoses.

Studies in young adults have suggested that low vitamin D levels are associated with a higher risk of a subsequent diagnosis of type 1 diabetes [21,22], but the evidence in children mostly relies on proxy measures such as vitamin supplementation [23] or cod liver oil consumption [24]. Some studies have reported lower vitamin D levels in children with newly diagnosed [25,26] or pre-existing [27–29] type 1 diabetes than in controls without diabetes but a recent large study comparing cases with non-diabetic siblings did not confirm this finding [30]. Ecological analyses of ultraviolet radiation data have reported associations with type 1 diabetes incidence [31,32] although these have been weak and inconsistent. Our study investigated the rather different question of whether or not there were observable short term effects of sunshine hours or of temperature (both assessed as deviations from the norm) on the number of cases diagnosed per month.

The large geographical coverage of some EURODIAB centres such as Norway means that obtaining relevant meteorological data is difficult, particularly for sunshine hours since fewer meteorological stations collect this information, and in general data for a single station nearest the centre’s largest concentration of population was selected for this analysis. Sunshine hours can be a rather poor proxy for sun exposure, and in some countries consumption of oily fish may also have a significant impact on vitamin D levels. The standardisation of sunshine hour measurements across centres could be an additional concern, but this should have less impact on our analysis which focuses mainly on within centre comparisons.

Vitamin D turnover in the body has a half-life of approximately 2 months [33], and a large observational study in the United States reports an August peak and February trough in the proportion of samples with 25-hydroxyvitamin D [25(OH) D] results exceeding 25 ng/mL [34]. This provided the rationale for incorporating a lag in the relationship between sunshine hours and diagnoses, but this lag did nothing to strengthen the relationship between sunshine hours and numbers of diagnoses in our dataset.

The unlagged temperature analysis showed a similar but marginally more significant relationship with diagnoses than did sunshine hours. The deviations from monthly norms for these two meteorological variables are correlated, but our findings are not suggestive of an effect of sunshine hours distinct from temperature. Our significant temperature finding could result from an acceleration [35] or overload [36] effect on an already-ongoing beta cell destruction being unmasked in periods of increased blood glucose or insulin resistance induced by low temperature. Another possible mechanism is that our temperature finding possibly reflects the role of some other relevant environmental factor linked with temperature, such as increased physical activity or healthier eating, which may decelerate a child's rate of progression to diagnosis.

In summary, our analysis confirms previously-reported features of seasonality in the month of type 1 diabetes diagnosis, but we observed significant deviations from a sinusoidal pattern in many centres. We did not detect any important role for deviation in sunshine hours or in average temperature from the monthly norm in explaining the departures from sinusoidal pattern in the numbers of cases diagnosed each month.

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Conflict of interest

None of the authors declares any conflict of interest in relation to this article.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Contributions

CCP has coordinated the group since 2010, undertook the statistical analysis and wrote a first draft of the report. EG maintained contact with the study centres and assembled and validated the data for analysis. AG set up the collaboration and coordinated the group until 1998 and together with GGD established the registration methodology. GS coordinated the group from 1998 to 2009. Remaining authors established and/or maintained the registration process in the different centres and validated the ascertainment level. All authors commented on a draft of the report and approved the final manuscript.

References

1. Lévy-Marchal C, Patterson C, Green A (1995) Variation by age group and seasonality at diagnosis of childhood IDDM in Europe. The EURODIAB ACE Study Group. Diabetologia 38:823–830

2. Moltchanova EV, Schreier N, Lammi N, Karvonen M (2009) Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. Diabet Med 26:673–678

3. The DIAMOND Project Group (2006) Incidence and trends of childhood Type 1 diabetes worldwide 1990 –1999. Diabet Med 23:857–866

4. Patterson CC, Gyürüs E, Rosenbauer J, et al (2012) Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. Diabetologia 2012;55:2142–2147

5. Mooney JA, Helms PJ, Jolliffe IT, Smail P; Scottish Study Group for the Care of Diabetes in the Young (2004) Seasonality of type 1 diabetes mellitus in children and its modification by weekends and holidays: retrospective observational study. Arch Dis Child 89: 970–973

6. Dahlquist G, Mustonen L (1994) Childhood onset diabetes - time trends and climatological factors. Int J Epidemiol 23:1234–1241

7. Hyppönen E (2010) Vitamin D and increasing incidence of type 1 diabetes—evidence for an association? Diabetes Obes Metab 12:737–743

8. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C (2011) Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol 347:106–120

9. Chakhtoura M, Azar ST (2013) The role of vitamin D deficiency in the incidence, progression, and complications of type 1 diabetes mellitus. Int J Endocrinol 2013:148673

10. Grassly NC, Fraser C (2006) Seasonal infectious disease epidemiology. Proc Biol Sci 273:2541–2550

11. Hii YL, Rocklov J, Ng N (2011) Short term effects of weather on hand, foot and mouth disease. PLoS One 6:e16796

12. Stene LC, Rewers M (2012) Immunology in the clinic review series; focus on type 1 diabetes and viruses: the enterovirus link to type 1 diabetes: critical review of human studies. Clin Exp Immunol 168:12–23

13. Suarez L, Barrett-Connor E (1982) Seasonal variation in fasting plasma glucose levels in man. Diabetologia 22:250–253

14. Wasmuth HE, Hess G, Viergutz C, Henrichs HR, Martin S, Kolb H (2000) Non-specific viral infections as possible synchronising events of the manifestation of type 1 diabetes. Diabetes Metab Res Rev 16:177–178

15. Green A, Gale EAM, Patterson CC (1992) Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE study. Lancet 339:905–909

16. Edwards JH (1961) The recognition and estimation of cyclic trends. Ann Hum Genet 25:83–87

17. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B (2013) Time series regression studies in environmental epidemiology. Int J Epidemiol 42:1187–1195

18. Schwartz J, Spix C, Touloumi G, et al (1996) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. J Epidemiol Community Health 50(Suppl 1):S3–S11

19. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L (2010) Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. BMJ 341:c3823

20. Gillespie KM, Gale EA, Bingley PJ (2002) High familial risk and genetic susceptibility in early onset childhood diabetes. Diabetes 51:210–214

21. Gorham ED, Garland CF, Burgi AA, et al (2012) Lower prediagnostic serum 25-hydroxyvitamin D concentration is associated with higher risk of insulin-requiring diabetes: a nested case-control study. Diabetologia 55:3224–3227

22. Munger KL, Levin LI, Massa J, Horst R, Orban T, Ascherio A (2013) Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. Am J Epidemiol 177:411-419

23. Zipitis CS, Akobeng AK (2008) Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child 93:512–517

24. Stene LC, Joner G and the Norwegian Childhood Diabetes Study Group (2003) Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 78:1128–1134

25. Pozzilli P, Manfrini S, Crinò A, et al (2005) Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 in patients with newly diagnosed type 1 diabetes. Horm Metab Res 37:680–683

26. Borkar VV, Devidayal, Verma S, Bhalla AK (2010) Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr Diabetes 11:345–350

27. Greer RM, Portelli SL, Hung BSM, et al (2013) Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. Pediatr Diabetes 14:31–41

28. Bin-Abbas BS, Jabari MA, Issa SD, Al-Fares AH, Al-Muhsen S (2011) Vitamin D levels in Saudi children with type 1 diabetes. Saudi Med J 32:589–592

29. Bener A, Alsaied A, Al-Ali M, et al (2009) High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. Acta Diabetol 46:183–199

30. Thorsen SU, Mortensen HB, Carstensen B, et al (2013) No difference in vitamin D levels between children newly diagnosed with type 1 diabetes and their healthy siblings: a 13-year nationwide Danish study. Diabetes Care 36:e157–e158

31. Sloka S, Grant M, Newhook LA (2010) The geospatial relation between UV solar radiation and type 1 diabetes in Newfoundland. Acta Diabetol 47:73–78

32. Elliott JC, Lucas RM, Clements MS, Bambrick HJ (2010) Population density determines the direction of the association between ambient ultraviolet radiation and type 1 diabetes incidence. Pediatr Diabetes 11: 394–402.

33. Jones G (2008) Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 88:582S-586S.

34. Kasahara AK, Singh RJ, Noymer A (2013) Vitamin D (25OHD) serum seasonality in the United States. PLoS One 8:e65785.

Table 1 Tests for seasonality in month of diagnosis of Type 1 diabetes in 23 EURODIAB centres using aggregated data over the 20 year period 1989–2008

Centre	Region	Period	Number of cases	General (11df) test of seasonal variation			Sinusoidal (2df) test of seasonal variation				Lack of fit (9df) test
				χ^2	P	Dec-Feb[a]	χ^2	P	Ampl[b]	Peak[c]	P
Austria	Whole nation	1989-2008	3372	50.7	<0.001	27.4%	29.6	<0.001	±13%	Dec	0.01
Belgium	Antwerp	1989-2008	448	32.3	0.001	31.5%	4.5	0.11	±14%	Nov	0.001
Croatia	Zagreb	1989-2008	339	12.6	0.32	24.8%	4.0	0.14	±15%	Nov	0.47
Czech Republic	Whole nation	1989-2008	4883	61.7	<0.001	26.1%	36.3	<0.001	±12%	Dec	0.003
Denmark	4 counties Whole nation	1989-1998 1999-2008	385 2402	55.2	<0.001	27.4%	15.6	<0.001	±11%	Dec	<0.001
Germany	Baden Württemberg	1989-2007	4804	70.7	<0.001	26.2%	44.3	<0.001	±14%	Dec	0.002
Germany	Düsseldorf region (7 districts) North Rhine-Westphalia	1989-1998 1999-2008	595 6331	103.0	<0.001	27.5%	73.5	<0.001	±15%	Dec	0.001
Germany	Saxony	1998-2008	921	32.3	0.001	27.9%	14.5	0.001	±18%	Dec	0.04
Hungary	18 counties	1989-2008	3239	92.4	<0.001	29.7%	75.2	<0.001	±22%	Dec	0.05
Lithuania	Whole nation	1989-2008	1396	73.6	<0.001	27.2%	52.7	<0.001	±28%	Dec	0.01
Luxembourg	Whole nation	1989-2008	229	24.2	0.01	32.3%	8.8	0.013	±28%	Jan	0.08
Macedonia	Whole nation	1989-2008	447	36.7	<0.001	30.6%	33.2	<0.001	±39%	Dec	0.94
Montenegro	Whole nation	1996-2008	252	24.4	0.01	28.6%	14.6	0.001	±34%	Jan	0.37
Norway	8 counties Whole nation	1989-2003 2004-2008	1380 1504	57.0	<0.001	27.7%	34.7	<0.001	±16%	Dec	0.008
Poland	Katowice	1989-2008	1719	80.3	<0.001	27.7%	63.2	<0.001	±27%	Dec	0.05
Romania	Bucharest	1989-2008	534	15.7	0.15	27.3%	7.9	0.02	±17%	Jan	0.55
Slovenia	Whole nation	1989-2008	715	31.7	0.001	27.6%	15.0	0.001	±21%	Dec	0.06
Spain	Catalonia	1989-2008	2527	65.1	<0.001	28.2%	46.5	<0.001	±19%	Feb	0.03
Sweden	Stockholm county	1989-2008	1978	34.7	<0.001	26.7%	12.9	0.002	±11%	Feb	0.01
Switzerland	Whole nation	1991-2008	2220	29.5	0.002	27.2%	12.9	0.002	±11%	Jan	0.06
United Kingdom	Northern Ireland	1989-2008	2043	59.9	<0.001	29.4%	50.9	<0.001	±22%	Dec	0.44
United Kingdom	Oxford	1989-2008	2288	68.7	<0.001	30.2%	31.9	<0.001	±17%	Jan	<0.001
United Kingdom	Yorkshire	1989-2008	3018	94.6	<0.001	30.2%	78.9	<0.001	±23%	Dec	0.07

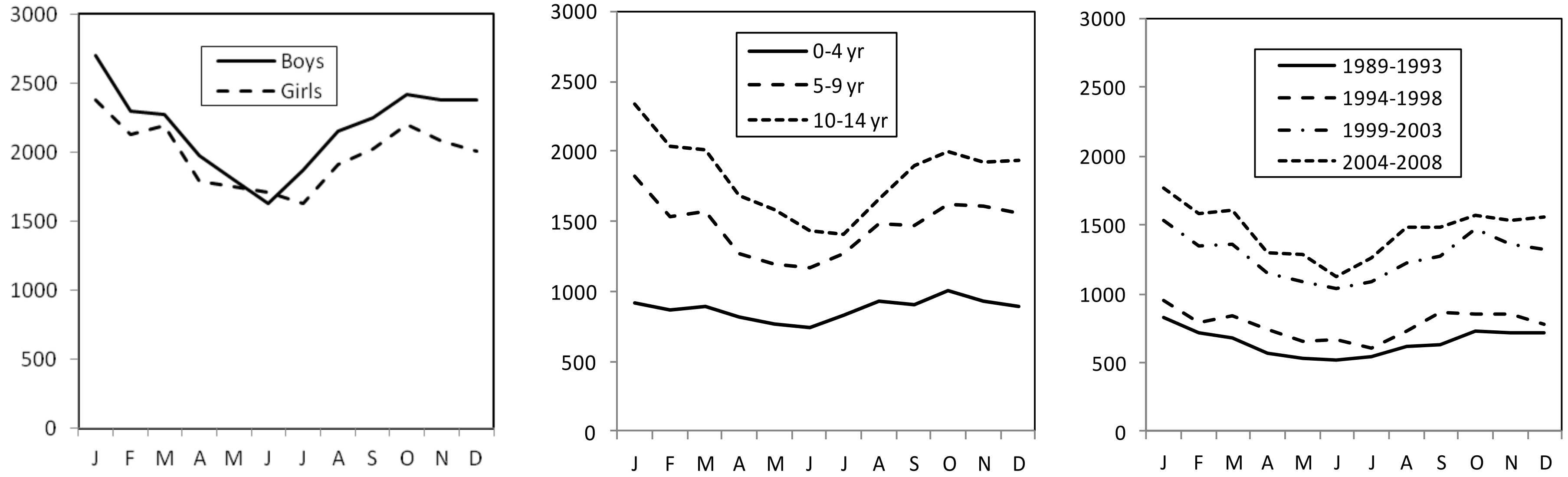
χ^2 = Chi-square statistic
df =degrees of freedom
[a] Dec-Jan = Percentage of cases in winter months
[b] Ampl = Amplitude of fitted sinusoidal pattern
[c] Peak = Peak month of fitted sinusoidal pattern

Table 2 Risk of type 1 diabetes diagnosis in relation to deviations in sunshine hours and average temperature from long-term monthly norms. Results were obtained by pooling estimates from separate Poisson regression models for each of the 23 centres. Poisson regression used the 240 monthly counts of diagnoses in the 20 year period as dependent variable and included terms for long-term sinusoidal seasonal pattern, linear trend and number of weekend days in the month as independent variables in addition to the deviations from the norm in meteorological variables.

		Random effects meta analysis results		
	Lag (months)	Relative risk (95%CI)	P	I^2
Sunshine hours	0	0.992 (0.984, 1.001)	0.09	0%
(per 30 hr above	1	0.999 (0.989, 1.008)	0.75	7%
monthly average)	2	1.006 (0.995, 1.017)	0.31	28%
	3	1.001 (0.991, 1.012)	0.85	24%
Temperature	0	0.992 (0.985, 1.000)	0.04	30%
(per °C above	1	0.999 (0.991, 1.006)	0.69	31%
monthly average)	2	1.005 (0.997, 1.013)	0.20	33%
	3	1.006 (0.997, 1.015)	0.17	43%[a]

[a] Heterogeneity test was significant (P<0.05)

Figure 1



Tests for heterogeneity in seasonal effect between sexes

General test: $\chi^2=37.5$, *df*=11; $P<0.001$

Sinusoidal test: $\chi^2=16.1$, *df*=2; $P<0.001$

Tests for heterogeneity in seasonal effect between age-groups

General test: $\chi^2=96.3$, *df*=22; $P<0.001$

Sinusoidal test: $\chi^2=68.3$, *df*=4; $P<0.001$

Tests for heterogeneity in seasonal effect between periods

General test: $\chi^2=44.4$, *df*=33; $P=0.09$

Sinusoidal test: $\chi^2=7.05$, *df*=6; $P=0.32$

Figure Legends

Figure 1 Seasonal variation by gender, age-group and calendar period in pooled results from all 23 EURODIAB centres. Monthly counts were aggregated over the 20 year period and adjusted for the number of days in the month.

Electronic Supplementary Material

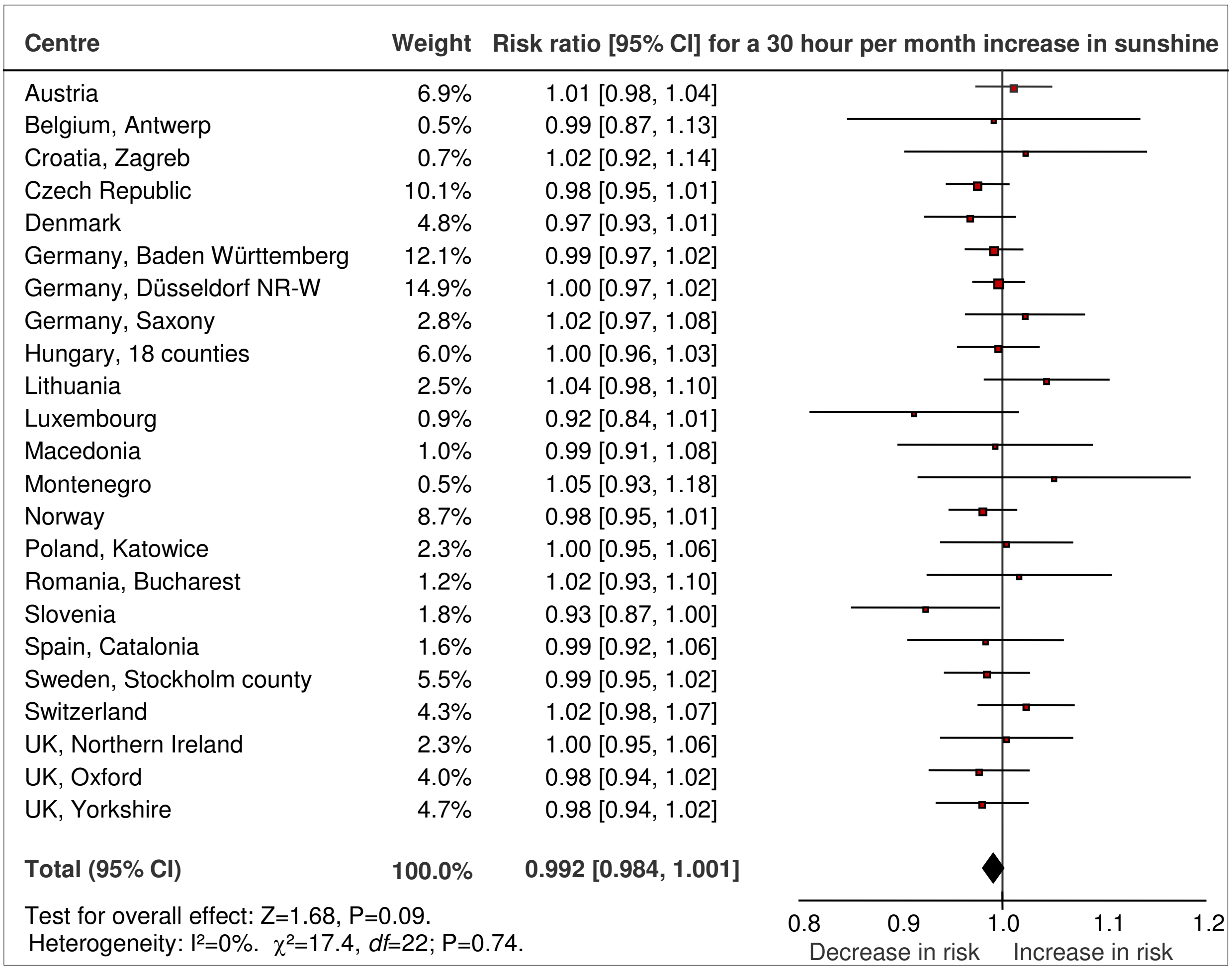
ESM Table 1 Summary of meteorological data for the period 1989-2008 by centre

Centre – Station location	Sunshine (hr)		Temperature (^{o}C)	
	Average[a]	Range[b]	Average[a]	Range[b]
Austria – Vienna	166	209	10.7	20.0
Belgium (Antwerp) – Antwerp	134	180	11.0	14.6
Croatia (Zagreb) – Zagreb	166	223	12.5	20.3
Czech Republic – Prague	145	190	8.8	19.0
Denmark – mainland average	136	192	8.7	14.8
Germany (B W) – Stuttgart	149	167	9.7	17.8
Germany (N R-W) – Düsseldorf	132	159	11.0	15.3
Germany (Saxony) – Dresden	143	171	9.6	18.2
Hungary (18 counties) – Budapest	170	218	11.8	21.4
Lithuania – Vilnius	144	243	7.0	21.1
Luxembourg – Luxembourg	139	193	9.6	16.9
Macedonia – Skopje	189	264	12.9	23.6
Montenegro – Podgorica	208	227	16.0	21.5
Norway – Oslo	142	200	6.9	19.1
Poland (Katowice) – Katowice	139	197	8.6	19.8
Romania (Bucharest) – Bucharest	182	243	11.8	24.4
Slovenia – Ljubljana	161	230	11.1	20.6
Spain (Catalonia) – Barcelona	209	159	16.2	15.8
Sweden (Stockholm) – Stockholm	154	241	7.8	19.2
Switzerland – Zürich	134	195	9.6	18.1
UK (Northern Ireland) – Armagh	103	109	9.1	10.1
UK (Oxford) – Oxford	136	161	11.0	12.9
UK (Yorkshire) – Bradford	108	138	9.7	11.8

[a] Mean – average of the 240 monthly values in the 20 year period

[b] Range – difference between the maximum and minimum of the 12 monthly averages (usually July average - January average)

ESM Figure 1 Rate of childhood type 1 diabetes diagnosis in 23 European centres in relation to monthly sunshine hours relative to the seasonal norm in the same month (unlagged); estimates from centres were combined by inverse variance weighted random effects meta-analysis.

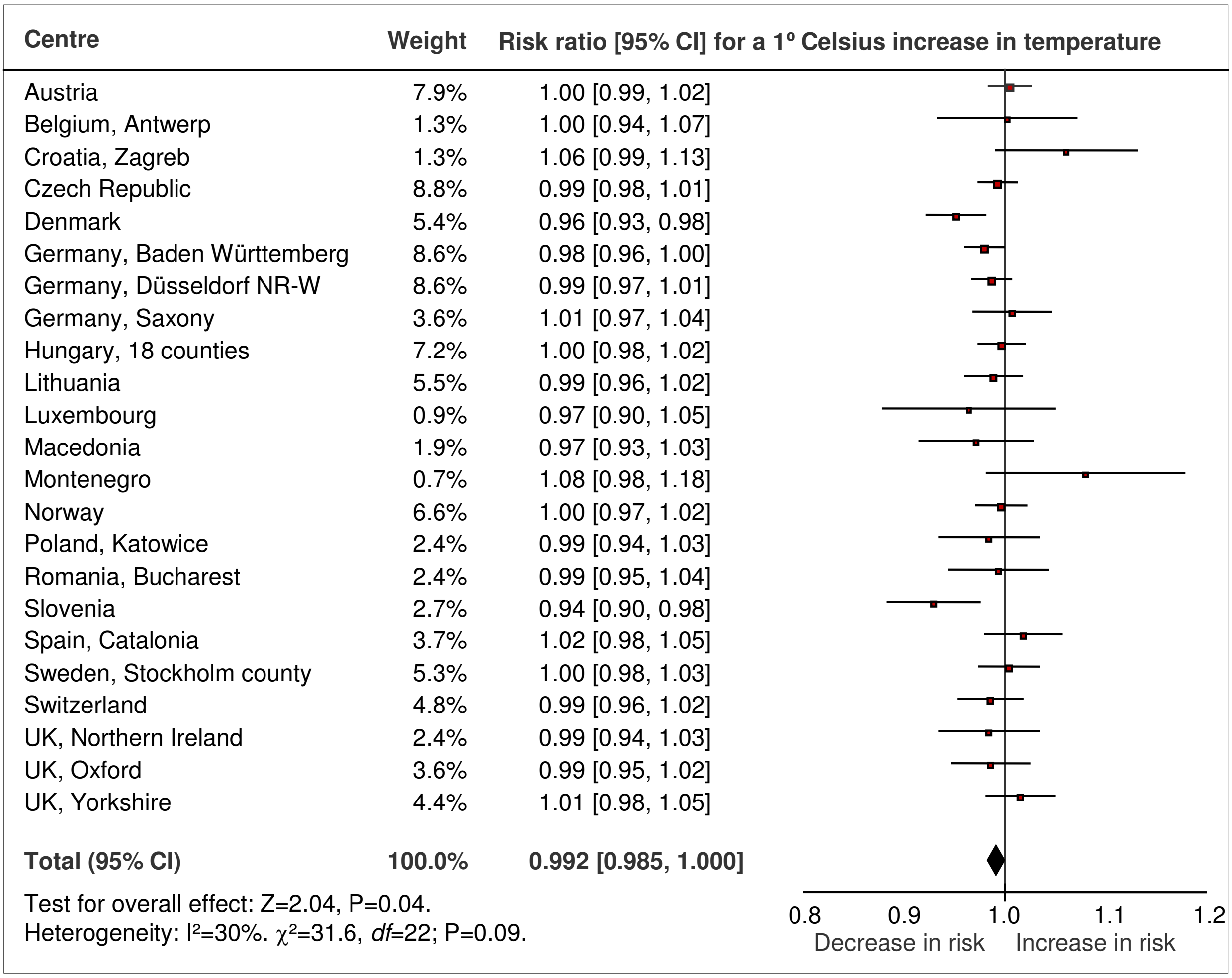


Centre	**Weight**	**Risk ratio [95% CI] for a 30 hour per month increase in sunshine**
Austria	6.9%	1.01 [0.98, 1.04]
Belgium, Antwerp	0.5%	0.99 [0.87, 1.13]
Croatia, Zagreb	0.7%	1.02 [0.92, 1.14]
Czech Republic	10.1%	0.98 [0.95, 1.01]
Denmark	4.8%	0.97 [0.93, 1.01]
Germany, Baden Württemberg	12.1%	0.99 [0.97, 1.02]
Germany, Düsseldorf NR-W	14.9%	1.00 [0.97, 1.02]
Germany, Saxony	2.8%	1.02 [0.97, 1.08]
Hungary, 18 counties	6.0%	1.00 [0.96, 1.03]
Lithuania	2.5%	1.04 [0.98, 1.10]
Luxembourg	0.9%	0.92 [0.84, 1.01]
Macedonia	1.0%	0.99 [0.91, 1.08]
Montenegro	0.5%	1.05 [0.93, 1.18]
Norway	8.7%	0.98 [0.95, 1.01]
Poland, Katowice	2.3%	1.00 [0.95, 1.06]
Romania, Bucharest	1.2%	1.02 [0.93, 1.10]
Slovenia	1.8%	0.93 [0.87, 1.00]
Spain, Catalonia	1.6%	0.99 [0.92, 1.06]
Sweden, Stockholm county	5.5%	0.99 [0.95, 1.02]
Switzerland	4.3%	1.02 [0.98, 1.07]
UK, Northern Ireland	2.3%	1.00 [0.95, 1.06]
UK, Oxford	4.0%	0.98 [0.94, 1.02]
UK, Yorkshire	4.7%	0.98 [0.94, 1.02]
Total (95% CI)	**100.0%**	**0.992 [0.984, 1.001]**

Test for overall effect: Z=1.68, P=0.09.

Heterogeneity: I^2=0%. χ^2=17.4, *df*=22; P=0.74.

ESM Figure 2 Rate of childhood type 1 diabetes diagnosis in 23 European centres in relation to average daily temperature relative to the seasonal norm in the same month (unlagged); estimates from centres were combined by inverse variance weighted random effects meta-analysis.



Centre	**Weight**	**Risk ratio [95% CI] for a 1° Celsius increase in temperature**
Austria	7.9%	1.00 [0.99, 1.02]
Belgium, Antwerp	1.3%	1.00 [0.94, 1.07]
Croatia, Zagreb	1.3%	1.06 [0.99, 1.13]
Czech Republic	8.8%	0.99 [0.98, 1.01]
Denmark	5.4%	0.96 [0.93, 0.98]
Germany, Baden Württemberg	8.6%	0.98 [0.96, 1.00]
Germany, Düsseldorf NR-W	8.6%	0.99 [0.97, 1.01]
Germany, Saxony	3.6%	1.01 [0.97, 1.04]
Hungary, 18 counties	7.2%	1.00 [0.98, 1.02]
Lithuania	5.5%	0.99 [0.96, 1.02]
Luxembourg	0.9%	0.97 [0.90, 1.05]
Macedonia	1.9%	0.97 [0.93, 1.03]
Montenegro	0.7%	1.08 [0.98, 1.18]
Norway	6.6%	1.00 [0.97, 1.02]
Poland, Katowice	2.4%	0.99 [0.94, 1.03]
Romania, Bucharest	2.4%	0.99 [0.95, 1.04]
Slovenia	2.7%	0.94 [0.90, 0.98]
Spain, Catalonia	3.7%	1.02 [0.98, 1.05]
Sweden, Stockholm county	5.3%	1.00 [0.98, 1.03]
Switzerland	4.8%	0.99 [0.96, 1.02]
UK, Northern Ireland	2.4%	0.99 [0.94, 1.03]
UK, Oxford	3.6%	0.99 [0.95, 1.02]
UK, Yorkshire	4.4%	1.01 [0.98, 1.05]
Total (95% CI)	**100.0%**	**0.992 [0.985, 1.000]**

Test for overall effect: Z=2.04, P=0.04.
Heterogeneity: I^2=30%. χ^2=31.6, *df*=22; P=0.09.