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ORIGINAL ARTICLE

Age-period-cohort modelling of type 1 diabetes incidence rates among children included in the EURODIAB 25-year follow-up study

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Abstract

Aims Specific patterns in incidence may reveal environmental explanations for type 1 diabetes incidence. We aimed to study type 1 diabetes incidence in European childhood populations to assess whether an increase could be attributed to either period or cohort effects.

Methods Nineteen EURODIAB centres provided single year incidence data for ages 0–14 in the 25-year period 1989–2013. Case counts and person years were classified by age, period and cohort (APC) in 1-year classes. APC Poisson regression models of rates were fitted using restricted cubic splines for age, period and cohort per centre and sex. Joint models were fitted for all centres and sexes, to find a parsimonious model.

Results A total of 57,487 cases were included. In ten and seven of the 19 centres the APC models showed evidence of non-linear cohort effects or period effects, respectively, in one or both sexes and indications of sex-specific age effects. Models showed a positive linear increase ranging from approximately 0.6 to 6.6%/year. Centres with low incidence rates showed the highest overall increase. A final joint model showed incidence peak at age 11.6 and 12.6 for girls and boys, respectively, and the rate-ratio was according to sex below 1 in ages 5–12.

Conclusion There was reasonable evidence for similar age-specific type 1 diabetes incidence rates across the EURODIAB population and peaks at a younger age for girls than boys. Cohort effects showed nonlinearity but varied between centres and the model did not contribute convincingly to identification of environmental causes of the increase.

Keywords Diabetes type 1 · Children · Europe · Incidence · Age-period-and cohort model

Introduction

Type 1 diabetes is an autoimmune disease in which the insulin producing cells of the pancreas are attacked and destroyed leading to insulin deficit. Type 1 diabetes is often diagnosed during childhood and the incidence has been increasing in both Europe and worldwide [1]. A genetic component exists but the rise in incidence cannot be explained by genetic changes alone and points to additional environmental triggers/factors. Evidence supporting infection, vitamin D, nutritional and toxic risk factors remains inconclusive [2]. Even though a role for early environmental factors in the aetiology of childhood type 1 diabetes is clear, the failure to date to identify strong environmental risk factors and the potential interplay between environmental and genetic factors makes interpretation difficult [2]. Some environmental factors may operate even as early as at birth while others more likely have a role in precipitating the clinical diagnosis in those whose pancreas's insulin production is already compromised. The increasing trends in incidence that have been observed almost universally since the middle of the last century point clearly to a prominent role for environmental risk factors [2]. Such factors may vary depending on calendar period, time of birth and with geographic location. Attempts to ascribe these trends to either period effects (i.e. effects specific to certain calendar years) or to cohort effects (i.e. effects specific to particular birth cohorts) have

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consequently led to mixed findings. Some earlier attempts to study age, period and cohort effects in type 1 diabetes incidence in European countries gave no clear picture of a dominant period or cohort effect [3–14].

The aim of this study is to apply age-period-cohort modelling to 25 years of incidence data collected by the EURODIAB registers of childhood type 1 diabetes to assess if nonlinear period or cohort effects are present. Most previous publications have used relatively coarse divisions of age, period and cohort, usually in five-year groups. All centres in this analysis had 25 years of incidence data and were able to supply incidence data and annual population estimates by single years of age permitting a finer classification of data by age, period and cohort than in previous publications.

Material and method

Data

The type 1 diabetes incidence data used in this analysis has previously been reported as part of the 25-year analysis of EURODIAB data [15]. This is a collaborative group of type 1 diabetes registers that has been recording new cases diagnosed under the age of 15 years in geographically defined populations since 1989 using a standardised protocol. This analysis is based on incidence data from 19 centres from 16 European countries that met the requirements of providing annual population data by single years of age and all but two centres included incidence data over a 25-year period. Cases were validated by the individual centres against a secondary data source, using capture-recapture methods. Ascertainment rates were mostly above 90% for all centres and for all the years [15].

Cases

From the EURODIAB database we used data for all persons diagnosed with type 1 diabetes before age 15 in the 25-year period 1989–2013 (incl.). Numbers of cases were tabulated by centre, sex, age at diagnosis, date of diagnosis (period) and date of birth (cohort) in 1-year intervals. Tabulation units by age, period *and* cohort are normally referred to as Lexis triangles [16]. Nationwide Danish case data were only available in the original EURODIAB dataset from year 1996, but for this analysis anonymised data from year 1989–1995 were added from the Danish National Patient Register in order to cover the entire 25-year period.

Person time

From the EURODIAB database we obtained the background population size in 1-year age classes 0–14 for each year in the 1989–2013 period. From these population sizes we computed the person-time in Lexis triangles (classification by age, period and cohort, see Electronic Supplementary Material (ESM) for further details).

Statistical models

With counts and person-years in Lexis triangles, we assigned the mean age (age at follow-up), period (date of follow-up) and cohort (date of birth) to each triangle [16] (detailed explanation in ESM). Rates were modelled using a Poisson likelihood assuming constant rates within each Lexis triangle. The quantitative effects of age, period and cohort were modelled using smooth parametric curves parametrized by natural (restricted cubic) splines. Knots for the splines were placed at percentiles equally spaced between the fifth (second for age) and ninety-fifth for each of the three variables for the cases in the data set pooled over all centres. This approach allocates four parameters to each nonlinear part of the effects. The approach differs from traditional age-period-cohort modelling that uses data classified only by age and period, and in the modelling assigns one parameter to each level of age, period and cohort. Our approach models each effect by the same number of parameters and hence makes the tests for nonlinearity between period and cohort more comparable.

Separate APC models

First, we fitted age (A), age-drift (Ad), age-period (AP), age-cohort (AC) and age-period-cohort (APC) models for the incidence rates, separately for each centre and sex. Drift represents the linear trend in rates which can equally well be ascribed either to periods or cohorts. Separate effects of age, period and cohort were extracted by constraining the period effects to be 0 on average with 0 slope (thereby assigning the drift effect to cohorts), and the cohort effect to be 0 at 1–1-1995 [16]. Since we model the variables as quantitative variables, the reference is a specific date and not a period. To assess the relative importance of period and cohort effects likelihood-ratio tests were used to assess if there was evidence of nonlinear period and cohort effects by comparing AP and AC models both to the Ad model and to the APC model (i.e., comparing AP versus Ad or APC versus AC for nonlinear period effects and comparing AC versus Ad or APC versus AP for nonlinear cohort effects).

Models for all centres

The 38 separate APC models one for each centre and sex can also be regarded as a joint model for all centres and both sexes, including an interaction between centre and sex on one hand with additive effect of age, period, and cohort on the other. This general model was compared to successively simpler models with specified common effects across centres and sexes, with the aim of identifying a simpler model describing incidence rates across all centres. We focused on variation in age-effects between boys and girls and variation in period and cohort effects between centres.

We assessed the contribution to the test statistics from each centre and sex. The following hypotheses were tested (p-values shown in figure ESM 3):

- nonlinear effect of period in any centre (the same set of tests as the first hypothesis evaluated for centre and sex separately above).
- nonlinear effect of cohort in any centre.
- different nonlinear cohort effects between boys and girls within each centre.
- different linear cohort component between boys and girls within each centre.
- different age-effects across centres, separately for each sex.
- different boy/girl rate-ratio between centres.
- nonlinear cohort effects.

In the final model we used parametric bootstrap to estimate the ages at maximal incidence for boys and girls as well as the difference between the ages at maximal incidence, the ratio of the peak incidences and the age of lowest boy to girl rate-ratio. A complete and detailed description of all models and test procedures is available in the ESM. All analyses were conducted using R version 3.6.3, and Epi package version 2.40 (https://CRAN.R-project.org/package=Epi). Aggregated data are available after reasonable request for external analysis.

Results

Background

In total 57,487 cases were registered in the 19 participating centres during the 1989–2013 period with case number ranging from 312 in Luxembourg to 6,930 in Baden Württemberg, Germany. Incidence rates varied across centres from a minimum of 5.5 per 100,000 in North Macedonia to a maximum of 31.8 per 100,000 in Stockholm County, Sweden. There were rises in incidence rate in all 19 centres during the period with the rate of increase varying from 0.6% per annum in Catalonia, Spain, to 6.6% per annum in Katowice, Poland (Table 1).

Age, period and cohort modelled separately in each centre

The initial analysis was by age-period-cohort models separately for each centre and sex, using smooth spline functions to represent the potentially nonlinear effects of age, period and cohort. The knots used for the splines were at 1.3, 5.6, 9.0, 11.6 and 14.2 years for age, at 1991.0, 1998.0 2003.6, 2008.4 and 2013.0 for period and at 1980.4, 1989.0, 1994.6, 1999.7 and 2007.2 for cohort. Visual representations of models fitted for single centres are shown in Fig. 1. Cohort effects seemed relatively consistent between boys and girls in the same centre but differed considerably from centre to centre. Comparison of p-values for nonlinearity of period and cohort (Table 2, figure ESM 2) showed smaller p-values for cohort effects with more cohort tests achieving significance at the conventional 5% significance level than period tests (29 vs. 17). Akaike's information criterion also favoured cohort models over period models; 10 centre-by-sex combination preferred a cohort (AC) model, only 5 a period (AP) model, but 12 preferred the full APC model; the drift model was favoured by 10 of the remaining 11 combinations. (ESM table 3).

Age, period and cohort modelled jointly across centres

The joint models for all centres were simplified in a number of steps (described in the ESM). Based on Akaike's information criterion for a sequence of models (ESM table 3) we found that a model with a) separate age-effects for boys and girls, but common for all centres and b) separate nonlinear cohort effects for each centre, but common for boys and girls, gave an adequate description of the rates in all centres. The estimates from this model are shown in Fig. 2. The age-specific rates from the joint model are shown with reference to date of birth 1995-1-1 in the Czechia. Fitted age-specific rates peak at age 11.6 (11.5; 11.7) for girls and age 12.6 (12.5; 12.9) for boys, and incidence rates are highest for girls in ages 5–12 but tend to be substantially higher for boys than for girls from age 12 to 14. The cohort effects on the right side of Fig. 2 show both the change in incidence rates by date of birth and also the relative size of incidence rates

Table 1 Cases and person-years for each centre, crude rates (per 100,000 PY), average annual change in rates (%) and estimated doubling time for incidence rates (years) with 95% confidence intervals

Centre	N	PY	Rate/100,000 PY 95% CI	Change/yr (%) 95% CI	Doubling time (yr) 95% CI
Austria (A1)	4,593	33,301,836	13.8 (13.4; 14.2)	4.5 (4.0; 4.9)	15.9 (14.5; 17.5)
Belgium, Antwerp (B1)	610	4,096,929	14.9 (13.8; 16.1)	2.3 (1.2; 3.5)	30.1 (20.3; 57.9)
Czechia (Z2)	6,522	42,847,152	15.2 (14.9; 15.6)	4.6 (4.2; 4.9)	15.5 (14.4; 16.7)
Denmark (D1)	5,458	24,044,552	22.7 (22.1; 23.3)	1.9 (1.6; 2.3)	36.0 (30.1; 44.7)
Germany, Baden WÜrttemberg (M2)	6,930	41,257,185	16.8 (16.4; 17.2)	4.2 (3.9; 4.6)	16.8 (15.5; 18.3)
Germany, DÜsseldorf (M1)	1,847	9,576,835	19.3 (18.4; 20.2)	3.6 (2.9; 4.3)	19.7 (16.6; 24.2)
Lithuania (K1)	1,861	16,300,848	11.4 (10.9; 11.9)	5.5 (4.9; 6.2)	12.8 (11.5; 14.6)
Luxembourg (L1)	312	2,024,618	15.4 (13.8; 17.2)	2.8 (1.1; 4.4)	25.4 (16.0; 61.2)
North Macedonia (Y3)	584	10,630,736	5.5 (5.1; 6.0)	4.9 (3.7; 6.1)	14.5 (11.7; 19.1)
Norway (N2)	6,348	22,016,528	28.8 (28.1; 29.6)	2.1 (1.7; 2.4)	33.5 (28.7; 40.3)
Poland, Katowice (W3)	2,360	19,319,272	12.2 (11.7; 12.7)	6.6 (6.0; 7.2)	10.8 (9.9; 11.9)
Romania, Bucharest (R1)	714	8,364,720	8.5 (7.9; 9.2)	5.7 (4.7; 6.8)	12.4 (10.5; 15.1)
Slovenia (Y1)	949	8,161,117	11.6 (10.9; 12.4)	3.9 (3.0; 4.8)	18.3 (14.9; 23.8)
Spain, Catalonia (S1)	3,446	25,192,792	13.7 (13.2; 14.1)	0.6 (0.2; 1.1)	109.6 (64.3; 371.0)
Sweden, Stockholm county (X1)	2,704	8,514,463	31.8 (30.6; 33.0)	2.3 (1.8; 2.9)	30.3 (24.5; 39.5)
Switzerland (1991–2013) (V1)	3,020	27,522,732	11.0 (10.6; 11.4)	3.2 (2.7; 3.8)	21.8 (18.6; 26.3)
UK, Northern Ireland (U1)	2,652	9,283,187	28.6 (27.5; 29.7)	2.8 (2.3; 3.4)	24.8 (20.8; 30.6)
UK, Oxford (U2)	2,920	13,345,573	21.9 (21.1; 22.7)	1.2 (0.7; 1.7)	59.1 (41.3; 103.8)
UK, Yorkshire (1989–2012) (U4)	3,657	16,286,872	22.5 (21.7; 23.2)	3.2 (2.7; 3.7)	21.9 (18.9; 26.0)
All centres	57,487	342,087,946			

[1]Includes data from 1989–2013 from all centres but two: Switzerland and UK (Yorkshire) where time periods are given in the table. The centre code is used in Fig. 3

between centres. Even though we are describing the secular trend with a cohort effect, it is possible that some linear component of this is a period (calendar time) effect; it is well known that it is not possible to separate out such effects [17]. We see a clear pattern of increasing rates by time, but also it seems that the curves converge, so that the centres with the lowest rates have the steepest increases. This is illustrated in Fig. 3 by plotting the annual drift versus the cumulative risk of type 1 diabetes for persons 0–15 years born 1980-1-1. We also indicated the doubling time of rates corresponding to the annual drifts and there was a strong negative relationship between drift and 1980 cumulative risk: centres with cumulative risk around 1/1000 and 3/1000 exhibit doubling times in the vicinity of 15 and 30 years, respectively (Fig. 3).

Discussion

Based on age-period-cohort modelling we found an overall increasing incidence in type 1 diabetes among children across the 19 European centres included in our analysis. We observed a tendency towards dominance of cohort effects over period effects, but this finding was not consistent. The nonlinear cohort effects and the absolute magnitude of rates varied between centres, while the shape of the age incidence curves was similar between centres. In addition, different age incidence curves were found for boys and girls with a higher incidence in girls than boys from approximately age 5 to 12 years and a higher incidence in boys than girls from age 12. An inverse relationship between the magnitude of drift and the cumulative incidence was observed, but this could be partially explained by the recent levelling off in incidence rate increases in higher-risk countries [15] as well as regression towards the mean.

Previous studies of APC modelling in type 1 diabetes are summarised in Table ESM 1. The first studies used data in the 1960–1980s and did not separate out a drift effect [9, 10, 13]. Of later studies that did include a drift term, the UK Yorkshire register 1978–1990 found the best fitting model included drift and nonlinear period terms but no cohort effects [11]. A subsequent analysis over an extended period (1978–2000) identified a cohort effect for the years

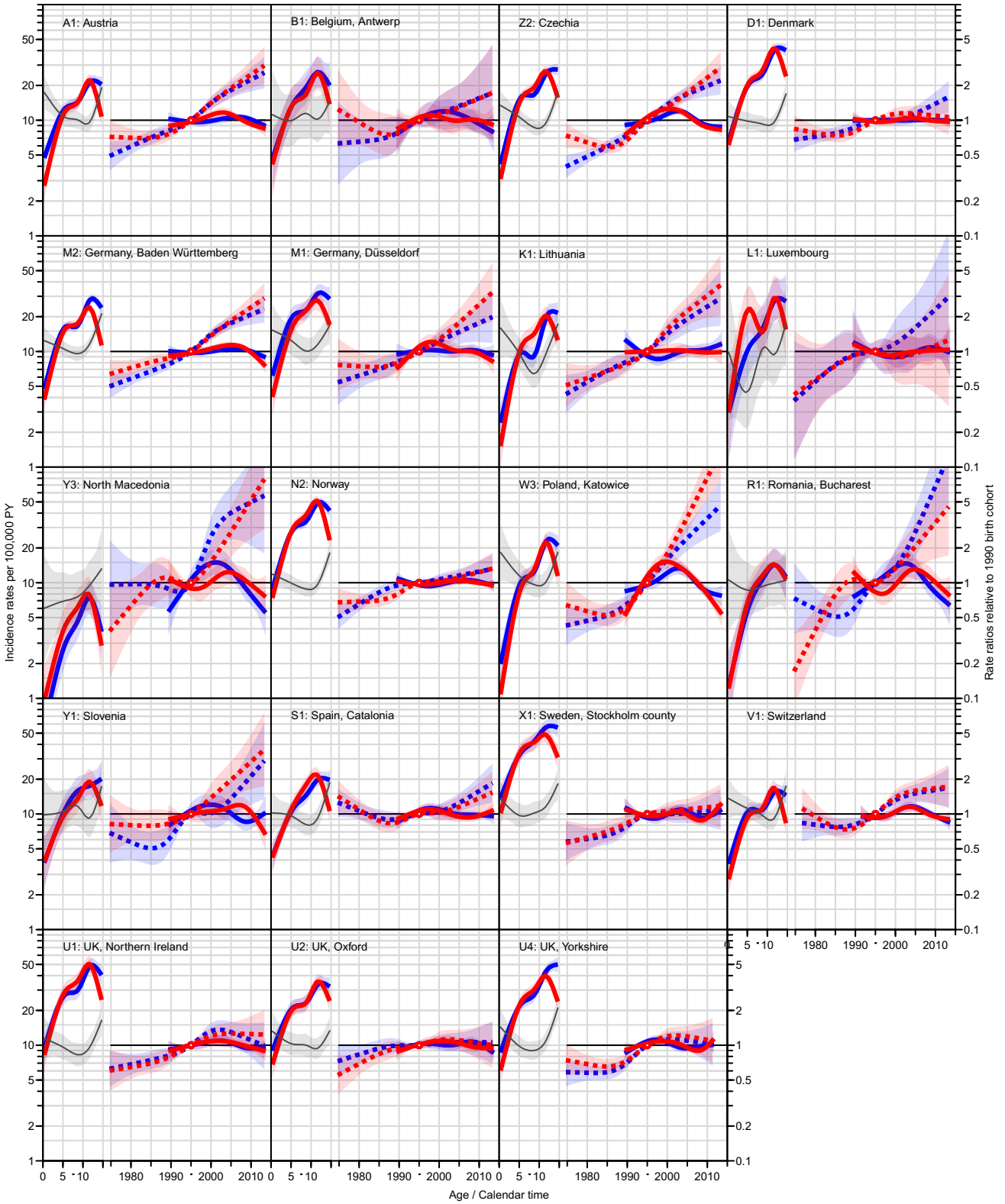

Fig. 1 Estimates from separate APC-models for boys (blue) and girls (red) from each centre. Legend: Left side panels are Age specific incidence rates. The gray curves are the boys/girl rate ratios. Right side panel are cohort and period effects represented as rate ratios for each centre relative to the 1995 cohort using dotted and solid curves, respectively

Table 2 Tests for period and cohort curvature (against the drift and the APC model, see footnote) and estimates of annual drift (%/year) for each centre and sex (derived from separate APC models)

	Boys					Girls				
	p-values				Drift (%/y)	*p* values				Drift (%/y)
Centre	P | d	C | d	P | C	C | P	Slope (95% CI)	P | d	C | d	P | C	C | P	Slope (95% CI)
Austria	0.182	0.140	0.204	0.157	4.7 (4.0; 5.3)	0.221	0.123	0.008	0.004	4.5 (3.8; 5.2)
Belgium, Antwerp	0.168	0.542	0.356	0.952	3.2 (1.3; 5.0)	0.973	0.581	0.856	0.474	2.0 (0.2; 3.8)
Czechia	0.976	0.335	0.997	0.357	2.0 (1.4; 2.5)	0.072	0.001	0.700	0.015	1.8 (1.2; 2.4)
Denmark	0.005	0.033	0.136	0.657	5.1 (4.1; 6.1)	0.334	0.033	0.989	0.141	5.5 (4.5; 6.6)
Germany, Baden Württemberg	0.953	0.905	0.906	0.854	4.1 (1.5; 6.7)	0.991	0.794	0.971	0.763	1.6 (-0.8; 4.1)
Germany, Düsseldorf	0.926	0.987	0.893	0.962	3.7 (2.7; 4.6)	0.306	0.739	0.056	0.158	4.0 (2.9; 5.2)
Lithuania	0.077	0.032	0.123	0.052	4.7 (4.2; 5.2)	0.006	0.450	0.000	0.003	4.0 (3.4; 4.5)
Luxembourg	0.119	0.066	0.174	0.098	2.0 (1.4; 2.5)	0.056	0.017	0.568	0.201	2.1 (1.6; 2.7)
North Macedonia	0.390	0.080	0.021	0.004	7.3 (5.5; 9.2)	0.127	0.092	0.056	0.040	6.2 (4.5; 7.9)
Norway	0.459	0.028	0.185	0.010	1.1 (0.4; 1.8)	0.062	0.002	0.244	0.008	0.8 (0.1; 1.5)
Poland, Katowice	0.236	0.013	0.389	0.023	2.6 (1.7; 3.4)	0.074	0.070	0.391	0.376	2.8 (1.9; 3.7)
Romania, Bucharest	0.100	0.240	0.378	0.789	0.8 (0.0; 1.5)	0.010	0.010	0.387	0.388	1.5 (0.7; 2.4)
Slovenia	0.423	0.005	0.105	0.001	3.1 (2.3; 3.9)	0.446	0.060	0.074	0.009	2.8 (2.0; 3.6)
Spain, Catalonia	0.014	0.055	0.016	0.063	3.2 (2.4; 4.0)	0.064	0.001	0.098	0.001	3.4 (2.5; 4.3)
Sweden, Stockholm county	0.003	0.710	0.000	0.051	7.2 (6.2; 8.3)	0.001	0.481	0.000	0.000	8.7 (7.5; 9.9)
Switzerland (1991–2013)	0.050	0.038	0.150	0.115	2.1 (1.2; 2.9)	0.099	0.779	0.061	0.540	2.1 (1.3; 3.0)
UK, Northern Ireland	0.389	0.157	0.214	0.083	4.3 (2.9; 5.8)	0.272	0.419	0.090	0.144	4.0 (2.7; 5.4)
UK, Oxford	0.328	0.150	0.004	0.002	6.0 (3.9; 8.2)	0.952	0.175	0.326	0.045	5.5 (3.7; 7.3)
UK, Yorkshire (1989–2012)	0.000	0.003	0.000	0.234	5.2 (4.6; 5.7)	0.000	0.016	0.000	0.000	4.6 (4.1; 5.2)

p-values: P|d: adding nonlinear period effect to drift model; C|d: adding nonlinear cohort effect to drift model; P|C: adding nonlinear period effect to cohort model; C|P: adding nonlinear cohort effect to period model

1990 and 1995 relative to the 1980 birth cohort, although it was unclear if the analysis adjusted for period effects [8]. A study including a broader age-range (0–30 years) from Italy (Turin) covering 1984–1996 [4] found only evidence of significant drift and no period or cohort effects. Similar findings were obtained from multicentre data in Italy in the under 15-year age-group during 1990–2003 [5] and in data from Italian region of Abruzzo during 1989–2008 [3]. However, data from the Italian island of Sardinia during 1989–2009 [18] reported a significant improvement in model fit when cohort and period effects were included though findings were only significant in girls.

A Danish study [12] of children age 0–14 years from 1970 to 2000 reported significant drift, and a significant nonlinear cohort effect from 1980. An analysis of data from children age < 15 from Norway for the periods 1973–1982 and 1989–2003 showed significant cohort and period effects [14]. Their analyses suggest that cohort effects may predominate over period effects; however, absence of data between the years 1983 and 1988 complicates the interpretation. Further analysis of Swedish registry-based incidence data for cases diagnosed under 35 years of age during 1983–2007 [7] found that nonlinear cohort effects contributed more significantly to a model containing age and drift than did nonlinear period effects. However, it was noted that these cohort effects might have been attributable, at least in part, to higher levels of ascertainment of the incidence in older age-groups in the early years of the study.

Overall, in previous studies (table ESM 1), where it was possible to make the assessment, cohort effects were more significant than period effects. However, these analyses fitted a model term for each category of age, period or cohort whereas we utilised spline methodology with even number of knots. The use of categories means the number of cohorts usually exceeded the number of periods, why the P values for cohorts were typically for tests with larger numbers of degrees of freedom and therefore disadvantaged relative to the P values for periods.

In theory the presence of nonlinear period or cohort effects could provide important clues about key environmental risk factors. Nonlinear cohort effects might be indicative of important obstetric or perinatal risk factors exerting their influence near to the time of birth. On the other hand,

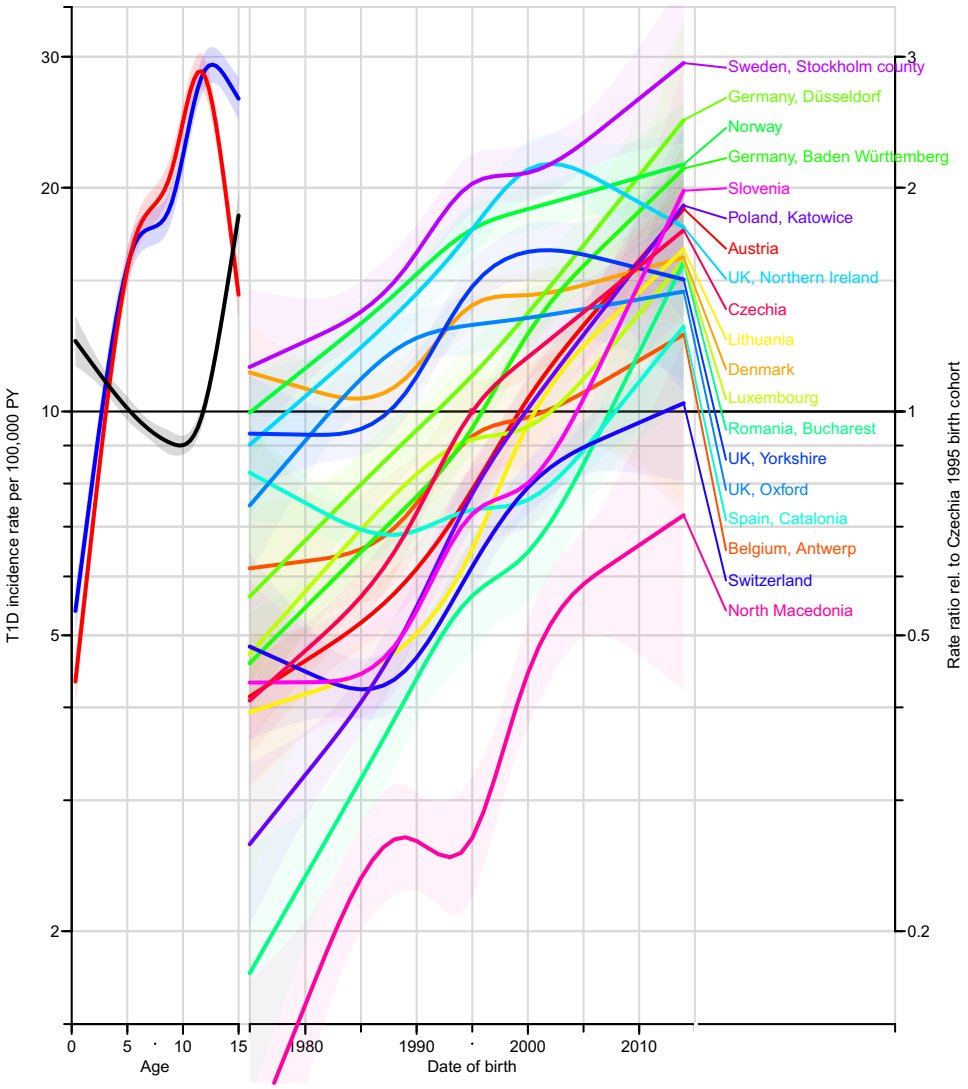

Fig. 2 Estimated curves from the joint model for type 1 diabetes incidence rates from 19 centres. The left panel curves are age-specific incidence rates for boys (blue) and girls (red), and the boys/girl rate ratio (black). Right panel curves are RRs relative to Czechian birth cohort 1995. Shaded areas represent 95% confidence intervals

nonlinear period effects could be explained by risk factors operating closer to the time of diagnosis. The overall picture of our analyses points to nonlinear cohort effects and only small nonlinearities in period effects but this was not consistent in all 19 centres, and our results provide little insight into the relative importance of risk factors in early life and near the time of diagnosis. Variation in the significance of nonlinear cohort effects from centre to centre may suggest that risk factors are country specific in type or size. The difference in incidence rates between countries and regions decreased over time and we found a steeper overall increase in countries with lowest average incidence rate (including North Macedonia, Romania, Lithuania, Poland, and Slovenia). This might be explained by environmental changes with the development of modern societies at different time points across Europe. Factors such as early dietary and obesity patterns have previously been found to have a smaller impact. Growing up in a clean environment (the hygiene hypothesis) with less exposure to microbial products and infections has been suspected to give lower stimulation of the immune system and thereby higher risk of autoimmune diseases; however, the evidence that exist is from proxy measures such as number of siblings, attending day care and living in urban or rural areas are imprecise and susceptible to confounding [2].

Vaccinations have also been speculated to have an impact through modifying effects for the developing immune system in early childhood [19], potentially manifesting as cohort effects. However, from meta-analysis, there was no evidence to suggest an association between any of the routine childhood vaccinations investigated (11

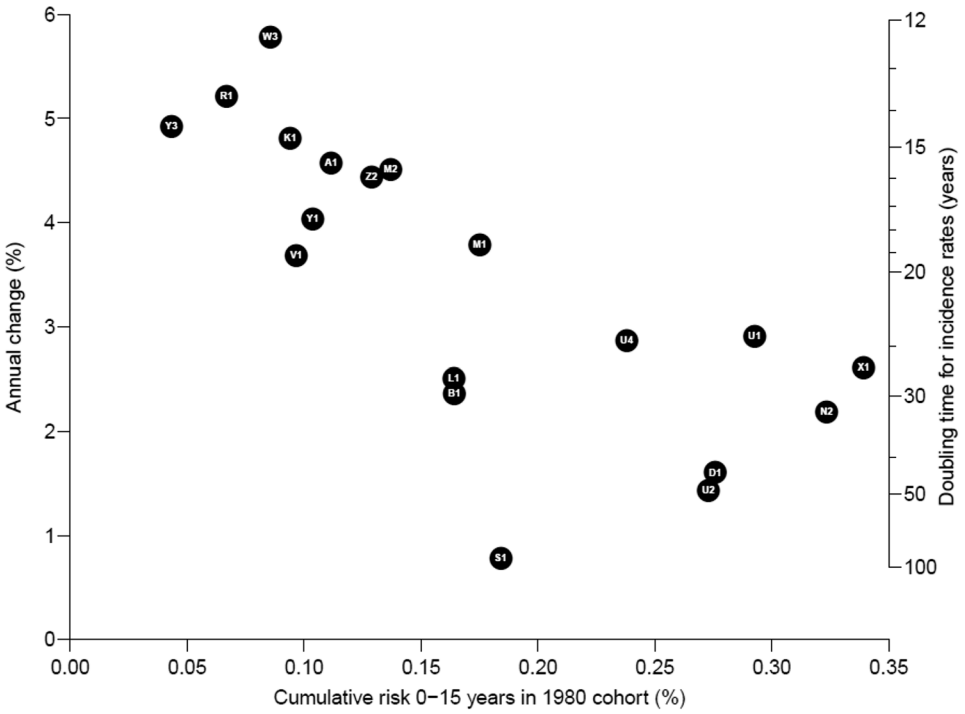

Fig. 3 Relationship between the cumulative risk and annual average change in rate of type 1 diabetes from model with linear cohort effects for each centre. Legend: (Each centre is presented as centre codes—see Table 1 for country and corresponding code). Estimated annual drift versus cumulative risk of type 1 diabetes at age 15 in persons born 1980-1-1 (average for boys and girls) from the model with linear cohort e_ects for each centre. The vertical axis on the right is just a transformation of the drift to the doubling time for rates. The lower increase in high incidence countries may be caused by levelling off

types including measles, mumps and rubella) and type 1 diabetes [19]. A recent publication using interrupted time series analysis reported a reduction in childhood type 1 diabetes incidence rate coinciding with the introduction of rotavirus vaccination in Australia but needs to be interpreted cautiously [20]. Most likely any protection offered by rotavirus immunisation would initially manifest as a cohort effect rather than as a period effect. Unfortunately, with the exception of Austria [21, 22], few of our centres had routine rotavirus vaccination during the period of our analysis, so there is little evidence from our study to study such an effect. Observational studies comparing rates of type 1 diabetes in rotavirus vaccinated and unvaccinated children, although potentially subject to selection bias, should help clarify the issue although currently they show divergent conclusions [23–25].

Our finding of a general later incidence peak-age in boys compared to girls is speculated to be due to later age of puberty and thereby later growth spurt. The slower decline in incidence rate across age among boys from the peak (as shown in Figs. 1 and 2) results in male preponderance of new cases in the adolescent years, at least in European populations.

The strengths of our study include unique data in a large cohort of covering populations from 16 European countries with data collected over a 25-year period. The completeness of data is high with the majority of centres reporting ascertainment rates exceeding 90% (15). The case definition relies on a clinical judgement, however, we consider the risk of misclassification very low. Even though type 2 diabetes in children and adolescents is increasing, the clinical distinction between the two of diabetes is generally not difficult in young persons. The number of cases of type 2 diabetes and monogenic diabetes that may be misclassified is considered very low and does not seriously threaten the validity of our results [15].

With our data from 19 European centres we modelled type 1 diabetes incidence trends in children with a common age pattern for all centres showing later peak incidence age for boys than girls. We show a significant overall rise in incidence by birth year with the individual centre incidences converging over time. The picture is not entirely consistent across centres but points to a slight dominance of cohort effects over period effects and thereby to the importance of early-life risk factors over risk factors nearer the time of diagnosis. However, our APC modelling can only describe incidence patterns and does not shed light on the environmental causes of the increasing incidence.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00592-022-01977-x.

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Declarations

Conflict of interest All authors declare that there is no conflict of interest.

Ethical approval All data are anonymous and based on aggregated data, with no requirementof ethical approval.

Consent to participate The data are register based and do not require consent from individual persons with diabetes.

Informed consent This article does not need informed consent to use registry data.

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