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RESEARCH ARTICLE

Early infant feeding and risk of type 1 diabetes mellitus – a nationwide population-based case–control study in pre-school children

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Abstract

Background The evidence on the role of environmental factors in the development of type 1 diabetes is conflicting. Reducing potential bias and the variety of exposures, we investigated the association between type 1 diabetes risk and nutritional and environmental exposures in pre-school children.

Methods This nationwide population-based case–control study included 760 cases under 5 years of age newly diagnosed with type 1 diabetes during 1992–1995. From the general population, 1871 controls were randomly selected and individually matched on age (±1 year), sex, and residence. Information on infant diet, foetal, perinatal and socio-economic factors, and familial diabetes was obtained by a parent-administered questionnaire. Data were analysed by multiple conditional logistic regression.

Results Duration of breastfeeding and age at introduction of bottle-feeding were inversely associated with type 1 diabetes risk according to a dose-response relationship (trend test $p < 0.05$). Adjusted odd ratios (95% CI) for a long breastfeeding period and a late introduction of bottle-feeding (≥5 month *versus* <2 weeks) were 0.71 (0.54–0.93) and 0.80 (0.62–1.04), respectively. Familial type 1 diabetes, maternal age >40 years, and low birth weight were found more frequently among diabetic than among control children. Current cow's milk consumption, higher social status, and a larger family were associated with a reduced diabetes risk. Up to one half of the diabetic cases in the population could be attributed to modifiable exposures.

Conclusions Our findings indicate that infant feeding is associated with type 1 diabetes risk and that a considerable part of new type 1 diabetic cases is potentially preventable. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords type 1 diabetes mellitus; case–control study; environmental factors; infant feeding; birth weight; familial type 1 diabetes; social status

Introduction

The aetiopathogenesis of type 1 diabetes is characterized by a specific destruction of the insulin-producing pancreatic β-cells due to a T-cell mediated autoimmune process with a probably extended asymptomatic pre-diabetic phase [1]. The underlying chronic autoimmune reaction is considered to appear in genetically predisposed subjects triggered or promoted by environmental factors. A genetic predisposition to type 1 diabetes is indicated by the higher recurrence risk among relatives of patients with type 1 diabetes [2]

and genetic risk is predominantly conferred by well-established HLA-genes [1]. The important role of environmental determinants in the aetiology of the disease is suggested by the low concordance rate among monozygotic twins [3], the geographical variation of type 1 diabetes incidence between and within countries [4,5], the continuous rise of the incidence, which has occurred in many populations during past decades [5,6], and the adaptation in diabetes risk in migrant populations [7].

Environmental exposures suggested to play a role in the type 1 diabetes autoimmune process are nutritional factors, viral infections, foetal and perinatal influences (e.g. birth weight, maternal age), increased childhood growth, socio-economic conditions, and psychosocial stress factors [8]. In particular, among nutritional factors a short breastfeeding period and an early introduction of customary formulas or cow's milk to infant's diet have been associated with an increased risk of diabetes in ecological and analytical epidemiological studies [9–21]. The cow's milk hypothesis was further supported by both animal studies and immunological studies in humans [22]. However, several analytical epidemiological studies, did not confirm these associations [23–27], and the evidence hence cannot be regarded as fully conclusive. Two meta-analyses led to inconsistent results, either concluding that there is evidence for a weak causal relation [17], or attributing the observed weak associations to methodical shortcomings of studies [18]. Inconsistent findings of epidemiological studies could be owing to a great variety of factors. But when assessing potentially weak associations, small and even moderate sample sizes might lead to diverse results between studies due to sample variation.

The present study was designed to evaluate the impact of early infant-feeding patterns and other environmental factors on the risk of type 1 diabetes in a large nationwide population-based case–control study in Germany focussing on children under 5 years of age. Assuming the variety of putative relevant exposures to increase with lifetime, the restriction to pre-school children can be expected to limit the number of potential confounding factors. Since parents of children under 5 years can be assumed to recollect their feeding practice and other exposures during infancy more precisely, the age restriction may also help to reduce recall bias concerning dietary history and other data recollected.

Materials and methods

Selection of cases and controls, method of data collection

Cases were defined as children newly diagnosed with type 1 diabetes mellitus under 5 years of age between 1st July 1992 and 31st December 1995 and permanently residing in Germany at the time of diagnosis. Cases were prospectively registered by the nationwide active hospital-based surveillance system ESPED covering all paediatric departments in Germany by means of reporting cards [28]. Reporting physicians were asked for information on sex, dates of birth and diagnosis, and place of residence by a mailed standardized questionnaire, or a telephone interview, if necessary. Completeness of ascertainment was estimated as 85% [28].

For each participating case non-diabetic control children – four during the first 6 months of the study and six thereafter to increase the number of participating control families – were randomly selected from the general population by local registration offices in the respective district, individually matched on age (±12 month), sex, and place of residence. When selected control families did not participate in the study no additional controls were selected for compensation.

Data on relevant exposures were asked from parents by means of a self-administered standardized questionnaire identical for case and control families. Owing to laws on protection of personal data, both hospitals and local registration offices were not allowed to provide the study group with names and addresses of diabetic patients or selected control subjects. Therefore, questionnaires together with information on the study had to be mailed to reporting paediatricians and registration offices with the request to forward the study material to case and control families. Questionnaires for case families were sent out immediately after registration of new diabetic cases, i.e. shortly after diabetes onset. In case of non-response the procedure was repeated up to two times. Directly after return of a case questionnaire, questionnaires for parents of potential control children were sent to the respective local registration office, wherefrom the material was forwarded to the selected control families. Thus, case and control children were under 5 and 6 years of age, respectively, when the questionnaire was completed. When questionnaires of case or control children were returned with incomplete data, complementary information was sought for through a telephone interview.

Questionnaire data

In the questionnaires, basic information was collected on sex, age (date of birth), date of diagnosis, and place of residence. History of diet was taken through questions on the duration of overall breastfeeding and age at first introduction of breast milk substitutes (predefined categories: <2 weeks, 2–6 weeks, 7 weeks–4 months, 5–6 months, ≥7 month), age at introduction of solid foods to infant feeding (<3, 3–4, 5–6, ≥7 month), type of breast milk substitutes fed during the first year of life, and current level of customary fresh cow's milk intake (no intake <200, 200–400, ≥400 mL/d) before diagnosis in cases or completion of the questionnaire in controls. As putative ante- and perinatal risk factors mother's customary tobacco and coffee consumption during pregnancy, parents' age at birth of the index child, child's weight at birth, and birth order (number of

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older siblings) were recorded. Additional information was obtained on the child's medical history and child's current weight at completion of the questionnaire. Predefined categories were used to assess these exposures (Table 2), except for child's birth weight (taken in g) and child's current weight (taken in kg).

As proxy for child's psychosocial stress, information was recorded on single-parent status and the family's last change of residence. Further questions addressed recent smoking habits of parents, and the family size (number of children). Genetic predisposition to type 1 diabetes was covered through family history of type 1 and type 2 diabetes in siblings, parents, and grandparents. According to common epidemiological practice, a case of diabetes in the family was classified as type 1, if the disease was characterized as such type in the questionnaire or the disease occurred before the age of 30 and insulin treatment was started within 1 year after diagnosis. All other reported cases were classified as type 2 diabetes.

Family's social status was assessed by obtaining information on the parents' highest achieved educational level (school not finished, primary, secondary or tertiary school, university degree) and the current occupational status (skilled or unskilled worker, non-manual employee in low, middle or high position, self-employed, housewife/houseman, unemployed, in occupational education). Following a scheme used in various studies in Germany [29], codes for education and occupational status were combined to an unweighted additive index of social status. If one social indicator was missing, the code for the other one was doubled. The mean of maternal and paternal social score was used as family score. According to the original scheme [29] the family social score was categorized into five social groups each including about one fifth of the study population. Finally, combining the second to fourth quintiles a three level social score was defined indicating low, middle, and high social status. Missing data on the social status were included as fourth category.

The local ethics committee and the government authorities for the protection of personal information approved the study.

Study sample

Questionnaires were sent to 1069 case families and 4385 control families. Altogether, 774 case and 1881 control families returned a questionnaire. Diabetic cases with transient neonatal or secondary diabetes as well as adoptive or foster children were excluded from the study. Further, cases and selected controls, which were siblings of already included case or control children, were excluded in order to include only one child per family in the study. In total, 14 cases and 10 controls were excluded leaving 760 cases (71%) and 1871 (43%) controls for analyses (Table 1). Owing to non-participation, the number of controls per case ranged between 1 and 6. Of the matched sets, 26.7% had one control, 29.2% two controls, 23.8% three controls and 20.3% four or more controls. Of diabetic children, 55.4% were male and of non-diabetic controls, 54.3% were male. Mean age (SD) of cases and controls was 3.0 (1.2) and 3.3 (1.2) years, respectively.

Statistical analysis

Birth weight was categorized according to common definitions [30,31]. Analysis of child's weight was restricted to cases with an indication of weight recorded after the first week and within 3 months after diagnosis in order to minimize systematic bias due to dehydration at presentation and to beware weight data of cases to be upwardly biased by the anabolic effect of insulin treatment. Current weight was transformed to a standard deviation score (SDS) using sex- and age-specific German reference data that have been estimated according to the LMS-method [32,33] and subsequently categorized (Table 2).

Descriptive analyses were performed for all exposure variables separately for diabetic case and non-diabetic control children. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using conditional logistic regression models to evaluate associations between exposures and type 1 diabetes risk [34]. In consideration of the variety of analysed factors, the final multiple model was obtained through a stepwise backward elimination procedure that started with a model including all exposures with $p < 0.25$ in simple logistic regression and that iteratively excluded regression terms based on the respective χ^2-statistic in using a threshold of $p > 0.25$. Goodness-of-fit of the final multiple model was assessed through a generalized likelihood-based coefficient of determination R^2 [35]. To estimate adjusted population attributable risks (PARs) explanatory variables of the final model were appropriately recorded (high risk categories *versus* others), where required, to represent risk factors with two categories only and then jointly analysed by a multiple conditional logistic model. Applying adjusted ORs ORad from this model and the exposure prevalence in diabetic children P(E|D) adjusted population attributable risks with 95% CIs were estimated according to Greenland [36]: $PAR = P(E|D) \times (ORad-1)/ORad$. χ^2-statistics were used to test

Table 1. Participation rates of cases and controls

Questionnaires	Cases	Controls
Sent out	1069	4385
Returned	774 (72.4%)	1881 (42.9%)
Excluded from analysis	14	10
due to: Sibling of already included	4	5
case or control children	–	–
Adoptive or foster child	4	5
Transient neonatal diabetes	4	–
Cystic fibrosis	1	–
Data insufficient	1	–
Included in analysis	760 (71.1%)	1871 (42.7%)

Table 2. Odds ratio estimates based on simple conditional logistic regression

Exposure variable	Cases ($N = 760$) % (n^a)	Controls ($N = 1871$) % (n^a)	Conditional logistic regression OR (95%CI)	p^b
Overall duration of breastfeeding				<0.001[c]
<2 weeks	28.2 (214)	20.3 (380)	1.00	
2–6 weeks	19.3 (147)	16.3 (305)	0.89 (0.68–1.17)	0.416
7 weeks–4 months	19.2 (146)	20.9 (391)	0.69 (0.53–0.90)	0.007
≥5 months	33.3 (253)	42.4 (792)	0.57 (0.45–0.72)	<0.001
			Trend: 0.83 (0.77–0.89)	*<0.001*[d]
Age at introduction of formulas/cow's milk				<0.001[c]
<2 weeks	32.6 (247)	25.5 (473)	1.00	–
2–6 weeks	19.5 (148)	15.6 (290)	1.02 (0.78–1.33)	0.880
7 weeks–4 months	18.6 (141)	22.0 (408)	0.68 (0.53–0.88)	0.004
≥5 months	29.3 (222)	36.9 (684)	0.63 (0.50–0.79)	<0.001
			Trend: 0.84 (0.78–0.91)	*<0.001*[d]
Kind of bottle-feeding during first year of life				0.047[c]
None	10.4 (78)	14.1 (258)	1.00	–
Cow's milk protein free formula	2.8 (21)	3.1 (56)	1.18 (0.66–2.10)	0.571
Hypoallergenic formula	8.1 (61)	8.5 (156)	1.41 (0.93–2.13)	0.110
Customary cow's milk formula	71.2 (534)	65.8 (1207)	1.53 (1.15–2.04)	0.004
Cow's milk	7.5 (56)	8.6 (158)	1.29 (0.86–1.95)	0.224
Age at introduction of solid food (months)				
≤4	56.8 (426)	50.4 (921)	1.00	
≥5	43.2 (324)	49.6 (905)	0.78 (0.65–0.93)	0.006
Current cow's milk consumption (mL/day)				<0.001[c]
None	20.0 (151)	14.3 (266)	1.00	
<200	33.3 (252)	32.6 (606)	0.67 (0.51–0.87)	0.003
≥200	46.7 (353)	53.1 (989)	0.56 (0.44–0.72)	<0.001
			Trend: 0.77 (0.68–0.86)	*<0.001*[d]
Familial type 1 diabetes				
No	90.1 (685)	98.9 (1851)	1.00	–
Yes	9.9 (75)	1.1 (20)	12.80 (7.17–22.87)	<0.001
Familial type 2 diabetes				
No	77.5 (589)	78.6 (1470)	1.00	–
Yes	22.5 (171)	21.4 (401)	1.05 (0.85–1.29)	0.664
Social status				<0.001[c]
Low	26.1 (198)	15.8 (296)	1.00	–
Middle	55.1 (419)	59.9 (1120)	0.59 (0.48–0.74)	<0.001
High	16.7 (127)	22.8 (427)	0.46 (0.35–0.61)	<0.001
Missing	2.1 (16)	1.5 (28)	0.86 (0.44–1.66)	0.647
			Trend[e]*: 0.67 (0.59–0.78)*	*<0.001*[d]
Maternal age at child's birth (years)				0.002[c]
≤20	5.4 (40)	2.9 (53)	1.97 (1.25–3.12)	0.004
21–25	25.7 (192)	23.1 (421)	1.20 (0.97–1.48)	0.098
26–40	68.1 (509)	73.7 (1342)	1.00	–
>40	0.8 (6)	0.2 (4)	5.07 (1.39–18.50)	0.014
Paternal age at child's birth (years)				0.053[c]
≤20	1.5 (11)	0.7 (12)	2.34 (1.00–5.46)	0.049
21–25	15.4 (113)	12.1 (215)	1.28 (0.98–1.66)	0.069
26–45	80.8 (594)	85.4 (1514)	1.00	–
>45	2.3 (17)	1.7 (31)	1.48 (0.79–2.74)	0.218
Birth Weight (g)				0.033[c]
<2500	5.8 (43)	3.8 (70)	1.70 (1.13–2.58)	0.012
2500–2999	16.9 (126)	14.6 (267)	1.26 (0.98–1.60)	0.067
3000–3999	64.5 (481)	69.9 (1277)	1.00	–
≥4000	12.9 (96)	11.7 (214)	1.19 (0.90–1.57)	0.219
Current weight (SD-score)				0.283[c]
< −2	1.8 (7)	1.9 (32)	1.05 (0.38–2.93)	0.925
−2– < −1	7.8 (31)	9.6 (166)	0.65 (0.42–1.01)	0.054
≥ −1 and ≤1	74.0 (293)	72.5 (1250)	1.00	–
>1–2	14.1 (56)	13.6 (234)	1.09 (0.77–1.54)	0.636
>2	2.3 (9)	2.4 (42)	0.75 (0.35–1.61)	0.455
Mother's coffee consumption during pregnancy (cups/day)				0.340[c]
None	25.0 (186)	23.3 (424)	1.00	–
1–2	48.3 (359)	48.1 (873)	0.91 (0.73–1.13)	0.386
≥3	26.6 (198)	28.6 (519)	0.83 (0.64–1.07)	0.142
			Trend: 0.91 (0.80–1.03)	*0.142*[d]

Table 2. (*Continued*)

Exposure variable	Cases ($N = 760$) % (n^a)	Controls ($N = 1871$) % (n^a)	Conditional logistic regression OR (95%CI)	p^b
Mother' s smoking during pregnancy (cig./day)				0.825[c]
None	85.4 (645)	84.1 (1558)	1.00	–
1–9	11.1 (84)	12.1 (224)	0.93 (0.71–1.22)	0.600
≥10	3.4 (26)	3.8 (71)	0.91 (0.57–1.46)	0.710
			Trend: 0.95 (0.78–1.14)	*0.552*[d]
Mother's current smoking status				
No	71.8 (532)	73.5 (1344)	1.00	–
Yes	28.2 (209)	26.5 (485)	1.09 (0.90–1.33)	0.372
Father's current smoking status				
No	57.8 (411)	59.0 (1026)	1.00	–
Yes	42.2 (300)	41.0 (712)	1.07 (0.89–1.28)	0.482
Change of residence during recent 2 year				
No	81.0 (606)	84.3 (1542)	1.00	–
Yes	19.0 (142)	15.7 (287)	1.25 (0.99–1.57)	0.056
Single-parent family				
	92.4 (701)	94.7 (1766)	1.00	–
	7.6 (58)	5.3 (99)	1.49 (1.05–2.10)	0.025
Number of children in family				0.004[c]
1	39.7 (302)	34.5 (645)	1.00	–
2	43.8 (333)	45.3 (847)	0.84 (0.69–1.02)	0.082
≥3	16.4 (125)	20.3 (379)	0.66 (0.51–0.84)	0.001
			Trend: 0.82 (0.72–0.92)	*0.001*[d]
Number of older siblings in family				0.076[c]
0	55.0 (418)	51.6 (965)	1.00	–
1	32.9 (250)	34.2 (640)	0.89 (0.74–1.08)	0.237
≥2	12.1 (92)	14.2 (266)	0.74 (0.57–0.97)	0.030
			Trend: 0.87 (0.77–0.98)	*0.026*[d]

[a]There are varying numbers of missing values for exposure variables.
[b]p-value of χ^2-test.
[c]Global χ^2-test for difference among categories of exposure variable.
[d]χ^2-test for trend across categories of exposure variable.
[e]Category 'missing' was excluded for analysis of trend.

for significance of associations. In order to test for a linear trend in ORs (on the log-scale) across categories of an exposure variable, e.g. to test for an increase in the strength of an association with increased level of exposure or with increasing duration of exposure (so-called dose-response relationship), χ^2-trend tests were carried out by modelling exposure variables in logistic models as linear continuous terms, as usual. Trend tests were performed for duration of breastfeeding, age at introduction of formulas/cow's milk, current cow's milk intake, social status, number of children in the family, number of older siblings in the family and mother's coffee consumption and smoking during pregnancy. The level of statistical significance was 5%.

Both duration of breastfeeding and age at first exposure to breast milk substitutes are of special concern with respect to the aetiology of type 1 diabetes. Since on principle it cannot be determined from epidemiological data, which of both factors is the more important and putative causal one, these exposures were not jointly included into one regression model, thus at the same time avoiding the problem of high collinearity (Spearman correlation here 0.84). The aforementioned multiple procedures were performed separately in two models including duration of breastfeeding or age at first exposure of breast milk substitutes.

Statistical analyses were performed with SAS (SAS for Windows, Release 8.2, SAS Institute Inc. Cary, NC, USA) or STATA (StataCorp. 2001. Stata Statistical Software: Release 7.0 College Station, TX: Stata Corporation).

Results

Simple logistic regression analyses

The risk of type 1 diabetes was inversely related to the duration of breastfeeding, to children's age at their first exposure to formulas/cow's milk or solid food, to the amount of current cow's milk intake, to the family's social status, to the number of children living with the family, and to the child's rank in the birth order of siblings (Table 2). There was a significant linear trend in the ORs (log-scale) for breastfeeding duration ($p < 0.001$), age at introduction of formulas/cow's milk ($p < 0.001$), current cow's milk intake ($p < 0.001$), social status ($p < 0.001$), number of children in the family ($p = 0.001$), and number of older siblings in the family ($p = 0.026$), indicating a dose-response relationship for these exposures.

Feeding of customary cow's milk formula during the first year of life was associated with a significantly increased risk, unlike other kinds of bottle-feeding. Further, familial type 1 diabetes, older mother's or younger parents' age at child's birth, low birth weight, single-parent family, and a family's residence move during recent 2 years (the latter only in tendency) were related to a higher diabetes risk. Type 1 diabetes risk was only slightly increased among children with high birth weight. No significant association was found between type 1 diabetes and familial type 2 diabetes, current child's weight-SDS, mother's coffee consumption and smoking habits during pregnancy, or the parents' current smoking status.

When age (in years) was included in each conditional logistic model in order to adjust for the non-perfect age-matching of cases and controls – on average controls were about 4 months older than cases – OR estimates were similar (data not shown).

Multiple logistic regression analyses

Irrespective of whether duration of breastfeeding or age at the introduction of bottle-feeding was included, the procedure of stepwise backward elimination resulted in a final model that comprised seven additional explanatory variables and explained an effectual proportion of the outcome variation ($R^2 = 14\%$, Table 3). Estimates of adjusted ORs and PARs for these shared variables of the two alternative final models were not substantially different. Thus, only those estimates based on the models including duration of breastfeeding are presented (Tables 3 and 4).

Adjusted OR estimates and trend tests confirmed the inverse relationship between the risk of type 1 diabetes and duration of breastfeeding, age at introduction of bottle-feeding, the current level of cow's milk intake, the number of children in the family, and the family's social status (Table 3). The influence of a familial type 1 diabetes was also validated. There was observed no significant interaction between infant feeding practice and family history. Maternal age at delivery was still influential, but a significantly increased risk was solely found in children born to mothers above 40 years of age. Young maternal age was no longer associated with an elevated risk. Low birth weight remained in tendency to be associated with an increased diabetes risk. The adjusted OR associated with a change of residence during recent 2 years was not statistically significant.

When additionally adjusting for age (in years) in each multiple model OR estimates did not change substantially (data not shown).

Estimates of the preventable proportion of cases in the population related to a short breastfeeding period (<5 month), young age at introduction of bottle feeding (<5 month) or less than three children in families ranged between 16–19% (Table 4). Family history of type 1 diabetes, low familial social status, low (<2500 g) or high birth weight (≥4000 g) and

Table 3. Adjusted odds ratio estimates based on multiple conditional logistic regression

Exposure variable	OR (95%CI)	p^c
Overall duration of breastfeeding[a]		0.049[d]
<2 weeks	1.00	–
2–6 weeks	0.97 (0.72–1.31)	0.862
7 weeks–4 months	0.85 (0.63–1.13)	0.255
≥5 months	0.71 (0.54–0.93)	0.012
	Trend: 0.89 (0.82–0.97)	*0.008*[e]
Age at introduction of formulas/cow's milk[b]		0.053[d]
<2 weeks	1.00	–
2–6 weeks	1.15 (0.86–1.54)	0.347
7 weeks–4 months	0.82 (0.62–1.09)	0.168
≥5 months	0.80 (0.62–1.04)	0.092
	Trend: 0.91 (0.84–0.99)	*0.035*[e]
Current cow's milk consumption[a] (mL/day)		0.001[d]
None	1.00	–
<200	0.65 (0.49–0.88)	0.005
≥200	0.60 (0.46–0.79)	<0.001
	Trend: 0.80 (0.70–0.91)	*<0.001*[e]
Familial type 1 diabetes[a]		
No	1.00	–
Yes	12.53 (6.77–23.18)	<0.001
Social status[a]		0.003[d]
Low	1.00	–
Middle	0.71 (0.55–0.91)	0.006
High	0.55 (0.40–0.76)	<0.001
Missing	0.81 (0.38–1.72)	0.578
	Trend[f]*:0.74 (0.63–0.87)*	*<0.001*[e]
Maternal age at child's birth[a] (years)		0.079[d]
≤20	1.45 (0.87–2.43)	0.157
21–25	0.99 (0.78–1.25)	0.912
26–40	1.00	–
>40	4.57 (1.20–17.40)	0.026
Change of residence during recent two years[a]		
No	1.00	–
Yes	1.10 (0.86–1.42)	0.434
Number of children in family[a]		0.054[d]
1	1.00	–
2	0.86 (0.69–1.06)	0.155
≥3	0.71 (0.53–0.94)	0.018
	Trend: 0.84 (0.73–0.96)	*0.011*[e]
Birth Weight[a] (g)		0.085[d]
<2500	1.51 (0.96–2.38)	0.077
2500–2999	1.27 (0.97–1.66)	0.080
3000–3999	1.00	–
≥4000	1.28 (0.94–1.73)	0.113

[a]Results were derived from the model including overall duration of breastfeeding, current cow's milk consumption, familial type 1 diabetes, social status, maternal age, change of residence, number of children, and birth weight analysis included 719 cases and 1735 controls, $R^2 = 0.137$.
[b]Results were derived from the model including age at introduction of formulas/cow's milk, current cow's milk consumption, familial type 1 diabetes, social status, maternal age, change of residence, number of children, and birth weight analysis included 718 cases and 1725 controls, $R^2 = 0.137$; OR estimates for the other variables from this model were similar to the presented estimates from the model including duration of breastfeeding.
[c]p-value of χ^2-test
[d]Global χ^2-test for difference among categories of exposure variable.
[e]χ^2-test for trend across categories of exposure variable.
[f]Category 'missing' was excluded for analysis of trend.

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Table 4. Population attributable risk estimates based on adjusted odds ratio estimates from multiple conditional logistic regression

Exposure variable	OR (95%CI)	p^c	PAR (95%CI)
Overall duration of breastfeeding[a]			
≥5 months	1.00	–	–
<5 months	1.40 (1.13–1.73)	0.002	0.190 (0.129–0.282)
Age at introduction of formulas/cow's milk[b]			
≥5 months	1.00	–	–
<5 months	1.30 (1.04–1.61)	0.019	0.160 (0.101–0.254)
Current cow's milk consumption[a]			
Yes	1.00	–	–
None	1.67 (1.29–2.16)	<0.001	0.082 (0.052–0.127)
Familial type 1 diabetes[a]			
No	1.00	–	–
Yes	12.29 (6.66–22.66)	<0.001	0.088 (0.065–0.120)
Social status[a]			
Other	1.00	–	–
Low	1.50 (1.19–1.91)	<0.001	0.085 (0.054–0.135)
Maternal age at child's birth[a] (years)			
21–40	1.00	–	–
≤20 or >40	1.77 (1.10–2.83)	0.018	0.026 (0.012–0.057)
Change of residence during recent 2 years[a]			
No	1.00	–	–
Yes	1.11 (0.87–1.42)	0.413	0.018 (0.006–0.053)
Number of children[a]			
≥3	1.00	–	–
<3	1.29 (1.00–1.66)	0.049	0.188 (0.112–0.316)
Birth Weight[a] (g)			
3000–3999	1.00	–	–
<3000 or ≥4000	1.30 (1.05–1.60)	0.015	0.081 (0.048–0.134)

[a]Results were derived from the model including overall duration of breastfeeding, current cows's milk consumption, familial type 1 diabetes, social status, maternal age, change of residence, number of children, and birth weight; analysis included 719 cases and 1735 controls, $R^2 = 0.129$.
[b]Results were derived from the model including age at introduction of formulas/cow's milk, current cows's milk consumption, familial type 1 diabetes, social status, maternal age, change of residence, number of children, and birth weight; analysis included 718 cases and 1725 controls, $R^2 = 0.126$; OR and PAR estimates for the other variables from this model were similar to the presented estimates from the model including duration of breastfeeding.
[c]p-value of χ^2-test.

lack of current cow's milk consumption each accounted for about 8–9% of new diabetic cases. Population attributable risks due to young or older maternal age at delivery or change of residence were estimated to be low.

Discussion

This large population-based case-control study in pre-school children showed that a long duration of breast-feeding, late introduction of bottle feeding, current cow's milk consumption, higher family's social status, and a greater number of children in the family were associated with a reduced risk of type 1 diabetes, even after adjusting for confounding. Children with a family history of type 1 diabetes, low birth weight children (<2500 g), and children born to mothers above 40 years of age were shown to bear a higher diabetes risk. Estimates of population attributable risks indicated a short breastfeeding period, an early introduction of bottle feeding, low or high birth weight (<2500 or ≥4000 g), and a small family each to account for 16–23% of diabetic cases in the population. Overall, up to one half of diabetic cases in the population were potentially attributable to modifiable exposures.

In this study, a large number of incident cases and controls have been collected from a narrowly defined age group during a short period, thus reducing cohort effects and potential variation of the outcome variable due to unknown background factors. Controls were individually matched and randomly selected from the general population, which is considered a suitable choice for a population-based case series [34]. In comparison to previous case-control studies, this study has the advantage that questionnaires were sent out to children with early diabetes onset only and were completed by case families shortly after onset and followed by a telephone interview, when data were incomplete. The confinement to pre-school children can be presumed to limit the number of potential confounding factors and in particular to reduce recall bias with respect to the history of diet and other exposures recollected, because parents of children under 5 years of age should recollect respective data more precisely than those of older children. Nevertheless, the retrospective collection of exposures by parent-administered questionnaires may have caused some misclassification due to recall bias. A further shortcoming is the lower response rate among control families compared to case families – probably due to the indirect contacting of control families via local registration offices – with a potential selection.

Both selection and recall bias could have affected the observed associations. However, data on breastfeeding duration among control children were in good agreement with reported data [37]. In addition, results have been adjusted for socio-economic status, which is known to be associated with both study participation rates and dietary habits in infancy [37]. Differential recall and misclassification between parents of diabetic and non-diabetic children cannot completely be ruled out, but it seems very unlikely to account for the observed associations, particularly relating to feeding habits in infancy. Non-differential recall bias would only have weakened the associations. A major strength of this study is the comprehensive statistical analysis unlike in many previous studies, which could be performed owing to the large number of cases and controls. We performed a stepwise backward elimination procedure simultaneously considering most of the investigated exposures to select the relevant explanatory variables of the diabetes risk and to estimate respective adjusted ORs. The final multiple models explained a considerable part of the variation in the data according to estimates of the coefficient of determination. Respective estimates are lacking in previous studies. Further, we estimated adjusted population attributable risks based on adjusted ORs for the first time – to our knowledge – in this research context.

Our results on infant diet adds to the body of evidence on the protective role of a long breastfeeding duration and a late introduction of breast milk substitutes from epidemiological studies [9–21]. The observed linear trend in ORs (on the log-scale) across categories of breastfeeding duration and age at introduction of breast milk substitutes, e.g. the observed dose-response relationship between infant feeding and the diabetes risk indicates that the association is rather real than due to bias or other methodical problems [18,34]. However, it cannot be ruled out that the observed association is at least partially due to recall or selection bias. The effect of infant feeding on diabetes risk was not modified by familial type 1 diabetes. Concordantly, this association has previously been indicated not to be modified by HLA-associated genetic risk [13,19,27,38]. Though short breastfeeding and early introduction of bottle-feeding (<5 months) increased diabetes risk only moderately, in agreement with previous meta-analyses [17,18], the proportion of new diabetic cases in the population attributable to these exposures may be of considerable size (PAR $\approx$ 20%). However, data on infant feeding habits are scarce for Germany. Thus, it can hardly be assessed whether changes in infant feeding habits actually contributed to the increase in diabetes incidence observed in Germany [5,28,39].

Earlier retrospective studies did not consistently find evidence for a protective effect of breastfeeding and late exposure to formulas or cow's milk [23–27]. Recent prospective investigations, which were not subject to recall bias, also produced conflicting evidence on the association between infant diet and the risk of β-cell autoimmunity. Some studies did not find an association between diabetes autoimmunity and breastfeeding duration or early cow's milk introduction [40–43], whereas other studies did [44,45]. However, some of these retro- and prospective studies exhibited methodical shortcomings: Small numbers of cases, rather limited information on infant feeding practices, possibly too close matching, and short observation periods may have limited the power to detect moderate associations [15,26,27,40–42,46]. Recently, a randomized double-blind dietary intervention pilot trial in newborns genetically at increased risk for type 1 diabetes provided first evidence that casein hydrolysate formulas may protect against the development of islet cell autoimmunity [47].

Infant diet has been hypothesized to be involved in the initiation of the type 1 diabetes autoimmune process by impairing the maturation of the gut-associated immune system and/or by providing antigens cross-reactive to islet cell antigens (molecular mimicry) [22]. However, infant diet may affect diabetes risk as well through pathways according to the recently raised 'accelerator hypothesis' or the 'overload hypothesis' (e.g. *via* increased birth weight, accelerated growth, increased weight gain) [48], because breast-fed children are well known to show less rapid growth and to be less likely to develop childhood adiposity than bottle-fed children [49]. One study showed both early age at introduction of infant formula and increased weight gain to be independently associated with increased diabetes risk [50].

Results on the association between type 1 diabetes risk and early exposure to solid foods or current cow's milk intake confirm previous findings [11,13,19,51], although there are conflicting reports [14,27]. The observed inverse association of current milk intake with the diabetes risk could have partly been caused by selection bias, because the participation rate was lower among controls than cases in our study, and participants of this type of studies are known to be more educated people behaving differently, in particular with respect to diet. Further, cases were somewhat younger than controls on average, what could have contributed to the lower milk intake observed among cases, because the collected data on current customary cow's milk intake among cases could refer to an earlier time point than among controls. However, the inverse association held after adjustment for social status and age. Recent prospective studies found associations between increased β-cell autoimmunity and early or late introduction of cereals/gluten or early introduction of fruits and roots into infant diet [41–43]. Unfortunately, we had no information on the age at first exposure to different food categories.

A positive family history of type 1 diabetes has consistently been reported to raise type 1 diabetes risk among relatives [2,9,11,20,21,23,51,52]. But reported ORs varied considerably, partly due to different age groups investigated or different definitions of familial type 1 diabetes. We estimated an OR of about 13, even higher than the risk among the under 5s in a Swedish

study [11]. A case of type 2 diabetes in the family was not associated with an increased type 1 diabetes risk in our study, in line with some [52] but not all investigations [11,21].

Epidemiological evidence on the association between socio-economic status and type 1 diabetes risk in children is fairly conflicting, possibly owing to different study designs or differing methods for assessing social status. Positive [15,19,51] and inverse associations [10–14,16,21,25,53] have been reported. In this study a higher social status was more prevalent among control families indicating yet unknown protective factors associated with high social status. Therefore, the growing social disparities observed in Germany during the last decade could have potentially accounted for the diabetes incidence increase [28]. However, the observed association could have been affected at least partially by selection bias, because different response rates between case and control families may be differentially associated with social status.

Crowded households (overcrowding), a greater number of siblings, and a higher birth order have been observed to be associated with a reduced risk for type 1 diabetes in case-control and recent cohort studies [14,15,23,54]. Our study confirmed these inverse associations, although after multiple adjustment the relationship only held for the number of children, thus indicating the effect of birth order (number of older siblings) to be due to confounding by family size. The 'hygiene hypothesis' presumes infections in early life to support the maturation of the immune system [53]. Actually, day care attendance, potentially associated with an increased infectious load, has been indicated to be protective against type 1 diabetes in a recent meta-analysis, in particular in children less than 5 years of age [55]. A larger family might mediate similar protective mechanisms. According to the PAR estimate, about 20% of new diabetic cases below 5 years in the population are attributable to small families. Thus, the decreasing number of children in families observed in developed countries during past decades could have accounted for the observed rise in diabetes incidence. But a lower number of children in case families could also be a consequence of the disease, because parents of a child with a chronic disease like type 1 diabetes might be less likely to have more children. The inverse association between family size or birth order and type 1 diabetes risk has not been supported consistently [9,10,16,25,53].

There is a considerable body of evidence that higher maternal age at child's birth (mostly >35 years) is associated with a higher risk of type 1 diabetes [10,11,15,16,20,53,56], although there are other studies not supporting a suchlike association [12–14,23,26,51]. Concordantly with the majority of studies, we found a higher proportion of case than control children born to mothers older than 40 years. Recent cohort studies showed a log-linear increasing risk with rising maternal age [31,54,57]. But in line with others [58], we observed an elevated crude risk also in children of very young mothers (≤20 years) indicating a J-shaped association. Further, children of very young fathers had a higher crude risk, in keeping with some [12,23] but not all previous reports [15,54]. But it cannot be excluded that the association between parental young age and diabetes risk observed in our study is due to selection bias. Apart from this, maternal age at first childbirth has increased in developed countries during past decades. Thus, maternal age could have contributed to the rise in incidence of type 1 diabetes. The influence of maternal age may partly be attributed to social determinants, because higher maternal age is likely to be associated with higher education, which is known to affect a child's early life exposures like infant diet, neonatal care, or exposure to infections or vaccinations. But we found a significant effect of maternal age even after adjustment for social status pointing at further relevant factors associated with pregnancy in older age that possibly could increase diabetes risk by impairing normal maturation of the immune system in offspring [57]. However, according to our PAR estimate (2.5%) only a small proportion of diabetic cases may be attributable to maternal age, unlike previously reported [56,57].

Results on the association between birth weight and type 1 diabetes risk are conflicting. Some studies observed an increased risk in children with high birth weight and a lower type 1 diabetes risk among children with low birth weight [31,59,60]. The association between birth weight and diabetes risk was almost linear. But other studies observed also low birth weight to be associated with an increased risk [61–63] and an earlier onset age [64,65], while others found no association [23,30,53]. In concordance with the Taiwan study [61], our study indicated at least in tendency a U-shaped association, with a stronger relation for low birth weight. It cannot be ruled out that the observed association is affected by selection bias, but data on birth weight of children reported by the families are likely to be rather valid, because in Germany each child's birth weight is recorded in the child's examination book (It contains child's medical information on birth and general development milestones according to the German schedule of preventive medical check-ups during childhood). Low birth weight children have been found to show a postnatal catch-up growth in infancy associated with a higher risk for adiposity and insulin resistance in subsequent childhood [66]. Further, increased weight gain and growth in infancy and childhood have been observed to increase the risk for type 1 diabetes [50,67,68] and to be associated with an earlier onset age [64,65,69]. Thus, low birth weight might affect type 1 diabetes risk like high birth weight via increased adiposity and growth in early childhood, in accordance with the 'overload hypothesis' [48]. However, since birth weight has been rising in developed countries, low birth weight is actually unlikely to mainly account for the rapidly increasing incidence of type 1 diabetes [5,6]. But interestingly, both low birth weight and increased weight gain in infancy among children with postnatal catch-up growth have been reported to be associated with specific genotypes that also confer higher risk of

type 1 diabetes (HLA-DQ8/DQ2, class I-allele at insulin gene (INS) variable number of tandem repeats (VNTR)) [70–72]. Therefore, these risk genotypes might at least in part affect type 1 diabetes risk along the above mentioned pathway.

Although children with type 1 diabetes have been reported to show an increased weight gain before onset of the disease in childhood [50,67–69], type 1 diabetic children have not consistently been reported to be overweight at diagnosis in comparison to reference children. While an earlier study found weight-SDS to be lower at diabetes diagnosis [73], recent studies reported an increased weight-SDS and BMI-SDS in children at diagnosis of type 1 diabetes [64,74], another recent study found no difference in weight-SDS and BMI-SDS in comparison to a reference population [69]. In our study, type 1 diabetic children were also heavier at onset (precisely, analysis included diabetic children with weight data recorded one week until 3 months after diagnosis) when compared to a German reference population (mean weight-SDS at onset: 0.17, 95% CI: 0.08–0.26), but not when compared to age-matched control children of the study (mean weight-SDS: 0.13, 95% CI: 0.07–0.20). Likewise, there was found no overall significant association between weight-SDS and diabetes risk in logistic regression. But the onset of diabetes can be associated with true weight loss beyond dehydration, so that weight measured to close to diagnosis possibly underestimates the true weight. Due to our finding, results of earlier studies comparing weight of type 1 diabetic children at onset only with a reference population data [64,69,74] may be questioned, because reference populations might not have matched diabetic cases appropriately with respect to calendar period or geographical region, as it was the case in our matched case-control study.

Stressful events in early life have been observed to be associated with an increased type 1 diabetes risk [11,16,21,25,75]. Suchlike events have been hypothesized to accelerate a pre-existing autoimmune process [75]. Concordantly, in this study children living with only one parent or with residence change during recent 2 years were at increased risk of type 1 diabetes according to simple regression analysis. In particular, the association with house move is unlikely to be a consequence of the disease, because qualified diabetes care is provided throughout the country, but may be due to selection bias. Overall, the epidemiological evidence on the relation of family status or removal and diabetes risk is conflicting [9,10,15,16,53].

Consistent with some previous studies [16,23,76] we observed no difference in coffee consumption and smoking during pregnancy between mothers of case and control children. On the contrary, maternal coffee consumption has also been reported to be associated with an elevated diabetes risk, and cigarette smoking during pregnancy with an increased or reduced risk [21,51]. Parent's current smoking was not related to diabetes risk in our study, as reported previously [25,76].

Taken together, performing comprehensive statistical analyses this large nationwide population-based case-control study in pre-school children widely confirms previously known influencing factors of type 1 diabetes. Differing findings could be due to a variety of methodical factors (e.g. study design, sample size, data collection, age range of study participants, confounding factors) or to truly different impacts of environmental factors between populations, possibly depending on a varying genetic background or gene–environment interactions. In particular, results indicated infant feeding to be associated with type 1 diabetes risk. Within the given design, it was not possible to differentiate, whether some inherent component of the breast milk or the exposure to breast milk substitutes is the causative factor. Importantly, a considerable part of new type 1 diabetic cases in the population was indicated to be attributable to alterable environmental exposures and thus potentially preventable.

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Conflict of interest

None declared.

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