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ARTICLE

The effect of birth order and parental age on the risk of type 1 and 2 diabetes among young adults

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Abstract
Aims/hypothesis The aim of this study was to examine the effects of birth order and parental age on the risk of type 1 and type 2 diabetes among Finnish individuals aged 15–39 years.
Methods Data on all cases of type 1 diabetes (n=1,345) and type 2 diabetes (n=1,072), diagnosed between 1992 and 1996, were collected from four sources: standardised national reports from diabetes nurses, the National Hospital Discharge Register, the Drug Prescription Register and the Drug Reimbursement Register. Information on matched controls and the family members of all study subjects were obtained from the National Population Registry. The odds ratios (ORs) for both types of diabetes were estimated using a conditional logistic regression model.
Results There was a U-shaped relationship between maternal age and the risk of type 2 diabetes in the offspring: the risk was higher in children born to young and old mothers compared with children born to mothers aged around 30 years. The children born second (OR 0.76, 95% CI 0.62–0.94), third (OR 0.73, 95% CI 0.55–0.95), or fourth (OR 0.66, 95% CI 0.47–0.94) had a lower risk of type 2 diabetes than the first-born children. Maternal age, paternal age, and birth order did not have an effect on the risk of type 1 diabetes in the individuals aged 15–39 years at the time of diagnosis.
Conclusions/interpretation Maternal age and birth order are both associated with the risk of early-onset type 2 diabetes. However, part of these associations may be due to low birthweight. In this study neither parental age nor birth order showed a significant association with the risk of type 1 diabetes diagnosed after 15 years of age.

Keywords Birth order · Diabetes · Maternal age · Paternal age · Young adults

Abbreviations
ICD International Classification of Diseases
OR odds ratio

Introduction

Type 1 diabetes mellitus is caused by immune-mediated destruction of the pancreatic beta cells leading to an absolute deficiency in endogenous insulin [1]. This process, which occurs in genetically susceptible individuals, is triggered by environmental factors [2]. The underlying, mediating environmental factors are not known, although several factors have been proposed, including viral infections [3], dietary factors such as cow's milk protein and gluten [4], environmental toxins [5], increased weight gain in infancy [6] and antenatal factors such as maternal age [7] and birth order [8]. Data on the aetiology of type 1 diabetes are largely based on studies of type 1 diabetes cases

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diagnosed in children younger than 15 years. However, type 1 diabetes can develop at any age [9, 10] and the incidence of type 1 diabetes in adults follows different patterns compared with that in children [11]. The information on aetiological factors obtained from the childhood cases may not be applicable to type 1 diabetes with a later onset.

The number of cases of type 2 diabetes diagnosed in adolescents and children is rising [12]. Type 2 diabetes is characterised by insulin resistance and relative insulin deficiency [1]. The role of the genetic predisposition in the development of type 2 diabetes is significant, and concordance in monozygotic twins is approximately 70% [13]. In addition to genetic susceptibility, type 2 diabetes is prominently associated with obesity [14] and low physical activity [15]. Antenatal factors are also important in the aetiology of type 2 diabetes, and low birthweight is an acknowledged risk factor for type 2 diabetes and related conditions [16].

An increased risk of type 1 diabetes in childhood has been associated with a high maternal age at birth [7, 17–20]. Weaker associations between type 1 diabetes risk and high paternal age at conception have been found [17, 20], but this association has not always been significant after adjusting for maternal age and other confounding factors [8]. Studies on the effects of birth order on the risk of type 1 diabetes have produced inconsistent results. Increasing birth order has been reported to decrease the risk of type 1 diabetes in childhood [17, 19, 20]. In contrast, among children of parents with type 1 diabetes the risk of type 1 diabetes was lowest in the first-born [21]. Furthermore, the effect of birth order is modified by maternal age [8]. A large family-based study reported a 15% risk reduction per child born [20], but the methods used in the study were subsequently criticised [22, 23]. The data on the influence of parental age and birth order on type 2 diabetes are scarce. We found only one study, carried out in the 1990s, reporting that a birth order above four might be a risk factor for type 2 diabetes [24].

Previous studies of antenatal factors have been carried out among patients with type 1 diabetes diagnosed under the age of 21 years [7, 17–20]. In a study conducted in the UK, increasing birth order had a protective effect only against type 1 diabetes diagnosed before 5 years of age [17], and in a Swedish study high maternal age was a risk factor for diabetes only among children diagnosed under 10 years of age [7].

The association of parental age or birth order with late-onset type 1 diabetes or early-onset type 2 diabetes has not to our knowledge been studied previously. In this study we have examined the effect of parental age and birth order on the risk of type 1 and type 2 diabetes among individuals aged 15–39 years at the time of diagnosis.

Methods

Diabetic patients The patients were diagnosed with type 1 or type 2 diabetes at the age of 15–39 years between 1992 and 1996 and were resident in Finland at the time of diagnosis. The National Advisory Board on Health Care Ethics approved the study plan. Four different data sources were used to capture the cases:

1. New cases of diabetes mellitus diagnosed in individuals aged 15–39 years were reported by diabetes nurses in Finnish hospitals and primary care diabetic clinics to the National Public Health Institute in Finland using standardised forms. The date of diagnosis of diabetes and the date of treatment initiation were included in the forms.
2. The Drug Reimbursement Register of the Social Insurance Institute contains information on persons entitled to free-of-charge medication for diabetes. Glucose-lowering agents (insulin and oral medication) prescribed by a physician are free of charge in Finland and are subject to the approval of a physician at the Institute who reviews each case history. Patients who apply for free-of-charge medication must attach a detailed medical statement prepared by the treating physician, who provides data to confirm the diagnosis of diabetes.
3. The Drug Prescription Register of the Social Insurance Institute includes all prescriptions prescribed in Finland since late 1994. All the class A10 drugs in the WHO Anatomical Therapeutic Chemical Classification and Defined Daily Dose classification (drugs used in diabetes; insulin and analogues, blood glucose lowering drugs, other drugs used in diabetes) [25] prescribed up to the end of 1996 were reviewed.
4. The hospital discharge diagnoses for patients who have been admitted to the hospital ward (up to four diagnoses per visit) are included in the Finnish National Hospital Discharge Register maintained by the National Research and Development Centre for Welfare and Health. The treating physicians assign the diagnostic codes using the International Classification of Diseases [26] (ICD-9 until 1995 and ICD-10 from 1996 onwards). The Finnish versions of the ICD-9 also included information about the type of diabetes.

The classification of diabetes was based on the information obtained from the data sources: the clinical diagnosis of the treating physician (the Finnish National Hospital Discharge Register), detailed information of medication (the registers of the Social Insurance Institution) and the standardised national reports from the diabetes nurses. The data obtained from the registers were linked using the unique personal identification number assigned to every

Finnish resident. The inclusion criterion was a consistent diagnosis from at least two data sources, and the date of diagnosis was set as the date of the first entry in any one of these registers. The methods for the classification of diabetes have been described in detail previously [27]. In total, 4,478 individuals who fulfilled the inclusion criterion were identified from these four data sources, 485 of whom could not be reliably classified as having type 1 or type 2 diabetes and were excluded from the study. There were also 1,268 patients with gestational diabetes and 216 patients who were categorised as having 'other specific type of diabetes' according to the American Diabetes Association definition [28] who were also excluded. Altogether, 1,388 individuals with type 1 diabetes (mean age at diagnosis 26 years), and 1,121 individuals with type 2 diabetes (mean age at diagnosis 34 years) were identified by this method. This number comprises all type 1 and type 2 diabetes cases identifiable from the registers for the period between 1992 and 1996 in patients aged 15–39 years in Finland. The degree of ascertainment estimated using the capture–recapture method [29] for type 1, type 2 and undefined type of diabetes was 88% overall [27].

Data on the parents of the patients in the study, including their date of birth, were obtained from the National Population Register. Due to a lack of this information a further 43 patients with type 1 diabetes and 49 patients with type 2 diabetes were excluded. Therefore, 1,345 individuals with type 1 diabetes and 1,072 individuals with type 2 diabetes were included in the analysis of parental age. Among these patients, information on the birth dates of the siblings was available from the National Population Register for 1,272 patients with type 1 diabetes and 943 patients with type 2 diabetes, and these were included in the analysis of birth order.

Control individuals Two nondiabetic control individuals matched by birth date, birth place and sex were obtained from the National Population Register for each diabetic subject. For 33 patients with type 1 diabetes and 34 patients with type 2 diabetes only one control was found. The nondiabetic status of the controls was confirmed by computer linkage with the Hospital Discharge Register and the registers of the Social Insurance Institution. The number of controls included in the study was 2,657 for the type 1 diabetes group and 2,110 for type 2 diabetes group. For cases with information available on the birth dates of the siblings the number of controls was 2,532 for type 1 diabetes and 1,898 for type 2 diabetes.

Statistical methods Data for type 1 diabetes and type 2 diabetes were analysed separately using a conditional logistic regression model [30]. Cases were matched to one to two controls on date of birth, place of birth and sex. A p value of <0.05 was considered significant. All statistical analyses were performed using R software [31].

Results

Both categorical birth order adjusted for maternal age and maternal age alone had an effect on the risk of type 2 diabetes. The interaction between birth order and maternal age was also tested but not found to be significant. Maternal age was highly correlated with paternal age (ρ= 0.8), and so further analysis was carried out using maternal age alone. In preliminary data analysis, the effect of maternal age on the risk of the offspring developing type 2 diabetes between 15 and 39 years of age was found to have a U-shaped pattern. Therefore, a quadratic term was added to the model. The quadratic model (Fig. 1a) also displayed a slightly better fit than a linear model, as measured by Akaike's information criterion. In the model, age was treated as a continuous variable. The baseline for maternal age was chosen to be 25.5 years, which was the mode (i.e. most frequent or typical) for maternal age in the data. The analysis showed that, compared with the baseline, the risk of type 2 diabetes in children born to very young or old mothers was significantly higher, whereas the lowest risk was observed at a maternal age of around 30 years (Fig. 1a). The p values were 0.02 for both the linear and the quadratic terms. The results for maternal age in categories (Table 1) suggest a quadratic relationship for both type 1 and type 2 diabetes. However, contrary to the analysis for type 2 diabetes, the quadratic term was not significant for type 1 diabetes. Second- [odds ratio (OR) 0.76, 95% CI 0.62–0.94], third- [OR 0.73, 95% CI 0.55–0.95], and fourth-born children [OR 0.66, 95% CI 0.47–0.94] had a significantly lower risk of type 2 diabetes than first-born children (p<0.05) (Table 1, Fig. 2a). Birth orders six through 12 were pooled into one category because of their

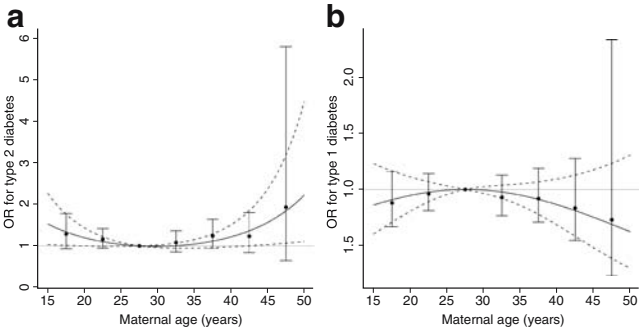

Fig. 1 ORs for type 2 (**a**) and type 1 (**b**) diabetes according to maternal age. Estimated continuous models (black line) with 95% CIs (dashed lines). The categorical models (circles) with 95% CIs (error bars) support the quadratic fit for both type 2 and type 1 diabetes. The quadratic term for the continuous model in **a** was found to be significant

Table 1 ORs for type 1 and type 2 diabetes by maternal age and birth order adjusted for maternal age

Maternal age (years)	Type 1 diabetes				Type 2 diabetes			
	Cases, *n*	Controls, *n*	OR	95% CI	Cases, *n*	Controls, *n*	OR	95% CI
15–19	95	201	0.88	0.67–1.16	75	125	1.28	0.93–1.78
20–24	406	803	0.96	0.81–1.14	330	626	1.16	0.95–1.42
25–29	431	824	1.00		273	602	1.00	
30–34	237	486	0.93	0.77–1.13	185	385	1.08	0.86–1.36
35–39	112	229	0.92	0.71–1.19	114	206	1.24	0.94–1.64
40–44	34	74	0.83	0.54–1.28	50	91	1.23	0.84–1.80
>44	4	10	0.73	0.23–2.34	7	7	1.93	0.64–5.81
Birth order								
1st	559	1,081	1.00		436	771	1.00	
2nd	400	795	0.94	0.79–1.11	227	501	0.76*	0.62–0.94
3rd	171	341	0.96	0.76–1.22	127	295	0.73*	0.55–0.95
4th	76	169	0.81	0.59–1.12	66	166	0.66*	0.47–0.94
5th	34	66	0.93	0.58–1.48	48	82	0.99	0.65–1.50
6th+	32	85	0.70	0.44–1.11	39	84	0.68	0.43–1.06

*$p<0.05$

low frequencies in the data. Paternal age and the ratio of paternal age to maternal age did not differ between type 2 diabetic patients and control subjects (data not shown).

In the analysis of the risk of type 1 diabetes there was no significant effect of examined covariates (maternal age, birth order, paternal age or paternal/maternal age ratio) on the risk of type 1 diabetes (Table 1, Figs 1b and 2b).

Discussion

There are no previous studies focusing on the effects of both parental age and birth order on the risk of type 1 or type 2 diabetes diagnosed between 15 and 39 years of age. The most important finding of this study was that, although the effects of birth order and maternal age were correlated, both maternal age at delivery and the birth order of the offspring had an effect on the risk of early-onset type 2 diabetes in the offspring. The observed effect of maternal age was not linear. Furthermore, within the family the second-, third-, and fourth-born children had a lower risk than the first-born child. We did not find any associations of parental age or birth order with the risk of type 1 diabetes diagnosed between 15–39 years of age. This is contrary to the findings from some previous studies carried out among childhood onset cases of type 1 diabetes [8, 18–20]. On the other hand, our results are consistent with studies in which the effects of maternal age [7] and birth order [17] were limited only to the very young-onset cases of type 1 diabetes.

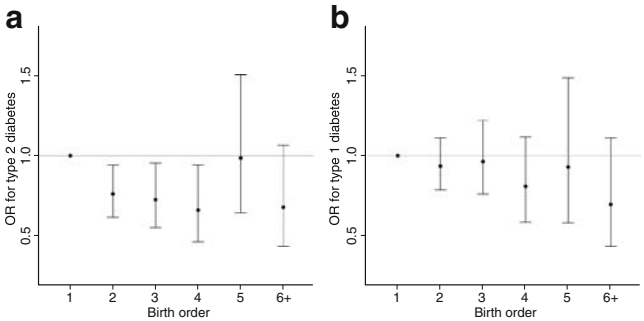

Fig. 2 ORs for type 2 (**a**) and type 1 (**b**) diabetes with onset between 15 and 39 years of age by birth order adjusted for maternal age. Categorical model with 95% CI (error bars)

The national healthcare registers in Finland that were used to capture and classify cases have been reported to be highly reliable [32, 33]. The majority of all confirmed cases of type 1 or type 2 diabetes diagnosed in individuals aged between 15 and 39 years during 1992–1996 nationwide were included in this study. The classification of the type of diabetes was done using multiple data sources (and confirmed from the medical statements prepared for applications for free-of-charge medication when necessary), thus avoiding the possible misclassification that could occur if the classification were based on the age of disease onset alone. All patients with gestational diabetes, secondary forms of diabetes or undefined diabetes were excluded from the analyses.

The National Population Register comprises basic information on all residents in Finland, including the unique personal identification numbers of family members. This provides an accurate link to family members; however, it was only possible to detect nuclear families, and half-siblings were not included in the analyses. As a result, the sizes of the families in this study were smaller than in reality, and the number of first-borns was exaggerated. However, it is unlikely that this had any influence on the results, because the same was true for the control families.

The potential effects of parental diabetes were not possible to examine in this study, and as there is significant genetic predisposition to both types of diabetes, it can be assumed that there were more diabetic parents in the families of the diabetes cases than in the control families.

Low birthweight, influenced by the genetic potential of the fetus and the external conditions in utero, increases the subsequent risk of type 2 diabetes [16]. The conditions in utero are modified by several factors, including maternal age, parity and nutrition. The birthweight of the child is generally presumed to increase with parity and is lowest in the first-born child [34, 35]. In addition, intrauterine growth retardation and prematurity, both resulting in low birthweight, are more frequent at the extremes of maternal age [36]. It could therefore be expected that the risk of type 2 diabetes would also be highest in the first-born children and in the children of very young and old mothers. Our results are in accordance with this, although the differences found in this study were not very large. However, in Finland, the incidence of type 2 diabetes is increasing, on average, by 7.9% per year in the young adult population [27], whereas the changes in maternal age and family size are much smaller—the average age of primiparae in Finland has increased gradually from 24.7 years in 1960 to 27.9 years in 2005 [37]. Therefore, it seems that the effects of maternal age and birth order play only a minor role in the risk of type 2 diabetes in young adulthood, and fail to explain the increasing incidence of type 2 diabetes in this age group.

The aetiology and pathophysiology of type 1 diabetes that develops after childhood are not well understood. Compared with childhood-onset type 1 diabetes, late-onset type 1 diabetic patients seem to have higher C-peptide values at diagnosis [38], disease progression is slower [39], and there are differences in epidemiological patterns [11]. It has been suggested that the environmental factors that trigger type 1 diabetes might be different in adult-onset disease [39]. Our results consistently indicate that the previous results on antenatal factors affecting the risk of type 1 diabetes in children cannot be applied to type 1 diabetes diagnosed after 15 years of age.

In conclusion, maternal age and birth order both influence the risk of early-onset type 2 diabetes in the offspring, suggesting that the disease process begins early in life. However, part of these associations may be due to low birthweight. In this study, neither parental age nor birth order showed a significant association with the risk of type 1 diabetes with onset after 15 years of age.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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