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Paternal smoking is associated with a decreased prevalence of type 1 diabetes mellitus among offspring in two national British birth cohort studies (NCDS and BCS70)

André M. Toschke[1,*], Anna Ehlin[2], Berthold Koletzko[3] and Scott M. Montgomery[2,4,5]

[1] Division of Pediatric Epidemiology at the Institute of Social Pediatrics and Adolescent Medicine, Ludwig-Maximilians-University Munich, Munich, Germany
[2] Enheten för klinisk epidemiologi, Institutionen för medicin vid Karolinska sjukhuset, Karolinska Institutet, Stockholm, Sweden
[3] Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[4] Clinical Research Centre, Örebro University Hospital, Örebro, Sweden
[5] Department of Primary Care and Social Medicine, Imperial College, London, UK

Abstract

Aims: An association between paternal age and type 1 diabetes (IDDM) among their offspring was recently reported as well as transgenerational responses in humans. This paper aims to assess the association of markers for prenatal exposures with IDDM.
Methods: We analysed data from two birth cohorts in Great Britain on 5214 cohort members from the National Child Development Study (NCDS) and 6068 members of the 1970 British Birth Cohort Study (BCS70) with full information on IDDM and explanatory variables using multivariate logistic regression.
Results: IDDM prevalence was 0.7% (95% CI 0.5–1.0%; n = 38) in the NCDS and 0.4% (95% CI 0.3–0.6%; n = 27) in the BCS70 cohort. Paternal age was not associated with IDDM possibly due to lack of sample power. Unexpectedly, a lowered prevalence of IDDM was observed among offspring of smoking fathers in both cohorts, with a combined odds ratio of 0.44 (95% CI 0.25–0.75). This association could not be explained by maternal smoking prior to, during or after pregnancy, number of siblings, parental social class, maternal and paternal age, or cohort. Maternal smoking in pregnancy did not alter the IDDM prevalence among offspring.
Conclusions: This unexpected finding may be explained by germ-line mutations or other mechanisms associated with paternal smoking. This phenomenon should be investigated and these results should not be used as a justification for smoking. Paternal exposures may be important in determining IDDM risk.

Keywords: Environment and public health; environmental pollution; glucose metabolism disorders; variation (genetics).

*Corresponding author (current address):
Dr. A.M. Toschke, MPH, MSc
Senior Lecturer in Health Services Research
King's College London
Department of Public Health Sciences
Division of Health and Social Care Research
Floor 7 Capital House
42 Weston St
London SE1 3QD
UK
Tel: +44 (0) 207 848 6261
Fax: +44 (0) 207 848 6620
E-mail: michael.toschke@kcl.ac.uk

Introduction

Recently an association of type 1 diabetes mellitus (type 1 DM) with paternal age was reported implicating germ line mutations or possibly transgenerational responses in humans [1, 8]. A possible explanation for the association with father's age is through germ-line mutations as these accumulate with increasing age [4]. Some germ-line mutations may influence the risk of type 1 DM in offspring. Further evidence that paternal smoking influences the health and development of offspring comes from the association of paternal smoking prior to conception with altered growth patterns among offspring [15].

Our *a priori* hypothesis was that if germ-line mutations are implicated in the etiology of type 1 DM, then paternal exposures associated with increased risk of mutations, specifically smoking, may influence the risk of type 1 DM in offspring.

In order to assess the impact of possible prenatal or early postnatal exposures on type 1 diabetes mellitus we analysed data from two national longitudinal birth cohort studies, the National Child Development Study (NCDS) and the 1970 British Birth cohort study (BCS70). We examined paternal smoking and paternal age as risks for type 1 DM in offspring. We also investigated risks associated with maternal smoking; this has been associated with type 2 diabetes [13].

Methods

Study population and data sources

The National Child Development Study (NCDS) began as a Perinatal Mortality Survey to examine social and obstetric factors

associated with stillbirth and infant mortality among the babies born in Great Britain from 3–9 March 1958 [5]. Details on birth and pregnancy were available for 17,414 (98%) participants including medical records and interviews of mothers by midwives. Follow-up information of survivors was obtained at ages 7, 11, 16, 23, 33 and 42 years. Biases associated with sample attrition have tended to be small, although in the more deprived social groups have become underrepresented over time [6]. Details of the study are reported elsewhere [6]. The 1970 British Cohort Study (BCS70) was planned as a national birth cohort study including all children born in Great Britain from 5–11 April 1970. Follow-up information of all available survivors was collected at 5, 10, 16, 26, and 30 years of age. The biases associated with attrition are similar to those in NCDS [6].

The analysis was confined to cohort members with complete information on type 1 diabetes mellitus and *a priori* considered covariates leaving 5214 cohort members from NCDS and 6068 cohort members from BCS70 available for analysis.

Measures

Overall, nine covariates were analysed with respect to an association with type 1 diabetes, namely sex, paternal smoking, maternal smoking in pregnancy, postnatal maternal smoking, number of siblings, maternal and paternal age and social class. Information on paternal smoking was available as part of follow-up collection at 16 years for NCDS and five or ten years for BCS70 cohort members. Paternal smoking status was categorised as smokers and non-smokers with respect to possible imprecise digit preference for number of cigarettes smoked. Social class derived from occupation and classified according to the Registrar General's social class was divided in low social class (<IIIm and below) and high social class. The Registrar General's social class covers seven categories of occupation: I, professional occupations; II, managerial and technical occupations; III, skilled occupations divided into (N) non-manual or (M) manual; IV, partly-skilled occupations; and V, unskilled occupations. Pre- and postnatal maternal smoking was dichotomised. Parental age was dichotomised at a cut off at 30 years of age for mothers and fathers.

Statistical analysis

Prevalence of type1 diabetes was calculated. Corresponding exact confidence intervals were based on the binomial distribution [3]. Crude and adjusted odds ratios and their respective confidence intervals were calculated using logistic regression analysis. Paternal smoking, maternal smoking in and during pregnancy, sex, maternal age, paternal age, number of siblings, social class and cohort (NCDS or BCS70) were *a priori* considered in the multiple regression model.

All calculations were carried out with the software package SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

The prevalence of type 1 diabetes mellitus was slightly higher in the NCDS cohort with 0.7% (95% CI 0.5–1.0%; n=38) compared to 0.4% (95% CI 0.3–0.6%; n=27) for the BCS70 cohort. Table 1 shows the general study population characteristics.

No association between diabetes and postnatal maternal smoking, maternal and paternal age, number of siblings or social class could be observed (Table 2). In addition, maternal smoking prior to or during pregnancy, had no impact on offspring's prevalence of type1 diabetes (data not shown).

In both cohorts, a difference in prevalence could be observed between female and male cohort members with 0.4% (95% CI 0.3–0.6%) and 0.7% (95% CI 0.5–0.9%), for males and females, respectively, when the cohorts were combined. Among those with diabetes, 22 (34%) of 65 had a father who smoked, compared with 5795 (51.7%) of 11,217 of those without diabetes. If the offspring's biological father smoked, the prevalence of type 1 diabetes was significantly reduced: 0.8% (95% CI 0.6–1.0%) for offspring of non-smoking fathers and 0.4% (95% CI 0.2–0.5%) for offspring of smoking fathers. This association could not be explained by the potential confounding factors as the odds ratios remained statistically significant after adjusting for maternal smoking, social class, maternal and paternal age, number of siblings and cohort (NCDS or BCS70) (Table 2). The multivariate analysis yielded an approximately halved risk for type 1 diabetes among offspring of paternal smokers (OR 0.48; 95% CI 0.29–0.80; Table 1).

This paper is concerned with pre-natal exposures associated with paternal smoking. However, as smoking was only recorded after the cohort members' births we have investigated the stability of paternal smoking behaviour over time and reported age at commencement of smoking. For BCS70, information on paternal smoking was available at children's age of five and ten years (Table 3). The proportion of smokers was similar for both ages, with a high kappa value for the dichotomised smoking variable of 0.75 (95% CI 0.73–0.76). Reported number of cigarettes smoked varied with time, producing a kappa value of 0.34 for the following categories: non-smoking, up to ten cigarettes, 10–20 cigarettes, 20–30 cigarettes and 30 or more cigarettes per day. In BCS70 88.5% (95% CI 87.3–89.7%) of smoking fathers started smoking by the age of 20 years.

Discussion

The prevalence of type 1 diabetes mellitus was slightly higher among British residents born in 1958 compared with British residents born in 1970 possibly due to longer follow-up. Maternal smoking prior, in, and during pregnancy, number of siblings, parental social class, maternal and paternal age were not associated with type 1 diabetes. Our *a priori* hypothesis predicted an increase in type 1 DM risk associated with paternal smoking, but this research revealed the opposite: a lowered prevalence of

Table 1 General characteristics of parents and offspring.

	n (%)		
	NCDS (n = 5214)	BCS70 (n = 6068)	Both cohorts (n = 11,282)
Offspring's characteristics			
Type 1 diabetes	38 (0.7)	27 (0.4)	65 (0.6)
Male sex	2619 (50.2)	3018 (49.7)	5637 (50.0)
More than one sibling	785 (15.1)	1728 (28.5)	2513 (22.3)
Parent's characteristics			
Paternal smoking	2899 (55.6)	2918 (48.1)	5817 (51.6)
Maternal smoking in pregnancy	1626 (31.2)	2527 (41.6)	4153 (36.8)
Postnatal maternal smoking	2370 (45.5)	2218 (36.6)	4588 (40.7)
Maternal age at birth > 30 years	1357 (26.0)	1131 (18.6)	2488 (22.1)
Paternal age at birth > 30 years	2198 (42.2)	2036 (33.6)	4234 (37.5)
Low social class (Registrar General's class > III)	3888 (74.6)	4164 (68.6)	8052 (71.4)

type 1 diabetes could be observed among offspring of smoking fathers. This association could not be explained by postnatal environmental tobacco exposure (maternal smoking after pregnancy), maternal smoking prior, and during pregnancy, number of siblings, parental social class, maternal and paternal age, or cohort. Additionally, it should be emphasised that a chance finding (type 1 error) is unlikely as the results were consistent across both cohorts with odds ratios of 0.4 for NCDS and 0.5 for BCS70. Although the direction of the association is not what we predicted, germ-line mutations or other mechanisms associated with paternal smoking may account for this phenomenon.

We could not observe an association between high paternal age and type 1 diabetes, whereas such an association was recently reported by two other studies [1, 8]. This may be due to lack of sample power since the reported sample size was up to 10 times higher with 991 [1] and 647 [8] type 1 diabetes cases and the adjusted reported effect was moderate with a relative risk of 1.5 for fathers of at least 35 years of age [1, 8].

Methodological considerations

Information on smoking was prospectively obtained through interviews avoiding recall bias and possible confounding associated with retrospective interviews of subjects. Results from other studies suggest that self reported smoking is accurate in general [14], although digit preference appears to be a problem if the precise number of cigarettes is an issue [10]. Since our analysis focused on a dichotomised smoking status, self-reported questionnaires should allow for sufficient classification of smokers and non-smokers.

Table 2 Unadjusted and adjusted results for paternal smoking and offspring's type 1 diabetes mellitus.

Explanatory variable	Odds ratio for type 1 diabetes mellitus (95% CI)			
	NCDS (n = 5214)	BCS70 (n = 6068)	Both cohorts (n = 11,282)	
	Adjusted	Adjusted	Crude	Adjusted
Paternal smoking (y/n)	0.37 (0.18–0.75)	0.54 (0.24–1.27)	0.48 (0.29–0.80)	0.44 (0.25–0.75)
Maternal smoking in pregnancy (y/n)	1.35 (0.58–3.12)	1.45 (0.52–4.04)	1.00 (0.61–1.67)	1.38 (0.71–2.67)
Postnatal maternal smoking (y/n)	1.10 (0.49–2.49)	0.66 (0.21–2.02)	0.91 (0.55–1.50)	0.91 (0.47–1.78)
Male sex	1.56 (0.81–3.01)	1.72 (0.79–3.76)	1.61 (0.97–2.65)	1.61 (0.97–2.65)
Maternal age at birth > 30 years	0.77 (0.31–1.91)	1.50 (0.42–5.27)	0.97 (0.54–1.76)	0.96 (0.46–2.02)
Paternal age at birth > 30 years	0.93 (0.42–2.06)	0.55 (0.18–1.67)	0.91 (0.55–1.52)	0.76 (0.40–1.45)
More than 1 sibling	2.39 (1.12–5.11)	1.02 (0.39–2.64)	1.24 (0.71–2.16)	1.63 (0.90–2.97)
Low social class (Registrar General's class > III)	0.75 (0.37–1.51)	0.99 (0.43–2.27)	0.84 (0.50–1.41)	0.84 (0.49–1.43)
1970 cohort (reference 1958 cohort)	–	–	0.61 (0.38–0.99)	0.50 (0.30–0.84)

Table 3 Paternal smoking behaviour in BCS70.

Paternal smoking at children's age 5 years	Paternal smoking at children's age 10 years	
	No	Yes
No	3722	441
Yes	600	3522

Cohen's kappa: 0.75 (95% CI 0.73–0.76).

We hypothesised that paternal smoking *prior to conception* may influence type 1 DM risk. However, information on paternal smoking prior to pregnancy was not available for either cohort. To investigate whether fathers who smoked were likely to have done so prior to conception of their offspring, we undertook two sets of analysis; to investigate the stability of paternal smoking over time and into the age at which fathers began smoking. Smoking behaviour did not substantially change for a time interval of five years between interviews in BCS70. This indicates that our measures of smoking at later ages indicate that smoking at an earlier age is probable in the majority, as attempts to give up smoking are rarely successful [9]. We found that the majority of fathers who smoked began to smoke by the age of 20 years and thus, the majority are likely to have smoked prior to conception. Additionally, the information on parental smoking was reported by the parents themselves, increasing reliability of these measures as they are not subject to reporting or recall bias associated with, for example, case/control status.

Differential loss of smoking fathers indicating social and cultural circumstances seems to be unlikely as causal explanation, as adjustment for social class, which is associated with smoking and a good indicator of cultural and material circumstances, did not notably alter the association.

Potential confounding due to factors that vary with smoking status such as diet cannot be ruled out. Since maternal smoking showed no association with type 1 diabetes in offspring, it seems more likely that this association specifically operates through the father. Additionally, the local restriction to one country and inclusion of cohort members born at similar time intervals in the year minimises the potential of confounding due to factors that vary across different countries or seasonal dependent associations.

Reverse causation due to fathers with type 1 DM giving up or not starting smoking seems to be unlikely, since exclusion or adjustment for fathers (BCS70) or first-degree relatives (NCDS) with diabetes did not change the results (data not shown).

Differential selection bias due to analysis limited to those with complete information as an explanation of our results seems unlikely, since proportions of key variables were comparable to the entire population with available information on these variables: type 1 diabetes 0.6% in restricted sample compared with 0.6% in entire sample, paternal smoking with 52% (restricted sample) and 54% (entire sample), Registrar General's class < IIIm with 72% (restricted sample) and 73% (entire sample). Additionally, distributions of parental age were similar: mean of mother's/father's age was 26.7/29.5 years in the restricted sample and 26.7/29.9 in the entire sample.

Assessment of diabetes type was based on whether cohort members injected insulin or not. Although not a perfect marker of type 1 DM, it is reasonably reliable at such young ages and the vast majority who reported this are likely to have the disease. Further evidence that this assessment successfully identifies type 1 DM and not type 2, is that maternal smoking is not associated with our marker of type 1 DM: a previously reported association of maternal smoking with type 2 DM in offspring [13]. Additionally, the association with paternal smoking was specific to type 1 and not type 2 diabetes mellitus, for which no association could be observed to paternal smoking (data not shown).

Possible biological mechanisms

Our reason for considering paternal smoking as a risk for type 1 DM was because of previously reported associations of type 1 DM with paternal age [1, 8]. Greater age is associated with accumulating germ-line mutations. For example, there is an increased occurrence of Crouzon's syndrome and Pfeiffer's syndrome among offspring of old fathers [7]. Smoking increases mutation risk, indicated by the risk of early pregnancy loss associated with fathers who are heavy smokers [18]. Cigarette smoking has been shown to accelerate damage to telomeres [17]. These are the regions in genetic material between genes, which offer some protection against damage to the genes; thus, telomere damage associated with smoking may increase the risk of germ-line mutations. Due to these findings paternal smoking might increase the risk of type 1 DM through a mechanism involving germ cell mutations. However, the observed association was not in the predicted direction, but germ-line mutations may help to explain our findings.

Since pre- and postnatal environmental exposure to tobacco products through mother's smoking did not affect prevalence of type 1 diabetes, the positive association between paternal smoking and decreased prevalence of type 1 diabetes associations with fathers' smoking are not confounded by mothers' smoking, supporting a role for paternal germ cells. Since the main contribution of paternal germ cells to the offspring after conception is delivery of genetic information, germ-line mutations could play a possible role. Germ-line mutations are likely to be related to paternal smoking: These findings point to the potential role of tobacco inhaled products on sperm production, sperm quality and interrelated germ-line mutations. Since these possible mutations could not be balanced by maternal chromosomes,

these mutated genes may be dominant. Another study using birth cohort material has reported an association between paternal smoking prior to conception of offspring and growth [15]. The authors interpreted this association as a male-line transgenerational response. Since sperm cells are still dividing after births and maternal egg cells do not, the described association might reflect that the prenatal risk to sperm cells by environmental factors might be larger than to ova.

Other mechanisms are possible, including the influence of direct exposure of the offspring to tobacco smoke. Paternal smoking was associated with an increased risk of atopy in a population-based study [11]. Atopic diseases have been reported to be protective against type 1 diabetes possibly due to immunological mechanisms [2, 12, 16]. Thus, paternal smoking could potentially alter type 1 diabetes risk through modified immunological responses.

Although we found a reduced prevalence of type 1 diabetes associated with paternal smoking, this finding may not be considered as a reason for men to smoke, due to the numerous health risks, such as cardiovascular disease and lung cancer, related to smoking. However, these findings suggest to further study the association between paternal smoking, type 1 diabetes, immunological function in offspring, as well as possible studies on smoking and spermatogenesis. In particular, studies on smoking and spermatogenesis could provide an insight into genetic mechanisms involved into development of type 1 diabetes. Paternal exposures may be important in the etiology of type 1 DM.

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