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Parental diabetes and birth weight of offspring: intergenerational cohort study

Elina Hyppönen, George Davey Smith, Chris Power

According to the fetal insulin hypothesis, shared genetic factors lead to suboptimal prenatal growth and to insulin resistance in the parent's later life.¹ If this is true, we expect non-insulin dependent diabetes in parents to be associated with lower birth weight among their offspring. Some evidence supports an inverse association between birth weight of offspring and paternal diabetes.^{2,3} The association between fetal macrosomia and a mother's diabetes during pregnancy has been established,⁴ however this is likely to be caused by acute metabolic effects. We used data from the large cohort study of British births in 1958 to evaluate whether a father's non-insulin dependent diabetes or a mother's diabetes starting after childbirth is associated with the birth weight of their offspring.

Participants, methods, and results

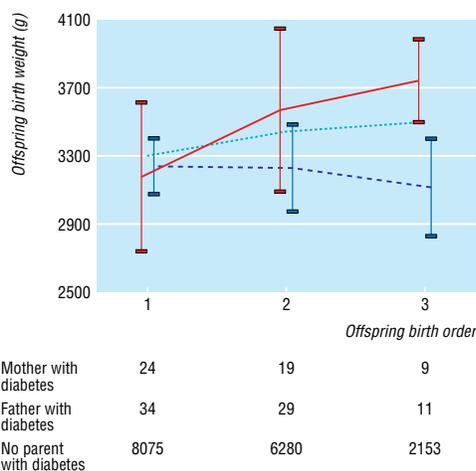
Members of the cohort were born during the week 3-9 March 1958.⁵ Between 1999 and 2000, 96 cohort members reported having diabetes (controlled by diet or tablets). We excluded participants with other types of diabetes (n=100).

Of the 11 276 participants contacted at age 41 years, 3777 mothers and 4364 fathers gave information on the birth characteristics for at least one (range 1-9) singleton liveborn child. A total of 34 men with diabetes had had children, and 24 women had become diabetic after childbirth. We used random effects models on birth weight (adjusted for gestational age) to allow for dependence between a parent's subsequent births. North Thames Multicentre Research Ethics Committee approved the 41 year survey.

The offspring of the fathers with diabetes weighed on average less by a difference of -186 g (95% confidence interval -330 g to -44 g) than other children (figure). Father's adult height or social class did not explain the association between a father's diabetes and the birth weight of his offspring. The child's birth order made no difference to the effect of a father's diabetes on the birth weight of his offspring (P=0.21).

The mean difference in the birth weight of offspring between diabetic and non-diabetic women (133 g; -29 g to 296 g) was not significant (P=0.11), but there was a positive interaction between mother's diabetes and child's birth order (P<0.001) (figure). The association between mother's diabetes and offspring birth weight seen in second born and subsequent births was not seen for first born babies (difference +15 g; -172 g to 202 g). The data showed a decrease in birth weight per year from birth to the onset of diabetes in the mother (change per year of -54 g; -147 g to 38 g).

When we restricted the analysis to first born babies born at least 10 years before the onset of the mother's diabetes (n=17), offspring had lower birth weight (decrease of 156 g; -377 g to 65 g).



Birth weight of offspring as a function of birth order for parents with or without diabetes; numbers relate to each birth order. Error bars are 95% confidence intervals

Comment

Diabetes in fathers and the birth weight of their offspring are strongly associated, according to data from the 1958 birth cohort. Our finding is consistent with reports of increased risk of non-insulin dependent diabetes for the fathers of children with low birth weight in native Americans and Swedish populations.^{2,3}

In contrast to the paternal effect, diabetes in the mother increases the birth weight of offspring.⁴ The association between maternal diabetes and the child's birth weight, however, is likely to reflect immediate effects of the mother's metabolic control, possibly masking genetic effects operating in the opposite direction. We observed some evidence for a lower birth weight for offspring of the mothers who were likely to have been free of metabolic disturbances related to diabetes at the time of childbirth.

The interaction between birth order and diabetes for mothers (not fathers) may also reflect the different intervals between the onset of diabetes and the timing of births. Our findings support the hypothesis that common genetic factors contribute both to the risk of non-insulin dependent diabetes and decreased prenatal growth.¹

We thank Leah Li for computational advice and Peter Shepherd for advice on the data. We took data from the National Child Development Survey's composite file including selected perinatal data and sweeps one to five, Centre for Longitudinal Studies, Institute of Education, National Birthday Trust Fund, National Children's Bureau, City University, Social Statistics Research Unit, and Data Archive Distributor, Colchester, Essex.

Contributors: EH drafted the paper and carried out statistical analyses. All authors participated in developing the idea, evaluation of the results, and contributed to the final version of the paper. EH is guarantor.

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Incidence of coronary heart disease in a health authority in London: review of a community register

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Strategies to reduce deaths from coronary heart disease need to take into account clinical presentation of the disease.¹⁻⁴ We used a coronary heart register to examine non-fatal and fatal presentations of the disease in a health authority in outer London.

Methods and results

Bromley Health Authority employs 151 general practitioners with a total of 295 584 patients on their lists. The Bromley coronary register prospectively identified all incidences of coronary heart disease in people aged 16-74 from September 1996 to August 1997 for men and from September 1996 to May 1998 for women.

The health authority invited general practitioners to refer new cases of suspected exertional angina to a daily "rapid access" clinic for patients with chest pain at Bromley Hospital. All patients using the clinic and cardiology outpatients were screened. Inpatients admitted to the hospital through its emergency department were screened and followed up on the ward until diagnosis. The two coroner's offices for the authority identified sudden deaths in the community and inpatient deaths that had been reported to them. The authority provided data on all Bromley residents admitted to hospitals in England and Wales with ICD-9 (international classification of diseases, ninth revision) codes for coronary artery disease (410-414). We retrospectively audited a random 8/59 general practices for new prescriptions of nitrates (for angina); we found four missed cases during the registration period. Ethical approval was provided by Bromley local research ethics committee.

A panel of three consultant cardiologists reviewed the patients' presenting history, clinical examination, electrocardiogram, results of blood tests, results of tests measuring stress during exercise, myocardial perfusion scans, and necropsy information where available; they did not review coronary angiograms. The cardiologists classified cases as sudden cardiac death (death attributed

to coronary artery disease), acute myocardial infarction (typical history and resting electrocardiogram changes and creatine kinase concentrations twice the normal upper limit), unstable angina (typical chest pain at rest or rapidly worsening exertional pain without raised creatine kinase concentrations), or exertional angina (typical history and information from exercise testing or perfusion scanning, which was available in 92% of cases) (table 1). To test whether decisions were reproducible, 100 randomly selected cases (about 10% of the total) were reclassified; agreement was good (Cohen's $\kappa=0.86$).

We found 378 cases of men and 242 cases of women who first presented with coronary heart disease, all in the age group 25-74; we found no cases aged 16-24. The incidence of the disease was 414/100 000 population per year in men and 147/100 000 population per year in women. Incidences were greater in older people in both sexes, and at all ages they were significantly higher in men.

Comment

Most coronary heart disease presents in treatable form. Considerable potential exists to reduce the risk of recurrent disease and specifically to prevent patients with angina and well preserved ventricular function from progressing to myocardial infarction and death.⁵ We found that 86% of men and 87% of women present alive to medical services with their first presentation of coronary heart disease; 54% of men and 65% of women have preserved myocardium.

We thank the coroners for their help.

Contributors: SJS ran the clinic for people with chest pain; KFF primarily wrote the paper; DAW designed and supervised the study, reviewed cases, and contributed to the manuscript; KS and AS ran the register; MW did the statistical analysis; and FA and EL reviewed the cases. All authors reviewed and revised the manuscript. DAW is guarantor.

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Incidence of coronary heart disease per 100 000 population per year in people aged 25-74 in Bromley Health Authority

Presentation	Men		Women	
	Incidence (95% CI)	%	Incidence (95% CI)	%
Exertional angina	172 (146 to 201)	41	77 (63 to 91)	52
Acute myocardial infarction	133 (110 to 159)	32	32 (24 to 42)	22
Sudden cardiac death	57 (43 to 75)	14	19 (13 to 27)	13
Unstable angina	52 (39 to 70)	13	19 (13 to 27)	13