Journal of Epidemiology and Community Health 1991; 45: 299–301

Effect of fathers' age and birth order on occurrence of congenital heart disease

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Abstract

***Study objective*—The aim was to examine if there is an effect of fathers' age and of birth order on the occurrence of congenital heart disease.**

***Design*—This was a hospital based case-referent study including use of birth defects surveillance data.**

***Subjects*—Subjects were 497 cases of congenital heart disease aged between 3 months and 5 years, born in Beijing and Hebei Province, China; 6222 children without congenital heart disease serve as reference baseline.**

***Measurements and main results*—With stratified analysis and logistic regression analyses, congenital heart disease was found to be associated with fathers' age <25 years (odds ratio 2·63), independent of mothers' age and of birth order. There was also evidence to show a higher birth order effect on the occurrence of congenital heart disease independent of parental ages.**

***Conclusion*—Higher birth order and fathers aged <25 years were both independently associated with some categories of congenital heart disease and with congenital heart disease overall.**

Congenital heart diseases are very common and cause many deaths and disabilities in infants and children. The effect of maternal and paternal characteristics on the occurrence of congenital heart disease has only been addressed by a few workers, for example Kenna *et al*[1] and Rothman *et al*,[2] with contradictory results. In order to improve perinatal preventive services and to promote studies on the aetiology of birth defects, the effect of parental ages and of birth order on the occurrence of congenital heart disease in Beijing and Hebei Province, China, was examined epidemiologically in 1988.

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Accepted for publication January 1991

Methods

STUDY SUBJECTS

Case group

Criteria of inclusion for study cases were as follows. (1) Diagnosis was one of five commonly seen types of congenital heart disease: ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, and pulmonary stenosis, all without Down's syndrome. (2) Patients born in Beijing and Hebei were enrolled from cardiology wards and cardiology outpatient departments in six large hospitals from March to November, 1988. These were almost the only places where cardiac operations could be done in this area. (3) Diagnosis of congenital heart disease was based on invasive (operation or cardiac catheterisation) and/or non-invasive (physical examination, ECG, *x* ray, and B ultrasonography or Doppler echocardiography) findings. (4) Subjects were Beijing or Hebei residents aged <5 years.

Non-case group

This group included two kinds of control. (1) Hospital controls: by group matching, 222 eligible inpatients from medical and surgical wards of the participating hospitals were defined as controls if they were aged 3 months to 5 years, were without heart trouble, and were resident in Beijing or Hebei. (2) Community referents: from a dataset of around 47 000 total births in Beijing and one region of Hebei Province (October 1986 to September 1987) collected by Beijing Medical University Birth Defects Surveillance Programme, 6000 newborns without birth defects were drawn by systematic sampling to form a new community referents data set.

DATA COLLECTION

During both face to face interview with the mother and/or the father and in the mail survey, the same structured questionnaire was used. The principal items were parental ages at time of birth, and past and present obstetric history (parity, outcome of pregnancy, etc.). The interviewers were one of the authors (SYZ) and four trained nurses.

The response rate to the mail questionnaires was 82·7% (182/220) after one or two letters, and 156 (71% of 220) questionnaires were complete and usable. The comparability between cases and non-cases was very good with regard to sex (male 54% *v* 52%), place of residence (Beijing 69·8% *v* 69·5%) and low birth weight (6·2% *v* 5%).

ANALYTIC METHODS

The ordinary χ^2 test was used to compare the distribution of birth order and parental ages in the case and non-case groups. The frequent finding of a correlation among parental ages and birth order prompted us to attempt to differentiate various effects on the occurrence of congenital heart disease. Hence, unconditional logistic regression analysis was performed separately for four congenital heart disease categories (see below) and for overall congenital heart disease to detect independent risks. Regression was used to relate paternal and maternal ages (in single years) and birth order (count) to whether a birth defect occurred (d = 1 or 0).

The following cases were dropped from the analysis of specific types of congenital heart disease: (a) any case in which ventricular or atrial septal defect, patent ductus arteriosus, or tetralogy of Fallot was not the only anomaly present; (b) pulmonary stenosis and other categories which were relatively infrequent. In total 422 cases were involved in these analyses. The logistic model was as follows:

$$\ln \frac{P(\chi)}{1-P(\chi)} = \text{logit}[pr(d=1/x)] = \alpha + \sum_{k=1}^{3} Bk \cdot Xk$$

Stratified analyses (Mantel-Haenszel) were performed with data on birth order and parental ages.

Results

The years of birth of the cases and hospital controls were 1983–1988, and the 6000 referent controls were born in 1986 and 1987. During these periods there was no great change in government policy on family size which was likely to have affected the parity composition of the sample.

Table I Comparison of parental ages and birth order in case and non-case groups

Groups	No of subjects	Fathers' age (years)				Mothers' age (years)				Birth order		
		<25	25–29	30–34	35–	<25	25–29	30–34	35–	1	2	3–
Case	497	145	266	72	14	211	228	51	7	390	86	21
Non-case	6222	957	3959	1065	241	2328	3176	604	114	5678	485	59
			$\chi^2=64{\cdot}107$				$\chi^2=6{\cdot}114$				$\chi^2=98{\cdot}811$	
			$p<0{\cdot}001$				$p>0{\cdot}05$				$p<0{\cdot}001$	
OR		2·27	1				NA			1	2·86	
95% CI		1·85–2·79					NA				2·27–3·60	

OR = odds ratio; CI = confidence interval; NA = not assessed

Table II Logistic regression analyses of birth order and parental ages versus congenital heart disease

	Regression coefficient	OR	95% CI of OR
	Ventricular septal defect		
Birth order	1·044	2·840*	2·220–3·634
Paternal age	−0·159	0·853*	0·803–0·906
Maternal age	0·011	1·014	0·958–1·074
	Patent ductus arteriosus		
Birth order	0·202	1·224	0·611–2·453
Paternal age	−0·135	0·874*	0·796–0·960
Maternal age	0·058	1·060	1·008–1·115*
	Tetralogy of Fallot		
Birth order	1·240	3·454*	2·396–4·980
Paternal age	−0·166	0·847*	0·770–0·932
Maternal age	0·046	1·047	0·987–1·112
	Atrial septal defect		
Birth order	0·760	2·139*	1·109–4·126
Paternal age	−0·108	0·898	0·780–1·034
Maternal age	0·033	1·034	0·932–1·150
	Overall congenital heart disease		
Birth order	1·082	2·951*	2·434–3·579
Paternal age	−0·171	0·843*	0·807–0·879
Maternal age	0·034	1·035	0·997–1·074

OR = odds ratio; CI = confidence interval
*Odds ratios with significant 95% confidence interval

Table III Summary of independent effects on occurrence of different types of congenital heart disease (CHD), based on logistic regression

Category of CHD	No of cases	Independent effects		
		Birth order	Fathers' age	Mothers' age
VSD	254	risk	protective	no
PDA	69	no	protective	trivial risk
TOF	67	risk	protective	no
ASD	32	risk	no	no
Overall CHD	422	risk	protective	no

VSD = ventricular septal defect; PDA = patent ductus arteriosus; TOF = tetralogy of Fallot; ASD = atrial septal defect

UNSTRATIFIED DATA ANALYSIS

From the unstratified data comparison it was found that the fathers' age and the birth order distributions, but not the mothers' age, were significantly different in the case group from the non-case group (table I).

Crude data analysis of both birth order and paternal age with respect to the prevalence of congenital heart disease showed a significantly higher probability of congenital heart disease with increasing birth order and with young fathers (<25 years), as shown in the bottom of table I.

LOGISTIC REGRESSION ANALYSES

The results are displayed in detail in table II, with an overview of the various effects in table III. There was a clearly increased risk of Fallot's tetralogy, ventricular septal defect, atrial septal defect, and/or overall congenital heart disease when birth order was 2 or higher, and when fathers were <25 years old. The likelihood of the offspring getting congenital heart disease can be roughly estimated from the data in table II. For instance, birth order 2 or higher appears to increase the overall risk of congenital heart disease in babies nearly two fold (1·95 times), independent of parental ages (odds ratio 2·95). The risk of fathering a baby with any form of congenital heart disease will probably increase by 19% per year younger than age 24 years, since odds ratio = 0·84 (1/0·84 = 19%).

STRATIFIED ANALYSIS

Stratified analysis controlling either for fathers' or mothers' age consistently showed a substantial independent birth order effect, with odds ratios of 3·54 and 3·27 respectively (tables IV, V). Table VI shows that when birth order was 1 and father younger than 25 years, the risk of fathering babies with a heart defect was indeed increased, while in the second stratum the odds ratio of 1·44 was not statistically significant. So apart from birth order as a confounder, there was a little interaction between young fathers' age and birth order. A similar stratified analysis adjusting for mothers' age also showed the consistent effect of a very young father on the occurrence of congenital heart disease, which was independent of mothers' age (data not shown).

Discussion

All patients with congenital heart disease in this study were diagnosed by cardiologists. All interviewers received specific training before participation. Twenty nine out of 360 (18%) questionnaires went through duplicate surveys by different observers. The Kappa test was satisfactory ($\kappa = 0{\cdot}92$, $Z = 37{\cdot}58$, $p < 0{\cdot}01$). Eighteen of 256 subjects surveyed by mail had been re-examined in the outpatient departments, and the agreement rate on items in the questionnaire was 98·5%. However, the representativeness of the data was not very satisfactory, because some severe cases might

Table IV Stratified analysis of birth order, adjusting for paternal age

Age of father (years)	*Birth order*	*Case*	*Non-case*	*OR*	*95% CI*
<30	1	351	4673		
	2–	60	243	3·3	2·4–4·5
30 and	1	39	301		
over	2–	47	1005	4·0	2·5–6·4
		497	6222	ORmh = 3·54	2·7–4·5

OR = odds ratio; ORmh = Mantel-Haenszel OR; CI = confidence interval

Table V Stratified analysis of birth order, adjusting for maternal age

Age of mother (years)	*Birth order*	*Case*	*Non-case*	*OR*	*95% CI*
<30	1	368	5192		
	2–	71	312	3·2	2·4–4·3
30 and	1	22	486		
over	2–	36	232	3·4	1·9–6·2
		497	6222	ORmh = 3·27	2·5–4·2

OR = odds ratio; ORmh = Mantel-Haenszel OR; CI = confidence interval

Table VI Effect of father's young age on heart defects, controlling for birth order

Birth order	*Father's age (years)*	*Case*	*Non-case*	*OR*	*95% CI*
1	<25	137	928	2·77	2·21–3·47
	25–	253	4750		
2–	<25	8	29	1·44	0·59–3·40
	25–	99	515		
		497	6222	ORmh 2·63	2·12–3·27

OR = odds ratio; ORmh = Mantel-Haenszel OR; CI = confidence interval

have died before enrolment and also because very mild cases of congenital heart disease were undetected in our series. The fact that the community referents may have contained a few real cases of congenital heart disease probably did not matter very much.

In contrast to MacMahon's report of 1952,[5] several more recent investigations have found that birth order >2 consistently increases the risk of having congenital heart disease, for example Fallot's tetralogy,[1] patent ductus arteriosus,[2] and all congenital heart disease.[6] With respect to effect of birth order and of paternal age, logistic regression and the Mantel Haenszel procedure used in this study generated mutually supportive results which favour the previous evidence that birth order >2 is a risk factor, and suggest that low paternal age is also associated with increased risk. These findings were very similar for ventricular and atrial septal defects, patent ductus arteriosus, and Fallot's tetralogy, except that birth order appeared to have little effect on the risk of patent ductus arteriosus. This similarly argues for the homogeneity of congenital heart disease as a group.

With regard to maternal age effect, our data agreed with what MacMahon reported in 1952, that there is no association between congenital heart disease and elderly mothers. The fathers' age effect presents a somewhat complicated issue. With the Mantel-Haenszel procedure and logistic regression, Lian *et al*[3] reported that men aged 35+ or 40+ years had an increased risk of fathering babies with congenital heart disease, especially babies with ventricular and atrial septal defects. However, the present work showed not the slightest evidence to support an "elderly father" effect. However, the effect of younger fathers' age (less than 25 years) on the occurrence of congenital heart disease overall and of ventricular septal defect, patent ductus arteriosus, and Fallot's tetralogy in particular, has not, so far as we are aware, been reported before. The study by Lian *et al*[3] did not look at the effect of young fathers.

As the results of this study may be biased, the strongly suggestive effect of young fathers and high birth order on the occurrence of congenital heart disease in offspring is well worth reassessing. Clarification of these issues would certainly help in the investigation of causes of congenital heart disease and guide activities related to birth planning.

The authors wish to express their thanks to clinical staff of Beijing Municipal Children Hospital, Fu-Wai Hospital, Beijing, An-Zen Hospital, Beijing, Beijing Medical University First Hospital, and Hebei Medical College Second and Third Hospitals for their kindness and great assistance, without which this work could hardly have been carried out.

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