

## Parental cigarette smoking and the risk of congenital heart septal defects

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**Key words:** case-control study; smoking; pregnancy; septal defects.

**Summary.** The objective of this study was to determine the association between parental cigarette smoking and the risk of congenital heart septal defects in Kaunas infant population in 1995–2005.

**Material and methods.** An epidemiological case-control study was conducted. The study comprised 261 newborns with congenital heart septal defects (cases) and 1122 randomly selected newborns without any defects (controls), born in Kaunas city during 1995–2005. Information on potential risk factors of newborns' health was collected through an interview with parents using standardized questionnaires. Multivariate logistic regression analysis was used to assess the association between parental smoking and septal defects while controlling for possible confounders.

**Results.** According to the validated registry, 371 newborns with congenital heart malformations were born in Kaunas city during 1995–2005; 70.3% of cases had ventricular and/or atrial septal defects. After adjustment for possible confounding factors – maternal education, social status, marital status – a statistically significant relationship was observed between parental smoking and congenital heart septal defects. Parental, maternal, and paternal smoking was significantly associated with a 2.27-fold (adjusted OR=2.27; 95% CI, 1.49–3.46), 2.2-fold (adjusted OR=2.20; 95% CI, 1.01–4.79), and 1.45-fold (adjusted OR=1.45; 95% CI, 1.03–2.03) increased risk of defects if compared with nonsmoking parents.

**Conclusions.** According to the results of our study, parental smoking was significantly associated with an increased risk of congenital heart septal defects in infants.

### Introduction

Congenital heart defects are among the most common birth defects (1, 2), and they remain a major cause of death in infancy and childhood (3). The prevalence of congenital heart defects is estimated to be 4 to 10 cases per 1000 live births (1, 2, 4, 5), and the most frequent types of these malformations are septal defects (2, 6, 7). The part of ventricular and atrial septal defects closes spontaneously within the first year of life (8); other children with congenital defects require surgical intervention (8, 9).

The etiology of most congenital heart anomalies is unknown. About 85% of these defects are caused by complex interaction between environmental teratogens and genetic factors (1). It is considered that the effects of harmful environmental factors on female organisms may cause the occurrence of birth defects (10), especially if they are affected during critical period, i.e., from three months before pregnancy through the end of the first trimester (11).

Scientific studies have reported that maternal smoking during pregnancy is associated with an increased risk of congenital heart defects (12, 13) and septal defects (6). However, other studies have not found a significant association of maternal smoking with all septal defects (14). Relatively few studies have examined the relationship between congenital heart malformations and risk of parental smoking (13, 15, 16). According to data of the validated registry in Kaunas city during 1995–1998, paternal and maternal smoking increased the risk of congenital heart defects (13), but the importance of a hazardous habit in the risk of septal defects in infants has not been evaluated. The objective of this study was to determine the association between parental cigarette smoking and risk of congenital heart septal defects in Kaunas infant population in 1995–2005.

### Material and methods

In this study, we analyzed data from a case-control

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study on the risk of congenital heart defects in Kaunas infant population born during 1995–2005. We used the database of the Kaunas newborns' register, containing information on newborn's birth date, gender, health status, and mother's residence. This database served as an initial source for the registration of congenital heart malformations. To register all the cases of congenital heart defects, diagnosed at delivery or later, we analyzed all available information from outpatient and inpatient settings of Kaunas city.

A total of 261 cases with confirmed clinical diagnosis of septal heart defects (International Classification of Diseases, 10th revision, codes Q21.0–Q21.1) were selected from the database. The control group comprised 1122 randomly selected infants without any defects.

Information on potential risk factors of newborns' health was collected by using standardized questionnaires through a personal interview of case and control mothers at their home or by telephone. The questionnaire recorded information on selected risk factors, such as maternal age at delivery, education, marital status, occupation, health risk behaviors (maternal and paternal smoking). Mothers were divided into groups by age (less and 19 years, 20–29 years, 30–34 years, 35 years and older), educational level (primary or basic; secondary; and advanced vocational or higher), marital status (married or cohabiting and single), and occupation (office workers, housewives, workers, professional workers, farmers, and students). Data on parental smoking, its duration before and during pregnancy, and number of cigarettes smoked were collected. Information about hazardous habits was estimated by respondents' answers.

Analysis was performed using the statistical package SPSS 13.0 for Windows. The distribution of selected risk factors of newborns' health between cases and controls was assessed; crude and adjusted odds ratios (OR) along with 95% confidence intervals (CI) were calculated. A value of  $P < 0.05$  was considered statistically significant. The Mantel-Haenszel technique was used to estimate the association between maternal smoking and septal defects in infants while controlling for educational level. Multivariate logistic regression analysis was used to assess the relationship between parental smoking and congenital anomalies while controlling for possible confounders. The variables that were detected as statistically significant in the univariate analysis and considered as potential confounders were included into the multivariate models.

## Results

According to the validated registry data, 371 newborns with congenital heart defects were born in Kaunas city during 1995–2005. The most common cardiac malformations were ventricular and atrial septal defects. They represented 70.3% of all registered cardiovascular malformations. There were 79 (21.3%) cases with ventricular septal defects (Q21.0), and 39 (10.5%) newborns had atrial septal defects (Q21.1). One hundred forty-three (38.5%) newborns had septal defects with other cardiovascular malformations; of the 143 cases, 27 (7.3%) had both (ventricular and atrial) septal defects.

Sociodemographic characteristics of case and control mothers are shown in Table 1. According to our data, the mean maternal age at delivery was similar for cases and controls ( $27.61 \pm 5.56$  years and  $27.35 \pm 5.55$  years, respectively). Being single/unmarried was associated with an increased risk of septal defects. The odds ratio for single mothers to deliver infants with septal defects was 1.76 (95% CI, 1.14–2.71;  $P < 0.01$ ) if compared to married or cohabiting women.

According to our results, the risk of delivering a newborn with septal defects was 4.02-fold higher among mothers with primary or basic education (95% CI, 2.12–7.61;  $P < 0.001$ ), while women with secondary education had a 1.48-fold increased risk (95% CI, 1.11–1.98;  $P < 0.01$ ) if compared with advanced vocational or higher education group. The analysis of maternal occupations showed that housewives and workers were more likely to deliver newborns with defects (OR=1.51; 95% CI, 1.05–2.15 and OR=1.54; 95% CI, 1.09–2.17, respectively;  $P < 0.05$ ) than office workers.

To assess association between septal defects in newborns and maternal smoking, analysis was performed. According to our data, 29.2% of case mothers smoked before the pregnancy and 6.1% during the first trimester (Table 2). Maternal smoking before pregnancy increased the risk of septal defects in infants from 2 to 3 times depending on duration of smoking and number of cigarettes smoked per day. The risk to deliver a newborn with defects was more than twice higher among women who smoked during the first trimester (OR=2.36; 95% CI, 1.27–4.37;  $P < 0.01$ ) if compared with nonsmoking women.

Our results showed that the association between septal defects and maternal smoking, while controlling for educational level, was statistically significant ( $P < 0.001$ ) (Table 3). Smoking women were more likely to deliver infants with septal defects (OR<sub>MH</sub>=2.05; 95% CI, 1.47–2.85) than nonsmoking women.

Table 1. The proportions of case and control mothers and odds ratios to deliver a newborn with septal defects according to maternal sociodemographic factors (a univariate analysis, 1995–2005)

Risk factor	Cases		Controls		Crude odds ratio	
	N (261)	%	N (1122)	%	OR	95% CI
Maternal age at delivery (years):						
20–29	161	61.7	683	60.9	1.00	
≤19	11	4.2	42	3.7	1.11	0.56–2.20
30–34	51	19.6	261	23.3	0.82	0.58–1.17
≥35	33	12.6	136	12.1	1.02	0.67–1.56
No data	5	1.9	0	0		
Marital status:						
Married or cohabiting	224	85.8	1038	92.5	1.00	
Single	32	12.3	84	7.5	1.76**	1.14–2.71
No data	5	1.9	0	0		
Maternal education:						
Advanced vocational/higher	138	52.9	741	66.0	1.00	
Secondary	99	37.9	357	31.9	1.48**	1.11–1.98
Primary/basic	18	6.9	24	2.1	4.02***	2.12–7.61
No data	6	2.3	0	0		
Occupation:						
Office worker	76	29.1	441	39.3	1.00	
Housewife	71	27.2	273	24.2	1.51*	1.05–2.15
Worker	84	32.2	316	28.2	1.54*	1.09–2.17
Farmer	1	0.4	4	0.4	1.45	0.16–13.15
Professional worker	3	1.1	20	1.8	0.87	0.25–3.00
Student	18	6.9	67	6.0	1.56	0.87–2.76
No data	8	3.1	1	0.1		

OR, odds ratio; CI, confidence interval; \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

Table 2. The odds ratios for septal defects associated with maternal smoking among newborns (a univariate analysis, 1995–2005)

Risk factor	Cases		Controls		Crude odds ratio	
	N (261)	%	N (1122)	%	OR	95% CI
Maternal smoking <sup>a</sup> :						
No	175	67.0	945	84.2	1.00	
Yes	76	29.2	177	15.8	2.31***	1.69–3.17
No data	10	3.8	0	0		
Maternal smoking (cigarettes/day) <sup>a</sup> :						
None	175	67.0	945	84.2	1.00	
<10	58	22.3	152	13.6	2.06***	1.46–2.90
10–20	15	5.8	25	2.2	3.24***	1.67–6.27
>20	3	1.1	0	0		
No data	10	3.8	0	0		
Duration (in years) of smoking before pregnancy:						
None	175	67.0	945	84.2	1.00	
1–2 years	13	5.0	38	3.4	1.84	0.96–3.53
3 years	12	4.6	21	1.9	3.08**	1.49–6.38
≥4 years	51	19.6	117	10.4	2.35***	1.63–3.39
No data	10	3.8	1	0.1		
Maternal smoking during pregnancy:						
No	102	39.1	602	53.7	1.00	
Yes	16	6.1	40	3.6	2.36**	1.27–4.37
No data	143	54.8	480	42.7		

OR, odds ratio; CI, confidence interval; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; <sup>a</sup>smoking before and during pregnancy.

Table 3. The association between maternal smoking and congenital heart septal defects among newborns while controlling for educational level (stratified analysis)

Risk factor (education/smoking)	Cases (N)	Controls (N)	OR (95% CI)
Advanced vocational/higher nonsmoking	113	661	1.00
Advanced vocational/higher smoking	24	80	1.75* (1.06–2.88)
Secondary nonsmoking	56	269	1.00
Secondary smoking	40	88	2.18** (1.36–3.50)
Primary/basic nonsmoking	6	15	1.00
Primary/basic smoking	12	9	3.33 (0.92–12.01)
			OR <sub>MH</sub> =2.05*** (1.47–2.85)

OR, odds ratio; OR<sub>MH</sub>, Mantel-Haenszel odds ratio; CI, confidence interval; \* $P<0.05$ ; \*\* $P<0.01$ ; \*\*\* $P<0.001$ .

We also examined the relationships between paternal and parental smoking and the risk of septal defects in infants. According to our results, majority of case fathers (62.4%) and control fathers (56.2%) smoked (Table 4); paternal smoking increased the risk of septal defects from 1.5 to 3 times depending on the duration of smoking and smoking intensity.

More than one-fifth (21.5%) of infants whose both parents were smokers had the diagnosis of congenital septal defects (Table 5). Smoking of both parents was statistically significantly associated with an increased risk of birth defects (OR=2.63; 95% CI, 1.76–3.93;  $P<0.001$ ) as compared with nonsmoking parents.

Maternal smoking when the father did not smoke was associated with a 2.47-fold greater risk to have unhealthy newborns (OR=2.47; 95% CI, 1.15–5.31;

Table 4. The odds ratios for septal defects associated with paternal smoking among infants (a univariate analysis, 1995–2005)

Risk factors	Cases		Controls		Crude odds ratio	
	N (261)	%	N (1122)	%	OR	95% CI
Paternal smoking:						
No	80	30.7	484	43.1	1.00	
Yes	163	62.4	630	56.2	1.56**	1.16–2.09
No data	18	6.9	8	0.7		
Paternal smoking (cigarettes/day):						
None	80	30.7	484	43.1	1.00	
<10	85	32.6	330	29.4	1.55**	1.11–2.18
10–20	65	24.8	274	24.5	1.43*	1.00–2.05
>20	13	5.0	26	2.3	3.02**	1.49–6.13
No data	18	6.9	8	0.7		
Duration (in years) of paternal smoking:						
None	80	30.7	484	43.1	1.00	
2–3 years	12	4.6	42	3.8	1.72	0.87–3.42
≥4 years	148	56.7	588	52.4	1.52**	1.13–2.05
No data	21	8.0	8	0.7		

OR, odds ratio; CI, confidence interval; \* $P<0.05$ ; \*\* $P<0.01$ .

Table 5. The association between parental smoking and congenital heart septal defects among newborns (1995–2005)

Risk factors	Cases		Controls		Crude odds ratio		
	N (261)	%	N (1122)	%	OR	OR <sup>1</sup>	OR <sup>2</sup>
Neither parent smokes	66	25.3	456	40.6	1.00	1.00	1.00
Only father smokes	106	40.6	483	43.1	1.52* (1.09–2.12)	1.47* (1.05–2.06)	1.45* (1.03–2.03)
Only mother smokes	10	3.8	28	2.5	2.47* (1.15–5.31)	2.32* (1.07–5.03)	2.20* (1.01–4.79)
Both parents smoke	56	21.5	147	13.1	2.63*** (1.76–3.93)	2.34*** (1.54–3.56)	2.27*** (1.49–3.46)
No data	23	8.8	8	0.7			

OR, odds ratio; OR<sup>1</sup>, adjusted odds ratio for maternal education; OR<sup>2</sup>, adjusted odd ratios for maternal education, marital status, occupation; CI, confidence interval; \* $P<0.05$ ; \*\*\* $P<0.001$ .

$P < 0.05$ ) and paternal smoking when the mother did not smoke increased the risk by 1.5 times (OR=1.52; 95% CI, 1.09–2.12;  $P < 0.05$ ).

Table 5 presents the results of the multivariate logistic regression models. According to our data, the adjustment for potential confounding variables had little effect on the magnitude and statistical significance of the odds ratios.

A statistically significant association between congenital heart defects (ventricular and atrial) and parental smoking was identified in the first logistic regression model, while controlling for maternal education.

Adjustment for maternal education, social status, and marital status in the second – the final multivariate model – did not affect the relationship between parental cigarette smoking and risk of septal defects in newborns, although the odds ratios decreased but remained statistically significant. Our results indicated that parental, maternal, and paternal smoking significantly increased the risk of congenital defects (OR=2.27, 95% CI, 1.49–3.46; OR=2.20, 95% CI, 1.01–4.79; and OR=1.45, 95% CI, 1.03–2.03, respectively) if compared with nonsmoking pairs.

## Discussion

We performed an epidemiological case-control study to confirm the hypothesis that parental smoking is related to an increased risk of septal defects in newborns. We analyzed some environmental factors that may influence the risk of these anomalies and used logistic regression models to evaluate results.

According to our data, parental smoking or at least smoking of one of the parents was one of the risk factors associated with birth defects. The data about respondents' hazardous habits were subjective. Furthermore, in this study, information was collected mostly from mothers who could provide inaccurate information about intensity and duration of their and fathers' smoking.

Smoking is one of the most harmful factors to the reproductive system and fetal development. Scientists have showed that maternal smoking during pregnancy is associated with spontaneous abortions, placental complications, intrauterine growth retardation, preterm birth, perinatal mortality, sudden infant death syndrome, and congenital malformations (12, 17–21). According to results of our epidemiological study, maternal smoking increased the risk of septal defects. These results are partially consistent with findings of the study by Malik et al., who reported that women who smoked anytime during the month before pregnancy to the end of the first trimester were more likely

to deliver infants with septal defects if compared with nonsmoking mothers. Analysis of their data showed a stronger association of heavy maternal smoking ( $\geq 25$  cigarettes per day) with septal defects (OR=2.06; 95% CI, 1.20–3.54) (6). By contrast, the study by Kallen, using the Swedish Registry data, found that maternal smoking during pregnancy was not significantly associated with all septal defects but was associated with an increased risk of atrial septal defects (14).

We cannot easily compare our findings with previous studies as we did not analyze association between each subgroup of septal defects separately and maternal smoking. Similarly, there are differences in methodology, sample sizes, potential confounders, and misclassification of exposure.

According to our multivariate logistic regression analysis, parental or paternal smoking was significantly associated with the risk of septal defects in infants if compared to the nonsmoking group. However, it is difficult to compare these data since there are few studies that evaluated the role of parental smoking in this group of defects. In the Baltimore-Washington Infant Study, paternal smoking was not statistically significantly associated with an increased risk of membranous ventricular septal defects (22), but most scientists reported that toxic compounds and teratogenic, carcinogenic, and mutagenic components in smoke of active and passive smoking adversely affect the reproductive system and may also cause disorders of embryogenesis (23, 24).

The findings of our study showed that smoking women with lower levels of education had an increased risk of having newborns with congenital cardiac septal defects. Some researchers reported that low-educated women were more likely to smoke that could negatively affect the health of their newborns (21, 25). Our univariate analysis showed that some social factors had a relationship with an increased risk of birth defects. These results confirmed the conclusions of other researchers that adverse maternal socioeconomic factors (education, income, and occupation) increased the risk of perinatal deaths, premature births, and fetal growth disorders (26–28).

Although this epidemiological case-control study included only newborns of Kaunas city population, but its results confirmed that parental smoking or at least smoking of one of the parents before pregnancy and during pregnancy increased the risk of congenital cardiac septal defects. Therefore, not only smoking mothers but also parents should quit smoking when planning families and particularly avoid these harmful agents during pregnancy. The findings of our study are essential for public health, as parental smoking

can be the most preventable risk factor that is associated with congenital heart malformations. Additionally, further studies are needed in Lithuania to evaluate interactions between parental smoking and genetic polymorphisms in relation to the risk of congenital heart defects.

### Conclusion

The results of univariate and multivariate logistic regression analyses in this study showed a significant association between parental smoking, either maternal or paternal, and the risk of congenital heart septal defects in infants.

## Tėvų rūkymas ir įgimtų širdies pertvarų defektų rizika

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**Raktažodžiai:** atvejo-kontrolės tyrimas, rūkymas, nėštumas, pertvaros defektai.

**Santrauka.** *Tyrimo tikslas.* Nustatyti ryšį tarp tėvų rūkymo ir įgimtų širdies pertvarų defektų formavimosi rizikos Kauno miesto vaikų populiacijoje 1995–2005 m.

*Metodika.* Atliktas epidemiologinis atvejo-kontrolės tyrimas. Tirtųjų kontingentas – 261 naujagimis, turintis įgimtas širdies pertvarų formavimosi ydų (atvejai) ir 1122 atsitiktinės atrankos būdu atrinkti naujagimiai, neturintys jokių apsigimimų (kontrolinė grupė), gimę 1995–2005 m. Kauno mieste. Surinkti duomenims apie veiksnius, galinčius turėti įtakos apsigimimų rizikai, buvo atlikta naujagimių tėvų apklausa. Nustatant ryšį tarp tėvų rūkymo ir pertvarų defektų rizikos, iškraipančių veiksmų kontrolei naudota daugiaveiksni logistinė regresinė analizė.

*Rezultatai.* Naujagimių patikslinto registro duomenimis, 1995–2005 m. Kauno mieste užregistruotas 371 naujagimis, kuriam buvo diagnozuotos įgimtos širdies ydos. 70,3 proc. visų užregistruotų įgimtų širdies anomalijų sudarė skilvelių ir prieširdžių pertvaros defektai. Įvertinus galimus iškraipančiuosius veiksnius (t. y. motinos išsimokslinimą, socialinę bei šeimos padėtį), nustatytas statistiškai patikimas ryšys tarp tėvų rūkymo ir naujagimių įgimtų širdies pertvarų defektų rizikos. Abiejų tėvų rūkymas minėtų anomalijų riziką didino 2,27 karto (ŠS=2,27; 95 proc. PI 1,49–3,46), motinos – 2,2 karto (ŠS=2,20; 95 proc. PI 1,01–4,79), tėvo – 1,5 karto (ŠS=1,45; 95 proc. PI 1,03–2,03) lyginant su nerūkančiais tėvais.

*Išvados.* Įgimtų širdies pertvarų defektų formavimosi rizika reikšmingai susijusi su tėvų rūkymu.

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