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ORIGINAL ARTICLE

Maternal malnutrition, environmental exposure during pregnancy and the risk of non-syndromic orofacial clefts

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OBJECTIVE: To explore the risk factors of non-syndromic orofacial clefts.

SUBJECTS AND METHODS: A case–control study was conducted in China, 537 infants born with non-syndromic cleft lip with/without cleft palate, 176 infants born with cleft palate (CP), and 221 normal controls were recruited to participate in a questionnaire based study to identify risk factors related to maternal nutrition.

RESULTS: Single-factor Chi-square analysis identified 12 factors as significantly related to non-syndromic orofacial clefts ($P < 0.05$). Multiple logistic regression showed five of these factors were associated with non-syndromic orofacial clefts, male gender and maternal passive smoking during early pregnancy were risk factors for non-syndromic orofacial clefts (OR = 1.86 and 11.42; 95%CI: 2.28–2.69 and 6.87–19.00, respectively), whereas maternal weight gain during pregnancy and folic acid supplementation during early pregnancy were protective (OR = 0.15 and 0.67; 95%CI: 0.034–0.63 and 0.44–1.00, respectively).

CONCLUSIONS: Our data may provide references for cleft lip and CP prevention programs, and counseling programs in China.

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Keywords: non-syndromic oral clefts; cleft lip with or without palate; cleft palate only; logistic regression analysis

Introduction

Non-syndromic cleft lip with or without cleft palate (NSCL/P) is one of the most common congenital malformations in humans. The worldwide overall incidence of clefts is estimated to be 1/700, with wide variability among races across populations (Murray, 2002). Lower birth prevalences are seen among black people, while the highest incidences are seen among American Indians, Japanese and Chinese (Vanderas, 1987; Forrester and Merz, 2004) . The birth prevalence of NSCL/P is 1.82/1000 live births in China (Xiao, 1989). It is known that NSCL/P is a complex and heterogeneous congenital malformation and its occurrence is associated with several environmental and genetic risk factors, with interactions between them very likely. Many epidemiological investigations and animal experiments have confirmed exposure to environmental risk factors during early pregnancy, such as smoking, drinking, vitamins deficiency, viral infection can increase risk of cleft lip with or without cleft palate (CP) (Little *et al*, 2004; Shaw *et al*, 2005; Wang *et al*, 1995; Kotch and Sulik, 1992; Nandor *et al*, 2006; Grewal *et al*, 2008; Jia *et al*, 2009, 2010). However, environmental factors vary across geographical location, racial makeup of the population and over time. Here, a case–control analysis was undertaken to analyze the relationship between the epidemiological features (relative environmental factors) and non-syndromic orofacial clefts from a Chinese population.

Methods

Data collection

The case group contains 713 NSCL/P and CP cases collected at the Department of Cleft Lip and Palate Surgery, West China College of Stomatology, Sichuan University, between 2008 and 2010. Control group contained information from maternal questionnaires on 221 normal children (having no congenital malformation, no family history of genetic disease and being born in the same region) who visited West China Women's and Children's Hospital, Sichuan University during the same period. Informed consent was obtained from the parents of the case and control child prior to enrollment. This hospital-based case–control study was approved by the institutional review board of Sichuan University. To assess non-syndromic status of cases, all probands were

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screened for the presence of associated anomalies or syndromes by a physician, and only those determined to have an isolated cleft were included in this study. Patients and their parents were asked about general information (gender, month and year of birth, birth weight), maternal age at birth, pregnant history, parents' occupation, maternal age at birth, maternal weight change during pregnancy, maternal reaction to pregnancy (nausea or vomiting), parents' environmental exposure factors during early pregnancy (including maternal multivitamins, calcium and folic acid supplementation, maternal smoking and passive smoking, maternal drinking, paternal smoking history), family history of NSCL/P among first and second relatives, of parents and many other detailed information. Occupational history of parents is presented in Table 1.

Statistical analysis

All data on patients were transferred to a window-based personal computer, and statistical analysis was carried out using the statistical package for social science, version 11.0 (SPSS Inc, Chicago, IL, USA). Single factor Chi-square analysis, *T*-test analysis and multiple logistic regression analysis were used to analyze the relationship between environmental factors and risk of NSCL/P. P value < 0.05 was considered statistically significant.

Results

Family history

Among the 713 patients, 81 patients had positive family history (11.36% of all cases), including 73 patients with NSCL/P and eight patients with CP. The difference between these two case groups was significant ($\chi^2 = 10.78$, $P = 0.001$) (Table 2).

Gender

The gender distribution of cases and normal controls are presented in Table 2. Patients with NSCL/P included more men than women, whereas patients with CP and normal controls had more women than men. Chi-square analysis showed significantly differences between NSCL/P and normal controls (OR = 2.14, 95%CI:

Table 1 Occupational distribution of the parents

	Mothers' occupation		*Fathers' occupation*	
Type of occupation	*Case (%)*	*Control (%)*	*Case (%)*	*Control (%)*
No job	174 (24.4)	44 (19.9)	127 (17.8)	3 (1.4)
Agriculture and gardening	122 (17.1)	23 (10.4)	156 (21.9)	40 (18.1)
Office work	79 (11.1)	57 (25.8)	52 (7.3)	38 (17.2)
Teacher	33 (4.6)	29 (13.1)	37 (5.2)	15 (6.8)
Mechanical Engineering	10 (1.4)	13 (5.9)	110 (15.4)	21 (9.5)
Factory worker	64 (9.0)	6 (2.7)	112 (15.7)	20 (9.0)
Doctor and Nurse	23 (3.2)	3 (1.4)	10 (1.4)	4 (1.8)
Scientists and engineers	2 (3)	8 (3.6)	22 (3.1)	8 (3.6)
Cook and waiter	28 (3.9)	0 (0)	26 (3.6)	14 (6.3)
Sales personnel	38 (5.3)	27 (12.2)	35 (4.9)	52 (23.5)
Student	0 (0)	1 (5)	26 (3.6)	6 (2.7)
Housewives	140 (19.6)	10 (4.5)	0 (0)	0 (0)

Table 2 Family history, gender distribution, and birth weight (g) among the groups

	CL/P (537)	*CP (176)*	*All clefts (713)*	*Control (221)*
Family history				
Positive (%)	73 (13.59)	8 (4.55)	81 (11.36)	–
Negative (%)	464 (86.41)	168 (95.45)	632 (88.64)	–
χ^2	10.778			
P	0.001			
Gender				
Male (%)	354 (65.92)	71 (40.34)	425 (59.61)	105 (47.51)
Female (%)	183 (34.08)	105 (59.66)	288 (40.39)	116 (52.49)
χ^2	22.22	2.04	10.06	
P	< 0.0001	0.15	0.0015	
OR	2.14	0.75	1.63	
95%CI	1.55–2.94	0.50–1.12	1.20–2.21	
Birth weight (g)				
Mean	3210.03	3070.91	3175.69	3593.89
Mean difference	383.86	522.98	418.20	
SE difference	28.88	43.80	26.78	
95%CI of the difference	327.16–440.56	436.71–609.25	365.63–470.78	
T	13.29	11.94	15.62	
P	0.000	0.000	0.000	

CL/P, cleft lip with or without cleft palate.

1.55–2.94), all non-syndromic orofacial clefts and normal controls (OR = 1.63, 95%CI: 1.20–2.21).

Birth weight

T-tests were used to compare the birth weight of the non-syndromic orofacial clefts and normal controls, with an average weight among NSCL/P, CP, and normal controls of 3210.03 g, 3070.91, and 3593.89 g, respectively. There was significantly different between cases and controls ($P < 0.0001$) (Table 2).

Maternal covariates

Maternal covariates used in multivariate models included parity (primiparous mother, one previous live birth, two previous live births, three previous live births, four previous live births); there were significantly differences between case groups and controls ($P < 0.0001$) (Table 3), and a larger proportion of cases were second or later births (Figure 1). The average maternal age was 26.53 years in the case group and 27.14 years in the normal control group. The maternal ages were divided into five groups among the 713 patients and 221 normal controls respectively: < 19 years of age; 20–24 years of age; 25–29 years of age; 30–34 years of age; more than 35 years of age. There was significantly different between the cases group and normal control group ($P < 0.0001$) (Table 3 and Figure 2).

Maternal weight change, reaction to pregnancy and environmental exposure factors during pregnancy

Maternal weight change during pregnancy was divided into two types: gain and decline. Statistical analysis showed any maternal weight change during pregnancy was associated with higher risk of having a non-syndromic orofacial cleft ($P < 0.005$) and maternal weight gain may be a protective factor for NSCL/P and CP (OR = 0.20 and 0.16; 95%CI: 0.06–0.60 and 0.045–0.56, respectively). Maternal passive smoking and paternal smoking were also risk factors for NSCL/P (OR = 9.23 and 1.92; 95%CI: 5.96–14.28 and 1.40–2.64, respectively) and CP (OR = 9.45 and 2.09; 95%CI: 5.73–15.60 and 1.40–3.13, respectively), mother's reaction to pregnancy was a risk factor for CP (OR = 1.82, 95%CI: 1.21–3.13). Whereas maternal multi-vitamins supplementation was protective for NSCL/P and CP (OR = 0.63 and 0.64; 95%CI: 0.45–0.87 and 0.42–0.97, respectively), calcium supplementation was also a protective factor for NSCL/P (OR = 0.66, 95%CI: 0.47–0.93) as was folic acid supplementation during early pregnancy for CP (OR = 0.52, 95%CI: 0.33–0.81) (Table 4).

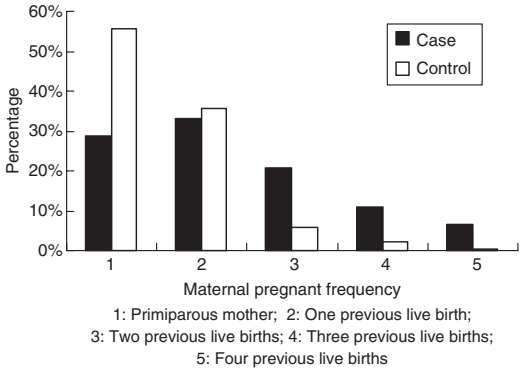

Figure 1 Maternal pregnant frequency

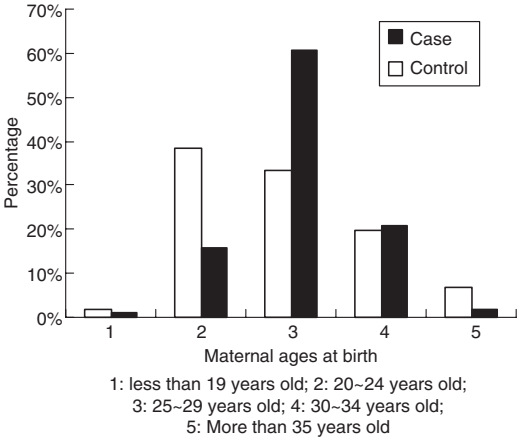

Figure 2 Maternal ages at birth

Table 3 Maternal characteristic with non-syndromic orofacial clefts

Maternal characteristics	*CL/P*	*CP*	*All clefts*	*Control*
Parity				
Primiparous mother	151	54	205	123
One previous live birth	181	54	235	79
Two previous live births	114	33	147	13
Three previous live births	58	21	79	5
Four previous live births	33	14	47	1
χ^2	80.087	57.038	105.52	
P	**0.000**	**0.000**	**< 0.0001**	
Age at birth				
< 19	8	5	13 (1.8%)	2 (0.9%)
20–24	200	73	273 (38.3%)	35 (15.8%)
25–29	176	63	239 (33.5%)	134 (60.6%)
30–34	113	27	140 (19.6%)	46 (20.8%)
> 35	40	8	48 (6.7%)	4 (1.8%)
χ^2	61.84	41.96	65.19	
P	**0.000**	**0.000**	**< 0.0001**	

CL/P, cleft lip with or without cleft palate; CP, cleft palate; Statistical significance values are given in bold.

Multiple logistic regression analysis of significant factors
Multiple logistic regression analysis of nine factors selected as 'significant' (gender, birth weight, maternal age at birth, maternal weight change during pregnancy, maternal multi-vitamin use, calcium and folic acid supplementation during early pregnancy, maternal passive smoking during early pregnancy and paternal smoking), were fit in a regression model. The regression coefficients estimated and OR (along with 95%CI) were calculated. Results showed maternal passive smoking during early pregnancy was risk factor for non-syndromic orofacial clefts (OR = 11.42; 95%CI: 6.87–19.00), and male gender had a high risk for non-syndromic orofacial clefts (OR = 1.86; 95%CI: 2.28–2.69). Whereas maternal weight gain during pregnancy and folic acid supplementation during early pregnancy were protective factors for non-syndromic orofacial clefts (OR = 0.15 and 0.67; 95%CI: 0.034–0.63 and 0.44–1.00, respectively), with exposure associated with a lower risk of having a child with a non-syndromic orofacial cleft (Table 5).

Discussion

The patients described in this study were recruited from the West China Stomatological Hospital of Sichuan University. This hospital is considered one of the largest CL and CP repair centers in China, and it has several unique characteristics. Because it is a referral center for much of western and southern China, it receives patients from many provinces and from all socioeconomic backgrounds.

Parents' occupation usually determines their exposure to many potentially environmental risk factors. Many studies have shown if mothers come in contact with certain chemicals, this can increase the risk of cleft lip and palate in the child. Aliphatic aldehydes, ethyl ether, aliphatic acids, trichloroethylene and pesticides can increase risk of CP (Cordier *et al*, 1997; Lorente *et al*, 2000; Chevrier *et al*, 2006). Some studies showed the incidence of CL/P was associated with less specific environmental factors, such as parental socio-economic status. If mothers who have no regular employment also have lower socio-economic status, the risk of occurrence of CL/P was higher than among mothers with regular employment and income.

Because of many confounding factors and the many categories of parental occupation, we found no relationship between occurrence of cleft lip and palate and parents' occupation in this study (Table 1). However, the case group did have more parents were engaged in agriculture or factory work, and farmers may be exposed to pesticides and other chemical substances which can lead to born birth defects including orofacial clefts.

As expected, the present study showed men were at higher risk of NSCL/P than women (Table 2). Also as

Table 4 Single-factor Chi-square analysis between non-syndromic orofacial clefts and environmental exposure factors during the first trimester

	CL/P					*CP*					*Control*	
Environmental exposure factors	*Yes*	*No*	*P*	*OR*	*95%CI*	*Yes*	*No*	*P*	*OR*	*95%CI*	*Yes*	*No*
Maternal weight change during pregnancy	502[a]	35[b]	**0.002**	**0.20**	0.06–0.60	162[a]	14[b]	**0.002**	**0.16**	**0.045–0.56**	218[a]	3[b]
Maternal pregnancy reaction	287	250	0.43	1.14	0.83–1.56	114	62	**0.004**	**1.82**	**1.21–2.74**	111	110
Maternal smoking	15	522	0.17	3.15	0.71–13.88	3	173	0.66	1.90	0.31–11.49	2	219
Maternal passive smoking	302	235	**< 0.0001**	**9.23**	**5.96–14.28**	100	76	**< 0.0001**	**9.45**	**5.73–15.60**	27	194
Maternal drinking	29	508	0.24	0.69	0.37–1.27	8	168	0.22	0.57	0.24–1.36	17	204
Maternal multi-vitamins supplementation	151	386	**0.006**	**0.63**	**0.45–0.87**	50	126	**0.043**	**0.64**	**0.42–0.97**	85	136
Maternal calcium supplementation	132	405	**0.019**	**0.66**	**0.47–0.93**	50	126	0.33	0.81	0.52–1.24	73	148
Maternal folic acid supplementation	158	379	0.071	0.74	0.53–1.02	40	136	**0.004**	**0.52**	**0.33–0.81**	80	141
Paternal smoking	325	212	**< 0.0001**	**1.92**	**1.40–2.64**	110	66	**< 0.0001**	**2.09**	**1.40–3.13**	98	123
Paternal drinking	261	276	0.30	0.84	0.61–1.15	92	84	0.92	0.97	0.66–1.45	117	104

[a]Gain.
[b]Decline.
CL/P, cleft lip with or without cleft palate; CP, cleft palate; Statistical significance values are given in bold.

Table 5 Multiple logistic regression analysis

	Regression coefficient	χ^2	*P*	*OR*	*95%CI*
Male	0.62	10.78	**0.001**	**1.86**	**1.283–2.69**
Birth weight	0.002	94.27	**0.000**	**1.002**	**1.002–1.003**
Maternal age at birth	0.006	0.068	0.794	1.006	0.96–1.05
Maternal weight addition	−1.93	6.64	**0.010**	**0.145**	**0.034–0.63**
Maternal multivitamins supplementation during early pregnancy	−0.29	1.85	0.174	0.75	0.49–1.14
Maternal calcium supplementation during early pregnancy	−0.034	0.022	0.882	0.97	0.62–1.51
Maternal folic acid supplementation during early pregnancy	−0.41	3.91	**0.048**	**0.67**	**0.44–1.00**
Maternal passive smoking during early pregnancy	2.44	88.14	**0.000**	**11.42**	**6.87–19.00**

Statistical significance values are given in bold.

expected, children with CL/P had a lower birth weight than normal control children, and there was significantly different between these two groups ($P < 0.0001$) (Table 2). Many scholars believe children with cleft lip and palate have a lower birth weight compared with normal liveborns, with more severe malformations having even lower weight at birth (Becker *et al*, 1998).

Maternal malnutrition during pregnancy can increase risk of having a CL/P. Some studies have shown children with CL/P have a much lower weight compared with normal children of the same developmental age. During infancy, children with CL/P have a much lower weight compared with normal children, because the CL/P itself impacts feeding and cleft children are prone to respiratory tract infections. This gap between CL/P children and normal children generally narrows gradually before preschool stage.

It is generally accepted increasing parity increases risk of a woman giving birth to child with a CL/P, perhaps because an excessive number of abortions may lead to reproductive organ damaged and dysfunction. Messer *et al*, (2010) showed slightly larger proportion of cases were born to women with three or more prior births in Texas during 1999–2003, and the mothers of children with CL/P were older than control mothers (Messer *et al*, 2010). Czeizel and Tusnadi (1971) found that non-first-born children with CL/P are much more and severe than first-born children with CL/P (Czeizel and Tusnadi, 1971). Bille *et al* (2005) found both high maternal age and high paternal age were associated with increased risk of CL/P, higher paternal age but not maternal age increased the risk of CP only (Bille *et al*, 2005), all these results are consistent with our study (Table 3).

The development of the fetus, nutritional status, lifestyle, genetic background and mental state all affect maternal weight change during pregnancy. A certain mount of weight gain indicates a healthy state of the fetus. Excessive weight gain or insufficient weight gain will both have impact on the fetus, but there is no precise weight change during pregnancy was significantly associated with occurrence of clefts. In this study, there was difference between the case group and control group (Table 4), inadequate weight gain may reflect fetal abnormalities.

Many studies have identified a relationship between environmental risk factors and NSCL/P. Maternal multivitamin use was inversely associated with CL/P but to a lesser extent cleft palate only, the volume of evidence on dietary folate, fortification and biochemical and genetic measures of folate status is substantially less; the evidence suggests no association exists, but there is substantial heterogeneity between studies (Johnson and Little, 2008). Our questionnaire covered use of maternal vitamins including folic acid supplementation during the early pregnancy, and multiple logistic regression analysis showed dietary folate was a protective factor (OR = 0.67, 95%CI: 0.44–1.00) (Table 5), which may decrease risk being non-syndromic orofacial clefts.

Alcohol consumption was considered as a risk factor for NSCL/P (Munger *et al*, 1996; Romitti *et al*, 1999; Shaw and Lammer, 1999), maternal smoking during early pregnancy had a positive association with CL/P and CP, but there was evidence of a dose–response relationship for both types of cleft (Little *et al*, 2004). Our study showed no significant association between maternal drinking and smoking during early pregnancy and risk of non-syndromic orofacial clefts. An effect of passive smoking could not be excluded among mothers who did not smoke themselves (Wang *et al*, 1995). In our study, multiple logistic regression analysis showed maternal passive smoking during early pregnancy may substantially increase the risk of having a child with a non-syndromic orofacial clefts (OR = 11.42, 95%CI: 6.87–19.00).

These data represent basic conditions in western China. Children with CL/P have significant difference in sex ratio, birth weight, and maternal weight gain during pregnancy compared with normal control children. Environmental factors play an important role in the incidence of CL/P, supplementation with vitamin and folic acid can decrease the risk of CL/P, and maternal passive smoking can increase risk. Strengthening prenatal care and reducing environmental exposure can reduce the incidence of CL/P.

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Author contributions

Z-L Jia has analyzed the data, written and revised the manuscript. B-Shi has designed the experiment. C-H Chen, J-Y Shi, J Wu and X Xu all have collected the questionaires.

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