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Original Article

Assessment of non-syndromic orofacial cleft severity and associated environmental factors in Saudi Arabia: A cross-sectional study

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ABSTRACT

Objective: To evaluate the relationship between different environmental risk factors and the severity of cleft lip with/without palate (CL ± P) and cleft palate (CP) in Saudi Arabia.
Methods: This was a cross-sectional national study, of government hospitals in 10 cities distributed across major regions of Saudi Arabia, from June 2020 to June 2021. All newborns with CL ± P or CP were clinically examined and evaluated for cleft phenotype severity using the LAHSHAL classification system. Various environmental factors were evaluated by interviewing parents using a validated questionnaire. The severity of CL ± P and CP was evaluated in relation to environmental factors.
Results: We recruited 174 patients with non-syndromic orofacial cleft (NSOFC); 122 (70.1 %) had CL ± P and 52 (29.9 %) had CP. After adjusting the odds ratios by ordinal regression for CL ± P and logistic regression analysis for CP, environmental factors that significantly increased the severity of CL ± P were family history of NSOFC, maternal illnesses, and maternal medication use (P = 0.02, adjusted odds ratio [AOR]:2.70; P = 0.002, AOR:3.70; and P = 0.03, AOR:2.14, respectively). Folic acid supplementation in the first trimester significantly reduced the severity of CL ± P and CP (P = 0.001, AOR:0.18 and P = 0.001, AOR:0.012, respectively).
Conclusion: The severity of CL ± P was affected by some maternal exposures during the 3-month pre-gestation period. Therefore, our results suggest the possibility of controlling the severity of NSOFC.

1. Introduction

Non-syndromic orofacial cleft (NSOFC) is the most common craniofacial anomaly (Mossey and Modell, 2012), with a recent global prevalence of 1.47/1000 live births (Panamonta et al., 2015). NSOFC has two main categories: cleft lip with or without palate (CL ± P), ranging from complete bilateral cleft lip and palate to incomplete unilateral cleft lip, and cleft palate (CP), which can be complete or

Abbreviations: AOR, Adjusted odds ratio; BCCLP, Bilateral complete cleft lip and palate; BICLP, Bilateral incomplete cleft lip and palate; CCP, Complete cleft palate; CI, Confidence intervals; CP, Cleft palate; ICP, Incomplete cleft palate; NSOFC, Non-syndromic orofacial cleft; OR, Odds ratios.

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incomplete (Mossey and Modell, 2012, Panamonta et al., 2015). A wide range of geographic and ethnic differences exist in the prevalence and etiology of NSOFC (Mossey and Modell, 2012, Panamonta et al., 2015). Its prevalence in Saudi Arabia, reported previously in three major cities, was 1.17/1000 live births (Sabbagh, 2015, Sabbagh et al., 2015b).

The etiology of NSOFC is multifactorial, involving both genetic and environmental components, as well as interactions between the two (Mossey and Modell, 2012). Several studies have linked environmental factors, such as socioeconomic status, parental age, consanguinity (Sabbagh et al., 2014), family history, maternal medication use, stress, infections, and maternal nicotine exposure during the 3-month pre-gestation period and the first trimester, to the development of oral clefts (Lie et al., 1994, Bille et al., 2005, Shahrukh Hashmi et al., 2010, Jia et al., 2011, Lin et al., 2012, Carmichael et al., 2014, Sabbagh et al., 2015a, Sabbagh et al., 2015b, Sabbagh et al., 2016, Jamilian et al., 2017, Shi et al., 2023). However, few studies have investigated the severity of NSOFC and related environmental risk factors. The only reported assistive environmental risk factors are parental age and family history. Although a positive relationship was reported, both factors were evaluated without considering other factors or excluding confounders, which might have reduced the strength of the evidence (Sivertsen et al., 2008, Hermann et al., 2018).

Therefore, this study aimed to evaluate the relationship between different environmental risk factors and the severity level of CL ± P and CP.

2. Materials and methods

2.1. Participants

This study focused on NSOFC cases in maternity wards in government hospitals across the five major regions of Saudi Arabia from November 1, 2020, to November 1, 2021. We identified 29 hospitals, including those affiliated with the Ministry of Health, university hospitals, and Ministry of National Guard hospitals. Infants born with syndromic orofacial clefts (OFCs) were excluded (Supplementary table 1). As the lack of a similar study prevented us from adopting a predetermined sample size, the sample power was calculated after the recruitment of participants. Nevertheless, this study included all NSOFC infants born in government hospitals during the study period, which can be considered the entire study population.

2.2. Methods

Ethical approval was obtained from the Research Ethics Committees of King Abdulaziz University Faculty of Dentistry (257–07-21) and King Fahad Armed Forces Hospital (REC 391) and the Institutional Review Boards of the Ministry of National Guard at King Abdullah International Medical Research Center (H-01-R-005), Ministry of Health in Riyadh (H-01-R012), and Ministry of Health in Jeddah (H-02-J-002). At each hospital, the research coordinator was notified immediately after a newborn was diagnosed with NSOFC. The research coordinator contacted the parents, explained the study, and arranged an appointment at the hospital (neonatal unit). Parents signed a consent form on the day of the appointment and were interviewed using a research questionnaire.

2.2.1. Research questionnaire

The research questionnaire comprised three sections as follows:

- Infants' general information and sociodemographic data, including parental age at birth grouped according to Herkrath et al. (Herkrath et al., 2012), who suggested that the risk of NSOFC rises when fathers are 40 years and older (<40 and ≥ 40 years) and mothers are 35 years and older (<35 and ≥ 35 years); parental educational level (less or more than high school); and family monthly income grouped according to Saudi salary ranges: low (≤6,000 SR), middle (6,000–16,000 SR), and high (≥16,000 SR) (Human Resources Development Foundation).
- Pregnancy history during the 3-month pre-gestation period and the first trimester. This included yes/no questions on maternal exposure to medications, folic acid, fever, different illnesses including severe acute respiratory syndrome coronavirus infection and parental smoking.
- Maternal exposure to stress during the 3-month pre-gestation period and first trimester using a validated (Norbeck, 1984, Talal AlSharif et al., 2023) modified life events questionnaire (seven life events). It included yes/no questions on stressful life events, such as problems with family, neighbors, or friends; changes in marital status and family residence; work status leaves or change; and maternal reporting of parents being robbed. If the mother had been exposed to any previous life stress events, she was considered to be exposed to stress. This questionnaire has been validated previously (Norbeck, 1984, Talal AlSharif et al., 2023).

2.2.2. Clinical examination

Newborns with NSOFC were examined by a pediatrician and geneticists in pediatric neonatal or plastic surgery units using lighting and mirrors to identify the cleft type according to the LAHSHAL classification system (Kriens, 1991, Houkes et al., 2023). The severity of CL ± P was evaluated according to the cleft extension and number of affected sites and was grouped into a scale ranging from levels 1 to 6, "1″ being the mildest and "6" being the most severe.

- Level 1: Unilateral incomplete cleft lip (UICL)
- Level 2: Unilateral complete cleft lip (UCCL)
- Level 3: Unilateral incomplete CL ± P (UICLP)
- Level 4: Unilateral complete CL ± P (UCCLP)
- Level 5: Bilateral incomplete CL ± P (BICLP)
- Level 6: Bilateral complete CL ± P (BCCLP)

In addition, CP severity was evaluated according to cleft extension and grouped to:

- Level 1: Incomplete CP (ICP)
- Level 2: Complete CP (CCP)

2.2.3. Content validity, reliability, and ascertainment

Six experts rated the research tool validity on a 1–4 scale, yielding a content validity index of 0.95. Moreover, online meeting with each medical institution coordinator ensured clarity and comprehension of the data collection form, affirming the tool's effectiveness.

2.3. Statistical analysis

The research coordinator used SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY). Descriptive data were presented as frequencies and percentages. The non-parametric Mann–Whitney *U* test was used to compare environmental factors and CL ± P severity. Chi-square and Fisher's exact tests were used to examine the relationship between environmental factors and the severity of CP. Ordinal logistic regression analysis was used to calculate odds ratios (ORs) and 95 % confidence intervals (CIs) for environmental factors and their estimated degree of association with CL ± P severity, and binary regression analysis was used to calculate ORs and 95 % CIs for CP severity. Statistical significance was set at $P \leq 0.05$.

3. Results

Among the 177 NSOFC infants born during the study period, 98.3 % of parents responded, with only three declining participation. Of the 174 included newborns with NSOFC, 40 (23 %) were from the Central Region, 67 (38.5 %) from the Western Region, 22 (12.6 %) from the

Eastern Region, 24 (13.8 %) from the Northern Region, and 21 (12.1 %) from the Southern region. Additionally, 94 (54 %) were male and 80 (46 %) were female. There were 122 newborns with CL ± P, grouped by level of severity to: 25 (20.5 %) with UICL, 4 (3.3 %) with UCCL, 45 (36.9 %) with UICLP, 26 (21.3 %) with UCCLP, 6 (4.9 %) with BICLP, and 16 (13.1 %) with BCCLP. Of the 52 newborns with CP, 28 (53.8 %) had ICP and 24 (46.2 %) had CCP.

Table 1 shows NSOFC sub-phenotypes distribution based on sociodemographic data, and their relationship with CL ± P and CP severity. Sociodemographically, 51.5 % of the patients were from middle-income families, 72.9 % had fathers under 40 years, and 71.8 % had mothers under 35 years at birth. The proportion of infants with NSOFC and parental consanguinity was 62.6 %, and 34.5 % had a family history of NSOFC.

The prevalence of severe CL ± P was higher in infants with consanguineous parents than in those with non-consanguineous parents, and the prevalence of severe CL ± P correlated significantly consanguineous parents (P = 0.026). The prevalence of severe CL ± P was higher in infants with a family history of NSOFC than in those without. Moreover, severe CL ± P significantly correlated with a family history of NSOFC (P = 0.000). Moreover, severe CL ± P and CP significantly correlated with having a family history of NSOFC (P = 0.006).

Maternal exposure to illness was reported by 43 (35.2 %) among infants with CL ± P and 18 (48.1 %) among those with CP. The prevalence of severe CL ± P was higher in infants whose mothers reported illnesses, maternal fever, and exposure to medication during the 3-month pre-gestation period and the first trimester than in those whose mothers did not, but the difference was significant only for exposure to medication (P < 0.001). In CP cases, the severity of CP significantly correlated with mothers reporting illnesses (P = 0.001) and fever (P = 0.014) in the 3-month pre-gestation period and the first trimester. Furthermore, the severity of CL ± P and CP significantly correlated with mothers not taking folic acid during the 3 months' pre-gestation and the first trimester (P < 0.001). See Table 2.

The prevalence of severe CL ± P and CP was higher in patients whose mothers reported experiencing stress during the 3-month pre-gestation period and/or first trimester than in those whose mothers did not; however, the difference was not significant (P = 0.413 for CL ± P and P = 0.266 for CP).

Ordinal logistic regression analysis was performed for all variables and their relationship with CL ± P severity (Table 3). Three factors were identified as significant predictors of CL ± P severity: maternal illness (P = 0.002; adjusted OR [AOR]: 3.70), maternal ingestion of medication (P = 0.03, AOR: 2.14), and family history of NSOFC (P = 0.02, AOR: 2.70). Conversely, the severity of CL ± P was reduced by folic acid supplementation (P < 0.001, AOR: 0.18).

Binary logistic regression analysis was performed for all variables and their relationships with CP severity (Table 3). CP severity was significantly reduced by folic acid supplementation (P < 0.001; AOR: 0.012). Although not significant, the severity of CP was lower in men than in women (P = 0.14; AOR: 0.22) and in fathers under 35 years than older (P = 0.14; AOR: 0.31). However, CP severity increased with a positive family history of NSOFC (P = 0.22; AOR: 3.53), maternal exposure to stress (P = 0.25; AOR: 2.16), and maternal exposure to illnesses (P = 0.08; AOR: 3.87). However, this association was not significant.

Maternal illness was chosen for sample size power assessment, revealing a mean difference of 0.88, with a 94.15 % power for a sample size of 43 (exposed) and 97 (not exposed).

4. Discussion

This study explored links between sociodemographic/environmental factors and NSOFC severity (CL ± P and CP). Results showed maternal illnesses, medicating, and family history were linked to higher CL ± P severity. Conversely, folic acid supplementation was associated with lower CP severity.

Although the severity of congenital anomalies can increase with certain risk factors (Christianson, 1980, De Santis et al., 2007, Carlson et al., 2009, Jordan et al., 2016), this is one of the few studies to evaluated the relationship between NSOFC severity and environmental risk factors. Unfortunately, with an increase in the severity of the anomalies, the suffering, consequences, and burden of the disease also increase.

This study revealed a higher prevalence of severe CL ± P was associated with younger parental age; although this association was not significant, it differed from a previous study's finding regarding an association between older parents and the severity of CL ± P (Hermann et al., 2018). In addition, 62.9 % of patients with NSOFC reported consanguinity, which was similar to the prevalence reported by El Mouzan et al., El-Hazmi et al., and Sabbagh et al. in Saudi populations (54.4 %, 57.0 %, 57.7 %, and 65.9 %, respectively) (El-Hazmi et al., 1995, El Mouzan et al., 2008, Sabbagh et al., 2015a, Sabbagh et al., 2015b), indicating that the sample resembles the NSOFC population and that the study has good generalizability. The prevalence of severe CL ± P was significantly higher in infants with consanguineous parents than in those with non-consanguineous parents. This suggests that consanguinity is related to the pattern and severity of the NSOFC phenotypes, which supports genetic involvement in CL ± P severity (Sabbagh et al., 2014, Saeed et al., 2019, Al Mahdi et al., 2020). Furthermore, the prevalence rates of severe CL ± P and CP were significantly higher in infants with a family history of clefts, which support the findings of a survey conducted by Sivertsen, et al. in 2008 (2008).

Furthermore, a greater than threefold increase in AOR was found for the severity of CL ± P or CP with mothers reporting exposure to illnesses in their 3-month pre-gestation and first trimester periods. This increase was also found by studies that reported an increased NSOFC prevalence

Table 1
Distribution of NSOFC sub-phenotypes according to sociodemographic factors and their relationship to CL ± P and CP severity.

Socio-demographic factors		CL ± P N (%)	CL ± P severity		CP N (%)	CP severity		
			Mean Rank	P-Value		ICP N (%)	CCP N (%)	p-value
Gender	**Male**	73 (59.8)	57.63	**0.126**	21 (40.4)	13 (43.3)	8 (36.4)	**0.613∝**
	Female	49 (40.2)	67.27		31 (59.6)	17 (56.7)	14 (63.6)	
Paternal age	**< 40 years**	87 (71.3)	59.13	**0.226$**	40 (76.9)	21 (75)	19 (79.2)	**0.772∝**
	≥ 40 years	35 (28.7)	67.39		12 (23.1)	7 (25)	5 (20.8)	
Maternal age	**< 35 years**	86 (70.5)	59.81	**0.397$**	40 (76.9)	21 (75)	18 (75)	**1.000∝**
	≥ 35 years	36 (29.5)	65.54		12 (23.1)	7 (25)	6 (25)	
Consanguinity	**Yes**	72 (59)	67.49	**0.020*$**	37 (71.2)	18 (64.3)	19 (79.2)	**0.238∝**
	No	50 (41)	52.87		15 (28.8)	10 (35.7)	5 (20.8)	
Family history of NSOFC	**Yes**	42 (34.4)	79.73	**< 0.001*$**	21 (21.2)	4 (14.3)	17 (70.8)	**0.006*∝**
	No	80 (65.6)	51.93		31 (78.8)	24 (85.7)	7 (29.2)	
Total N (%)		122 (100)			52 (100)	28 (100)	24 (100)	

CL ± P: cleft lip with or without palate, CP: cleft palate, ICP: incomplete cleft palate, CCP: complete cleft palate.
∝ Chi-square Test, **$** Mann-Whitney U Test, MR: mean rank, *Significance value P ≤ 0.05.

Table 2
Distribution of NSOFC sub-phenotypes according to maternal exposure factors and their relationship to CL ± P and CP severity.

Maternal exposure to [E]		CL ± P N (%)	CL ± P severity		CP N (%)	CP severity		
			Mean Rank	P-value		ICP N (%)	CCP N (%)	P-value
Maternal illness	**Yes**	43 (35.2)	74.49	**0.919[$]**	18 (48.1)	5 (17.9)	13 (54.2)	**< 0.001*[¥]**
	No	97 (79.5)	53.91		27 (51.9)	23 (82.1)	11 (45.8)	
Maternal fever	**Yes**	26 (21.3)	62.71	**0.731[$]**	2 (21.2)	5 (17.9)	12 (50)	**0.014*[¥]**
	No	96 (78.7)	61.14		41 (78.8)	23 (82.1)	12 (50)	
Medication	**Yes**	49 (40.2)	73.53	**< 0.001*[$]**	11 (21.2)	5 (17.9)	6 (25)	**0.735[¥]**
	No	73 (59.8)	53.42		41 (78.8)	23 (82.1)	18 (75)	
Folic acid supplementation	**Yes**	80 (65.6)	52.68	**< 0.001*[$]**	29 (55.8)	24 (85.7)	5 (20.8)	**< 0.001*[¥]**
	No	42 (34.4)	78.30		23 (44.2)	4 (14.3)	19 (79.2)	
Maternal Stress	**Yes**	78 (63.9)	63.40	**0.413[$]**	4 (7.7)	2 (7.1)	2 (8.3)	**0.266[¥]**
	No	44 (36.1)	58.14		48 (92.3)	26 (92.9)	22 (91.7)	
Maternal smoking	**Yes**	2 (1.6)	77.75	**0.537[$]**	29 (55.8)	12 (42.9)	14 (58.3)	**1.000[∝]**
	No	120 (98.4)	61.23		23 (44.2)	16 (57.1)	10 (41.7)	
Paternal Smoking	**Yes**	74 (60.7)	63.50	**0.602[$]**	32 (61.5)	15 (53.6)	17(70.8)	**0.202[∝]**
	No	48 (39.3)	60.20		20 (38.5)	13 (46.4)	7 (29.2)	
Total N (%)		122 (100.0)			52 (100.0)	28 (100.0)	24 (100.0)	

CL ± P: cleft lip with or without palate, CP: cleft palate, UICL: unilateral incomplete cleft lip, UICL: unilateral complete cleft lip, UICLP: unilateral incomplete cleft lip, UCCLP: unilateral complete cleft lip, BICLP: Bilateral incomplete cleft lip, BCCLP: Bilateral complete cleft lip.
∝ Chi-square Test. ¥ Fisher Exact Test. $ Mann-Whitney U Test. MR: mean rank, [E] Maternal-exposure during the 3-months pregestation and 1st trimester periods *Significance value P ≤ 0.05.

Table 3
Ordinal logistic regression and binary logistic regression analysis showing the most significant factors related to CL ± P and CP severity, respectively.

Factors		CL ± P			CP		
		P-value	AOR	95 % Cl	P-value	AOR	95 % Cl
Gender	**Male**	0.15	0.59	0.28–1.22	0.14	0.22	0.03–1.63
	Female		1			1	
Paternal age	**< 40 years**	0.06	0.43	0.18–1.04	0.47	0.31	0.01–7.61
	≥ 40 years		1			1	
Maternal age	**< 35 years**	0.79	0.89	0.37–2.13	0.73	1.57	0.11–22.14
	≥ 35 years		1			1	
Consanguinity	**Yes**	0. 16	1.70	0.80–3.58	0.91	1.14	0.11–12.5
	No		1			1	
Family history of NSOFC	**Yes**	0.02*	2.70	1.16–6.28	0.22	3.53	0.46–26.86
	No		1			1	
Maternal illnesses [E]	**Yes**	0.002*	3.70	0.72–8.38	0.08	3.87	0.83–18.04
	No		1			1	
Maternal Fever [E]	**Yes**	0.73	1.14	0.53–2.47	0.66	1.51	0.22–10.17
	No		1			1	
Maternal medication [E]	**Yes**	0.03*	2.14	1.05–4.38	0.74	0.60	0.03–12.29
	No		1			1	
Folic acid supplementation [E]	**Yes**	< 0.001*	0.18	0.08–0.38	< 0.001*	0.012	0.002–0.073
	No		1			1	
Maternal stress [E]	**Yes**	0.29	1.44	0.72–2.90	0.25	2.16	0.56–8.22
	No		1			1	
Paternal smoking [E]	**Yes**	0.56	0.81	0.40–1.63	0.59	1.65	0.25–10.58
	No		1			1	

CL ± P: cleft lip with or without palate, CP: cleft palate [E] Maternal-exposure during the 3-months pregestation and 1st trimester periods *Significance value P ≤ 0.05.

in mothers exposed to illnesses compared to the prevalence of NSOFC in infants (Inchingolo et al., 2022, Shi et al., 2023). Pathogens could be vertically transmitted from the mother through the placenta, thereby affecting the developing fetus. Infection, toxin release, pathogens invading the developing embryonic tissue, and inflammatory responses could result in birth defects, including NSOFC (Kim et al., 2009, Redline, 2012, Chan and Smith, 2018).

Maternal exposure to medications reportedly has teratogenic effects. Folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption, and specific receptor- or enzyme-mediated teratogenesis could explain the effects of medication on the developing fetus (van Gelder et al., 2010). Our study showed that medication was related to the severity of CL ± P. Previous studies have reported a significantly increased CL ± P risk in infants whose mothers use amoxicillin in the pre-gestation period (Lin et al., 2012, Howley et al., 2020).

The prevalence of severe CL ± P and CP was significantly higher in infants with NSOFC whose mothers did not take folic acid supplements. A *meta*-analysis by Badovinac et al. found a relationship between folic acid use and CL ± P based on five prospective studies (Badovinac et al., 2007). Furthermore, folic acid-containing supplements and/or multivitamins reduce the risk of CL ± P and CP by approximately 28 % and 20 %, respectively (Carinci et al., 2005). Further studies are needed to evaluate the amount, type, duration, and dosage of antibiotics and to clarify their effects on infant development.

This study had some limitations. The frequency of exposure was insufficient to definitively determine several environmental etiological risk variables, such as maternal smoking. Therefore, a larger sample size is required to verify our results. Moreover, the sample size for CP should be increased to further verify its risk factors. However, these aspects are worth exploring because of their relevance to the design of community prevention programs and future research. Another limitation of this study is recall bias. To limit this type of bias, we interviewed parents as soon as the infants were born.

5. Conclusion

Maternal illnesses, maternal medicating during the first trimester, and a family history of NSOFC significantly correlated with higher CL ± P severity. Folic acid supplementation in the first trimester significantly correlated with a lower severity of CL ± P and CP. Future prospective cohort studies are recommended to assess the effects of environmental factors on NSOFC severity during the first trimester of pregnancy. Community prevention programs that alter a range of lifestyle and behavioral variables may be beneficial for controlling the severity and probability of NSOFC.

Ethical statement

Ethical approval was obtained from the Research Ethics Committees of King Abdulaziz University Faculty of Dentistry (257-07-21) and King Fajad Armed Forces Hospital (REC 391) and the Institutional Review Boards of the Ministry of National Guard at King Abdullah International Medical Research Center (H-01-R-005), Ministry of Health in Riyadh (H-01-R012), and Ministry of Health in Jeddah (H-02-J-002).

CRediT authorship contribution statement

Sultan Musaad Alghamdi: Methodology, Writing – original draft. **Rana Abdullah Alamoudi:** Methodology, Writing – original draft, Writing – review & editing. **Najla Sulaiman Alrejaye:** Methodology. **Fatma Dawood Abdulhameed:** Methodology. **Reema Mahdi Alhussain:** Methodology. **Latifa Yousef AlGudaibi:** Methodology. **Heba Jafar Sabbagh:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sdentj.2023.12.009.

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