ASPI | Afarand Scholarly Publishing Institute; Turkey
ISSN: 2345-2897; Health Education and Health Promotion. 2024;12(1):47-52. 10.58209/hehp.12.1.47

Analysis of Maternal Risk Factors Associated with Non-Syndromic Orofacial Cleft Among Newborns at Celebes Cleft Center in Makassar

ARTICLE INFO

Article Type
Original Research

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How to cite this article
Rusdi B, Abdullah AZ, Wahiduddin W, Maria IL, Salmah U, Nazaruddin B. Analysis of Maternal Risk Factors Associated with Non-Syndromic Orofacial Cleft Among Newborns at Celebes Cleft Center in Makassar. Health Education and Healt Promotion. 2024;12(1):47-52.

ABSTRACT

Aims Non-syndromic orofacial cleft (NSOFC) is a congenital facial anomaly of cleft lip, cleft palate, or both, most commonly affecting the craniofacial region and oral cavity. The etiology is multifactorial, combining endogenous (genetic) with environmentally influenced exogenous factors. This study aimed to determine and analyze the risk factors for the incidence of NSOFC.

Materials & Methods This case-control study was conducted at Celebes Cleft Center in Makassar. The case group consisted of 80 newborns with cleft lip and palate, and the control group consisted of 106 newborns without cleft lip and palate. Data collected included sex, type of NSOFC, age of respondents, educational level, risk factors for NSOFC incidence from patient medical records and interview results. Data were collected in an Excel table and analyzed using the Stata program using the Chi-square test and multiple logistic regression

Findings The results showed that NSOFC mostly occurred in newborns of male gender (58.75%). The most common type of NSOFC was cleft lip accompanied by cleft palate then cleft lip, and the least was cleft palate. Maternal risk factors that were significant for the incidence of cleft lip and palate/NSOFC were maternal occupation (OR=25.037; 95%CI=5.812-222.113; p<0.001), family history of orofacial cleft (OR=11.666; 95%CI=1.493-522.396; p=0.005), history of tobacco smoke exposure during pregnancy (OR=2.64; 95%CI=1.355-5.187; p=0.002). The most dominant risk factor was maternal occupation.

Conclusion The type of maternal occupation, family history of orofacial cleft, and maternal history of tobacco smoking are risk factors for the incidence of lip and palate cleft or NSOFC.

Keywords Cleft Lip; Palate; Cleft Palate; Risk Factors

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Article History
Received: November 2, 2023
Accepted: January 11, 2024
ePublished: January 20, 2024

CITATION LINKS

[1] Variation of non-syndromic cleft lip/palate in Yayasan Surabaya cleft lip/palate ... [2] Parental exposures and risk of nonsyndromic orofacial clefts in ... [3] A case-control study of environmental exposures for nonsyndromic cleft of the lip ... [4] Distribution and risk factors of cleft lip and palate on patients from a sample ... [5] Risk factors for oral clefts: A population-based case-control study ... [6] Assessment of the correlation between various risk factors and orofacial cleft disorder spectrum: ... [7] Family history and socioeconomic risk factors for non-syndromic cleft lip and ... [8] Parent's occupation and isolated orofacial clefts in ... [9] A case-control study of environmental risk factors for nonsyndromic cleft of the lip and/or ... [10] Oral clefts, consanguinity, parental tobacco and alcohol use: A case-control ... [11] Incidence of cleft lip and palate and risks of additional ... [12] Orofacial clefts: A worldwide review of the ... [13] Maternal risk factors associated with the development of cleft lip and cleft palate in ... [14] Global, regional and national burden of orofacial clefts from 1990 to 2019: ... [15] Indonesian Basic Health Research in 2018 ... [16] Indonesian Basic Health Research in 2013 ... [17] TSouth Sulawesi Province Report in Indonesian Basic Health Research in 2018 ... [18] The impact of orofacial clefts on quality of life and healthcare use ... [19] Maternal risk factors for oral clefts: A case-control ... [20] Family history and risk factors for cleft lip and palate patients and ... [21] Parental age as a risk factor for non-syndromic oral clefts: A ... [22] Paternal occupation and risk of birth defects in ... [23] Family history in non-syndromic orofacial clefts: Is there ... [24] Identification of exogenous risk factors for non-syndromic maternal ... [25] Environmental and genetic risk factors of nonsyndromic and syndromic cleft lip ...

Introduction

Congenital anomalies refer to abnormal structures or malformations that arise from errors in fetal development and are observable at birth. These anomalies are a significant cause of prenatal, perinatal, and infant mortality and morbidity, with orofacial clefts (OC) being among the most prevalent [1].

Orofacial clefts represent the most frequent congenital malformation in the craniofacial and oral regions, leading to considerable medical and social challenges [1, 2]. The spectrum of orofacial cleft phenotypes includes cleft lip (CL), cleft lip and/or palate (CL/P), and cleft palate (CP), which can be further categorized into non-syndromic (isolated) and syndromic, the latter being associated with other anomalies [3].

A syndromic orofacial cleft is linked to a specific monogenic disorder or chromosomal anomaly and may also be influenced by environmental factors. In contrast, the causes of non-syndromic orofacial clefts (NSOFCs) are largely unknown, though it is generally believed that they result from interactions between genetic factors and environmental influences [2-5].

The causes of NSOFC are multifactorial, encompassing both genetic variations, including chromosomal abnormalities and syndromes, and environmental factors [6]. The occurrence of non-syndromic CL/P has been connected to various risk factors. Environmental influences, either independently or together with genetic factors (such as transforming growth factor (TGF-α)/TGF-β, *BCL3*, and *MSX1*), are thought to account for approximately 60% of CL/P cases [6]. Risk factors, such as socioeconomic status, maternal age at pregnancy, maternal education level, occupation type, residential location, history of abortion, maternal blood pressure, smoking during pregnancy, alcohol intake, use of anticonvulsants and retinoic acid, exposure to home decoration pollutants, and parental occupation have been shown to affect the occurrence of non-syndromic CL/P [2, 4, 7-9].

The prevalence of orofacial clefts ranges from 1 in 500 to 1 in 2500 births, varying by geographic location, ethnicity, and genetic background. The global incidence of non-syndromic CL/P is 1.4 per 1000 births, with Caucasians experiencing it at approximately 1 in 1000 births [10]. A study conducted by Hagberg in 1998 in Stockholm, Sweden, reported an incidence rate of 2 per 1000 births. Asian populations faced the highest risk, with 14 per 10,000 births, followed by Europe at approximately 6 per 10,000 births, and the lowest rates were observed in individuals of European descent, at 4 per 10,000 births [11-13].

A global decrease in orofacial cleft occurrences was noted in a study by Wang *et al.* in 2023, utilizing data from the Global Burden of Disease study in 2019. This research revealed that the incidence of orofacial clefts declined from 3.61 per 100,000 in 1990 to 2.98 per 100,000 in 2019. Despite this overall reduction, the highest incidence rates in both 1990 and 2019 were reported in low- to middle-income countries. Mortality rates associated with orofacial clefts decreased from 0.18 per 100,000 in 1990 to 0.04 per 100,000 in 2019, with all deaths occurring in low- to middle-income regions. The disease burden, measured in disability-adjusted life years (DALYs), also showed a decline from 19.63 per 100,000 in 1990 to 7.51 per 100,000 in 2019, with high- to middle-income countries demonstrating the most significant reduction in trend [14].

In Indonesia, classified as a low- to middle-income country, the prevalence of orofacial cleft is reported to be 0.12%, or 1.2 per 1000 births, according to the National Basic Health Research conducted in 2018. This rate marks an increase from the 2013 National Basic Health Research findings, which recorded a prevalence of 0.08% or 0.8 per 1000 births. These statistics highlight that orofacial cleft cases remain a significant challenge in Indonesia. Furthermore, the 2018 National Basic Health Research indicated that the prevalence in South Sulawesi province was slightly below the national average at 0.10% or approximately 1 per 1000 births. Although lower, this rate is still considerably high for congenital cleft incidences [15-17].

Individuals with CL/P face social and economic challenges that significantly impact their and their families' quality of life over the long term. They are more susceptible to various health issues, including difficulties with mastication, speech and hearing, and an increased risk of ear infections, which elevate the morbidity and mortality rates [18]. Economically, the treatment for Americans with CL/P is estimated to incur lifetime medical costs of about 100,000 dollars per person. Addressing orofacial clefts requires long-term, phased treatment involving collaboration across multiple disciplines, including dentistry, surgery, pediatrics, and psychology.

This study assessed the risk factors for orofacial cleft incidence in patients at the Celebes Cleft Center in Makassar.

Materials and Methods

Study Design and Population

This study utilized an analytic observational approach with a case-control design, conducted in South Sulawesi province in conjunction with the lip cleft social service provided by the Celebes Cleft Center Foundation in Makassar from July to October 2023.

Sampling and Selection of Cases and Controls

For case sampling, this study employed a saturated sampling technique, wherein the entire population under investigation was chosen as research subjects. Control samples were selected after establishing the number of case subjects. Controls were then

identified using a simple random sampling from the same hospital, maintaining a 1:1 ratio of cases to controls. The minimum sample size determined for this study was 154 individuals, comprising 77 cases and 77 controls, to evaluate maternal risk factors influencing the incidence of NSOFC at the Celebes Cleft Center in Makassar City. This sample size calculation utilized the "OpenEpi" online statistical software, employing the Fleiss method with continuity correction for an unmatched case-control study, assuming a two-sided α of 0.05, a beta (β) of 0.20, and a hypothetical proportion of exposure in cases and controls of 0.625 and 0.40, respectively, with an additional 10% added to account for other variables.

Cases included children registered with the Cleft Lip Charity at the Celebes Cleft Center who had been diagnosed with NSOFC (CL, CL/P, CP) as confirmed by medical records. Mothers of these children were interviewed by researchers to gather data according to the study variables. Inclusion criteria for cases were children aged 0-5 years with available medical records who were willing to participate in the research questionnaire. Controls consisted of children from the same location as the cases who did not have NSOFC. Suitable controls were randomly chosen from the general hospital population in the same area in Makassar. The exclusion criteria for both cases and controls were children with other deformities or those who did not complete the questionnaire.

Variables, Tools, and Data Collection Techniques

This study utilized secondary data sourced from the patient records at Yayasan Celebes Cleft Center in Makassar City, which included information on age, gender, the highest educational level of parents, family history of orofacial cleft, history of smoking or exposure to tobacco smoke, alcohol consumption during pregnancy, and pesticide exposure history. Primary data were gathered through direct interviews with pregnant women and the control group, using an interview questionnaire divided into two sections: respondent characteristics and maternal risk factors. The characteristics covered the age and education level of the mother, while the second section focused on maternal risk factors/predictive variables, such as age during pregnancy, occupation, family history of NSOFC, smoking or exposure to tobacco smoke, alcohol consumption during pregnancy, and pesticide exposure history. The interview findings were categorized into high and low risk based on the responses.

Ethical Considerations

The research received approval from the Department of Epidemiology, Faculty of Public Health, Hasanuddin University, under certificate number: 23144/UN4.14.8/PT.01.04/2023, and ethical clearance from the Faculty of Public Health, Hasanuddin University, with the number: 4509/UN4.14.1/TP.01.02/2023.

Data analysis

All analyses were conducted using Stata 14.2 (StataCorp, 2015). Univariate analysis results were displayed in tables to outline the characteristics of respondents, case distribution, and study variables. For bivariate analysis, the Chi-square test was utilized, and Fisher's exact test was applied when the Chi-square test's criteria were not met (when the number of data points was less than 5) to identify variables significantly affecting the incidence of NSOFC with a significance threshold set at p=0.05. Additionally, the association between two events or factors was evaluated using the odds ratio (OR). The multivariate analysis involved a multiple logistic regression test employing a stepwise method to determine the variables most significantly impacting the incidence of NSOFC at the Celebes Cleft Center in Makassar. The strength of associations was reported as OR with 95% confidence intervals (CI).

Findings

Respondent Characteristics and Case Distribution

The total sample included 201 respondents, comprising 81 cases and 120 controls, collected between July and August 2023. However, due to incomplete data, 1 case and 14 control subjects were excluded, leaving 80 case subjects and 106 control subjects for analysis. Table 1 illustrates the distribution of NSOFC cases, indicating a higher prevalence in male babies (58.75%) and a greater frequency of the lip and palate gap phenotype group (38.75%).

Table 1. Frequency of non-syndromic orofacial cleft cases

Parameter	Values
Gender	
Male	47(58.75)
Female	33(41.25)
Total	80(100.00)
Types of NSOFC	
Cleft lip	28(35.00)
Cleft lip and palate	31(38.75)
Cleft palate	21(26.25)
Total	80(100.00)

Table 2. Frequency of cases and controls based on their characteristics

Parameter	NSOFC Incident		Total
	Cases (n=80)	Control (n=106)	
Age (year)			
15-24	30(37.50)	40(37.74)	70(37.63)
25-35	46(57.50)	60(56.60)	106(56.99)
34-50	4(5)	6(5.66)	10(5.38)
Education			
Elementary school	21(26.25)	3(2.83)	24(12.90)
Junior high school	9(11.25)	6(5.66)	15(8.06)
Senior high school	36(45.00)	33(31.13)	69(37.10)
Diploma	3(3.75)	15(14.15)	18(9.68)
Bachelor's degree	11(13.75)	45(42.45)	56(30.11)
Master's degree/PhD	0(0)	4(3.77)	4(2.15)

Regarding the age distribution of all research participants, the majority fell within the 25-35 year age group (51.08%). The educational background of respondents showed significant differences between groups; in the case group, the majority were high school graduates (45%), whereas in the control group, most had completed undergraduate degrees (42.45%; Table 2).

Risk Factors for the Incidence of NSOFC

In the bivariate analysis, the association of NSOFC in children with maternal age during pregnancy (OR=0.723; CI 95%=0.278-1.881), history of tobacco use during pregnancy (OR=1.392; 95%CI=0.016-105.306), and history of pesticide exposure (OR=1.53; 95%CI=0.529-4.519) was not statistically significant (p>0.05). However, a significant correlation was found between the occurrence of NSOFC in newborns and factors such as maternal occupation (OR=25.037; 95%CI=5.812-222.113), a family history of orofacial cleft (OR=11.666; 95%CI=1.493-522.396), and exposure to tobacco smoke (OR=2.64; 95%CI=1.355-5.187) (p-value<0.05 for all) (Table 3).

Table 4 presents the results from the multivariate analysis of independent variables, indicating that maternal history of orofacial cleft (OR=27.47; 95%CI=6.25-120.75; p<0.05) and occupational risks (OR=15.43; 95%CI=1.849-128.79; p<0.05) were the most impactful variables on the incidence of NSOFC at the Celebes Cleft Center.

Table 3. Frequency of risk factors for non-syndromic orofacial cleft (NSOFC) based on independent variables

Independent variables	NSOFC Incident		Total		
	Cases (n=80)	Control (n=106)	p-Value	OR	95%CI
Maternal age at pregnancy			0.903	0.964	0.513-1.805
High risk	34(42.50)	46(43.40)			
Low risk	46(57.50)	60(56.60)			
Mother's occupation			<0.001	25.037	5.812-222.113
High risk	26(32.50)	2(1.89)			
Low risk	57(67.50)	104(98.11)			
Family history of orofacial clefts	8(10)	1(0.94)	0.004	11.666	1.493-522.396
High risk	72(90)	105(99.06)			
Low risk					
Mothers with a history of smoking during pregnancy			0.84	1.392	0.016-105.306
High risk	1(1.25)	1(0.94)			
Low risk	79(98.75)	105(99.06)			
History of tobacco smoke exposure during pregnancy			0.002	2.64	1.355-5.187
High risk	37(46.25)	26(24.53)			
Low risk	43(53.75)	80(75.47)			
Mothers with a history of pesticide exposure during pregnancy			0.37	1.53	0.529-4.519
High risk	10(12.5)	9(8.49)			
Low risk	70(87.5)	97(91.51)			

Table 4. Results of multivariate analysis of independent variables

Independent variables	OR	95%CI (LL-LU)	p-Value
Mother's occupation	27.47	6.25-120.75	0.00
Family history of orofacial clefts	15.43	1.849-128.79	0.01
History of tobacco smoke exposure during pregnancy	-	-	0.08

Discussion

The study found a higher prevalence of NSOFC among male children, aligning with studies conducted in Iran by Golalipour *et al.* [19] and Jamilian *et al.* [20], which reported a generally higher occurrence in males than females, though without a significant statistical correlation between gender and the incidence of oral cleft. A study by Cheshmi *et al.* [6] reported a slight variance, with about 53% prevalence in females. This discrepancy highlights the need for further investigation to understand the cause of these differences.

This study observed a predominance of the lip and palate gap type of NSOFC. This finding is consistent with research by Leite *et al.* [10], Lin *et al.* [3], and Xu *et al.* [9], which also reported a higher distribution of NSOFC in the lip and palate cleft, single lip cleft, and the least in single palate cleft. A study by Triwardhani *et al.* [1] in Indonesia confirmed similar results, with approximately 69% of NSOFC cases presenting with a cleft lip and palate phenotype.

This study determined that the maternal age during pregnancy did not significantly influence the incidence of NSOFC (p=0.903), and high-risk maternal age (<25 years and >35 years) was identified as a protective factor (OR=0.964), though not statistically significant. This finding aligns with Golalipour *et al.* [19], who also found no association between maternal age and the incidence of NSOFC. However, this contrasts with two other studies that identified a significant link between maternal age during pregnancy and NSOFC incidence (<19 years and >30 years) [3, 9].

Further, studies by Cheshmi *et al.* [6] and Jamilian *et al.* [20] indicated that maternal age during pregnancy generally had no significant effect across most categories, with the exception of the age group >34 years (p<0.001). These findings concur with prior

meta-analysis research, which suggested that mothers over 40 years of age have a 28% increased risk of having children with NSOFC [21]. Additional studies are required to explore why older pregnant mothers are at an elevated risk of giving birth to children with NSOFC.

The occupation of high-risk mothers was found to increase the risk of NSOFC in children by 25.037 times compared to mothers engaged in low-risk occupations. This is consistent with a study by Schnitzer *et al.* [22] in Atlanta, USA, which highlighted farmers as a primary occupation associated with NSOFC incidence. Other high-risk occupations include fishermen and heavy laborers, suggesting a close relationship with chemical exposure. Contrarily, research in Greece indicated no significant link between maternal occupation and the high-risk category concerning the incidence of NSOFC in children, although this study was limited by a small sample size [2].

Research into the genetic links to familial predisposition towards clefts started in 1942, when Fogh-Andersen observed a higher occurrence of orofacial clefts in the families of affected individuals, suggesting that hereditary factors could influence the prevalence of clefts [23]. This study supports the notion that mothers belonging to a high-risk category or with a family history of orofacial cleft are 11.666 times more likely to have children with NSOFC compared to mothers without such a family history. This finding aligns with prior research indicating a significant risk of NSOFC in children due to family history [3, 7, 9, 20]. With numerous studies highlighting the influence of genetics on NSOFC, further investigation into the specific genetic contributions to cleft prevalence is warranted.

The current study did not identify any respondents who consumed anticonvulsants before or during pregnancy. This absence might be attributed to the study's small sample size and the relatively low incidence of epilepsy, which typically necessitates anticonvulsant medication, in eastern Indonesia. Future studies would benefit from larger sample sizes and more rigorous sampling strategies.

In this research, respondents exposed to smoke, whether actively or passively, were grouped together. Findings revealed that mothers classified as high-risk were 2.64 times more likely to have children with NSOFC than those in the low-risk category.

Similar findings were reported in other studies [24], noting that passive smoking during pregnancy could slightly increase the risk of NSOFC in offspring compared to active smoking (OR=1.14), with the risk escalating if the pregnant women also smoked actively (OR=1.51).

Additionally, a study in Brazil indicated no significant correlation between smoking during the first trimester of pregnancy and the occurrence of orofacial clefts, whereas exposure to tobacco smoke was significantly associated with NSOFC incidence (p=0.001; OR=1.70; 95%CI=1.09-2.97) [10].

Research conducted by Nahas *et al.* [4] revealed that according to their logistic regression model, children of mothers who smoked during pregnancy had a higher likelihood of developing NSOFC (OR=2.00; CI=95%) compared to those whose mothers did not smoke. This finding aligns with other research, where bivariate analysis indicated a significant association between both active and passive smoking during pregnancy and the incidence of NSOFC in children (p<0.001) [9]. The role of smoking, whether active or passive, during pregnancy as a risk factor for NSOFC has been extensively examined. Despite this, the specific pathomechanism linking smoking to the etiology of NSOFC remains unclear, though it is suspected that genetic modifications may play a part in the epigenetic manifestation of this condition.

Exposure to chemicals, including those from cosmetic products, cleansers, and pesticides, has been associated with an increased risk of developing orofacial clefts [25]. This research investigated the impact of pesticide exposure during pregnancy on mothers and discovered that it heightened the risk of NSOFC in children by 1.53 times compared to mothers who were not exposed to pesticides, although the finding was not statistically significant. Similarly, studies in China have shown that pesticide exposure during pregnancy raised the risk of NSOFC in children by 1.25 times, albeit without statistical significance. Moreover, this study explored the effect of pesticide exposure in fathers, finding a significant association with the incidence of NSOFC. This result suggests the need for further investigation into whether paternal pesticide exposure could indirectly influence the mother, thereby becoming a risk factor for NSOFC [5]. These outcomes differ from previous research, such as the study by Xu *et al.* [9], which used logistic regression to demonstrate that pesticide exposure significantly increases the risk of NSOFC in children (p<0.006, OR=8.90, 95%CI=1.81-43.59), and Mirilas *et al.* [2] indicated that children of mothers exposed to pesticides had a risk factor of 1.83 (95%CI=0.61-5.47). Although not all past studies consistently report the same patterns of orofacial cleft incidence, numerous research has identified pesticide exposure as a risk factor for congenital anomalies in newborns. Future research will require more precise exposure indicators and larger sample sizes to further address this issue.

This case-control study has several limitations. Conducted at the Celebes Cleft Center in Makassar, its findings may not be generalizable to other regions in Indonesia. Additionally, the study was unable to determine whether the exposure preceded the outcome. Thus, a longitudinal study is necessary to establish a causal relationship. Recall bias represents another potential limitation. However, a significant strength of this study is its large sample size relative to previous research.

Conclusion

The type of maternal occupation, family history of orofacial cleft, and maternal history of tobacco smoking are risk factors for the incidence of lip and palate cleft or NSOFC.

Acknowledgments: This article is the result of Budiman Rusdi's master's thesis in epidemiology entitled "Analysis of maternal risk factors for cleft lip and palate / non-syndromic orofacial cleft incidence in infants in celebes cleft centre in Makassar City". The researchers of this study would like to thank all the participants in this research and the Director of Celebes Cleft Center in Makassar City.

Ethical Permissions: The Ethical clearance was obtained from the Faculty of Public Health, Hasanuddin University (4509/UN4.14.1/TP.01.02/2023).

Conflicts of Interests: There are no conflicts of interests.

Authors' Contribution: Rusdi B (First Author), Introduction Writer/Methodologist/Main Researcher/Discussion Writer/Statistical Analyst (30%); Abdullah AZ (Second Author), Introduction Writer/Methodologist/Discussion Writer (20%); Wahiduddin W (Third Author), Introduction Writer/Discussion Writer (20%); Maria IL (Fourth Author), Assistant Researcher (10%); Salmah U (Fifth Author), Methodologist/Discussion Writer/Statistical Analyst (10%); Nazaruddin B (Sixth Author), Introduction Writer/Discussion Writer (10%)

Funding/Support: No financial support was received.

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