

## Risk Factors Associated with Cleft Etiology: A Multicenter Experience

Adesina Oluwafemi Adewale, BDS, FMCDS<sup>1\*</sup>, Rasheedat Ojikutu, BDS, FWACS<sup>1</sup>, Olubi Olawale MBBS, FWACS<sup>2</sup>, Adenuga-Taiwo Olugbenga, BDS, FWACS<sup>3</sup>, Opaleye Taofiq, BDS FWACS<sup>1</sup>, Adesina Opeyemi Olufeyisola, PhD<sup>4</sup>

<sup>1</sup>Department of Oral and Maxillofacial Surgery, Lagos state University College of Medicine, Lagos state University College of Medicine 1-5 Oba- Akinjobi Rd GRA Ikeja, Lagos, Nigeria

<sup>2</sup>Department of Ear, Nose and Throat, Lagos state University College of Medicine, Lagos state University College of Medicine 1-5 Oba- Akinjobi Rd GRA Ikeja, Lagos, Nigeria

<sup>3</sup>Department of Restorative Dentistry, Lagos state University College of Medicine, Lagos state University College of Medicine 1-5 Oba- Akinjobi Rd GRA Ikeja, Lagos, Nigeria

<sup>4</sup>Department of Medical Laboratory Science, Babcock University, 121103, Ilishan-Remo, Ogun State, Nigeria

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\*Corresponding author: Adesina Oluwafemi Adewale

Department of Oral and Maxillofacial Surgery, Lagos state University College of Medicine, Lagos state University College of Medicine 1-5 Oba- Akinjobi Rd GRA Ikeja, Lagos, Nigeria

### Abstract

**Background:** The etiology of cleft lip and palate is complex and thought to involve genetic influences with variable interactions from environmental factors. Although genetic and environmental triggers are important for syndromic cleft lip and palate, the etiology of the more common non-syndromic (isolated) forms remains poorly understood. Recognition of etiology, risk factors and natural history is essential to define how prevention and treatment should be planned and implemented. **Objective:** This study is aimed at assessing the possible risk factors in the etiology of patients presenting with cleft lip and palate. **Materials and methods:** A total of 254 children (children 12 years and below) for cleft surgery at three surgical centers (Mercyland orthopedic Hospital, Galaxy Medical Center and Shifa Royal Hospital) in the North Eastern under the Smile Train, project for a 2-year period (January 2021 to December 2022) were included in this study. A self-administered questionnaire was prepared to fill in data about the patients' gender, family history of cleft, consanguineous marriages, maternal risk factors. Ages of the children were ascertained in months and years as told by the parents. Paternal and maternal ages were also recorded. Statistical analysis was done using the Statistical Package for Social Sciences (IBM) 23.0 version. The significant level was set at a p value of  $\leq 0.05$  at 95% confidence interval. **Results:** Median age at presentation was 4 months, varying from  $<1$  months to 12 years. The gender distribution was 133 (52.4%) males and 121 (47.6%) females (M:F = 1:0.9). Majority (214, 84.3%) of the affected children belonged to low socioeconomic group while only a few (12, 4.7%). High proportion of mothers between the age of 26 to 35 years (42.5%) was observed, but no association was found between maternal age and clefts ( $p=0.331$ ). There was evidence of association between paternal age  $>35$  years old and cleft ( $p=0.005$ ). **Conclusion:** This study revealed a strong association between consanguineous marriage, low socioeconomic status and persistent maternal fever during the first trimester and cleft. Increasing paternal age was also found to increase the risk of cleft. The relevance of this study is for public health workers and clinicians to be equipped with adequate information to provide useful counseling to parents particularly those with history of cleft. It may also provide adequate information for policy makers when making policies of public health concerns.

**Keywords:** Risk, Cleft, Etiology, Multicenter.

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## INTRODUCTION

Cleft lip and palate are considered as one of the most common birth defects that result in medical, psychological, and social problems in affected individuals and their families. The etiology of cleft lip

and palate is complex and thought to involve genetic influences with variable interactions from environmental factors [1]. However in developing countries where prenatal care is less advanced or less available, religious and cultural beliefs regarding causation of clefts include witchcraft, God's will, and

engaging in a behaviour associated with causal power (e.g. looking at a child with a facial deformity when pregnant) [2].

Although genetic and environmental triggers are important for syndromic cleft lip and palate, the etiology of the more common non-syndromic (isolated) forms remains poorly understood [3, 4]. Many studies have shown that monozygotic twins (60%) have considerable higher concordance rate than dizygotic twins and siblings (5-10%) [5, 6]. Chromosomal aberrations and single gene mutations are frequently associated with the development of cleft lip and palate; single gene mutation being more prevalent than the chromosomal abnormalities [7].

The occurrence of cleft lip and palate has been linked to several environmental factors. These factors include deficiency of vitamins such as folic acid in pregnancy [8]. Teratogenic effect of several drugs such as hydantoin, sodium valproate, trimethadion, tranquilizers, and alcohol is well-known. Children born to mothers suffering from diabetes mellitus or phenylketonuria are at higher risk of developing CL/P and advanced maternal age [9, 10]. Development of fever more than 40°C, during the 1st 8 weeks of gestation causing facial clefts in the developing fetus has also been reported [9].

Recognition of etiology, risk factors and natural history is essential to define how prevention and treatment should be planned and implemented [11].

This study is aimed at assessing the possible risk factors in the etiology of patients presenting with cleft lip and palate.

## METHODOLOGY

A total of 254 children (children 12 years and below) who were among those who presented for cleft surgery at three surgical centers (Mercyland orthopedic Hospital, Galaxy Medical Center and Shifa Royal Hospital) in the North Eastern under the Smile Train, project for a 2-year period (January 2021 to December 2022) were included in this study.

After taking oral consent of the parents accompanying the patient, a detail history followed by clinical examination was performed.

A Self-administered questionnaire was prepared to fill in data about the patients' gender, family history of cleft, consanguineous marriages, maternal risk factors. Ages of the children were ascertained in months and years as told by the parents. Paternal and maternal ages were also recorded.

Risk factors were defined as those intrauterine insults that have been clearly shown to be associated with the development of Oro-facial cleft in the fetus,

like intake of anticonvulsant drugs by the mother during 1<sup>st</sup> three months of gestation, Smoking, alcohol ingestion, lack of folic acid consumption during pregnancy and overt diabetes mellitus in the mother. History of developing persistent high grade fever by the mother for at least 3 days during the 1st three months of pregnancy. Exposure to X-ray and CT scan during pregnancy.

A marriage was said to be consanguineous if the parents had at least one ancestor in common.

Children with cleft were classified into four groups according to anatomical site, i.e., children with cleft lip alone (CL), children with cleft palate alone (CP) and children having Cleft lip and palate (CL/P) and Bilateral cleft lip and palate (BCLP).

The socioeconomic status of the affected families was carefully ascertained on the basis of the occupation and educational attainment of the parents using the method and classification described by Oyedeji (1984) [12].

Statistical analysis was done using the Statistical Package for Social Sciences (IBM) 23.0 version. The significant level was set at a p value of <math>0.05</math> at 95% confidence interval.

## RESULT

A total of 254 children with cleft patients who presented at the maxillofacial clinic for the first time were analysed, Median age at presentation was 4 months, varying from <math><1</math> months to 12 years. The gender distribution was 133 (52.4%) males and 121 (47.6%) females (M:F = 1:0.9) Table 1.

Of the 254 children, 111 cases (43.7%) were Unilateral cleft lip only, followed by cases of Unilateral cleft lip and palate which was 73 (28.7%). The least number of cleft belonged to isolated cleft palate comprising of 32 cases (12.6%) Figure 1.

Majority (214, 84.3%) of the affected children belonged to low socioeconomic group while only a few (12, 4.7%) were born into families in the upper socioeconomic group Figure 2.

Most probable cause of cleft was recorded in 43.7% of the cases which was due to sickness of the mother during first trimester with persistent fever. 49 (19.3%) cases of the cleft cases were born from Consanguineous marriages. Drug ingestion other than routine antenatal drugs in first trimester examples Metronidazole and Tetracycline to stop stooling was recorded in 41 cases. Few number of cases was recorded in paternal family history, maternal family history, diabetes in mothers of the patients and families having other children with cleft Table 2.

Table 3 shows distribution of cleft according to type and parental age. High proportion of mothers between the age of 26 to 35 years (42.5%) was observed, but no association was found between

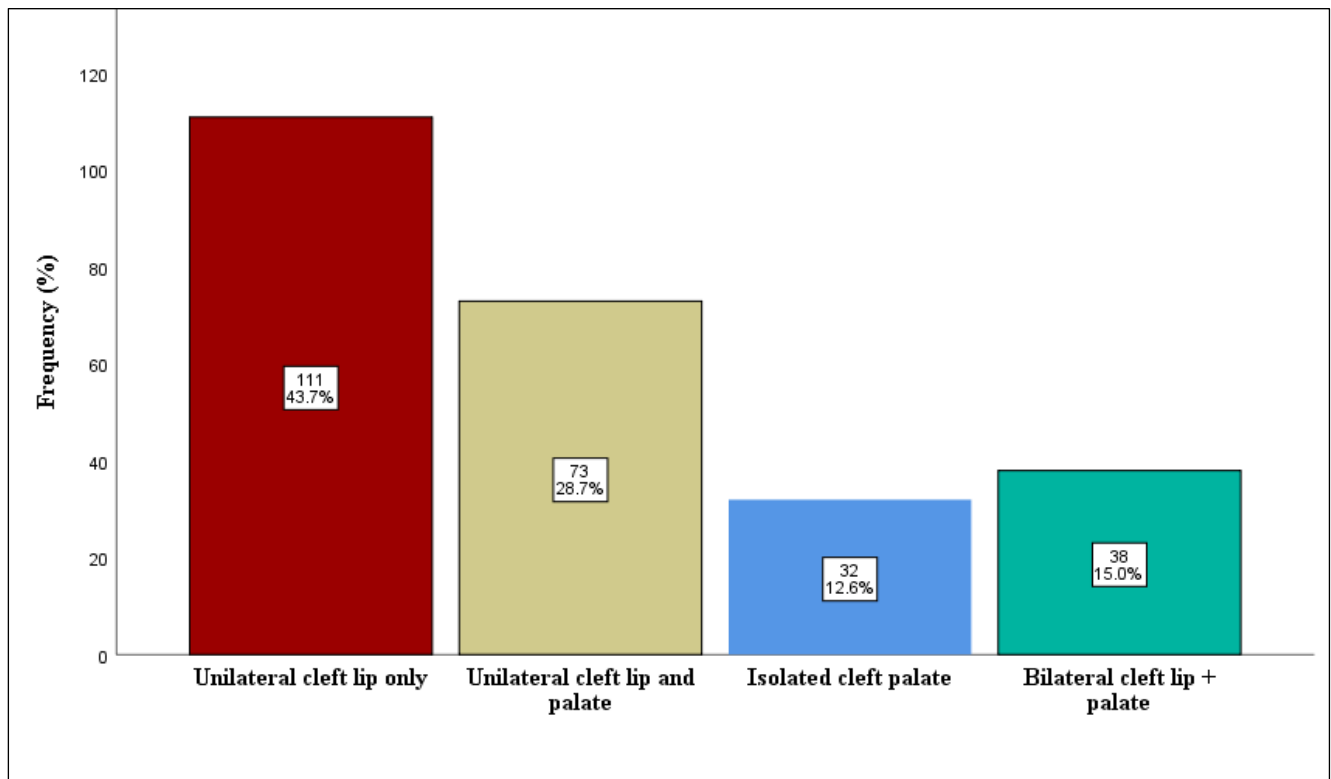
maternal age and clefts ( $p=0.331$ ). It was also observed that most of the men were greater than 35 years old (63.8%). There was evidence of association between paternal age >35years old and cleft ( $p=0.005$ ).

**Table 1: Socio-demographic characteristics of patients**

Variable	Frequency (n=254)	Percentage
<b>Age group (Years)</b>		
≤1 months	90	35.4
1-6 months	53	20.9
6-12 months	65	25.6
1-5 years	28	11.0
6-12 years	18	7.1
Median (Q1-Q3)	4 (1.0-13.0)	
<b>Gender</b>		
Male	133	52.4
Female	121	47.6

**Table 2: Risk factor of cleft among patients**

Variable	Frequency (n=254)	Percentage
<b>Any other sibling with cleft</b>	8	3.1
<b>Consanguineous marriage</b>	49	19.3
<b>Sickness at first trimester</b>	143	43.7
<b>Maternal family history of cleft</b>	7	2.8
<b>Paternal history of cleft</b>	6	2.4
<b>Exposure to radiation during pregnancy</b>	7	2.8
<b>Presence of chronic medical condition in mothers</b>	5	2.0
<b>Drug ingestion other than routine antenatal drugs in first trimester</b>	41	16.1



**Figure 1: Showing distribution of cleft type among patients**

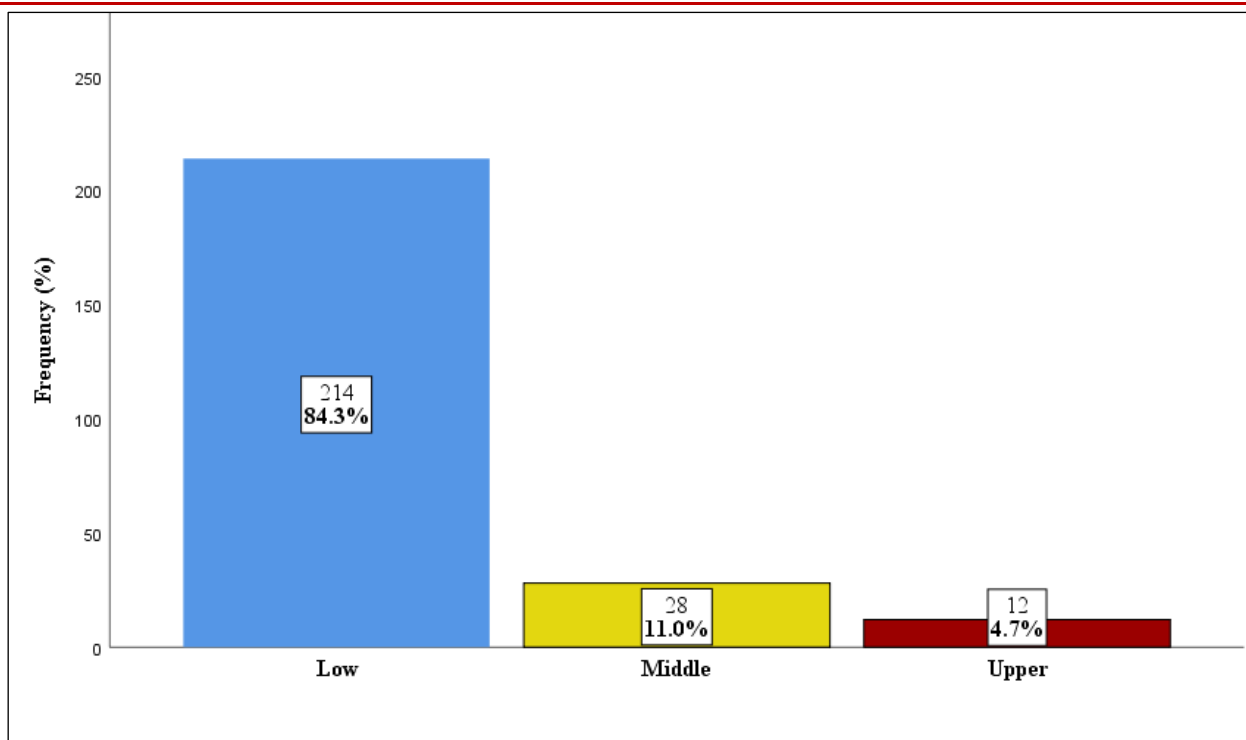


Figure 2: Social class of patients

Table 3: Maternal and paternal age of patients

	Maternal age (years)			p value	Paternal age (years)			p-value
	≤25 (n=78)	26-35 (n=108)	>35 (n=68)		≤25 (n=11)	26-35 (n=81)	>35 (n=162)	
Unilateral cleft lip only	37(47.4)	51(47.2)	23(33.8)	0.115	5(45.5)	42(51.9)	64(39.5)	0.005*
Isolated cleft palate	6(7.7)	11(10.2)	15(22.1)		1(9.1)	8(9.9)	23(14.2)	
Unilateral cleft lip and palate	22(28.2)	33(30.6)	18(26.5)		4(36.4)	24(29.6)	45(27.8)	
Bilateral cleft lip ± palate	13(16.7)	13(12.0)	12(17.6)		1(9.1)	7(8.6)	30(18.5)	

## DISCUSSION

The etiology of CL/P has been extensively studied in industrialized countries and is heterogeneous with increasing evidence that these anomalies are multifactorial in nature. However the etiology of the more common non-syndromic (isolated) forms remains poorly understood [3, 4]. Gender, geographical location, nationality, nutritional, tobacco use, use of antiepileptic drugs, alcohol consumption, low birth weight, Pesticides, and contaminated water sources have all been hypothesized as factors increasing the incidence rate of CL/P in newborns [13, 14].

This study revealed a higher incidence of Cleft Palate and Cleft lip and Palate among females and a male dominance for CL. This is contrary to the findings in studies from Europe, Middle-East, India and USA [15, 16], while another found no significant difference between the incidence of Cleft lip between genders [17]. The frequency of bilateral cleft lip and palate was low with male dominance, this is contrary to the studies in South India and Iran [16, 17].

This study has also revealed an association between genetic and environmental factors as risk factors in the etiology of cleft in the cleft patients that were analysed. These patients presented with one or more of these risk factors. Our experience in this study is contrary to the findings of other researchers who have classified etiology into environmental, genetic or untraceable [18, 19].

The environmental factors causing Cleft lip and palate are diversified. Some of the notable risk factors which are environmental in nature in this study are mothers having persistent fever during the first trimester of their pregnancy, ingestion of drugs other than those prescribed especially metronidazole and tetracycline used to stop stooling during first trimester, exposure to radiation and chronic medical condition mainly diabetes of the mothers during pregnancy.

Maternal fever is common during pregnancy. 1 in 5 women report having experienced fever on at least

1 occasion while being pregnant [20]. This research showed that 43.7% of the mothers had persistent fever during the first trimester of their pregnancies. It has been reported that the development of fever more than 40°C, during the 1st 8 weeks of gestation has high-risk of causing facial clefts in the developing fetus [9]. However, reviewed studies, found little evidence to support a dose–response relationship with temperature [21]. Chambers *et al.*, has also suggested an increased risk by increasing duration of the fever [22]. Fever in the fetal environment has been hypothesized to interrupt protein synthesis and enzyme production, which results in cellular processes (e.g. proliferation, migration, differentiation, apoptosis) becoming altered or dysfunctional [23].

Authors confirmed the Oro-facial cleft inducing effect of phenytoin, carbamazepine, oxy-tetracycline, and thiethylperazine and suggested a possible association between Oro-facial clefts and oxyprenolol and amoxicillin [24]. However Nielsen *et al.*, who investigated the association between antibiotic use in early pregnancy and the risk of isolated Oro-facial clefts in a Danish nation-wide cohort study, antibiotic use in early pregnancy is not a major risk factor for isolated Oro-facial clefts [25]. In this study 41(16.1%) of routine ingestion of tetracycline and metronidazole was observed in the mothers in their first trimester. These drugs were self-medicated to treat watery stooling. Metronidazole was teratogenic in some early animal studies, but this has proved difficult to reproduce. However Odile *et al.*, in their study confirmed metronidazole as very effective in treating bacterial vaginosis and trichomoniasis in pregnancy and offers no teratogenic risk [26]. This drug should however be used during pregnancy only if the benefit outweighs the risk.

Furthermore, a meta-analysis approach of parental age showed that fathers 40 years or older have a 58% higher probability of having a child with cleft palate (CP); for mothers over 40 years of age, the probability is 28% higher for CP and 56% higher for CLP. In the present study, we found no association between maternal age and clefts ( $p=0.115$ ).

However mothers between 26 and 35 have higher risk of having a child with cleft. This findings is supported by Paulo Henrique Pimenta de Carvalho *et al.*, [27]. In Contrary the study of James *et al.*, revealed a significant association between maternal age and Oro-facial cleft ( $<0.05$ ) [28]. This study also revealed an increased risk of cleft with paternal age. Studies performed by Shaw, Baird, Vieira, DeRoo also confirmed that maternal age is related to oral cleft risk; however not in all older studied maternal groups clefts occur [29, 30].

Various epidemiological observation have laid the foundation of role of genetics in etiology of cleft lip

and palate. Consanguineous marriage is allowed in the Northern part of Nigeria and it is not uncommon to see blood relations getting married to one another. However, the health implication especially as it affects child survival is however not known by many of those who are involved [31]. Parents of 49(19.1%) children were consanguineously married. The fundamental disadvantage of consanguinity is the emergence of rare recessive homozygous disorders, which otherwise may not appear in an out bred population [32]. Other studies have reported the same association between parental consanguinity and Oro-facial cleft [33-35].

Family history involving any present or past members of family can induce a higher risk of having baby with a cleft [36]. We reported a low incidence of positive family history with 3.1% of other siblings with cleft, 2.8% of maternal family history of cleft and 2.4% of paternal family history of cleft. Figueiredo found that family history of clefts was strongly associated with increased cleft [37]. González showed that the highest risk for cleft lip and/or palate was associated with variables related to family history background [38].

We found that 214 (84.3%) of the parents in our study are of low socio-economic status. It thus seems reasonable to suggest that a positive association exists between the socio-economic status of a family and the risk of having a child with Cleft. This may further suggest the nutritional status of the mothers during pregnancy. Habib [39] was of the opinion that nutrition of a pregnant woman was probably the link between the social class and the incidence of Cleft lip and palate. Emotional stress has also been associated with pregnant women in the lower social class. Leading to release of excess cortisone which may increase the risk of having a child with cleft [39].

## CONCLUSION

This study revealed a strong association between consanguineous marriage, low socioeconomic status and persistent maternal fever during the first trimester and cleft. Increasing paternal age was also found to increase the risk of cleft. The relevance of this study is for public health workers and clinicians to be equipped with adequate information to provide useful counseling to parents particularly those with history of cleft. It may also provide adequate information for policy makers when making policies of public health concerns.

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