**DOI:** https://doi.org/10.54393/pjhs.v7i6.2814

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 7, Issue 06 (June 2026)

**Original Article**

OPEN ACCESS

# Cleft Lip and Palate: Analyzing the Impact of Family History and Cousin Marriages

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## ARTICLE INFO

***Keywords:***
Cleft Lip and Palate, Family History, Cousin Marriages, Maternal Folic Acid Intake

***How to Cite:***
Anjum, R., Mehmood, S., Nagi, A. H., & Chaudhry, S. (2026). Cleft Lip and Palate: Analyzing the Impact of Family History and Cousin Marriages: Cleft Lip and Palate: Family History and Cousin Marriages. Pakistan Journal of Health Sciences, 7(6), 105-110. https://doi.org/10.54393/pjhs.v7i6.2814

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Received Date: 29th January, 2025
1st Revision Received: 11th December, 2025
2nd Revision Received: 19th December, 2025
3rd Revision Received: 23rd December, 2025
Acceptance Date: 18th April, 2026
Published Date: 30th June, 2026

## ABSTRACT

Cleft lip and palate (CLP) are prevalent birth disorders and have significant impacts on the individuals and their families. **Objectives:** To identify the trends of cleft lip and palate and to examine the effects of family history and the marriage of cousins. **Methods:** This cross-sectional study was carried out in the Department of Oral Pathology, University of Health Sciences, Lahore. Four hundred children between the ages of 0 and 20 years were included. The following data were taken: demographic and clinical, such as age, sex, type of cleft, maternal folic acid intake, family history of cleft lip and/or palate or other congenital anomalies, and parental consanguinity. **Results:** The mean age of the participants was 55.79 ± 54.3 months. Among them, 214 (53.5%) were male, and 186 (46.5%) were female. In terms of cleft pattern, cleft lip and palate were most common, affecting 247 (61.8%) individuals, compared to those with only cleft lip or cleft palate. A positive family history was reported in 89 (22.3%) of the cases. Only 60 (15%) of the mothers had taken folic acid during pregnancy, and cousin marriages were noted among the parents of 309 (77.3%) children. **Conclusions:** CLP is more commonly observed in individuals with a positive family history and those whose parents are biologically related. A considerable proportion of affected children had parents who were cousins, suggesting that consanguinity may be a contributing factor to CLP. Additionally, a significant number of mothers did not receive folic acid supplementation during pregnancy, which is a modifiable risk factor.

## INTRODUCTION

A cleft of the lips, palate, or both is the most common congenital anomaly of the orofacial complex in a newborn. CLP is a serious health issue with more than 10 million victims worldwide [1]. The greatest number of these anomalies concerns the Chinese births; the next ones are India and Indonesia. Pakistan has the largest number of infants born with a cleft lip or cleft palate after Indonesia [2]. One of the numerous affected craniofacial elements and oral structures is the hard palate due to these congenital defects [3]. The world is experiencing an alarming trend of the total number of people with clefts in their mouths and cheeks as the population continues to grow and the overall life expectancy is rising [4]. These conditions are being encountered at different frequencies across geographical areas among all ethnicities, sexes, and socioeconomic strata. The management involves several surgical procedures and extended multidisciplinary treatment that cause great psychological stress to the afflicted individuals and their families [5]. Cleft lip and palate are a multifactorial and complex development in its formation, which incorporates both a genetic predisposition and environmental exposures. In some cases, chromosomal abnormalities related to inheritable syndromes can also contribute to it [6]. A

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positive family history of CLP is an established risk factor of CLP; exposures to environmental risk factors like cigarettes and alcohol, prescription drugs, and illicit drugs, and an advanced maternal age at birth are some of the established risk factors of CLP [7]. Eighty-seven patients with orofacial clefts were studied in an Iranian study, and considerable relationships were observed between the presence of an orofacial cleft and consanguineous marriage of the parents, aggregation of clefts in families, and folic acid intake [8]. These patterns in the framework of hereditary background and consanguinity are analyzed as bringing important information to the genetic and environmental aspects of cleft lip and palate to develop more effective interventions, early diagnostics, and optimal management strategies.

Although the association of consanguineous marriage and congenital anomalies is well established, little data are available about the contribution of cousin marriage and maternal folic acid consumption to the occurrence and prevalence of cleft lip (CL) and cleft palate (CP) in Pakistan. This study aims to determine the distribution patterns of cleft lip and palate as well as to evaluate the influence of familial history and cousin marriages on the incidence of cleft lip and palate.

## METHODS

A cross-sectional study was conducted in the Department of Oral Pathology at the University of Health Sciences, Lahore, from January 2020 to December 2021, after getting formal institutional approval (Approval No. UHS/REG-20/ERC/146; dated 15th January 2020), and the research was conducted in accordance with the Declaration of Helsinki. A non-probability convenience sampling approach was used to enroll children diagnosed with non-syndromic cleft lip and/or palate (NSCL/P) who presented to CLAP Hospital, Lahore. The study consisted of 400 participants between 0 and 20 years of age. Despite the fact that the sample size was determined by practical considerations and not as a result of a statistical power calculation, it is comparable to those reported in related published studies. All ethical requirements were carefully observed. As the study population consisted of minors, written informed consent was obtained from parents or legal guardians, and verbal or written assent was obtained from children capable of comprehension, generally those older than seven years. Participants with syndromic cleft lip and/or palate, incomplete clinical documentation, or unclear diagnostic information were excluded. The data collected were composed of demographic and clinical variables, including age, gender, cleft type, folic acid intake by mothers, and positive family history of cleft lip and/or palate or other birth defects. An established criterion was used for categorization of Parental consanguinity into first-cousin, second-cousin, or more distantly related unions and was determined through structured interviews with parents without any genetic testing or official medical documentation, and classifications were based entirely on self-reported familial data.

SPSS version 26 was used to record and analyze the data. Descriptive statistics were performed to summarize age, gender distribution, cleft types, folic acid intake, and family history. Associations between cleft type and variables such as folic acid intake and family history were assessed using Chi-square tests or Fisher's exact tests, and assumptions for these tests (such as minimum expected cell counts) were checked before analysis. A p-value≤0.05 was set as statistically significant.

## RESULTS

The mean age was 55.79 ± 54.3 months. Out of 400 patients, there were 214 (53.5%) male and 186 (46.5%) female. Regarding the pattern of cleft lip and palate, CLP was the most prevalent, observed in 247 cases (61.8%), exceeding the occurrences of cleft lip only and cleft palate only. A familial occurrence of the condition was reported by 89 participants, accounting for 22.3% of the study population. Folic acid was taken by the mothers of 60(15%) children only, and cousin marriages were observed in the parents of 309(77.3%) children (Table 1).

**Table 1:** Distribution of Demographic Variables

| Variables | Frequency (%) |
|---|---|
| **Gender** | |
| Male | 214 (53.5%) |
| Female | 186 (46.5%) |
| **Cleft Lip and Palate Pattern** | |
| Cleft Lip and Palate | 214 (53.5%) |
| Cleft Lip Only | 117 (29.3%) |
| Cleft Palate Only | 69 (17.3%) |
| **Family History** | |
| Positive | 89 (22.3%) |
| Negative | 311 (77.8%) |
| **Folic Acid** | |
| Yes | 60 (15%) |
| No | 340 (85%) |
| **Cousin Marriages** | |
| Yes | 309 (77.3%) |
| No | 91 (22.8%) |

The study presents the distribution of CLP patterns based on gender, family history, maternal folic acid intake, and cousin marriages; however, no significant associations were found (Table 2).

**Table 2:** Association among the Demographic Variables

| Variables | Cleft Lip and Palate | Cleft Lip Only | Cleft Palate only |
|---|---|---|---|
| **Gender** | | | |
| Male | 121 (56.5%) | 57 (27%) | 36 (16.3%) |

**DOI:** https://doi.org/10.54393/pjhs.v7i6.2814

| | | | |
|---|---|---|---|
| Female | 93 (50.5%) | 60 (32.2%) | 33 (17.2%) |
| p-value | 0.13 | 0.17 | 0.71 |
| RR (CI) | 1.35 (0.913-2.01) | 0.744 (0.48-1.14) | 0.90 (0.538-1.52) |
| **Folic Acid Intake by Mothers** | | | |
| Yes | 35 (60%) | 15 (25%) | 10 (15%) |
| No | 179 (52.6%) | 102 (3.8%) | 59 (17%) |
| p-value | 0.41 | 0.40 | 0.94 |
| RR (CI) | 1.2 (0.72-2.1) | 767 (0.40-1.43) | 0.9729 (0.466-2.02) |
| **Cousin Marriages** | | | |
| Yes | 167 (54%) | 91 (29.7%) | 51 (16.2%) |
| No | 47 (52.7%) | 26 (28.5%) | 18 (18.6%) |
| p-value | 0.68 | 0.82 | 0.42 |
| RR (CI) | 1.01 (0.689-1.75) | 1.06 (0.633-1.77) | 0.783.43-1.4) |
| **Family History** | | | |
| Yes | 49 (55%) | 25 (28%) | 15 (16.8%) |
| No | 165 (53.3%) | 92 (30%) | 54 (16.7%) |
| p-value | 0.73 | 0.74 | 0.96 |
| RR (CI) | 1.084 (0.675-1.7) | 0.91 (0.54-1.54) | 98 (0.52-1.85) |

RR: Relative Risk CI: Confidence Interval

Analysis of gender, maternal folic acid intake, cousin marriage, and family history showed no statistically significant association with the type of orofacial cleft. The distribution of cleft lip and palate, cleft lip only, and cleft palate only was similar in both males and females, with all p-values > 0.05. Likewise, maternal folic acid use did not significantly influence cleft type, and relative risks for all categories crossed unity. No meaningful differences were observed between children from consanguineous versus non-consanguineous marriages, nor between those with or without a positive family history, as reflected by non-significant p-values and wide confidence intervals. Overall, none of the evaluated factors demonstrated a significant association with cleft subtype in this cohort.

## DISCUSSION

Cleft lip and palate are widely occurring congenital anomalies that are caused by a complex interplay between a predisposition that is hereditary and the environmental exposures, whereby the underlying mechanisms are not always well understood. The children who are affected often face self-esteem issues and difficulty getting along with others. They may have scars on their face and talk differently, which could influence their attitude towards themselves. They may become awkward with the people around them or may be regarded as being treated unjustly or bullied. As well, communicating well due to difficulty in speaking may be a challenge and have an impact on friendship and school performance. The best thing to do is begin speech therapy at the earliest stage, and with the help of medical care and encouragement from others, a majority of individuals are capable of leading a normal, successful life. Stigmatization and increased acceptance of people can also be achieved by assisting the community to understand more about cleft conditions. In this research, the boys (as compared to girls) were more affected by cleft lip and palate, with an average age of 55.79 and a standard deviation of 54.3 months. This is unlike some other studies, which have found more girls being affected. The variations in the way the body parts develop in both boys and girls, such as hormones that influence the formation, may be behind the fact that more boys are affected. There is research that claims the palate may take longer to form in early growth in girls, making them prone to a cleft palate. The delayed palatal fusion in embryogenesis in females has been postulated to predispose to developmental disturbances, and therefore, predispose the onset of cleft palate malformation [9]. Conversely, research conducted in Pakistan has similarly documented a higher frequency of orofacial clefts in males, who comprised 60% of cases compared with 40% in females [10]. Similarly, another study identified a total of 2,089 children meeting the inclusion criteria, with 1,311 male and 778 female. In female, orofacial clefts primarily occur during the late embryonic period and usually involve only the secondary palate, often due to fusion defects. In contrast, clefts in male are more prevalent during both the early and late embryonic stages. These clefts often affect both the primary and secondary palates and are typically caused by differentiation abnormalities or a combined fusion and differentiation disturbance [11]. The cases of cleft lip and cleft palate were found in the current study in a larger number based on palate, and then cleft lip, and finally cleft palate. A study carried out in Pakistan depicted a higher prevalence of cleft lip only, then cleft palate only, and cleft lip and palate, respectively. Out of the 540 patients with the condition of the OFC, 123 were afflicted with cleft lip alone, 233 with cleft lip and palate, and 178 with cleft palate. Cleft lip and cleft lip and palate patients were characterized by a greater number of male patients, whereas cleft palate was characterized by more female patients [12]. A different study illustrated the CL:CLP: CP ratio to be 4.7:7.1:1[13]. The existing evidence also points to the idea that women of children with orofacial clefts (OFC) tend to have nutritional deficiencies and a lack of folic acid. Prenatal vitamins and folic acid are advised for women of childbearing age, both before and during pregnancy, in case of an unplanned pregnancy [14]. In the current study, only 60 (15%) female took folic acid during their pregnancy. Samuel Trezena noted a slight trend in the occurrence of complete non-syndromic cleft palate (NSCP) among children with a family history of NSCP, those whose mothers took some form of medication in pregnancy, or those with certain systemic alterations. Although these differences were statistically insignificant, they should still be considered while examining the development of cleft types [15]. They reported that 25% of patients had oral clefts in their families, which is significantly more than the

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2.9 % prevalence in Spain and 7 % in Brazil [16, 17]. In a study conducted in Brazil, the predominance of a family history of non-syndromic oral clefts (NSOC) among individuals with non-syndromic cleft palate (NSCP) was 33.2%. Probably, this could have been due to differences in sample size of the studies [18]. The present research could not find any significant correlation between CP and consanguineous marriages. The other studies also highlight consanguineous marriage as a risk factor with an OR of nearly 3, meaning that children born to such marriages are more susceptible to developing complex cleft lip [19, 20]. It is possible that the absence of meaningful association between consanguineous marriages and cleft lip and palate reported in this research could be explained by a number of methodological and population-related factors. These are a lack of adequate sample size to elicit minor effects, a more inclusive definition of consanguinity, and an inherent genetic heterogeneity in the study sample in comparison to previous studies. Also, the outstanding confounding variables, reporting or categorizing relationships with family members, and potential selection bias because of a hospital-based sample could have diminished the capacity to find a true association. The discrepancy with the previously published results could also be due to variability caused by gene-environment interaction and natural differences between studies. Autosomal recessive disorders, such as rare or novel syndromes, can be caused by consanguineous marriages, and thus, it is vital to create awareness among the population on the dangers involved. Consanguinity in rural settings also offers various social gains, including increased female autonomy, better marriage stability, less domestic violence and violence, improved knowledge with the in-laws, and economic benefits, including reduced dowry payments, lower divorce rates, and land retention [21, 22]. Genetically, consanguinity arises from a reduced genetic diversity caused by a limited pool of close relatives. Given that more than 90% of the human genome is shared among individuals, the impact of consanguineous marriages on genomic sequencing is minimal. If two siblings have children, the resulting child will have fewer unique genetic contributions, increasing the likelihood of inheriting harmful recessive genes [23]. Offspring of consanguineous parents tend to have higher rates of homozygosity. Loss-of-function (LoF) mutations, which cause complete gene inactivation or malfunction, often occur in autozygous regions of the genome. Studying consanguineous offspring with specific clinical traits can help identify mutations responsible for diseases. However, most genes in the human genome are either unrelated to established disorders or have undiscovered roles, which is a major focus of extensive sequencing research. While many genes are associated with orofacial clefts, only a few are linked to well-defined cleft phenotypes [24]. Consistent with other studies, research in Iran showed a statistically significant link between consanguinity and the occurrence of oro-facial clefts [20]. However, a study from Saudi Arabia did not establish this relationship [25]. Additionally, a significant link between the incidence of cleft defects and family history was reported in another study conducted in Brazil and Saudi Arabia, which is also observed in the present study [26]. First and second-degree family histories of clefts had a higher risk compared to third-degree relatives. However, a study from India reported a significant correlation between cleft defects and family history [27]. Among 538, consanguinity was found in 284 parents; more of the patients were reported with cleft lip and palate [22]. In other countries, including Iran, where consanguineous marriage is common and culturally valued, the acceptance of consanguineous marriages in society contributes to the increased risk of congenital anomalies. To overcome this challenge, the policymakers in the health sector ought to issue preventive policies to reduce consanguineous marriages. It is important to adopt genetic counseling and involve prominent leaders in the community in the design and implementation of health programs [28]. Increased incidents of cleft lip and palate (CLP) are being observed in children born to similar parents, and this has significant implications for health care and society. When a child has CLP, families tend to have huge financial and social problems due to the high costs of surgeries, continuous medical treatment, and other auxiliary services. These problems demonstrate the significance of providing more genetic guidance and enhancing the health activities of the population. Informing the population about the genetic risks of close family marriages and providing them with access to counseling can be used to lessen the effects of CLP and other genetic issues in societies where such marriages are prevalent.

Although this research did not show any decisive relationship, the number of individuals that were researched was too low, and the manner in which the research was conducted may have made it difficult to notice an actual relationship. This must be taken as a limitation, and further research on bigger groups is required to prove these findings.

## CONCLUSIONS

This study did not find a strong link between close family relationships or the mother taking folic acid during pregnancy and the occurrence of cleft lip and/or palate. Although many affected children were born to closely related parents and a lot of mothers didn, Äôt take folic acid, these factors didn, Äôt clearly increase the risk of CLP in this group. The lack of clear results could be because of a small sample size, how relationships were classified, or other factors not considered. So, when

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interpreting these results, it's important to be careful, and larger, more detailed studies are needed to better understand the role of consanguinity and folic acid in CLP. Overall, the study shows that cleft lip and palate are influenced by many factors, both genetic and environmental. It's important to address both inherited risks and other influences in preventing and managing this condition. Improving genetic counseling, increasing awareness about close family marriages, and encouraging folic acid use during pregnancy are key steps. More research is needed to understand the biological reasons behind CLP and to develop better ways to prevent and treat it.

## Acknowledgement

The authors acknowledge the staff at Cleft Lip and Plate Hospital (CLAP), Lahore, Pakistan, for their support and cooperation.

## Authors' Contribution

Conceptualization: SM, SC
Methodology: RA, AHN, SC
Formal analysis: RA, SM, SC
Writing and Drafting: RA
Review and Editing: RA, SM, AHN, SC

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

## Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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