



The Geographical Factors in Cleft Lip and Cleft Palate among Infants as Congenital Anomalies over West Bengal: A Systematic Review and Meta-Analysis

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Abstract

Cleft of lip and palate provided most common consecutive congenital anomalies which affect the mouth and related structures of human being. The cleft occurs when certain body parts and structures do not fuse together during fetal development. The clefts have a complex etiology with genetic and environmental playing role. It is seen that about 20% of birth defects are caused by genetic or hereditary factors and about 10% of birth defects are caused by environmental factors such as infection, radiation, pollution, biomedical and hazardous waste and drugs *etc.* The frequencies of different genetic disorders depend upon various factors such as genetic background of the population and the type of environment to which the population is exposed. This article main aims to the review and analysis in the point of geographical mind of congenital anomalies associated with cleft lip and palate among Infants.

Keywords: Congenital Defects, Cleft lip and Palate, Infants, Geographical analysis, Environmental factors.

Background

Cleft lip and cleft Palate are the most common facial congenital defects [1-3]. Facial structure over human beings has been gained remarkable scientific interest worldwide over the past decades [4-8]. Single or multiple defects in one or many organs of the child results increasing mortality rate [4-8]. It is seen from investigations that about 3 % of the million annual births are affected by major structural and functional defects per year in world [9-10]. Birth defects causes by a genetic infection [6, 11-12] or environmental factors [13] but the majority of all congenital disorders still have no exact detectable cause [14]. About 20% of birth defects are caused by genetic or hereditary factors and about 10% of birth defects are caused by environmental factors such as infection, radiation, pollution, biomedical and hazardous waste and drugs *etc.* [13-17]. The frequencies of different genetic disorders depend upon

various factors such as genetic background of the population and the type of environment to which the population is exposed [13-17]. These environmental factors can cause death, severe birth defects on the developing baby depending on when during pregnancy the exposure occurs [18-19]. Thus, medical science has identified the cause of about 30% of birth defects [14]. That means about 70% remain without a straightforward cause. These birth defects have multi-factorial causes, or the causes are simply unknown [17]. Multi-factorial means that the defect is caused by a complicated combination of both genetic and environmental factors. In this regards, researchers across the globe are busy searching newly protocols over defects to efficiently reduce concentration of congenital malformations of human beings through sustainable ways. In this aspect, in recent decades, congenital heart defects (CHDs) and cleft lip and palate (CL/P) were identified as most common types of congenital defects [20-23]. Congenital heart disease (CHD) is an abnormality in morphological structure and functional metabolism caused by abnormal development of the heart and large blood vessels during the embryonic period or a congenital deformity in which the orifices that are present during the foetal period and are used for blood circulation remain open after birth [24]. However, from the literature review it is seen that orofacial clefts (OFC) are also very common birth defects worldwide with an incidence of 1.7 per 1000 babies being diagnosed with OFC [20-23]. Among these, cleft lip and cleft palate (CL/P or cleft lip/palate) are most common in India [25-28]. From the literature survey, only a few research works are found related to cleft lip and cleft Palate which is most common facial congenital defects in India. CL/P is a common congenital anomaly with complex etiology, involving genetic and environmental factors [22, 29-30]. Our studies have identified associations between different health problems and environmental pollution [31-35]. Clefts can involve the lip and/or the roof of the mouth (palate). It seems that CL/P varies considerably in occurrence with wide variability across geographic origin, racial and ethnic groups as well as environmental exposures and socioeconomic status (SES) [31-37]. Although, it is not a major cause of mortality in our countries, CL/P does cause considerable morbidity to affected children who goes beyond the obvious disfigurement of face and extends to repeated infections, social stigma, and mental impairment that affect the speech, hearing, and teeth formation.

It is seen that the overall worldwide prevalence of cleft lip with or without the cleft of palate is 9.92 per 10,000. The prevalence of cleft lip is 3.28 per 10,000, and that of the cleft lip and palate together is 6.64 per 10,000 [38]. Lowest incidence occurs in Native American tribes of Montana, USA, which is 1:2076 [39]. In India, approx birth rate is estimated to be 24.5 million births per year and prevalence of clefts cases are somewhere between 27,000 and 33,000 cases per year [25-28]. Inequalities exist, both in access to and qualities of cleft care with distinct differences among urban versus rural areas. Due to this inequality along with lack of awareness has lead to the accumulation of untreated clefts of the lip and palate leading to a significant health care problem in India [25-28].

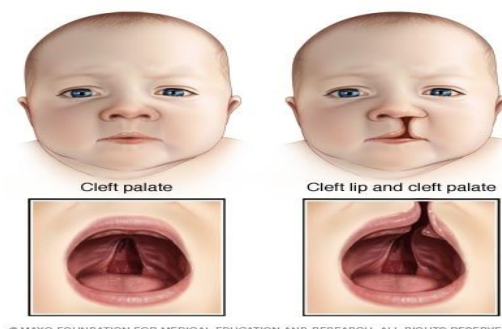


Figure 1: Congenital anomalies associated with Cleft Lip and Cleft Palate among infants due to genetic and environmental factors

Indian sub continent being a geographically and economically different region than others, the demographic, prenatal and clinical profile of the clefts cases found in this region also differs. The condition in tropical countries like India becomes even worse due to poverty and illiteracy. However, India being economically a developing country

is expanding the medical facilities available in the rural area. The various geographically difficult regions such as mountainous region of North and North-eastern India and plains of the Central Indian and the Southern region have diverse culture, religion and living standards. Due to insufficient, ineffective and disproportionate penetration of health care facilities the population at large have suffered a lot in terms of basic health care facilities. However, certain NGOs and government agencies by means of various health projects have done excellent work overall but still lot of rural masses are deprived of quality and good health care. Various studies have shown that due to improvement of economic condition, literacy rate and more importantly the improvement in health care infrastructure are resulting in better care of cases suffering from cleft disease. In addition, due to lack of awareness and illiteracy rate, the patients of cleft remain untreated or misguided by some quacks [40]. But also despite the general improvement of the environment there is lack of interdisciplinary treatment approach at majority of the centres, and hence there is a need for better and effective collaboration among the specialist for the health care needs of the cleft cases [41].

Overall incidence of cleft lip and palate is approximately 1 in 600 to 800 live births (1.42 in 1000) and isolated cleft palate occurs approximately in 1 in 2000 live births. Thus, the typical distributions of cleft types are [28]:

1. Cleft lip alone – 15%
2. Cleft lip and palate – 45%
3. Isolated cleft palate – 40%.

Many researches through their studies have revealed the genetic complexity in Indian children suffering from oral cleft lip and palate [42-46]. India being one the fastest developing country is covered with many young and enthusiastic researchers who are struggling hard in their laboratory to find the genetic reasons along with the environmental effects resulting in oral clefting in Indian population.

The frequency of occurrence of cleft lip and cleft palate differs with regard to gender and side of clefting. Cleft lip is more common in males at a 2:1 male to female ratio, whereas a cleft palate is more common in females with a ratio of 1:2 male to female [47]. Approximately 90% of clefts are unilateral [37]. Among unilateral cases of CL/P, left-sided clefts are common (66%) than right-sided clefts at a 2:1 ratio of left- to right-sided clefts [47]. Figure 2 shows the prevalence of cleft lip and cleft palate.

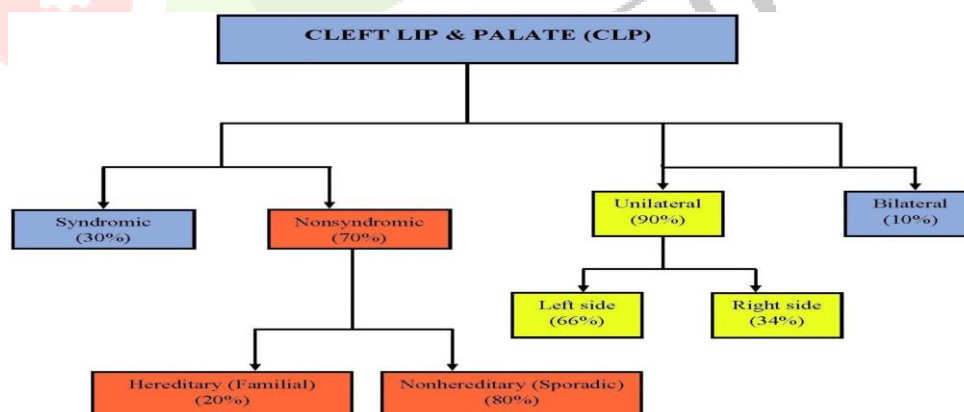


Figure 2. Prevalence of Cleft Lip and Palate (CLP) [30]

The epidemiological studies have reported, adult patients with CL/P may suffer from various difficulties such as esthetics, difficulty in speech, hearing, and psychosocial problems. These individuals may have episodes of depression, low self-esteem and low emotional development even after achieving satisfactory cosmetic, functional, and speech therapy. Many adults will reach a point at which they refuse take the final stages of dental and other surgical treatment. All these problems associated life-long impact on the quality of life of the CL/P patients.

It was noted that about 49.9% of CLP group and 12.4% of Non-CLP group admitted that they received inadequate support from strangers which is shown in Figure 3 and 4 [48]. About 40.4% of CLP group and 15.6% of NCLP group reported that they received inadequate support from authorities, thus affecting the relationship with authorities. 34.3% of CLP group and 15.6% of NCLP group reported that they received inadequate support from their subordinates, thus affecting the relationships with subordinates. 40% of CLP group and 12.5% of Non-CLP group reported of inadequate support affecting the relationships with equals. Nearly 40.5% of CLP group and 12.5% of Non-CLP reported that they received less support even from their friends, thus affecting the relationships with friends. About 18.6% of CLP group reported that they received less support from their parents and children, thus affecting the child–parent relationships.

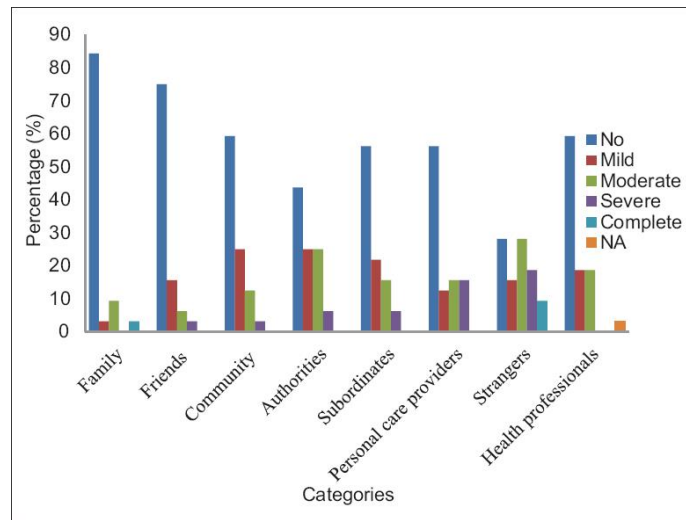


Figure 3. Percentage of population facing environmental barriers with support and relationship in cleft lip and palate group across different categories [48]

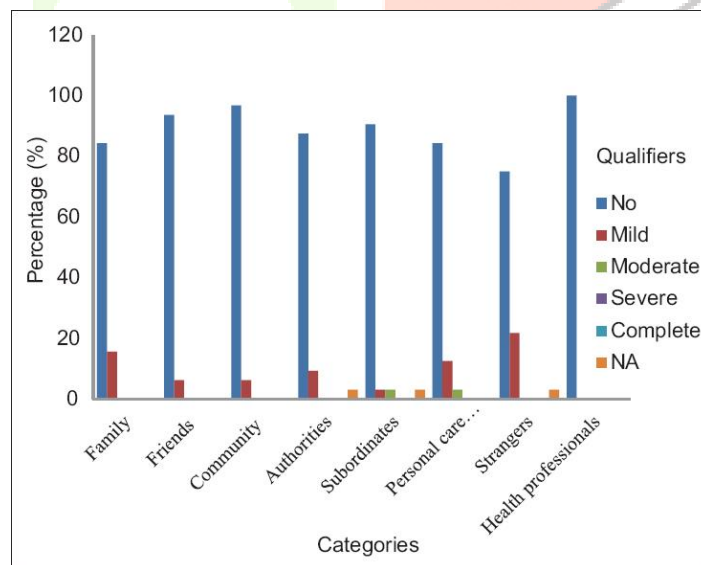


Figure 4: Percentage of population facing environmental barriers with support and relationship in noncleft lip and palate group across different categories [48]

In this article we have reported the risk factors for the cleft lip and palate CL/P, emphasizing environmental contamination and other associated factors leading to the cleft lip and cleft palate among infants (less than 5years) in West Bengal.

Objectives

The objectives of the present study are as follows:

1. To assess and investigate the associated congenital factors leading to on cleft lip and cleft palate among infants.
2. To evaluate the issues related to this disability among the children.
3. To study the genetic profiles of disability person individually. After that the aim of setting up such centres should be to provide quality comprehensive & multidisciplinary treatment for patients belonging to sections of society with cleft and craniofacial anomalies.
4. To collect the data on the patients from various medical College of West Bengal, India.
5. To suggest and give awareness against the negative effects of consanguinity and about the hazardous effects
6. To suggest sustainable pathways and some awareness programmes with help of Doctors, Government health authorities along with the NGOs
 - a. For the society in general; and
 - b. For the affected children

Through which they may have better life opportunities.

Some of the well-known environmental factors in our study areas over West Bengal in India

West Bengal, state of India, located eastern part of the country. The majority of West Bengal's people live in rural villages. Of those living in urban areas, more than half reside in greater Kolkata. West Bengal is now divided in 23 districts. As per the statistics of 2011 census, West Bengal has a literacy rate of 77.08%. Out of the total population of 91,276,115 people, 61,538,281 people re literate in the state. The literacy rate of the male population in the state is 81.69%. However, amount of females, literacy rate is 70.54%. So, the environmental risk factors such as maternal exposure to tobacco, tobacco smoke, alcohol, poor nutrition, viral infection, improper medications, and teratogens at the workplace and home in early pregnancy are focused as some of the important etiological factors. The role of maternal nutrition and, multivitamins in particular, in orofacial clefts cases remains unclear. Furthermore, assessments of dietary intake or biochemical measures of nutritional status of OFC cases are challenging and often not available among the many impoverished populations suffering from the highest rates of orofacial clefts disease. The main environmental factors which has been reported to possibly increasing the risk of orofacial clefts cases is tobacco smoking, alcohol consumption, solvents and agricultural chemicals as well as unwanted air pollution.

Recently over West Bengal it is seen that the heavy metals exposure such as lead, nickel, mercury, cadmium, among other substances and pollutant particles act as another risk factors for congenital malformations such as CL/P. Breathing pollution during early pregnancy is linked to a higher risk for certain serious multi-factorial birth defect causing congenital anomalies like Cleft Lip and Cleft Palate.

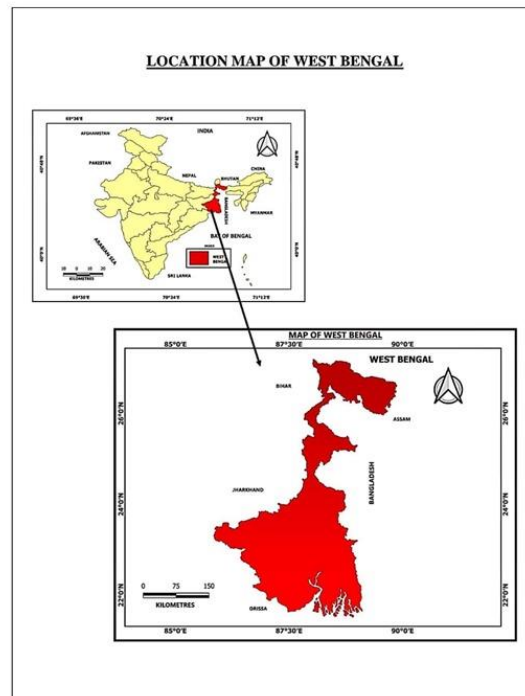


Figure 5: Geographical location for our study area

Geographic factors influencing the congenital anomalies

It is quite important to notice that prevalence of orofacial clefts (OFC) world-wide and it's related with geographic, climate, and socio-epidemiological factors is still a focus of many studies. It is seen that a very important ethnic and social dependence factors arise from the investigation which has been reported to possibly increasing the risk of orofacial clefts cases [49-52]. Geographic factors have a great meaning in orofacial cleft predisposition, occurrence and treatment methods. Although this study did not establish causal relationships, it showed the spatial interaction between Because of habits, social conditions, drug abuse as well as tobacco and alcohol consumption in different geographic regions during pregnancy is highly related with hereditary disease occurrence and predisposition. If more risk factors accumulate it is more possible for many diseases to appear. Several epidemiological studies showed an increased prevalence of CL/P in patients whose mothers were exposed to smoking, alcohol consumption (binge levels), antiepileptic medications, Corticosteroids, nutritional deficiencies (folic acid) and infectious diseases during pregnancy may adversely affect the intrauterine environment during embryogenesis. These environmental factors found to increase the risk of a risk factor for non-syndromic cleft lip with or without cleft palate (NSCL/P).

Exposure to risk factors in pregnancy such as alcohol may induce cleft lip and palate. When alcohol is combined with other factors, such as tobacco, drugs, and also other socio-geographic factors cleft risk is greatly higher [31-35]. Miller *et al.* 2006 study performed in Russian region Murmansk in baby homes and orphanages suggest that geographic region of Murmansk and its greater expression of prenatal exposure to alcohol. Because of that children's growth, maturation and even occurring symptoms are more common. Tobacco intake seems to have the most serious influence on OFC according to Lebbly *et al.*, 2010.

It is observed from literature that low social status with abuse of tobacco, alcohol and/or drug addiction have a great effect on predisposition to orofacial clefts, and also use during pregnancy is causing not only orofacial clefts but also other congenital syndromes and malformations. Genetic factors involved in orofacial clefts are still being considered in serious studies being performed world-wide [36-37].

Other factors such as diet including folic acid, vitamins, zinc and other microelements have a great effect on pregnancy. Some authors also point out that drinking cola and tea might have some influence on pregnancy. Drugs, medicine, corticosteroids, antibiotics and local and general agents used in pregnancy have a great effect on orofacial clefts predisposition.

An environmental study has documented a relationship between heavy metals exposure such as lead, nickel, mercury, cadmium, among other substances, and risk of congenital malformations such as CL/P [53]. Recent studies have found evidence of the influence of environmental pollution on CL/P, specifically ozone and PM2.5 [54]. The mothers who were exposed to air pollution and chlorinated solvents during the first two months of pregnancy as having increased risk of delivering children with CL/P [55-56]. Some socio demographic factors like social exclusion, low economic and educational level, and geographical marginalization have been related to increased incidence of CL/P [57].

In domains such as health services, education training systems, and policies CLP population revealed that they were dissatisfied with the services. It could be attributed to many factors such as awareness in the family about the condition, motivation and support of the family members, literacy level in the family, and socioeconomic status SES of the family. Further, it is assumed that lack of knowledge about the available treatment options and schemes provided by the local administration could have possibly limited the CLP group in seeking support of the health systems/policy for treatment. A major proportion of population in CLP group face barriers due to attitudes of individuals in their community such as authorities, strangers, friends, and family members. It is evident from the results that CLP group encounters barriers in the environment due to the negative attitude of people in their community. It is possible that the attitudes of all these individuals in the community can influence the individuals with CLP negatively

Conclusion

We conclude that there are many factors which can be involved in orofacial clefts predispositions. Improving our knowledge about the risk factors and potential risk factors leading to oral clefts can be very useful in their prevention Education of future mothers about behaviours before and during pregnancy, which can increase the risk of oral clefts is very important. It might cause decrease in the orofacial clefts occurrence and improve local health systems, however lack of information and people's lack of education might have a great impact on orofacial clefts. Nationwide social awareness programs should be planned that focuses on the environmental factors associated with the congenital factors leading to on cleft lip and cleft palate. It is also important to sincerely collect qualitative as well as quantitative information about defected infants at our examined areas so that there is a strong need for developing educational programme to prevent the health hazards. In India large number of NGOs, government health agencies and health policies and institutes are all time trying to address the problem of treatment and quality care of OFC cases. There is wide acceptance among various health agencies that an improvement in birth defects research, surveillance, and registration and quality treatment is required. Therefore, the community health society will conduct regular for general awareness programme regarding prevention of this congenital malformations or defects.

Reference

1. A. Jugessur, P. Farlie, N. Kilpatrick, The genetics of isolated orofacial clefts: From genotypes to subphenotypes, *Oral Dis.* 15, **2009**, 437–453;
2. P. A. Mossey, J. Little, R. G. Munger, M. J. Dixon, W. C. Shaw, Cleft lip and palate, *Lancet.* 374, **2009**, 1773–1785
3. P. Mossey, J. Little, Addressing the challenges of cleft lip and palate research in India, *Indian J. Plast. Surg.*, 42, **2009**, 9–18.
4. V. K Diwana, G Gupta, R. Chauhan, K. Mahajan, A. Mahajan, R. Gupta and K. Mahajan, Clinical and epidemiological profile of patients with cleft lip and palate anomaly: 10-year experience from a tertiary care center in the sub-himalayan state of Himachal Pradesh in Northern India, *J. Nat. Sc. Biol. Med.*, 10, **2019**, 82-86
5. J. Dvivedi, S. Dvivedi, A clinical and demographic profile of the cleft lip and palate in Sub-Himalayan India: A hospital-based study, *Indian J. Plast. Surg.*, 45, **2012**, 115-120
6. P. Bhide and Anita Kar, A national estimate of the birth prevalence of congenital anomalies in India: systematic review and meta-analysis, *BMC Pediatrics*, 18, **2018**, 175
7. I. Pavlovic, D. Plecas, S. Plesinac, J. Dotlic and N. Stojanovic, *Vojnosanitetski Pregled*, 77, **2020**, 317-323
8. K. Saleem, T. Zaib, W. Sun and S. Fu, Assessment of candidate genes and genetic heterogeneity in human non syndromic orofacial clefts specifically non syndromic cleft lip with or without palate, *Heliyon*, 5, **2019**, e03019.
9. C. A. Bacino, “Common Genetic Problems in the Newborn”: ch 10, *Manual of Neonatal Care*, Cloherty JP, eds. 17th ed. 111-123
10. H. Dolk, M. Loane and E. Garne, The prevalence of congenital anomalies in Europe, *Adv. Exp. Med. Biol.*, 686, **2010**, 349–64
11. *World Health Organization (WHO)*. Congenital anomalies. Fact sheet; **2016** Available from: <http://www.who.int/mediacentre/factsheets/fs370/en>
12. D. M. Webber, S. L. MacLeod, M. J. Bamshad, G. M. Shaw, R. H. Finnell, S. S. Shete, J. S. Witte, S. W. Erickson, L. D. Murphy¹ and C. Hobbs, Developments in Our Understanding of the Genetic Basis of Birth Defects, *Birth Defects Research (Part A)*, 103, **2015**, 680–691
13. N. B. Thimmadasiah and T. K. Joshi, India: country report on children’s environmental health, *Rev Environ Health*, **2020**.
14. A. Khan, I. Khan, Suleman, K. Zahid and G. Nabi, A Comprehensive Review on Various Aspects of Genetic Disorders, *Journal of Biology and Life Science*, 6, **2015**, 111-118.

15. P. R. Gandhi, H. D. Vora, H. J. Vasavada, M. T. Patelia, P. L. Popatiya and N. Vora, A study of gross congenital malformation at birth, *Int J Contemp Pediatr.*, 6, **2019**, 1019-1022.
16. A. Kawalec, K. Nelke, K. Pawlas and H. Gerber, Risk factors involved in orofacial cleft predisposition – review, *Open Med.*, 10, **2015**, 163-175
17. M. A. Mannan, S. Afroze, S. K. Dey, S. C. Moni, M. K. H. Shabuj, I. Jahan, S. N. Sultana, M. Shahidullah, Birth Defect and it's Impact in Neonatal Health : A Review, *Bangladesh J. Child Health*, 43, **2019**, 49-58
18. R. Francine, S. Pascale and H. Aline, Congenital anomalies: prevalence and risk factors. *Univ. J. Public Health*, 2, **2014**, 58–63
19. C. I. Oliveira and A. C. Fett-Conte. Birth defects: risk factors and consequences. *J. Pediatr. Genet.*, 2, **2013**, 85–90
20. S. chatterjee¹, S. Dutta, S. Ghosh, S. Das and N. Bhattachary, Congenital Heart Disease in the Pediatric Population in Eastern India: A Descriptive Study, *Indian Pediatrics*, 57, **2020**, 174-175
21. K. P. Allagh, B. R. Shamanna, G. V. S. Murthy, A. R. Ness, P. Doyle, S. B. Neogi, H. B. Pant and Wellcome Trust- PHFI, Folic Acid project team Birth Prevalence of Neural Tube Defects and Orofacial Clefts in India: A Systematic Review and Meta-Analysis, *Plos One*, **2015**
22. F. M. Gasca-Sanchez, J. Santos-Guzman, R. Elizondo-Dueñaz, G. M. Mejia-Velazquez, C. Ruiz-Pacheco , D.Reyes-Rodriguez, E.Vazquez-Camacho, J. A. Hernandez-Hernandez, R. C. Lopez-Sanchez , R. Ortiz-Lopez , D. Olvera-Posada and A. Rojas-Martinez, Spatial Clusters of Children with Cleft Lip and Palate and Their Association with Polluted Zones in the Monterrey Metropolitan Area, *Int. J. Environ. Res. Public Health*, 16, **2019**, 2488
23. D. Pujari, S. Charmode and H. S Kadlimatti, The Study Of Cleft Lip And Palate In North Karnataka Region, *Int. J. Anat. Res.*, 6, **2018**, 6014-6017.
24. S. Zaidi and M. Brueckner, Genetic and Genomics of Congenital Heart Disease, *Circulation Research*, 120, **2017**, 923-940.
25. R J. Maller, The Impact of Cleft Lip and Palate Repair Surgery on Cognitive and Academic Outcomes for Teens in India, *Master's Theses*. 1074, <https://repository.usfca.edu/thes/1074>
26. S.W. Ghonmode, A. R. Kalaskar, R. R. Kalaskar, R. Chole, P. Bhushan and F. M. Ali, Vista Of Cleft Lip And Palate In India, *J. Evolution Med Dental Sci*. 1, **2012**, 1102-1110
27. P. K. Neela, S. G.Reddy, A.Husain and V. Mohan, Association of cleft lip and/or palate in people born to consanguineous parents: A 13-year retrospective study from a very high-volume cleft center, *J. Cleft Lip Palate Craniofac. Anomal*, 6. **2019**, 33-37
28. S. Gaurishankar, Textbook of orthodontics. 1st ed. Paras Medical Publication; 2011.

29. N. Setó-Salvia and P. Stanier, Genetics of cleft lip and/or cleft palate: Association with other common anomalies, *Eur. J. Med. Genet.*, 57, **2014**, 381–393
30. J. C Murray, Gene/environment causes of cleft lip and/or palate, *Clin. Genet.*, 61, **2002**, 248–256
31. M. Acosta, D. Percastegi and B. Flores, Frecuencia y factores de riesgo en labio y paladar hendidos del Centro Médico Nacional «La Raza», *Rev. Mex. Cirugía Bucal Maxilofac.*, 9, **2017**, 109–112
32. C. Barrera and N. Mezarobba, Maternal risk factors associated with cleft lip with or without cleft palate: A review. *Int. J. Odontostomat.*, 10, **2016**, 359–368
33. A.T. Hoyt, M.A. Canfield, P.A. Romitti, L.D. Botto, M.T. Anderka, S.V. Krikov, M. K. Tarpey and M. L. Feldkamp, Associations between maternal periconceptional exposure to secondhand tobacco smoke and major birth defects, *Am. J. Obstet. Gynecol.* 215, **2016**, 613
34. I. Gonçalves and S. Koifman, Oral clefts, consanguinity, parental tobacco and alcohol use: A case-control study in Rio de Janeiro, Brazil. *Braz. Oral Res.*, 23, **2009**, 31–37
35. Y. Liu, B. Wang, Z. Li, L. Zhang, J. Liu and A. Ren, Indoor air pollution and the risk of orofacial clefts in a rural population in Shanxi province, China, *Birth Defects Res. Part A Clin. Mol. Teratol.*, 106, **2016**, 708–715
36. G. H. D. Casado and G. J. D. Grávalos. Orofacial closure defects: Cleft lip and palate. A literature review. *Semergen.*, 39, **2013**, 267-271
37. L. A Brito, L. A Cruz, K. M Rocha, L. K Barbara, C. B Silva and D. F Bueno, et al. Genetic contribution for non-syndromic cleft lip with or without cleft palate (NS CL/P) in different regions of Brazil and implications for association studies, *Am. J. Med. Gene.t A.*, 155A, **2011**, 1581-1587
38. J. C. Murray, Gene environment causes of cleft lip and/or palate. *Clin. Genet.*, 61, **2002**, 248–56.
39. Global Strategies to Reduce the Health Care Burden of Craniofacial Anomalies. Report of WHO meetings on International Collaborative Research on Craniofacial Anomalies. Geneva, Switzerland, **2000**.
40. N. Vasan, Management of children with clefts of the lip or palate: An overview. *N. Z. Dent. J.*, 95, **1999**, 14-20
41. A. Gopalakrishna, K. Agrawal, A status report on management of cleft lip and palate in India, *Indian J. Plast. Surg.*, 43, **2010**, 66-75.
42. U. Radhakrishna , U. Ratnamala, M. Gaines, S. Beiraghi, D. Hutchings, J. Golla, S. A Husain, P.S Gambhir, J. J. Sheth, F. J. Sheth, G. K. Chetan, M. Naveed, J. V Solanki, U. C. Patel, D. C. Master, R. Memon, G. S. Antonarakis, S. E Antonarakis, S. K. Nath.

- Genomewide Scan for Nonsyndromic Cleft Lip and Palate in Multigenerational Indian Families Reveals Significant Evidence of Linkage at 13q33.1-34, *Am. J. Hum. Genet.*, 79, **2006**, 580–585
43. P. Jindal, G. Khurana, S. Dvivedi, J. P. Sharma, Intra and postoperative outcome of adding clonidine to bupivacaine in infraorbital nerve block for young children undergoing cleft lip surgery, *Saudi J. Anesthesia*, 5, **2011**, 289–294.
44. J. Murthy, L. V. K. S. Bhaskar, Current concepts in genetics of nonsyndromic clefts, *Indian J. Plast. Surg.*, 42, **2009**, 68–81.
45. B.T. Chiquet, S. S. Hashmi, R. Henry, A. Burt, J. B. Mulliken, S. Stal, M. Bray, S. H. Blanton and J.T. Hecht, Genomic screening identifies novel linkages and provides further evidence for a role of MYH9 in nonsyndromic cleft lip and palate, *Eur. J. Hum. Genet.*, 17, **2009**, 195–204.
46. S. Beiraghi, S. K. Nath, M. Gaines, D. D. Mandhyan, D. Hutchings, U. Ratnamala, K. McElreavey, L. Bartoloni, G. S. Antonarakis, S. E. Antonarakis, U. Radhakrishna, Autosomal Dominant Nonsyndromic Cleft Lip and Palate: Significant Evidence of Linkage at 18q21.1, *Am. J. Hum. Genet.*, 81, **2007**, 180–188.
47. A. N Mahamad Irfanulla Khan, C. S Prashanth, N. Srinath, Genetic etiology of cleft lip and cleft palate, *AIMS Molecular Science*, 7, **2020**, 328–348
48. S. R. M. Reddy, B. Subramaniyan ., R. Nagarajan, Studying the impact of cleft of lip and palate among adults using the international classification of functioning, disability and health framework, *J. Cleft Lip Palate Craniofac. Animal*, 4, **2017**, 125-137
49. K. Kallen, Maternal smoking and orofacial clefts. *Cleft Palate-Craniofac J.*, 34, **1997**, 11–16
50. Munger RG, Romitti PA, et. al., Maternal alcohol use and risk of orofacial cleft birth defects., *Teratology.*, 54, **1996**, 27–33
51. Holmberg PC, Hernberg S, Kurppa K, Rantala K, Riala R. Orofacial clefts and organic solvent exposure during pregnancy, *Int. Arch. Occup. Environ. Health.*, 50, **1982**, 371–376
52. T. Nurminen, K. Rantala, K. Kurppa, P. C. Holmberg, Agricultural work during pregnancy and selected structural malformations in Finland, *Epidemiology*, 6, **1995**, 23–30.
53. N. Spinder, J. E. Bergman, H. Marike, R. C. Vermeulen, H. Kromhout and E. K DeWalle, Maternal occupational exposure and oral clefts in offspring, *Environ. Health*, 16, **2017**, 1–11.
54. Y. Zhou, S.M. Gilboa, M. L. Herdt, P. J. Lupo, W. D. Flanders, Y. Liu, M. Shing, M. A. Canfield and R.S. Kirby, Maternal exposure to ozone and PM2.5 and the prevalence of orofacial clefts in four U.S. states, *Environ. Res.*, 153, **2017**, 35–40.

55. B. F. Hwang and J. J. Jaakkola, Ozone and other air pollutants and the risk of oral clefts. *Environ. Health Perspect.*, 116, **2008**, 1411–1415
56. I. P. Krapels, G. A. Zielhuis, F. Vroom, L.T. de Jong, A. M. Kuijpers, A. B. Mink van der Molen and R. P. Steegers, Eurocran Gene-Environment Interaction Group. Periconceptional health and lifestyle factors of both parents affect the risk of live-born children with orofacial clefts, *Birth Defects Res. A Clin. Mol. Teratol.*, 76, **2006**, 613–620.
57. G. Acuña-González, C. E. Medina-Solis, G. Maupome, M. Escobedo-Ramirez, J. Hernandez-Romero, M.L. Marquez-Corona, A. J. Islas-Marquez and J. J. Villalobos-Rodelo, Family history and socioeconomic risk factors for non-syndromic cleft lip and palate: A matched case-control study in a less developed country, *Biomedica*, 31, **2011**, 381-391.

