

## The Prevalence of Cleft Lip and Cleft Palate and Related Risk Factors among Iranian Children from 2000 to 2016: a Literature Review

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### Abstract

#### Background

Cleft lip and cleft palate (also, known as or facial clefts), are amongst the most common congenital deformities affecting the jaw and face as well as the most common defects associated with lip and palate. Thus, the current study was an attempt to investigate the prevalence and risk factors of or facial clefts in Iranian children.

#### Materials and Methods

The present study, was conducted through a systematic search for articles recorded in the internal database (SID, IranMedex and Magiran), and external authoritative databases (Google scholar, PubMed, Science Direct, MEDLINE, CINAHL and EMBASE) using the keywords including "cleft lip", "Iranian", "cleft palate", and "children" from 2000 to 2016. Then, 61 articles were collected. 47 studies with associated incidence or prevalence of cleft lip and cleft palate were included.

#### Results

According to the findings of the review of the studies conducted in Iran, it is revealed that the prevalence of cleft lip and cleft palate was from 0.78 to 2.14 in Iranian children. It was revealed that several factors contributing to the development of this disorder consist of Family history (  $P < 0.001$ ), Antibiotics, (  $P < 0.001$ ), Stress in the first trimester of pregnancy ( $P=0.048$ ), BMI before pregnancy ( $P=0.036$ ) Seasonal factors ( $P= 0.03$ ), and Consanguineous marriage ( $P=0.02$ ).

#### Conclusion

According to the results of the present study, the prevalence of cleft lip and cleft palate is high in Iran in comparison with international studies. Furthermore, the prevalence of this disorder is reported to be higher in males than females. Therefore, it is recommended arrange the practical programs in order to help parents eliminate or diminish the factors that affect the prevalence of this disorder and complications.

**Key Words:** Children, Cleft lip, Cleft palate, Iran, Prevalence.

\*Please cite this article as: Jafari A, Zarea K, Mehregan N. The Prevalence of Cleft Lip and Cleft Palate and Related Risk Factors among Iranian Children from 2000 to 2016: a Literature Review. Int J Pediatr 2017; 5(4): 4687-97. DOI: **10.22038/ijp.2016.7180**

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Received date: Dec.17, 2016; Accepted date: Jan. 22, 2017

## 1- INTRODUCTION

The greatest asset of any country is its next generation of healthy, wise, intelligent, and creative children. Congenital malformations are a major factor making such a great asset inefficient. Cleft lip and palate with the incidence of 1 in every 700 live births, is one of these malformations (1). Cleft lip and cleft palate are one of the most common congenital defects which may happen with different percentages of prevalence in different societies. Its prevalence in Iran is estimated to be approximately 1/1 in 1000 live births for children (2). Cleft palate (CP), is a common congenital defect which makes serious problems for cleft-affected children (3). Or facial cleft i.e., cleft lip (CL), cleft palate (CP), and both together cleft lip and cleft Plate (CLP), are the most common congenital anomalies of the head and neck which can affect the lips, jaw bones, hard palate, and soft palate. Several problems can be observed in the cleft-affected patients including dental abnormalities, malocclusion, malformations of the face and nose, and feeding, respiratory, hearing, and speech problems (4). Cleft lip and cleft palate are the congenital abnormality affecting 3 in 1000 live births (5).

Cleft lip and cleft palate are one of the most common congenital anomalies caused by the abnormal facial growth during fetal life (6). Cleft lip with or without cleft palate and cleft palate (CP), are the most common malformations in newborns. Asians are at higher risk for or facial clefts, followed by Caucasians and African Americans (7, 8). In Iran, its prevalence is varied from 0.93 to 1.03 per each 1,000 births (9). According to the statistics, among every 700 live births in America, one infant has or facial clefts. Thus, annually 5,000 infants are born with cleft lip and palate in America; this means that every two minutes an infant with cleft lip and cleft palate draws its first breath

(10). Isolated cleft lip or cleft lip with a cleft palate is among craniofacial congenital anomalies and usually occurs one in a thousand births (11). Predisposing characteristics of CL and CP can be determined by parental genome and may be identified in parental phenotype (12).

Although these disorders have mostly genetic factors, approximately 20% of them are caused due to environmental factors and teratogens during the embryonic period which are all preventable. Some of these factors include consanguineous marriages, taking medications, seasonal fluctuations, alcohol consumption, smoking, maternal obesity and overweight, and genetic factors such as race, ethnicity (1, 4, 10, 13).

One of the big challenges for an infant born with cleft lip and cleft palate is articulation and normal speech production (14). These anomalies emerged in the syndrome and non-syndrome forms and the identification of its related risk factors is so, complicated (2). According to different complications of the disease, it seems that its etiology be a combination of genetic and environmental factors (15). Numerous studies have revealed that 70% of cleft lip and/or cleft palate (CL/P), cases are non-syndrome and the remaining 30% are related to structural abnormalities outside the cleft region (16). When a cleft palate/lip is diagnosed, nutrition may be a major concern for parents. Feeding difficulties appear at birth due to the impairment of sucking and swallowing functions caused by changes in the anatomic structure; thus, at this stage, monitoring infants' feeding and weight gaining is a top priority (17).

The prevalence of this defects reported to be more in males than in females; moreover, children with cleft lip and cleft palate are often suffering from hearing and speech impairments and language production (18). Cleft palate is the most

common congenital anomalies. Patients with cleft palate often need various forms of surgery and other complicated procedures (19). The patients with cleft lip and/or cleft palate (CL/P) are susceptible to various dental abnormalities (i.e., those are related to the teeth number, shape, size, growth, and root formation), more than the general population (20).

However, there is a few of study on children with cleft lip and palate in Iran. Furthermore, there is a very small number of review articles revealing the overall statistics of the prevalence of cleft lip and cleft palate in Iran. Nevertheless, there is a very high number of Iranian children with cleft lip and cleft palate disorder who will undoubtedly face lots of problems relating to their defect in their future life. The current study aimed to determining the prevalence of cleft lip and palate in Iranian children and identifying the related risk factors.

## 2- MATERIALS AND METHODS

The current study is a review article which is carried out through a systematic search for articles recorded in the internal databases [such as Magiran, IranMedex and SID, using the keywords including "cleft palate", "cleft lip", "prevalence/incidence", and "children"], and also in the external authoritative databases [such as Google scholar, PubMed, Science Direct, MEDLINE, CINAHL and EMBASE], using the keywords including "cleft lip", "Iranian", "cleft palate", and "children" from January 2000 to February 2016.

At first, data was extracted by two researchers independently in a form include; name, author, year of publication, place of study, course of study, type of study, number of live births, the number of children with cleft lip and cleft palate, incidence per 1,000 live births. The third researcher were reviewed the final results. If one of researcher disagreed with each

other about the extracted information, they tried to sharing their results with third person to reaching an agreement. A total of 40 articles in international bases, and 21 papers from internal bases were found in the internal data base. After reviewing the articles 47 article (28 article from the foreign bases and 19 from the domestic bases), were entered into the final analysis. Four articles were review and others were original.

Inclusion criteria were incidence of cleft lip and cleft palate in Iranian children and factors affecting of cleft lip and cleft palate from 2000 to 2016.

Fourteen articles of which were not related to the subject or did not examine the prevalence or incidence of cleft lip and cleft palate, were excluded. At the final, the data were extracted form 47 selected articles and entered into a separate file (**Figure.1**).

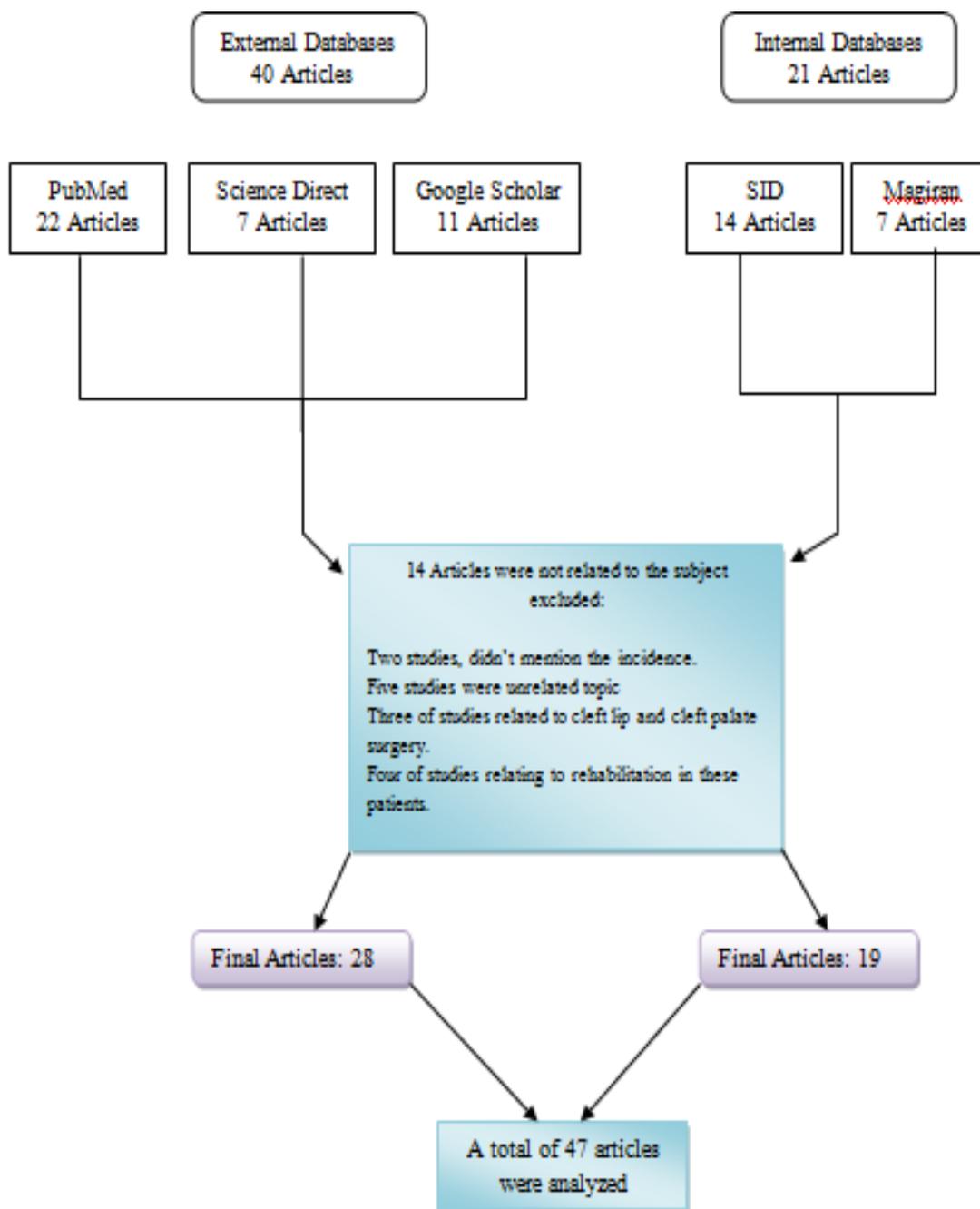
## 3- RESULTS

According to the articles, this study is an attempt to express the prevalence of cleft lip and cleft palate in Iranian children during the January 2000 to February 2015. The final results are presented in **Table.1** and **Table.2**.

According to the results obtained from studies conducted in the prevalence of cleft lip and cleft palate between 0.78 and 2.14 of Iranian children reported the lowest prevalence in the city of Babol and the highest prevalence was reported in Tehran (**Table.1**).

In previous studies, it was revealed that there was a significant positive correlation between the incidence of cleft lip and cleft palate and seasonal factors, marriage, family, family history, use of antibiotics, stress and BMI before pregnancy (**Table.2**).

(Note: the tables 1 and 2, are shown at the end of article).



**Fig.1:** The strategy of searching databases

#### 4- DISCUSSION

In this study, we assessed the prevalence of cleft lip and cleft palate and its associated risk factors among Iranian children from 2000 to 2016. So that one of the most common congenital jaw and face was cleft lip and cleft palate, more than ten million people worldwide are living with

the diseases (9,15). These abnormalities may be occurring alone in the lip, lip and palate and, palate. It is usually follow a multifactorial inheritance pattern (15). According to studies conducted in Iran, the prevalence of cleft lip and cleft palate are from 0.78 to 2.14 in 1000 live birth. The

prevalence of cleft lip and cleft palate in different areas in the world by some researchers are reported as follows:

Moreover, in a study by Cooper et al., the prevalence of syndrome cleft lip and cleft palate is reported to be 1.30 in China, 1.34 in Japan, 1.47 in other Asian countries, and 1.33 in the whole Asia per 1,000 live births. Besides, they report that the prevalence of non-syndrome cleft lip and cleft palate are 1.20, 1.18, 1.22, and 1.19 in China, Japan, other Asian countries, and the whole of Asia, respectively (31). Moreover, the prevalence of cleft lip and cleft palate in the several international studies were 1.39 (32), 1.76 (33) and, 1.53 (34), per 1,000 live births. In a study conducted by Tanaka et al., it was reported to be 7.75 per 10,000 live births in America, and 7.94 per 10,000 live births at the international level (35). In most studies, the prevalence of cleft lip and cleft palate is very different, so, various factors can affect it; some of these factors consist of seasonal fluctuations, consanguineous marriages, taking medications, hypoxia, alcohol consumption, smoking, maternal obesity and over-weight, and agricultural pesticides (1, 4, 10). In a review study conducted in Iran, a positive association is reported between maternal obesity and the incidence of cleft lip and cleft palate (1).

In Watkins et al.'s study, a positive association is observed between maternal obesity and birth defects and anomalies (36). Villamor et al., found a positive association between maternal overweight and the incidence of cleft lip and cleft palate (37). Cedergren and Kallen also, report a positive relationship between maternal Body mass index (BMI), and the incidence of cleft lip and cleft palate (38). Smoking is another factor that plays an important role in the incidence of this complication. In the study done by Little et al., there can be observed a statistically significant positive association between maternal smoking and cleft lip and palate

(39). It is an inevitable fact the oxygen supply to the human embryo is a very crucial issue during embryonic development. Webster and Abela, demonstrate that there is a relationship between cleft lip and cleft palate anomaly and hypoxia (40).

In Jahanbin et al.'s investigation, the highest incidence of cleft palate is reported to occur in the fall, but the most prevalence of cleft lip and cleft palate is observed in males in the spring and in females in the winter (9). In a study by Elliott et al., more births are reported to be in March through August (41). Yassaei et al., realize the prevalence of cleft lip occurs more in summer than in other seasons (13). Noorbakhsh et al., reported there is statistically significant between the use of antibiotics and stress during the first trimester of pregnancy and the incidence of cleft lip and cleft palate (1).

A study showed that the infants of pregnant women treated with amoxicillin, phenytoin, and oxprenolol are at increased risk of cleft lip and cleft palate (42). Carmichael and Shaw, perform a study in California and express that at least one stressful event during the periconceptional period is associated with the incidence of cleft lip and palate (43). In terms of gender, the prevalence of clefts is different at different regions of Iran. In the study conducted by Jamilian et al. (27), cleft lip and cleft palate are more prevalent in females, but in most studies clefts' prevalence is higher in males than females (4, 44-47).

In some studies, revealed that a positive correlation between consanguineous marriages and the prevalence of cleft lip and cleft palate (10, 11, 15, 28), but Gonza et al., assert there is no statistically significant relationship between these two variables in their study (48). Due to the Islamic culture in which any consumption of alcohol is strictly prohibited, statistics

on alcohol consumption are not available in the present survey conducted in Iran; but, the study by Grewal et al., reported a positive relationship between alcohol consumption and childhood disorders (49). Baumann et al., also, approve alcohol consumption and smoking increase the risk of deformities in infants (50).

It is worth mentioning that there is a positive relationship between pesticides and cleft lip and cleft palate (23). Moreover, Jahanbin et al., reported that using chemical fertilizers and pesticides in agriculture can be a predisposing factor for the incidence of orofacial clefts; also, most rate of children with cleft lip and cleft palate accrued in the fall season (9). González et al. also, reported there is a significant association between pesticides and the prevalence of cleft lip and palate (48). Azimi and Karimian mentioned to consanguinity as a factor for cleft lip and cleft palate (15). Noorbakhsh et al., stated that having a positive family history, use of antibiotics, stress and BMI before pregnancy were noted for this disorder (1).

#### **4-1. Study Limitations**

Lack of accessing to some international database and also unpublished papers can limit generalizability of our finding.

#### **5- CONCLUSIONS**

According to the results obtained from studies conducted in the prevalence of cleft lip and cleft palate between 0.78 to 2.14 among Iranian children, reported the lowest prevalence in the city of Babol and the highest prevalence was reported in Tehran. In previous studies, it was revealed that there was a significant positive correlation between the incidence of cleft lip and palate and seasonal factors, marriage family, family history, used of antibiotics, stress and BMI before pregnancy.

The majority of internal researches are retrospective, and based on the evaluation of the existing data of patients' pedigrees; thus, it can be said that there is no study which accurately examine the prevalence of cleft lip and cleft palate and its related risk factors. Accordingly, due to the high rate of prevalence of cleft lip and cleft palate in Iran, comprehensive study at the national level is needed to prevent this anomaly which enjoys different complications and bad consequences for infants.

**6- CONFLICT OF INTEREST:** None.

#### **7- ACKNOWLEDGMENTS**

We would like to express our deepest appreciation to all those who assisted us in conducting this study. A special gratitude librarians of Ahvaz nursing school, whose contribution in stimulating suggestions and encouragement were of great help.

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**Table-1:** Characteristics of studies conducted in Iran on the prevalence of cleft lip and cleft palate among Iranian children (2000- 2016)

References & Authors	Year of Publication	Study population	Study period	Study type	Number of live birth	Number of cases	Incidence in 1,000 live births
Rajabiyani and sherkat (21)	2000	Shiraz	1991-1976	Cross sectional	19369	20	1.03
Tafazzoli et al.(22)	2001	Qazvin	1997	Retrospective	6531	7	1.07
Golalipour et al. (23)	2003	Gorgan	1997-2000	The prospective	19545	20	1.02
Ghasempour and keshvari (24)	2003	Babol	1996-2000	Retrospective	14036	11	0.78
Rajabiyani and aghaei (25)	2005	Shiraz	1993-2003	-	147608	119	0.80
Mohajerani et al. (26)	2005	Tehran	1991-2001	Analytical-descriptive	87838	131	1.49
Golalipour et al. (11)	2005	Gorgan	1997-2003	Cross sectional	37951	37	0.97
Jamilian et al. (27)	2007	Tehran	1998-2005	Retrospective	11651	25	2.14
Sadri and Ahmadi (28)	2007	Tehran	1994-2002	Case-control description	147500	193	1.3
Yaseei et al. (13)	2010	Yazd	2003-2006	Cross sectional	65236	56	0.86
Khazaei et al. (4)	2010	Kermanshah	2001-2008	Descriptive-retrospective	59500	98	1.65
Zandi and heydari (29)	2011	Hamedan	1993-2008	Cross sectional	143589	146	1.016
Jalili et al. (30)	2012	Tehran	2004-2008	Description	57526	103	1.79
Kiyanifar et al. (8)	2015	Mashhad	1982-2011	Cross sectional	28519	54	1.9

**Table-2:** Finding, conclusion and related factors of studies on cleft lip and cleft palate among Iranian children

Author (s)	Location	Type of Study	Findings	Conclusion	Related risk factors
Jahanbin et al. (2008) (9)	Khorasan Razavi Mashad	A retrospective study	The highest birth rates of the patients with cleft palate was in the autumn, but cleft lip and palate showed a different seasonal trend.	These seasonal trends may act as an indicator to investigate the environmental factors which are effective in the multi factorial etiology of cleft lip and cleft palate. the highest combined incidence of cleft lip and palate was in the spring and autumn for males and in the winter for females.	Seasonal factors (Prevalence of Cleft Lip and Palate)  P= 0.03
Azimi and Karimian (2009) (15)	Tehran	A retrospective study	A total of 7374 pedigrees of all the patients including 63 pedigrees of the patients with CL±P (including 92 patients) and 36 pedigrees of the patients with CP (including 44 patients) were studied.92% of patients had syndromic and non-syndromic CL±P and 44% of patients had syndromic and non-syndromic isolated cleft palate.	The prevalence of consanguineous marriage of parents of patients with syndromic cleft lip or palate seemed to be significantly (P = 0.02) higher than its prevalence among parents of non-syndromic patients. Moreover, among non-syndromic patients, the prevalence of consanguineous marriages of parents of CL±P patients was significantly (P = 0.02) higher than its prevalence in patients with isolated CP.	Consanguineous marriage P=0.02
Noorbakhsh et al. (2010) (1)	Esfahan	A combined retrospective and case-control study	A total of 149 children with cleft lip and palate under three years and 151 healthy children under three years were studied. The percentage frequency of family history of cleft lip and palate in the case group was 26.9% and in the control group was 1.3% (P<0.001). furthermore, the frequency of use of antibiotics during the first trimester of pregnancy was 26.2% in the case group and 7.9% in the control group (P<0.001).	In this study, factors such as family history, antibiotics, stress, and BMI before pregnancy were positively associated with the incidence of cleft lip and palate.	Family history, P < 0.001 Antibiotics, P < 0.001 in the first Stress trimester of pregnancy, P=0.048 BMI before pregnancy P=0.036