

# Incidence of cleft lip and palate in Iran

## A meta-analysis

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### ABSTRACT

**الأهداف:** عمل تحليل بعدي من أجل التحقق من الدراسات التي أُجريت عن الحالات المصابة بالشفة الأرنبية، وانشقاق الحنك، وانشقاق الشفة مع أجزاء من الحنك بين حديثي الولادة في إيران

**الطريقة:** أُجري هذا التحليل البعدي في جامعة أصفهان للعلوم الطبية، أصفهان، إيران وذلك خلال الفترة من مايو إلى ديسمبر 2009م، حيث شمل التحليل 11 دراسة، وقد تضمنت البيانات كافة الحالات المصابة بالشفة الأرنبية وانشقاق الحنك في الفترة من 1978م إلى يونيو 2009م. لقد قمنا بتطبيق وزن معكوس التباين من أجل تقدير خلاصة التأثير العشوائي، وكذلك من أجل عمل الرسم البياني للتحليل البعدي، وقد قمنا أيضاً بحساب التحليل البعدي التراكمي للبيانات المنشور. وفيما يخص التحيز النشرى للدراسات فقد تم التحقق منه من خلال اختبارات الكشف عن التحيز المتمثلة باختباري إبيغير، وبيغ.

**النتائج:** لقد وصل مجموع الحالات التي توصلنا إليها في 11 دراسة إلى 1.0 / 1000 (95% مدى الأمان الإحصائي: 0.5-1.5). وأشارت نتائج الدراسة إلى أنه لم يكن هناك تحيز نشري بين مجموع الدراسات التي شملها التحليل البعدي (القيمة الاحتمالية لاختبار بيغ كانت 0.53، فيما كانت لاختبار إبيغير 0.23).

**خاتمة:** أثبتت الدراسة أن نسبة الإصابة بانشقاق الشفة والحنك كانت ضئيلة في المجتمع الإيراني مقارنةً بالبلدان الأخرى.

**Objectives:** To investigate meta-analysis of published data on overall incidence of cleft lip, cleft palate, and cleft lip and palate of newborns in Iran.

**Methods:** This meta-analysis was carried out at the School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran between May 2009 and December 2009. Our data were consisted of all incidences of cleft lip and palate from 1978 to June 2009, and we selected 11 studies. Inverse-variance weighting was implemented to calculate the random effect summary estimates and to produce a forest plot. Cumulative meta-analysis on

published data was calculated and grouped. Publication bias was checked using both Begg's and Egger's test.

**Results:** Pooled incidence from 11 studies was 1.0/1000 (95% confidence interval: 0.5-1.5). There was no evidence of publication bias among the 11 studies (p-values for Begg's test was 0.53 and for Egger's test was 0.23).

**Conclusion:** The incidence of cleft lip and palate in Iran was lower compared to other countries.

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Cleft lip (CL), cleft palate (CP) and cleft lip and palate (CLP) are the most common congenital anomalies that affect the orofacial region and remain a significant public health burden.<sup>1,2</sup> Orofacial clefts (CL/P) commonly affect the lip, alveolar ridge, and hard and soft palates. Problems associated with these anomalies are dental problems, malocclusion, nasal deformity, feeding, and ear and speech difficulties.<sup>3</sup> Affected infants require multidisciplinary surgical and non-surgical care from birth to adulthood. Thus, apart from being a burden on families, orofacial clefts impose a considerable cost to the health system and other related services.<sup>3,4</sup> Etiology of orofacial clefts is multifactorial and includes both environmental and genetic factors.<sup>5</sup> Cleft

lip occurs more frequently in males (80%); its incidence increases slightly with maternal age and varies among populations. The frequency of isolated CP is much lower than CL; it occurs more often in females (67%) and is not related to maternal age.<sup>6</sup> Incidence of CLP ranges from 1/500 to 1/2000 live births, depending on the population. In general, Native American and Asian populations have the highest incidence, Caucasians are placed in the middle, and with Africans the lowest.<sup>7-9</sup> While most of the epidemiological studies have been carried out in the USA, Europe or other developed countries, it is believed that Asians are at higher risk than Whites or Blacks.<sup>7,10</sup>

Cleft lip and palate is more common than the Down syndrome, in many regions of the world. Every 2 minutes, a child with CLP is born in the world, 660 children daily and 235 thousand new cases are seen annually. The incidence of CLP varies according to geographic location, race and socio-economic condition.<sup>11,12</sup> Literature review of scientific journals showed different incidence reports for this anomaly in various area of Iran. There is no national registration system for orofacial clefts in Iran, but many children hospitals and dentistry schools have studied these anomalies. Different studies reported various incidences (0.77 to 3.37/1000 live births) for these defects.<sup>13,14</sup>

To our knowledge, there is no meta-analysis study on such studies in Iran. A meta-analysis can provide valuable information on trends in incidence of such condition using available data, and it seems important for healthcare system to know about orofacial clefts incidence. Thus, the present study was aimed to investigate about the pooled incidence of such condition using all available national data.

**Methods.** This meta-analysis study was performed during May 2009 to December 2009 in School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran. Relevant reports were collected on the “cleft lip”, “cleft palate” and “cleft lip and palate” in both national and international databases including the Iranian Scientific Information Database (SID),<sup>15</sup> indexing articles published in the Iranian biomedical journals (Iranmedex),<sup>16</sup> Pubmed,<sup>17</sup> ISI web of science<sup>18</sup> and Iranian Research Institute of Information and Documentation (Irandoc), which indexed thesis abstracts.<sup>19</sup> The references in each study were also reviewed. The information on incidence of orofacial clefts (CP+CL+CLP) among live births were included from 1978 to June 2009. Exclusion criteria were insufficient or irrelevant data and incorrect methodology; also if a study had multiple publications (Persian and English). We included only the one with one result.

**Collection of data.** Six studies were identified using ISI web of science. Of these, 4 were selected and reviewed.<sup>10,14,20,21</sup> In Gotalipour et al<sup>22</sup> study, we selected the Persian version. One study did not report relevant data.

Four studies were found through Pubmed search; they were same as ISI<sup>10,14,20,21</sup> and 5 studies were excluded. Out of the 11 studies from SID, 5 were selected and reviewed,<sup>22-26</sup> we excluded the 6 studies due to insufficient data and the other were animal cases.

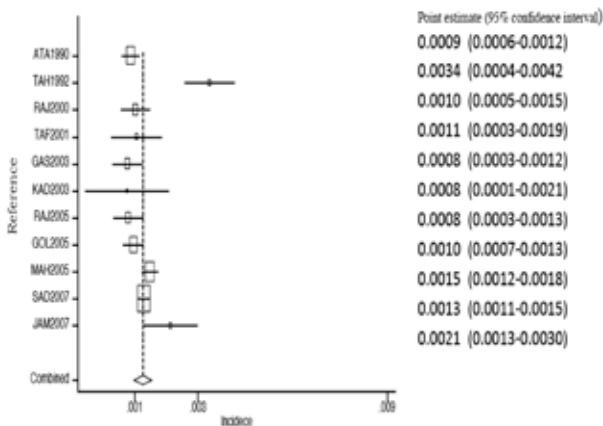
Forty-six studies were found on the iranmedex website and after reviewing their title and abstracts, 6 studies were selected, in which 5 of them had same as SID.<sup>13, 22-26</sup> Out of the 46, 40 were not relevant. Six thesis abstracts were found in the Irandoc website, only one study was selected,<sup>27</sup> the other 5 were excluded due to unreported incidence of the anomaly. Overall, 11 studies were selected for meta-analysis (Table 1).

**Data extraction.** Information including period and area of study, incidence, and total number of newborn were extracted. The data were analyzed using Stata software (Version 8). The proportion of live births suffered from CL/P, and the related standard error were calculated using binomial distribution. In order to investigate the heterogeneity among the results of included studies, we used Cochran Q and we found significant variations between studies. We used inverse-variance weighting to calculate random effect summary estimates and to produce a forest plot. Such graph shows both point estimate and 95% confidence interval for each study and pooled estimate of meta-analysis. The pooled estimate was the weighted (using inverse of variance of each study) average of estimated prevalence of included studies. In order to investigate the temporal trend in incidence of CL/P, we used the cumulative meta-analysis. First, we sorted out all studies by year, using the Stata software, and we incorporated one additional study in each analysis. Such analyses show the cumulative results at the time of each study that had been published. In order to find whether some small studies have been missed in our searched strategy, we checked the publication bias using both Begg's and Egger's test.

**Results.** Table 1 shows the Iranian studies of orofacial clefts. Eleven studies (5 Persian articles, 5 English articles, and one thesis) were selected according to the selection criteria. The largest sample size was found in Rajabian and Aghaei<sup>20</sup> and Sadri and Ahmadi<sup>26</sup> studies. Figure 1 shows the estimated pooled incidence of orofacial clefts. The cumulative incidence of CL/P ranged from 0.77/1000 to 3.37/1000. Using a random effect model (p-value for heterogeneity <0.001), the

**Table 1** - Iranian studies of orofacial cleft that included in this meta-analysis (N=11 studies).

References	Year of publication	Study population	Study period	Incidence in 1000 live birth	Number of live birth	Number of cases
Atarod <sup>27</sup>	1990	Tehran	1989	0.88	45081	40
Taher <sup>14</sup>	1992	Tehran	1983 to 1988	3.37	21138	79
Rajabian & Sherkar <sup>10</sup>	2000	Shiraz	1976 to 1991	1.03	19396	20
Tafazzoli et al <sup>23</sup>	2001	Qazvin	1997	1.07	6531	7
Ghasempour & Keshvari <sup>24</sup>	2003	Babol	1995 to 1999	0.78	14036	11
Kadkhodayan & Naghib Zadeh <sup>13</sup>	2003	Mashhad	1996 to 2000	0.77	16847	13
Rajabian & Aghaei <sup>20</sup>	2005	Shiraz	1993 to 2003	0.8	147608	119
Golalipour et al <sup>22</sup>	2005	Gorgan	1997 to 2003	0.97	37951	37
Mohajerani et al <sup>25</sup>	2005	Tehran	1991 to 2000	1.49	87838	131
Sadri & Ahmadi <sup>26</sup>	2007	Tehran	1994 to 2002	1.3	147500	193
Jamalian et al <sup>21</sup>	2007	Tehran	1998 to 2005	2.14	11651	25



**Figure 1** - Forest plot of incidence of orofacial cleft in Iranian studies. ATA - Atarod<sup>27</sup>, TAH - Taher,<sup>14</sup> RAJ - Rajabian & Sherkar,<sup>10</sup> TAF - Tafazzoli et al,<sup>23</sup> GAS - Ghasempour & Keshvari,<sup>24</sup> KAD - Kadkhodayan & Naghib Zadeh,<sup>13</sup> GOL - Golalipour et al,<sup>22</sup> MAH - Mohajerani et al,<sup>25</sup> SAD - Sadri & Ahmadi,<sup>26</sup> JAM - Jamalian et al<sup>21</sup>

pooled incidence from 11 studies for which the reference populations were available was 1.0/1000 (95% CI: 0.5-1.5). The cumulative incidence from 1976 to 2005 (study period) showed no evident trend. Using Begg's and Egger's test, there was no evidence of publication bias among 11 studies (*p*-value for Begg's test=0.53 and *p*-value for Egger's test=0.23).

**Discussion.** In this meta-analysis study about the incidence of CL/P in Iran, all national and international data base before June 2009 were evaluated. Seventy-eight related studies were evaluated according to including and excluding criteria. Only 11 studies had sufficient data for meta-analysis. The CL/P incidence in Iran was 1.0/1000 (95%CI: 0.5-1.5). There was no evidence of publication bias. In addition, the cumulative incidence

showed no trend. World Health Organization profile of CL/P in Islamic Republic of Iran,<sup>28</sup> which was based on data from previous 2 studies, reported 1.03/1000 and 2.14/1000 live births, respectively.<sup>10,21</sup> Our findings on CL/P incidence in Iran was 1.0/1000 and we confirmed one of them. According to the reports from different countries, the present incidence was higher compared to Saudi Arabia (0.3/1000 live births),<sup>29</sup> and lesser compared to other countries such as Jordan (1.39/1000 live births),<sup>30</sup> Pakistan (1.91/1000 live births),<sup>31</sup> and Republic of Korea (1.81/1000 live births).<sup>32</sup> Also, Asian populations have reported higher values: 1.30/1000 live births from China and 1.34/1000 from Japan.<sup>9</sup> The etiology of orofacial clefts is complex, heterogeneous and multifactorial and include both environmental and genetic factors.<sup>5,33</sup> Many teratogenic agents and factors in pregnancy are claimed to cause clefting, such as maternal smoking,<sup>4</sup> maternal hypoxia,<sup>34</sup> season of gestation,<sup>35</sup> and maternal diabetes mellitus.<sup>36</sup> We did not investigate the affecting factors of orofacial cleft in our study. It is necessary to define these factors in Iranian population.

Limitations of this study were unreported incidence of CL/P, other reports mentioned that Iranian studies were restricted to north, center, Southwest and Northeast of country, with no studies from other areas of Iran, and no evidence in cumulative incidence suggests that there is no change in risk related to such conditions.

In conclusion, the results of this study showed that the incidence of CL/P in Iran was lower (1.0/1000 births) compared to other countries. Further studies are required to examine the risk factors for orofacial clefts in Iranian populations.

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