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Prevalence of Orofacial Clefts among Live Births in China: A Systematic Review and Meta-Analysis

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Abstract

Background—Orofacial clefts (OFCs) are common human birth defects in China. However, studies on the prevalence of OFCs present inconsistent results. The overall prevalence and geographic distribution of OFCs are poorly described in China. Thus, we conducted a systematic review and meta-analysis to estimate the prevalence of OFCs.

Methods—The systematic review and meta-analysis were conducted on the basis of an established protocol (PROSPERO 2015: CRD42015030198). We systematically searched for articles in four electronic databases, including Embase, PubMed, Wanfang Database, and China National Knowledge Infrastructure (CNKI) to identify relevant studies about prevalence of OFCs in China. Meta-analysis, including subgroup analysis, was conducted to estimate the pooled prevalence.

Results—A total of 41 studies published between 1986 and 2015 were included in our analysis. The sample size ranged from 2,586 to 4,611,808 live births. The random-effects model of meta-analysis showed that the overall prevalence of OFCs in China was 1.4 per 1000 live births (95% confidence interval [CI], 1.1–1.7). In subgroup analysis based on geographic regions, we found that OFC prevalence in Southwest (2.3 per 1000 live births, 95% CI, 1.1–4.7) was higher than that in other regions of China. There were no significant time trends of OFCs during the study period (p -value = 0.47).

Conclusion—The overall prevalence of OFCs in China was 1.4 per 1000 live births. No significant secular trend of prevalence has been found in this analysis. Further studies need to be conducted to explore the etiology of OFC to better control the risk of this common birth defect.

Keywords

orofacial clefts; prevalence; systematic review; meta-analysis

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Additional Supporting information may be found in the online version of this article.

Introduction

Orofacial clefts (OFCs) represent a large proportion of birth defects. Approximately 1 in 700 live births is affected by OFC worldwide (Rahimov et al., 2012). OFCs require multi-disciplinary interventions, including reconstructive surgeries, dental care, speech and language therapy, hearing intervention, and psychological counseling (Berger and Dalton, 2009). Despite the development of surgical and dental techniques, OFCs still create substantial medical, psychological, and economic burdens for cases and their families (Christensen and Mortensen, 2002; Sank et al., 2003). In addition, it has been reported that OFCs are also associated with increased risk of other major causes of death (Christensen et al., 2004).

Determining accurate estimates of OFC prevalence among live births is of great importance for studies of the burden and etiology of the disease. Chinese people are reported to have a higher prevalence of OFCs among live births compared with other racial groups (Cooper et al., 2006). However, the estimated prevalence has been reported to be from 0.9 to 2.0 per 1000 births (Zou and Wang, 2012; Yang et al., 2015). This uncertainty could reflect the heterogeneity of OFC. In terms of subtypes, OFC can be subdivided into three anatomically distinct types: cleft lip alone (CL), cleft palate alone (CP), and cleft lip and palate (CLP) (Leslie and Marazita, 2013). CL and CLP are often grouped into cleft lip with or without cleft palate (CL/P) according to their similarities in epidemiologic characteristics and embryological development (Mangold et al., 2011).

Moreover, the complexity of estimating the prevalence of OFCs may also come from whether the syndromic forms have been included or not. At least 275 congenital syndromes have orofacial clefting as a primary feature which are Mendelian disorders, while nonsyndromic OFCs refer to those of isolated clefting (Leslie and Marazita, 2013). The prevalence of syndromic OFCs is much lower compared with nonsyndromic forms. In addition, ethnic and geographic variations, and whether to include stillbirths and abortions, can also be other sources of inconsistency of prevalence estimation (Vanderas, 1987; Marazita, 2012; Saad et al., 2014).

The prevalence of OFCs varied among different geographic regions in China (Zou and Wang, 2012; Yang et al., 2015). Moreover, few studies have been conducted to investigate the secular trend of OFC in China. To better understand the epidemiologic pattern of OFC in China, we conducted a systematic review and meta-analysis to estimate the prevalence of OFCs and describe its geographic distribution among live births in China.

Materials and Methods

The systematic review and meta-analysis were conducted on the basis of an established protocol (PROSPERO 2015: CRD42015030198).

SEARCH STRATEGY

We systematically searched for available articles in four electronic databases, including Embase, PubMed, Wanfang Database, and China National Knowledge Infrastructure

(CNKI). Search was limited to the publication year from January 1, 1980, to December 31, 2015. Searches were done in parallel by two reviewers. Free text words were applied to Wanfang Database and CNKI, while of Medical Subject Headings (Mesh) terms and free text words were combined to search PubMed and Embase. Detailed search strategies for each database were summarized in Supporting Table S1, which is available online.

INCLUSION AND EXCLUSION CRITERIA

We included descriptive studies and cohort studies with accurate raw data about the prevalence of OFCs which were conducted among live births in China and published between 1980 and 2015. We excluded duplicates within and among the databases and the studies focusing on treatment of congenital malformations and animal models. We also excluded case reports, case series, and studies irrelevant to OFC.

STUDY SELECTION AND DATA EXTRACTION

According to the criteria of inclusion and exclusion, two reviewers independently screened each study by the title, the key words, and the abstract. The full text of studies meeting criteria of inclusion were retrieved and screened by two reviewers. Screening results of every step were compared. Two reviewers extracted the information from each included study independently and the results were compared after extraction. In the process of selection and extraction, disagreements were resolved by discussion or by the third reviewer. We extracted information including the first author, the publication year, the province, the source of sample, the study design, the number of OFCs, and the number of live births. OFC in this study referred to all types of clefts (CP, CL, or CLP; syndromic or nonsyndromic forms). When the information for subgroup analysis was missing from the original studies, the corresponding authors were contacted by emails once a week. If the authors did not reply to the emails after sending the second email, the study was excluded from the related subgroup analysis.

RISK OF QUALITY ASSESSMENT

We used a checklist with nine items adapted from an assessment tool for prevalence studies, which was originally developed by Damian Hoy et al from Leboeuf-Yde and Lauritsen tool (Hoy et al., 2012). The nine items included representation for national population, representation for target population, sampling method, response rate, data collection, case definition, same mode of data collection, prevalence period, and precise parameter. Each item was assessed as low or high risk of quality according to the predefined criteria (Supporting Table S2). For each item, if the article met the criteria, it was defined as low risk and one point was scored, otherwise it was defined as high risk and zero point was scored. The point for each item added up to a total score. Articles with total score being at least seven points were defined as high quality, while total score of four to six points or zero to three points was defined as medium quality or low quality, respectively.

DATA ANALYSIS AND STATISTICAL METHODS

Prevalence was derived from the number of OFCs divided by the number of live births, and the 95% confidence interval (CI) for the prevalence in each study was calculated based on the logit-transformed metric.

The meta-analysis was conducted for the pooled estimates. Statistical difference of the prevalence across included studies was tested by I^2 statistic and Q statistic for heterogeneity. If statistically significant heterogeneity was absent, the pooled estimate and the 95% CI would be calculated using a fixed-effect model, and if significant heterogeneity was present, the random-effects model was adopted.

The subgroup analysis was conducted based on predefined variables including sources of samples (hospital-based studies, or community-based studies), study designs (cross-sectional study, monitoring study, or historical data analysis), study year, the provinces, sample size, geographic regions, economic conditions, and subtype of clefts (CP, CL/P) to explore possible sources of heterogeneity among different studies. Moreover, 20 provinces with prevalence data available were included and categorized into seven subgroups based on their geographic regions (Lv, 2016).

Egger's test was conducted to assess the publication bias for the overall prevalence. A funnel plot was applied to graphically assess the potential publication bias.

The graph of risk of quality assessment was conducted with Review Manager (Version 5.2). The graph of OFC prevalence in different provinces was drawn through Adobe Photoshop CS6. We performed all the data analysis using "meta" package in R (Version 3.2.0). I^2 statistic of more than 50% and P -value of less than 0.05 were regarded as statistical significance for all tests.

Results

GENERAL INFORMATION ABOUT THE INCLUDED STUDIES

We retrieved 4080 studies from four databases, of which 41 studies were finally eligible for inclusion (Fig. 1). The majority of the studies were written in Chinese, while seven were in English. The included studies were published between 1986 and 2015. The sample size ranged from 2,586 to 4,611,808 live births. Only one study was a nationwide study, which was an analysis on national monitoring data from 1986 to 1987. The other 40 studies were conducted in 20 different provinces in China. The detailed information of the included studies was showed in Supporting Table S3.

RISK OF QUALITY ASSESSMENT

The assessment of risk of quality showed that all studies included in our analysis presented high quality, with total score ranging from seven points to eight points (Supporting Table S4, Supporting Fig. S1). Figure 2 summarized the percentage of the included studies for each item of the assessment tool.

OVERALL PREVALENCE

All included studies reported the prevalence of OFCs among live births. The pooled prevalence of OFCs was 1.4 per 1000 live births (95% CI, 1.1–1.7; Fig. 3). While $I^2 = 98.7\%$ (p -value < 0.05), the random-effect model was adopted in our study.

SUBGROUP ANALYSIS

The results of subgroup analysis were summarized in Table 1 and the forest plots were presented in Supporting File S1. The pooled prevalence of studies obtained in hospital-based studies was 1.3 per 1000 live births (95% CI, 1.2–1.6; $I^2 = 92.8\%$), which was similar to prevalence estimated in community-based studies (1.3 per 1000 live births; 95% CI, 0.9–1.9; $I^2 = 99.3\%$). Although study design did not influence the estimation of prevalence statistically (test statistics for heterogeneity = 1.11, p -value > 0.05), the prevalence of OFCs based on historical data analysis (1.5 per 1000 live births; 95% CI, 1.2–1.8) was higher than that in cross-sectional studies (1.1 per 1000 live births; 95% CI, 0.7–1.9) and monitoring studies (1.4 per 1000 live births, 95% CI; 1.1–1.7). In addition, the prevalence estimated by larger scale studies (sample size > 150,000; prevalence = 0.8 per 1,000 live births) was significantly lower compared with small scale studies (sample size < 10,000; prevalence = 2.3 per 1000 live births; p -value < 0.05).

There was statistically significant variation among studies conducted in different provinces (p -value < 0.05). OFC prevalence by different provinces across China is shown in Figure 4 and Supporting Table S5. The OFC prevalence in Chongqing (5.1 per live births; 95% CI, 1.3–20.4) and Ningxia (2.8 per 1000 live births; 95% CI, 1.9–4.0) was higher than that in other provinces. In subgroup analysis based on geographic regions, the OFC prevalence was the highest in Southwest (2.3 per 1000 live births; 95% CI, 1.1–4.7), followed by Northeast (2.2 per 1000 live births; 95% CI, 0.3–15.8), and the lowest prevalence was observed in Central China (1.1 per 1000 live births; 95% CI, 0.7–1.8) and East China (1.1 per 1000 live births; 95% CI, 1.0–1.2). Although there was no statistically significant difference between prevalence of studies conducted in diverse economic conditions, prevalence of provinces with high level economic condition (1.4 per 1000 live births; 95% CI, 1.2–1.7) was higher than those with low level economic condition (1.3 per 1000 live births; 95% CI, 0.7–2.1; p -value = 0.71).

In our analysis, there was no statistically significant difference of annual OFC prevalence during the study period (p -value = 0.47). The results of annual OFC prevalence were summarized in Supporting Table S6.

Nine studies reported prevalence of OFCs according to different subtypes of clefts (CP, CL/P), the pooled prevalence of CL/P was 0.8 per 1000 live births (95% CI, 0.5–1.4; $I^2 = 98.8\%$), while the prevalence of CP was 0.3 per 1000 live births (95% CI, 0.2–0.4; $I^2 = 89.7\%$).

PUBLICATION BIAS

The Egger's test suggested the risk of publication bias was at low level ($t = 1.2265$; p -value = 0.2274), while the funnel plot developed based on original studies was not symmetrical absolutely (Supporting Fig. S2).

Discussion

In this meta-analysis, 41 studies published from 1986 to 2015 were included. The overall prevalence of OFCs was 1.4 per 1000 live births (95% CI, 1.1–1.7) in China. We also found that OFC prevalence in Southwest (2.3 per 1000 live births; 95% CI, 1.1–4.7) and Northeast (2.2 per 1000 live births; 95% CI, 0.3–15.8) was higher than those in other regions of China. There were no significant time trends of OFC during the study period.

The meta-analysis in our study indicated that the prevalence of OFCs among live births in China was lower than the prevalence of OFCs reported by Cooper et al. (1.53 per 1000 live births) or by Panamonta et al. (1.56 per 1000 live births) (Cooper et al., 2006; Panamonta et al., 2015). The potential reason may include the sample sizes of the original studies. Studies with larger sample size represented lower pooled estimates in our study (Table 1). To better describe the burden of OFC in China, we only included original studies that reported OFCs among live births in the analysis. It has been reported that stillbirths may have approximately three times higher prevalence of OFCs than live births (Panamonta et al., 2015). Therefore, whether to include stillbirth or abortion may influence the prevalence of OFC.

It has been reported that Chinese, Koreans, and other Asian populations had higher prevalence of OFCs than other racial groups, such as Americans and Africans (Cooper et al., 2006). The prevalence of OFCs in Thailand and Korean was 1.51 per 1000 live births and 1.109 per 1000 live births, respectively (Lee et al., 2015; Chowchuen et al., 2016). The prevalence of OFCs was 0.82 per 1000 live births among Germans and 1.21 per 1000 live births among British people (EUROCAT, 2014), which was lower than the prevalence of OFCs in our analysis.

The prevalence of OFCs varied across studies conducted in different provinces, and among the provinces, OFC prevalence was among the highest in Chongqing and Ningxia. To explore possible sources of heterogeneity, we divided the 20 provinces into different subgroups according to their geographic regions and economic conditions. In subgroup analysis based on geographic regions, the OFC prevalence was higher in the southwest and northeast than in other regions. Possible reasons for the variation of OFC prevalence by geographic regions may include environmental exposures and lifestyle risk factors. Although no statistically significant difference of OFC prevalence was found in the stratified analysis based on different levels of economic conditions, studies conducted in regions with higher level of economic conditions showed higher OFC prevalence compared with those with lower economic levels.

However, a study conducted by Dai et al. (2003) found a lower OFC prevalence in urban areas compared with rural areas. Moreover, it is hard to make a feasible comparison among

these findings because the definition of economic condition differed among studies. Consistent associations of the role of economic conditions on OFC have not been established. In addition, sparse data were provided by the included studies for many provinces, including five provinces in northern China, three provinces in western China, and three provinces in central and southern China. Further studies need to be conducted to explore the incidence and prevalence of OFC.

There were no obvious time trends of prevalence of OFCs in our study, which was similar to what was observed by Dai et al. (2010). Therefore, better prevention and control strategies are needed to control the prevalence of OFCs among live births in China. In subgroup analysis based on sources of samples, more hospital-based studies were included, and the community-based studies had more subjects. It has been reported that whether samples were collected from hospitals or communities can influence the prevalence of OFCs (Wang et al., 2012). However, the prevalence estimated by hospital-based studies was similar to that observed by community-based studies. Moreover, there was no statistically significant difference among different study designs in our analysis. Most included studies applied random sampling or conducted a census to collect data, which could be the reason for no major heterogeneity among studies with diverse sources of samples and study designs.

All studies included in our analysis were evaluated as high quality in the assessment of risk of quality. Among the included 41 studies, only 1 was a nationwide study, which collected monitoring data from 29 different provinces in China and was a good representation for national population. Another 40 studies were conducted in 20 different provinces in China, which were assessed as high risk of quality on the item of “representation for national population.” Some original studies did not apply any diagnostic criteria or failed to use recognized criteria in their studies, which resulted in approximately half of the included studies being defined as high risk of quality on the item of “case definition” in the assessment of risk of quality. Because CP is less noticeable externally, lack of diagnostic criteria may have some effect on the prevalence estimation of OFC.

There are still some limitations for this analysis. First, although studies conducted in 20 different provinces were included in our analysis, the pooled sample size is still relatively small for the Chinese population. Second, prevalence of cleft types, including anatomical groups (CP, CL, and CLP) and syndromic/non-syndromic forms, was not estimated in this study because few included studies reported relevant data. This partly reflected the quality of original studies, most of which focused on the estimation of the prevalence of OFCs but ignored other important clinical and/or etiological information of this congenital orofacial malformation. In addition, we could not analyze the prevalence of OFCs according to different ethnicities in China due to unavailable data in the original articles. Finally, most original studies failed to report missing rates, which may influence the pooled estimates of prevalence in our study.

In summary, further studies are required to confirm the pooled prevalence of OFC among live births in China. More studies need to be conducted to advance the understanding of the genetic and environmental risk factors for OFC so as to develop better prevention and control strategy for this common birth defect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1.
Flow chart of study selection.

FIGURE 2.
Risk of quality assessment for all included studies.

FIGURE 3.

Overall prevalence of orofacial clefts among live births in China.

FIGURE 4.
Prevalence of orofacial clefts in different provinces in China

TABLE 1

Results of Subgroup Analysis

Prevalence of orofacial clefts in China						
Subgroup	No. of studies	No. of orofacial clefts	No. of live births	Prevalence ^a	95% CI ^a	I ² (%)
Source of sample						
Hospital-based	22	3,887	2,867,017	1.3	1.2–1.6	92.8
Community-based	19	6,420	7,965,581	1.3	0.9–1.9	99.3
Study design						
Cross-sectional study	16	3,259	5,660,833	1.1	0.7–1.9	98.7
Monitoring study	20	3,724	2,654,943	1.4	1.1–1.7	96.4
Historical data analysis	5	3,324	2,516,822	1.5	1.2–1.8	92.7
Sample size						
<10,000	11	205	66,838	2.3	1.3–4.1	93.1
10,001–50,000	13	545	299,794	1.5	1.0–2.3	95.1
50,001–100,000	6	556	472,055	1.2	1.0–1.4	81.6
100,001–150,000	2	213	292,166	0.7	0.6–0.9	54.8
>150,000	9	8,788	9,701,745	0.8	0.6–1.1	99.6
Subtype of clefts						
CP	9	998	2,941,731	0.3	0.2–0.4	89.7
CL/P	9	2,421	2,941,731	0.8	0.5–1.4	98.8
Region						
Central China	6	471	559,836	1.1	0.7–1.8	95.5
East China	9	4,266	3,451,680	1.1	1.0–1.2	90.9
North China	6	2,792	4,809,746	1.3	0.7–2.3	98.1
Northeast	2	156	155,625	2.2	0.3–15.8	99.1
Northwest	7	261	499,396	1.3	0.5–3.3	98.1
South China	4	93	62,507	1.3	0.8–2.2	79.3
Southwest	6	271	73,151	2.3	1.1–4.7	96.1
Economic condition						
High level ^b	24	5,184	4,181,288	1.4	1.2–1.7	96.4
Low level ^b	16	3,126	5,430,653	1.3	0.7–2.1	98.8

^a Per 1000 live births.^b According to whether the per capita gross domestic product of each province in 2014 was higher or lower than the national average (7591 dollars) in China (National Bureau of Statistics of China, 2015).
CP, cleft palate; CL/P, cleft lip with or without cleft palate.