Systematic Review and Meta-Analysis of the Birth Prevalence of Orofacial Clefts in Low- and Middle-Income Countries

Abstract

Background

In the last comprehensive review of the literature published in 2002 little information on the prevalence of orofacial clefts was available from low- and middle-income countries (LMICs).

Objective
To analyse published data on the birth prevalence of cleft lip and/or palate (CL/P) from (LMIC).

Design
Systematic review of the literature and meta-analysis of data from original papers on the birth prevalence of CL/P in LMIC between 1990 and 2014. Secondary inclusion criteria were developed to analyse lower quality studies from countries with scarce data.

Main Outcome Measure
Birth prevalence of undifferentiated CL/P (with or without associated syndrome or other anomaly).

Results
28 studies met strict inclusion criteria. Among 31,475,278 total births, the pooled birth prevalence of undifferentiated CL/P was 1.38 per 1,000 births (95%CI: 1.20-1.56). Four studies met criteria for secondary analysis, providing data on 75,627 births, with a pooled prevalence of 0.75 CL/P cases per 1,000 births (95%CI: 0.56-0.95). Comparison of studies was limited by variable definitions of cases and of the reference population, and inconsistent reporting of outcomes. There is significant heterogeneity in the findings.

Conclusions
In LMIC, approximately 1 in every 730 children is born with CL/P. To optimise comparability across settings, future research should use a standard classification system and standard criteria for data collection and presentation. As clefting is associated with deprivation, understanding the true scale, risks and preventive measures for orofacial clefts in LMIC is a matter of both scientific and humanitarian importance.

Key words: Systematic review, birth prevalence, cleft lip, cleft palate, low- and middle-income countries

Introduction

Orofacial clefts (OFC) are among the most common congenital disorders worldwide. Clefts have a significant impact on the health, development, quality of life and survival of affected individuals and their families, even in settings where specialised, early care is widely available and accessible (Lockhart 2003, Hunt et al. 2005). The birth prevalence of OFC is a crucial component in the estimation of burden of disease, effect of risk factors, and provision of care. As we enter an era of preventative medicine, it is important to be able to estimate the efficacy of interventions such as surgery and rehabilitation, as well as the effect that terminations of pregnancy have on the prevalence figures for OFC.

International umbrella registries gather registry data from hospital and population-based registries in several countries. Examples include the European Surveillance of Congenital Anomalies (EUROCAT), the Latin American Collaborative Study of Congenital Malformations (ECLAMC)(Castilla and Orioli 2004), and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)(Botto et al. 2006). These registries provide insight on the epidemiology across the globe, including prevalence and proportion of different kinds of clefts over time, genetic and environmental risk factors, and the effect of interventions on prevalence. However, there are large gaps in registry data from low and middle income countries (LMIC), limiting our ability to design and undertake effective public health and clinical interventions for the prevention of clefts and treatment for affected children.

Reports from registry data internationally suggest wide variations in birth prevalence of cleft lip and/or cleft palate (CL/P) across settings. Reports of isolated cleft lip with or without cleft palate (CL±P) show a 7 fold range from 3.4 to 22.9 per 10,000 live births, while reports of isolated cleft palate only (CP) range from 1.3 – 25.3 per 10,000 live births, a 20 fold variation (Mossey et al. 2009). Detection of the latter (CP) at birth requires specialist training, is less consistent, and therefore ascertainment is almost certainly a factor in the variation in CP prevalence.

A systematic review of CL/P prevalence up to the year 2000 found that approximately 1 in 700 children worldwide are born with an orofacial cleft (Mossey and Little 2002). This figure remains the best estimate to date (Mossey and Modell 2012). The purpose of the current systematic review is to present and analyse published data from low- and middle-income countries, in order to update the previous systematic review, address some significant gaps and obtain a better understanding of the current burden of this disorder in low- and middle-income settings.

Methods

Search strategy and selection criteria

Due to marked variation in reporting, the outcome measure is birth prevalence of undifferentiated CL/P. Undifferentiated CL/P is defined as all CL/P, including isolated clefts, those associated with syndromes, and those associated with other anomalies. Regional comparisons are made to evaluate patterns in prevalence across settings.

We identified LMIC participating in international umbrella registries. For countries without birth registry data, we undertook a systematic review. As studies in all settings variably include live births, stillbirths, and less frequently, terminations of pregnancy, no restrictions were made for birth outcomes. We applied no language restrictions. Studies with a median date of data collection between 1990 and 2014 were included; the 10 year overlap with the previous systematic review was done to improve validity of the findings. Major and selected geographically-focused online databases were searched for publications, including PubMed/Medline, EMBASE, Latin American and Caribbean Health Science (LILACS), IndMED, Africa-Wide Information, Open Grey and the New York Academy of Medicine Grey Literature Report. The last search was performed on 27 June 2014.

Search terms included multiple variants of "cleft lip" or "cleft palate" or "orofacial cleft" or "harelip", and "epidemiology" or "prevalence" or "rate", and comprehensive search terms for low and middle income settings based on the World Bank classification of the world's economies in 2014 (World Bank 2014). The search terms used for PubMed are provided in Annex 4 in the web appendix. Medical Subject Headings terms were used when available, and snowball searching was used to identify additional studies by screening the reference list of retrieved studies. Selected studies from high income Middle Eastern countries were also included, and the titles of their respective references were screened.

Studies were included in the main analysis if they reported of the birth prevalence of OFCs from a defined population, demonstrated systematic ascertainment of cases, stated the number of cases and the population denominator, and spanned at least one full calendar year. For detailed inclusion and exclusion criteria, refer to web appendix Annex 2.

To address the problem of gaps in data, a secondary analysis was undertaken of lower quality studies from countries in geographical regions with no data meeting inclusion criteria. This included smaller studies of less representative populations, such as studies from single tertiary care facilities or specialist maxillofacial surgery clinics.

Studies meeting inclusion criteria were abstracted onto a standard data extraction form, which had been piloted and refined. Studies were reviewed and data was abstracted by AK. Recorded study characteristics included the time period, study country and sub-region, study design, reference population, the birth prevalence of isolated OFCs, birth prevalence of OFCs associated with syndromes, birth prevalence of OFCs associated with other malformations, and overall population prevalence of OFCs. Where available, data were extracted for subtypes of clefts, including cleft lip with cleft palate (CLP), cleft lip (CL) and

isolated cleft palate only (CP), and breakdown of these by sex. Other variables for which data were extracted included risk factors such as consanguinity or previous family history of cleft. When possible, authors were contacted for missing data from studies in order to maximise the number of studies that met inclusion criteria. The completed data extraction form was reviewed by HB and PAM, and in the case of queries or differences, an agreement was negotiated.

The risk of bias was assessed for each individual study based on the data source, method of ascertainment, quality of ascertainment, population included in the study, and any special characteristics of the population. Studies which were deemed to be at high risk of bias, and therefore unlikely to be representative of the regional or national population, were excluded from the main analysis. The studies included in this review presented data on a wide range of variables in an inconsistent manner, however nearly all studies provided figures for undifferentiated oral clefts (i.e. where the category and /or cleft type was not specified). As such, the primary meta-analyses were performed on the prevalence of undifferentiated CL/P. Data from studies which did not specify if the population included isolated or undifferentiated CL/P were classified as undifferentiated. For studies presenting data exclusively on isolated CL/P, the figures provided were included in the total pooled meta-analysis of studies providing data on undifferentiated CL/P; this method will lead to an underestimation of the prevalence of isolated CL/P, if the percentage of isolated CL/P is calculated from the pooled figures obtained by meta-analysis. A separate meta-analysis was done for studies providing data on isolated CL/P as part of the sensitivity analysis.

The inclusion of less representative studies from areas with no other available data in a secondary analysis was done because these studies provide the only available data for their respective countries, and thus provide a glimpse, however imperfect, into the epidemiology of CL/P in these regions. In order to allow for comparison between studies meeting strict inclusion criteria and second tier inclusion criteria and thus evaluate for potential effects of bias, figures from each tier are presented separately.

Statistical analysis
Statistical analysis was performed in Stata version 11.2 (StataCorp, College Station, Texas, USA). The pooled birth prevalence of undifferentiated orofacial clefts was generated using the metan command, which performs meta-analysis using the inverse-variance method. Weights were calculated using random effects analysis. Due to known ethnic variations in the prevalence of clefting, pooled prevalence estimates were generated by GBD geographical super-region (Murray et al. 2012). For China, where national and regional level data were available, meta-analysis was performed to compare the pooled national level studies to the regional pooled prevalence (Web appendix Annex 3, Figure 3). Heterogeneity was evaluated by using the Q and the I^2 statistics.

The sensitivity of the findings was evaluated by examination of the differences between the pooled prevalence of studies in the main analysis to lower quality studies from regions with limited data, and between studies presenting data on isolated cases versus those presenting undifferentiated cases. Results were compared with those reported by the EUROCAT and ECLAMC umbrella registries. EUROCAT has documented a stable birth prevalence and high ascertainment from participant registries since 1980, and as such, it serves as a reliable and valid registry for comparison (EUROCAT 2002). ECLAMC includes data from LMIC in Latin America, hence it is particularly useful for comparison with other LMIC settings.

Role of the funding source

The study design, data collection, analysis, interpretation of data and writing of the manuscript was undertaken independently, with no input from the study sponsors. All authors had full access to all the data in the study and they shared responsibility for the decision to submit for publication. The systematic review was undertaken as part of a larger study of the global birth prevalence of selected congenital disorders initiated by the World Health Organization (Lim et al. 2012).

Results

Search results

The literature search yielded 2,117 titles. After removing duplicates, the titles and abstracts of the remaining 1303 publications were screened for potential eligibility. 12 further studies were identified through secondary searches of the references of included papers. A total of 113 papers were reviewed in full text, of which 28 studies met strict inclusion criteria for the main analysis, and 4 met second tier inclusion criteria (Web appendix Annex 2, Figure 3, Flow diagram). All studies meeting second tier criteria came from Sub-Saharan Africa (Uganda, Sudan, Kenya, and Malawi). Table 1 provides an overview of the studies.

The pooled total study population in the main analysis is 31,475,278 births from 12 countries, of which 34,653 were identified to have CL/P. The total pooled population is 1.38 per 1,000 births (95%CI: 1.20-1.56), or 1 in 730 births. Tables 2A-B in the web appendix provide an overview of the findings of studies which provided data on cleft subtypes, and web annex Table 1 provides data on findings by strict and secondary inclusion criteria.

Table 1 and Figure 3A. illustrate the findings across GBD super-regions. There is wide variation in CL/P prevalence between regions and significant heterogeneity within each super region. East Asia and Pacific demonstrates the highest regional prevalence, with 1.69 CL/P cases per 1,000 births (95%CI: 1.48-1.90). All studies from this region were conducted in China, and 8 of the 12 studies provided data from a birth defects registry. Interestingly, meta-analysis of the three nation-wide studies, all of which took data from the National

Birth Defects Monitoring System, provides a lower CL/P prevalence, at 1.49 per 1,000 live births (95%CI: 1.15-1.83) (Web appendix Annex 3, Figure 3A) when compared with the provincial studies, for which the pooled prevalence was 1.80 per 1,000 births (95%CI: 1.37-2.23) (Web appendix Annex 3, Figure 3B). The national studies presented data on infants ≥ 28 weeks gestation, and two studies specified that this included both live born and stillborn infants.

South Asia and North Africa/Middle East were found to have similar reported birth prevalence of 1.28 cases per 1,000 births (95%CI: 0.84-1.72) and 1.22 (95%CI: 0.93-1.50) respectively. The prevalence reported from Sub-Saharan Africa was significantly lower, at 0.73 cases per 1,000 births (95%CI: 0.47-0.98). The data from these studies is significantly heterogeneous, and while they met strict inclusion criteria, ascertainment was variable. One of the studies calculated prevalence by comparing cases operated in 7 large Smile Train centres in Nigeria to the birth rates in the relevant regions(Butali et al. 2014). As such, it misses all undiagnosed and unoperated cases in the relevant regions, and all cases in other regions, and thus underestimates the actual birth prevalence. Interestingly, when the lower quality studies from the secondary analysis are included, the total pooled prevalence increases slightly to 0.75 cases per 1,000 births (95%CI: 0.56-0.94). This is still markedly below the figures for all other regions of the globe. The paucity of data from Sub-Saharan Africa reflects a severe lack of data from this region and an increased risk of bias in the data included in our analysis.

Latin America and the Caribbean are represented in this systematic review by only two Mexican studies. A number of Central and South American countries participate in a regional registry, ECLAMC (Castilla and Orioli 2004). These data were not included in this review, as the focus is to gather data from areas with significant gaps in high quality data on the birth prevalence of OFCs. Meta-analysis of the Mexican studies showed a birth prevalence of 0.96 per 1,000 births (95%CI: 0.74-1.18) (Figure 3A, and web appendix Annex 3, Figures 1-2).

Iran: a sub-study

Four of the six studies from the North Africa and Middle East super-region were from Iran. They presented data from four different parts of the country between 2005 and 2010: the northwest, southwest, and central regions, and Tehran. A meta-analysis of these studies demonstrated a birth prevalence of 1.0 cases of undifferentiated CL/P per 1,000 births (95%CI: 0.76-1.24) (Web appendix Annex 3, Figure 4). A previous meta-analysis of 11 Iranian studies by Khazaei et al (2011) also showed a birth prevalence of 1 case per 1,000 births (95%CI: 0.5-1.5) (Khazaei et al. 2011).

Sensitivity

The pooled prevalence of studies meeting strict inclusion criteria was markedly higher than those included in the secondary analysis (1.38 compared with 0.75 CL/P cases per 1,000 births). All second tier studies were from Sub-Saharan Africa, and included a total of 59 CL/P cases from a pooled population of 75,627 births (Web appendix Annex 3, Table 1 and Figure 1). The secondary analysis included studies from single tertiary care facilities, and thus were at risk for presenting a falsely high prevalence in a poorly generalisable population. However, given the high morbidity and mortality in untreated CL/P patients and the limited access to care in these settings, it is also possible that studies from referral facilities may underestimate the true population prevalence.

Interestingly, studies that specifically presented isolated CL/P demonstrated a similar prevalence to the combined pooled prevalence in studies of isolated and associated CL/P. The pooled prevalence of CL/P from the nine studies which provided data on isolated CL/P was 1.37 per 1,000 births (95% CI: 0.89-1.85). Studies presenting undifferentiated CL/P (i.e. total CL/P with or without associated malformations or syndromes) had a pooled prevalence of 1.4 per 1,000 births (95% CI: 1.21-1.58). Figure 3B-C display the forest plots for these respective meta-analyses. While both demonstrate marked heterogeneity, the studies presenting isolated CL/P have notably narrower confidence intervals.

Discussion

A number of factors are known to affect the prevalence orofacial clefts, including genetic factors such as ethnicity and family history of clefting, as well as environmental factors such as maternal smoking and in-utero exposure to seizure medications (Hill et al. 1988, Kallen 2003, Mossey et al. 2009, Kucik et al. 2012, Lie, Wilcox, and Skjaerven 2001, Sabbagh et al. 2014). There is some evidence for deprivation being a risk factor for clefting, however the precise elements of deprivation, and underlying mechanism remains poorly understood (Durning et al. 2007, Clark et al. 2003). Careful study of the epidemiology of clefting in resource limited settings may help us to understand this and provide insight into how best to intervene in order to attenuate the risk of children being born with a cleft of the lip or palate.

The findings in our systematic review are indicative of a nuanced prevalence in orofacial clefts, and support the findings from large umbrella registries that the prevalence and nature of clefting is influenced by local genetic predisposition and environmental factors (EUROCAT 2002, Group 2010). The heterogeneity found in our systematic review may be partly due to differences in ascertainment, however the heterogeneity within regions and even within countries, as evidenced by the meta-analysis of Iranian studies, is also seen in long-standing umbrella registries such as EUROCAT (EUROCAT 2002) and ECLAMC (Table 2). Furthermore, subtypes of clefts, laterality of cleft, and the prevalence of associations is known to vary across populations (EUROCAT 2002, Mossey and Modell 2012, Chung and

Myrianthopoulos 1968). The diversity in presentation of clefts makes classification and monitoring challenging, even in high income settings with well-established birth defect registries. Furthermore, difficulties in identifying children with cleft palate are likely lead to under-ascertainment even in high income settings. Study of clefting in individual populations with multiple source ascertainment and including terminations of pregnancy will be required to establish true birth prevalence in different settings.

The high prevalence of CLP in East and South Asian children is in keeping with previous observations (Mossey and Little 2002, Siva Raju 2000, Brydon et al. 2014). The strength and the meaning of the findings from Sub-Saharan Africa are less certain. There were very few studies from this large geographical region, and only 3 of the 7 studies met strict inclusion criteria. Resource limitations across the continent hamper ascertainment and provision of care. Infants in these areas are often born at home, and their families often face significant barriers in access to care, including limited financial resources, distance to health facilities, and limited skilled paediatric health workers. Sub-Saharan Africa is thought to have a lower prevalence of clefting for genetic reasons. Previous studies have identified that people of African descent have lower prevalence of CL/P, even after moving to a different part of the world (Croen et al. 1998, Chung and Myrianthopoulos 1968, Kucik et al. 2012, Canfield et al. 2014). The lower prevalence identified in the Sub-Saharan African studies may be related to a combination of poor ascertainment and lower genetic predisposition to clefting in this population.

The similarity in prevalence of isolated CL/P and combined pooled prevalence of undifferentiated CL/P is surprising, as isolated cases are only a subset of all clefts. Up to 71% of clefts are thought to be isolated, and approximately 29% are associated with other anomalies or syndromes (Mossey and Modell 2012). As such, it would be expected that studies measuring isolated and associated clefts together as a single group would find a higher prevalence than those measuring only isolated cases. The studies of isolated CL/P were undertaken in several different regions, including East Asia, the Middle East, and Sub-Saharan Africa, and all met strict inclusion criteria (Figure 3B). The comparatively high pooled prevalence in studies of isolated CL/P is likely due to more careful ascertainment in these studies rather than higher predisposition to clefting in the diverse study populations. Furthermore, this finding suggests that the overall pooled prevalence in this systematic review underestimates the true prevalence of undifferentiated CL/P worldwide.

While the overall figure for CL/P prevalence is similar to that of the previous systematic review, a careful comparison is not possible due to significant differences in the data presented and the method of analysis. The previous review was more comprehensive, in that it included data from high, middle, and low income settings, and it included registry data as well as epidemiological studies.

Validity

As we sought to include studies from places where registry data is not available, we did not include registry data from LIMC countries participating in the ECLAMC registry.

In 2002, EUROCAT reported a regional prevalence of undifferentiated CL/P at 1.52 per 1000 births (95% CI 1.49-1.55). The prevalence of isolated CL/P was 1.0 per 1,000 births (95%CI: 0.5-1.5). These figures include live births, stillbirths and terminations of pregnancy. Significant variation was seen across geographical regions within and between countries, with the lowest reported rate in El Valles, Spain, at 0.63 cases per 1,000 births, and the highest in Finland at 2.62 per 1,000 births (EUROCAT 2002). It must be noted that there are ethnic and environmental exposure differences between EUROCAT member registry populations and those from the studies included in the systematic review.

ECLAMC data is somewhat more varied, with prevalence figures ranging from 2.68 per 1,000 births in Bolivia to 1.18 in Uruguay (Table 2). ECLAMC collects data from hospital registries which participate voluntarily in the umbrella registry. Chile, Argentina, Brazil and Colombia each have several hospital registries participating in ECLAMC, and are thus most likely to be representative of their respective national populations and therefore the most reliable data for comparison. Combined data from ECLAMC registries for undifferentiated CL/P during the years 2000-2013 gives a prevalence of 1.87 cases per 1,000 births (combined stillborn and live born). This prevalence is markedly higher than the findings from the two Mexican studies included in our systematic review.

The ECLAMC figures for Argentina are higher than those registered in the Argentina National Registry of Congenital Anomalies (RENAC). Table 3 in the web appendix provides RENAC prevalence figures for total OFCs and subtypes for the years 2010-2013. While ECLAMC includes data from a few Argentinian hospital-based registries, RENAC is a national registry with a broader catchment, including all hospitals with 1000 or more births/year as well as specialist hospitals (Groisman et al. 2013). There are likely to be variations in quality of ascertainment and differences in prevalence based on the level of specialisation of hospitals participating in the two registries.

Heterogeneity

Significant heterogeneity was observed in the total pooled estimate (I^2 = 99.5%; Q-statistic, p<0.001). Marked heterogeneity was also observed in most of the regional pooled estimates and in the pooled estimate of studies meeting first tier inclusion criteria (Web appendix Annex 3, Figures 1-2). There was also substantial heterogeneity amongst studies from Sub-Saharan Africa (I^2 = 85.2%; Q-statistic, p<0.001). There are insufficient studies from most regions to assess for heterogeneity due to changes in prevalence over time

There are many potential sources of heterogeneity, the most likely of which are inconsistent and limited ascertainment of cases within and between countries and regions, and variable methods of data collection and reporting, which lead to registration bias. Only two studies used more than one source of ascertainment. As such, there is large room for error, particularly in failure to detect isolated cleft palate only, which is a challenge even in high income settings with specialised health care workers. Tables 2A-B in the web appendix give an overview of the studies which provided data on cleft subtypes. Cleft palate was notably absent or surprisingly low in a number of these studies. Accurate ascertainment in low- and middle-income settings is hampered by a limited number of skilled workers in obstetrics and paediatrics, with subsequent limited access to maternal and newborn care, and eventual diagnosis and treatment.

Another source of heterogeneity is the variability in the size of the studies, ranging from 6,621 births to 12,058,550 births. Furthermore, clefts were defined variably, particularly in regard to the reporting of isolated versus associated CL/P. Finally, the definitions of the reference population were variable; some studies included live births only, while others variably included stillbirths, terminations and fetal deaths. Taken together, these differences in the definition of cases and the reference population are likely to contribute to the heterogeneity seen in the overall findings presented here.

Limitations

There are a number of limitations in our systematic review which reflect large gaps in prevalence data that persist in low- and middle-income settings. The factors described above which contribute the heterogeneity between studies above also limit the strength of the findings. Furthermore, studies used varied and often unclear definitions of cases and of the study population. While studies with very poor ascertainment were excluded, the included studies had variable quality of ascertainment, even in those which met strict inclusion criteria. The assumption was made that the data presented was for all children born with clefts, including those with syndromes and other malformations. Accordingly, the figures presented here are those for undifferentiated CL/P, and a meta-analysis of studies that specifically provided data on isolated CL/P was performed to evaluate the sensitivity of the overall findings. As only a few studies provided information on cleft subtypes and sex distribution, these were not statistically analysed.

It is not clear how to interpret the data included in the secondary analysis. The studies were undertaken in referral facilities and therefore risk overestimating the true birth prevalence of CL/P. Simultaneously, the settings are characterised by significant barriers to care, which are likely to lead to miss children who never receive care, are never referred, or die before they reach a referral centre, thus leading to underestimation of the true prevalence. At this time, they provide a best estimate where no other data is available.

Implications for future research

The findings and the limitations of this systematic review demonstrate that the greatest need is for research that is comparable across settings. While establishing registries is the gold standard, it is a time and resource-intensive task which is less likely to be prioritised or sustainable in LMICs.

For countries with severe resource limitations, a good alternative would be to undertake population-based studies, as the studies included in this review have done. However, in order to be a useful resource for inter-centre comparisons, such studies must be comparable. A recent initiative to standardise the classification of cleft subtypes has been undertaken at the WHO collaborating centre for craniofacial anomalies at the University of Dundee, UK, by replacing the ICD-10 classification for OFC (which is considered by clinicians to be unfit for purpose), and recommending an alternative based on that described by Kriens in 1989 as the LAHSHAL system. It may be possible for this to be adopted internationally (McBride et al. 2015).

Annex 1 in the web appendix provides a suggested structure for future data collection and reporting. In order to ensure comparable data, studies should adopt clear and broadly used definitions when reporting outcomes, and they should explicitly state this in the text of eventual publications.

Ultimately, the objective in reporting on CL/P must be, from both the scientific and humanitarian viewpoints, to advance our knowledge and understanding of causative factors of orofacial clefts, to enable the design and implementation of primary preventative measures. Developing a clear understanding of the true scale of the problem and the nuances in different populations is the first step towards this goal.

Conclusion

Using the best evidence available to date, it appears that in low- and middle-income settings, 1 in every 730 children is born with a cleft lip and/or palate. Although prevalence studies in these settings have increased in number and improved during the past 15 years, the data presented remains limited and difficult to compare, and the findings from this systematic review should be interpreted with caution. Future research should use a standard classification system, with standard criteria for data collection and presentation, in order to optimise comparability across settings. Research should also include health economics data in order to estimate the cost of treatment as compared with that of potential preventive measures. As there is an association between deprivation and CL/P, understanding the true scale of clefting and associated risk factors for children born in low- and middle-income settings is a matter of both scientific importance and one of social justice.

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