Cleft lip and/or palate and associated risks in lower-middle-income countries: A systematic review

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Abstract

Objective: To identify and review published data on the risks associated with cleft lip and/or palate (CL/P) in lower-middle-income countries (LMICs).

Design: A systematic review of literature was performed on electronic databases using the PRISMA-P. Literature on risks associated with CL/P in LMICs, from 2010 to 2020 were included.

Results: Seventeen studies met the inclusion criteria. All studies adopted an observational study design. Biological and environmental risks were identified. Maternal and paternal age (n=7) and low socioeconomic status (n=5) were the most prominently associated environmental risk factors. A strong association was identified between family history of cleft (n=7) and CL/P occurrence.

Conclusion: Environmental risk factors are now being investigated more than biological risk factors in LMICs, aiding health care workers in the early identification of possible cumulative effects of risks in CL/P. Contextually-relevant tools are recommended to promote early identification of at-risk infants.

Keywords

Cleft lip and/or palate, biological risks, environmental risks, lower-middle-income country, systematic review.

Introduction

Every year, an estimated 303 000 newborns worldwide die within the first four weeks after birth due to congenital anomalies (World Health Organization, 2020). Approximately 94% of congenital anomalies occur in lower-middle-income countries (LMICs) due to the interplay of various environmental and genetic risk factors (World Health Organization, 2020). Cleft lip and/or palate (CL/P), an established risk factor for communication and developmental difficulties, is the most common congenital craniofacial anomaly with a prevalence rate of approximately 1 in 700 live births worldwide (World Health Organization, 2006), and 1 in 730 live births in LMICs (Kadir et al., 2017). This high prevalence rate could be due to the biological and environmental risks individuals in LMICs are exposed to, as well as the complex heterogeneity of individuals presenting with CL/P, including genetic and environmental factors (McKinney et al., 2016; Wang et al., 2016; Angulo-Castro et al., 2017; Kummer, 2020; Maranhão et al., 2020).

Exposure to various environmental risks such as maternal alcohol consumption, maternal smoking, insufficient folic acid supplementation, maternal diabetes, and living in a low socioeconomic environment, places unborn infants at greater risk of having CL/P (Alfwaress et al., 2017; Angulo-Castro et al., 2017; Kozma et al., 2019; Maranhão et al., 2020).

CL/P is a genetically complex condition as more than 17 genes are associated with non-syndromic orofacial clefts (Jamilian et al., 2017; Kummer, 2020). Various genes also interact with environmental risks, giving rise to the gene-environment interplay found in non-syndromic cleft lip and/or palate [NSCL/P] (Wang et al., 2016; Maranhão et al., 2020). The *MTHFR, MTR,* and *MTRR* genetic polymorphisms, which are responsible for encoding folate metabolism enzymes, may increase the risk of NSCL/P (Wang et al., 2016). These genetic polymorphisms may damage DNA, which leads to a folate deficiency, thus further contributing to the development of NSCL/P in utero (Wang et al., 2016). Therefore, insufficient folic acid

supplementation possibly due to food insecurity (Bailey et al., 2015) and the contribution of the above-mentioned genes, lead to a cumulative effect in the presence of CL/P in infants. Infants living in LMICs are subject to more adverse environmental and biological risks than those in high-income countries (Samuels et al., 2012; Black et al., 2017; Spencer et al., 2019). Living in extreme poverty increases the likelihood of being exposed to multiple risk factors, which are associated with biological risks, such as preterm birth and low birth weight (Black et al., 2017; Zar et al., 2019). These biological risks result in a combination of neurodevelopmental outcomes that negatively impact infant development (Pascal et al., 2018). Additionally, international registry data, which provide insight into the global epidemiology of orofacial clefts, presents with large gaps in LMICs research due to barriers in access to health care, leading to inadequate identification of risk factors and a presumed higher CL/P prevalence rate in these settings (Kadir et al., 2017). The interplay between environmental factors, biological factors and childhood development, highlights the importance of early identification of risk factors for CL/P in LMICs (Samuels et al., 2012; McKinney et al., 2016; Kummer, 2020). A comprehensive description of prevalent risks in this setting combined with an understanding of the aetiology of CL/P will allow for the development of well-timed and individualised early intervention strategies (Maranhão et al., 2020). This study aimed to systematically review the recent literature of the risks associated with CL/P in LMICs.

Method

Protocol Development

Guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols [PRISMA-P] (Shamseer et al., 2015) were used to document the review process and results. This protocol was registered on the international prospective register of systematic reviews (CRD42020193875).

Search Strategy

Studies were identified by electronic searches on the following databases: Pubmed, MEDLINE (Proquest), Scopus, Cochrane Libraries, and Web of Science Core Collection, in May 2020. Literature published from 2010 to 2020 were included. Key search terms included variants of "cleft lip and palate", as well as "associated risk factors", "lower-middle-income country", "non-syndromic", and "syndromic". Appendix A provides supplementary material on the results each search phrase obtained from the different databases. The reference lists of included articles were hand searched for other eligible articles. Studies were screened for inclusion using predefined criteria.

Eligibility Criteria

The PICO synthesis tool was utilised to evaluate the eligibility criteria (Methley et al., 2014; Shamseer et al., 2015).

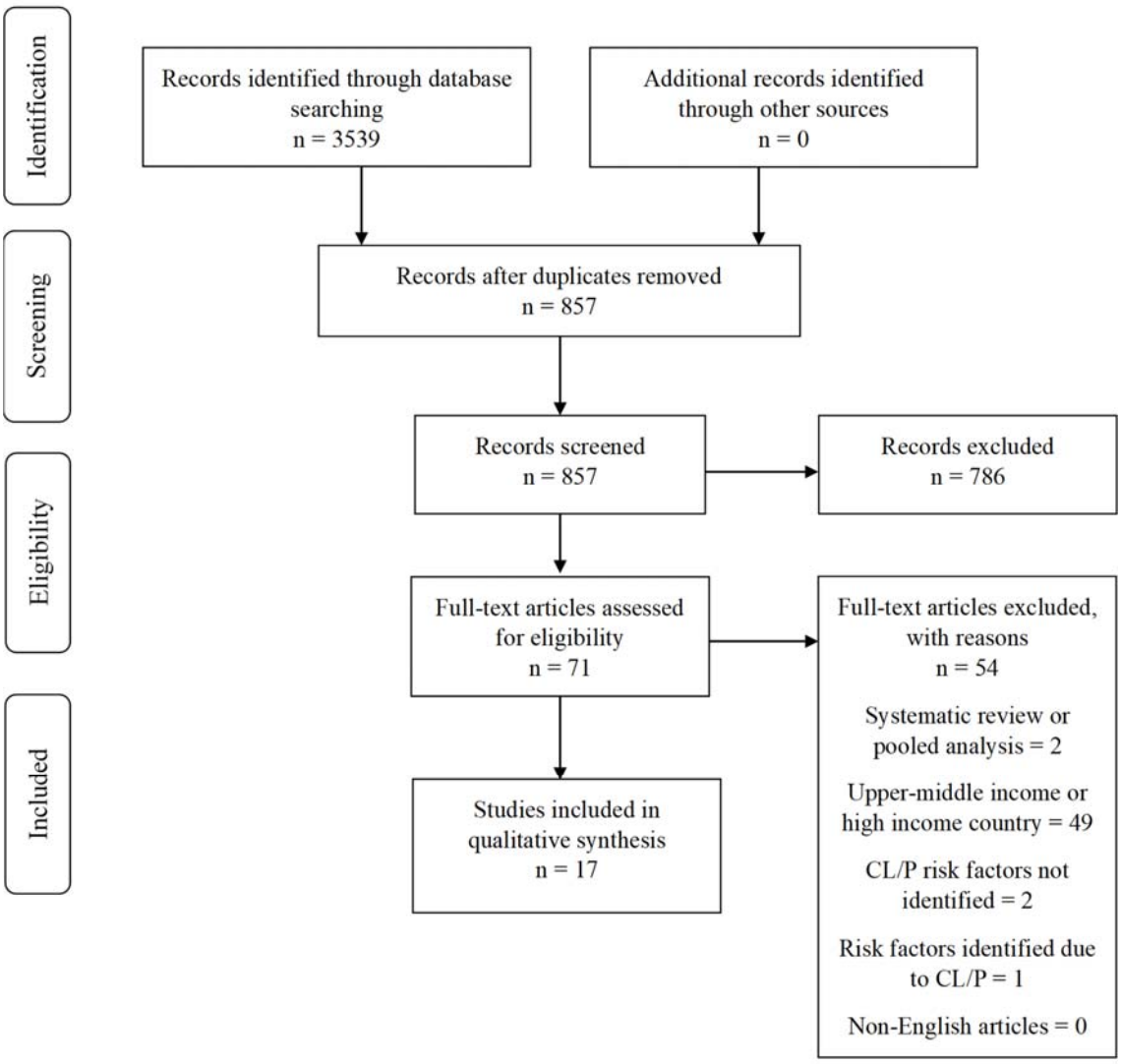
Inclusion criteria: Studies were selected if participants were diagnosed with a CL/P. Gender and age of participants were not restricted. Studies utilising human participants were included. Studies conducted in countries classified as lower-middle-income, low-middle-income or low income, were included (The World Bank, 2020). Studies were included if the type of risk factor, i.e. biological risks or environmental risks, were investigated to determine an association in presence of CL/P. The review aimed to explore risks associated with CL/P, thus non-syndromic and syndromic as well as studies on bilateral and unilateral CL/P were included. Peer-reviewed, observational studies were also included in this review.

Exclusion criteria: Studies were excluded if the design included systematic reviews, study protocols, or pooled analysis (n=2); due to translation limitations, studies not available in English were excluded (n=0); if countries were classified as upper-middle-income or high income, studies were excluded (n=49); studies were excluded if identified risks were associated with a group of congenital anomalies and not directly associated with CL/P (n=2).

Study selection

DistillerSR was used to screen and select studies obtained from the keyword search.(Evidence Partners, 2020) Titles and abstracts were first screened against the inclusion and exclusion criteria. Full texts were independently obtained and evaluated for the second screening by the primary researcher (K.K). A second researcher (J.V.D.L) evaluated 20% of the studies, while a third reviewer (C.V) mitigated any discrepancies. The study selection process according to the PRISMA-P is summarised in Figure 1.

Figure 1. Outcome of search process according to the PRISMA-P.



Data extraction and evaluation

Data were extracted from the final 17 articles by a single researcher (K.K). The extracted information included the following data items: title, authors, year of publication, country in which data were collected, type of cleft present, number of participants including controls, type of participants (newborns, young children, adolescents, or adults) as well as participants' age range, study design, the American Speech-Language-Hearing Association (ASHA) level of evidence (American Speech-Language-Hearing Association [ASHA]., 2004), and the type of associated risks. A second and third reviewer (J.V.D.L and C.V) evaluated data extracted for consistency and clarity (Shamseer et al., 2015).

To allow for a comprehensive evaluation of the data, a qualitative and quantitative comparison was undertaken of the category of risk factors (environmental, biological, or both) as well as the specific type of risk factors identified to be significantly associated with the presence of a CL/P. Thematic analysis of qualitative data was conducted to analyse, organise and synthesise the information extracted from the selected studies (Clarke and Braun, 2014). Main themes were identified through a deductive approach and sub-themes through an inductive approach by the primary researcher (K.K) (Vaismoradi et al., 2013; Clarke and Braun, 2014). The second (J.V.D.L) and third (C.V) reviewer evaluated the relevance of each theme and sub-theme and consensus was reached through reflective thoughts and examining the raw data (Vaismoradi et al., 2013). The themes and sub-themes were coded (Supplementary Material: Appendix B) and reviewed by all three reviewers.

Risk of bias

The Newcastle-Ottawa Scale (NOS) for case-control studies and cohort studies, as well as an adapted version of the NOS for cross-sectional studies, were used to evaluate the quality of non-randomised studies included in this review (Wells et al., 2014). Each study was independently appraised by the initial reviewer (K.K) while a second (J.V.D.L) and third

reviewer (C.V) rated 20% of the included studies. The third reviewer (C.V) also mitigated in situations of disagreement. The same articles were reviewed by the three reviewers and a 100% consensus was reached.

Results

Study results

A total of 3539 studies were identified during the initial database search. No additional studies were identified by searching references of included articles. After title and abstract screening and exclusion of duplicates, the full-text of 71 studies were screened. Of these, 17 studies were deemed eligible for inclusion by two reviewers (K.K and J.V.D.L) based on predefined criteria. A third reviewer (C.V) mitigated and 100% consensus was achieved. Figure 1 provides a summary of the study selection results.

Study characteristics

The characteristics of the 17 studies are presented in supplementary material: Appendix B. The majority of the studies were conducted at a single centre in either a LMIC (n=10), a low-income country (n=5) or in both (n=2). All studies adopted an observational design (n=17). Study sample size ranged from three to 754 with an average of 235 participants. Participants across studies ranged from newborns to adults with a mean age ranging from a few days to 50 years old. The evidence of all included studies were rated using the ASHA level of evidence [Supplementary material: Appendix B] (American Speech-Language-Hearing Association [ASHA]., 2004). Fifteen (88.23%) of the studies achieved a high evidence level rating of IIb, while two (11.76%) achieved a low evidence level rating of III. Neither publication nor selection bias was noted in and across the selected studies.

Risk of bias assessment

The risk of bias assessment is summarised and presented in Table 1. A star rating system is employed when evaluating the methodologic quality using the NOS, which is based on three

perspectives: selection, comparability, and exposure or outcome. Scores ranged from zero stars (worst) to nine stars (best). Twelve studies obtained a moderate methodologic quality of five (n=3) to six stars (n=9), while five studies obtained a high methodologic quality of seven (n=4) to eight (n=1) stars. An average of six stars was achieved, indicating a moderate quality of evidence across all studies included.

Table 1. Risk of bias assessment results

Author(s)	Selection	Comparability	Outcome/ exposure	Total quality
	NOS for case-controlled studies			
Aldhorae et al., 2014	**	**	***	7
Ali & Hamid, 2019	*	**	**	5
Bui et al., 2018	*	**	***	6
Bui et al., 2018	*	**	***	6
Dien et al., 2018	**	**	***	7
Eshete et al., 2020	**	**	**	6
Figueiredo et al., 2014	*	**	***	6
Figueiredo et al., 2015	*	**	***	6
Kalaskar et al., 2013	*	**	**	5
Mbuyi-Musanzayi et al., 2018	**	**	***	7
Mendonca, 2020	*	**	**	5
Neogi et al., 2017	*	**	***	6
	NOS for cohort studies			
Buyu et al., 2012	**	**	***	7
Fasunla et al., 2014	***	**	*	6
Kumari et al., 2013	***	**	*	6
	NOS for cross-sectional studies			
Gendel et al., 2019	**	**	**	6
Omo-Aghoja et al., 2010	****	**	**	8

Abbreviations: NOS, Newcastle-Ottawa Scale

Table 2. Environmental and biological risk factor sub-themes associated with CL/P

Risk factor sub-themes	n*	%	Association (n)**	No association (n)***
Environmental risk factors				
– Maternal and paternal age (25 to <35 years old)	10	58.8	7	3
– Maternal and second-hand/passive smoking	8	52.9	4	4
– Low socioeconomic status	5	29.4	5	0
– Prenatal maternal alcohol use	5	29.4	2	3
– Low maternal education level	4	23.5	4	0
– Consanguineous marriage	4	23.5	3	1
– Food consumption	4	23.5	4	0
– Prenatal maternal use of medication (prescribed and herbal)	4	23.5	3	1
– Prenatal complications (e.g. threatened abortion)	3	17.6	3	0
– Prenatal maternal exposure to chemicals, minerals and/or radiation	3	17.6	3	0
– Prenatal maternal intake and lack of folic acid supplementation	3	17.6	2	1
– Prenatal maternal intake and lack of multivitamin supplementation	3	17.6	2	1
Biological risk factors				
– Family history of cleft	7	41.1	7	0
– Maternal chronic illness (e.g. hypertension)	6	35.2	5	1
– Birth order (second to last born)	4	29.4	3	1
– Sex of offspring	3	17.6	3	0
– Genetics	3	17.6	3	0
– Maternal and infant homocysteine level	1	5.8	1	0
– Family history of cancer	1	5.8	1	0

* n; total number of studies that evaluated specified risk factors.
** Association (n); number of studies that found an association.
*** No association (n); number of studies where no association was found.

Risk factor outcomes

Due to the range of outcomes that were evaluated and differences among outcomes, a meta-analysis of the study results was not undertaken. Table 2 indicates the risk factor sub-themes identified, the number of articles that identified these risks as contributing to the presence of CL/P, as well as how many articles identified a direct association or no association with the

presence of CL/P. Direct association between CL/P and risk factors was identified through multivariable analysis (Table 2). For reporting purposes, adjusted models were used when both models and adjusted models were reported on in the included studies.

Category risk factors

Three main themes were identified across a total of 17 articles. The majority of the studies (n=10; 58.82%) investigated both biological and environmental risk factors as potential risks for CL/P. Four studies (23.52%) investigated only environmental risks, while three studies (17.65%) investigated only biological risk factors.

Environmental risks

Twelve sub-themes related to environmental risk factors were identified. All 12 risk factors were concluded to be associated with CL/P while six risk factors were identified as not being associated with a CL/P.

Biological risks

Seven sub-themes related to biological risk factors were identified. An association among these seven biological risk factors and CL/P was identified, of which the most common was a family history of a cleft. Maternal chronic illness and birth order were the second and third most common biological risk factor, respectively, to show an association.

Discussion

Evidence illustrates that CL/P is a complex, heterogeneous and multifactorial disorder (Buyu et al., 2012; Kalaskar et al., 2013; Bui et al., 2018a) as demonstrated by the variety of biological and/or environmental risk factors found in this systematic review. LMICs present with higher birth rates as well as higher mortality rates compared to high-income countries (The World Bank, 2021a; The World Bank, 2021b) making it difficult to analyse risks from high-income countries in LMICs. Infants in LMICs are exposed to a multitude of risk factors which may lead to poor developmental outcomes (Black et al., 2017) as well as the occurrence of a CL/P.

In order to understand the complexity of an established risk factor, such as CL/P, in addition to other risk factors in a specific context, the current systematic review aimed to identify which specific risks were associated with CL/P in LMICs. To date, no systematic review has investigated the risks associated with CL/P in LMICs.

Low socioeconomic status (SES) was reported to be statistically significantly associated with CL/P in four studies [$p < 0.05$] (Bui et al., 2018a; Bui et al., 2018b; Ali and Hamid, 2019; Gendel et al., 2019). The type of cleft has been linked to different SES levels, as cleft lip (CL) was found to be more prevalent in a low SES population (Gendel et al., 2019). Two studies found associations between the lack of prenatal folic acid supplementation with the occurrence of a CL (Ali and Hamid, 2019; Gendel et al., 2019). Therefore, a possible link between SES, prenatal folic acid intake and cleft type exists. This requires further investigation as many mothers in LMICs may have limited access to adequate prenatal care and, therefore, folic acid supplementation.

Living below the poverty line has been associated with nutritional deficiencies due to a lack of access to nutritious food (Kalaskar et al., 2013; Alkerwi et al., 2015; Allen et al., 2017). Ingestion of clay ($p < 0.0001$), Kapolowe fish [$p < 0.0001$] (Mbuyi-Musanzayi et al., 2018), caffeinated drinks [AOR = 1.68; 95% CI, 0.53-5.37] (Dien et al., 2018), and vegetarianism [AOR = 4.47; 95% CI, 1.83-10.98; $p = 0.001$] (Neogi et al., 2017) were associated with the presence of CL/P. Contact with heavy metals due to eating contaminated food or drinking polluted water is a risk individuals in rural areas are exposed to and has been linked to CL/P (Figueiredo et al., 2015; Mbuyi-Musanzayi et al., 2018). Mothers with a low SES may be less likely to receive guidance regarding appropriate nutrition during pregnancy due to poor access to health care (Figueiredo et al., 2015; Bui et al., 2018a; Mbuyi-Musanzayi et al., 2018; Gendel et al., 2019; Eshete et al., 2020). Low SES further negatively impacts the quality of education individuals receive. Poor maternal education leads to the occurrence of CL/P (Figueiredo et al.,

2015; Mbuyi-Musanzayi et al., 2018; Ali and Hamid, 2019) as many mothers only have basic education and may not have awareness of environmental risk factors that may lead to negative pregnancy outcomes.

Caffeinated drinks may lead to maternal hyper-homocysteine levels, which are associated with NSCL/P (Kumari et al., 2013; Dien et al., 2018). A study by Kumari et al. (2013) found higher homocysteine levels are required for NSCL/P to manifest in females than compared to males. Hyper-homocysteine has also been closely related with an increased risk of cancer, not specific to gender (Hasan et al., 2019). A recent study found a statistically significant association ($p < 0.001$) between a family history of cancer and CL/P (Bui et al., 2018b). These findings indicate a possible biological link between CL/P, a family history of cancer, and elevated homocysteine levels. Studies have supported this finding as the *MTHFR C667T* gene polymorphism has been identified as a biological risk across all three factors (Kumari et al., 2013; Wang et al., 2016; Hasan et al., 2019).

Two studies (n=2; 11.76%) solely investigated gene polymorphisms and the risk of CL/P. *1q32.2, 10q25, 17q22* (Figueiredo et al., 2014) as well as *8q24, 9q22, 10q25,* and *13q31* (Aldhorae et al., 2014) gene loci were identified to be statistically significant biological risk factors. The underrepresentation of genome-wide association studies in LMICs may be limited due to inadequate funding, inappropriate access to required infrastructure, and few skilled health care professionals and researchers.

The majority of the studies (n=7; 41.17%) identified a family history of a cleft to be strongly associated with CL/P, especially across first or second degree relatives (Buyu et al., 2012; Figueiredo et al., 2014). Studies conducted in Brazil (Maranhão et al., 2020), Mexico (Angulo-Castro et al., 2017), China (Xu et al., 2015; Xu et al., 2018; Hong et al., 2020), and Thailand (McKinney et al., 2016) have found similar results, restating the biological origin of CL/P regardless of SES. Additionally, consanguineous marriage was associated with an increase in

the occurrence of a CL/P (Bui et al., 2018a; Bui et al., 2018b; Ali and Hamid, 2019). The presence of both consanguinity and a familial history may lead to a cumulative effect in the occurrence of CL/P.

A study conducted in the Netherlands determined that CL/P was more common in males while cleft palate (CP) was more common in females (Pool et al., 2020). While one study concluded similar results (Bui et al., 2018a), other studies identified CL/P, CL, and/or CP to be more prevalent in females (Omo-Aghoja et al., 2010; Kalaskar et al., 2013; Mbuyi-Musanzayi et al., 2018; Ali and Hamid, 2019) and CLP, cleft lip and alveolus, and CP to be prevalent in males (Mbuyi-Musanzayi et al., 2018; Ali and Hamid, 2019). Due to the interplay between genetics and the environment, genetic testing in LMICs is important as this population may be exposed to additional environmental risk factors, such as poverty and lack of nutritious food, in comparison to individuals in high-income settings.

Maternal and paternal factors play a key role in the occurrence of a cleft. Maternal smoking (Bui et al., 2018b; Mendonca, 2020) and paternal smoking (second- and third-hand smoke) (Figueiredo et al., 2015; Bui et al., 2018a) were associated with CL/P. This is in agreement with several studies conducted in upper-middle income countries (Campos Neves et al., 2016; Angulo-Castro et al., 2017; Hong et al., 2020). Two studies (n=2; 11.76%) identified an association between maternal alcohol consumption and CL/P [$p < 0.0001$ and $p < 0.772$ respectively] (Omo-Aghoja et al., 2010; Mbuyi-Musanzayi et al., 2018), while three studies determined no association (Buyu et al., 2012; Figueiredo et al., 2015; Ali and Hamid, 2019). Similar results have been noted from studies conducted in upper-middle income countries (Campos Neves et al., 2016; Angulo-Castro et al., 2017; Xu et al., 2018; Maranhão et al., 2020; Hong et al., 2020). Maternal age older than 25 years (Omo-Aghoja et al., 2010; Figueiredo et al., 2015; Mbuyi-Musanzayi et al., 2018; Gendel et al., 2019), paternal age older than 35 years (Omo-Aghoja et al., 2010; Mbuyi-Musanzayi et al., 2018; Gendel et al., 2019), prenatal

maternal use of antibiotics and herbal medication (Omo-Aghoja et al., 2010; Gendel et al., 2019), prenatal complications (Bui et al., 2018a; Bui et al., 2018b; Eshete et al., 2020), and prenatal exposure to diagnostic x-rays were identified as associated risk factors in the presence of CL/P (Eshete et al., 2020). LMICs are greatly impacted by diseases such as HIV/AIDS, with the type of intervention being ARVs. One study identified no statistically significant association between ARVs and clefts (Fasunla et al., 2014). Based on findings, limited studies have investigated an association between HIV, ARVs and CL/P (Sufiawati et al., 2020). Future prospective research using large samples should investigate this possible association.

Gestational hypertension [n=2; 11.76%] (Bui et al., 2018a; Bui et al., 2018b), pregestational hypertension [n=2; 11.76%] (Figueiredo et al., 2015; Gendel et al., 2019), asthma [n=2; 11.76%] (Gendel et al., 2019; Eshete et al., 2020), gestational seizures [n=1; 5.88%] (Figueiredo et al., 2015), and hypothyroidism [n=1; 5.88%] (Gendel et al., 2019) were maternal illness associated with the occurrence of CL/P. Through the use of medication and proper nutrition, these maternal illnesses are manageable. However, many child-bearing mothers may not have access to these treatment options due to economic disadvantages; thus increasing the possible occurrence of CL/P.

Three studies (n=3; 17.64%) identified birth order as a possible risk factor, as children born with a CL/P were less likely to be the first born (Buyu et al., 2012; Figueiredo et al., 2014; Neogi et al., 2017). A possible explanation for this is that advanced maternal age may be associated with birth order, as the older a mother is the more likely an infant is to be the second, third or last born; however, this was not a statistically significant finding (Figueiredo et al., 2015). Another explanation may be that high parity was associated with a low SES as many expecting mothers may not have access to information regarding the risks of moderate to high parity (Eshete et al., 2020).

This systematic review identified that environmental risk factors are now more frequently being investigated, but the cumulative effect of risks associated with CL/P is not yet a research focus in LMICs. Due to the variability in the specific environmental and biological risk factors investigated, a meta-analysis could not be conducted. To increase the generalisability of the results, a meta-analysis is required in future when more studies in LMICs have emerged. In order to provide holistic intervention, future research may investigate the gene-environment interplay associated with CL/P in LMICs and whether these interactions are more prevalent within the CL/P population in such settings. High mortality rates in conjunction with a lack of registry data in LMICs (Kadir et al., 2017) leads to the presentation of incomplete statistics, therefore additional risk factors may not have yet been identified and many at-risk infants are not being identified early. Thus the mentioned risk factors should form part of a mandatory prenatal risk assessment in order to inform health professionals, such as speech-language therapists and community health nurses, of families that may require additional support and counselling. The early identification of risks ensures that families receive timeous and appropriate intervention. Early identification of risks may also encourage a change in health care policies as well as the efficient allocation of human and financial resources. Future research should investigate the cumulative effect of associated risks on the development of infants with CL/P.

Limitations

Frequent limitations mentioned within studies included (1) parental self-report of risk factors, thus parents may not have provided honest information; (2) due to the ascertainment of exposure, recall bias needed to be accounted for; (3) selection of control participants may have not been from the same hospital or the sample size may have been limited, thus studies may be subjected to selection bias. Limitations of the current systematic review include possible

language bias as only articles written in English were included. Investigating the cumulative effect of risks was limited due to the variability in the types of outcomes explored.

Conclusion

Within the last decade, multiple studies have investigated environmental and/or biological risk factors in the presence of CL/P. Findings from the current systematic review identified multiple risks associated with CL/P in LMICs. Lower-income countries, when compared to high-income countries, are faced with major barriers such as poverty, poor infrastructure, and a lack of skilled health care professionals (Kadir et al., 2017). There is a need for more research in lower-middle income settings in order to develop contextually relevant tools that may promote the early identification of at-risk infants.

Declaration of Conflicting Interests

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