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

Kayla Kruppa (15069819)

Dissertation submitted in fulfilment of the requirements for the degree MA (Speech-Language Pathology) in the Department of Speech-Language Pathology and Audiology

Faculty of Humanities

University of Pretoria

Supervisor: Dr Esedra Krüger

Co-supervisors: Prof. Jeannie van der Linde and Mrs Carlien Vorster

March 2021

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FACULTY OF HUMANITIES

DEPARTMENT OF SPEECH-LANGUAGE PATHOLOGY AND AUDIOLOGY

Declaration of originality

Full name: **Kayla Kruppa**

Student number: **u15069819**

Degree: **MA Speech-Language Pathology**

1. I understand what plagiarism is and am aware of the University's policy in this regard.
2. I declare that this **dissertation** is my own original work. Where other people's work has been used (either from a printed source, Internet or any other source), this has been properly acknowledged and referenced in accordance with departmental requirements.
3. I have not used work previously produced by another student or any other person to hand in as my own.
4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

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27/03/2021

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Acknowledgements

I would like to give my sincere and heartfelt thanks to:

Dr Krüger, thank you for the time you have spent and the knowledge you have imparted to me regarding the cleft lip and palate population. Your love and passion for the cleft lip and palate community is inspiring and has allowed my love for this special population to grow.

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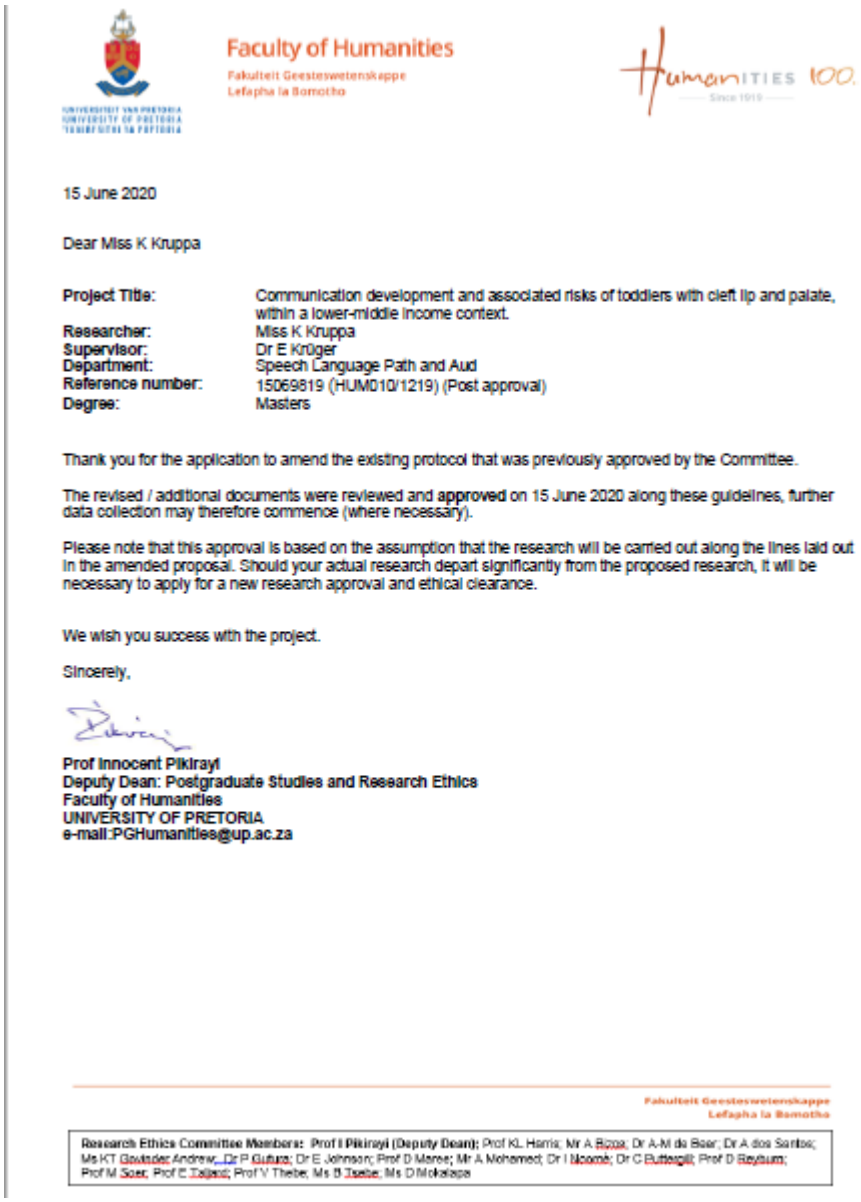
ASHA	American Speech and Hearing Association
DistillerSR	Distiller Systematic Review
CL	Cleft lip
CL/P	Cleft lip and/or palate
CP	Cleft palate
EI	Early identification
HCPs	Health care professionals
LBW	Low birth weight
LMICs	Lower-middle-income countries
NOS	Newcastle-Ottawa Scale
NSCL/P	Non-syndromic cleft lip and/or palate
PICO	Population, Intervention, Comparison and Outcome
PTB	Preterm birth
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol
SES	Socioeconomic status
SLTs	Speech-Language Therapists

Ethical clearance letter from Faculty of Humanities



Faculty of Humanities
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Humanities 100
Since 1919

15 June 2020

Dear Miss K Kruppa

Project Title:	Communication development and associated risks of toddlers with cleft lip and palate, within a lower-middle income context.
Researcher:	Miss K Kruppa
Supervisor:	Dr E Krüger
Department:	Speech Language Path and Aud
Reference number:	15069819 (HUM010/1219) (Post approval)
Degree:	Masters

Thank you for the application to amend the existing protocol that was previously approved by the Committee.

The revised / additional documents were reviewed and **approved** on 15 June 2020 along these guidelines, further data collection may therefore commence (where necessary).

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the amended proposal. Should your actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely,

Prof Innocent Pikirayi
Deputy Dean: Postgraduate Studies and Research Ethics
Faculty of Humanities
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Fakulteit Geesteswetenskappe
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Research Ethics Committee Members: Prof I Pikirayi (Deputy Dean); Prof KL Harris; Mr A Bizos; Dr A-M de Boer; Dr A dos Santos; Ms KT Govinder Andrew; Dr P Gufura; Dr E Johnson; Prof D Maree; Mr A Mohamed; Dr I Ncomb; Dr C Puttergill; Prof D Reyburn; Prof M Soer; Prof E Taljard; Prof V Thebe; Ms B Tsebe; Ms D Mokalapa

Abstract

UNIVERSITY OF PRETORIA

DEPARTMENT OF SPEECH-LANGUAGE PATHOLOGY AND AUDIOLOGY

Initials and surname	K. Kruppa
Supervisors	Dr E Krüger Prof. Jeannie van der Linde Mrs Carlien Vorster
Date	March 2021
Title	Cleft lip and/or palate and associated risks in lower-middle-income countries: A systematic review

Abstract:

Background: Cleft lip and/or palate (CL/P) is a complex, heterogeneous disorder which occurs due to the interplay between environmental and biological risk factors. Individuals in lower-middle-income countries (LMICs) are exposed to a multitude of risk factors resulting in a greater occurrence of CL/P. Research and knowledge of which risk factors are associated with CL/P in LMICs may aid health care professionals such as speech-language therapists in low-income countries in the early identification of at-risk infants.

Objective: To identify and review published data on the risks associated with CL/P in 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 was 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. Regarding biological 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, hindering health care workers in the early identification (EI) of the possible cumulative effects of risks in CL/P. Contextually-relevant tools are recommended to promote the EI of at-risk infants.

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

Chapter 1: Introduction

Chapter aim:

The aim of this chapter is to discuss pertinent literature about cleft lip and/or palate within lower-middle income countries. Chapter 1 concludes with the rationale, research question, clarification of terminology used throughout the study, as well as an outline of the chapters contained in the dissertation.

1.1. Introduction

Every year, an estimated 303 000 newborns worldwide die within the first four weeks after birth due to congenital anomalies (World Health Organization, 2020a). 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, 2020a). 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 one in 700 live births worldwide (World Health Organization, 2020b), and one in 730 live births in LMICs (Kadir et al., 2017). This high prevalence rate could be due to the biological and environmental risk factors individuals in LMICs are exposed to, as well as the complex heterogeneity of CL/P (Angulo-Castro et al., 2017; Kummer, 2020; Maranhão et al., 2020; McKinney et al., 2016; Wang et al., 2016).

Orofacial clefts are characterised by anomalies in the structure of the nose, upper lip, alveolus, hard palate and soft palate (Zajac & Perry, 2017). An orofacial cleft can occur in isolation, giving rise to a cleft lip (CL) or a cleft palate (CP), or can occur as a cleft lip and/or palate [CL/P] (Kummer, 2020). A CL/P occurs when parts of the lips, alveolus and palate fail to fuse during development, and varies in severity (Kummer, 2020). The embryological development of these facial structures occurs between six to nine weeks of gestation (Kummer, 2020). If any of these embryological processes are disrupted by genetic and/or environmental factors, an orofacial cleft may occur (Kummer, 2020; Zajac & Vallino, 2017). The timing of the development and the

aetiology of a CL/P indicates that prenatal identification of associated risk factors may be warranted.

It has been well documented that environmental factors such as prenatal maternal alcohol consumption, prenatal maternal smoking, insufficient prenatal folic acid supplementation, maternal diabetes, and living in a low socioeconomic status (SES), increases the possible occurrence of a CL/P in infants (Alfwaress et al., 2017; Angulo-Castro et al., 2017; Campos Neves et al., 2016; Kozma et al., 2019; Maranhão et al., 2020; McKinney et al., 2016). A parental and maternal age of >35 years is now also associated with a greater risk of CL/P or a CP (Herkrath et al., 2012; Maranhão et al., 2020). However, a study conducted in Brazil has indicated that only advanced paternal age, more specifically 40 years and older, is associated with the presence of a CL/P (de Carvalho et al., 2016), while another study found no association between maternal and paternal age and the presence of CL/P (Campos Neves et al., 2016). Literature states that pregnancy at an age of 40 years and older increases the risk of gestational diabetes, possibly leading to a greater chance of CL/P (Bouzaglou et al., 2020; Ornoy et al., 2015).

CL/P is a genetically complex condition. A high occurrence of CL/P has been identified in children with a family history of orofacial clefts (Jamilian et al., 2017). Furthermore, CL/P and CL is more common in males than in females (Alfwaress et al., 2017; Campos Neves et al., 2016). To date, 17 genes have been associated with non-syndromic orofacial clefts (Kummer, 2020). The most common genetic markers are included from the interferon regulatory factor 6 (*IRF6*) and the methylenetrahydrofolate reductase (*MTHFR*) gene, as well as the *8q24* gene loci (Aldhorae et al., 2014; Assis Machado et al., 2018; Wang et al., 2016; Wattanawong et al., 2016). Various genes interact with environmental risk factors, giving rise to the gene-environment interplay found in non-syndromic cleft lip and/or palate [NSCL/P] (Leslie & Marazita, 2013; Maranhão et al., 2020; Wang et al., 2016). The *MTHFR,* 5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*)*,* and 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*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 occurrence of NSCL/P (Wang et al., 2016). Therefore, this genetic predisposition, coupled with the additional risk of insufficient

maternal folic acid supplementation, possibly due to food insecurity, (Bailey et al., 2015) could lead to the presence of CL/P.

Children living in LMICs are subject to more adverse environmental and biological risk factors than children in high-income countries (Black et al., 2017; Samuels et al., 2012; Spencer et al., 2019). An estimated 663 million children are living in poverty and 385 million are living in extreme poverty (UNICEF, 2016). Living in extreme poverty increases the likelihood of being exposed to multiple risk factors, such as food insecurity, environmental contaminants, violence and family stress (Black et al., 2017). Various environmental risks are associated with biological risk factors. Food insecurity and maternal substance abuse, for example, are associated with other biological risk factors, such as preterm birth (PTB) and low birth weight [LBW] (Zar et al., 2019). Both PTB and LBW may result in a combination of sub-optimal neurodevelopmental outcomes, such as cognitive delays, motor delays, cerebral palsy, blindness, and hearing impairment (Pascal et al., 2018); thereby negatively impacting child development. Furthermore, maternal alcohol consumption is a known causal factor for Fetal Alcohol Spectrum Disorder and multiple pre- and postnatal co-occurring comorbidities (Popova et al., 2016). Research indicates that food insecurity and maternal substance abuse also leads to the occurrence of a CL/P (McKinney et al., 2016). Prenatal exposure to environmental risk factors may therefore lead to a variety of disorders including CL/P. Due to the multiple risk factors infants in LMICs are exposed to, the prenatal identification of risk factors may allow health care professionals (HCPs) and families to plan more effective future intervention for infants at risk of CL/P as well as allow the development of registry data (Kadir et al., 2017; McKinney et al., 2016; Samuels et al., 2012).

International registries provide insight into the global epidemiology of orofacial clefts, including prevalence, genetic and environmental risk factors, as well as the impact of intervention on the prevalence of CL/P (Kadir et al., 2017). However, when observing registry data from LMICs, large gaps in research are present. These gaps limit adequate identification of risk factors and the design and implementation of effective interventions (Kadir et al., 2017). These large gaps may be attributed to the barriers in access to health care, which include limited financial resources, distance to health care facilities, and limited skilled (HCPs) in LMICs (Kadir et al., 2017; Samuels et al., 2012). Therefore, no true representation of CL/P within the LMIC population is

available (Kadir et al., 2017). Risk factors may be overlooked or generalized from research conducted in high-income countries to individuals in LMICs, therefore warranting further investigation.

Determining risk and protective factors are crucial in order to establish individualised and holistic intervention goals (Guralnick, 2020). Folic acid supplementation and taking multivitamins during pregnancy is considered a protective factor in the occurrence of a CL/P (Angulo-Castro et al., 2017; Maranhão et al., 2020). However, many expecting mothers in LMICs have inadequate access to prenatal care and experience food insecurity, which may lead to micronutrient deficiencies (Bailey et al., 2015; Jensen et al., 2017; Samuels et al., 2012). Food insecurity and micronutrient deficiencies increase the risk of a CL/P (McKinney et al., 2016). LMICs are often subjected to poor water supply and sanitation, increasing the risk of infectious diseases such as diarrhoea; thereby contributing to the poor micronutrient status (Bailey et al., 2015; Spencer et al., 2019). Furthermore, alcohol and tobacco are consumed and used more frequently by individuals in LMICs, than those in high-income countries (Allen et al., 2017). Prenatal exposure to maternal smoking and the presence of a CL/P is well-documented (Angulo-Castro et al., 2017; Campos Neves et al., 2016; Maranhão et al., 2020; McKinney et al., 2016). The evidence regarding CL/P and exposure to maternal alcohol consumption is divided. Various studies suggest no association between prenatal alcohol exposure and the presence of a CL/P (Bell et al., 2014; Campos Neves et al., 2016), while other studies found a significant association between this risk factor and CL/P (Angulo-Castro et al., 2017; Hao et al., 2015; Maranhão et al., 2020). The majority of the studies investigating risks associated with CL/P have been conducted in upper-middle-income or high-income countries. Many of these risk factors may or may not be present in LMICs and, therefore, calls for an investigation.

The interplay between environmental factors, biological factors and childhood development, highlights the importance of early identification (EI) of risk factors for CL/P in LMICs (Kummer, 2020; McKinney et al., 2016; Samuels et al., 2012). A comprehensive description of prevalent risk factors combined with an understanding of the aetiology of CL/P will allow for enhancing of early intervention approaches (Maranhão et al., 2020). Specific early intervention approaches and tailored strategies should be developed by speech-language therapists (SLTs) and allied HCPs for

infants at risk of CL/P in LMICs, in order to mitigate future communication and developmental delays. Research conducted in Sub-Saharan Africa found that many cleft lip and palate centres did not provide intervention from a multidisciplinary team approach due to a lack of skilled allied HCPs (Hlongwa et al., 2019). The same study also identified that centres located in the rural provinces of South Africa could not provide speech-language therapy (Hlongwa et al., 2019). Thus, even in an upper-middle-income country such as South Africa, infants with CL/P are not receiving comprehensive and team-based early intervention services. Furthermore, treatment for CL/P is often viewed as a sub-speciality in some professions and few professions regard themselves as equipped to provide optimal intervention to this population (Ghabrial & Bütow, 2020).

Due to the heterogeneous nature of CL/P, risk factors may be identified by various HPCs, such as specific genes by a geneticist. When these specialist HCPs, such as geneticists, are not available to provide services to vulnerable populations, key risk factors may be overlooked and an infant may be at a greater risk for CL/P. Research and knowledge of which risk factors are associated with CL/P in LMICs may aid HCPs such as SLTs in low-income countries in the EI of at-risk infants. Thus, the following research question was posed: Which risk factors significantly associated with CL/P in LMICs have been identified in literature in the last ten years (2010-2020).

1.1. Clarification of terminology

Cleft lip and/or palate (CL/P): An orofacial cleft can occur in isolation giving rise to a cleft lip (CL) only or a cleft palate (CP) only. When an orofacial cleft does not occur in isolation the term cleft lip and/or palate (CL/P) is used. A CL/P occurs when parts of the lips, alveolus and palate fail to fuse during embryological development. CL/P is classified as bilateral or unilateral and can be due to a syndrome or can be termed nonsyndromic when no associated syndrome occurs. In the case of the latter, the term *nonsyndromic cleft lip and/or palate (NSCL/P)* is applied (Kummer, 2020; Zajac & Vallino, 2017).

Environmental risk factors: Absent or limited early experiences in health care, parental care, and exposure to physical and social stimulation may affect development (American Speech-Language-Hearing Association [ASHA], 2008). Risk factors include maternal personal characteristics (e.g., maternal age, maternal diabetes, and

maternal substance abuse), as well as family and economic characteristics [e.g., socioeconomic status and access to health care] (Alfwaress et al., 2017; Angulo-Castro et al., 2017; Hermann et al., 2018; Maranhão et al., 2020; L. F. Xu et al., 2015).

Biological risk factors: Biological risk factors are genetically inherited disorders (e.g. CL/P) as well as a history of adverse prenatal, perinatal, and neonatal events (e.g. PTB and LBW), which may influence a young child's typical development (ASHA, 2008; Kummer, 2020).

1.2. Outline of chapters

A brief outline of the content in each of the chapters of the dissertation is presented as follows:

- **Chapter 1:** Introduction to the topic, discussion of literature pertaining to the topic and the presentation of the research question and rationale, and clarification of terminology used in the dissertation.
- **Chapter 2:** A detailed discussion of the method used in the study.
- **Chapter 3:** Research article submitted to *The Cleft Palate-Craniofacial Journal* (27 November 2020). The format of chapter 3 was structured according to the author guidelines of the journal and therefore differs from that of the rest of the dissertation.
- **Chapter 4:** Clinical and theoretical implications, strengths and weaknesses of the study, as well as future research recommendations.

Chapter 2: Method

Chapter aim:

This chapter states the aim of the research study and describes the research design, study criteria, search strategy, risk of bias assessment, and the data extraction and synthesis procedures.

2.1. Research aim

To identify and review recent published literature on the risks associated with CL/P in LMICs.

2.2. Research design

A systematic review of recent literature (2010 - 2020) was conducted to investigate risk factors associated with the occurrence of CL/P in LMICs. Systematic reviews provide the latest information on a given topic to readers in order to support the development of evidence-based guidelines and appropriate clinical decision making (Moher et al., 2015). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines statement was followed while conducting this systematic review (Moher et al., 2015). PRISMA-P provides a minimal set of 17 items for reporting and preparing systematic reviews and meta-analysis (Moher et al., 2015). These items encourage complete and transparent reporting in systematic reviews (Moher et al., 2015).

2.3. Registration

This research study was registered with PROSPERO (CRD42020193875), an international database of systematic review protocols related to health, social care, and international health-related development (Schiavo, 2019). Systematic reviews are registered with PROSPERO in the initial stages in an attempt to avoid possible duplication and encourage transparency, by allowing comparison between reported methods and those planned in the protocol (Schiavo, 2019; Shamseer et al., 2015) [PRISMA-P checklist, Item 2; Appendix A].

2.4. Ethical considerations

Ethical clearance was obtained for this study from the Research Ethics Committee of the Faculty of Humanities, University of Pretoria (Appendix B). Various journal articles were included in this systematic review and therefore the inclusion of human research participants did not apply to this study minimising the ethical implications of the study.

The current study recognised the following standards of ethical conduct:

2.4.1. Plagiarism

The current study referenced all consulted sources according to the American Psychological Association (American Psychological Association, 2017). The study acknowledged all resources and did not claim ownership of other researchers' work (American Psychological Association, 2017). In order to avoid plagiarism, all sources contributing to this study were carefully cited and a detailed reference list was included at the end of the manuscript and this dissertation.

2.4.2. Meta-bias

Selective reporting bias refers to the subjective selection of studies with more statistically significant results (Drucker et al., 2016). This systematic review attempted to reduce selective reporting bias by establishing search strategies before commencing the review. These strategies included keyword searches that were agreed upon by the three reviewers, generating inclusion and exclusion criteria, as well as including three reviewers to independently evaluate the inclusion of 20% of the studies. Publication bias refers to the publication of positive results over negative results by authors and editors (Dwan et al., 2013; Joober et al., 2012). The exclusion of statistically nonsignificant data may result in a systematic review being biased towards positive results (Drucker et al., 2016). Therefore, publication bias was reduced by searching several databases with a variety of search terms in order to obtain a large number of relevant articles for review. Thus, ensuring that both studies with statistically significant and insignificant results were equally evaluated and considered for inclusion. Grey literature was included in order to further reduce publication bias throughout the systematic review (Paez, 2017).

2.5. Data collection procedures

2.5.1. Eligibility criteria

In the current systematic review, the search was limited to studies conducted in the last 10 years (2010 – 2020), as the researcher intended to review the most recent published literature on the risks associated with CL/P. The Population, Intervention, Comparison, and Outcome (PICO) synthesis tool, which provides a comprehensive list of search results, was utilised to evaluate the eligibility criteria (Methley et al., 2014; Shamseer et al., 2015) [PRISMA-P checklist, Item 8; Appendix A].

Population: Studies were selected if participants were diagnosed with an orofacial cleft, namely a CL, a CP, or a CL/P. No limit was placed on the gender or age of the participants. 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 risk factors or environmental risk factors, were investigated to determine an association with the occurrence of a CL/P.

Exposure: Studies that investigated risk factors prenatally were included. This included a family history of CL/P, maternal risk factors, low birth weight and/or preterm birth, and environmental risk factors such as exposure to second-hand smoke. To ensure an accurate representation of risks associated with the CL/P population, non-syndromic and syndromic as well as bilateral and unilateral CL, CP and CL/P studies were included.

Study design: Various research designs were eligible for inclusion in the current systematic review and included observational studies such as cohort studies and case-control studies. Only peer-reviewed studies were included in this systematic review. Grey literature was included as the reference list of the included studies were hand-searched.

2.5.2. Exclusion criteria

Studies were excluded if:

- The design included systematic reviews, study protocols, or pooled analysis;
- Studies were not available in English;
- The study was considered an animal study;
- Countries were classified as upper-middle-income or high income;

- Identified risks, such as malnutrition, were associated with various congenital anomalies and not directly associated with CL/P.

2.5.3. Information sources

Five electronic databases were searched in May 2020 by the researcher. The specific databases that were selected included: PubMed, MEDLINE (Proquest), Scopus, Cochrane Libraries, and Web of Science Core Collection. These databases were identified and searched due to their relevance in health care related topics. The reference lists of the articles found were further hand-searched to identify and include articles that were not identified during the primary search. The last search was conducted at the end of June 2020. Information regarding electronic sources was in accordance with Item 9 of the PRIMISA-P checklist [Appendix A] (Shamseer et al., 2015).

2.5.4. Search strategy

Concept mapping was applied to enhance the search strategy. A concept map refers to a visual method that qualitatively represents the information required to understand the relationship between concepts (Wilson et al., 2016). The search strategy included the study population using keywords, terms and Boolean operators [PRISMA-P checklist, Item 10; Appendix A]. Various combinations of keywords were used across the different databases in order to visualise and identify the association between the search terms (Wilson et al., 2016).

The following keyword combinations were searched:

1. “Cleft lip and palate” OR “cleft lip” OR “cleft palate” OR “orofacial clefts” AND (“associated risk factors”)
2. “Cleft lip and palate” OR “cleft lip” OR “cleft palate” OR “orofacial clefts” AND (“associated risk factors”) AND (“non-syndromic” OR “syndromic”)
3. “Cleft lip and palate” OR “cleft lip” OR “cleft palate” OR “orofacial clefts” AND (“lower-middle-income setting” OR “lower-middle-income countries” OR “lower-middle-income context”)

Electronic search strategy with limits

Table 2.1 indicates the number of responses obtained from each database using combinations of the keywords and phrases indicated previously.

Table 2.1: Number of results each search phrase obtained from different databases

	PubMed	**Medline (Proquest)**	**Scopus**	**Cochrane Libraries**	**Web of Science Core Collection**	**Total**
Selected fields	Title/ abstract	Abstract	Title/ abstract/ keyword	Title/ abstract/ keyword	Topic (Title/ abstract/ keyword)	
Search terms	**Number of responses**					
(cleft lip and palate) AND (associated risk factors)	430	15	504	4	326	**1 279**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (associated risk factors)	577	24	504	8	409	**1 522**
(cleft lip and palate) AND (associated risk factors) AND (non-syndromic OR syndromic)	136	2	104	0	90	**322**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (associated risk factors) AND (non-syndromic OR syndromic)	185	5	104	1	95	**390**
(cleft lip and palate) AND (associated risk factors) AND (non-syndromic OR syndromic) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	0	0	0	0	0	**0**
(cleft lip and palate) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	3	1	0	0	3	**7**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	4	1	0	0	4	**9**
(cleft lip and palate) AND (associated risk factors) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	0	0	0	0	0	**0**
Total number of results	**1 335**	**48**	**1 216**	**13**	**927**	**3 539**

2.5.5. Study selection

The final study selection was achieved through two levels of the PRISMA-P statement (PRISMA-P checklist, Item 11b and 11c; Appendix A). *Distiller Systematic Review* (DistillerSR) was used throughout the two levels. The primary researcher (K.K) hand searched the five databases. The initial level encompassed the screening of titles and abstracts and the removal of duplicate studies. Unrelated studies were excluded and the remaining related studies qualified for full-text review, forming the second level. The second level included the full-text review of studies according to the eligibility criteria set out by the primary researcher (K.K). The reference list of the 17 included studies was hand searched, by the primary researcher, to identify relevant articles, which acted as a secondary literature review. Thereafter, the studies were compared against the eligibility criteria. Fifty-four articles were excluded: The study was conducted in upper-middle-income or high-income countries (n=49); the study design was a systematic review or a pooled analysis (n=2); the study did not identify risk factors directly related to CL/P but rather identified risk factors associated with a group of congenital anomalies (n=2), the study investigated risks which occurred due to CL/P (n=1). A total of 17 articles were accepted for synthesis (Figure 1).

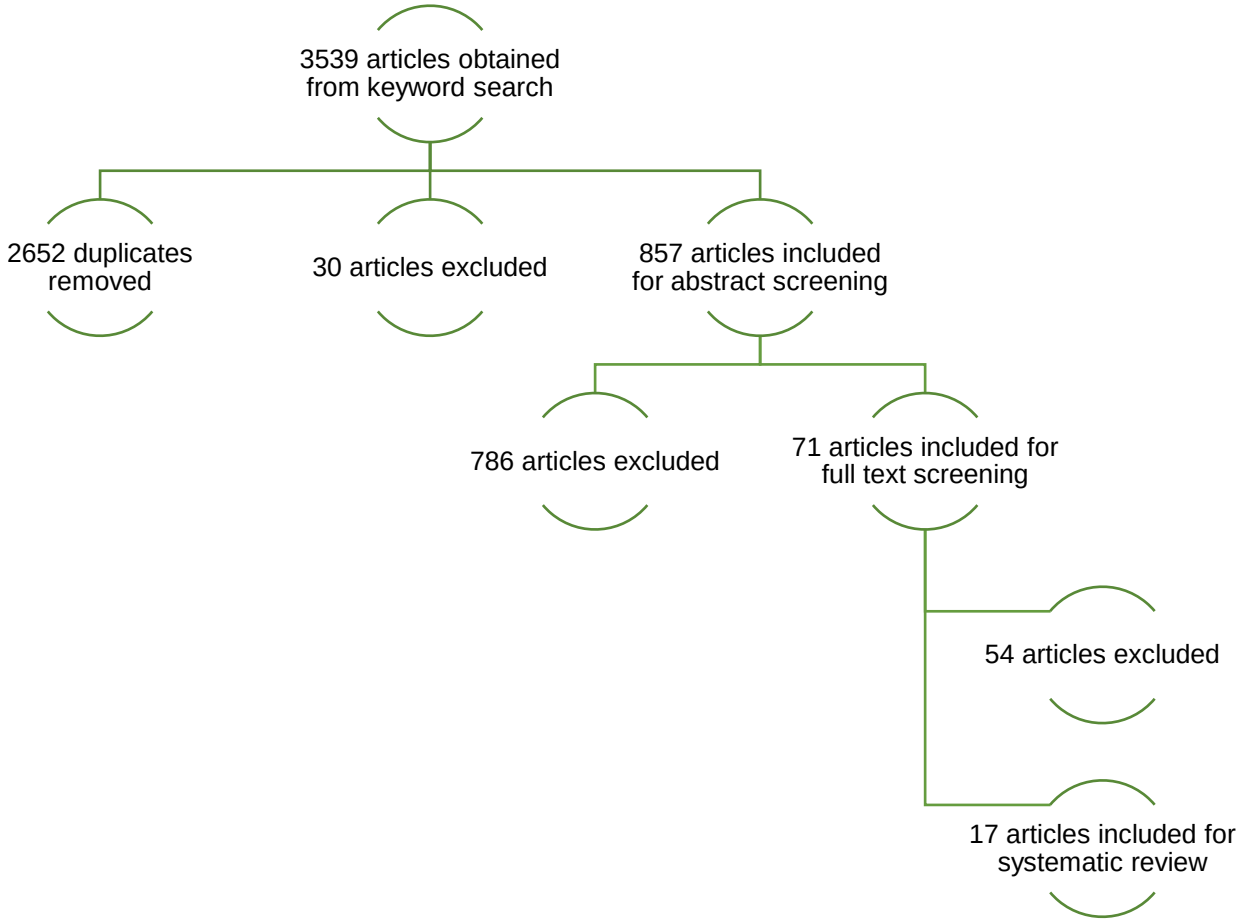

Figure 1: Figure illustrating the number of results obtained and the number of results excluded and included at each phase.

2.5.6. Data management

DistillerSR, an online software program, was used to select and evaluate the relevant studies for this systematic review. This tool provides real-time collaboration with reviewers and includes title and abstract screening, full-text review, and elimination of citation duplicates (Evidence Partners, 2020). Furthermore, DistillerSR allows for risk of bias assessment, extraction of study characteristics, as well as data and reference exportation (Evidence Partners, 2020). DistillerSR was used following Item 11a on the PRISMA-P checklist (Appendix A).

2.5.7. Data extraction

The primary objective of this review was to retain articles identifying risks associated with CL/P within LMICs. Therefore, the final 17 studies were analysed and relevant data were extracted according to the eligibility criteria by the primary researcher (K.K).

Utilising a data extraction form, relevant data items were extracted (Supplementary material Appendix B). No piloting of the data extraction form was conducted.

In accordance with Item 12 on the PRISMA-P checklist (Appendix A), the following were included: title of the article, 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 the participants' age range, study design (case-control study, cohort study or cross-sectional study), level of evidence, and the type of category associated risks. A second and third reviewer evaluated the data extracted for consistency and clarity (Shamseer et al., 2015).

Level of evidence

The included studies' level of evidence was evaluated by using the ASHA level of evidence rating scale (ASHA, 2004). This rating scale is widely accepted and rate studies on four levels. Level IV indicating the lowest form of quality evidence and level I indicating the highest quality evidence (ASHA, 2004). The researcher appraised the included studies while a second investigator reviewed the results to ensure accuracy and consistency of data (Supplementary material Appendix B). No inconsistent ratings were obtained. Table 2.2 provides an outline of the ASHA levels of evidence used to rate the studies in this review.

Table 2.2: Levels of evidence (ASHA, 2004)

Level	Description
I	Well-designed meta-analysis of >1 randomised controlled trial.
Ib	Well-designed randomised controlled study.
IIa	Well-designed controlled study without randomisation.
IIb	Well-designed quasi-experimental study.
III	Well-designed non-experimental study, i.e. correlation and case studies.
IV	Expert committee report, consensus conference, clinical experience of respected authorities.

2.5.8. Risk of bias

Assessing the risk of bias is an essential step in systematic reviews as it is equivalent to internal validity (Bero et al., 2018). Systematic reviews should minimise bias to ensure a valid review (Joober et al., 2012; Shamseer et al., 2015). Therefore, assessing the risk of bias is crucial and is in accordance with the PRISMA-P checklist, Item 14 (Appendix A).

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). The NOS utilises a 'star system' on which studies are judged based on three broad categories: study group selection; comparability of the groups; and the ascertainment of the exposure or the outcome of interest (Wells et al., 2014). Stars were awarded to high-quality characteristics while no stars were awarded to low-quality characteristics within each category. Therefore, the higher the number of stars, the greater the quality of evidence (Wells et al., 2014). The content validity of this rating scale has been well established (Wells et al., 2014). Recent literature has found that the adapted version of the NOS for cross-sectional studies, presents with good inter-rater reliability when compared to another appraisal tool (Moskalewicz & Oremus, 2020). Similar results have been found for the NOS for case-control and cohort studies (Wells et al., 2014). Each study was appraised independently by the researcher while a second reviewer and a third reviewer rated 20% of the included studies. The third reviewer also mitigated in situations of disagreement. The same articles were reviewed by the three reviewers and a 100% consensus was reached. This approach demonstrates inter-rater reliability within the current systematic review. The risk of bias outcomes are presented in Table 2.3, 2.4 and 2.5 and is in accordance with the PRIMSA-P checklist, Item 17 (Appendix A).

Table 2.3: Outcomes of the Newcastle-Ottawa Scale for case-control studies (n=12)

Newcastle-Ottawa Scale for case-control studies

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.

	Selection			Comparability		Exposure		
Article	**Is the case definition adequate?**	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis controlled for confounders**	**Ascertainment of exposure**	**Same method of ascertainment for case and controls**	**Non-response rate**
Aldhorae, K. A., Böhmer, A. C., Ludwig, K. U., Esmail, A. H. A., Al-Hebshi, N. N., Lippke, B., Gölz, L., Nöthen, M. M., Daratsianos, N., Knapp, M., Jäger, A., & Mangold, E. (2014). Nonsyndromic cleft lip with or without cleft palate in Arab populations: Genetic analysis of 15 risk loci in a novel case-control sample recruited in Yemen. Birth Defects Research Part A - Clinical and Molecular Teratology, 100(4), 307–313. https://doi.org/10.1002/bdra.23221	Yes, with independent validation.*	Potential for selection bias.	No description	Controls have no history of the disease.*	Study controls for (a) patients of Yemen ethnicity; (b) exclusion of patients with a syndromic malformation, mental retardation or other anomalies.**	Secure record.*	Yes*	Same rate for both groups.*
Ali, M. A. M., & Hamid, M. M. M. (2019). Risk Factors of Non-Syndromic Orofacial Clefts in Sudan during 2016-2017. Annals of Medical and Health Sciences Research, 9(1), 472–477.	Yes, with self-report.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) mothers (aged 15 - 47 years); (b) infants with non-syndromic orofacial clefts; (c) infants with no congenital anomalies.**	Interview not blinded to case/control status.	Yes*	Same rate for both groups.*

Article	Selection			Comparability		Exposure		
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis controlled for confounders**	**Ascertainment of exposure**	**Same method of ascertainment for case and controls**	**Non-response rate**
Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., & Taub, P. J. (2018). Association Between Cleft Lip and/or Cleft Palate and Family History of Cancer: A Case-Control Study. Annals of Plastic Surgery, 80(4), S178–S181. https://doi.org/10.1097/SAP.0000000000001331	Yes, with record linkage and self-report.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) individuals with CLP; (b) have no history of a CLP repair.**	a) Secure record.* b) Interview not blinded to case/control status.	Yes.*	Same rate for both groups.*
Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., & Taub, P. J. (2018). Maternal Tobacco Exposure and Development of Orofacial Clefts in the Child. Annals of Plastic Surgery, 81(6), 708–714. https://doi.org/10.1097/SAP.0000000000001665	Yes, with record linkage.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) infants with an orofacial cleft (0 - 3 years old); (b) exclusion of infants with any repaired orofacial cleft; (c) infants attending Bashir Hospital/ Cleft Hospital.**	a) Secure record.* b) Interview not blinded to case/control status.	Yes*	Same rate for both groups.*
Dien, V. H. A., McKinney, C. M., Pisek, A., & Pitiphat, W. (2018). Maternal exposures and risk of oral clefts in South Vietnam. Birth Defects Research, 110(6), 527–537. https://doi.org/10.1002/bdr2.1192	Yes, with independent validation.*	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for infants (<18 months old); (a) attend the Ho Chi Minh City Hospital; (b) diagnosed with CLP or CP: (c) with or without other diagnosed anomalies not part of syndrome.**	a) Secure record.* b) Interview not blinded to case/control status.	Yes*	Same rate for both groups.*

Article	Selection			Comparability		Exposure		
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis controlled for confounders**	**Ascertainment of exposure**	**Same method of ascertainment for case and controls**	**Non-response rate**
Eshete, M., Butali, A., Abate, F., Hailu, T., Hailu, A., Degu, S., Demissie, Y., Gravem, P. E., Derbew, M., Mossey, P., Bush, T., & Deressa, W. (2020). The Role of Environmental Factors in the Etiology of Nonsyndromic Orofacial Clefts. Journal of Craniofacial Surgery, 31(1), 113–116. https://doi.org/10.1097/SCS.0000000000005924	Yes, with independent validation.*	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) mothers of children born with non-syndromic orofacial cleft; (b) agreed to participate; (c) exclusion of children with syndromic orofacial clefts or family history of clefts.**	Interview not blinded to case/control status.	Yes*	Same rate for both groups.*
Figueiredo, J. C., Ly, S., Raimondi, H., Magee, K., Baurley, J. W., Sanchez-Lara, P. A., Ihenacho, U., Yao, C., Edlund, C. K., van den Berg, D., Casey, G., DeClerk, Y. A., Samet, J. M., & Magee, W. (2014). Genetic risk factors for orofacial clefts in central africans and Southeast Asians. American Journal of Medical Genetics, Part A, 164(10), 2572–2580. https://doi.org/10.1002/ajmg.a.36693	Yes, with record linkage and self-report.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for children (birth - 3 years old) with; (a) isolated CLP; (b) accompanied by biological parent (>18 years old); (c) receiving treatment from Operation Smile Inc.**	a) Secure record.* b) Interview not blinded to case/control.	Yes.*	Same rate for both groups.*
Figueiredo, J. C., Ly, S., Magee, K. S., Ihenacho, U., Baurley, J. W., Sanchez-Lara, P. A., Brindopke, F., Nguyen, T. H. D., Nguyen, V., Tangco, M. I., Giron, M., Abrahams, T., Jang, G., Vu, A., Zolfaghari, E., Yao, C. A., Foong, A., Declerk, Y. A., Samet, J. M., & Magee, W. (2015). Parental risk factors for oral clefts among Central Africans, Southeast Asians, and Central Americans. Birth Defects Research Part A - Clinical and Molecular Teratology, 103(10), 863–879. https://doi.org/10.1002/bdra.23417	Yes, with record linkage and self-report.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for children (birth - 3 years old) with; (a) isolated CLP; (b) accompanied by biological parent (>18 years old); (c) receiving treatment from Operation Smile Inc.**	a) Secure record.*b) Interview not blinded to case/control status.	Yes*	Same rate for both groups.*

Article	Selection			Comparability		Exposure		
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis controlled for confounders**	**Ascertainment of exposure**	**Same method of ascertainment for case and controls**	**Non-response rate**
Kalaskar, R., Kalaskar, A., Naqvi, F. S., Tawani, G. S., & Walke, D. R. (2013). Prevalence and evaluation of environmental risk factors associated with cleft lip and palate in a central Indian population. Pediatric Dentistry, 35(3), 279–283.	Yes, record linkage.	Consecutive or obviously representative series of cases.*	Hospital controls.	Controls have no history of the disease.*	Study controls for infants (a) with non-syndromic CLP or CP; (b) who attend the Department of Pedodontics and Preventive Dentistry.**	Interview not blinded to case/control status.	Yes*	Same rate for both groups.*
Mbuyi-Musanzayi, S., Kayembe, T. J., Kashal, M. K., Lukusa, P. T., Kalenga, P. M., Tshilombo, F. K., Devriendt, K., & Reychler, H. (2018). Non-syndromic cleft lip and/or cleft palate: Epidemiology and risk factors in Lubumbashi (DR Congo), a case-control study. Journal of Cranio-Maxillofacial Surgery, 46(7), 1051–1058. https://doi.org/10.1016/j.jcms.2018.05.006	Yes, with independent validation.*	Potential for selection bias.	Community* & Hospital controls.	Controls have no history of the disease.*	Study controls for (a) newborns with CLP; (b) newborns without CLP; (c) born in the same maternity ward; (d) live in the same neighbourhood.**	a) Secure record.* b) Interview not blinded to case/control status.	Yes*	Same rate for both groups.*
Mendonca, V. J. (2020). Maternal Folic Acid Intake and Risk of Nonsyndromic Orofacial Clefts: A Hospital-Based Case–Control Study in Bangalore, India. Cleft Palate-Craniofacial Journal, 57(6), 678–686. https://doi.org/10.1177/1055665619893214	Yes, based on self-report.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) mothers of live-born infants with non-syndromic orofacial clefts; (b) mothers who are older than 18 years old; (c) gave consent to participate; (d) mothers who were not taking medications associated with clefts.**	Interview not blinded to case/control status.	Yes*	Same rate for both groups.*

Article	Selection			Comparability		Exposure		
	Is the case definition adequate?	**Representativeness of the cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on the basis of the design or analysis controlled for confounders**	**Ascertainment of exposure**	**Same method of ascertainment for case and controls**	**Non-response rate**
Neogi, S. B., Singh, S., Pallepogula, D. R., Pant, H., Kolli, S. R., Bharti, P., Datta, V., Gosla, S. R., Bonanthaya, K., Ness, A., Kinra, S., Doyle, P., & Gudlavalleti, V. S. M. (2017). Risk factors for orofacial clefts in India: A case–control study. Birth Defects Research, 109(16), 1284–1291. https://doi.org/10.1002/bdr2.1073	Yes, with record linkage.	Potential for selection bias.	Hospital controls.	Controls have no history of the disease.*	Study controls for (a) infants with non-syndromic CLP (0 - 4 months old); (b) exclusion of structural or chromosomal malformations.**	a) Secure record.* b) Interview not blinded to case/control status.	Yes*	Same rate for both groups.*

Table 2.4: Outcomes of Newcastle-Ottawa Scale for cohort studies (n=3)

Newcastle-Ottawa Scale for cohort studies

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.

Article	Selection			Comparability		Outcome		
	Representativeness of the exposed cohort	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest was not present at the start of the study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur?**	**Adequacy of follow up of cohorts**
Buyu, Y., Manyama, M., Chandika, A., & Gilyoma, J. (2012). Orofacial clefts at Bugando Medical Centre: Associated factors and postsurgical complications. Cleft Palate-Craniofacial Journal, 49(6), 736–740. https://doi.org/10.1597/10-202	Truly representative of the average individual with an orofacial cleft in the community.*	No description of the derivation of the non-exposed cohort.	Secure record/ Structured interview.*	No.	Study controls for (a) individuals with a CLP or CP or CL; (b) aged 2 days - 41 years old; (c) have no history of CL/P repair.**	a) Record linkage.* b) Self-report.	Yes (4 weeks after surgery).*	Complete follow-up - all subjects accounted for.*
Fasunla, A. J., Ogunbosi, B. O., Odaibo, G. N., Taiwo, B., Nwaorgu, O. G. B., Olaleye, D. O., Murphy, R. L., Adewole, I. F., Kanki, P., & Akinyinka, O. O. (2014). Cleft palate in HIV-exposed newborns of mothers on highly active antiretroviral therapy. Oral Surgery, 7(S1), 102–106. https://doi.org/10.1111/ors.12117	Somewhat representative of the average HIV-exposed infant with an orofacial cleft in the community.*	Drawn from the same community as the exposed cohort.*	Secure record.*	No.	Study controls for (a) HIV-exposed newborns; (b) born to mothers of HAART.**	Record linkage.*	No.	No statement.

Article	Selection			Comparability		Outcome		
	Representativeness of the exposed cohort	**Selection of non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest was not present at the start of the study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur?**	**Adequacy of follow up of cohorts**
Kumari, P., Ali, A., Sukla, K. K., Singh, S. K., & Raman, R. (2013). Lower incidence of nonsyndromic cleft lip with or without cleft palate in females: Is homocysteine a factor? Journal of Biosciences, 38(1), 21–26. https://doi.org/10.1007/s12038-013-9298-7	Selected group of users.	Drawn from the same community as the exposed cohort.*	Secure record.*	Yes.*	Study controls for (a) congenital malformations; (b) kidney-related diseases & other related diseases.**	Independent blind assessment.*	No.	No statement.

Table 2.5: Outcomes of the Newcastle-Ottawa Scale adapted for cross-sectional studies (n=2)

Newcastle-Ottawa Scale adapted for cross-sectional studies

Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.

Article	Selection				Comparability	Outcome	
	Representativeness of the sample	**Sample size**	**Non-respondents**	**Ascertainment of the exposure**	**Subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.**	**Ascertainment of the outcome**	**Statistical test**
Gendel, A. A. A., Sayed, S. A. M., Mohamme, B. H., & Mohemed, A. A. (2019). Maternal risk factors associated with the development of cleft lip and/or palate in sudan. International Journal of Scientific and Technology Research, 8(12), 129–145.	Selected group of users.	Justified and satisfactory *	No description of the response rate or the characteristics of the responders and the non-responders.	Non-validated measurement tool, but tool is described *	Study controls for (a) Sudanese mothers of children with non-syndromic orofacial clefts; (b) who willing participated. **	Self-report (questionnaire) *	Statistical test is clearly described and appropriate.*
Omo-Aghoja, V. W., Omo-Aghoja, L. O., Ugboko, V. I., Obuekwe, O. N., Saheeb, B. D. O., Feyi-Waboso, P., & Onowhakpor, A. (2010). Antenatal determinants of oro-facial clefts in southern Nigeria. African Health Sciences, 10(1), 31–57. https://doi.org/10.4314/ahs.v10i1.55938	Somewhat representative of the average in the target population *	Justified and satisfactory *	No description of the response rate or the characteristics of the responders and the non-responders.	Validated measurement tool.**	Study controls for all patients who (a) present with an orofacial cleft; (b) attend the hospital; (c) provided consent to participate. **	Self-report (questionnaire) *	Statistical test is clearly described and appropriate.*

2.6. Reliability and validity

Reliability is the consistency with which a measuring tool yields a certain, consistent result when the concept being measured has not changed (Leedy et al., 2019). Validity is the suitability of tools or data (Leung, 2015). The integrity of the evidence in the current systematic review was ensured by adhering to the guidelines stipulated in the PRISMA-P Statement Checklist (Moher et al., 2015). These guidelines ensured that a complete systematic review was obtained. Furthermore, five electronic databases in conjunction with multiple search terms from peer-reviewed journals were included. Relevant studies were critically analysed and synthesised based on the stipulated inclusion criteria as well as obtaining consensus between the three reviewers. The level and quality of the data were determined through independent ratings by three investigators. A hundred per cent agreement was reached amongst all three reviewers indicating that minimal bias was present throughout the review process. Selective reporting bias was avoided by discussing the potential bias between the three investigators and ensuring that all results, not only those desired, were reported (Shamseer et al., 2015). Independent blind reviews were conducted of 20% of the included articles by two investigators, demonstrating inter-rater reliability within the study.

2.7. Data analysis

A qualitative and quantitative comparison was performed of the category risk factors and the specific type of risk factors that were identified from literature to be associated with the presence of a CL/P. Thematic analysis is often used in qualitative research and interprets implicit and explicit data items (Clarke & Braun, 2014). Thematic analysis was employed to identify, analyse and interpret information extracted from the included studies (Clarke & Braun, 2014). The primary researcher employed a deductive approach to identify main themes and an inductive approach to identify sub-themes (Clarke & Braun, 2014; Vaismoradi et al., 2013). Themes and sub-themes were evaluated for relevance and coded by the researcher (Supplementary material Appendix B) and reviewed by two other investigators. Consensus was reached through reflective thoughts and examination of the raw data (Clarke & Braun, 2014; Vaismoradi et al., 2013). Due to the range of outcomes that were evaluated and differences among outcomes, a meta-analysis of the study results was not undertaken. An article was identified to have a direct association if the risk factors were determined

through the development of a multivariable analysis, thus only the specific risk factors which were found to be associated with CL/P after being adjusted for other variables, were discussed.

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Chapter 3: Research article

Chapter aim:

This chapter contains an article based on the research project. The article was resubmitted to "The Cleft Palate-Craniofacial Journal" with revisions on 16 March 2021 (Appendix C). The format of this chapter differs to that of the rest of the dissertation as the journal specified guidelines for the formatting of the article.

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, 2020a). 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, 2020a). 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 (Angulo-Castro et al., 2017; Kummer, 2020; Maranhão et al., 2020; McKinney et al., 2016; Wang et al., 2016).

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] (Maranhão et al., 2020; Wang et al., 2016). 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 (Black et al., 2017; Samuels et al., 2012; 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 (Kummer, 2020; McKinney et al., 2016; Samuels et al., 2012). 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.

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 (Guest et al., 2012)(Guest et al., 2012)(Guest et al., 2012)(Guest et al., 2012)(Clarke & Braun, 2014; Guest et al., 2012). Main

themes were identified through a deductive approach and sub-themes through an inductive approach by the primary researcher (K.K) (Clarke & Braun, 2014; Vaismoradi et al., 2013). 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.

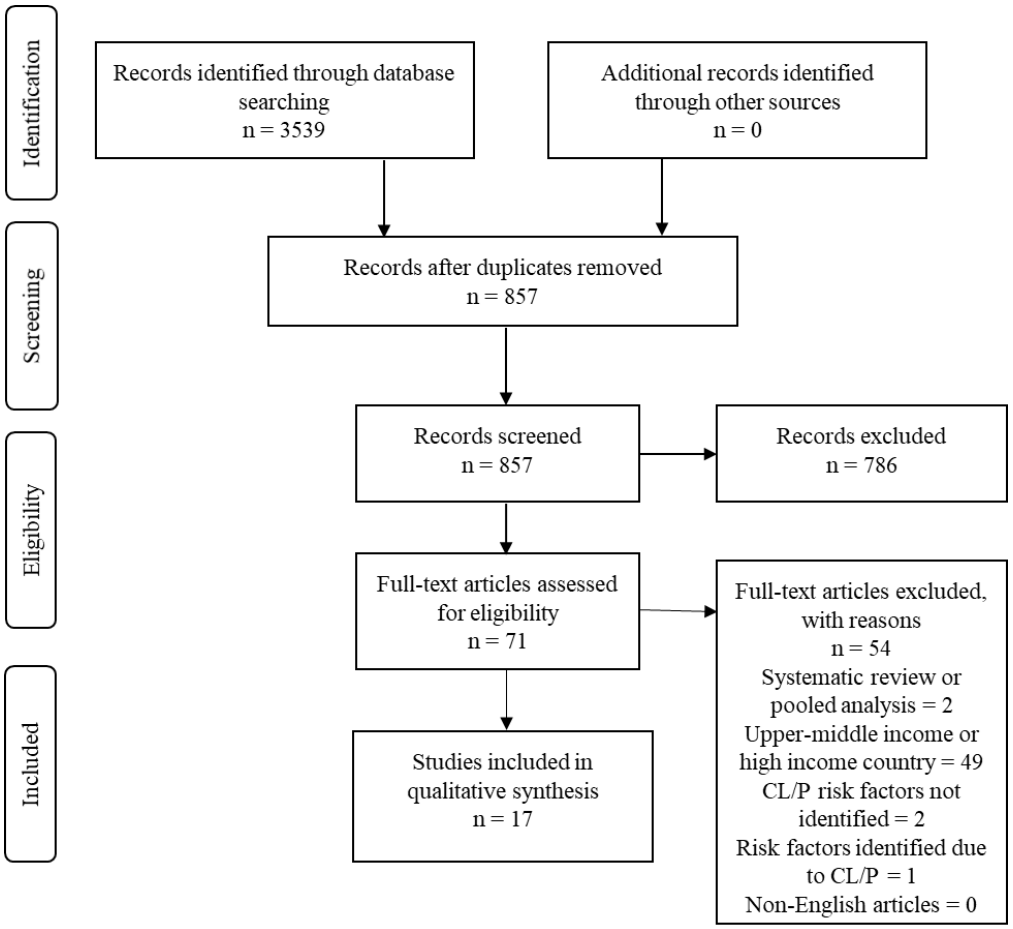

Figure 1. Outcome of search process according to the PRISMA-P.

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.

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. An article was identified to have a direct association if the risk factors were determined through the development of a multivariable analysis, thus only the specific risk factors which were found to be associated with CL/P after being adjusted for other variables, were presented in Table 2. Articles for which no multivariable analysis was developed, it was assumed that no adjustment was required and that the risk factors identified were associated with CL/P.

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.

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

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 (Bui et al., 2018b; Buyu et al., 2012; Kalaskar et al., 2013) as demonstrated by the variety of biological and/or environmental risk factors found in this systematic review. LMICs present with higher birth rates and higher mortality rates compared to high-income countries (The World Bank, 2021b, 2021a). These rates are related to socioeconomic and structural factors, thus making it difficult to analysis 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 in addition to risk factors already present the current systematic review aimed to identify which specific risk factors are associated with CL/P. 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 [$p < 0.05$] (Ali & Hamid, 2019; Bui et al., 2018b, 2018a; 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 & 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 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 (Alkerwi et al., 2015; Allen et al., 2017; Kalaskar et al., 2013). 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 (Bui et al., 2018b; Eshete et al., 2020; Figueiredo et al., 2015; Gendel et al., 2019; Mbuyi-Musanzayi et al., 2018). Low SES further negatively impacts the quality of education individuals receive. Poor maternal education leads to the occurrence of CL/P (Ali & Hamid, 2019; Figueiredo et al., 2015; Mbuyi-Musanzayi et al., 2018) as many mothers only have basic educational skills and may not have the knowledge regarding which environmental risk factors lead to negative pregnancy outcomes.

Caffeinated drinks may lead to maternal hyper-homocysteine levels, which are associated with NSCL/P (Dien et al., 2018; Kumari et al., 2013). A study by Kumari et al. (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).

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

A recent study found a statistically significant association ($p < 0.001$) between a family history of cancer and CL/P (Bui et al., 2018a). 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 (Hasan et al., 2019; Kumari et al., 2013; Wang et al., 2016).

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 (Hong et al., 2020; D. P. Xu et al., 2018; L. F. Xu et al., 2015), 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 (Ali & Hamid, 2019; Bui et al., 2018b, 2018a). 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., 2018b), other studies identified CL/P, CL, and/or CP to be more prevalent in females (Ali & Hamid, 2019; Kalaskar et al., 2013; Mbuyi-Musanzayi et al., 2018; Omo-Aghoja et al., 2010) and CLP, cleft lip and alveolus, and CP to be prevalent in males (Ali & Hamid, 2019; Mbuyi-Musanzayi et al., 2018). 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., 2018a; Mendonca, 2020) and paternal smoking (second- and third-hand smoke) (Bui et al., 2018b; Figueiredo et al., 2015) were associated with CL/P. This is in agreement with several studies conducted in upper-middle income countries (Angulo-Castro et al., 2017; Campos Neves et al., 2016; 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] (Mbuyi-Musanzayi et al., 2018; Omo-Aghoja et al., 2010), while three studies determined no association (Ali & Hamid, 2019; Buyu et al., 2012; Figueiredo et al., 2015). Similar results have been noted from studies conducted in upper-middle income countries (Angulo-Castro et al., 2017; Campos Neves et al., 2016; Hong et al., 2020; Maranhão et al., 2020; D. P. Xu et al., 2018). Maternal age older than 25 years (Figueiredo et al., 2015; Gendel et al., 2019; Mbuyi-Musanzayi et al., 2018; Omo-Aghoja et al., 2010), paternal age older than 35 years (Gendel et al., 2019; Mbuyi-Musanzayi et al., 2018; Omo-Aghoja et al., 2010), prenatal maternal use of antibiotics and herbal medication (Gendel et al., 2019; Omo-Aghoja et al., 2010), prenatal complications (Bui et al., 2018b, 2018a; 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., 2018b, 2018a), pregestational hypertension [n=2; 11.76%] (Figueiredo et al., 2015; Gendel et al., 2019), asthma [n=2; 11.76%] (Eshete et al., 2020; Gendel et al., 2019), 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 illness are manageable. However, many child-bearing mothers may not have access to these treatment options due to the economic disadvantages they are exposed to; 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 research. 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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Supplementary material

Supplementary material for this article is available online.

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Supplementary material appendix A. Number of results each search phrase obtained from different databases

	PubMed	**Medline (Proquest)**	**Scopus**	**Cochrane Libraries**	**Web of Science Core Collection**	**Total**
Selected fields	Title/ abstract	Abstract	Title/ abstract/ keyword	Title/ abstract/ keyword	Topic (Title/ abstract/ keyword)	
Search terms	**Number of responses**					
(cleft lip and palate) AND (associated risk factors)	430	15	504	4	326	**1 279**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (associated risk factors)	577	24	504	8	409	**1 522**
(cleft lip and palate) AND (associated risk factors) AND (non-syndromic OR syndromic)	136	2	104	0	90	**322**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (associated risk factors) AND (non-syndromic OR syndromic)	185	5	104	1	95	**390**
(cleft lip and palate) AND (associated risk factors) AND (non-syndromic OR syndromic) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	0	0	0	0	0	**0**
(cleft lip and palate) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	3	1	0	0	3	**7**
(cleft lip and palate OR cleft lip OR cleft palate OR orofacial cleft) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	4	1	0	0	4	**9**
(cleft lip and palate) AND (associated risk factors) AND (lower-middle-income countries OR lower-middle-income setting OR lower-middle-income context)	0	0	0	0	0	**0**
Total number of results	**1 335**	**48**	**1 216**	**13**	**927**	**3 539**

Supplementary material appendix B. Study characteristics and level of evidence

Article title	Authors	Year	DOI, website or PMCID	Country (LMIC)	Type of cleft (CL, CP, CLP)	Number of participants including controls	Participants & participant age range	Study design	Level of evidence (ASHA, 2004)	Outcomes (category risk factor & specific associated risk factors)
Antenatal determinants of oro-facial clefts in Southern Nigeria	Omo-Aghoja, V. W., Omo-Aghoja, L. O., Ugboko, V. I., Obuekwe, O. N., Saheeb, B. D. O., Feyi-Waboso, P., Onowhakpor, A.	2010	PMC2895797	Nigeria	CP, CLP	Case: 60	Newborns, children & adults 5 days - 37 years old	Transverse, cross-sectional	IIb	**Biological risks** Family history (p-value < 0.250) **Environmental risks** Maternal age (OR=3.14, CI=1.14 – 8.69) Parental age (OR=1.33, CI=0.52 – 5.25) Alcohol consumption (p-value=0.772) Low SES (p-value=0.689) Medication consumption (OR=2.35, CI=0.58 – 4.47)

Association between cleft lip and/or cleft palate and family history of cancer: A case-control study	Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., Taub, P. J.	2018	10.1097/SAP.0000000000001331	Pakistan	CLP	Case: 137 Control: 147	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Family history of cancer (AOR=5.17, CI=1.57 – 17.03, p-value < 0.001) Maternal chronic illness (AOR=1.34, CI=0.44 – 4.05, p-value = 0.02) **Environmental risks** Smoking parent (AOR=2.12, CI=1.05 – 4.28, p-value = 0.001) Consanguineous marriage (AOR=1.53, CI=0.83 – 2.82, p-value = 0.03) Prenatal complications (AOR=4.60, CI=1.21 – 17.54, p-value = 0.01) Low SES (p-value < 0.001)
Cleft palate in HIV-exposed newborns of mothers on highly active antiretroviral therapy	Fasunla, A.J., Ogunbosi, B.O., Odaibo, G.N., Taiwo, B., Nwaorgu, O.G.B., Olaleye, D.O., Murphy, R.L., Adewole, I.F., Kanki., P., Akinyinka ,O.O.	2014	10.1111/ors.12117	Nigeria	CP	HIV-exposed: 126 HIV-unexposed: 121 Case with cleft: 3	Newborns < 37 weeks old	Qualitative, descriptive study (case report)	III	**Environmental risks** Medicine consumption (OR=10.95, CI=0.94 – 126.84; p-value = 0.07)

Genetic risk factors for orofacial clefts in Central Africans and Southeast Asians	Figueiredo, J. C., Ly, S., Raimondi, H., Magee, K., Baurley, J. W., Sanchez-Lara, P. A., Ihenacho, U., Yao, C., Edlund, C. K., van den Berg, D., Casey, G., DeClerk, Y. A., Samet, J. M., Magee, W., 3rd	2014	10.1002/ajmg.a.36693	DR Congo, Vietnam, Philippines	CLP	260	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Genetics: rs10787738 (p = 4.98) rs7987165 (p = 6.1)
Low incidence of nonsyndromic celft lip with or without cleft palate in females: Is homocysteine a factor?	Kumari, P., Ali, A., Sukla, K. K., Singh, S. K., Raman, R.	2013	10.1007/s12038-013-9298-7	India	CLP	Case: 318 Controlled: 281	Infants & young children Case: 1 - 9 years old. Controlled: 3 - 12.5 years old	Retrospective, cohort	IIb	**Biological risks** Homocysteine (OR=1.99, CI=1.42 – 2.77) Genetics (OR=4.9, CI=1.2 – 20.2)
Maternal exposures and risk of oral clefts in South Vietnam	Dien, V. H. A., McKinney, C. M., Pisek, A., Pitiphat, W.	2018	10.1002/bdr2.1192	South Vietnam	CL, CP, CLP	Age & gender matched Case: 170 Controlled: 170	Infants < 18 months old	Hospital-based case-control	IIb	**Environmental risks** Food consumption (OR=5.89, CI=1.08 – 32.00)
Maternal folic acid intake and risk of nonsyndromic orofacial clefts: A hospital-based case–control study in Bangalore, India	Mendonca, V. J.	2020	10.1177/1055665619893214	India	CP, CLP	Case: 106 Control: 212	Infants, Case: birth - 9 months old. Infants, Control: birth - 3 months old	Hospital-based, case-control	IIb	**Environmental risks** Intake of multivitamin supplementation (AOR=2.93, CI=1.84 – 4.69) Smoking parent (AOR=8.16, CI=1.60 – 41.58)
Maternal tobacco exposure and development of orofacial clefts in the child: A case-control study conducted in Pakistan	Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., Taub, P. J.	2018	10.1097/SAP.0000000000001665	Pakistan	CL, CP, CLP	Case: 297 Control: 131	Newborns, children & adults, Case: 1 day - 25 years old. Newborns & toddlers,	Retrospective, case-control	IIb	**Biological risks** Maternal illness (AOR=1.59, CI=0.60 – 4.22)

							Control: 1 day - 3 years old			**Environmental risks** Smoking parent (AOR=1.89, CI=1.10 – 3.26) Consanguineous marriage (AOR=1.79, CI=1.13 – 2.85) Prenatal complications (AOR=2.36, CI=1.43 – 3.88) Low SES (AOR=1.36, CI=0.70 – 2.66)
Maternal risk factors associated with the development of cleft lip and/or palate in Sudan	Gendel, A. A. A., Sayed, S. A. M., Mohamme, B. H., Mohemed, A. A.	2019	https://www.researchgate.net/publication/338139231_Maternal_Risk_Factors_Associated_with_the_Development_of_Cleft_Lip_and_or_Palate_in_Sudan	Sudan	CL, CP, CLP	Case: 280	Infants & children 1 - < 10 years old	Case descriptive, cross-sectional, hospital-based	III	**Biological risks** Family history (p-value = 0.025) Maternal illness (Chi-square = 4.961, p-value = 0.042) Gender (Chi-square = 12.857, p-value = 0.001) **Environmental risks** Low SES (p-value = 0.003) Medication consumption (Chi-square = 8.718, p-value = 0.007) Folic acid supplementation (Chi-square = 4.973, p=0.042) Maternal age (24.3%, CI=20.06 – 28.51)

Low maternal education (n=183; 65.4%)

Non-syndromic cleft lip and/or cleft palate: Epidemiology and risk factors in Lubumbashi (DR Congo), a case-control study	Mbuyi-Musanzayi, S., Kayembe, T. J., Kashal, M. K., Lukusa, P. T., Kalenga, P. M., Tshilombo, F. K., Devriendt, K., Reychler, H.	2018	10.1016/j.jcms.2018.05.006	DR Congo	CP, CLP	Geographically matched Case: 162 Control: 162	Infants Birth - 1 years old	Case-control	IIb	**Biological risks** Family history (p-value < 0.0007) Gender (males: 52%; females: 48%; ratio: 1.08) **Environmental risks** Alcohol consumption (Maternal: AOR=19.301, CI= 1.890 – 197.095; paternal: AOR=18.748, CI=3.939 – 89.229) Food consumption (AOR=38.269, CI=9.328 – 157.010) Maternal age (OR=0.744, CI=0.256 – 2.156) Paternal age (OR=1.864, CI=0.590 – 5.885) Low maternal education (AOR=9.480, CI=2.012 – 44.676) Exposure to chemicals (AOR=130.3, CI=13.2 – 1286.9)

Nonsyndromic cleft lip with or without cleft palate in arab populations: genetic analysis of 15 risk loci in a novel case-control sample recruited in Yemen	Aldhorae, K. A., Böhmer, A. C., Ludwig, K. U., Esmail, A. H., Al-Hebshi, N. N., Lippke, B., Gölz, L., Nöthen, M. M., Daratsianos, N., Knapp, M., Jäger, A., Mangold, E.	2014	10.1002/bdra.23221	Yemen	CLP	Case: 242 Control: 420	Not indicated in study.	Case-control	IIb	**Biological risks** Genetics: rs987525 (OR_{Het}=1.74, CI=1.22 – 2.47; OR_{Hom}=2.47, CI=1.55 – 3.93) rs4460498 (OR_{Het}=1.18, CI=0.75 – 1.85; OR_{Hom}=1.99, CI=1.25 – 3.16) rs4752028 (OR_{Het}=1.84, CI=1.28 – 2.66; OR_{Hom}=1.38, CI=1.38, CI=0.38 – 4.96) rs8001641 (OR_{Het}=1.22, CI=0.87 – 1.71; OR_{Hom}=2.99, CI=1.72 – 5.20)
Orofacial clefts at Bugando Medical Centre: associated factors and postsurgical complications	Buyu, Y., Manyama, M., Chandika, A., Gilyoma, J.	2012	10.1597/10-202	Tanzania	CL, CP, CLP	94	Newborns, children & adults 2 days old - 41 years old	Cohort study	III	**Biological risks** Family history (Chi-square = 27.7, p-value < .001) Birth order (Chi-square = 21.0, p-value < .001) †**Environmental risks**
Parental risk factors for oral clefts among Central Africans, Southeast Asians, and Central Americans	Figueiredo, J. C., Ly, S., Magee, K. S., Ihenacho, U., Baurley, J. W., Sanchez-Lara, P. A., Brindopke, F., Nguyen, T. H. D., Nguyen, V., Tangco, M. I., Giron, M.,	2015	10.1002/bdra.23417	DR Congo, Vietnam, Philippines, Honduras	CP, CLP	Case: 430 Control: 754	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Family history (AOR=4.7, CI=3.0 – 7.2) Pregestational hypertension (AOR=2.6, CI=1.3 – 5.1)

	Abrahams, T., Jang, G., Vu, A., Zolfaghari, E., Yao, C. A., Foong, A., Declerk, Y. A., Samet, J. M., Magee, W., III									Gestational seizures (AOR=2.9, CI=1.1 – 7.4) **Environmental risks** Maternal age (AOR=1.2, CI=1.0 – 1.3) Maternal education (primary school: AOR=2.4, CI=1.6 – 2.8; secondary school: AOR=1.6, CI=1.2 – 2.2) Smoking parent (AOR=1.5, CI=1.1 – 1.9) Exposure to chemicals (agricultural chemicals: AOR=2.7, CI=1.1 – 6.7; industrial chemicals: AOR=3.9, CI=2.0 – 7.6)
Prevalence and evaluation of environmental risk factors associated with cleft lip and palate in a central Indian population	Kalaskar, R., Kalaskar, A., Naqvi, F. S., Tawani, G. S., Walke, D. R.	2013	http://search.ebscohost.com.uplib.idm.oclc.org/login.aspx?direct=true&db=ddh&AN=87856059&site=ehost-live&scope=site	India	CP, CLP	Case: 88 Control: 88	Mothers 15 - 47 years old	Case-control	IIb	**Environmental risks** Food consumption (Chi-square, p-value = .00) Medicine consumption (Chi-square, p-value = .00)

Risk factors for orofacial clefts in India: A case–control study	Neogi, S. B., Singh, S., Pallepogula, D. R., Pant, H., Kolli, S. R., Bharti, P., Datta, V., Gosla, S. R., Bonanthaya, K., Ness, A., Kinra, S., Doyle, P., Gudlavalleti, V. S. M.	2017	: 10.1002/bdr2.1073	India	CLP	Geographically matched Case: 157 Control: 628	Infants, Case: birth - 4 months old Newborns, Control: birth - 2 days old	Hospital-based, matched case-control	IIb	**Biological risks** Family history (AOR=15.48, CI=4.36 – 54.96) Birth order (AOR=2.55, CI=1.25 – 5.21) **Environmental risks** Food consumption (AOR=4.47, CI=1.83 – 10.98)
Risk factors of non-syndromic orofacial clefts in Sudan during 2016-2017	Ali, M. A. M., Hamid, M. M. M.	2019	http://search.ebscohost.com.uplib.idm.oclc.org/login.aspx?direct=true&db=a9h&AN=136630644&site=ehost-live&scope=site	Sudan	CL, CP, CLP	Case: 144 Control: 144	Mothers 11 - 50 years old	Descriptive, case-control	IIb	**Biological risks** Family history (OR=6.95, CI=4.68 – 7.26, p-value = 0.003) **Environmental risks** Maternal education (p-value = 0.001) Lack of folic acid supplementation (p-value = 0.018) Low SES (p-value = 0.042) Consanguineous marriage (OR=2.70, CI=2.03 – 3.37, p-value = 0.003)

The role of environmental factors in the etiology of nonsyndromic orofacial clefts	Eshete, M., Butali, A., Abate, F., Hailu, T., Hailu, A., Degu, S., Demissie, Y., Gravem, P. E., Derbew, M., Mossey, P., Bush, T., Deressa, W.	2020	: 10.1097/SCS.0000000000005924	Ethiopia	CL, CP, CLP	Case: 359 Control: 401	Infants & toddlers A few days - 4 years old	Unmatched, case-control	IIb	**Biological risks** Maternal illness (AOR=0.194, CI=0.053 – 0.712) **Environmental risks** Prenatal complications (AOR=0.179, CI=0.091 – 0.352) Exposure to radiation (AOR=0.375, CI=0.142 – 0.990)

OR = odds ratio
AOR = adjusted odds ratio
OR_{Hom} = odds ratio homozygous
OR_{Het} = odds ratio heterozygous
CI = confidence interval
SES = socioeconomic status
† = category risk factor investigated but no risk factors were found to be associated with CL/P

Chapter 4: Implications and conclusion

Chapter aim:

This chapter aims to provide a brief summary of the main findings, the theoretical and clinical implications of the findings, a critical discussion of the strengths and limitations of the systematic review, and future research recommendations based on the findings. Finally, a conclusion of the study is provided.

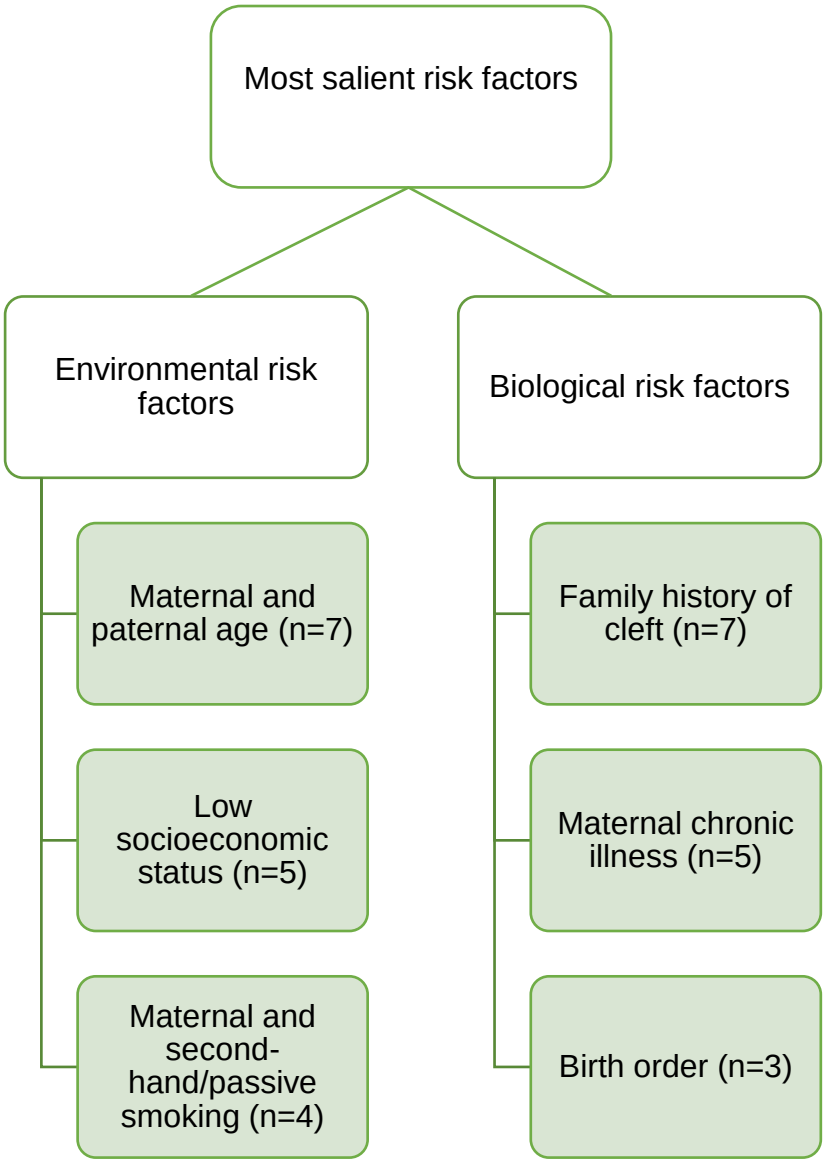
4.1. Summary of results

The current study's objective was to identify and review recently published literature on the risks associated with CL/P in LMICs. Bias was reduced throughout the systematic review by employing an explicit and reproducible methodology (Higgins et al., 2019), namely the PRISMA-P guideline. To the knowledge of the researcher after an extensive literature review, no recent systematic review could be found that investigated the risks associated with CL/P in LMICs.

Findings from the current systematic review identified multiple risks associated with CL/P in LMICs. When compared to high-income countries, low-income countries are faced with major barriers to service delivery such as poverty, poor infrastructure, and a lack of skilled health care professionals (Kadir et al., 2017). However, while investigating risk factors associated with CL/P, it was found that infants in LMICs are exposed to similar environmental risk factors, such as maternal smoking and alcohol consumption, and biological risk factors, for example, gender, and a family history of a cleft, when compared to individuals in upper-middle-income and high-income countries (Ali & Hamid, 2019; Angulo-Castro et al., 2017; Bui et al., 2018b; Buyu et al., 2012; Figueiredo et al., 2014, 2015; Maranhão et al., 2020; Mbuyi-Musanzayi et al., 2018; Pool et al., 2020). Indicating that the specific risk factors identified in the current systematic review may be applicable to low-resourced areas in upper-middle-income and high-income countries. However, due to the additional risk factors infants in LMICs face and also the cumulative effect of multiple environmental and biological risks in this setting i.e. poverty and inadequate access to prenatal health care, infants in these countries may be at a greater risk for CL/P than in high-income settings.

Figure 2 provides a brief overview of the most salient environmental and biological risk factors significantly associated with CL/P in LMICs that were identified in the systematic review.

Figure 2: Salient environmental and biological risk factors for CL/P in LMICs



4.2. Clinical and theoretical implications

Evidence illustrates that CL/P is a complex, heterogeneous and multifactorial disorder (Bui et al., 2018b; Buyu et al., 2012; Kalaskar et al., 2013). This was demonstrated by the variety of environmental and/or biological risk factors related to CL/P found in this systematic review. Infants and young children with a CL/P are at a greater risk for communication and developmental delays, which may be exacerbated by the

presence of multiple risk factors in LMICs (Cavalheiro et al., 2019; Claassen et al., 2016; Lancaster et al., 2020). The cumulative effect of these risk factors on communication development should therefore be investigated as infants and young children may be exposed to many of these risk factors at once.

Awareness of the risk factors associated with CL/P should form the foundation of preventative programs nationwide. Recent literature identified that parents of children with CL/P experience a lack of social support services, which includes public awareness (Hlongwa & Rispel, 2018). Due to a lack of awareness, many families and children with CL/P are subjected to stigmatization, which negatively impacts a family's participation within the community as well as the family's socio-emotional well-being (Adeyemo et al., 2016; Guralnick, 2013). One study conducted at a tertiary care hospital in India found that approximately 98% of participants were unaware of the association between passive smoking and the occurrence of CL/P, indicating that there is a lack of general public awareness regarding specific risks related to CL/P (Patturaja & Leelavathi, 2019). Public awareness programs driven by local community health care workers should focus on educating mothers and the public about the causes and prevention of CL/P (Adeyemo et al., 2016; Patturaja & Leelavathi, 2019).

The benefits of maternal prenatal folic acid and multivitamin supplementation and the protective effect in CL/P occurrence has been well researched (Dien et al., 2018; Hong et al., 2020; Mendonca, 2020; Xu et al., 2018; Zhou et al., 2020). Access to adequate prenatal health care in LMICs is often limited due to financial restrictions and the distance between rural communities and health care facilities (Kadir et al., 2017). Thus, limited access to multivitamins in LMICs may be increasing the risk of CL/P. Government policies should be aimed at providing all women of child-bearing age with sufficient prenatal health care while prioritising women in rural communities. Expecting mothers from a lower SES are more likely to have unplanned pregnancies due to a lack of planning behaviour such as information-seeking, and therefore their intake of folic acid during the preconception and pregnancy period may be limited (Stern et al., 2016). Public awareness programs regarding preventative health care should be implemented and strengthened in low resource communities by educating expecting mothers about the benefits of folic acid and multivitamin supplementation, in order to reduce the possibility of having an infant with a CL/P (Eshete et al., 2020; Gendel et al., 2019; Mendonca, 2020). Local government should prioritise the health of mothers

of child-bearing age by ensuring that access to adequate prenatal care is readily available in rural communities. This may be achieved by training community health care workers in the screening of mothers for high risk factors. The reduction of these biological risk factors may decrease the negative cumulative effect on communication disorders in infants with CL/P.

Due to the possible communication delays infants with CL/P face, health care policies should promote the EI of infants at-risk for CL/P by means of a routine prenatal risk assessment. This assessment should ideally be administered by HCPs working in prenatal clinics. The implementation of a prenatal risk assessment will inform allied HCPs, such as SLTs and community health nurses, of families that may require additional support and counselling. The EI of at-risk infants will ensure that families receive effective and timeous intervention and could result in appropriate referral to an interdisciplinary team (American Cleft Palate-Craniofacial Association [ACPA], 2018). EI of at-risk infants will allow SLTs to provide specialised early intervention regarding feeding, language development, and speech development, as many infants with CL/P present with delays across these developmental areas (Cavalheiro et al., 2019; Groenewald et al., 2013; Lancaster et al., 2020; Visser et al., 2018). Furthermore, EI programs will ensure that at-risk infants are monitored well during the period of optimal neural plasticity and that early intervention can be well-timed and individualised. However, high travel costs to health care facilities, lack of awareness of CL/P, poor patient health and poor financial support are barriers many patients in LMICs face (Massenburg et al., 2016; Samuels et al., 2012). Therefore, optimal early intervention and EI services may still not be possible in low-resourced areas due to environmental barriers. Local government should support the training of more HCP that are involved in multidisciplinary teams to ensure that families in LMICs receive optimal EI services.

The multiple risk factors identified to be associated with CL/P in LMICs emphasises the need to provide holistic intervention for infants with CL/P and their families. Many families living in rural communities do not receive multidisciplinary care (Hlongwa et al., 2019). This may be due to the few specialised craniofacial teams in LMICs, as well as few skilled professionals and allied health care workers, such as SLTs (Ghabrial & Bütow, 2020; Massenburg et al., 2016; Prathanee et al., 2020; Sommer et al., 2020). Therefore, access to care for all families and infants, which should form part of government policies and is the responsibility of the health care system, is not readily

available. In contrast, the United Kingdom, a high-income country, has an implemented policy that guarantees CL/P care is centralised and provided by a multidisciplinary team (Scott et al., 2014). This policy states that the majority of care for families and infants with CL/P be provided at a specialised cleft care centre while secondary services, such as speech-language therapy, are geographically located near the main centre to ensure all individuals receive optimal care. The centralisation of services within the United Kingdom is in line with national policies and provides early, individualised intervention for families and their children (Scott et al., 2014). Thus, the care families and children with CL/P receive are evidence-based and follow the guidelines set by international associations (ASHA, 2008). An explanation for the lack of cleft care policies in LMICs may be that more pressing concerns, such as malnutrition and HIV/AIDS, are the current health care priority of local government.

The specific risk factors identified to be associated with the occurrence of a CL/P provides insight into the global epidemiology of CL/P, which allows for the expansion of registry data in LMICs (Kadir et al., 2017). This will, furthermore, provide HCP with specific data related to individuals in low-income settings, hindering the generalization of risk factors from upper-middle-income and high-income countries to LMICs. Thus, allowing for the development of more individualised early intervention services for this at-risk population.

The risk factors identified in this systematic review may be of value to practising HCP in primary health care facilitates, such as SLTs who are involved in the assessment and intervention of communication difficulties in infants with CL/P. The findings of this study highlight risk factors that need to be taken into account when working with this population. The financial restrictions encountered by many families in LMICs, leading to limited intervention sessions, emphasises the need for coaching of parents by SLTs to ensure optimal intervention is received (The Hanen Centre, 2016). Current practising SLTs should advocate for developmental monitoring of infants with CL/P in order to minimise the long-term impact of communication delays on an infant's quality of life, thereby redirecting the allocation of financial and human resources.

SLTs receive undergraduate training in the field of craniofacial disorders. However, many practising SLTs do not feel confident in the assessment and intervention of the CL/P population (Ghabrial et al., 2020). Undergraduate SLT training in LMICs should include knowledge of the specific environmental and biological risk factors associated

with CL/P in LMICs, and the impact of these risk factors on communication development. Furthermore, more training opportunities, in the form of workshops and online courses, should be available to practising SLTs regarding the holistic assessment and management of potential communication delays in this at-risk population

4.3. Strengths and limitations

The current systematic review presented with various strengths. The study adhered to the PRISMA-P guidelines, which is a valid and reliable research methodology protocol and limits possible bias (Shamseer et al., 2015). The eligibility criteria that were stipulated before the data synthesis commenced, ensured that all risk factors were associated with the occurrence of CL/P. Therefore, risks that occurred due to the presence of CL/P, i.e. feeding difficulties, were eliminated. The risk of bias of each study was independently evaluated by the researcher, which ensured consistency across results, and 20% of the studies were evaluated by two additional reviewers to strengthen the inter-rater reliability of the review (McHugh, 2012). Furthermore, the systematic review only included literature published in the last ten years ensuring that the most recent studies would be synthesised and discussed.

Limitations were also present in this review. A meta-analysis of the results could not be conducted due to the variability in the specific types of environmental and biological risk factors each study investigated. A meta-analysis is conducted by employing statistical techniques in order to summarise results of multiple studies (Shamseer et al., 2015). As a meta-analysis could not be conducted, generalisability of results may be difficult. The review mainly included studies with observational designs, limiting the variety of study designs synthesised in this review. Thus, causality between risk factors could not be determined

4.4. Future research recommendations

The review identified that environmental risk factors are now frequently being investigated in LMICs. Limited research regarding biological risk factors was identified in this systematic review of literature of the last ten years. An explanation for this limited research may be due to the fact that research regarding biological risk factors is older and was thus not included in the recent ten-year search. While researchers are currently more interested in environmental risk factors and their impact on CL/P in

the last ten years. While there is data on the biological and environmental risks, it appears that the cumulative effect of risks associated with CL/P is not yet being investigated. In order for the SLT to provide holistic intervention to infants with CL/P and their families, the cumulative impact of risk factors within the family system needs to be investigated (Guralnick, 2013). Future research should aim to investigate the impact that the cumulative effect of multiple biological and environmental risk factors have on parent-child interaction patterns, family orchestrated child experiences and the health and safety provided by the family to a child with CL/P in LMICs (Guralnick, 2013).

Maternal smoking and/or alcohol use are well established risk factors which lead to prenatal complications such as LBW and PTB (Bird et al., 2017; Zar et al., 2019). However, literature regarding the link between maternal smoking and/or alcohol consumption and CL/P is varied. The impact that these risk factors have on a child's general development may be exacerbated by the presence of a CL/P. In order to reduce the long-term negative impact on a child's development, future research should be conducted on the association between maternal smoking and/or maternal alcohol consumption and the presence of a CL/P.

Limited studies have been conducted in LMICs regarding the genetic component of CL/P. This may be due to several reasons including limited trained genomic scientists, lack of infrastructure, and the expensive nature of genetic research (Sirisena & Dissanayake, 2019; Tekola-Ayele & Rotimi, 2015). Future research should focus on the development and implementation of undergraduate and postgraduate specialised genomic training programs to ensure that this gap within the medical field is filled (Sirisena & Dissanayake, 2019).

The interplay between the environment and genetics and the role this interaction plays in the occurrence of CL/P is not yet well understood but has been addressed by various studies in upper-middle-income countries (Assis Machado et al., 2018; Estandia-Ortega et al., 2014; Garland et al., 2020). The cumulative effect of multiple environmental risk factors infants in LMICs are exposed to may increase the possibility of a negative interaction with gene polymorphisms, placing an infant at a greater risk for CL/P and communication delays in these settings. Therefore, future studies should investigate the gene-environment interaction associated with CL/P in LMICs and

whether specific combinations of these interactions are more prevalent in these settings.

Children exposed to specific risk factors, such as prenatal maternal smoking or maternal alcohol consumption, experience delayed communication development (Hendricks et al., 2019; Hernández-Martínez et al., 2017). Regarding CL/P, studies have concluded that children with CL/P also presented with delayed communication development (Cavalheiro et al., 2019; Groenewald et al., 2013; Lancaster et al., 2020). Thus, if a child is exposed to several risk factors in addition to the CL/P, a greater communication developmental delay may be present. Future research should be conducted regarding the communication development of infants with CL/P and whether the presence of associated risk factors increases the possibility of developmental communication delays. Such research will provide SLTs with guidelines throughout the assessment and management of children with CL/P and will allow for appropriate adaptation of evidence-based intervention programs.

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, future research should explore the implementation of a prenatal risk assessment for infants at-risk for CL/P on a larger scale, by utilising longitudinal studies across various high-income, middle-income and low-income communities, to ensure the validity and reliability of the prenatal risk assessment. The development and implementation of a prenatal risk assessment will enhance the EI of infants at-risk for CL/P and will allow for timeous early intervention.

4.5. Conclusion

Within the last decade, multiple studies have investigated environmental and/or biological risk factors associated with the presence of CL/P with more research now emerging about the environmental risks associated with CL/P than before. In order for SLTs to provide holistic intervention to the CL/P population, more research is required in lower-middle-income settings in order to develop contextually-relevant tools to allow for the EI of infants at-risk for CL/P. Investigating the cumulative effect of the multitude of environmental and biological risks infants with CL/P in lower-middle-income settings face will allow cleft team members and other allied health care staff to provide

comprehensive and coordinated early intervention services in areas that require it most.

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Appendices

Appendix A: PRISMA-P Checklist

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	15
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	N/A
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	9-13
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	13
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	16-17
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	17-18
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18-19
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	21
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	20
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	20

Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	21-22
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	N/A
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	23
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	32
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	24

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix B: Ethical clearance letter from Faculty of Humanities

Faculty of Humanities
Fakulteit Geesteswetenskappe
Lefapha la Bomotho

15 June 2020

Dear Miss K Kruppa

Project Title:	Communication development and associated risks of toddlers with cleft lip and palate, within a lower-middle income context.
Researcher:	Miss K Kruppa
Supervisor:	Dr E Krüger
Department:	Speech Language Path and Aud
Reference number:	15069819 (HUM010/1219) (Post approval)
Degree:	Masters

Thank you for the application to amend the existing protocol that was previously approved by the Committee.

The revised / additional documents were reviewed and **approved** on 15 June 2020 along these guidelines, further data collection may therefore commence (where necessary).

Please note that this approval is based on the assumption that the research will be carried out along the lines laid out in the amended proposal. Should your actual research depart significantly from the proposed research, it will be necessary to apply for a new research approval and ethical clearance.

We wish you success with the project.

Sincerely,

Prof Innocent Pikirayi
Deputy Dean: Postgraduate Studies and Research Ethics
Faculty of Humanities
UNIVERSITY OF PRETORIA
e-mail:PGHumanities@up.ac.za

Fakulteit Geesteswetenskappe
Lefapha la Bomotho

Research Ethics Committee Members: Prof I Pikirayi (Deputy Dean); Prof KL Harris; Mr A Bizos; Dr A-M de Bear; Dr A dos Santos; Ms KT Govinder Andrew; Dr P Gultura; Dr E Johnson; Prof D Maree; Mr A Mohamed; Dr I Noomè; Dr C Puttergill; Prof D Reyburn; Prof M Soer; Prof E Taljard; Prof V Thebe; Ms B Tsebe; Ms D Mokalapa

Appendix C: Confirmation of submission to The Cleft Palate-Craniofacial Journal

The Cleft Palate-Craniofacial Journal

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

Journal:	*The Cleft Palate-Craniofacial Journal*
Manuscript ID	CPCJ-20-0546.R1
Manuscript Type:	Original Article
Keywords:	Etiology, Maternal factors, Prenatal development, Epidemiology
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.