The epidemiology of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago and characteristics of multi-disciplinary team cleft care pathways, globally.

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ABSTRACT

Introduction

Orofacial clefts (OFCs) are the most prevalent craniofacial anomaly (CFA) worldwide, with birth prevalence varying significantly across different geographic regions and ethnic groups. In terms of management, there are also global disparities in the quality and access to comprehensive cleft care through a multidisciplinary (MDT) approach. This is reflected within Small Island Developing States (SIDS) like the Caribbean country, Trinidad and Tobago. Despite its high-income status and universal healthcare system providing free healthcare to its citizens, it faces specific healthcare challenges to other members of the United Nations' SIDS such as a lack of specialised professionals, infrastructure and quality health services such as a national cleft service. Moreover, the Caribbean, often grouped with Latin America as "Latin America and the Caribbean (LAC)", is frequently overlooked by international non-profit organisations focused on developing cleft care within low-middle income countries in South and Central America, leaving Caribbean countries with higher income status without similar support. This lack of international influence and interest in developing care for cleft patients within the Caribbean is thought to be at least in part due to the absence of up-to-date epidemiological evidence. Updating the evidence on the epidemiology of orofacial clefts and craniofacial anomalies in Trinidad and Tobago is therefore expected to enhance both local and international efforts aimed at improving cleft care in the country and across the Caribbean region. Additionally, in an ambition to map the characteristics of a cleft care pathway appropriate for introducing a MDT approach to comprehensive cleft care that is sustainable and scalable in low-resource settings such as Trinidad and Tobago and other SIDS, a scoping review approach to systematically reviewing the literature is deemed appropriate.

This work supports the United Nation's Sustainable Development Goals, specifically targets 3.8 and 3.C in achieving access to essential healthcare services and increasing health development in developing countries especially in SIDS.

Aims and objectives

The overall aims of this thesis were to:

1) Explore the epidemiology of orofacial clefts (OFCs) and other craniofacial anomalies in Trinidad and Tobago; and

2) Appraise the literature on MDT care pathways for the management of patients with OFCs globally and use the information found to suggest characteristics of a care pathway appropriate for introducing basic MDT cleft care in low-resource settings that is sustainable and scalable.

To achieve this, the objectives were to:

1. Determine the birth prevalence (incidence) of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago and explore associated factors that might be linked to these anomalies through an epidemiological study following a cross-sectional, retrospective, quantitative, observational design.
2. Identify the characteristics of an ideal MDT cleft care pathway and facilitating factors and challenges to its implementation; and
3. Define characteristics of a basic, sustainable MDT cleft care pathway that can be implemented.

Methods

The aims and objectives were addressed through two pieces of work.

The first was an epidemiological study with an observational quantitative cross-sectional design, over a 5-year retrospective period (2018-2022). Birth prevalence was determined using data extracted from Trinidad and Tobago's digital national birth registry database. The numbers of craniofacial anomalies identified in the database for the country's different Regional Health Authorities (RHAs) were verified through searching a variety of data sources including hospital files/records and nursing admission notes at each RHA's Neonatal Intensive Care Unit (NICU) during that period. To explore the evidence-based associated risk factors that might be linked to OFCs, hospital records of babies and their mothers were searched. For each baby

identified as being born with an OFC, a healthy newborn closely matched (by sex and birth month) was randomly selected within the same RHA to form study and control groups. Birth prevalence and the samples were presented using descriptive statistics. Logistic regression models were used to assess which factors are more strongly linked with the birth of a baby with an OFC.

The second was a scoping review conducted following the Joanna Briggs Institute (JBI) guidelines. To identify eligible sources of evidence, multiple electronic databases were searched along with hand-searching for grey literature. Only data sources focused exclusively on the management (which includes both diagnosis and treatment from all clinical specialities) of non-syndromic orofacial cleft were considered. Studies were screened by two independent reviewers using the pre-determined eligibility criteria and any disagreements resolved with a third (experienced) reviewer.

Results

The birth prevalence of the most common craniofacial anomaly, orofacial clefts, within the population of Trinidad and Tobago was found to be 0.64 per 1000 births. Other craniofacial anomalies were poorly reported as only 3 cases of micrognathia were reported by a single RHA. This study also encountered missing data and inconsistently available and ambiguous data suggesting that record-keeping needs improvement and optimisation in the areas of patient history documentation, craniofacial anomaly surveillance and orofacial cleft classification. Although only a limited number of variables were appropriate for analysis, significant predictors of OFCs were still identified (gestational age; birth weight; birth length; maternal age; maternal medical history within normal limits; gravida; para). This study's findings suggest that the likelihood of a birth with an OFC decreases with gestational age, birth weight, birth length and if there is a maternal medical history within normal limits. Also, the likelihood of a birth with an OFC increases with maternal age and number of pregnancies. When analysed together, only maternal medical history within normal limits and gravida remain significant suggesting these are the stronger predictors which might themselves

be influencing the other variables. The analysis suggests that a mother with a normal medical history is 91% less likely to give birth to a baby with an OFC. Women with a higher gravida are 74% more likely to give birth to a baby with an OFC. This study also emphasises that development is required to establish a basic cleft MDT care pathway that introduces comprehensive cleft care for these individuals, as an observational finding revealed the absence of a standardised multidisciplinary pathway providing comprehensive cleft care.

The scoping review identified 34 sources suitable for synthesis and interpretation. Overarching themes/ characteristics of MDT cleft care pathway were identified within the included sources of evidence as a statement of goals, infrastructure, MDT composition, supporting documents for the delivery of safe, quality cleft care, cleft care timeline and facilitating factors to optimising the care pathways. Using these characteristics, an ideal cleft care pathway was defined and suggestions were proposed for a basic cleft care pathway capable of introducing comprehensive cleft care in low-resource settings.

Conclusions

In conclusion, this thesis updates the epidemiological evidence on the most common craniofacial anomaly, orofacial clefts, within the population of Trinidad and Tobago. It outlines the steps necessary to support future epidemiological studies on craniofacial anomalies in this population. Additionally, it provides initial suggestions for the characteristics of a care pathway suitable for introducing basic multidisciplinary team (MDT) cleft care that is sustainable and scalable in low-resource settings, while acknowledging that further review and appraisal involving stakeholders is required to develop recommendations.

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LIST OF ABBREVIATIONS

CARICOM Caribbean Community

CCCC Comprehensive Cleft Care Centre

CFAs Craniofacial anomalies

CL cleft lip

CLP Cleft lip and palate

CL/P Cleft lip with or without palate

CPO Cleft palate only

CPW care pathway

CRANE Cleft Registry and Audit Network

ECLAMC Latin America Collaborative Study of Congenital Malformations

ERHA Eastern Regional Health Authority

FAS Foetal Alcohol Syndrome

HFM Hemifacial microsomia

HPE Holoprosencephaly

ICBDSR International Clearinghouse for Birth Defects Surveillance and Research

ICD International Statistical Classification of Diseases and Related Health Problems

IPDTOC International Perinatal Database of Typical Orofacial Clefts

LAC Latin America and the Caribbean

LDC Least developed country

LMIC Low-middle income country

MSH Mobile surgical hospital

NAM nasoalveolar moulding

NCRHA North Central Regional Health Authority

NICU Neonatal Intensive Care Unit

NWRHA North West Regional Health Authority

OFC Orofacial cleft

OR Odds ratio

RHA Regional Health Authority

UN SDGs United Nations Sustainable Development Goals

SIDS Small Island Developing States

STROBE Strengthening the Reporting of Observational Studies in Epidemiology

SWRHA South West Regional Health Authority

TCS Treacher Collins Syndrome

TRHA Tobago Regional Health Authority

T&T Trinidad and Tobago

CHAPTER 1 INTRODUCTION

Orofacial clefts (OFCs) are the most common craniofacial anomaly worldwide. The World Health Organization (WHO) reports a global prevalence of 1 in 700 births, varying widely within different populations (Mossey and Little, 2002).

It is recognised that effective and efficient management of OFCs requires a multidisciplinary team (MDT) of specialised professionals following a protocol of comprehensive cleft care (Kassam et al. 2020). However, the reality is that there are global disparities in quality and access to cleft care. For example, in developed countries like the United Kingdom, there are multiple standardised Cleft Centres focused on delivering comprehensive care through a MDT approach. In contrast, no such centres exist in the Caribbean region (World Health Organization (WHO) 2018).

Moreover, the Caribbean, often grouped with Latin America as “Latin America and the Caribbean (LAC)”, is frequently overlooked by international non-profit organisations focused on developing cleft care. These organisations typically prioritise low-middle income countries in South and Central America, leaving Caribbean countries, many of which are high-income yet still developing, without similar support (Yan et al. 2023). The lack of international influence and interest in developing care for cleft patients within the Caribbean is thought to be at least in part due to the absence of up-to-date epidemiological evidence.

Trinidad and Tobago, with a population of approximately 1.5 million, is a cosmopolitan and ethnically diverse country with origins traced to African, South Asian, Middle Eastern and Chinese populations (UNFPA 2024). The incidence of OFCs within Trinidad’s multi-ethnic 830,000 population was last reported in 1963 to be as high as 1 in 500 births in some racial groups and 1 in 1,600 for others (Robertson 1963). It is a high-income developing country that is the hub for medical care and tertiary education within the Caribbean. However, despite its high-income status and universal healthcare system providing free healthcare to its citizens, it faces specific healthcare challenges to other members of the United Nations’ Small

Island Developing States (SIDS) such as a lack of specialised professionals, infrastructure and quality health services such as a national cleft service.

Updating the evidence on the epidemiology of orofacial clefts and craniofacial anomalies in Trinidad and Tobago is expected to enhance both local and international efforts aimed at improving cleft care in the country and across the Caribbean region. This effort could pave the way for future projects, including the establishment of a comprehensive database that tracks information on children born with these anomalies, similar to the CRANE (UK Cleft Registry and Audit Network) database. Such a resource would not only stimulate interest from international cleft-focused organisations but also contribute valuable data to the global research landscape. By addressing the current gaps in ethnic and racial diversity in studies, this work could significantly enhance the relevance and applicability of orofacial cleft and craniofacial research.

Additionally, in an ambition to map the characteristics of a cleft care pathway appropriate for introducing basic MDT cleft care that is both sustainable and scalable, a scoping review approach to reviewing the literature is deemed appropriate.

This work has received approval from Trinidad and Tobago's Ministry of Health and supports the United Nation's Sustainable Development Goals, specifically targets 3.8 and 3.C[1] in achieving access to essential health-care services and increasing health development in developing countries especially in SIDS.

[1] SDG Target 3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all; SDG Target 3.C Health workforce: Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States.

Organisation of thesis

The thesis is presented in Chapters 2-7 with the following structure:

- Chapter 2 provides a review of the literature, organised into two sections. The first section provides a background overview of craniofacial anomalies, while the second delves into the existing research regarding the epidemiology of orofacial clefts, the most common type of craniofacial anomaly.
- Chapter 3 lists the aims and objectives of this thesis.
- Chapter 4 investigates the epidemiology of orofacial clefts (OFCs) and other craniofacial anomalies in Trinidad and Tobago through an observational epidemiological study determining the birth prevalence of these conditions. It also examines potential associated factors that might be linked to these anomalies over a retrospective period.
- Chapter 5 undertakes a critical evaluation of the literature on multidisciplinary team care pathways for the management of patients with orofacial clefts through a scoping review approach.
- Chapter 6 provides a summary of the thesis, integrating the two pieces of work presented in Chapters 4 and 5 and consolidating the main findings.
- Chapter 7 displays recommendations for future research.

CHAPTER 2 LITERATURE REVIEW

2.1 Introduction

This chapter serves as a review of the literature on the epidemiology of orofacial clefts and other craniofacial anomalies as well as their management.

Here epidemiology is defined as the branch of medical science that investigates the distribution, determinants and the application to control that disease or disorder (Brachman 1996). Epidemiological research helps to understand how many there are with a disease/disorder, if those numbers are changing and how the disorder affects that population (NIDCD 2011).In the definition of epidemiology, “distribution” refers to descriptive epidemiology, covering time (when), place (where), and person (who). Whereas “determinants” refers to analytic epidemiology, generally including the causes (including agents), risk factors (including exposure to sources), modes of transmission (why and how) epidemiology, but does not include the resulting public health action (CDC 2012; Parritz and Troy 2017). In this literature review, determinants are covered under “aetiology” and management of each craniofacial anomaly is discussed in tandem.

This literature review is narrated under the following sections:

- Section 2.2: Background
    - 2.2.1 Healthcare in Trinidad and Tobago
    - 2.2.2 Craniofacial anomalies
    - 2.2.3 The most common craniofacial anomaly: orofacial clefts
- Section 2.3: Global distribution of orofacial clefts
- Section 2.4: Summary

2.2 Background

2.2.1 Healthcare in Trinidad and Tobago

Trinidad and Tobago's Ministry of Health leads the health sector which is a two-tier healthcare system, comprising both public and private facilities. The division of public healthcare and service provision to Regional Health Authorities (RHAs) ensures geographic coverage of public healthcare is free to everyone in Trinidad and Tobago and is paid for by the Government and taxpayers (Pan American Health Organization (PAHO) 2009; The UN Refugee Agency 2024).

Like other member states of the United Nations, Trinidad and Tobago (T&T) is committed to achieving Universal Health Coverage (UHC) which guarantees all individuals access to a comprehensive range of quality health services without financial hardship (World Health Organization 2023b). However, despite being classified as a high-income country, it is still a developing nation (The World Bank 2024). Specifically, it is a Small Island Developing State (SIDS), that shares common healthcare challenges with other member countries, including limited healthcare services and infrastructure, a shortage of specialists, and an oversupply of medical interns. This paradox underscores the urgent need for enhanced specialist training opportunities to meet the healthcare demands of an aging population and chronic disease treatment (Kamis 2020). Goal 3 of the United Nations Sustainable Development Goals emphasises achieving UHC and access to quality healthcare. In the Caribbean, barriers to these goals include infrastructural challenges, a lack of skilled health professionals, and fiscal vulnerabilities (Kamis 2020; United Nations 2024c; United Nations 2024b)

Currently, there are no formalised cleft care services in T&T and little data exists on the subject in the Caribbean. The absence of resources further complicates efforts to align with UHC principles and the UN Sustainable Development Goals. While there have been strides in equitable access to essential health services, significant gaps remain, particularly in cleft palate surgical repair (Carlson et al. 2016). In summary, Trinidad and Tobago's healthcare system faces unique challenges that require targeted efforts to achieve UHC, enhance health equity, and improve health outcomes for its citizens and the wider Caribbean region.

2.2.2 Craniofacial anomalies

Craniofacial anomalies (CFAs) represent a diverse and complex group of congenital deformities of the bones and associated soft tissues of the skull and face. Collectively, CFAs are the most common birth defects in humans and are a major cause of infant mortality and childhood morbidity (Mossey et al. 2003; Farhan et al. 2020). Although the prevalence of this group of developmental disorders varies considerably across geographic areas and ethnic groupings, they share far-reaching consequences on affected individuals, their families and society.

Orofacial clefts (OFCs) are the most common CFA globally and reducing its healthcare burden is the focus of the WHO's International Collaborative Research on Craniofacial Anomalies report (World Health Organization (WHO) 2002). Similarly, OFCs are the focus of many non-profit organisations' surgical outreach programmes. According to the world's largest cleft-focused global non-governmental organisation, Smile Train, their efforts are directed toward OFCs rather than other CFAs, in order to be more effective and productive. They assert that clefts, once treated, never return and that the cleft surgery is a safe and highly effective low-cost intervention that yields immediate transformative results (Smile Train 2024e).

While this thesis focuses on OFCs, which are comprehensively reviewed in Section 2.2.3, it is important to acknowledge that OFCs form part of a wider group of CFAs, many of which share embryological pathways with OFCs or frequently co-occur with cleft lip and/or palate as part of their phenotype. The WHO's Global Strategies report (2002) highlights several such CFAs. Accordingly, this section presents a brief overview of selected CFAs relevant to OFCs, providing context for their inclusion and reflecting the interconnected nature of craniofacial conditions within global craniofacial health and service delivery.

2.2.2.1 Otomandibular anomalies

Brief description

Otomandibular anomalies are characterised by congenital malformations affecting the mandible and the auditory system. They include all disorders involving ear hypoplasia or agenesis and mandibular hypoplasia and may coexist with other malformations (Pereira et al. 2011). Examples of otomandibular anomalies include the conditions hemifacial microsomia (HFM) and Treacher Collins Syndrome (TCS). TCS, a key otomandibular anomaly, frequently presents with cleft palate, and hemifacial microsomia shares embryological pathways relevant to OFCs (Ramanathan 2021; Posnick, 2000).

Global birth prevalence

Hemifacial microsomia is the second most common congenital craniofacial defect after cleft lip and palate, affecting 1 in every 3,500-4,000 live births (Facial Palsy UK (FPUK) 2023). TCS is much less common with reports of 1 in every 50,000 live births (0.02-0.05 per 1000 births) (World Health Organization (WHO) 2002; Trainor and Andrews 2013).

Aetiology

HFM and TCS result from abnormal development of the first and second branchial arches during foetal development. Disruptions in this process can stem from genetic defects, teratogens, maternal smoking, hormonal therapy, vascular injury, and certain maternal conditions like diabetes, hypothyroidism, and coeliac disease, leading to hypoplasia or aplasia. Genetic factors associated with HFM include various chromosomal abnormalities such as trisomy 10p and deletions on chromosomes. TCS is associated with mutations in three genes: TCOF1, POLR1C, and POLR1D. These genes are crucial for producing proteins that regulate the early development of bone and tissue cells during pregnancy(Trainor and Andrews 2013; NHS Foundation Trust 2020; Facial Palsy UK (FPUK) 2023; Young and Spinner 2023; Barbosa et al. 2024).

Clinical features and complications

Hemifacial microsomia is a congenital condition characterised by facial asymmetry and deformities, primarily affecting one side of the face more than the other. The most notable features include asymmetry of the jaw, eyes, facial soft tissues, ear abnormalities and speech impairment. Severe cases may also involve abnormalities in other body systems, particularly the spin, kidneys and heart (Young and Spinner 2023).

Children with TCS have a characteristic appearance due to the problems with their cheekbones, jaw and eye sockets forming. Typical features include bilateral downslanted palpebral fissures, malar hypoplasia and micro- or retrognathia. Hypoplasia of the facial bones (maxilla, mandible) and clefting of the palate can lead to respiratory and feeding challenges, while ear abnormalities may cause conductive hearing loss. Other clinical features include dental anomalies in 60% of individuals with TCS. Less common features include choanal stenosis or atresia (NHS Foundation Trust 2020).

Management

Otomandibular anomalies require a multidisciplinary team approach with surgical specialties and other healthcare professionals to address conditions unique to the individual such as hearing or feeding impairments. HFM and TCS often require surgical procedures to treat the various components of asymmetry. This may involve mandibular and/or ear reconstruction or fat grafting to help with correcting face shape(NHS Foundation Trust 2020; Young and Spinner 2023).

2.2.2.2 Craniosynostosis

Brief description

At birth, cranial sutures are normally not fused to facilitate the baby's passage through the birth canal and allow expansion and normal brain growth. Craniosynostosis refers to the premature fusion of one or more cranial sutures. It may be congenital or observed later, often during the first year of life. Syndromic craniosynostoses such as Apert and Crouzon syndromes often co-occur with cleft palate, linking them to OFCs within craniofacial service delivery (Kolar and Salter, 1997).

Global birth prevalence

Craniosynostosis anomalies are the second major group of craniofacial malformations. Birth prevalence has risen with time from 0.3 to 0.4-0.5 per 1000 (World Health Organization, 2002; Kajdic et al. 2018).

Aetiology

The aetiology is not known but thought to be a combination of genes and environmental factors and sometimes related to genetic disorders.

Clinical features

In craniosynostosis, premature fusing of the sutures affects normal brain and skull growth, which may result in an atypically shaped skull and increased intracranial pressure. It is commonly classified based on the number of sutures involved (simple vs complex) or association with syndrome (syndromic vs non-syndromic). Syndromes that present with craniosynostoses include Apert, Crouzon and Pfeiffer.

Complications

If untreated, complications of the respiratory and neurologic systems occur. The most common signs in infants with this condition include changes in the shape of the head and face, increased irritability, noticeable scalp veins, high-pitched cry, poor

feeding, projectile vomiting, increasing head circumference. Later complications include seizures, blindness, headaches, developmental delays and cognitive impairment.

Management

Early diagnosis is key to preventing complications and surgery is typically the recommended treatment to reduce intracranial pressure and prevent or correct deformities of the face and skull bones.

2.2.2.3 Stickler syndrome

Brief description

Stickler syndrome encompasses a range of hereditary conditions that impact connective tissues, which provide support and structure to various organs, particularly those in the face, ears, eyes and joints. Stickler syndrome is an autosomal dominant genetic disorder that can affect anyone, though individuals with a family history are at greater risk (O'Brien and Phillips 2023; Cleveland Clinic 2024c). Stickler Syndrome is a significant syndromic cause of cleft palate (Stickler et al. 1965).

Global birth prevalence

Some sources report that the birth prevalence is about 1 to 3 cases per 7,500 to 10,000 newborns according to Cleveland Clinic, or 0.1 per 1,000 births according to the World Health Organization ((World Health Organization (WHO) 2002; Cleveland Clinic 2024).

Aetiology

Stickler syndrome is caused by a genetic mutation in one of six collagen-related genes: COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, or COL9A3. These genes are crucial for producing collagen, which provides flexibility and strength to connective tissues. When mutated, collagen formation is impaired, particularly affecting the development of bones and other connective tissues leading to the characteristic features of Stickler syndrome(O'Brien and Phillips 2023; Cleveland Clinic 2024c).

Clinical features and complications

There are six types of Stickler syndrome, with increasing severity of symptoms as the types increase in number. Stickler syndrome therefore varies widely among individuals, with few experiencing all associated symptoms. Common issues include bone and joint problems like flexible joints, scoliosis, and arthritis; ear and hearing challenges such as hearing loss; and ocular issues like severe near-sightedness, detached retina, or cataracts. Additional symptoms may involve breathing difficulties,

deafness, feeding challenges in infants, and learning issues stemming from vision and hearing problems. Many affected children also exhibit facial characteristics like cleft palate, micrognathia and a flattened face with a small nose. In addition to complications such as joint problems, ocular issues, hearing loss, breathing difficulties like obstructive sleep apnoea, feeding and speech issues associated with cleft palate, these individuals may experience learning challenges from vision and hearing impairments (Cleveland Clinic 2024c).

Management

There is no consensus clinical diagnostic criteria for Stickler syndrome that has been published (O'Brien and Phillips 2023). Diagnosis may involve genetic testing to analyse blood or tissue samples for mutations, imaging to reveal abnormalities in bones and joints, a physical exam to assess symptoms in the face, ears, eyes, and joints, and vision and hearing tests to identify any related issues.

Treatment for Stickler syndrome depends on an individual's specific symptoms. While there is no cure for the condition, it does not impact life expectancy. Early diagnosis and management of symptoms are crucial for achieving the best outcomes, particularly when addressing issues such as a detached retina, joint abnormalities or a cleft palate (Cleveland Clinic 2024c).

2.2.2.4 CHARGE Association

Brief description

CHARGE association (also known as CHARGE syndrome or Hall-Hittner syndrome) is a rare genetic disorder that impacts multiple areas of the body. Its abbreviation stands for several characteristic features: coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear abnormalities. Individuals may experience a unique combination of these malformations, which can lead to serious, life-threatening health issues, especially during infancy (Facial Palsy UK (FPUK) 2020). CHARGE syndrome can present with cleft lip and/or palate among its constellation of features (Blake et al. 1990).

Global birth prevalence

It has been reported to affect approximately 1 in 10,000 newborns (0.1 per 1000 births) (World Health Organization (WHO) 2002). The death rate is the highest in the first year of life and children with CHARGE have been shown to have a 70% survival rate to five years of age (Blake 1998).

Aetiology

CHARGE syndrome is a genetic condition caused by a mutation in the CHD7 gene, located on chromosome 8. This gene is vital for the development of various foetal tissues, including the eyes and inner ears. Approximately 60-65% of individuals with CHARGE syndrome have this mutation, most often as a new occurrence with no prior family history. For parents who have one child with CHARGE, the chance of having another affected child is about 1-2%. However, the risk may be as high as 50% for the children of individuals with CHARGE (National Institutes of Health National Library of Medicine (NIHNLM) 2017).

Clinical features

CHARGE syndrome is characterised by a distinct set of clinical features and complications that can often be identified at birth. Major traits include coloboma, a keyhole-shaped eye defect that can impact vision; choanal atresia, a blockage in the nasal passages; and various ear anomalies, which can lead to hearing loss and balance issues. Many individuals also experience cranial nerve dysfunction, resulting

in loss of smell, facial palsy, and swallowing difficulties. In addition to these primary features, children with CHARGE syndrome may exhibit minor characteristics such as heart defects, cleft lip and palate, genital differences, kidney abnormalities, and growth deficiency. Other notable traits include characteristic facial features such as asymmetry and a flat mid-face, upper body hypotonia and additional medical concerns like chronic ear problems and spine deformities (Facial Palsy UK (FPUK) 2020).

Management

Diagnosis primarily relies on clinical evaluation rather than genetic testing, which is not always conclusive. Some babies may receive a diagnosis immediately, while for others, it may take years to connect the various medical signs. Common neonatal emergencies related to CHARGE syndrome include cyanosis due to congenital heart defects and bilateral posterior choanal atresia. Therefore, it is crucial for all patients suspected of having CHARGE syndrome to undergo a cardiology consultation. Some cases may necessitate tracheostomy to manage chronic airway difficulties, aspiration or gastroesophageal reflux disease. Children with CHARGE syndrome often require extensive medical management for feeding difficulties, frequently needing jejunostomy or gastrostomy feeding tubes. Treatment is customised to address each individual's unique medical challenges and typically involves a multidisciplinary team of specialists, including ENT doctors, cardiologists, and endocrinologists. Many infants will need comprehensive medical and educational interventions, including surgeries for conditions like choanal atresia and orofacial clefts, which are usually performed at specific developmental stages. Ongoing treatments may also address facial palsy and hormonal deficiencies that can impact puberty and bone health. Overall, the management of CHARGE syndrome is thorough and may require long-term care and support. In terms of prognosis, patients are particularly vulnerable during their first year of life, often facing a higher risk of infections, frequent hospitalisation and complex surgeries, including congenital heart surgery. In late childhood through adulthood, common causes of death include infection, aspiration, and obstructive sleep apnoea. Additionally, widespread bilateral coloboma, poor vision, brain malformations, and microcephaly

can contribute to a poorer prognosis (Facial Palsy UK (FPUK) 2020; Leviashvili et al. 2023).

2.2.2.5 Holoprosencephaly

Brief description

Holoprosencephaly (HPE) is a condition resulting from the abnormal development of the prosencephalon, or forebrain, leading to incomplete separation of the brain's left and right halves. There are several forms of HPE: in the alobar type, there is no separation; in the semilobar type, some separation exists; and in the lobar type, most of the brain is divided, but with incomplete separation. Its impact on affected children can vary widely, ranging from severe and life-threatening to mild and barely noticeable (Contact 2024; National Organization for Rare Disorders (NORD) 2024). Holoprosencephaly frequently includes midline facial anomalies such as cleft lip and/or palate (Solomon et al. 2010).

Global birth prevalence

HPE is the most common structural anomaly of the developing brain. It is estimated to occur in 1 in 250 foetuses during early development but most affected pregnancies end in miscarriages or stillbirth. It is rare in live births, with birth prevalence ranging from 1 in 8,000-16,000 live births (0.06-0.02 per 1,000 births) (Raam et al. 2011; Cleveland Clinic 2024).

Aetiology

This birth defect results from various causes, primarily linked to disruptions in the development of the first and second branchial arches formed by neural crest cells during the early weeks of pregnancy. The aetiology remains uncertain, but two primary theories propose vascular injury to the stapedial artery and anomalous migration of neural crest cells as contributing factors. Genetic abnormalities are significant in HPE, with about one-third of affected children having chromosomal disorders, notably trisomy 13, as well as other chromosomal changes such as trisomy 10p and microdeletions on chromosomes 12p13.33 and 22q11.2. Specific gene mutations (e.g., in SHH, SIX3, and TGIF1) can also disrupt brain development. Additionally, environmental factors like maternal diabetes, teratogens, and infections during pregnancy can elevate risk, although many cases lack identifiable intrauterine exposures. While some children may have identifiable genetic causes, the exact

origin of HPE remains unknown for many individuals, suggesting the potential for additional, yet undiscovered, genetic factors. The heterogeneous phenotypic presentation of HPE arises from these complex interactions among genetic and environmental influences (International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) 2024; National Organization for Rare Disorders (NORD) 2024).

Clinical features and complications

Children diagnosed with holoprosencephaly (HPE) may exhibit various challenges, including microcephaly (a small head), hydrocephalus (excess fluid in the brain), and developmental delays in milestones like sitting and walking. Epilepsy is common, with many experiencing seizures. Endocrine issues may arise, including low levels of thyroid, cortisol, or growth hormones, and diabetes insipidus affects three-quarters of affected children, leading to high sodium levels and excessive urination. Motor control problems can result in tight muscles, balance issues, and weakness, while sleep disturbances, such as insomnia or sleep apnoea, are also prevalent. Additionally, difficulties in regulating body temperature and feeding challenges often necessitate the use of feeding tubes. Facial deformities may include a flat nose with a single nostril, close-set eyes and cleft lip or palate. Some children may also display self-abusive behaviours like biting or scratching (Christie and Clegg 2021).

Management

HPE is typically diagnosed through ultrasound during pregnancy, although milder forms may go unnoticed until after birth. If a baby exhibits developmental delays, an MRI can be performed to confirm the diagnosis. There is no cure or standard treatment for HPE. Instead, healthcare providers focus on managing each child's specific symptoms through a multidisciplinary approach. Common interventions include anti-seizure medications to control seizures, placement of a ventriculoperitoneal shunt to address hydrocephalus, and therapies to improve movement issues such as spasticity and dystonia. Additionally, surgical cleft repair and other plastic reconstructive surgery may be performed for cleft lip and palate or other facial abnormalities. Hormonal imbalances related to pituitary gland defects can be treated with medication, and children with feeding difficulties may benefit from

nutritional support measures, such as a gastrostomy tube(Raam et al. 2011; Christie and Clegg 2021; Cleveland Clinic 2024b).

2.2.3 The most common craniofacial anomaly: Orofacial clefts

2.2.3.1 Anatomy and clinical features

The term “orofacial cleft” (OFC) is an umbrella term describing a broad spectrum of pathologies that range from a small indentation to a large gap in the foetal face. OFCs can affect the lip, philtrum, alveolus and hard and soft palate to varying degrees (Cleveland Clinic 2024a).

Table 1 summarises the diverse OFC phenotypes which are broadly classified into three principal types: (1) cleft palate alone (CP; CPO); (2) cleft lip with or with or without cleft alveolus (CL+/-A); (3) cleft lip and palate (CLP).

Table 1 The different orofacial cleft phenotypes, their abbreviation and a list of exclusions (Lewis 2017; Huang et al. 2015)

Orofacial cleft phenotypes	Abbreviations found in the literature	Exclusions
Cleft lip	CL	Excludes: -cleft lip and alveolus -cleft lip and palate -cleft palate alone
Cleft lip with or without cleft alveolus	CL+/-A	Excludes: -cleft lip and palate -cleft palate alone
Cleft palate alone	CP; CPO	Excludes: -cleft lip -cleft lip and palate
Cleft lip and palate	CLP	Excludes: -cleft lip -cleft palate alone
Cleft lip with or without cleft palate	CL+/-P	Excludes -cleft palate alone
Cleft lip and/or cleft palate	CL/P	No exclusion

Cleft lip anatomy and clinical features

Cleft lip refers to clefting not affecting the palate, only the upper lip which can include the nose (Shetty et al. 2021). The terms used to describe a cleft lip are summarised in Table 2.

Table 2 Cleft lip clinical descriptors and explanations

Cleft lip clinical descriptor	Explanation/Description
Microform (also known as Forme Fruste)	A mild form of cleft lip that can appear as a groove in the lip with or without an accompanying notch in the lip vermillion
Partial or incomplete cleft lip	Either a small gap or an indentation in the upper lip
Complete cleft lip	The cleft lip continues into the nose
Laterality: Unilateral or bilateral	Affecting one side or both sides
Simonart's band	The name given to the band of tissue if present across the nasal sill in an otherwise complete cleft of the lip

The primary muscle of the lip is the orbicularis oris. It is divided functionally and anatomically into two components: deep; superficial. In conjunction with oropharyngeal muscles, the deep component of the orbicularis oris serves as a sphincter, functioning in swallowing. The superficial component inserts into the anterior nasal spine, alar base and skin to form the philtral ridges. Table 3 details the anatomical differences between cleft lips and a normal lip.

Table 3 Summary of the normal lip anatomy compared to a unilateral complete cleft lip and a bilateral complete cleft lip

Normal lip anatomy	Unilateral Complete cleft lip anatomy	Bilateral complete cleft lip anatomy
Labial skin	Non-fusion of the lip in the cleft region, the skin on both sides of the cleft is less projected or drawn out	Presence of one prolabium (the central lip element that is deficient in tissues) with bilateral lip elements
Philtral columns	Oblique philtral columns located on the non-cleft side with a discrepancy in length	No philtral columns present
White roll	On the lateral side of the cleft, the white roll gradually diminishes to about 2-3 m before it disappears. On the medial side of the cleft, the demarcation of the white roll is less clear	The white roll on the prolabium is rounded and not sharply defined
Mucosa	Thinner, finer mucosa with the absence of a labial glandular bed and deficient compressor muscles	Thinner, finer mucosa with the absence of a labial glandular bed and deficient compressor muscles
Orbicularis oris	No muscle crossing in the midline. Presence of an abnormal attachment at the alar base	The muscle runs bilaterally up into the alar bases but there is no muscle on the median lip element.

Cleft palate anatomy and clinical features

The palate (also known as the “roof of the mouth”), divides the nasal and oral cavities. It has two distinct parts: the hard palate (anterior bony portion) and the soft palate (posterior muscular portion).

The hard palate which is encased in a mucous membrane, enables sounds by providing a surface against which the tongue can be moved and it also functions to allow food to be chewed while breathing. The soft palate is made up of muscle fibers and connective tissue, ending in the uvula. When lowered or retracted during breathing, it facilitates airflow in and out of the nasal passages. In contrast, during the production of most sounds, the soft palate is raised, allowing the mouth to generate the sound. When elevated, it separates the nasal cavity and upper pharynx from the lower pharynx and mouth, which helps with swallowing food and creating a vacuum for drinking. If the soft palate is lowered, it results in the production of nasal sounds (Hopkins 2019).

Embryologically, the palate is also divided by the incisive foramen into the primary palate (or pre-maxilla) and the secondary palate. The primary palate develops first at week 5 of intrauterine life. It consists of structures anterior to the incisive foramen and includes that part of the anterior palate, the portion of the alveolar ridge containing the four incisor teeth and the upper lip. The secondary palate begins developing by week 6 of intrauterine life and consists of structures that are posterior to the incisive foramen. These structures include the hard palate posterior to the incisive foramen, the soft palate and uvula. The soft palate (velum) is a fibromuscular shelf made up of five muscles attached as a sling to the posterior portion of the hard palate. It functions to elevate the nasopharynx, effectively closing the communication from the nasopharynx to the oropharynx. It also serves as the anterior wall of the velopharyngeal port, a sphincter mechanism of which the posterior and lateral walls consist of the superior pharyngeal constrictor. This muscular valve aids in breathing, blowing, swallowing, and phonation. The velum consists of the tensor veli palatini muscle which tenses and depresses the soft palate and opens the eustachian tube; the levator veli palatini muscle which elevates the palate; the uvulus muscle which pulls the uvula cranially and anteriorly; and the glossopalatine and the

palatopharyngeus muscles, which draw the palate inferiorly and constrict the pharynx (Hopper et al. 2007). Together, the primary and secondary palates give rise to the hard and soft palates. Failure of the hard and/or soft palate to fuse gives rise to cleft palate (Hopkins, 2019). Clefting involving the secondary palate disrupts the palatal sling secondary to abnormal insertions of the soft palate muscles into the posterior margin of the remaining bony palate rather than the midline raphe. As a result, the affected individual loses velopharyngeal competence, which may lead to potential speech distortion, such as nasal air emission and hypernasality (Fisher and Sommerlad, 2011). Eustachian tube control is often lost as well, manifesting as recurrent otitis (Matsune et al. 1991).

The cleft palate may present with varying degrees of severity and can include the soft palate, hard palate and alveolus. The terms used to describe a cleft palate are summarised in Table 4.

Table 4 Terms used to describe a cleft palate

Cleft palate clinical descriptor	Explanation/description
Overt palatal cleft	A visible opening in the roof of the mouth that can be observed on intraoral inspection
Submucous cleft palate	Submucous cleft palate is a more subtle form of cleft palate that may grossly appear to be structurally intact but there are both muscular and bony deficits. The defects include a bony notch in the hard palate, a bluish line at the midline of the soft plate (zona pellucida),a bifid uvula.

2.2.3.2 Terminology used to describe OFC characteristics

Orofacial clefts include all variations of cleft lip and cleft palate and several classification schemes have been suggested for typical and atypical orofacial clefts. The features used to initiate the classification of an orofacial cleft include the laterality, completeness, severity (wide vs narrow), and presence of any abnormal tissue. Diminutive orofacial clefts may also be described as microform, occult, or minor. These characteristics used to refer to more specific variations within the broader categories of cleft phenotypes may also be referred to as sub-phenotypes (Tolarová and Cervenka 1998; Rozendaal 2013). This is summarised in Table 5.

Table 5 Description of the different orofacial cleft features (Tolarová and Cervenka 1998; Kosowski et al. 2012; Hopkins 2019)**.**

OFC feature	Explanation/description
Type	• Type refers to whether the OFC is of the cleft lip only (CL), cleft lip with cleft palate (CLP) or cleft palate only (CPO).
Laterality: median; paramedian; unilateral (right or left); bilateral	• A median (midline) cleft is rare and refers to a defect in the median line of the face. • Most OFCs are paramedian (unilateral or bilateral). • A unilateral cleft lip is identified when there is a separation or notching of the lip on one side of the face with the contralateral side being normal. • A bilateral paramedian cleft lip occurs when there is a separation of the lip on each side of the face, although the degree of discontinuity may differ between sides.
Symmetry	• A bilateral cleft lip may feature the same degree of clefting on each side (and thus be symmetric bilateral cleft lip) or may differ from side-to-side (asymmetric bilateral cleft lip).
Severity (wide vs narrow)	• Although the relationship between initial width and aesthetic outcome remains controversial, wider clefts pose a greater technical challenge. Cleft severity, specifically in terms of width, is categorised for surgical repair purposes and takes into account the upper lip, nose, primary palate and secondary palate. For example, a severe form of unilateral cleft lip and palate based on the primary palate component is a cleft width greater than 10mm.
Completeness (complete; incomplete), with or without presence of abnormal tissue	• Complete and incomplete clefts may be associated with a cleft palate. A complete cleft extends through the vermillion to the nostril potentially causing the affected nostril to widen and flare. Clefts affecting the palate may involve the primary palate (alveolar ridge and premaxilla) and/or the secondary palate (hard and soft palate). Complete cleft of the palate involves the length of the primary and secondary palate whereas incomplete cleft palate involves only the secondary palate. • Clefts may be described as incomplete when the gap does not reach the nostril and may be subtle enough to consist of just a notch in the vermillion border. • Cleft lip with the presence of abnormal tissue: In some cases of cleft lip, there may be an abnormal web-like piece of tissue that extends from the cleft side of the lip to the non-cleft side at the nasal sill. This abnormal tissue, known as a Simonart band, is distinct from an incomplete cleft and is not considered the same.
Presence of other congenital anomalies: isolated vs non-isolated	• OFCs may be classified as isolated or non-isolated. • Isolated describes a patient who has only an orofacial cleft without any accompanying malformations. In the literature, it can also describe a specific type of cleft occurring alone. For instance, an isolated cleft palate features an intact lip and alveolar ridge. • Non-isolated describes the presence of an orofacial cleft alongside other congenital malformations, with no consistent pattern that would be defined as a specific sequence or a syndrome.
Syndromic vs non-syndromic	• OFCs may be divided into 2 main subtypes: non-syndromic and syndromic. • Syndromic: Individuals with a syndromic OFC present with patterns of malformations and/or symptomatology that form a recognisable syndrome of known or unknown origin; hence the cleft is part of a syndrome. Syndromes associated with OFC include chromosomal abnormalities such as trisomy 13 or 18 and Mendelian disorders like Van der Woude Syndrome. • Non-syndromic; multiple non-syndromic: The various subsets of OFCs include those that do not belong to a recognisable syndrome but occur alongside different malformations which may involve but are not limited to, the eye, ear, head, neck, respiratory tract, gastrointestinal tract and musculoskeletal system. Cases of “multiple non-syndromic” CL/P and CPO may be classified as such simply by unrecognised syndromes or undocumented teratogenic exposures.

2.2.3.3 Registration and Classification systems

The clinical presentation (cleft morphology) of orofacial clefts (OFCs) is highly variable, making cleft classification crucial for studying their epidemiology, as these conditions are aetiologically heterogeneous. Accurately describing cleft types is essential for untangling the interactions between environmental and genetic risk factors that contribute to OFCs.

Throughout the history of cleft care, numerous classification systems have been developed and implemented to more accurately classify clefts and overcome limitations of existing systems. For example, the Veau classification was created to simplify the overly complex and impractical Brophy classification but does not consider cleft lip/alveolus and the morphological severity of palatal clefts. A global survey by Houkes et al. (2021) on cleft classification use found the most used systems to be the International Statistical Classification of Diseases and Related Health Problems (ICD-10), (35.5%), LAHSHAL (34%), Veau (32.5%), Kernahan's striped-Y (22.8%), and ACPA classification (21.3%) (Houkes et al. 2023). A brief overview of these systems is provided below.

The International Statistical Classification of Diseases and Related Health Problems (ICD)

It is important to distinguish between the registration and classification of clefts. Although the ICD is referred to as a "classification", it is actually a registration process for coding and categorising diseases as opposed to being designed for the primary purpose of classification (Houkes et al. 2023a). The medical classification list by the World Health Organization enables standardised codes that improve communication among healthcare providers, ensuring consistency in patient records and treatment approaches (World Health Organization (WHO) 2024).

The revisions of the current registration system, ICD-11 (11th Revision), aim to provide more precise descriptions and categorisations to improve diagnosis, tracking and treatment coding. The major differences between ICD-10 and ICD-11 are that the user-friendly ICD-11 offers more distinct coding for anatomical descriptions in terms of laterality, type, combination (e.g., cleft lip with cleft palate), associated

conditions. These updates help clinicians and researchers to more accurately document different types of clefts and their complexities, ultimately leading to better health data and patient care(World Health Organization (WHO) 2016). In summary, the ICD classification for clefts is crucial for effective clinical management, data collection, research, and communication in healthcare settings, playing a vital role in improving outcomes for individuals with cleft conditions (World Health Organization (WHO) 2024).

The LAHSHAL system

The LAHSHAL system is the most widely adopted classification system in the UK and is currently used in the outcomes registry for the American Cleft Palate and Craniofacial Association (Burg et al. 2016). It is compatible with ICD-10, enabling clefts to be coded for computer use, particularly on the CRANE register (The South West Cleft Service 2020). This palindromic classification uses the acronym "LAHSHAL" to describe the bilateral anatomy of the lip (L), alveolus (A), hard (H) and soft (S) palates from right to left, with the first character representing the patient's right lip and the last representing the left lip. Completeness of cleft is used indicated by a capital letter for a complete cleft or a small letter for an incomplete cleft. For example, "LAHS" describes a complete right-sided unilateral cleft lip, alveolus, hard and soft palate (Kriens 1991). An asterisk (*) is used in place of a letter to indicate the presence of a microform cleft in that specific location. For example, a full LAHSHAL code might read "*AHS---" indicating a microform cleft of the right lip, a complete cleft of the right alveolus (A), hard palate (H) and soft palate (S), with no cleft on the left side.

Advantages of the LAHSHAL system include its user-friendliness, accuracy and reproducibility, allowing clinicians with minimal training to consistently document cleft type, completeness, laterality and subtle cleft presentations, while also facilitating data entry into electronic patient records (McBride et al., 2013; McBride et al., 2016).

However, while it enables detailed recording and is compatible with ICD coding, it may require supplementary codes for associated syndromic associations (example, Pierre Robin Sequence) if used in isolation but is considered a minor limitation. The

LAHSHAL system remains superior due to its clarity, objective structure, and compatibility with digital systems, supporting its continued use for cleft classification in clinical and research settings.

Victor Veau Classification (Veau, 1931)

Veau classified clefts into four groups with increasing severity of clefting and was useful in describing clefting of the palate. Class I represents an isolated soft palate cleft, class II is a hard/soft cleft palate, class III is a unilateral cleft lip and palate and class IV is a bilateral cleft of the lip and palate (Houkes et al. 2023b).

This classification**,** historically has been influential in structuring cleft documentation and surgical planning as it is simple and easy for clinical descriptions of palatal clefts (Veau and Borel, 1931). However, this classification has limited scope as it primarily describes palatal clefts and does not capture cleft lip or alveolar clefts, lacks detail on laterality and the completeness of clefts, and cannot record microform clefts or subtle subphenotypes (McBride et al., 2016). Additionally, it is not compatible with modern digital registry systems, limiting its utility for detailed documentation and research requiring precise phenotypic data. These disadvantages mean that while Veau remains historically significant and clinically practical for palatal clefts, it is less suitable for contemporary research and registry needs requiring detailed and standardised cleft subphenotyping.

Kernahan's striped Y classification

The Kernahan 'striped Y' classification, uses the symbolic letter Y, where the upper arms denote the primary palate and the base signifies the secondary palate, with the most anterior part representing the lip. Affected areas are shaded dark to visually illustrate the type and extent of the cleft.

The main advantage of the Kernahan classification is its visual design which enhances understanding of cleft extent and location, making it particularly useful for teaching and initial clinical discussions (Houkes et al., 2023a). However, it has significant limitations, the most obvious being that it cannot be used for verbal communication or description in the text format or for computer archiving. It lacks detail regarding other important aspects such as associated anomalies and the darkened segments can be subjective, potentially leading to misinterpretation between practitioners (Houkes et al. 2023a; Oxford Reference 2024). Additionally, it lacks detail regarding associated anomalies and does not record the completeness or laterality of clefts, while the shading of segments can be subjective, leading to potential misinterpretation and variability between practitioners (McBride et al., 2016). These limitations mean that while the Kernahan 'striped Y' is helpful for visualising cleft patterns, it is less suitable for detailed clinical documentation, registry use, or research requiring precise phenotypic data.

The American Cleft Palate Association (ACPA) classification

According to Singh et al (2015), the ACPA classification by Harkins et al. places emphasis on embryology, recognising the independent mechanisms of development anterior and posterior to the incisive foramen. The classification system with six groups, was inspired by the concepts of Kernahan and Stark, encompassing both rare and common clefts. Harkins et al. further divided these groups according to the extent and sides of the clefts but this made the classification complex and challenging for the average cleft surgeon to recall, attributing to its lack of popularity (Agrawal 2014; Singh et al. 2015).

The main advantage of the ACPA classification is its strong embryological foundation, enabling clinicians and researchers to consider the developmental

origins of clefts while categorising cases, and its inclusivity of a wide spectrum of cleft types, including less common presentations. However, its significant disadvantage is its complexity**,** as the further subdivision of groups according to the extent and sides of clefts makes it challenging for the average cleft surgeon to recall and use consistently in clinical practice (Singh et al., 2015). This complexity has limited its popularity and practical utility in day-to-day clinical documentation and registry systems, making it less suitable for settings requiring a user-friendly and easily reproducible classification system (McBride et al., 2016).

Summary and Recommendation

In summary, while each classification system for OFCs has advantages, these systems have notable limitations in providing comprehensive, practical and objective classification for cleft care and research. The LAHSHAL system addresses many of these limitations by providing a user-friendly, anatomically descriptive, and bilaterally coded approach that aligns with clinical needs and digital record requirements. Therefore, LAHSHAL is favoured in this thesis as the recommended classification system for its balance of clarity, clinician utility, and objectivity in documenting OFCs for both clinical and research purposes.

2.2.3.4 Aetiology

Understanding of the aetiology and pathogenesis of OFCs remains relatively poor. This is a reflection of the complexity and diversity of mechanisms involved at the molecular level during embryogenesis as well as the multifactorial nature of OFCs with both genetic and environmental influences (Cobourne, 2004; Murray, 2002).

2.2.3.4.1 ***Developmental pathogenesis***

Orofacial development is a highly co-ordinated, well-timed multi-step process. It involves signalling pathways, transcriptional events, cellular proliferation, cell migration, apoptosis, differentiation, cell and tissue fusion (Nasreddine et al. 2021). It is a complex process resulting in the development of the mouth, lips, palate and nose and takes place during the 4th and 12th week of intrauterine life.

Embryologically, orofacial development involves the growth and fusion of prominences/processes summarised and illustrated in the Table 6 and Figure 1 below.

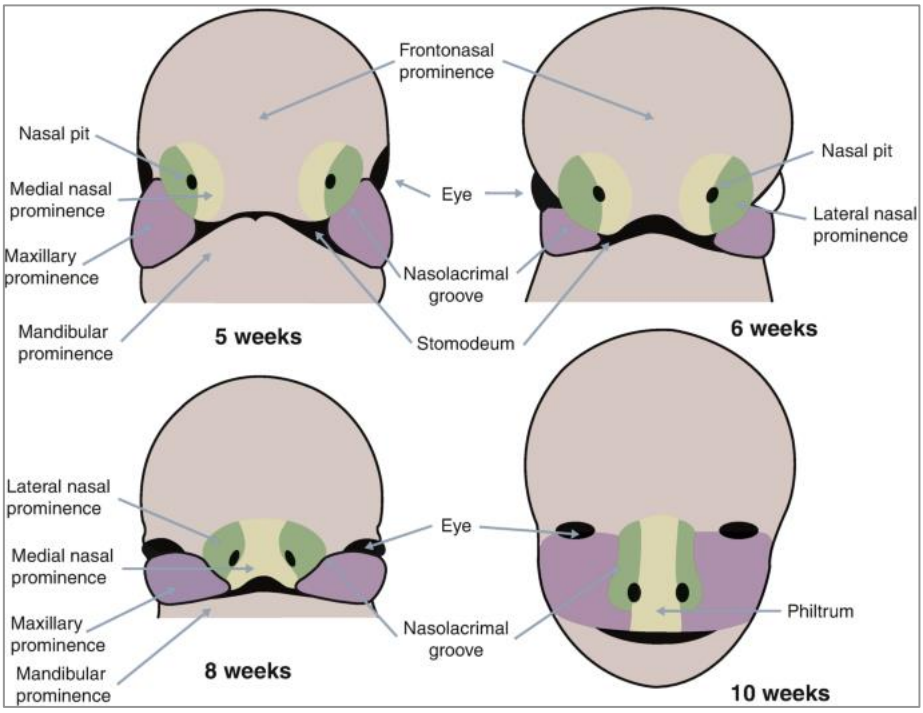

Figure 1 Illustration of facial development via growth and fusion of prominences (McLarnon 2023)

Table 6 A summary of the origin and contributions of the prominences to the adult face (Duke University Medical School 2016)

Embryonic structure	Embryonic origin	Orofacial structures formed
2 mandibular prominences (right and left)	1st pharyngeal arch neural crest mesenchyme	Lower portion of the face (mandible, lower lip)
2 maxillary prominences (right and left)	1st pharyngeal arch neural crest mesenchyme	Mandible, lip (lateral to the philtral column), orbital floor, inferior portion of the lateral nasal wall
1 frontonasal prominence (midline structure)	Cranial neural crest mesenchyme	Two nasal pits develop in the ventrolateral aspects of the frontonasal prominence, thereby forming 2 lateral and mesial nasal prominences
2 medial nasal prominences (midline structure)	Frontonasal prominence	Philtrum, medial upper lip, nasal tip, columella
2 lateral nasal prominences (right and left)	Frontonasal prominence	Lateral nasal ala and nasolacrimal groove

The face is derived from five prominences/processes: the frontonasal and two maxillary and mandibular prominences. During the 4th week of embryonic development, an area of thickened ectoderm on each side of the frontonasal prominence called the nasal placodes appear and are converted into two nasal pits by invagination. The nasal pits indent the frontonasal prominence and divide it into medial and lateral nasal prominences.

The term “clefting” describes a discontinuity between structures that otherwise would have joined to create a unified whole. At the embryological level, disruptions in the variety of mechanisms and events involved in orofacial development can result in clefting (Cobourne and DiBiase 2016; Dworan et al. 2023). Facial anomalies including orofacial clefts are the result of a multifactorial aetiology that causes disruption to the sequence of events in the development of embryonic facial prominences. The result is the development of cleft lip, cleft palate or both, and although cleft lip and palate often occur together, their embryologic origins are different.

Embryology of cleft lip

Normal lip development occurs between weeks 4-8 *in utero*. Following complex processes of cell differentiation, the upper lip and primary palate are formed by fusion of the maxillary and middle nasal processes. At the beginning, the maxillary prominences begin growing medially, fusing firstly with the lateral nasal prominences to form the lateral parts of the upper lip. During this time, the maxillary prominences also form the cheeks, while the lateral nasal prominences give rise to the alae of the nose. At around week 5, the maxillary prominences continue to grow medially and fuse with the medial nasal prominences on either side, bringing the nostrils closer. Fusion of the medial nasal prominences forms the intermaxillary segment which fuses with the maxillary prominences resulting in the formation of the philtrum, middle one-third of the upper lip, the primary palate, the central nose, the nasal septum during the 7th week. The heterogenous presentation of cleft lip is attribution to how fusion may fail: entirely or partially; unilaterally or bilaterally (Chadha and Beale 2023). For example, bilateral failure of the fusion between the maxillary and nasal prominences on both sides leads to a bilateral cleft lip, whereas failure on one side will result in a unilateral cleft lip (Babai and Irving 2023).

Embryology of cleft palate

In contrast to lip development, development of the palate occurs in two stages between the 5th and 12th week *in utero*. Consequently, cleft palate may occur in association with a cleft lip (CLP) or in isolation (CPO).

Cleft of both the lip and palate (CLP) can occur in the first stage of palate development. In this stage, the primary median palatal triangle is formed, derived from the merging of the two medial nasal processes originated from the median frontonasal process. This is completed by the 8th intrauterine week.

The second stage of palate development occurs during the 6th week *in utero*, when two lateral palatine processes or shelf-like outgrowths (palatal shelves) from the medial side of the maxillary processes form and lie vertically under the tongue. When the tongue starts to flatten and move inferiorly as a result of jaw development, the two palatal shelves elevate to a horizontal position and grow approaching each other above the tongue. The palatal shelves then fuse with each other and with the nasal septum and the hard palate. By the 12th week *in utero*, the hard palate is formed from the fusion of the bones extending from the maxilla and the palatine bone to the palatal shelves, while the posterior unossified part forms the soft palate and the uvula. Failure of elevation, contact or fusion of the palatal shelves results in cleft palate (Nasreddine et al. 2021; Babai and Irving 2023).Variation in the completeness of CPO occurs as a result of fusion of the secondary palate occurring in an anterior-to-posterior direction. Therefore, a complete CPO involves the entire secondary palate to the incisive foramen, whereas an incomplete CPO has varying degrees of intact hard and/or soft palate anterior to the cleft defect.

CPO may also occur with Pierre Robin Sequence (PRS). Previously named Pierre Robin Syndrome, PRS is now correctly named a sequence because one initial malformation leads to a sequential chain of events causing other anomalies. Around the 7th week *in utero,* the mandible typically grows ventrally and inferiorly. In PRS, mandibular growth is abnormal resulting in a small lower jaw (micrognathia/ mandibular hypoplasia) preventing the tongue from following the normal trajectory of resulting in downward displacement of the tongue (glossoptosis) that can fall back into throat causing upper airway obstruction. Understanding this is important as PRS

may initiate failure of the palatal shelves to elevate and fuse, resulting in a CPO that is often wide and 'U' shaped (Chadha and Beale 2023).

2.2.3.4.2 ***Genetic evidence***

The significant role that genes play in the development of normal craniofacial structures is evident from observations of monozygotic twins where the majority are phenotypically indistinguishable (Nasreddine et al. 2021).

2.2.3.4.2.1 Non-syndromic OFCs

Most OFC cases are non-syndromic. According to Murray (1995), non-syndromic orofacial clefting arises as a complex multifactorial trait being a myriad of Mendelian patterns exhibiting varying levels of penetrance, sex differences and environmental overlays, ultimately making gene identification difficult. Despite this, there is a variety of evidence to support underlying genetic factors as an influence in the risk of OFC development. Whole genome/exome analysis and genome-wide associated studies have identified genetic factors that contribute to the development of non-syndromic OFCs. Hereditary factors are estimated to be 90% effective in the development of non-syndromic OFCs (Grosen et al. 2010). Simultaneously, the genetic program is sensitive to post-conception disturbances such as exposure to teratogens (Schutte and Murray, 1999). An orofacial cleft population-based cohort study in Norway found that among first degree relatives, the relative risk of recurrence of cleft was 32 for any cleft lip and 56 for cleft palate only (Sivertsen et al, 2008).
Additionally, the risk of having a baby born with an OFC by an affected mothers and fathers was found to be similar (Sivertsen et al., 2008). However, the higher recurrence rates of cleft palate indicate a stronger genetic component associated with cleft palate than with cleft lip. Supporting this genetic aetiology, twin studies have also provided valuable insights (Mossey, 2011).

2.2.3.4.2.2 Syndromic OFCs (SCL/P)

As with all clinically recognisable syndromes, cases of syndromic CLP or CP can be broadly subdivided into those that occur as part of a characterised Mendelian disorder (resulting from a single gene defect), those arising from structural

abnormalities of the chromosomes, syndromes associated with known teratogens or those whose causation remains obscure and therefore currently uncharacterised (Cobourne 2004).

Over 500 Mendelian syndromes with OFCs are listed in the Online Mendelian Inheritance in Man (OMIM) database (Shkoukani et al., 2013). Van der Woude Syndrome was found to be the most common syndrome associated with OFCs, accounting or 2% of all OFC cases (Rizos, 2004). Cleft palate has been associated with 28-35% of individuals affected with Treacher Collins Syndrome (TCS) (Cobourne 2004). Although Holoprosencephaly (HPE) is relatively rare in live births with the majority of foetuses being miscarried, it is considered a significant congenital anomaly that is associated with cleft palate in foetuses that do go to term. Approximately 25% of the cases with the hereditary arthro-ophthalmopathy Stickler Syndrome, exhibit some form of midline clefting, including cleft palate (Snead and Yates, 1999; Cobourne 2004). A brief summary of the syndromes associated with OFCs is given in Table 7.

Table 7 Syndromes associated with OFCs (Cobourne 2004)

Syndrome	Typical clinical features	Description
Van der Woude Syndrome (VWS)	OFC, lower lip pits or fistula, dental anomalies	Autosomal dominant syndrome caused by a defect in IRF6 on chromosome 1
Treacher Collins Syndrome (TCS)	External and middle ear malformations, downsloping palpebral issues with colobomas of the lower eyelids, zygomatic and mandibular hypoplasia, cleft palate (clinical features are highly variable)	Autosomal dominant disorder caused by TCS gene (TCOF1) to human chromosome 5q32-q33.1.
Holoprosencephaly (HPE)	A developmental disorder that encompasses a spectrum of defects ranging from mild anomalies of midline patterning to a complete failure of forebrain division with associated cyclopia	Mutations in the gene encoding the Sonic hedgehog (SHH) signaling peptide have been associated with a HPE phenotype
Stickler syndrome	Disorder of collagen connective tissue associated with ocular, auditory, articular and craniofacial manifestations	Autosomal dominant disorder (Type 1 demonstrates linkage to the COL2A1 gene encoding type II collagen. Type 2 demonstrates mutations in the COLIIA1 that encodes type XI collagen).

2.2.3.4.2.3 Epigenetics

Epigenetics is described as the regulation of gene expression through reversible chemical modifications without affecting the DNA sequence (Kiefer, 2007;Uysal et al. 2023). Among the best-understood epigenetic modifications are histone modifications, which influence chromatin accessibility during transcription and DNA methylation. These processes play a critical role in regulating gene expression during palatal fusion (Garland et al., 2020; Beaty et al., 2011).

The expression of the several genes that are associated with NSCL/P is controlled by epigenetic modifications. Epigenetically controlled genes include transcription factors (*LHX8, PRDM16, PBX1, GSC, VAX1, MYC*), growth factors and their modulators (*WNT9B, BMP4, EPHB2, BICC1, DHRS2*), and microRNAs (miRNAs) including *MIR140* and *MIR300* (Alvizi et al. 2017; Gonseth et al. 2019; Howe et al. 2019; Xu et al. 2019; Zhao et al. 2019).

Maternal smoking is one example of an epigenetic factor linked to orofacial clefts. The risk of cleft lip and palate (CLP) significantly increases among children of mothers with the maternal glutathione S-transferase genotype who smoke (Van Rooij et al., 2001). Furthermore, Joubert et al. (2016) found that maternal smoking was associated with differential methylation of several genes related to OFCs, including MSX1, PDGFRA, GRHL3, ZIC2, and HOXA2. Additionally, Jugessur et al. (2009) reported that variants of the alcohol dehydrogenase gene ADH1C are associated with clefting.

Dietary folate also plays a role in epigenetic-mediated OFC. An epigenome-wide association study to investigate the correlation between epialleles and OFCs in the United States, led to the introduction of mandatory folate treatment in 1998 (Gonseth et al. 2019; Uysal et al 2023).

The significant role that genes play in the development of normal craniofacial structures is evident from observations of monozygotic twins where the majority are phenotypically indistinguishable (Nasreddine et al. 2021).

Whole genome and exome analyses, as well as genome-wide association studies, have identified genetic contributors to NSCL/P, estimating that hereditary factors account for about 90% of its development (Grosen et al., 2011). Simultaneously, the genetic program is sensitive to post-conception disturbances such as exposure to teratogens (Schutte and Murray, 1999). Contribution of epigenetic actors and gene-gene/environment interactions make the pathogenesis complex. As such it is not always possible to define the exact gene(s) involved.

2.2.3.4.2.4 Heritable Genetic Risk Factors

Heritable genetic risk factors contribute significantly to the aetiology of orofacial clefts (OFCs). These factors include a positive family history, consanguinity, and parental age, which influence the likelihood of OFCs through genetic predisposition, increased homozygosity, and the accumulation of de novo mutations associated with advanced parental age (Mossey et al., 2009; Dixon et al., 2011; Inchingolo et al., 2022).

a) Family history

As previously mentioned, a positive family history of OFCs is a recognised risk factor for OFCs (Khoury et al., 2007). Badr et al's (2020) retrospective study identifying 73 mothers with a positive family history of OFCs found the incidence of having a baby with an OFC as 9.3% (86-fold increase). This study acknowledged that incidence varied depending on many factors, including type of oral clefts in the family, the degree of relation of the foetus or baby to the family member who has the cleft and the number of siblings with OFCs.

b) Consanguinity

Consanguinity, defined as marriage between individuals who are closely related, has been strongly associated with an increased risk of orofacial clefts (OFCs). This association is attributed to the increased homozygosity of deleterious recessive alleles within families, which raises the likelihood of genetic anomalies contributing to

OFC development (Inchingolo et al., 2022). The risk is particularly notable in regions where consanguineous marriages are culturally prevalent, including parts of the Middle East, South Asia, and North Africa, where studies have shown a higher incidence of OFCs in offspring from consanguineous unions compared to non-consanguineous unions (Cheshmi et al., 2019; Silva et al., 2020). A definitive reference in this field is the systematic review and meta-analysis by Sabbagh et al. (2014), which analysed 16 studies involving 1.7 million births and demonstrated that parental consanguinity nearly doubles the risk of non-syndromic OFCs, with an overall odds ratio of 1.83 (95% CI: 1.31–2.54). While consanguineous marriage itself is a modifiable social practice, its role in OFC aetiology is mediated through genetic mechanisms, and therefore it is appropriately considered under heritable genetic risk factors (Mossey et al., 2009; Dixon et al., 2011; Inchingolo et al., 2022). Recognising consanguinity as a risk factor underscores the importance of genetic counselling and community education initiatives in high-prevalence regions to mitigate this risk.

c) Parental age

Higher parental (maternal and paternal) age has been associated with various birth defects, making it a significant focus for many researchers. The global investigation into the relationship between parental age and the risk of orofacial clefts (OFC) spans both high-income and lower-middle-income countries. In high-income nations, it is increasingly common for adults to delay parenthood (Mills et al., 2011). Advanced maternal age is particularly associated with chromosomal abnormalities (Ellegren, 2007; Martelli et al., 2010). Shaw et al. (1991) found that women over 39 years have double the risk of having a child with cleft lip and palate (CLP) compared to those aged 25 to 29. Conversely, Savitz et al. (1991) identified a connection between cleft palate (CPO) and younger mothers. Bille et al. (2005) highlight the need to consider paternal age when evaluating maternal age effects. Paternal age plays a critical role, as older fathers tend to have more mutations in sperm DNA, increasing the risk of various genetic syndromes (Ellegren, 2007). A 2022 systematic review on orofacial clefts in lower-middle-income countries identified paternal age over 35 as a significant risk factor (Kruppa et al., 2022; Omo-Aghoja et al., 2010; Mbuyi-Musanzayi et al., 2018; Gendel et al., 2019).

2.2.3.4.3 ***Environmental factors***

Numerous studies and systematic reviews have explored the relationship between environmental factors and orofacial clefts (OFCs). This section highlights the existing evidence for these associations, organised in a maternal history-taking format: demographics, maternal medical and drug history, maternal nutrition, maternal social history.

Many studies suggest that maternal risk factors play a significant role in the development of orofacial clefts (OFCs). Recent reviews have identified maternal smoking, passive smoking, alcohol, and multivitamin with folate supplementation as the environmental exposures best supported by evidence (Garland et al. 2020a; Garland et al. 2020b; Ji et al. 2020; Reynolds et al. 2020). Other maternal factors such as socio-economic status and education level have been suggested as OFC risk factors, although Mossey (2007) notes that such factors are broad environmental measures that are difficult to separate from combined effects of other factors such as maternal nutrition and health (Mossey 2007). Conflicting results in these other maternal factors might reflect complexity of the aetiology of OFCs and the difficulty in designing studies to capture environment-specific effects. Confounding factors such as co-exposures, genetic susceptibility, and socio-economic conditions may obscure true associations**,** making it challenging to isolate the independent effects of specific environmental risk factors. Additionally, much of the evidence regarding maternal environmental exposures relies on retrospective case-control studies, which are inherently limited by maternal recall bias and the potential for inaccurate reporting of exposures during pregnancy (Acosta et al., 2019; Sabbagh et al., 2023). These limitations highlight the need for well-designed prospective studies to better understand the role of environmental factors in OFC aetiology.

2.2.3.4.3.1.1 ***Maternal demographics***

Maternal BMI as an Environmental Risk Factor

Pre-pregnancy maternal weight is classified by level of body mass index (BMI; kg/m^2) and is classified as an environmental risk factor for orofacial clefts (OFCs), as it reflects

modifiable nutritional and metabolic conditions influencing embryonic development. The largest study of BMI in OFCs incorporated six large case-control studies from Northern Europe and the USA for analyses pooling the individual-level data. Cases included 4943 mothers of children with OFCs, and 10,592 controls (mothers of unaffected children). CLP and CPO were found to be associated with maternal pre-pregnancy obesity (BMI ≥ 35) compared with normal weight and marginally associated with maternal underweight. However, CL was not associated with BMI, suggesting that extremes of weight may have a specific effect on palatal development (Kutbi et al 2017). Maternal obesity may increase OFC risk through mechanisms including hyperglycaemia, systemic inflammation, and oxidative stress, while undernutrition may reflect deficiencies in essential micronutrients important for craniofacial development, reinforcing the categorisation of BMI as an environmental and modifiable risk factor for OFCs (Inchingolo et al., 2022; Mossey et al., 2009).

2.2.3.4.3.1.2 Maternal medical and drug history

a) Obstructive lung diseases and bronchodilators

A significant association between maternal bronchodilator use during the periconceptual period for control of symptoms of obstructive lung diseases (such as asthma and chronic obstructive lung disease (COPD) and the risk of cleft lip only was found after controlling for other risk factors. However, the authors acknowledge that they were uncertain whether the increased odds ratio observed was due to bronchodilators, the severity of the condition, or both, or were not related to each other (Munsie et al., 2011).

b) Anticonvulsant drugs

The role of anticonvulsant drugs in contributing to isolated oral clefts is well established. The use of anti-seizure medications during pregnancy, including lamotrigine, phenobarbital, phenytoin, sodium valproate, and benzodiazepines like diazepam, has been associated with a higher risk of oral clefts in offspring. While it is recognised that anticonvulsants can increase this risk, ongoing research is needed to fully understand the mechanisms involved. The data regarding the association between diazepam and orofacial clefts is inconsistent. In their review, Marinucci et al. analyse data from international studies on the combined genetic and environmental causes of cleft lip with or without cleft palate, highlighting both successes and challenges in identifying these underlying factors. They emphasise the need for further studies to clarify the effects of diazepam during gestation on the development of orofacial clefts (Marinucci et al., 2011). Similarly, the association between another anticonvulsant, lamotrigine, and oral clefts has been explored in research by Holmes et al., who observed an increased incidence of isolated cleft palate in infants exposed to lamotrigine during pregnancy. This suggests that infants exposed to this medication during the first trimester face a higher risk of developing isolated cleft palate or cleft lip deformities (Holmes et al., 2008).

c) Corticosteroid use

Corticosteroids are used to treat many diseases during pregnancy, such as inflammatory diseases but the association between their use and the risk of orofacial clefts in infants remains unclear. Carmichael et al's (2007) study investigating whether maternal corticosteroid use during pregnancy is associated with delivering an infant with an orofacial cleft, suggests a moderately increased risk of cleft lip/palate among women who use corticosteroids during early pregnancy stages (Carmichael et al. 2007). However, Park-Wyllie et al suggest that prednisone does not represent a major teratogenic risk in humans at therapeutic doses (Park-Wyllie et al. 2007). Hviid et al. (2011) found no increased risk of orofacial clefts linked to corticosteroid use, suggesting any observed associations may arise from multiple statistical comparisons. In a study by Park-Wyllie et al., which followed 184 women exposed to prednisone and 188 controls, no significant differences in major anomalies were noted, although there was a marginally increased risk of malformations after first-trimester exposure (Park-Wyllie et al. 2000). A summary of case-control studies indicated a significant odds ratio for oral clefts (3.35 [95% CI 1.97, 5.69]). Despite this, a prevalence study of 83,043 women in northern Denmark (1999–2009) found no association between early corticosteroid use and congenital malformations (Bjorn et al., 2014).

d) Antibiotic use

According to the study by Møgaard-Nielsen et al. (2012), which investigated the association between antibiotic use in early pregnancy and the risk of isolated orofacial clefts in a Danish nationwide cohort, antibiotic use during this period is not considered a major risk factor for isolated orofacial clefts. In contrast, the results of a study by Lin et al. suggest that maternal use of amoxicillin in early pregnancy may be associated with an increased risk of cleft lip, with or without cleft palate, particularly when used during the third month of gestation (Lin et al., 2012; Kawalac et al., 2015).

e) Antiemetic use

Nausea and vomiting affects about 70% of all women during their pregnancy, usually beginning in the first trimester at around 4-6 weeks, peaking between 8-12 weeks and ending by the 16th week of pregnancy. If severe and not improved after trying

lifestyle changes, anti-sickness medicine called an antiemetic, may be prescribed to use in pregnancy. This is often a type of antihistamine, usually used to treat allergies that is also effective as an antiemetic. In cases where a more severe form of pregnancy sickness called Hyperemesis Gravidarium occurs, there is the risk that the mother may become dehydrated and malnourished (NHS, 2024). The association may be explained by insufficient intake of some nutrients as a consequence of excessive vomiting (Zhu et al. 2023).

Ondansetron, a 5-HT3 receptor antagonist, although an excellent and effective antiemetic drug, it is authorised for management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and for the prevention and treatment of nausea and vomiting after surgery. Ondansetron may also be used as second line treatment of Hyperemesis Gravidarum. Although there is a growing body of evidence that does not suggest an increase in the risk of overall congenital malformations when used in pregnancy,

Epidemiological studies have identified a small increased risk of OFCs in babies born to women who used oral Ondansetron during the first trimester of pregnancy. Healthcare professionals are therefore advised that patients should be counselled on the risk and a final decision made jointly if there is a clinical need for Ondansetron use in pregnancy (British National Formulary, 2020;).

f) Viral infections (HSV, HIV and AIDS)

Viral infections such as HSV are very common and have a great influence in any hereditary disease occurrence. However, infections of HIV and AIDS in which pregnant women require antiretroviral prophylaxis, additional drugs are available to prevent vertical HIV transmission to the offspring from infected mothers. Association between antiretroviral prophylaxis and risk of oral clefts was investigated but no evidence was found to support an increased risk of cleft lip or palate among infants exposed to antiretroviral drugs during pregnancy (Carstos et al. 2012; Albano and Tilson; 2013).

g) Antineoplastic drugs

Kawalec et al (2015) acknowledges that although there is evidence regarding the association of antineoplastic drug use during pregnancy and the increased risk of

oral clefts and congenital malformations in offspring, the subject requires additional research.

2.2.3.4.3.1.3 Maternal Nutrition

a) Use of multivitamin containing folate during pregnancy

Among the environmental variables that decide the fate of the developing embryo, maternal nutrition is considered the most important (Graham 2000; Alade et al. 2022). In particular, micronutrients such as vitamins and minerals play a role in the cartilaginous and osseous growth of the craniofacial skeleton (Martiniakova et al. 2022).

Considerable circumstantial evidence exists relating maternal nutritional factors such as folic acid and vitamin B6 (pyridoxine) to the occurrence of OFCs but less evidence exists suggesting roles of vitamin B2 (riboflavin), vitamin A and Zinc. Supplementation with a multivitamin containing folate (MVF) during the periconceptual period is therefore implicated as reducing risk of OFCs (Wehby et al 2013; Wehby and Murray 2010).

Some retrospective case-control studies involving self-reported pre-conceptual MVF use, show consistent protective effects against OFCs (Gildestad et al., 2015; Murray and Wehby 2010). MVF use is also supported by studies on serum measurements that link increased OFC risk to mothers with deficiencies of vitamin B6, folic acid and vitamin B12. At least 0.4mg of folate once per day beginning at least one month prior to conception and continuing through the first trimester is recommended to reduce the risk of neural tube defects and OFCs.

A 2018 meta-analysis for supplementation with folate alone found a significant association with CL/P but no significant association for CPO. Notably, this same study indicated that MV intake (not specifically folate) was associated with a significantly decreased risk for CL/P and CPO (Jahanbin et al., 2018). A similar finding was seen in a meta-analysis conducted on the effect of folic acid fortification and the prevalence of OFCs, where a significant effect was seen only with the CL/P phenotype (Millacura et al. 2017).

These results were similar to those from a previous meta-analysis (Johnson & Little, 2008) as well as a more recent systematic review of 64 MVF studies (Zhou et al., 2020), indicating a synergistic effect of folic acid in combination with other vitamins as the more effective prevention of OFCs. MV supplementation in recommended dosages (0.4–0.8 mg) reduces the risk of having a baby with OFC by 30–35% in women of reproductive age (Marazita 2022).

There are many potential pathways in which Vitamin B6 protects against OFCs. It is the coenzyme in the degradation of homocysteine and it is vital in amino acid metabolism. This vitamin's role in cleft prevention is shown in animal studies where deficiencies in vitamin B6 alone have resulted in cleft palate and other birth defects in mice (WHO, 2002a). However, its role in human oral clefts has been uncertain. Munger et al's case-control study examined the association between maternal vitamin B6 and folate status and risk of CL/P. They concluded that poor maternal vitamin B6 status was consistently associated with an increased risk of CL/P in their Phillipine population (Munger et al, 2004).

Vitamin A plays a crucial role during embryogenesis, most importantly in the modulation of the upper lip and palate morphogenesis (Finnell et al., 2004). Although the teratogenic effect of excess or deficient vitamin A and its link to an increased risk of OFCs has been reported in animal studies, the threshold at which vitamin A becomes teratogenic in humans remains controversial (Finnell et al.,2004; Bastos Maia et al., 2019). This is because although the recommended daily dose during pregnancy is 800 µg/day (WHO, 2004), mean serum vitamin A levels remain within the physiologic range even at a dosage of 9,000 µg/day. Furthermore, foetal vitamin A levels do not increase significantly following maternal supplementation (Miller, Hendrickx, Mills, Hummler, & Wiegand,1998). Very few human studies have evaluated the specific effect of vitamin A and have concluded the protective effect of vitamin A on the risk of OFCs to be largely non-significant (Johansen et al.,2008; Mitchell et al.,2003; Werler et al., 1990). Only one study reported a statistically significant protective effect of vitamin A on CPO (Johansen et al.,2008). Further, studies have shown that vitamin A deficiency during pregnancy is likely to have different phenotypic effects depending on the stage of foetal development (Bastos Maia et al., 2019). Alade et al's meta-analysis acknowledged this and evaluated the

association between vitamin A use during the periconceptional period and the risk of giving birth to a child with OFCs among pregnant women (Alade et al. 2022). Like previous studies, their results showed a non-significant protective effect of vitamin A on the risk of giving birth to a child with OFCs among pregnant women but closer analysis of the phenotypes found a significant protective effect of vitamin A on the risk of CL/P and a nonsignificant effect on the risk of CPO. This is similar to the findings for folic acid supplementation (Millacura et al., 2017).

b) Zinc deficiency

Among the other micronutrients that pregnant women need besides folic acid, Zinc is one of the most important. It plays a significant role in foetal morphogenesis and differentiation as it is needed during protein synthesis, DNA synthesis, and cell division (Mahanani et al. 2022). Zinc's potential role in the aetiology of cleft was acknowledged in the WHO's 2002 document but studies were extremely limited and involved only few cases of orofacial clefts where no meaningful statistical analysis was possible (Soltan and Jenkins 1982; Stoll et al. 1999). Hozyasz et al (2005) suggested the role of low levels of zinc and elevated levels of copper in the aetiology of orofacial clefts. Their 2009 case-control study found the association of low zinc levels with copper levels only in the group of mothers of children with CL/P and that mothers with a low zinc whole blood concentration of 47.1micromol/L or less had a 2.5 times higher risk of having a child with an orofacial cleft than those with a higher concentration (Hozyasz et al. 2009). A 2022 review of the literature concluded that a definitive correlation between zinc deficiency and CL/P could not be made due to conflicting evidence (four articles reported a positive correlation while five articles reported no correlation), varied samples, methods and most articles having a moderate risk of bias (Mahanani et al. 2022).

2.2.3.4.3.1.4 Maternal social history

Social history is important in documenting lifestyle factors that may put a female at greater risk for giving birth to a baby with an OFC. Information pertinent to this section includes smoking history, alcohol use/consumption, occupation and stress levels.

a) Smoking history

Maternal smoking is considered a modifiable causal environmental factor for orofacial clefts (United States Department of Health and Human Services, 2014). Most studies today agree that maternal smoking whether active or passive (also referred to as second hand smoke) during the first trimester of pregnancy is associated with an increased risk of OFC (Marazita 2022).

The WHO referred to the association between OFC and maternal tobacco use as modest, acknowledging that many women, especially among technologically developing countries are exposed to passive smoking (World Health Organization 2002).

Fell et al's (2022) systematic review and meta-analysis acknowledged that other risk factors such as mother's age, obesity and alcohol intake during pregnancy are all strongly associated with smoking behaviour and failure of studies to adjust for such confounding factors place them at high risk of bias (Fell et al 2022). From the few studies deemed to be of good quality, Fell et al (2022) found a moderate association between maternal smoking and OFC with a population attributable fraction (PAF) of 4%. This suggests that should maternal smoking be eliminated, 4% of CL/P would not occur (Raut et al 2019). Similarly, according to the American College of OB/GYN's 2020 report, an estimated 6.1% of OFCs could be avoided by eliminating maternal smoking (ACOG Committee, 2020). Additionally, maternal smoking has been reported to have the largest adjusted PAF for CL/P (50%) and CPO (43%) when modifiable risk factors (such as maternal age, alcohol consumption, folic acid supplementation, obesity, maternal education, diabetes, fever) and nonmodifiable risk factors (such as sex and race) are considered.

Risk estimates from one of the largest studies published so far (Chung, Kowalski, Kim, & Buchman, 2000) in addition to three meta-analyses (Wyszynski, Duffy, & Beaty, 1997; Little et al., 2004; Xuan et al., 2016) showed that smoking increases the odds of clefting by a factor in the range of 1.29–1.37 for CL/P and by 1.22–1.32 for CP (Marazita 2022).

Meta-analyses indicated that maternal passive smoking exposure results in a 1.5-fold increase in risk of non-syndromic oral clefts (Sabbagh et al., 2015).

Several case-control studies where mothers were interviewed regarding their smoking history have determined smoking intensity specific effects. The smoking categories are none, 1–10, 11–20 and >20 cigarettes a day, or some slight modification of these dosage schemes. Chung et al's study did not distinguish between CL/P and CP but reported the odds for clefting estimated to increase by a factor of 1.50, 1.55 and 1.78 with smoking 1–10, 11–20, and 21 or more cigarettes per day, respectively, compared to no smoking (Chung et al 2000). This suggests that the highest dose of smoking (>20 cigarettes per day) has the strongest positive effect on OFC risk and may represent a threshold effect of more than 20 cigarettes needing to be smoked a day before a difference is noted in OFC aetiology. However, Fell et al (2022) concluded there to be insufficient evidence to support a dose-response effect of smoking due to recall/reporting bias from the dose of cigarettes per day being self-reported.

Although there is insufficient evidence to support a dose-response effect of smoking, this evidence is sufficient to support a causal relationship (Fell et al. 2022).

Mechanism of action:
Cigarette smoke comprises more than 4000 different compounds that can cause harm (Martelli et al. 2015). Although the exact mechanism is unknown, it is biologically plausible that maternal smoking could lead to CL/P as it is a common exposure and has been established as a risk factor for preterm birth, low birth weight and birth anomalies (Kureger and Rohrich, 2001; Hackshaw et al. 2011).
Hypoxia, smoking and CL/P have all been linked. There may be a direct interaction of the smoking products with neonatal tissue, causing nicotine-mediated

vasoconstriction and impairing angiogenesis leading to hypoxia which has been shown to disrupt palatal fusion in animal models (Vieira and Dattilo 2018).
Another theory is that smoking affects DNA methylation in the foetus, which could impact upon gene expression responsible for lip and palate formation (Lebby et al. 2010).

b) Alcohol use

As early as 1978, maternal consumption of alcohol during pregnancy was suggested as a potential environmental risk factor for oral clefts (Clarren and Smith 1989). Alcohol intake during pregnancy is a known teratogen (Carreras-Torres et al 2018; Taylor et al 2018) and cleft palate has been described as an associated defect in 10% of severe case of foetal alcohol syndrome (FAS) (Lemoine 1992; World Health Organization 2002). FAS represents the severe end of the foetal alcohol spectrum disorders and is characterised by distinctive craniofacial anomalies, including midfacial hypoplasia and in severe cases, cleft palate, linking prenatal alcohol exposure with cleft related phenotypes (Popova et al., 2017; Vorgias et al., 2023). However, evidence for maternal alcohol consumption as a risk factor for OFCs has been less consistent than the evidence for smoking. Two recent studies including a meta-analysis of 9 studies from 1950 to 2019 (Yin et al 2019) and a large-scale Japanese national birth cohort study including 73,595 mothers (Kurita et al., 2020) failed to find teratogenic associations between retrospective reports of periconceptional alcohol consumption and congenital malformations such as orofacial clefts (Kurita et al., 2020; Yin et al., 2019). Although recent meta-analysis reports no significant difference between drinking and non-drinking mothers in the risk of having a child with anon-syndromic orofacial cleft and no confirmatory evidence for the presence of a dose-response relation, Yin et al (2019) acknowledge that individually, some eligible studies suggested a positive correlation between binge drinking and occurrence of non-syndromic oral cleft. Yin et al (2019) conclude that although no concrete correlation between mild alcohol consumption during pregnancy and the occurrence of non-syndromic oral cleft was found, binge drinking during the first trimester should be avoided. The highest alcohol consumption category, referred to as binge drinking is usually defined as more than four drinks on any one occasion. Although, alcohol consumption studies reporting significant positive associations between the highest

alcohol consumption category exist (Munger et al., 1996; Romitti et al., 2007; Shaw & Lammer, 1999; Werler, Lammer, Rosenberg, & Mitchell, 1991), the WHO (2002) and Yin et al (2019) acknowledge that maternal alcohol consumption is retrospectively self-reported and precise alcohol consumption is difficult to evaluate as alcohol concentration varies widely among beverages. The WHO's report concluded that although maternal alcohol has been associated with risk of OFC, more consistent methods are needed for assessment of maternal alcohol intake that acknowledge the type and context of alcohol consumption (World Health Organization 2002).

c) Occupation

Associations have been suggested between an increased risk of orofacial clefts and maternal occupations such as hairdressing, health workers, the repair-services industry, industrial trade, agriculture and paternal occupations in the printing industry, as a painter, motor vehicle operator, fireman or farmer. It is important to note the study period as early studies that made these associations are not represented in subsequent studies (World Health Organization 2002). It should be noted that many of these studies involve limited number of subjects and authors acknowledge that determining multiple exposure via self-reported questionnaires requires associations to be interpreted cautiously (Chevrier et al. 2006). Furthermore, measures and regulations may have since been put in place to protect against potential adverse effects of exposure. For example, maternal occupational exposure to chlorinated solvents trichloroethylene and tetrachloroethylene during pregnancy have been suggested by case-control studies to play a role in the aetiology of orofacial clefts. They are known teratogens that are banned in the European Union and some parts of the United States except for authorised industrial use in some industries for removing grease from metal parts and as an ingredient in adhesives and paint remover but with safety controls to limit workplace exposures (CDC 2019; Wexler 2023).

d) Stress

During times of stress, the body releases cortisol. The effect of cortisol administration has shown to cause orofacial clefts in animal models and this association has also been studied in human models and blood cortisol levels. Two recently published meta-analyses assessed whether women who experience stressful life events such as death of a close relative during periconceptional period are at a higher risk of giving birth to a baby with an orofacial cleft (Tran et al. 2022; Talal AlSharif et al. 2023). Tran et al (2022) concluded only a weak positive association based on four case-control studies whereas Talal AlSharif et al's (2023) meta-analysis included 12 studies that when adjustments were made for potential confounders, found a statistically significant association with an increased risk for orofacial clefts for both CL/P and CPO. However, stress was not an objective assessment as a history of mood disorders in early pregnancy was used and questionnaires to assess stressful life events presented to mothers. A theory suggested to explain the mechanism of teratogenic effects on craniofacial development is that the mother's body redirects blood to vital organs and muscles during the fight and flight response, resulting in the placenta being temporarily hypoprofused leading to foetal damage (Wallace et al., 2011).

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2.2.3.4.4 ***Risk factors: Modifiable vs non-modifiable***

Inchingolo et al. (2022) discusses the multifactorial aetiology of orofacial clefts and categorisation of risk factors into non-modifiable and modifiable, consistent with wider literature (Mossey et al., 2009; Dixon et al., 2011; Sabbagh et al., 2023).

Non-modifiable risk factors are inherent and unchangeable. They include genetic polymorphisms, positive family history, ethnicity, and gender of the newborn**.** Genetic factors, particularly variations in genes involved in folate metabolism, alongside a family history of OFCs, significantly increase the likelihood of occurrence. Additionally, OFCs are more common in certain ethnic groups, including Asian and Indigenous populations, and tend to vary by sex, with cleft lip with or without palate (CL/P) being more frequent in males and cleft palate (CP) alone more common in females (Inchingolo et al., 2022).

Modifiable risk factors are those that can be influenced through lifestyle changes, medical interventions and public health measures to reduce OFC risk. They include those that can be addressed before conception, such as consanguinity, advanced or very young parental age,

low socioeconomic status, and poor nutritional status**.** There are also risk factors that are modifiable during pregnancy such as maternal smoking, alcohol use, certain medications, infections, obesity, and exposure to pollutants (Inchingolo et al., 2022)**.** Addressing these modifiable factors through preconception counselling, antenatal care, and health education offers important opportunities for reducing the incidence of OFCs, particularly in genetically susceptible populations.

2.2.3.4.5 Summary of understanding the aetiology of OFCs

To summarise, as evidenced in the literature, the aetiology of OFCs are multifactorial. It is understood that intrauterine environmental factors will influence foetal development in combination with the individual genetic background of the embryo and the aetiology therefore cannot be treated in isolation (Cobourne, 2004; Prescott et al., 2001). Among environmental factors, maternal smoking and exposure to environmental pollutants have shown a consistently strong association with increased OFC risk globally and represent key targets for prevention (Little et al., 2004; Sabbagh et al., 2023). In contrast, the role of folic acid supplementation in preventing OFCs appears to be modest, with limited and inconsistent evidence of a protective effect, particularly for cleft lip with or without palate (Wehby and Murray, 2010; Millacura et al., 2017). Understanding these multifactorial influences is essential for informing effective prevention strategies and counselling in clinical practice.

2.2.3.5 Management of orofacial clefts

OFCs can have a profound impact on a person's quality of life, which can lead to problems with feeding, speech, hearing, dentition (e.g tooth decay), neurodevelopmental disorders, psychological aspects and socialisation (Gomes et al., 2009; Wehby and Cassell, 2010; Smallridge et al., 2015; Waylen et al., 2015; Tillman et al., 2018). The physiological severity of these problems is not correlated with the severity and location of the cleft (Houkes et al. 2021).

2.2.3.5.1 Management of complications

Children with OFCs face a wide variety of medical issues and medical complications. These extend beyond the surgical correction of the congenital defect (Robin et al. 2006). The need for MDT reflects the wide-ranging impact of OFCs on feeding, growth, communication, the dentition, educational attainment and psychological integration, all requiring co-ordinated specialist management.

a) Airway and breathing

A subset of babies diagnosed with cleft will have airway-related issues. Co-existing choanal atresia, trachea-oesophageal fistulae and laryngomalacia all require input from a paediatric airway ENT specialist. Babies born with PRS, are particularly at risk of airway compromise and/or breathing difficulties especially during sleep because of mandibular retrognathia and associated glossoptosis. Risk is pronounced at birth and around 6 weeks postnatally where growth of disproportioned facial features can prompt decompensation of the airway. The airway issues often resolve as the mandibular growth 'catches up' during infancy and early childhood. In extreme cases, specialist input may be required to formally secure the airway but in the majority of cases positional manoeuvres (side lying) with the addition of a nasopharyngeal airway (NPA) on a short-to-medium term basis (if positioning alone is insufficient to support the airway) is adequate (Hartzell and Kilpatrick, 2014; Chadha and Beale, 2023).

b) Feeding problems

Feeding difficulties in babies with OFCs differ according to the location of the cleft pathology. Babies born with an isolated CL can often breastfeed or bottle feed as normal unless it is a more complete cleft that prevents the baby getting an adequate seal for an effective suck. Babies born with a CP can rarely generate sufficient intraoral pressure to suckle from either bottle or breast and their feeding difficulties broadly relate to (1) insufficient suckling (2) escape of food into the nose. There are two approaches to assist feeding: (1) reducing the need to suck (2) blocking off the nasal cavity from the oral cavity. Specialised feeding bottles are widely used within the UK but the use of orthodontic (orthopaedic) maxillary plates to close off the nasal cavity from the oral cavity is not common practice. Babies with increased work of breathing, such as those with PRS or those with additional difficulties may need a nasogastric tube (NGT). A small subset of children who have other feeding difficulties in addition to the cleft may be considered for more permanent enteral methods of feeding. Typically, there is no difference in the timeline for weaning a baby with a cleft. Food may pass into the baby's nose through a CP and cause sneezing but babies invariably learn to cope with this (Mitchell and Wood, 2000).

c) Speech difficulties

Children with OFCs are at risk for communication disorders due to the dysfunction of the levator veli palatini muscle phonation are affected. Retardation of consonant sound (p, b, t, d, k, g) is most common finding. Abnormal nasal resonance and difficulty in articulation are another characteristic feature in most individuals with cleft lip and palate (Timmons et al. 2001; Vyas et al. 2020; Mitchell and Wood, 2000). Management involves early assessment to determine oral and pharyngeal function and regular speech therapy.

d) Ear infections

Congenital conditions affecting the outer, middle, and inner ear structures are frequently observed, particularly in individuals with cleft palate, who are at an

increased risk for middle ear disease. This otological pathology can lead to hearing loss, which may be permanent or intermittent and can vary in severity from mild to profound. Such hearing impairments can significantly impact speech and language development, academic performance, and psychological and social well-being. The improper function of the tensor veli palatini muscle, responsible for opening the Eustachian tube, often contributes to the frequent occurrence of otitis media. Recurrent infections can result in hearing loss, further complicating the challenges faced by these individuals. Therefore, routine audiology surveillance is essential for those with craniofacial differences to monitor and address potential hearing issues effectively (ACPA, 2018; Mitchell and Wood, 2000; Sharma and Nanda, 2009; Vyas et al., 2020).

e) Dental problems

Children with CLP are known to have a variety of dental anomalies including missing or extra teeth, impacted teeth, misshapen teeth and a greater predisposition to dental caries. Preventative dental care and maintaining good oral health is particularly important in children with CLP to avoid the additional burden of preventable dental disease. It is also not uncommon for teeth to require extraction either because they are grossly carious, obstructing access (for other teeth to erupt or surgical procedures) or because they are supernumerary (extra) and serve little function. There is also lack of bone in cleft region compromising the prognosis and disrupting the eruption of the permanent teeth adjacent to the cleft, particularly the adult canine tooth, and challenges orthodontic dental alignment, jaw surgery and the replacement of missing teeth (Chadha and Beale, 2023).

f) Psychological considerations

As children become more self-aware of their facial differences, psychology input helps them to deal with questions from peers and strangers. Bullying is a common occurrence that can lead to a significant deterioration in self-concept and psychosocial integration and can manifest as behavioural pathology and mental

health problems. Psychological support also provides an aid to decision-making and managing expectations around treatments, particularly those pertaining to orthognathic surgery where the commitment to treatment and risks of surgery are significant (Chadha and Beale, 2023).

In summary, patients with orofacial clefts may face various complications, necessitating a multidisciplinary team approach to management. The treatment plan should be tailored to the individual needs of each child and may vary depending on the severity of the cleft and any associated conditions.

2.2.3.5.2 Terminology used to describe multidisciplinary team management of OFC

In terms of managing orofacial clefts, the literature references terms such as comprehensive cleft care, models of care, care pathways, protocols and guidelines. This section clarifies their meanings.

Comprehensive cleft care

Comprehensive cleft care refers to a multidisciplinary approach that addresses the diverse needs and challenges of individuals with an orofacial cleft throughout their development. It goes beyond surgical correction and includes a range of services to ensure optimal health, growth, and quality of life (Smile Train 2024a).

Models of care

Defines how health services are delivered, including the processes of care, organisation of providers and management of services, supported by the identification of roles and responsibilities of different platforms and providers along the pathways of care. Foundation-based cleft initiatives in low-resource settings and low-to middle-income countries are broadly classified as vertical, horizontal, or diagonal models with the former being the least sustainable and the latter being the most sustainable (Patel et al. 2012).

A) Vertical Care Delivery model

The vertical model provides a transient solution exemplified by surgical mission trips, where teams travel to areas with limited access to cleft care along with necessary supplies, surgical equipment and medications. Host countries are provided with needed transitory increase in workforce that helps decrease the burden of disease and temporarily addresses healthcare deficits. These initiatives can provide host countries with service delivery in areas with an untreated backlog of cases and provide expert consultation and the needed transitory increase in workforce to help decrease the burden of disease and address healthcare deficits. This model has been criticised for the following: lack of sustainability, potential disruption of local healthcare systems and infrastructure, not being cost-effective, adding financial

strain on the host country, possible alienation or dependence of host countries on the visiting teams (Hughes et al., 2012; Patel et al., 2012; Carlson et al., 2015; Kantar et al., 2019a).

B) The Horizontal Care Delivery model

This model focuses on expansion of service delivery, investing in the host country, developing and strengthening existing infrastructures with local authorities. It is appropriate where basic infrastructure and human resources are already available. The strength of this model lies in capacity building and sustainability. Advantages of the horizontal model include potential sustainability of care and empowerment of local teams. However, this model involves long-term investment and requires continuous follow-up until transition to cleft care autonomy can be achieved. Additionally, horizontal systems often need a significant amount of time to instil noticeable change and may fail in areas that are completely deprived of surgical expertise (Patel et al., 2012).

C) The Diagonal Care Delivery model

The diagonal care delivery model combines the advantages of the vertical and horizontal models. It provides vertical care through temporary workforce and resources needed on surgical missions while empowering local teams and investing in horizontal capacity building and transition to autonomy (Patel et al., 2012).

Patel et al. (2018) note that this approach is becoming increasingly popular among surgical organisations that provide cleft lip and palate care, such as Global Smile Foundation, Operation Smile and the European Cleft Organisation (ECO), as a means of balancing immediate service delivery with long-term health system strengthening (Mustakim et al., 2023; Chahine et al., 2021; Patel at al., 2018).

Recognised as the world's largest cleft-focused organisation, Smile Train has pioneered capacity-building within this model, focusing on training and equipping local surgeons to deliver comprehensive cleft sustainably within their communities. Since its founding in 1999, Smile Train has supported more than two million cleft surgeries globally, partnering with more than 1,000 hospitals to provide comprehensive cleft care for patients across 95 countries as of 2024 (Smile Train

2025; Smile Train, 2024). A clear example of the diagonal approach is the 2022 Smile Train and Kids Operating Room (KidsOR) partnership resulting in state-of-the art transformation of operating rooms in ten countries across Africa, providing surgeons and their teams with the infrastructure as well as the training needed to create sustainable cleft care services (Smile Train, 2022).

Through this approach, initial surgical mission trips have transitioned into sustainable cleft care centres, with examples including Operation Smile in India and Resurge International (formerly Interplast) in Nepal. The Guwahati Comprehensive Cleft Care Centre in India is a self-sustaining, comprehensive surgical centre, which focuses on cleft care, education, and outcomes research. In Nepal, Resurge International successfully launched a cleft care centre with an emphasis on patient safety, preservation of local culture, and the teaching of local surgeons. Their model progresses through the initial stages of “observation” and “integration,” with the ultimate goal of phasing out external support during the final “independence” stage (Campbell and Kreshanti, 2021).

Cleft care pathways, guidelines, protocols

A care pathway is a multidisciplinary plan of care, designed to improve patient outcomes, streamline processes, and enhance communication within the healthcare team. They can be used in various settings, such as hospitals, outpatient clinics, and community health programs(Rotter et al. 2019). Compared to a clinical protocol which is a step-by-step systematic approach to dealing with important issues and that must normally be followed exactly, a care pathway is flexible, patient centered, outcome focused and allows for interdisciplinary collaboration and a holistic approach to care(Picard 2022).

Clinical practice guidelines are evidence-based recommendations intended to aid clinicians in making informed decisions about patient care. They aim to standardise treatment approaches while remaining adaptable to individual patient circumstances and local healthcare settings. Interpretation of these guidelines is essential, as the strength of the underlying evidence and specific patient needs can influence their application. A Guidelines Advisory Committee often oversees the development and implementation of these guidelines, ensuring they reflect current research and clinical expertise. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument is commonly used to evaluate the quality and rigor of guidelines, helping to ensure they are reliable and effective for clinical use (Panteli et al. 2019).

In summary, a care pathway serves as the most appropriate framework for hospitals, countries and care providers to develop their own protocols. It recognises that a care pathway is a flexible guide as orofacial cleft patients require individualised, tailored care.

2.3 Global distribution of orofacial clefts

2.3.1 Introduction

Epidemiology is the branch of medical science that investigates the distribution, determinants and the application to control that disease or disorder. Epidemiological research helps to understand how many people in a population have a disease or disorder, if those numbers are changing and how the disorder affects that population (NIDCD 2011). In the definition of epidemiology, “distribution” refers to descriptive epidemiology, covering time (when), place (where), and person (who). Whereas “determinants” refers to analytic epidemiology, generally including the causes (including agents), risk factors (including exposure to sources), modes of transmission (why and how) epidemiology, but does not include the resulting public health action (CDC 2012; Parritz and Troy 2017).

Rationale for epidemiologic research in OFCs

Descriptive epidemiology is essential in identifying and quantifying the problem. It looks for trends, associations and inter-population differences, with the aim of supporting aetiological research and advancing the translational agenda. However, this is not possible in every country in the world and epidemiological research should seek to identify data gaps with a view to improve the situation. The list of complications faced throughout the life of those born with an OFC is extensive, requiring a host of clinical interventions within a multidisciplinary team. The medical, economic and psychosocial impact on the patients and the focus of contemporary OFC research is to improve the evidence base for treatment interventions that aim to optimise OFC quality of care and primary prevention. Descriptive epidemiology underpins both of these major areas (Mossey and Modell, 2012).

2.3.2 Birth prevalence

2.3.2.1 Terminology

In the context of describing the epidemiology of clefts, "birth prevalence" is typically the more accurate term. Birth prevalence refers to the number of cases of orofacial clefts that occur per live births within a specific population over a defined period, usually expressed per 1,000 or 10,000 live births. "Incidence," on the other hand, generally refers to the number of new cases that develop within a specified time period, which may not be as relevant for congenital conditions like clefts since they are present at birth. Therefore, for epidemiological studies on clefts, focusing on birth prevalence provides a clearer picture of their occurrence in the population (Cornel 1999).

2.3.2.2 Global prevalence

In 2012, Mossey and Modell reported the global prevalence of OFCs as approximately 1 in 700 live births, noting considerable ethnic and geographical variation (Mossey and Modell 2012a; Mossey and Little, 2002). Historically referenced by organisations and the literature, this “1 in 700” estimate stems from a comprehensive 2002 overview of OFC epidemiology by Mossey and Little, which includes a systematic literature search and a review of major international registries up to the end of the 20th century (Mossey and Little, 2002).

A more recent systematic review and meta-analysis by Salari et al. (2022), reports a lower estimate for global prevalence of OFCs of 1 in every 1000-1500 newborns worldwide, also acknowledging varying rates across ethnic and geographic areas. Although this figure has since been referenced by the WHO in their Global Oral Health Status Report and several other publications and cited by several publications, it is important to critically appraise Salari et al’s lower estimate before considering its application as a replacement for established prevalence figures (World Health Organization (WHO) 2022; Putri et al., 2024). Closer examination reveals that while the analysis included 69 studies, a substantial proportion (13 studies) were conducted in a single country and the majority of the data were derived from high-income countries and upper-middle-income settings. Representation from low- and lower-middle-income countries in Salari et al’s study is notably limited, despite these regions

having some of the highest reported prevalence rates of OFCs globally, particularly in South Asia (India, Nepal, Pakistan, Sri Lanka) and Southeast Asia (Philippines, Indonesia) (Kadir et al., 2017; Sarilita et al., 2021). This underrepresentation limits the generalisability of the findings.

Additionally, the meta-analysis reported extreme heterogeneity (I^2 = 99.9%), indicating substantial variation between included studies, and did not provide stratification by syndromic vs. non-syndromic clefts, ethnicity, or consistent regional healthcare factors. These methodological limitations, combined with regional sampling biases, reduce the validity of applying the reported figure as a “global prevalence” estimate.

Putri et al. (2024) similarly highlight that while OFCs remain highly prevalent globally, with substantial ethnic and geographic variation, gaps in registry data from low- and lower-middle-income countries continue to limit the representativeness of global prevalence estimates. They note that further systematic reviews incorporating bias assessment are needed to establish robust global figures, supporting the cautious stance taken in this thesis regarding the adoption of newer lower estimates without critical appraisal.

The figure reported by Salari et al. (2022) is acknowledged but is not adopted as a replacement due to methodological limitations, limited LMIC representation, and concerns regarding the mischaracterisation of the findings as globally representative. Therefore, the established prevalence figure of 1 in 700 live births will be used in this thesis to represent global OFC prevalence.

2.3.2.3 Regional and ethnic variability

The epidemiology of orofacial clefts shows significant variation based on ethnicity and geography, as highlighted by epidemiological data from the WHO, the International Clearinghouse Birth Defects Monitoring System (ICBDMS) and European Registration of Congenital Anomalies (EUROCAT), as presented in peer-reviewed literature (Mossey et al., 2009; WHO, 2002b; EUROCAT, 2002).

i. Asia

The highest birth prevalence of OFCs was found to be documented in Asia. Fourteen studies conducted across various regions in Asia reported prevalence rates ranging from 1.05 to 2.36 per 1,000 live births. Among these, two studies focused on Asia as a whole, while the remaining twelve examined specific countries, including Iran, Israel, Vietnam, Nepal, Saudi Arabia, Singapore, Sri Lanka, Japan, and China (Kobayasi 1958; Tanaka 1972; Cooper et al. 2006; de Alwis et al. 2007; Jamilian et al. 2007; Aqrabawi 2008; Tan et al. 2008; Jalili et al. 2012; Sabbagh et al. 2012; Silberstein et al. 2012; Singh et al. 2012; Hoang et al. 2013; Borno et al. 2014; Kianifar et al. 2015; Panamonta et al. 2015) .

ii. North America

The birth prevalence of OFCs in North America has been reported to range from 0.6 to 3.92 per 1,000 live births. This data comes from a systematic review of 12 studies on the prevalence of OFCs in Canada, the USA, and Mexico (Loretz et al. 1961; Tretsven 1965; Gilmore and Hofman 1966; Niswander and Adams 1967; Emanuel et al. 1973; Ching and Chung 1974; Lowry and Trimble 1977; Shaw et al. 2004; Conteras-Acevedo et al. 2012; Aggarwal et al. 2015; Matthews et al. 2015; Panamonta and Chowchuen 2015; Wang et al. 2015). It is important to note that Panamonta and Chowchuen classify Mexico as part of North America, while other reports place Mexico in Central America (Panamonta et al. 2015). Neither classification is wrong, as the unofficial United Nations geoscheme defines Central America as all countries south of the United States, though historically and politically, Mexico is generally considered part of North America (Britannica 2024).

iii. Europe and the United Kingdom

Earlier evidence from a systematic review of studies across Iceland, Finland, Denmark, Turkey, the Netherlands, and Poland, reported that the birth prevalence of OFCs in Europe ranged from 1.02 to 1.94 per 1,000 live births, reflecting variability in study methodologies and population contexts (Panamonta et al. 2015). More recent and comprehensive data from EUROCAT, which is widely regarded as one of the most robust congenital anomaly registries globally, report an average OFC prevalence of 1.52 per 1,000 live births (15.2 per 10,000) across its network, which covers over 30% of European births with high standards of data quality and ascertainment (EUROCAT, 2023).

Although the United Kingdom (UK) is no longer part of the EU, the Cleft Registry and Audit Network (CRANE) now operates as the UK's national registry within England, Wales, Scotland, Northern Ireland, collecting prospective data on children born with cleft lip and/or palate since January 2023. At the time of writing this literature review, although there is no current update for birth prevalence of OFCs for the UK that includes Scotland, there are estimates prior to 2023. Within England, Wales and Northern Ireland (excluding Scotland), similar to the birth prevalence of OFCs globally, the UK has been consistently reported at 1 in 700 live births, equating to around 1.4 per 1,000 live births (CRANE, 2024). In Scotland, cleft care data prior to 2023, was collected separately, with a slightly higher reported birth prevalence than the UK's CRANE average of approximately 1 in 600 live births (1.67 per 1,000) (Cleft Care Scotland, 2023).

iv. Oceania

Oceania is commonly regarded as a continent, encompassing the islands of the Central and South Pacific. It includes a range of islands, from larger ones like Australia, New Zealand, Papua New Guinea, and Fiji to smaller island nations such as Samoa, Tonga, and Kiribati. Panamonta et al. (2015) reported the birth prevalence of OFCs for Oceania to range from 1.21 to 1.73 per 1,000 live births but this was derived from four studies only conducted in Australia (Chi and Godfrey 1970; Brogan and Woodings 1974; Spry and Nugent 1975; Bell et al. 2013; Panamonta et al. 2015). In 2016, Thompson et al. reported a higher birth prevalence

of OFCs in New Zealand as 1.79 per 1000 live births (Thompson et al. 2016). From the literature, it appears that this region is deficient in epidemiological evidence on OFCs.

v. Latin America and the Caribbean (LAC)

According to the United Nations, there are 33 Member States of Latin America and the Caribbean (LAC). LAC is comprised of countries of the Caribbean (Haiti, Dominican Republic, Cuba, Jamaica, Trinidad and Tobago, Bahamas, Barbados, Saint Lucia, Grenada, St Vincent and the Grenadines, Antigua and Barbuda, Dominica, Saint Kitts and Nevis), Central America (Guatemala, Honduras, Nicaragua, El Salvador, Costa Rica, Panama, Belize, Mexico) and South America (Brazil, Colombia, Argentina, Peru, Venezuela, Chile, Ecuador, Bolivia, Paraguay, Uruguay, Guyana, Suriname)(United Nations 2024a).

South America

Panamonta et al.'s 2015 systematic review reports a birth prevalence of OFCs in South America at approximately 1 per 1,000 births. However, this estimate is based on only two studies, both conducted in Brazil, making it less representative of the overall OFC birth prevalence across South America (Menegotto BG and Salzano FM 1991; Souza and Raskin 2013). The birth prevalence of OFCs (CL/P and CPO) in other South American countries, including Argentina, Chile, Uruguay and Venezuela was reported in the WHO's 2002 International Collaborative Research on Craniofacial Anomalies meeting. The rates were recorded as 1.92, 1.48, 1.18, and 0.96 per 1,000 live births, respectively (World Health Organization 1998; World Health Organization (WHO) 2002). In 2019, a study published the birth prevalence of orofacial clefts (OFCs) in Colombia over a retrospective period of eight years, reporting a rate of 0.6 per 1,000 births. (Alonso and Brigetty 2019).

Central America

For Central America, the most recent reports on OFC birth prevalence are from Costa Rica, with a rate of 2.1 per 1,000 births for the period 1996-2021, Guatemala with 1 per 1,000 births, and Mexico with 0.9 per 1,000 births (González-Osorio et al. 2011; Figueroa et al. 2020; de la Paz Barboza-Argüello and Benavides-Lara 2024).

The Caribbean

Most of the epidemiological data on OFCs in the Caribbean region originates from Cuba and the Dominican Republic, with an additional report from Trinidad and Tobago dating back to 1963. Cuba provides the most recent epidemiological data, with a 2021 report from the Villa Clara Province documenting a birth prevalence of 0.78 per 1,000 births over a five-year retrospective period. During this time, 36 newborns with OFCs were identified out of a total of 46,007 births(Delgado Díaz et al. 2007; Torres Iñiguez et al. 2007; Reyes Bacardí et al. 2013; Taboada-Lugo et al. 2021).

Reports on birth prevalence of OFCs from Dominican Republic are from the years 1980, 1978, 1970. In 1980, Garcia-Godoy identified 439 infants born with clefts out of 704,410 live births over a three-year retrospective period, resulting in a birth prevalence of approximately 0.62 per 1,000 live births (Garcia-Godoy 1980). Previous reports on the prevalence of OFCs have ranged from 1 in 1,429 to 1 in 1,300 live births (or 0.7 to 0.77 per 1,000 births) (Garcia-Godoy et al. 1970; Castillo De Ariza 1978).

A report from 1963, available only as an abstract, provided data on clefts in the population of Trinidad and Tobago, which had about 830,000 people at the time. The report noted approximately 35 cases of clefting among 30,000 annual births, suggesting a birth prevalence of 1.2 per 1,000 live births. It also indicated a higher incidence among Indians, at about 1 in 500 births (or 2 per 1,000), compared to other racial groups, where the prevalence was 1 in 1,600 births (or 0.62 per 1,000). However, "other racial groups" were not clearly defined in the abstract (Robertson 1963).

In summary, the LAC region has a significant gap in studies reporting birth prevalence data specific to Caribbean countries, with the only available report from Trinidad and Tobago dating back over 60 years and lacking easy access to the full text.

vi. Africa

Panamonta and Chowchuen (2015) report the overall birth prevalence of OFCs (CL, CLP, CPO) in Africa as 0.3-1.65 per 1,000 live births. This is a review of 10 studies across Africa including Kenya, Nigeria, Uganda, South Africa, Zaire, Malawi, Sudan and Madagascar (Khan 1965; Gupta 1969; Robinson and Shepherd 1970; Iregbulem 1982; Morrison 1985; Ogle 1993; Msamati BC et al. 2000; Suleiman AM et al. 2005; Rakotoarison RA et al. 2012; Kesande T et al. 2014; Panamonta and Chowchuen 2015).

vii. General trends

In terms of ethnicity, many studies and systematic reviews reveal ethnic variation in the birth prevalence of OFC clefts. The highest rates have been documented in the Native North American Indians, followed by the Japanese and Chinese in the Far East, India, Aborigines, Scandinavia, parts of South America and Native Americans. The lowest rates have been documented in Africa, Southern Europe and African Americans (Mossey 2007; Panamonta and Chowchuen 2015).

The trends in terms of race are that OFCs is most common for White/Caucasian races, intermediate in Hispanics and lowest in Blacks (The Hispanic Ethnicity Birth Defects Workgroup 2000; Mossey 2007; Panamonta and Chowchuen 2015).

2.3.2.4 Registries and Surveillance Systems

The role of registries and surveillance systems in monitoring OFCs is critical for epidemiological research, service planning and quality improvement. Registries are organised systems that systematically collect individual-level data on specific health conditions, including information on occurrence, type, extent and treatment (EUROCAT, 2018; Gliklich et al., 2014). In contrast, surveillance systems focus on the ongoing, systematic collection, analysis and interpretation of health-related data, integrated with timely dissemination to support public health action (WHO, 2006). These systems may operate at a local, national or international level and may be hospital-based, population-based or a combination of both (WHO, 2006).

The European network of population-based registries for the epidemiological surveillance of congenital anomalies commonly referred to as EUROCAT, the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) and the Latin American Collaborative Study of Congenital Malformations (ECLAMC) operate as both registries and surveillance systems (Kadir et al., 2017). EUROCAT is widely regarded as the most robust congenital anomaly registry in the world, covering over 30% of births in Europe with high standards of data quality and ascertainment, enabling meaningful analysis and comparison across populations (EUROCAT, 2022). Some notable registries encountered within literature include the International Perinatal Database of Typical Orofacial Clefts (IPDTOC) which functions primarily as an international research registry and the Cleft Registry and Audit Network (CRANE) which operates as a national registry within the UK to support audit, quality improvement initiatives and service planning for cleft services (CRANE, 2024; IPDTOC, 2011).

Although the importance of registries and surveillance systems, as emphasised in the literature, cannot be overstated, they are not without deficiencies. Kadir et al. (2017) explain that international umbrella registries compile data from hospital and population-based registries across various countries. These registries provide valuable insights into global epidemiology, tracking the prevalence and types of clefts over time, identifying genetic and environmental risk factors, and assessing the impact of interventions on prevalence. However, reports from these international

registries indicate significant variations in the birth prevalence of OFCs across different settings (Kadir et al., 2017; Castilla and Orioli, 2004; McGoldrick et al., 2023). Deficiencies in registries include underreporting, variability in data collection practices, the use of hospital-based versus population-based registries, inconsistent diagnostic criteria and limited long-term follow up which can affect data completeness and regional comparability. For example, Castilla and Orioli (2004) highlight that due to pregnancy termination being largely prohibited across South America, the inability to legally include terminated pregnancies limits the data within the ECLAMC registry toward live births, thus potentially underestimating the true prevalence of congenital anomalies in the population (Castilla and Orioli, 2004). More recently, McGoldrick et al (2023) outlined several factors contributing to variations in reported birth prevalence data for OFCs using the ICBDSR registry compared to robust global estimates. Limitations of the ICBDSR registry include heterogeneity across countries, cultures and health systems where higher rates of elective terminations in some European countries led to lower live birth prevalence, while countries such as Malta where termination is illegal reported higher stillbirth rates instead. According to McGoldrick et al (2023), the inclusion of stillbirths in the denominator data within the ICBDSR registry may have contributed to the lower prevalence reported within their study (McGoldrick et al., 2023).

To conclude, although several registries and systems exist, standardisation in data collection and reporting is still needed to enable accurate estimation of the prevalence of different types of OFCs to truly facilitate meaningful comparisons across regions.

2.3.3 OFC characteristics

Prevalence of CL/P

Since 2002 there have been a number of significant international efforts through more systematic registry-based systems to record the prevalence of orofacial clefts. A study by EUROCAT analysed 6 million births across 23 registries in 14 European countries, identifying 5,449 cases of CL/P between 1980 to 2000. The overall prevalence of CL/P was 9.1 per 10,000 births, with 70.8% classified as isolated and 29.2% associated with either multiple congenital anomalies, chromosomal defects or recognised syndromes (Calzolari et al. 2007).

Data from the International Perinatal Database of Typical Orofacial Clefts (IPDTOC examined birth prevalence data for CL/P from 54 registries in 30 countries between 2000 and 2005, encompassing over 7.5 million births. An overall prevalence of 9.92 per 10,000 births was reported, closely aligning with findings from Calzolari et al. (2007). Of these cases, 76.8% were isolated, while 23.2% were associated with malformations in other systems (15.9%) or identified as part of a recognised syndrome (7.3%) (International Perinatal Database of Typical Oral Clefts (IPDTOC) Working Group 2011).

Prevalence of CPO

For CPO, the distribution among isolated cases, recognised syndromes and those associated with other birth defects, was 54.8, 27.2 and 18%, respectively (Cobourne 2012).

Relative proportions of different cleft types

European and US studies on non-syndromic clefts indicate unilateral CLP as the most commonly, representing 30-35% of all cases studied. Isolated CLP follows as the second most frequently reported, making up 20-25%. Bilateral CLP accounts for approximately 10%, while submucous and other types account for the remaining cases (Hagberg et al. 1997; Mossey and Modell 2012b).

Dysmorphological severity of cleft and additional malformations

The general trend in CL/P is that in those regions of the world with the highest cleft prevalence, there is also a higher ratio of CLP to CL. Conversely, in regions with the lowest cleft prevalence, the proportion of the more severe forms of clefting is correspondingly lower. This finding, first observed by Mossey and Little (2002) reviewing international data, has been confirmed in the IPDTOC study (2011) and is in agreement with a multifactorial model which would predict that the higher the overall CL(P) prevalence, the greater the genetic liability within that particular gene pool, and therefore the more CLP as opposed to CL (International Perinatal Database of Typical Oral Clefts (IPDTOC) Working Group 2011; Mossey and Modell 2012b).

The severity of CL/P appears closely linked to the presence of other malformations, showing a notable trend. According to Hagberg et al. (1997), the bilateral subgroup of orofacial clefts exhibits a higher incidence of additional malformations. Therefore, cases of bilateral cleft lip and palate should be carefully assessed for associated malformations, as the risk of having another significant malformation is three times greater compared to unilateral cleft lip (Hagberg et al. 1997; Mastroiacovo et al. 2011; Mossey and Modell 2012b).

Unilateral clefts and laterality

Cleft lip only (CL) tends to be unilateral (in about 90% of cases), with approximately two-thirds occur on the left side, regardless of sex, ethnicity or severity of defect (Fogh, 1942; Fraser and Calnan, 1961; Bonaiti et al. 1982; Tolarova, 1987; Jensen et al. 1988). In the IPDTOC study (2011), the proportion of bilateral cases was 10.3% among CL and 30.2% among CLP, with little variability across different registries and regions. In these registries, the side distribution (right or left) was documented in 1,264 out of a total 2,506 unilateral cases. The proportion of right side was 36.9% for CL and in 41.1% for CLP. While there is no definitive explanation for these differences, one proposed explanation suggests that blood vessels, supplying the right side of the foetal head, leave the aortic arch closer to the heart, and are perhaps better perfused by blood than those going to the left side (Johnston and Brown 1980; Mossey and Modell 2012b).

Clefts and associated malformations

From a global perspective there is variation in OFC with associated anomalies from as low as 21% (Milerad et al. 1997), 29% (Shafi et al. 2003), 31% (Rittler et al. 2011) and as high as 59.8% for CL/P and 71.1% for CP (Shaw et al. 2004).The higher figures reported by Shaw et al (2004) could be due to the inclusion of very minor defects whereas other studies defined a cleft with an associated malformation when only major structural defects were present. It should be noted that methodological differences hinder reliable comparison.

In terms of cleft type, CPO has the highest prevalence of associated defects, followed by CLP, with CL having the lowest (Fraser and Calnan, 1961; Stoll et al. 2000; Rawashdeh and Abu-Hawas, 2008; Rittler et al. 2011). Representative of this is a study conducted in North Eastern France that found the the rate of associated malformations as 46.7% in CPO, 36.8% in CLP and 13.6% in CL (Kallen et al 1996). However, Milerad et al. (1997) reported that CLP as being associated with the highest prevalence, followed by for CLP, followed by CPO and CL. In both studies, CL has the lowest prevalence of associated defects (Kallen et al. 1996; Milerad et al. 1997; Mossey and Modell 2012b). Some studies also subdivide CL/P into unilateral and bilateral groups when examining additional malformations and report an increase in additional malformations in the bilateral sub-group. All studies that analysed CLP and CL separately (Tolarova and Cervenka, 1998; Harville et al. 2005; Milerad et al. 1997; Stoll et al. 2000; Genisca et al. 2009) found the lowest prevalence of associated defects for isolated CL. Congenital heart disorders along with anomalies of the limbs and vertebral column, were the most commonly associated conditions with both CPO and CLP (Rittler et al. 2011; Milerad et al. 1997; Shafi et al. 2003; Rawashdeh and Jawdat 2008; Genisca et al. 2009). However, it is not made certain within the literature whether the frequent association between congenital heart disorders alongside other defects, including clefts, is genetically determined or if it is simply coincidental and non-specific (Rittler et al. 2011).

Sub-phenotypes

As our understanding of genetic aetiology continues to advance, in order to establish genotype-phenotype correlations, it will be crucial to differentiate between sub-phenotypes such as complete vs. incomplete clefts and classifications based on the involvement of the soft or hard palate. Growing evidence indicates significant epidemiological and genetic differences between cleft lip (CL) and cleft lip and palate (CLP). The different patterns of defects associated with CL and CLP, indicating different underlying mechanisms, suggest that CL and CLP reflect more than just variable degrees of severity, and that distinct pathways might be involved (Rittler et al. 2008). For example, a Norwegian study by Harville et al. (2005) found that 17% of infants with CLP also presented with additional defects, compared to only 9% of those with isolated CL (Harville et al. 2005).

In terms of gender, a UK study investigated the prevalence of cleft lip in CL/P and found that complete cleft of the lip in CLP patients was found to occur in 90% of males and 85% of females. In isolated cleft lip (CL) patients however, complete cleft of the lip were less common, affecting 39% of females and 25% of males and the ratio of complete to incomplete CL was higher in females (Carroll and Mossey 2012; Pool et al. 2020).

The prevalence of a Simonart's band in patients with CLP ranges from 21.9 to 31.2% (Smahel and Brejcha, 1983; Nordin et al. 1983; Semb and Shaw, 1992; Roberts-Harry et al.1996; Da Silva et al. 2006, Mossey and Modell, 2012). The last of these studies indicated a higher prevalence in bilateral CLP compared to unilateral CLP, with left-sided occurrences more common in UCLP and right-sided occurrences more common in unilateral CLP. Furthermore, the prevalence of Simonart's band in clefts of the lip and alveolus was much higher than in complete clefts of the primary and secondary palate (CLP). These epidemiological observations point to potential differences in their underlying causes (Mossey and Modell 2012b).

In general, the evidence suggests that CL/P occurs more in populations and CPO is less common. CPO shows less variation across ethnic groups populations of Asian origin have a higher incidence than Caucasian populations which, in turn, have a higher incidence than African populations (World Health Organization (WHO) 2002).

2.3.4 Sex distribution

One of the well-known epidemiological differences between CL/P and isolated CP is that males are more likely to have CL/P, while females are more likely to have CP. The sex ratio also varies depending on factors such as the severity of the cleft, the presence of additional malformations, the number of affected siblings in a family, ethnic background, and possibly paternal age (Mossey and Little, 2002; Mossey et al., 2009).

In white populations, the male-to-female ratio for cleft lip and palate is about 2:1 in favor of males (Mossey and Little, 2002). In Japanese populations, there is a significant male predominance in the CL(P) group, but this pattern is not seen in the cleft lip-only group (Fujino et al., 1963). Within white populations, the male predominance in CL(P) becomes more pronounced with increasing severity of the cleft, although this trend is less evident when multiple siblings are affected in the same family (Fogh, 1942; Niswander et al., 1972). On the other hand, the male predominance in CL(P) is reduced when the infant also has malformations in other organ systems (IPDTOC, 2011). While the exact reasons for these gender differences are not fully understood, it is suggested that differences in the timing of key developmental stages in craniofacial development may play an undefined role in their etiology (Burdi and Silvey, 1969).

2.4 Summary

Trinidad and Tobago, a high-income developing country, is committed to achieving Universal Health Coverage and the Sustainable Development Goals while already providing free healthcare. However, it faces challenges like other Small Island Developing States, such as inadequate infrastructure and a shortage of specialists. In the realm of craniofacial anomalies, the literature predominantly focuses on orofacial clefts which is a feature of many craniofacial anomalies.

In terms of epidemiology of orofacial clefts, Trinidad and Tobago's data is outdated, with only an abstract from 60 years ago highlighting a high birth prevalence in certain ethnic groups. The available literature highlights the existing knowledge gaps on the epidemiology in terms of distribution and determinants of orofacial clefts and other craniofacial anomalies for the population of Trinidad and Tobago.

In terms of management, the goal is to implement comprehensive cleft care through a multidisciplinary team (MDT) approach, with literature advocating for sustainable and scalable care models suitable for low- and middle-income countries (LMICs) but there does not appear to be any literature specific to introducing comprehensive cleft care via a cleft care pathway in low-resource settings.

CHAPTER 3 AIMS AND OBJECTIVES

The overall aims of this thesis were to:

1) Explore the epidemiology of orofacial clefts (OFCs) and other craniofacial anomalies in Trinidad and Tobago; and
2) Appraise the literature on MDT care pathways for the management of patients with OFCs globally and use the information found to suggest characteristics of a care pathway appropriate for introducing basic MDT cleft care in low-resource settings that is sustainable and scalable.

To achieve this, the objectives were to:

1. Determine the birth prevalence (incidence) of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago and explore associated factors that might be linked to these anomalies through an observational epidemiological study.
2. Identify the characteristics of an ideal MDT cleft care pathway and facilitating factors and challenges to its implementation; and
3. Define characteristics of a basic, sustainable MDT cleft care pathway that can be implemented.

CHAPTER 4 EPIDEMIOLOGICAL STUDY

Title: The epidemiology of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago

4.1 Abstract

Introduction

Orofacial clefts (OFCs) are the most common craniofacial anomaly (CFA) worldwide. However, birth prevalence of babies with OFCs varies significantly across geographic areas and ethnic groupings. As the last report on Trinidad and Tobago's multi-ethnic population was in 1963, this study explores the epidemiology of Orofacial clefts (OFCs) and other craniofacial anomalies (CFAs) in Trinidad and Tobago.

Objectives

To determine the birth prevalence (incidence) of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago and explore associated factors that might be linked to OFCs.

Methods

Ethical approvals were obtained for a retrospective observational quantitative cross-sectional study covering the 5-year period 2018-2022. Birth prevalence was determined using data extracted from Trinidad and Tobago's digital national birth registry database. The numbers of craniofacial anomalies identified in the database for the country's different Regional Health Authorities (RHAs) were verified through searching a variety of data sources including hospital files/records and nursing admission notes at each RHA's Neonatal Intensive Care Unit (NICU) during that period. To explore the evidence-based associated risk factors that might be linked to OFCs, hospital records of babies and their mothers were searched. For each baby identified as being born with an OFC, a healthy newborn closely matched (by sex and birth month) was randomly selected within the same RHA to form study and control groups. Birth prevalence and the samples were presented using descriptive statistics. Logistic regression models were used to assess which factors are more strongly linked with the birth of a baby with an OFC.

Results

A total of 47 babies were born with an OFC out of 73,941 registered births giving a birth prevalence of 0.64 per 1000 births. Three cases of micrognathia were reported by one RHA. Sex predilection could not be concluded. Furthermore, data collected on the characteristics and clinical features of patients with OFCs did not adhere to established OFC classifications and was described in an ambiguous manner. Many risk factors associated with OFCs were either not available for data collection or inconsistently available, resulting in only a limited number of variables used for analysis. Single analysis showed significant predictors of cleft (gestational age; birth weight; birth length; maternal age; maternal medical history within normal limits; gravida; para). The likelihood of a birth with an OFC decreases with gestational age, birth weight, birth length and if there is a maternal medical history within normal limits. The likelihood of a birth with an OFC increases with maternal age and number of pregnancies. When analysed together, only maternal medical history within normal limits and gravida remain significant suggesting these are the stronger predictors which might themselves be influencing the other variables. The analysis suggests that a mother with a normal medical history is 91% (OR 0.089) less likely to give birth to a baby with an OFC. Women with a higher gravida are 74% more likely to give birth to a baby with an OFC. Another finding was the absence of a standardised multidisciplinary pathway providing comprehensive cleft care.

Conclusion

This epidemiological study provides an update on the birth prevalence of orofacial clefts in Trinidad and Tobago. To support future large-scale epidemiologic craniofacial anomaly research, improvements in record-keeping practices are essential, particularly in patient history documentation, craniofacial anomaly surveillance and orofacial cleft classification. Additionally, development is required to establish a basic cleft MDT care pathway that introduces comprehensive cleft care to these individuals.

4.2 Introduction

The cost to individuals affected with craniofacial anomalies (CFAs), their families and society are considerable in terms of morbidity, health care and emotional disturbance. According to (Mossey et al. 2003), the ultimate humanitarian and scientific research objective in craniofacial anomalies (CFAs) is primary prevention but global collaboration is necessary. The most common CFA remains orofacial clefts (OFCs), occurring in approximately 1 in 700 live births and varying significantly across geographic areas and ethnic groupings (Mossey and Little, 2002).

Within Trinidad and Tobago's multi-ethnic population, OFC incidence was last reported in 1963. This high-income developing nation, also a small island developing state (SIDS), shares a significant challenge of many low- and middle-income countries (LMICs) of a gap in birth prevalence data (Mossey 2023). To address this gap and improve the global epidemiology picture, this study aims to explore the epidemiology of OFCs and other CFAs in Trinidad and Tobago through an observational epidemiological study.

Objectives

1. To determine the birth prevalence (incidence) of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago; and
2. To explore associated factors that might be linked to these anomalies.

4.3 Methods

Study design

This epidemiological study follows a cross-sectional, retrospective, quantitative, observational design. The retrospective period observed was five years, between January 1st 2018 to December 31st 2022. The design and the reporting of results follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline (Initiative 2023). There are two parts to this epidemiological study: Part A uses patient records to identify the incidence of orofacial clefts and other craniofacial anomalies: Part B explores risk factors associated with orofacial clefts within dyads consisting of babies born with an orofacial cleft (study group) and a closely matched control group of healthy newborns. Prior to data collection, the study was registered on Open Science Framework (https://osf.io/tz4us).

Setting, geographical coverage, study population

Data collection for this study was completed in four hospitals (Regional Health Authorities; RHAs) in Trinidad from May to July 2023.

As all births within the twin-isle Trinidad and Tobago, must be registered within Trinidad, the sample is limited to registered births. This includes babies born in the Private sector (such as private hospitals or private clinics) and any baby born with a congenital anomaly, as these babies are seen through a Neonatal Intensive Care Unit (NICU), which is within the Public Health Care service. It must be understood that as there are limited Specialists on the island, a baby born with a congenital anomaly within the Private sector, once alive, will be seen through a NICU in the Public Health Care service. As there are no Specialists such as a Neonatologist or Plastic Surgeon on the island of Tobago, a baby born with a congenital anomaly in Tobago will be seen through a NICU on the mainland Trinidad. Therefore, babies with a congenital anomaly that did not survive to be referred to a NICU are excluded from the sample.

Regarding geographical coverage, Trinidad and Tobago's Ministry of Health devolves the responsibility for providing public healthcare services through Regional Health Authorities (RHAs). These are five autonomous bodies (South West RHA, North Central RHA, North West RHA, Eastern RHA, Tobago RHA) that are represented as hospitals located throughout Trinidad and Tobago (Figure 2).

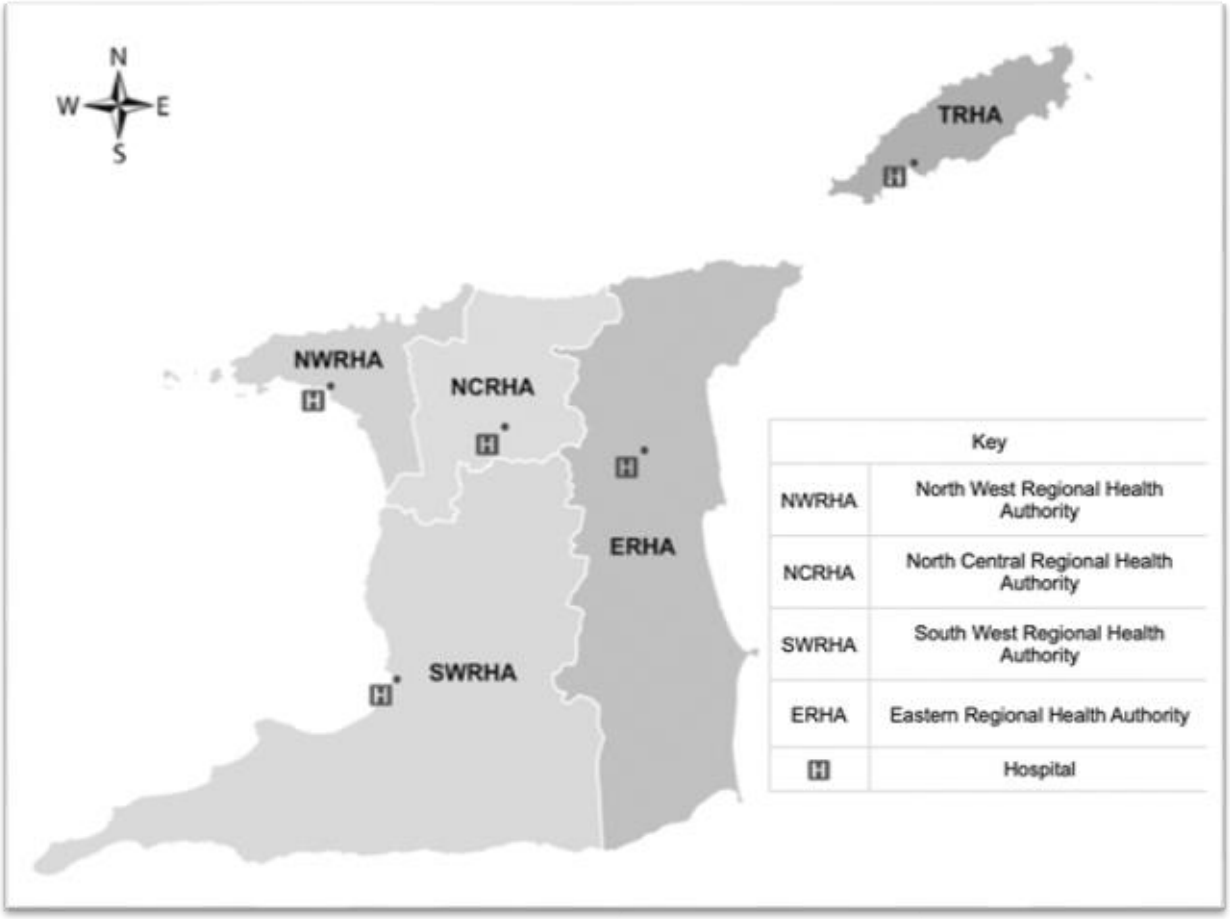

Figure 2 Illustration of Trinidad and Tobago's geographical coverage provided by the Regional Health Authorities (RHAs)

Each RHA requires a separate ethical approval for conducting research within, and not all RHAs have NICUs. For example, a NICU was only established in the Eastern RHA in April 2019. Therefore, the specific setting for this study is the Trinidad and Tobago RHAs with a NICU.

The population consists of babies and their birth mothers within Trinidad and Tobago. The sampling frame chosen to represent the population is women within

Trinidad and Tobago who gave birth between the retrospective five-year period of January 1st 2018, to December 31st 2022.

Ethical approval

Ethical approval was obtained from Trinidad and Tobago's Ministry of Health and four of the nation's RHAs (Tobago RHA excluded) (See Appendix 1).

Participants, groups, method of selection, data sources/measurement.

Data collected was anonymous and did not include patient identifiable information such as name or address. Data collection for each part of the study was as follows:

Part A

Trinidad and Tobago's digital national birth registry database was created in 2018. For each RHA annually, the database contains the total registered live births as well as the number of births diagnosed with a congenital anomaly. For one RHA (NWRHA), more details such as birth characteristics and relevant maternal history were available as part of a newly established congenital anomalies log on the database that began in 2019. No patient identifiable details are available on this database. This database was accessed to determine the country's total registered live births for the period January 1st 2018 to December 31st 2022 and the number of births recorded as having an orofacial cleft. To verify this data, the hospital files/records of babies admitted between 2018-2022 to the NICUs were also searched for an orofacial cleft or other craniofacial anomaly diagnosis. Where available, other data sources such as nursing admission logbooks (NWRHA, SWRHA, ERHA), congenital anomalies logbooks (SWRHA) and Plastic Surgery theatre lists for surgical cleft repairs (NCRHA) were also searched for admission of babies with craniofacial anomalies.

Part B

Part B of the study involved using web-based computer randomisation to sample an equal number of control group babies for variables within the data collection proforma of the babies with craniofacial anomalies. The groups

consisted of maternal hospital files/records of women who gave birth in Trinidad and Tobago between the retrospective period observed. Maternal hospital files contain information on the baby's birth and health until discharged from the hospital. For surviving babies born with an OFC, a file was created for care within NICU. Healthy newborns without an OFC would not be seen through NICU and would therefore not have a NICU file or a file of their own as they are discharged shortly after birth. Ad hoc observations of the care pathway for managing babies born with an OFC were also noted at this stage.

Study group (sample) and method of selection

The study group represents babies born with an OFC or other craniofacial anomaly with or without an associated syndrome. At each RHA's Records Department, all NICU patient files were requested for the retrospective period and hand-searched by two data collectors for a craniofacial anomaly diagnosis. Once a baby with a craniofacial anomaly was identified, their file along with their mother's file was requested. Where available, other data collection sources were used to supplement data collection on variables for the study group (such as nursing admission logbooks, congenital anomalies logbooks, past theatre lists for surgical cleft repairs performed by Plastic Surgery). In instances where the Records Department were unable to retrieve the OFC file with or without their mother's file, other data collection sources were used as the primary source for data collection.

Control group and method of selection

The control group represents healthy newborns without an OFC or other craniofacial anomaly. These files were obtained from the postnatal department as these mothers are routinely discharged after birth (no medical concerns requiring an extended hospital stay after giving birth). Once a baby included in the study group was identified, a closely matched control file (by sex and birth month) was requested from the RHA's Records Department, to ensure that the control group and the study group had similar characteristics and were directly comparable.

Therefore, each case in the study group, was individually matched by sex, birth month and geographic location (within the same RHA) to give a control. The control file was selected using randomisation with an online random sequence generator to reduce selection bias (www.randomizer.org). For example, if the case in the study group was a female baby born at SWRHA in February 2020 with an orofacial cleft, the files of mothers admitted to SWRHA's postnatal department (these mothers birthed healthy newborns) in February 2020 were requested and searched for female births. Those files obtained by the records department, were numbered by the researcher and using an online random sequence generator, a file for a healthy female newborn born in February 2020 at the same RHA was selected. For example, if the records department obtained 22 files of mothers admitted to the postnatal department in February 2020, those files were numbered 1-22 and the online random sequence generator was used to determine the number of the file to be included in the control group. Although this method has a low risk of bias, there was one instance where this was not possible. For example, at ERHA, only 1 female newborn was born during the same month and year as the case in the study group, therefore randomisation could not have been done and the file used.

Orofacial cleft associated risk factors (variables)

Variables consisted of evidence-based risk factors associated with an orofacial cleft. Risk factors identified a priori as potentially associated with the development of an orofacial cleft were grouped under the following headings: patient demographics, birth characteristics, orofacial cleft characteristics, family history, maternal history. Maternal history includes the following subheadings: maternal demographics, maternal medical and drug history, pregnancy history, maternal social history. This is summarised in Table 8. The data collection proforma consisting of these variables can be found in Appendix 2. The variables that were not available or found in patient records for collection were noted and addressed in the results

Table 8 Summary of variables addressing evidence-based risk factors associated with orofacial clefts

Variable							
Patient demographics	**Birth characteristics**	**Orofacial cleft characteristics**	**Family history**	**Maternal history**			
				Maternal demographics	**Maternal medical and drug history**	**Pregnancy history**	**Maternal social history**
-Lived/died status -Sex -Race/ethnicity	-Gestational age -Birth weight -Length -Head circumference -Method of delivery	-Presence of OFC -Presence of syndrome -Presence of associated congenital anomaly -Type (CL/P; CPO) -Laterality (bilateral; unilateral; side of face affected)	-family history of craniofacial anomaly -parental consanguinity -paternal age -paternal occupation	-Maternal age -BMI -socioeconomic level -education level	-Maternal medical history -use of multivitamin containing folate during pregnancy -excess vomiting during pregnancy -use of prescription (licit) drugs? -anaemia complicating pregnancy	-Number of pregnancies (gravida) -Number of times given birth to a viable child (para) -History of abortion	-smoking history -alcohol use -use of illicit drugs -occupation -stress

Statistical methods

Part A

Descriptive statistics were used to report the incidence of orofacial clefts and other craniofacial anomalies in Trinidad and Tobago.

Part B

Descriptive statistics were used to summarise the characteristics of the study and control groups and a logistic regression was used to assess which variables/factors are more strongly linked with the presence of a craniofacial anomaly. All statistical analyses were carried out in Jamovi version 2.3.28 (The jamovi project 2024).

Handling of missing data/unrecorded data for variables

This study defines missing data as variables not available to investigators that would have contributed to the final analysis had they been observed. Incomplete medical records with variables not being reported was anticipated. A holistic approach for addressing missing data was taken in the design phase (prior to the study), conduct phase (during the study) and in the analytic phase (after data collection was completed).

In the design phase, several data sources were retrieved and searched to fill in missing data and ensure that basic important variables (such as sex, gestational age, maternal age) were captured. During the conduct phase, to understand inconsistently recorded variables, the data collectors consulted clinicians and clinical staff involved in recording of the data that was retrospectively collected. This helped clarify and confirm assumptions on the missingness of data collected. In the analysis phase variables with insufficient variability for analysis were excluded. Details of the missing data procedure are presented in Table 9.

Table 9 Details of the missing data procedure

Phase of study	Handling of missing data
In the design phase	• Variables that were not adequately or consistently recorded were not included in the study.
In the conduct phase	• Clinicians and clinical staff involved in recording of data explained that positive findings for variables were recorded but where there was no record, it can be assumed that the variable was not present. Therefore, negative findings were not always reported. For example, for common history taking categories such as social history, a positive finding was recorded but the absence of a positive finding can be assumed to be a negative finding. Consequently, negative findings were assumed and not likely to be recorded. • Missing data for the following variables were confirmed to assume negative findings: – presence of syndrome – presence of associated congenital anomaly – no relevant maternal medical history recorded – use of licit drugs – anaemia complicating pregnancy – history of abortion – smoking history – alcohol use – use of illicit drugs • Missing data for the following variables could not be assumed as negative findings and were therefore excluded from the study: – use of multivitamins – excess vomiting during pregnancy
In the analysis phase	• Variables with any categories that had n<5 were excluded from the statistical analysis

4.4 Results

Part A: Incidence of craniofacial anomalies for the population of Trinidad and Tobago, 2018-2022

A total of 73,941 births were registered in Trinidad and Tobago for the five-year period 2018-2022. This includes births within the private hospitals/clinics and public sectors (TRHA, ERHA, NCRHA, NWRHA, SWRHA). Within this period, a total of 47 births were identified as having an orofacial cleft (OFC) giving an incidence of 0.64 orofacial clefts per 1000 births for the population of Trinidad and Tobago during 2018-2022.

A record of other craniofacial anomalies was only found at one RHA. SWRHA recorded other craniofacial anomalies such as micrognathia onto Trinidad and Tobago's digital national birth registry database for the 5-year period. A total of three cases of micrognathia were reported by SWRHA, one of which was associated with a high arched palate (born in 2018).

Geographically, the highest number of births with orofacial clefts were reported in the country's southern region at SWRHA (n=22), followed by the NCRHA (n=17), NWRHA (n=7), ERHA (n=1).

This is summarised in the Table 10.

Table 10 Craniofacial anomalies recorded over the 5-year period 2018-2022 nationally onto Trinidad and Tobago's digital national birth registry database

Year	National total births	Number of orofacial clefts recorded annually at each RHA				Number of orofacial clefts recorded nationally	Number of births recorded at SWRHA with other craniofacial anomalies
		ERHA	NCRHA	NWRHA	SWRHA		
2018	16849	NA	5	3	3	11	1
2019	15585	1	3	2	3	9	0
2020	15000	0	3	0	7	10	1
2021	14703	0	3	1	3	7	1
2022	11804	0	3	1	6	10	0
Total	73941	1	17	7	22	47	3

Geographically, the highest number of births with orofacial clefts were reported in the country's southern region at SWRHA (n=22), followed by the NCRHA (n=17), NWRHA (n=7), ERHA (n=1).

Sex split of the babies born with an OFC

Of the 47 births with OFCs recorded over the 5-year period, data on assigned sex was available for 41 out of 47 records. This is because 6 records at NCRHA (3 orofacial clefts in 2021 and 3 orofacial clefts in 2022) were recorded on the National Birth Registry Digital Database with no patient identifiable information. NCRHA did not allow access to patient files but they allowed access to Plastic Surgery cleft repair lists that contained information: sex, date of birth, surgical procedure. The 3 OFC births in 2021 and 3 OFC births in 2022 at NCRHA were not listed for surgery at the time of data collection (May-July 2023) and the sexes could not be identified. Of the 41 babies for which sex was recorded, 26 were female and 15 were male.

Orofacial cleft characteristics (type; laterality; side; presence of syndromes; presence of other congenital anomalies)

The study group sample of 30 OFCs consisted of 17 CL/P (57%) and 13 CPO (43%).

Of the 13 CPO recorded, females (n=8) were greater than males (n=5).

For 5 of the 13 CPO cases, “Pierre Robin Syndrome” was found within the data sources for the OFC patient with CPO. It must be noted that this was vague as the more appropriate term “Pierre Robin Sequence” was not documented in the data sources and no specification as to whether this was isolated or associated with a syndrome. Treacher Collins Syndrome was observed in 1 CPO case.

In general, of the 30 OFCs, congenital anomalies were also associated with 5 OFC patients. Description of the congenital anomalies are presented in Table 11. The table also serves to highlight the inconsistent and ambiguous description of the clinical features of OFC patients with terms such as “CL/P” or “dysmorphic features”.

Table 11 Description found recorded within the data sources for 5 OFC patients associated with congenital anomalies

Description of the congenital anomalies as noted for 5 OFC patients
CL/P with ventriculomegaly, absent corpus callosum
Bilateral CLP with polydactyly
Bilateral CLP with micrognathia, low set ears, cystic mass affecting left eye
CPO with macrocephaly, low set ears, widespread nipples, shield shaped chest
CPO with dysmorphic features

OFC laterality (unilateral or bilateral) and side of the face affected were variables inconsistently found/available for data collection. Laterality of OFCs were only found describing 3 of the 30 OFCs. This includes 1 bilateral CLP, 1 bilateral CPO, 1 unilateral CLP affecting the left side.

Part B: Associated risk factors

A study group of 30 OFC babies and a closely matched healthy control group were included for analysis. Excluded from the sample were 17 of the 47 identified OFC births and their respective 17 closely matched healthy newborns within the NCRHA. These records were considered unretrievable as they were not stored at NCRHA's main hospital but at the Records Department of the Mt Hope's Women's Hospital which required additional ethical approval to access.

It must also be noted that at NWRHA, 2 OFC files were unable to be located by the Records Department. They explained that files were not made for these OFC babies as they died shortly after admission to NWRHA NICU which was confirmed with death certificates on the date of admission. Additionally, as their mothers were not patients and the newborns were not delivered at the hospital, maternal files did not exist. However, for these 2 OFC births, nursing admission notes were available with the following information: date of birth; sex; OFC characteristics; relevant maternal medical history. As this information contributes to the mortality rate of OFC newborns and was sufficient to allow closely matched controls, they were included in part B of the study.

Reasons encountered for missing data on variables include incomplete written details within files, maternal file or file of an OFC baby being unavailable.

Descriptive analysis of associated risk factors

The characteristics of the sample of the study group (thirty babies born with OFC within the 2018-2022 period) and control group (thirty healthy newborns closely matched by sex and birth month) are summarised in Table 12. The availability of variables and consistency at which they were found for collection within patient records are summarised in Table 13 and detailed in Table 14.

Table 12 Characteristics of the sample for 30 orofacial cleft cases (study group) and 30 closely matched healthy newborns (control group)

ASSOCIATED RISK FACTOR	OROFACIAL CLEFT GROUP (STUDY GROUP)				HEALTHY NEWBORNS WITHOUT AN OROFACIAL CLEFT OR OTHER CRANIOFACIAL ANOMALY (control group)			
PATIENT DEMOGRAPHICS								
Lived or died status	**n**	**%**			**n**	**%**		
Alive	22	73			30	100		
Dead	8	27			0	0		
Sex*	**n**	**%**			**n**	%		
Female	19	63			19	63		
Male	11	37			11	37		
BIRTH CHARACTERISTICS								
	n	**Missing**	**Mean +/- SD [Median]**	**Min-Max**	**n**	**Missing**	**Mean +/- SD [Median]**	**Min-Max**
Gestational age (weeks)	22	8	38+/- 2.38 [38]	32.2-43.4	30	0	39+/-0.795 [39]	35.7-40
Birth weight (kg)	18	12	2.53 +/- 0.779 [2.63]	1.13-3.75	30	0	3.16+/-0.281 [3.22]	2.52-3.56
Birth length (cm)	8	22	48.4+/- 5.26 [50.8]	40-54	30	0	51.3+/-1.88 [52]	46-55
Head circumference (cm)	8	22	33 +/- 1.63 [32.5]	31-35	29	1	32.9+/-33 [1.17]	31-35
Method of delivery	**n**	**%**			**n**	**%**		
C section	11	100			12	40		
Vaginal	0	0			18	60		
Missing data/no record found	19				0			
MATERNAL HISTORY								
	n	**Missing**	**Mean +/- SD [Median]**	**Min-Max**	**n**	**Missing**	**Mean +/- SD [Median]**	Min-Max
Maternal age	22	8	32.2+/- 7.89 [32]	18-43	30	0	25.5+/-5.61 [24]	18-36
Maternal medical history	**n**	**%**			**n**	**%**		
Within normal limits	22	73			29	97		
Not within normal limits / presence of medical condition	8	27			1	3		
Use of multivitamin containing folate during pregnancy?*	**n**	**%**			**n**	**%**		
Yes	3	21			11	37		
No	11	79			19	63		
Missing data/no record found	16				0			
Excess vomiting during pregnancy*	**n**	**%**			**n**	**%**		
Yes	1	7			0	0		
No	13	93			30	100		
Missing data/no record found	14				0			
Anaemia complicating pregnancy*	**n**	**%**			**n**	**%**		
Yes	0	0			0	0		
No	16	100			30	100		
Missing data/no record found	14				0			
Use of prescription (licit) drugs*	**n**	**%**			**n**	**%**		
Yes	3	19			0	0		
No	13	81			30	100		
Missing data/no record found	14				0			
	n	**Missing**	**Mean +/- SD [Median]**	**Min-Max**	**n**	**Missing**	**Mean +/- SD [Median]**	Min-Max
Number of pregnancies (gravida)	16	14	3.38 +/- 2.78 [2]	1-10	27	3	1.78+/-0.801 [2]	1-3
Number of times patient has given birth to a viable child Para	16	14	2.38+/- 1.86 [2]	0-7	27	3	1.44+/-0.698 [1]	1-3
History of abortion*	**n**	**%**			**n**	**%**		
Yes	1	6			5	17		
No	15	94			25	83		
Smoking history*	**n**	**%**			**n**	**%**		
Yes	0	0			1	3		
No	15	100			29	97		
Missing data/no record found	15				0			
Alcohol use*	**n**	**%**			**n**	**%**		
Yes	0	0			1	3		
No	15	100			29	97		
Missing data/no record found	15				0			
Use of illicit drugs*	**n**	**%**			**n**	**%**		
Yes	0	0			1	3		
No	15	100			29	97		
Missing data/no record found	15				0			

* These variables were excluded from the analysis due to small sample sizes or lack of rigour in collecting the data

Table 13 Availability of variables (evidence-based risk factors associated with an orofacial cleft) and whether they were recorded (available for data collection) or not (information not available for data collection).

	Variable							
	Patient demographics	Birth characteristics	Orofacial cleft characteristics	Family history	Maternal history			
					Maternal demographics	Maternal medical and drug history	Pregnancy history	Maternal social history
Variable consistently found/available for data collection	-Lived/died status -Sex	-Gestational age -Birth weight -Length -Head circumference -Method of delivery	-Presence of OFC -Presence of syndrome -Presence of associated congenital anomaly		-Maternal age	-Maternal medical history	-Number of pregnancies (gravida) -Number of times given birth to a viable child (para) -History of abortion	
Variable inconsistently found/available for data collection			- Type (CL/P; CPO) -Unilateral/bilateral -Side of face affected			-Use of multivitamin containing folate during pregnancy? - Excess vomiting during pregnancy -Use of prescription (licit) drugs		-Smoking history -Alcohol use -Use of illicit drugs
Variable not found/ unavailable for data collection	-Race/ethnicity		-complete/incomplete	-History of craniofacial anomaly -Parental consanguinity -Paternal age -Paternal occupation	-BMI -Socioeconomic level -Education level -Maternal occupation	-Anaemia complicating pregnancy		-Occupation -Stress

Table 14 Description on the data available for variables that were not found or inconsistently found during this study

Variable	Availability for data collection
Race/ethnicity	This variable was not found to be available for data collection
Orofacial cleft characteristic of completeness	This was not found recorded
Family history: history of craniofacial anomaly; parental consanguinity; paternal age; paternal occupation	A record of family history was not found in any patient records
Maternal demographics: BMI, socioeconomic level, education level, maternal occupation	No data was found on variables BMI, socioeconomic level, education level and maternal occupation in either group across all data collection sources.
Maternal medical history	The variable “anaemia complicating pregnancy” was not recorded within any of the maternal control or study group files. It is assumed that if the mother experienced this it would have been documented. Of the 60 mothers of the 30 babies within the study group and 30 babies within the control group, only one record of vomiting during pregnancy was found. This was a mother to a newborn with an orofacial cleft (study group). This variable was not found to be recorded in any other files. Use of multivitamins containing folate during pregnancy: This variable was available for data collection for 14 mothers of OFC babies out of 30 in the study group. Only 3 out of 14 mothers (21%) were found to use multivitamins containing folate during pregnancy. For the control group, 11 out of 19 mothers of health newborns (37%) reported use of multivitamins containing folate during pregnancy.
Maternal social history	The maternal social history variables “smoking history”, “alcohol use” and “use of illicit drugs” were inconsistently found whereas “occupation” and “stress” were not found to be recorded within the files of mothers in either study or control group. The missing data for “smoking history”, “alcohol use” and “use of illicit drugs” was handled in the conduct phase (Table 9) where clinicians and clinical staff involved in recording the data confirmed that positive findings were recorded, and the absence of a positive finding can be assumed to be a negative finding. The data collected for the “smoking history” and “alcohol use” variables reflect this. Only one mother, within the control group, was found with a positive history of smoking, alcohol use and illicit and licit drug use. It was recorded under their medical history as “does drugs” with no further details.

Birth characteristics (lived/died status; gestational age; birth weight; length; head circumference; method of delivery)

From a sample of 30 orofacial clefts, 8 died shortly after birth and 22 lived. Of the 8 deaths, 3 were associated with other congenital anomalies. The associated congenital anomalies recorded in the 3 orofacial cleft patients were: ventriculomegaly, absent corpus callosum, cleft lip/palate; bilateral cleft lip and palate, micrognathia, low set ears, multiple congenital anomalies, cystic mass of the left eye; cleft palate with unspecified dysmorphic features. Among the control group 0 died.

In general, babies with an OFC were born earlier (38+/-2.38 vs 39+/-0.795 weeks), were of lower birth weight (2.53+/-0.779 vs 3.16+/-0.281 kg), shorter birth length (48.4+/-5.26 vs 51.3+/-1.88 cm) and of similar head circumference (33+/-1.63 vs 32.9+/-33 cm) than healthy newborn babies within the control group.

Babies with an OFC, seem to have more variability around the mean (greater standard deviation) and is likely due to smaller sample size.

The variable “method of delivery” was only found for 11 babies with an OFC within the study group of 30. All 11 OFC babies were delivered via C section. Method of delivery was well documented in all healthy newborns, revealing 40% (n=12) were delivered by C-section and 60% (n=18) were delivered vaginally.

Maternal history

The variable maternal age was available for 22 mothers in the study group and 30 mothers in the control group. Mothers of OFC babies were on average older (32.2+/-7.89 years) than mothers of healthy newborns (25.5+/-5.61 years).

The variable “maternal medical history” was available for 30 in the study group and 30 in the control group. Medical history was not within normal limits for 8 of 30 mothers of OFC babies, with the following conditions recorded: Diabetes Mellitus type 1 (n=1), hypertension (n=1), HIV or HAART (n=1), Diabetes Mellitus type 2 / HSV2 (n=1), Covid-19 (n=1), gestational diabetes (n=3). Only 1 mother of a healthy newborn had a recorded medical history of hypothyroidism.

Maternal records of “gravida” and “para” were consistently found. It must be noted that missing data on the variable “history of abortion” in the absence of a positive

finding was assumed to be a negative finding according to clinicians involved in recording of data into maternal files.

For 16 mothers of OFC babies (study group), the average number of pregnancies (gravida) was 3.38, the average number of births (para) was 2.38. For 30 mothers of healthy newborns (control group), the average number of pregnancies (gravida) was 1.78 the average number of births (para) was 1.44. From our data, more mothers of healthy newborns (5 out of 30; 17%) reported a history of abortion compared to mothers of OFC babies (1 out of 16; 6%).

Predictors of OFCs

To find which factors/variables were strongly linked with the presence of an OFC, logistic regression analysis was done. Table 15 shows the effect sizes for each variable appropriate for analysis from the single models and the multiple variables model; this included all the variables with p values < 0.1 in the single models and stepwise regression was used to create a final reduced model containing only statistically significant ($p<0.05$) variables. Variables with the largest p-values were removed at each step as follows: birth weight >maternal age>length>para number of live births>gestational age. The best predictors of OFC that were retained in the reduced model were: Maternal medical history within normal limits; number of pregnancies (gravida).

The logistic regression results suggest that a mother with a normal medical history is 91% (OR = 0.089) less likely to give birth to a baby with an OFC. Figure 3 shows the predicted probability of having a baby with an OFC for mothers with medical history within normal limits compared to those not within normal limits. Figure 3 suggests that for a mother with a medical history within normal limits, there is approximately 25% chance of giving birth to a baby with an OFC compared to a chance of approximately 80% for a mother without a normal medical history.

The results also suggest that the chances of women giving birth to a baby with an OFC increase by 74% (OR = 1.74) for each new gravida pregnancy experienced. Figure 3 shows the increased predicted probability of a baby with an OFC for each pregnancy.

Table 15 Logistic regression analysis of variables found appropriate for analysis

Associated risk factor (categorical)	Single Models				Multiple variables model				Stepwise deletion
	Orofacial cleft study group vs. Control group				Orofacial cleft study group vs. Control group				
	OR	CI (lower upper)	partial R	p	OR	CI (lower upper)	partial R	p	
	PATIENT DEMOGRAPHICS				PATIENT DEMOGRAPHICS				
Lived or died status									
Alive-dead	0.00000002	0.00-inf	0.148	0.99					
Gestational age (weeks)	0.641	0.418-0.983	0.078	0.041	0.798	0.441-1.444	0.29	0.456	5
	BIRTH CHARACTERISTICS				BIRTH CHARACTERISTICS				
Birth weight (kg)	0.098	0.020-0.483	0.215	0.004	0.088	0.00002-425.89	0.602	0.574	1
Birth length (cm)	0.757	0.578-0.991	0.13	0.042	1.398	0.501-3.90	0.584	0.522	3
Head circumference (cm)	1.067	0.569-2.00	0.001	0.84					
	MATERNAL HISTORY				MATERNAL HISTORY				
Maternal age (n=52)	1.157	1.05-1.271	0.163	0.003	0.939	0.713-1.24	0.59	0.654	2
Maternal medical history within normal limits									
Yes-No	0.095	0.011-0.815	0.086	0.032	0.089	0.008-0.973	0.238	0.047	
Number of pregnancies (gravida)	1.809	1.092-2.997	0.152	0.021	1.743	1.045-2.907	0.238	0.033	
Number of times patient has given birth to a viable child (para)	1.883	1.038-3.418	0.099	0.037	0.432	0.085-2.188	0.31	0.311	4

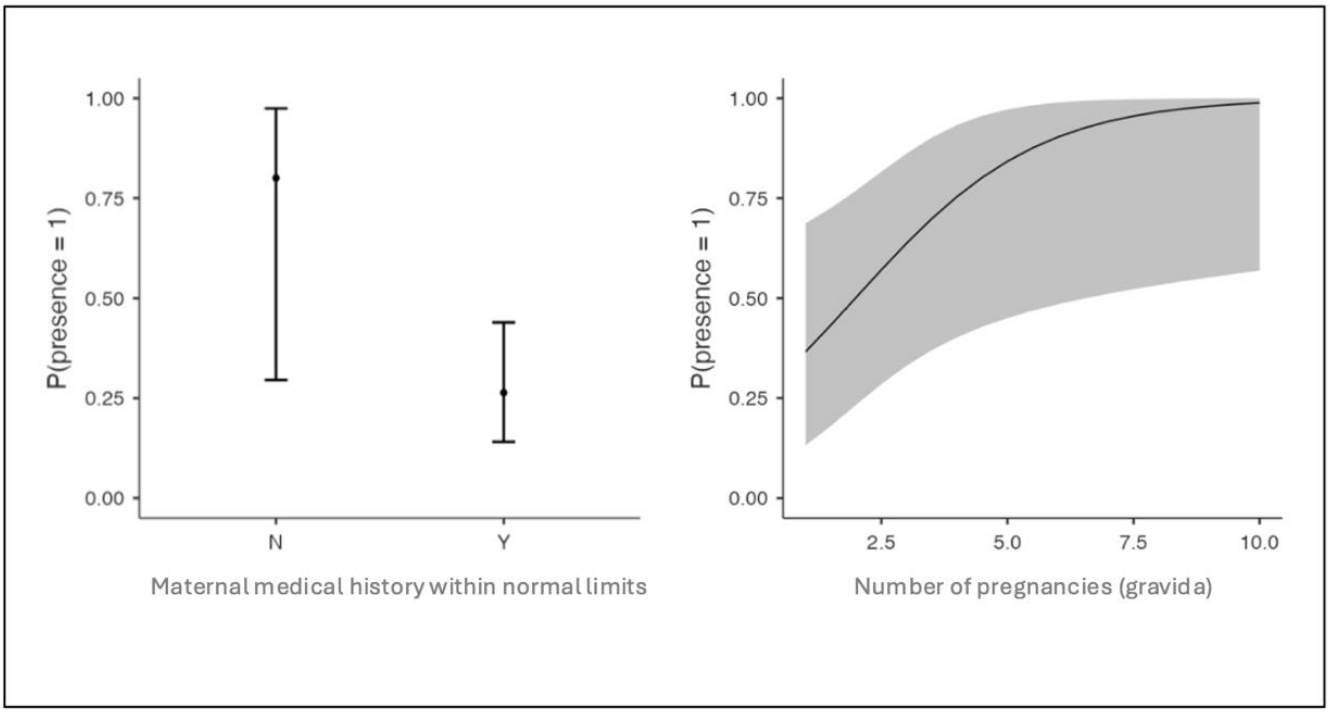

Figure 3 Predicted probabilities of OFCs from the final reduced logistic regression model containing maternal medical history within normal limits (left panel) and number of pregnancies (gravida) (right panel)

Observations of the care pathway for managing babies born with an OFC

The management of babies born with OFCs within Trinidad and Tobago begins with diagnosis. This is usually at or shortly after birth. Detection before birth is also possible via routine antenatal ultrasound scan which is a service available to the community through the RHAs but lacks a Foetal Medicine Specialist. Once an OFC is detected at birth, the baby is transferred to the RHA's NICU for feeding assessments and other investigations to rule out syndromes and associated malformations. The parents and family are counselled and supported by a Dietitian and referral made to Plastic Surgery where management is continued as an outpatient. There is only one major referral centre for NWRHA, NCRHA, ERHA, TRHA and a separate pathway for SWRHA. Discussions are held between the Neonatologist and Plastic Surgeon regarding planning for surgical repair.

While each RHA has a care pathway, at the time of writing this study, there is no care pathway that is standardised across all RHAs, providing a multidisciplinary team approach to comprehensive cleft care.

4.5 Discussion

Key results, interpretation, generalisability

Objective: To determine the birth prevalence of orofacial clefts and craniofacial anomalies in Trinidad and Tobago

The birth prevalence of OFCs was found to be 0.64 per 1000 births. This finding is approximately half of the 1.2 per 1,000 births reported by Robertson for the birth prevalence of orofacial clefts (OFCs) in the population of Trinidad and Tobago in 1963. Robertson's report highlighted that the birth prevalence of orofacial clefts (OFCs) varied by race and ethnicity, noting a higher incidence among East Indians at approximately 2 per 1,000 births, compared to 0.62 per 1,000 for "other racial groups." Although the full text of Robertson's study is unavailable and the term "other racial groups" is not defined in the abstract, the current birth prevalence of 0.64 per 1,000 births aligns closely with what was reported for those groups in 1963. Since then, the population has increased from 830,000 in 1963 to around 1.5 million in 2024, while the average annual births have decreased from approximately 30,000 to 15,000 (Robertson 1963; UNFPA 2024).

While there are few reports from other Caribbean countries for comparison, the current finding is similar to the Dominican Republic's 1980 report of 0.62 per 1,000 births, but it is lower than the most recent figure from Cuba, reported in 2021, which is 0.78 per 1,000 births (Garcia-Godoy 1980; Taboada-Lugo et al. 2021). Within the Latin American region, this finding is comparable to the birth prevalence reported for Colombia in 2019, which was 0.6 per 1,000 births.

Compared to the widely cited global prevalence figure of approximately 1 in 700 live births, which has been reported by Mossey and Little (2002) and remains the internationally recognised benchmark for OFC prevalence, the birth prevalence in Trinidad and Tobago appears lower. This global figure, based on comprehensive epidemiological reviews and analyses of international registry data, highlights that while Trinidad and Tobago's reported prevalence aligns with findings in some regional contexts, it is substantially below the global estimate, underscoring the need for further investigation into local factors influencing OFC prevalence (Mossey and Modell, 2012; Mossey and Little, 2002).

Link/association between geography and ethnicity

Ethnicity was not recorded in the data sources. Despite this, an interesting finding of this study is that nearly half of the OFCs recorded on T&T's digital national birth registry database over the 5-year period were reported in the country's southern region at SWRHA. SWRHA is located in the large city of San Fernando in Trinidad and has a significant East Indian population (Clarke CG, 2023; Gugolati, 2021). Similarly, Robertson's (1963) report on the racial incidence of OFCs in Trinidad found the highest incidence in the East Indian racial group. NCRHA reported the second highest number of OFCs. NCRHA and SWRHA both provide healthcare geographically for the region spanning both RHAs. This region is where Central Trinidad's population and cities such as Chaguanas and Cunupia resides and is not only are associated with a predominant East Indian population but also has the highest Hispanic or Latin American presence. This is because the twin-isle Trinidad and Tobago lies off the coast of Venezuela and is host to an estimate 40,000 Venezuelan refugees and migrants (Alsina, 2022). This study highlights the higher birth prevalence of 0.96 orofacial clefts (OFCs) per 1,000 births reported in the literature for Venezuela, noting its close proximity and potential influence on Trinidad and Tobago (World Health Organization 1998; World Health Organization (WHO) 2002). Although OFCs can occur in any race, our study's association is an important one as it supports the global consensus that OFCs have significant ethnic variation, with a higher incidence (birth prevalence) in people of Asian, Native American or Hispanic descent (Huang et al. 2024; Dixon et al. 2011).

Sex split of the babies born with an OFC

While existing literature highlights sex-based differences with OFCs, with CL/P occurring more often in males and CPO occurring more often in females, this study cannot conclude sex predilection (Pool et al., 2021). In this study, the female:male ratio of 1.7:1 was noted from 41 of the 47 babies identified as being born with an OFC. However, without information on sex ratio for the whole cohort and the type of OFC, conclusions regarding incidence of OFCs among the two sexes cannot reasonably be made.

Orofacial cleft characteristics (poor records, no classification agreed, inconsistent, ambiguous description) (type; laterality; side; presence of syndromes; presence of other congenital anomalies; completeness)

There is general perception that epidemiological research is hampered by a lack of sensitivity and specificity in grouping those with OFCs into sub-phenotypes (McBride et al. 2013). This is because major cleft phenotypes are heterogeneous entities as cleft lip with or without palate (CL/P) and cleft palate only (CPO) occur at distinct embryologic stages of development. For this reason, this study reports on OFCs as a broad encompassing term due to the ambiguity in the data found. For example, rather than a comprehensive description of the OFC identifying characteristics such as anatomical involvement, extent, laterality and completeness, to name a few, the recordings were vague such as "CL/P" referring to a cleft lip with or without a palate. Although this reduces the value and quality of this study's OFC data, it highlights an area requiring improvement prior to implementing future epidemiologic research. It also reminds the importance of comprehensive classification as both syndromic and non-syndromic OFCs have genetic and environmental aetiology (McBride et al. 2013). Although there is no international consensus on which of the many OFC classification systems should be used, the most widely used is the LAHSHAL classification for its comprehensiveness, intra and interrater reliability, reproducibility and ease of use with little training required (McBride et al. 2013; Houkes et al. 2021).

Objective: To explore associated factors that might be linked to these anomalies

In the study group of 30 OFC babies, 27% (8 out of 30 OFC babies) died shortly after birth. Without information on the number of deaths among the 47 babies born with an OFC over the 5-year period, neonatal mortality rate (NMR) for cleft-births could not be determined. This study was also unable to obtain information that would allow the population-based NMR to be determined for comparison.

In terms of OFC characteristics, although it was difficult to ascertain accurate clinical descriptions from the available data, anomalies were found to be associated only with CPO. Similar to existing evidence, Pierre Robin sequence was the most

common anomaly found to be associated with CPO (5 out of 13 CPO cases). CPO can also occur with a number of syndromes including van der Woude, Stickler, Treacher Collins and Apert syndrome but this study reports only one case of CPO associated with a syndrome which was Treacher Collins Syndrome (Cugno and Sommerlad, 2022).

Only a limited number of variables could be analysed as many were unavailable/missing or too few recorded within the study group for that period. Of the variables that could be used, on the single analysis, the following were significant predictors of OFCs: gestational age, birth weight, birth length, maternal age, maternal medical history within normal limits, number of pregnancies (gravida), number of times patient has given birth to a viable child (para).
When these variables are analysed together, only maternal medical history and number and gravida remain significant, suggesting these are the stronger predictors which might themselves be influencing the other variables.

In general, babies with an OFC were born earlier (38+/-2.38 vs 39+/-0.795 weeks), of lower birth weight (2.53+/-0.779 vs 3.16+/-0.281 kg), shorter birth length (48.4+/-5.26 vs 51.3+/-1.88 cm) and of similar head circumference (33+/-1.63 vs 32.9+/-33 cm) compared to healthy newborn babies within the control group. These findings of earlier gestational age, lower birth weight and shorter birth length for babies born with an OFC, are aligned with trends that have been described in various cleft subtypes around the world (Ács et al. 2024; Lei et al. 2009; Wyszynski et al. 2003; Becker et al. 1998). It must be noted that within the literature, studies link specific OFC subtypes with birth characteristics. For example, Becker et al's (1999) study reported no difference between body dimensions for babies with isolated cleft lip (CL) and healthy newborns but found that infants with isolated cleft palate (CPO), cleft lip and palate (CLP) or associated with Pierre Robin sequence tended to lighter and shorter (Becker et al. 1999). It is acknowledged that this study could not make such associations because of the quality of data collected.

Epidemiological and experimental studies suggest that maternal risk factors play a significant role in OFC development. Maternal age has been widely studied as a risk

factor for OFCs, with several studies finding a positive association with increasing maternal age for cleft lip with or without cleft palate, cleft palate, or both (Womersley and Stone, 1987; Saxen, 1974; Shaw et al. 1991). This study is consistent with those findings as mothers of OFC babies were on average, older (32.2+/-7.89 years) than mothers of healthy newborns (25.5+/-5.61 years). However, recent studies emphasise the importance of taking paternal age into account when analysing the effect of maternal age and this study lacked data on paternal age and could therefore not adjust for paternal age (Bille et al. 2005).

Logistic regression results suggest that for a mother with a medical history within normal limits, there is approximately 25% chance of giving birth to a baby with an OFC compared to a chance of approximately 80% for a mother without a normal medical history. This study's findings are higher than reported within the literature for mothers with a medical history within normal limits. This may be explained by major maternal risk factors that this study could not account for such as smoking and alcohol use. However, this broad finding of mothers without a normal medical history having a higher chance of a cleft birth is consistent with other studies (Angulo-Castro et al. 2017; Ács et al. 202; Ács et al. 2024).

Within the literature, there is much disagreement about the association of multigravidity with OFCs. Similar to other researchers that have observed a higher rate of cleft births among women with increased gravidity, this study's results suggest that the chances of women giving birth to a baby with an OFC increase by 74% (OR = 1.74) for each new gravida pregnancy experienced (Menegotto and Salzano, 1991; Lopez-Camelo and Orioli, 1996; Vieria and Orioli et al. 2002)

Strengths

As the first update of epidemiological evidence on orofacial clefts for the Caribbean twin-isle Trinidad and Tobago's population since Robertson's (1963) study more than six decades ago, there are many strengths to this study.

Firstly, Trinidad and Tobago's public healthcare system is free to everyone and is designed to enhance accessibility by ensuring geographical coverage of the country through different Regional Health Authorities. All births are free to be registered and must be done within 42 days of birth according to Chapter 44:01 of Trinidad and

Tobago's "The Registration of Births and Deaths Act". All babies born with a congenital anomaly such as a CFA are able to be seen through a NICU within a RHA for management. Although the country, like many Small Island Developing States (SIDS) lack Specialists, they provide their expertise and care through the RHAs. This is considered a strength contrary to less-developed countries where hospital care is more available to women from upper socioeconomic groups and all births are unlikely to occur in hospital and all newborns are unlikely to be assessed in a hospital setting. Interpretation of RHA-based data for this and future studies is therefore considered straightforward for this country as these factors support the proportion of births delivered in hospital being a close representative approaching 100% of the births for the general population. The sample of babies born with OFCs within this study is therefore thought to be a close representative for the population during that retrospective period.

Secondly, randomisation was done to individually select controls. To control confounders, cases and controls were matched by gender and birth month. As controls were selected within the same RHA, matching was also to geographic location.

Other strengths are that this study pooled data from several overlapping sources such as patient records/hospital files and nursing admission notes to reduce the amount of missing data. The use of multiple sources of ascertainment: Trinidad and Tobago's digital national birth registry database, nursing admission logbooks, congenital anomalies logbooks, Plastic Surgery theatre lists for surgical cleft repairs.

Limitations

This study is not without its limitations.

Missing data

Missing data was encountered within three areas of record keeping: patient history taking, CFA surveillance and OFC classification.

In terms of patient history taking, no uniform method of recording data for babies born with congenital anomalies, healthy newborns and mothers was found across

the 4 RHAs covering the public healthcare sector for this country. For all patients, record keeping was found to be inconsistent, not following a systematic or standardised approach, resulting in missing information from patient histories. Several potential confounders such as maternal smoking, alcohol consumption, diet intake were unable to be assessed as they were not routinely recorded within maternal hospital records. Patient history taking should follow a systematic and standardised format. It should include parental data for newborns such as paternal and maternal history. To ensure comprehensive history taking, future studies should employ a data collection proforma covering variables such as the one used to conduct this study (see Appendix 2).

CFA surveillance refers to the monitoring of patients with craniofacial anomalies including orofacial clefts. In 2018, Trinidad and Tobago's digital national birth registry database was started and was intended as the main data source. However, a variety of data sources (congenital anomalies logbook, newborn and maternal hospital files, nursing admission notes) that were not uniformly available across the RHAs, were used to verify, supplement and reduce the amount of missing data. A single data source of CFAs such as Trinidad and Tobago's digital national birth registry database should hold the data collected from a standardised proforma for all RHA's, introducing uniform, consistent data collection and maintaining geographic coverage. CFA surveillance should be linked to the birth registry database for the country to find healthy newborns and to be able to determine stillbirths, perinatal deaths (not requiring admission) for the country.

A thorough description of orofacial cleft characteristics or a clear implementation of an OFC classification and registration system, such as LAHSHAL and ICD-11 (previously ICD-10), was not evident in the available data sources. A range of heterogenous cleft phenotypes exist and the descriptions were vague, not considered accurate or true representations of the clinical picture. Consensus on reporting OFCs and clinical features of CFAs is needed to facilitate future research and international collaboration (Mossey et al. 2023). It is important to appreciate that CL(P) and CP differ not only anatomically and chronologically but also in developmental pathogenesis, and there are epidemiological and distinctive

differences in sex predilection. To be able to differentiate phenotypes also has implications for future clinical protocols, which may be determined not only by cleft type, but also by cleft severity.

The accuracy of the data recorded is uncertain

The accuracy of patient data entry must be mentioned, particularly given varied experience and knowledge of individuals responsible for entering critical information in different data sources varied.

Data collectors should undergo training in using the data collection proforma, assessment and recording of OFC characteristics and clinical features of other CFAs. They should be trained in comprehensive patient history taking, use of the CFA surveillance system and identifying OFC characteristics and clinical features of other CFAs. Training of data collectors is suggested as consensus is needed on cleft classification and the recording of obstetric history to reduce ambiguity. For example, “G2P1” means two pregnancies, one birth. In this study where mothers already gave birth to either babies with OFCs or healthy newborns, G2P1 suggests that the first pregnancy was not carried beyond 24 weeks gestation with the mother experiencing either a miscarriage or having a history of abortion. This data should not be left to assumption. Also, in this study, the presence of an OFC was recorded in data sources by a variety of medical personnel varying in expertise. Given that some minor forms of OFCs, such as submucous clefts, can be challenging to detect, it is important that those entering data are trained to recognise cleft characteristics (Kubon et al. 2007). Additionally, training in using the data collection proforma is essential to reduce information bias.

Other limitations

While logistic regression was used to assess associations between selected maternal and birth-related variables and the presence of orofacial clefts (OFCs), it is important to acknowledge the limitations of this approach in the context of the dataset’s deficiencies and structure. Logistic regression assumes accurate, complete, and sufficiently large datasets, and is most appropriate when variables are reliably recorded with minimal bias. In this study, significant missing data, inconsistencies in recording and small sample size obtained over five years limit the robustness of the regression outcomes. These limitations underscore the need for a longer observation period to increase the dataset and strengthen analyses in future studies.

Furthermore, the dataset did not reliably differentiate between cleft sub-phenotypes, specifically cleft palate only (CPO) and cleft lip with or without palate (CL/P), leading to these categories being pooled for analysis. This approach warrants caution, as CP and CLP are distinct entities with different embryological origins, risk factors, and epidemiological patterns. Pooling them obscures specific associations and dilute findings relevant to each sub-phenotype. Future analyses would benefit from maintaining these categories separately to enable more precise epidemiological and risk factor exploration.

Given the limitations in data quality, it may have been more appropriate to focus on detailed descriptive analysis (qualitative and quantitative) of the available variables to identify trends and contextual factors within the local setting rather than relying solely on logistic regression to infer associations. Such an approach would provide a clearer understanding of the patterns observed while acknowledging data limitations and avoiding over-interpretation of associations derived from incomplete or biased datasets.

It is also important to consider the potential limitations in case ascertainment within this study, particularly regarding cleft palate only (CPO) cases. Submucous or less severe forms of CPO may not be identified at birth and can remain undiagnosed until speech difficulties emerge later in childhood, leading to underreporting within birth registry and hospital-based datasets (Mossey and Modell, 2012). This under-ascertainment limits the accuracy of prevalence estimates and may affect the representativeness of associated analyses. To address these deficiencies, baseline records require strengthening, including the implementation of standardised clinical examination protocols at birth and routine checks during early childhood to improve detection rates. Government investment in prospective, population-based surveillance systems that follow pregnancies from antenatal stages through to at least one year postnatally would enable more complete case capture and accurate epidemiological assessment. Additionally, long-term studies conducted over ten years or more would provide robust data to inform health service planning and guide the development of cleft care pathways within Trinidad and Tobago and the wider Caribbean region.

Future work

To combat the limitations encountered in this study, the importance of audit and quality improvement projects must be emphasised. The focus of these projects should be to improve the three areas of record keeping: patient history taking, CFA surveillance, OFC classification. These projects aim to reduce missing data and achieve standardisation of record keeping across all RHAs. They set the groundwork for a prospective observational epidemiological study over a 10-year period to increase the dataset, given the small size of the dataset obtained over 5 years in the present study. To further reduce confounding bias with matching to a control group, maternal age should be matched in addition to the baby gender, birth month and geographic region, as done in Gili et al.'s (2012) case-control study. Suggestions outlined in this study should be implemented to reduce information bias (a single data source covering all RHAs, a data collection proforma covering all variables, trained data collectors). In so doing, future epidemiological evidence on OFCs and other CFAs from Trinidad and Tobago's multi-ethnic population can add a greater contribution to the global epidemiologic picture.

4.6 Conclusions

In conclusion, the updated birth prevalence for OFCs in the population of Trinidad and Tobago is 0.64 per 1000 births. Despite limitations such as missing data and a small dataset, variables were found appropriate for analysis. The likelihood of a birth with an OFC increases with earlier gestational age, lower birth weight, shorter birth length and maternal factors such as maternal age, a medical history that is not within normal limits and higher gravidity. Finally, in addition to observing the absence of a multidisciplinary care pathway providing comprehensive cleft care, three areas within record keeping were identified as requiring development through audit and quality improvement projects to facilitate further epidemiologic research within this population and international collaboration.

CHAPTER 5 SCOPING REVIEW

Title:

Characteristics of multidisciplinary team (MDT) care pathways for the management of orofacial clefts: A scoping review

5.1 Abstract

Background

Orofacial clefts (OFCs) are the most common craniofacial congenital anomaly worldwide. To be effective and efficient with management, a multidisciplinary team (MDT) of specialised professionals following a protocol of comprehensive cleft care is generally considered the best approach. Unfortunately, there are global inequalities in care, with countries such as Trinidad and Tobago having no MDT Cleft Service or structured cleft care pathway. Although a well-established and standardised cleft care pathway such as those in developed countries is the goal, a basic, sustainable MDT care pathway must first be established upon which it can grow. This scoping review systematically appraises the literature on MDT care pathways for the management of patients with OFCs globally.

Aims and Objectives

The aim was to use the information found to suggest characteristics of a care pathway appropriate for introducing basic, sustainable MDT cleft care.

The specific objectives were to review the literature to:

1. Identify the characteristics of an ideal MDT cleft care pathway and facilitating factors and challenges to its implementation;
2. Define characteristics of a basic, sustainable MDT cleft care pathway that can be implemented.

Methods

The Joanna Briggs Institute (JBI) guidelines were followed in this scoping review. The databases Ovid MEDLINE, Scopus, Cochrane Library and Latin American and Caribbean Health Sciences Library (Lilacs) were searched for publications. The reference list of all included sources of evidence were screened for additional studies. Cleft lip and palate associations around the world were contacted to identify unpublished guidelines. Only publications involving the management of solely the non-syndromic orofacial cleft phenotype were considered. Management from all clinical specialities within an MDT were considered. Management includes diagnosis and treatment from the speciality involved. Studies were screened by two independent reviewers using the pre-determined eligibility criteria and any disagreements resolved with a third (experienced) reviewer.

Results

This review identified 34 sources suitable for synthesis and interpretation. Overarching themes/ characteristics of MDT cleft care pathway were identified within the included sources of evidence as a statement of goals, infrastructure, MDT composition, supporting documents for the delivery of safe, quality cleft care, cleft care timeline and facilitating factors to optimising the care pathways. Using these characteristics, an ideal cleft care pathway was defined and suggestions were proposed for a basic cleft care pathway capable of introducing comprehensive cleft care in low-resource settings.

Conclusions

There is no global consensus on a standardised care pathway for management of babies born with an OFC. The evidence synthesised in this review allowed characteristics of an ideal OFC cleft care pathway to be defined as well as facilitating factors and challenges to its implementation to be identified. This structured review of the evidence makes initial suggestions for a basic care pathway and the next steps would be further review and appraisal involving stakeholders, to make recommendations.

Keywords:

Cleft lip and palate; guideline; management; pathway; orofacial cleft.

5.2 Introduction

Background:

Orofacial clefts (OFCs) are the most common craniofacial congenital anomaly worldwide (Mossey et al., 2009). To be effective and efficient with management, a multidisciplinary team (MDT) of specialised professionals following a protocol of comprehensive cleft care is the best approach (Kassam et al., 2020). Unfortunately, there are global inequalities in care. The reality is that the provision and access to comprehensive cleft care differs between developing and developed countries, with developing countries such as Trinidad and Tobago, despite their high-income status, lacking a multidisciplinary team approach to providing comprehensive cleft care. Like other Small Island Developing States (SIDS), this may be due specialist shortages, being overlooked by foundation-based cleft outreach programmes that often prioritise lower income countries, or the absence of evidence suggesting this as an area requiring development (Sharratt et al., 2020). Although well-established and standardised cleft care pathways such as those in developed countries are the goal for others such as SIDS and Least Developed Countries (LDCs), a basic, sustainable MDT care pathway must first be established upon which it can grow.

While the terms "care protocol" and "care pathway" are often used interchangeably, this review specifically focuses on care pathways. Care pathways can be defined as a way of providing a simple, clear outline of management, essentially, “what happens, when it happens and who is responsible” within a defined timeframe (Renard 2024). Care pathways effectively integrate standards and guidelines to inform decision-making, allow for the standardisation of care and has the potential to streamline multidisciplinary clinical practice. In contrast, protocols are more rigid, prescribing specific steps to follow(NHS Scotland 2023).

Rationale:
Due to the broad nature of a care pathway, it was considered appropriate to review the literature through a scoping review approach to give an overview of the information available on MDT care pathways for managing patients with OFCs globally and give a framework for the information to be mapped.

The aim was to use the information found to suggest characteristics of a care pathway appropriate for introducing basic MDT cleft care that is both sustainable and scalable.

The specific objectives were to review the literature to:

1) Identify the characteristics of an ideal MDT cleft care pathway, facilitating factors and challenges to its implementation;
2) Define characteristics of a basic MDT cleft care pathway that is sustainable, scalable and can be implemented in low-resource settings

It answers the following question: What are the characteristics of a basic MDT care pathway that is both sustainable and scalable, compared to an ideal MDT care pathway for the management of patients with orofacial clefts?

5.3 Methods

5.3.1 Protocol and registration

The protocol for this scoping review was pre-registered on 17/6/2024 on Open Science Framework (https://doi.org/10.17605/OSF.IO/VHMZK). The review was reported according to PRISMA-ScR checklist (Tricco et al., 2018) (see Appendix 3).

5.3.2 Eligibility criteria

Inclusion criteria

The categories for eligibility criteria were developed based on the Population, Concept, Context (PCC) framework recommended by the Joanna Briggs Institute (JBI) (Peters et al., 2022). This is described below.

Population (P)

The population refers to the multidisciplinary teams (for example the different healthcare providers/specialities/clinical disciplines) involved in the management of an orofacial cleft.

Concept (C)

The concept examined was the global MDT care pathways for the management of an orofacial cleft patient. As these were anticipated to vary in the extent of their complexity, this review maps the literature for different MDT care pathways for orofacial clefts into an ideal MDT care pathway and a basic, sustainable care pathway. The criteria for both pathways are outlined in Table 16. As the disciplines within the team have well-defined roles and deliver procedures at approximate timepoints throughout an orofacial cleft patient's life, the pathways highlight such interventions along a timeline. This review focused on recommendations, guidelines, guidance and policies for members (by discipline) of the team carrying out essential diagnosis and management procedures along the timeline of birth to adulthood. To support the development and progression from the basic, sustainable cleft care pathway to the ideal cleft care pathway, facilitating factors and challenges within the literature were highlighted in this review. For example, introducing an audit network was considered a facilitating factor and shortages in medical and surgical expertise are considered a challenge.

Context (C)

There were no restrictions on the place that care is delivered. Therefore, MDT care in all settings such as hospital, clinic, community and outreach will be considered.

Exclusion criteria

The search was restricted to articles and reports published in English. Papers pre-1990 were excluded as most major non-profit cleft lip and palate associations were founded circa 1990. Management of syndromic orofacial clefts and non-traditional, novel diagnostic techniques/procedures and treatments were excluded.

Table 16 Eligibility criteria for the article recommendations included in the MDT cleft care pathways

Ideal orofacial MDT cleft care pathway	Basic, sustainable orofacial MDT cleft care pathway
- Should include antenatal care - Evidence-based multidisciplinary treatment based on clinical practical guidelines that have led to standardisation of care. These are likely to be carried out through national level pathways and delivered in the form of a cleft service/centre (Frederick et al. 2022)	- May not include antenatal care - Sustainable models of orofacial cleft care that are likely to be delivered within settings that are not at national level. Examples include outreach settings, low-resource settings, resource constrained settings

5.3.3 Types of Sources

Sources considered included systematic reviews and descriptive observational study designs, including case series, individual case reports and cross-sectional studies. Lower levels of evidence, such as texts and opinion papers were also considered. Additionally, policies, guidance documents, guidelines, recommendations, relevant updated documents and unpublished work from cleft lip and palate associations were considered. Table 17 summarises the eligibility criteria discussed and agreed (by SJ, NI) to ensure consistency in the choice of articles.

Table 17 Summary of eligibility criteria for studies within this review

Inclusion criteria	Exclusion criteria
• Population: The different disciplines of the MDT who provide orofacial cleft care • Interventions: Reasons that the cleft patient must be seen/reviewed by the different disciplines within the MDT throughout their life (examples: consultation, assessments, reviews, interventions, treatments, surgeries) • Types of studies: -systematic reviews -descriptive observational study designs -case series -case reports -cross-sectional studies -recommendations -guidelines -guidance -policies • Context: care delivered within all settings: hospitals, clinics, community, outreach settings, resource constrained settings	• syndromic orofacial clefts • non-traditional, novel diagnostic techniques/procedures and treatments • non-English studies • no care setting specified • published pre-1990

5.3.4 Search

To identify studies, the following electronic databases were searched: MEDLINE, Scopus, The Cochrane Library, Latin American and Caribbean Health Sciences Literature (Lilacs).

The search strategy aimed to locate both published and unpublished studies. An initial limited search of MEDLINE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a comprehensive search strategy. Supported by a subject specialist librarian (advising on suitable terminology, databases), the full search strategy, including all identified keywords and index terms, was adapted for each database and/or information source (See Table 18). Database limits for English language were applied and the date range was limited to 1990-onwards. Forward and backward citation chaining was carried out for included studies, to identify relevant additional studies. Cleft lip and palate associations around the world were also contacted by website or publicly available email to identify unpublished guidelines.

Table 18 Search strategies

Electronic database	Initial limited search strategy	Comprehensive search strategy
Ovid MEDLINE	Ovid MEDLINE(R) ALL <1946 to forward> 1 Cleft Lip/ 2 Cleft Palate/ 3 cleft lip.tw. 4 cleft palate.tw. 5 orofacial cleft.tw. 6 1 or 2 or 3 or 4 or 5 7 guideline*.tw. 8 policy.tw. 9 policies.tw. 10 recommendation*.tw. 11 7 or 8 or 9 or 10 12 diagnosis.tw. 13 management.tw. 14 12 or 13 15 6 and 11 and 14	Ovid MEDLINE(R) ALL <1946 to June 14, 2024> 1 Cleft Lip/ 17564 2 Cleft Palate/ 23487 3 cleft lip.tw. 15780 4 cleft palate.tw. 13710 5 orofacial cleft.tw. 546 6 1 or 2 or 3 or 4 33296 7 guideline*.tw. 510881 8 policy.tw. 264005 9 policies.tw. 142037 10 recommendation*.tw. 368697 11 care pathway*.tw. 8103 12 Critical Pathways/ 8049 13 "Delivery of Health Care"/ 123096 14 Practice Guideline/ or Guideline/ 38662 15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 1244960 16 6 and 15 705 17 limit 16 to (english language and yr="1990 -Current") 644
Scopus	(TITLE-ABS-KEY ("cleft lip" OR "cleft palate" OR "orofacial cleft") AND TITLE-ABS-KEY (guideline* OR guidance OR policy OR policies OR recommendation*) AND TITLE-ABS-KEY (management OR diagnosis OR pathway OR "delivery of care "))	(TITLE-ABS-KEY ("cleft lip" OR "cleft palate" OR "orofacial cleft") AND TITLE-ABS-KEY (guideline* OR policy OR policies OR recommendation* OR "care pathway" OR "delivery of care"))
Cochrane	#1 MeSH descriptor: [Cleft Lip] #2 MeSH descriptor: [Cleft Palate] #3 ("cleft lip"):ti,ab,kw #4 ("cleft palate"):ti,ab,kw #5 (orofacial cleft):ti,ab,kw #6 (policy):ti,ab,kw #7 (policies):ti,ab,kw #8 (recommendation*):ti,ab,kw #9 (guideline):ti,ab,kw #10 (guidance):ti,ab,kw #11 {OR #1-#5} #12 {OR #6-#10} #13 #11 AND #12	ID Search Hits #1 MeSH descriptor: [Cleft Lip] this term only 436 #2 MeSH descriptor: [Cleft Palate] this term only 524 #3 ("cleft lip"):ti,ab,kw (Word variations have been searched) 855 #4 ("cleft palate"):ti,ab,kw (Word variations have been searched) 857 #5 (orofacial cleft):ti,ab,kw (Word variations have been searched) 28 #6 (policy):ti,ab,kw (Word variations have been searched) 13444 #7 (policies):ti,ab,kw (Word variations have been searched) 13439 #8 (recommendation*):ti,ab,kw (Word variations have been searched) 29965 #9 (guideline):ti,ab,kw (Word variations have been searched) 58445 #10 (care pathway):ti,ab,kw 3310 #11 MeSH descriptor: [Critical Pathways] explode all trees 326 #12 MeSH descriptor: [Delivery of Health Care] explode all trees67567 #13 MeSH descriptor: [Practice Guideline] explode all trees 0 #14 MeSH descriptor: [Guideline] explode all trees 0 #15 {OR #1-#5} 1238 #16 {OR #6-#14} 155109 #17 #15 AND #16 63
Lilacs	Cleft [Words] and guideline [Words]	(cleft) AND (guideline* OR policy OR policies OR recommendation* OR "care pathway" OR "delivery of care") AND (db:("LILACS") AND la:("en")) AND (year_cluster:[1990 TO 2024])

5.3.5 Selection of sources of evidence

Following the search, all identified citations were collated and uploaded into Mendeley© referencing software and exported into the web application Rayyan© software (Rayyan, Massachusetts, United States of America) to facilitate the screening process (Foekcler et al., 2022; Ouzzani et al., 2016). Rayyan© automatically detected duplicates which were then removed manually. The titles and abstracts of all remaining articles were screened against the eligibility criteria in Table 17 by two independent, blinded reviewers (SJ and TH). All potentially relevant sources as well as records that did not contain an abstract (title only) were passed on to full-text screening. The full text of selected citations was assessed in detail against the inclusion criteria by two independent reviewers (SJ and TH). Reasons for exclusion of sources of evidence at full text that did not meet the inclusion criteria were recorded and reported in the scoping review. Any disagreements that arose between the reviewers at each stage of the selection process were resolved through discussion with an experienced third reviewer (NI). The texts agreed for inclusion were given a unique ID to allow them to be identified within the data.

5.3.6 Data charting process

Data were extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers. The data extraction form is provided in Appendix 4. To ensure accurate data extraction, the data extraction tool was piloted with three papers retrieved from the search. This was done independently (by two reviewers) in duplicate and blind to one another. The data extracted were compared and disagreements resolved through discussion and the data extraction tool was amended as necessary. This allowed both calibration of the data extractors and piloting of the data extraction tool. The data extracted included specific details about the participants, concept, context, study methods and key findings relevant to the review question. The initial pilot form was amended to include the approximate timepoint of review/ages of the patient, the speciality that they are recommended to be seen by and the reason for that visit/appointment. This reflects the reality of a patient with an orofacial cleft where management begins

immediately after birth, extends through childhood into adulthood and involves multiple specialities.

5.3.7 Data items

A clinical care pathway is a tool to guide evidence-based healthcare (Rotter et al. 2019). By detailing steps of management, it allows for standardisation of care, potentially streamlining multidisciplinary clinical practice. Applying criteria from Kinsman et al's (2010) criteria and the European Pathway Association's characteristics of a care pathway, defining characteristics include statement of goals, key elements of multidisciplinary cleft care (team members and roles) and steps in the pathway with time-frames (Kinsman et al. 2010; Vanhaecht et al. 2007). These defining characteristics are the key data items looked for in our review of data sources. Although not considered a characteristic of a care pathway, additional items that go hand in hand and were anticipated to be found within studies on optimising care include "challenges" to implementing the ideal care pathway and potential solutions, referred to as "facilitating factors". From here on, these data items are referred to as themes and through reviewing the literature it is anticipated that sub-themes would be identified.

5.3.8 Synthesis of results

The results of the search and the study inclusion process are reported in full according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) Checklist (Tricco et al., 2018) (Appendix 3). The flow of information through the review process and selection of sources of evidence is depicted in Figure 4. The general characteristics of included studies and their relevant data are summarised in a table. The extracted data were mapped to MDT care pathways and their characteristics (for OFC care) are presented in tables as well as illustrative and descriptive formats. The challenges with moving from the basic, sustainable care pathway to the ideal care pathway and facilitating factors are presented in a narrative summary.

5.4 Results

5.4.1 Selection of Sources of Evidence

Figure 4 displays the flow of searches and resulting published papers from the searches and selection process. A total of 1856 published articles were retrieved from database searches and 1249 records remained after duplicate removal. Initial screening of the titles and abstracts resulted in 1107 sources being excluded because they did not report on the topic of interest. In total, 147 full-text records were retrieved. From these 124 were excluded as they did not report on a cleft care pathway or pertain to team members, their roles, or timing of involvement with care, leaving 23 eligible sources, comprising journal articles and one book chapter. Forward and backward citation chaining and a search of the grey literature identified a further 10 additional relevant sources for inclusion giving 34 sources that met the eligibility criteria for inclusion.

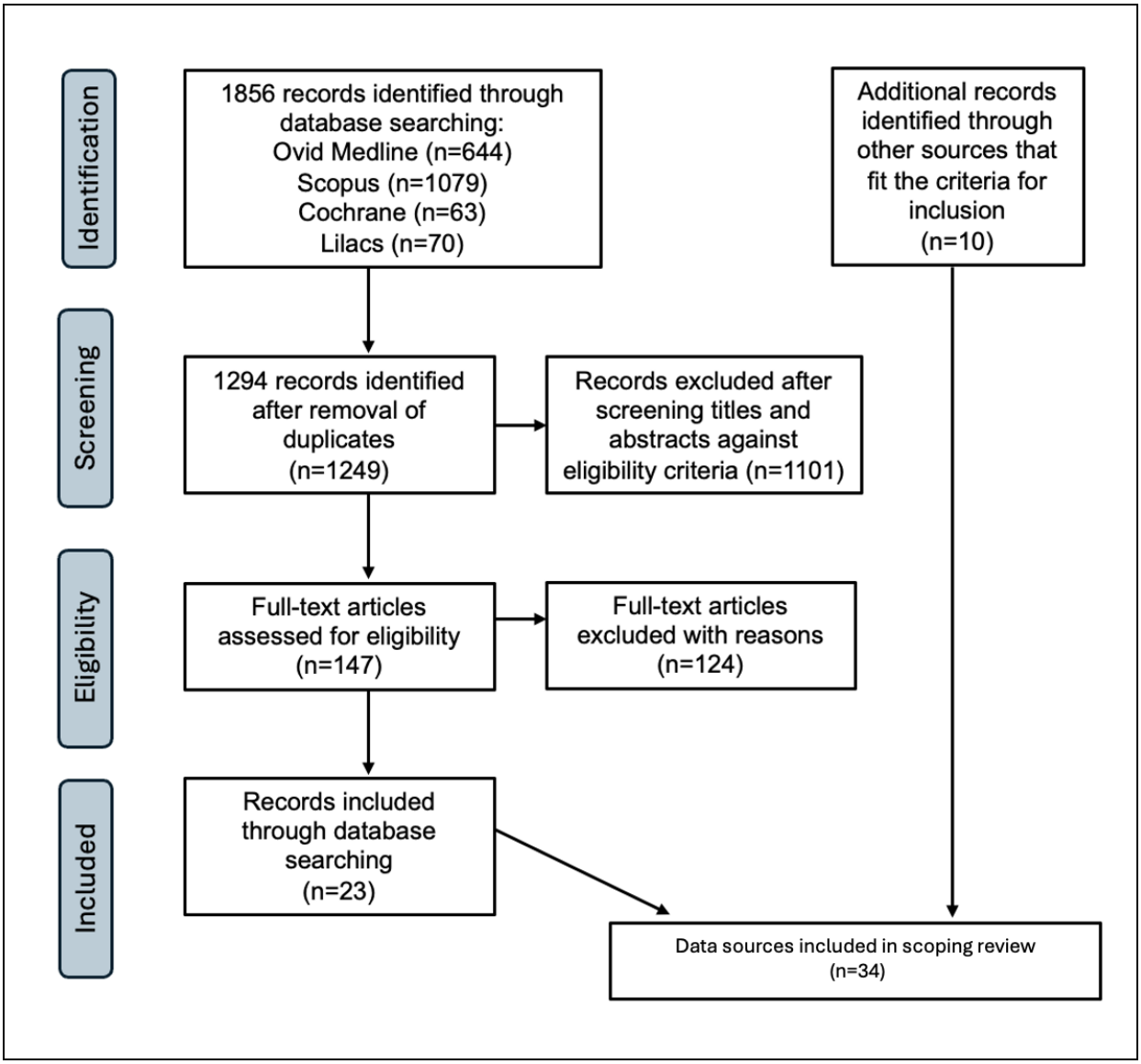

Figure 4 Scoping review flowchart of selection process adopted from PRISMA statement

5.4.2 Characteristics and results of sources of evidence

For each included source, the characteristics with citations are presented in Table 19 along with the data that were charted relating to this review's question and objectives. All data sources but two contained recommendations on the characteristics of an ideal orofacial cleft MDT care pathway and all but 12 presented characteristics of a basic, sustainable orofacial cleft MDT care pathway.

Table 20 provides a summary of key characteristics of the data sources reviewed. Publication dates of included data sources ranged from 2005 to 2024, with 2023

being the most common year for publication. The most common type of source was journal articles, while less common types included guidelines, policies, reports. The least frequently represented sources with only one each include a policy statement, standard, book chapter, guide and association website. Reports were on cleft care for global patient populations and on cleft care within developed countries (UK, Europe, USA, Canada, New Zealand, Netherlands, Germany, Israel. Cleft associations/organisations were associated with 18 of the 34 data sources. This scoping review included data sources on cleft care from all settings to create a comprehensive global overview. This means that even if a data source did not specify a particular setting, it was still eligible. Some sources reported on cleft care delivered within multiple settings, with the most common being within hospital environments, followed by services and clinics within hospitals, standalone clinics or centres dedicated to cleft care. Other settings reporting on cleft care include private healthcare systems, any setting capable of providing comprehensive cleft care, optimal settings with ample resources, and any environment involving health professionals in cleft lip and palate care. Reports on providing cleft care in resource-limited settings are also included.

The characteristics of care pathways that were examined as data items/themes in each data source revealed sub-themes and are represented in Table 21 and discussed in the “synthesis of results” section.

Table 19 Characteristics of sources of evidence included in the scoping review and their relevant data

Publication/ article unique ID	Author	Document title	Year	Document type: Policy; guideline; recommendations; guidance	Country	Association/ organisation	Setting	Summary of article	Relevant data of individual sources of evidence	
									Contains recommendations on the characteristics of an ideal orofacial cleft MDT care pathway (yes/no)	Contains suggestions on characteristics of a basic, sustainable orofacial cleft MDT care pathway (yes/no)
1	Chauhan, S	Protocols for management of cleft lip and palate around the world	2024	Journal article	Global	-	University Hospitals; Cleft Centres	A review of various protocols (procedures and their recommended timing/patient age) for the management of OFCs globally.	Yes -All protocols have the same statement of goals. -Cleft MDT composition: core/wider members of MDT and procedures in addition to key procedures. Example: recent protocols such as Netherland's 2022 Clinical Practice Guidelines show the inclusion of genetic testing, orthognathic surgery, rhinoplasty and revision surgical procedures.	Yes -All protocols have the same statement of goals -Cleft MDT composition: core member of MDT and key procedures derived from protocols that began with a basic MDT approach to cleft care. Example: the early beginnings of the Oslo Protocol suggests core members involved in cleft care as the Plastic Surgeon and the Orthodontist. Key procedures suggested as cleft lip and cleft palate surgical repair which were common to all protocols and guidelines.
2	CLAPA	Timeline	2024	Association website	UK	Cleft Lip and Palate Association (CLAPA)	NHS England Cleft Service (UK NHS Cleft Service)	A web page with the age ranges/approximate timing that a patient with a cleft lip and palate should be seen through the NHS England Cleft Service. The web page references information from the 2013 NHS England's policy titled "NHS Standard contract for cleft lip and/or palate services including non-cleft velopharyngeal dysfunction".	Yes -Cleft care timeline: Approximate ages and times (from before birth to 21+ years of age) that a baby born with a cleft lip and palate should be seen for management by the different disciplines involved in care through the NHS England Cleft Service, supports the ideal cleft MDT care timeline	No
3	Smile Train	Comprehensive Cleft Care Recommended Timeline	2024	Guideline	Global	Smile Train	All settings capable of providing comprehensive cleft care	A guideline for family education and clinical management of patients with cleft lip and/or palate, along with a recommended timeline.	Yes The recommended timeline is for comprehensive cleft care. Smile Train acknowledges that socioeconomic conditions may affect implementation across global patient populations.	No

4	ERN CRANIO	Clefts of the lip and palate: evidence based clinical practise guideline.	2023	Guideline	Europe	ERN CRANIO- – European Reference Network for rare craniofacial anomalies and ENT disorders	Europe	Evidence-based clinical practice guideline for the comprehensive management of cleft lip and/or palate, covering genetic diagnosis, surgical timing, feeding, orthodontics, hearing, psychosocial care, and organisation of care using a modular, updateable structure.	Yes Provides detailed guidance for structured, multidisciplinary, evidence-based cleft management.	Yes Guidelines on NAM
5	Welsh Health Specialised Services Committee (WHSSC)	Cleft Lip and/or Palate including Non-Cleft Velopharyngeal Dysfunction: All Ages	2023	Policy (NHS Standard Contract)	UK	Welsh Health Specialised Services Committee (WHSSC)	NHS Wales Cleft Service (UK NHS Cleft Service)	Outlines service configuration, identifies the key responsibilities and skill mix of the main team, the clinical pathways based on national policy and best practice.	Yes -Statement of goals provided for this MDT cleft care pathway -Cleft care timeline (before birth to >21 years supports the timeline for the ideal cleft care pathway -Facilitating factors: Outlines key performance indicators, clinical standards, quality requirements for audit	No
6	Chadha and Beale	UK cleft lip and palate care: a contemporary perspective	2023	Journal article	UK	-	UK multidisciplinary team cleft centre (UK NHS Cleft Service)	A general overview of UK cleft infrastructure, schedule of care, role of various members of the cleft MDT, with special emphasis on the role of the paediatrician.	Yes The care pathway for children born with cleft lip and palate supports the timeline for the ideal cleft care pathway. Facilitating factors to this care pathway were identified as a centralised service with a hub-and-spoke model of delivery, a Cleft Registry and Audit Network for quality assurance purposes and a research programme to address optimal treatment pathways.	Yes Acknowledges that most cleft palates and some lips are diagnosed soon after birth but the NHS cleft service schedule of cleft care begins with antenatal diagnosis at 18-21 weeks using 2D ultrasound where OFCs is one of the conditions screened in the Foetal Anomaly Screening Programme. This supports a suggestion for a characteristic of antenatal start of the basic, sustainable orofacial cleft MDT care pathway so that families can be supported if an antenatal diagnosis is made.

7	Chahine et al.	Quality Assurance Standards for Outreach Cleft Lip and Cleft Palate Repair Programs in Low-Resource Settings	2023	Journal article	Global	American Cleft Palate Craniofacial Association (ACPA), Global Smile Foundation (GSF)	Low-resource settings, low and middle-income countries (LMICs)	A proposal of updated quality assurance standards for outreach cleft repair that builds on work by the World Cleft Coalition and is based on ACPA quality standards, published literature, published protocols by GSF and the author's experience. Areas addressed include site assessment, team composition, quality assurance guidelines, safety checklists, emergency response protocols, outcomes evaluation.	Yes	Yes Recommends infrastructure standards, team composition standards for cleft care in outreach settings, guidelines, protocols and standards for quality cleft care
8	Dudding et al.	An introduction to the UK care pathway for children born with a cleft of the lip and/or palate	2023	Journal article	UK	-	UK multidisciplinary team cleft centre (UK NHS Cleft Service)	An outline of the clinical journey that a child born with an OFC in the UK will follow throughout their life, from antenatal diagnosis *in utero* to adulthood in terms of management by each subspeciality within the cleft MDT pathway. The care pathway described is based on a case study specific to the management of a patient born with a non-syndromic complete unilateral cleft lip and palate. This paper is the first to be published from a series of papers that are still to be published.	Yes -Key elements of MDT cleft care (infrastructure; - Cleft care timeline, facilitating factors to optimising the cleft care pathway identified as: 1) CRANE database that collects data from cleft centres, monitoring performance indicators against the established benchmarks, outcomes and the national average, produces annual reports and enforces processes aimed at improving the care of patients with cleft; 2) cleft research studies to improve patient outcomes.	No

9	O'Gara et al.	Interdisciplinary Team Care for Children with Facial Differences	2023	Journal article	USA, Canada	American Cleft Palate Craniofacial Association Commission on Approval of Teams (ACPA CAT)	Cleft Lip and Palate Clinic in Hospital	Addresses the six critical components to this interdisciplinary care: focus on the team's composition, the team's management and responsibilities, the inclusion of patient and family/caregiver communication, an ongoing commitment to cultural competence, the importance of psychosocial and social services provided for the child and family, and the dedication to outcomes assessment	Yes Supports the cleft team composition and roles	Yes Core disciplines named (surgeon; orthodontist; speech/language pathologist; access to psychologist) supports the core members of the MDT. The wider members of the MDT are considered the professionals that the team must establish access to (professionals in social work; dentistry; otolaryngology; audiology; genetics; primary paediatric medical care)
10	Parham et al.	Updates in Cleft Care	2023	Journal article	USA	ACPA	Cleft Lip and Palate Clinic in Hospital	Outlines the current standards of care in children born with OFCs and highlights ongoing advancements in the field	Yes Timeline supports ideal care pathway as it is follows current ACPA approved standards for cleft care	No
11	Mossey et al.	Oral Health in Comprehensive Cleft Care: Guidelines for oral health professionals and the wider cleft care team	2022	Guideline	Global	Smile Train; FDI World Dental Federation	Any setting where a patient with cleft lip and palate may be assessed by any health professional involved in their care	Oral health guidelines that follow a timeline from birth into adulthood for patients with an OFC. The guidelines should be referred to by cleft care providers (both oral health and non-oral health professionals) at each appointment.	Yes This guideline supports the delivery of oral health care by all care providers in a comprehensive cleft care pathway. It also supports the timeline with a list of all the providers involved in cleft care and the approximate age at which the child should undergo treatment with the comprehensive cleft care team	Yes This guideline supports the delivery of oral health care by all care providers in a comprehensive cleft care pathway.
12	Fell et al.	Adapting Elements of Cleft Care Protocols in Low- and Middle-income Countries During and After COVID-19: A Process-driven Review With Recommendations	2022	Journal article	Global	A multidisciplinary international working group of global organisations and affiliations involved in comprehensive cleft care including Cleft Collective, Transforming Faces, CLEFT charity, Operation Smile	Resource-constrained settings	A consortium of global cleft professionals, predominantly from low-middle-income countries, identified adaptions to cleft care protocols during and after COVID-19 as a priority learning area of need	Yes Identifies supporting documents for quality cleft care	Yes Identifies supporting documents for quality cleft care and the priority of surgical procedures and cleft care service

13	American Cleft Palate Association (ACPA)	Standards for Approval of Cleft Palate and Craniofacial Teams	2022	Peer-review standards of care	USA	ACPA	ACPA approved teams throughout USA and Canada found at Cleft centres, hospitals, comprehensive craniofacial clinics, universities	Peer-reviewed standards for the quality of care provided by interdisciplinary teams to patients with OFCs or craniofacial anomalies addressing team composition, management and responsibilities, caregiver communication, cultural competence, psychological and social services and outcomes assessment	Yes Current standards for cleft team composition states a minimum core team and their roles and outlines all the other disciplines that the team must maintain access to.	Yes States a minimum core team (a designated patient care coordinator, surgery, speech-language pathology, orthodontics) which supports suggestions for the MDT composition of a basic CPW.
14	Frederick et al.	An Ideal Multidisciplinary Cleft Lip and Cleft Palate Care Team	2022	Journal article	USA	-	An optimum setting with resources abound	A reflection on what an ideal organisation structure and care team composition for OFC care could be comprised of, considering OFC care team guidelines and recommendations from different countries	Yes Recommends the disciplines of the ideal MDT cleft care team and their roles	No
15	Campbell and Kreshanti	Comprehensive Cleft Care Centers: Scalable, Sustainable and Cost Effective Surgical Care	2021	Book chapter	USA	-	Low-resource setting; Universities; governmental hospitals; private healthcare systems; cleft centre; mobile surgical hospital	Discusses key elements in establishing and maintaining a successful comprehensive cleft care centre	No	Yes Supports suggestions on infrastructure and steps in a cleft care pathways with timeframes with a suggested timeline of surgical treatment for OFCs in low-resource settings.
16	Fowler et al.	The history of cleft services in New Zealand	2021	Journal article	New Zealand	-	Publicly funded multidisciplinary cleft units within 5 hospitals throughout New Zealand	Examines the history of cleft services in NZ, the role of the MDT to current cleft care pathway	Yes Outlines the cleft care pathway (team members, interventions, approximate ages) in New Zealand today which is adapted from CLAPA. This supports characteristics of the MDT composition and steps in cleft care pathway.	Yes Discusses the early beginnings of cleft centres in New Zealand which supports suggestions for core members of the MDT for essential procedures for the management of OFCs
17	Zimmerman et al.	What is the Impact of Prenatal Counseling on Postnatal Cleft Treatment? Multidisciplinary Pathway for Prenatal Orofacial Cleft Care	2021	Journal article	USA	-	A high-volume foetal diagnosis and treatment centre in Children's Hospital of Philadelphia (CHOP)	Presents the cleft care pathway at CHOP	No	Yes Supports suggestions on core clinical disciplines and procedures considered essential in a cleft care pathway

18	Mink van der Molen et al.	Clinical Practice Guidelines on the Treatment of Patients with Cleft Lip, Alveolus, and Palate: An Executive Summary	2021	Journal article	Netherlands	Medical Specialists for the Netherlands Society for Plastic and Reconstructive Surgery; Dutch Association for Otorhinolaryngology and Surgery of the Head and Neck; the Dutch Association of Orthodontists; the Dutch Scientific Association of Dentists; the Dutch Association for Oral and Maxillofacial Surgery	Not stated	This report describes clinical practice guideline (CPG) development and shares the main recommendations to optimise cleft care by a multidisciplinary working group of representatives from all relevant disciplines	Yes Gives recommendations for management of common problems affecting patients with OFCs along with time-frames. Also supports delivery of quality cleft care.	Yes Recommendations for quality cleft care
19	Kassam et al.	World Cleft Coalition International Treatment Program Standards	2020	Journal article	Global	Smile Train, GSF	All settings	Presents efforts to establish an internationally agreed set of minimum core practice and best practice guidelines, along with overarching principles to promote safe and comprehensive cleft care globally	Yes Refers to supporting documents for quality cleft care	Yes Refers to supporting documents for quality cleft care and recommends members of the cleft MDT that are considered minimum core standards and members of the team for best practice.
20	Operation Smile	Medical Global Standards 2020	2020	Report	Global	Operation Smile	Outreach setting	Presents global standards for surgical outreach cleft programs	Yes Guidance on quality cleft care	Yes Guidance on quality cleft care, supports time-frames for key surgical repair procedures that are appropriate for late-presenting patients
21	Watted et al.	Multidisciplinary treatment in cleft lip and palate patients	2020	Journal article	Germany, Israel	-	Not stated	Discusses the advantages and disadvantages of team management, presents a treatment protocol for cleft lip and palate, the members and their roles in a cleft team.	Yes Supports the members of the cleft team and their role and the interdisciplinary interaction	Yes Acknowledges that multdisciplinary approach is needed (basic CPW) but the interdisciplinary approach is the goal (ideal CPW).
22	Murthy	Burden of Care: Management of Cleft Lip and Palate	2019	Journal article	India	-	Cleft and Craniofacial Centre	Discusses protocol, morbidity and burden of care in the management of cleft	Yes Supports the ideal cleft care pathway	Yes Supports the basic care pathway by highlighting unnecessary interventions and the different burdens of care

23	ACPA	Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial differences	2018	Policy statement	USA	American Cleft Palate-Craniofacial Association (ACPA)	Hospital setting	Proposes specific recommendations for the composition of interdisciplinary teams, the role and timing of clinical practices of each discipline and procedures during the neonatal period and infancy for patients with an OFC.	Yes Lists the disciplines of a cleft MDT, their role and acknowledges that the specific team varies according to the availability of qualified personnel and by the type of cleft by the patient. Recommendations on diagnosis and management and approximate time-frames/ages are also outlined which supports the timeline for ideal care.	No
24	Oberoi et al.	Team Care Protocols for Individuals with Cleft Lip and Palate and Modified Protocols for Developing countries	2018	Journal article	Global: San Francisco USA; developing countries	-	University of California at San Francisco (UCSF) Craniofacial Centre; treatment centres in developing countries	Provides an overview of orthodontic aspects of management of individuals with OFCs as part of a modern OFC team and also discusses modified treatment protocols for treatment centres in developing countries	Yes Outlines the disciplines of the MDT for cleft lip and palate and the protocol followed with a focus on timely orthodontic treatment at University of California, San Francisco, USA. This supports the characteristics of cleft team composition and orthodontic management with time-frames.	Yes Makes suggestions for modifying treatment protocols to what practically can be achieved in treatment centres in developing countries. This supports suggestions for a basic cleft team composition and their roles.
25	European Committee for Standardization Technical Committee (CEN/TC)	Early care services for babies born with cleft lip and/or palate	2015	Report	Global: CEN national members (Europe, UK)	European Committee for Standardization (CEN national members: Europe, UK	Countries where national protocols need to be established	Specified recommendations for the care of babies born with an OFC at time of diagnosis and the year following birth or diagnosis (whichever is later), including referral processes, establishment of feeding, parental support and care pathways	Yes Team composition	Yes Care pathway including time-frames
26	Operation Smile	Operation Smile Resource Manual-Global Standards of Care	2015	Guide	Global	Operation Smile	Outreach setting	Presents global standards for surgical outreach cleft programs. The updated version of this document are the 2020 Global Standards of Care	Yes Guidance on quality cleft care	Yes Guidance on quality cleft care, supports time-frames for key surgical repair procedures that are appropriate for late-presenting patients
27	McIntyre	Management of patients with cleft lip and palate: Part 1: From antenatal diagnosis to primary surgery	2014a	Journal article	UK	-	Not stated	Article 1 of 3 discussing diagnosis and management from antenatal diagnosis until primary surgery	Yes Gives an overview of the UK's cleft infrastructure which supports the infrastructure of the ideal cleft CPW and outlines the health professionals in the cleft MDT. It also outlines the audit records that are collected from birth into adulthood.	No

28	McIntyre	Management of patients with cleft lip and palate: Part 2: From primary surgery to alveolar bone grafting	2014b	Journal article	UK	-	Not stated	Article 2 of 3 provides details of the care of patients with clefts from primary surgery through to alveolar bone grafting.	Yes Supports timeframe for ideal cleft care pathway	No
29	McIntyre	Management of patients with cleft lip and palate: Part 3: From age 10 to adulthood	2014c	Journal article	UK	-	Not stated	Article 3 or 3 discussing care into adulthood	Yes Supports timeframe for ideal cleft care pathway	No
30	Hartzell and Kilpatrick	Diagnosis and management of patients with clefts: A comprehensive and interdisciplinary approach	2014	Journal article	USA	American Cleft Palate-Craniofacial Association (ACPA)	Cleft team (clinic; hospital setting)	An overview of the specific multidisciplinary care OFC patients may receive including timing of evaluations, surgical and medical interventions and follow-up.	Yes Supports the team composition	Yes Supports the team composition
31	NHS England	NHS standard contract for cleft lip and/or palate services including non-cleft velopharyngeal dysfunction (all ages)	2013	Policy (NHS Standard Contract)	UK	NHS England	NHS England Cleft Service (UK NHS Cleft Service)	Service specifications for the delivery of cleft care within NHS England.	Yes Supports time-frames for diagnosis and management in comprehensive cleft care	No
32	Hussein et al.	Cleft lip and palate: The Multidisciplinary Management	2012	Journal article	Global: Palestine; USA; Turkey; Germany	-	Hospital cleft team	Gives an overview of the contemporary MDT approach of cleft lip and palate	No	Yes Protocol of timing for MDT treatment from birth to adulthood that excludes antenatal care and continuous care throughout adulthood
33	Robin et al.	The Multidisciplinary Evaluation and Management of Cleft Lip and Palate	2006	Journal article	USA	-	Multidisciplinary cleft clinic (MCC)	An overview on the workings of MCC clinics, the management issues for children with CFAs, how they are addressed by the members of the MCC.	Yes Lists healthcare personnel in a typical cleft clinic, common problems experienced by patients with OFCs and roles that the different disciplines play and uses the literature to support recommendations on approximate timing of operations and procedures. This supports the clinical disciplines, their roles. It refers to the ACPA's "Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial anomalies" published in 2000. This is has since been updated (ACPA, 2018).	No

34	Nahai et al.	The Management of Cleft Lip and Palate: Pathways for Treatment and Longitudinal Assessment	2005	Journal article	USA	ACPA and the Team Standards Committee	Not stated	An outline of management of patients with clefts from birth to young adulthood with emphasis on long-term planning and goals, continuity of care, timing and decision making,	Yes Supports team composition and roles	Yes Supports team composition and roles

Table 20 A summary of key characteristics of included sources

Data variable	Findings
Publication dates (mode (range))	2023 (2005-2024)
Most common source types	Journal article (22), guideline (2), policy (2), report (2) policy statement (1), standard (1), book chapter (1), guide (1), association website (1)
Locations/countries of data sources	Global (11), USA (10), UK (9) Netherlands (1), Canada (1), New Zealand (1), India (1), Germany (1), Israel (1), Europe (1)
Associations/Organisations in data sources	ACPA (6), Operation Smile (3), Smile Train (3), CLAPA (2), GSF (2), FDI World Dental Federation (1), WHSSC (1), Cleft Collective (1), Transforming Faces (1), CLEFT charity (1), CEN (1), UK NHS (1) Associations from Netherlands: Medical Specialists for the Netherlands Society for Plastic and Reconstructive Surgery (1), Dutch Association for Otorhinolaryngology and Surgery of the Head and Neck (1), the Dutch Association of Dentists (1), the Dutch Association for Oral and Maxillofacial Surgery (1).
Settings of cleft carer reported within data sources	Service/clinic within a hospital (9): Cleft lip and palate clinic in Hospital (3), publicly funded multidisciplinary cleft units within hospitals (1), UK NHS Cleft Service (5) Other hospital setting (6): hospital (2), University hospitals (3), governmental hospitals (1) Centres/clinics not in hospital setting (7): multidisciplinary cleft clinic (MCC)/Cleft centres/cleft and craniofacial centre (6), a high-volume foetal diagnosis and treatment centre (1) Other settings: private healthcare systems (1); all settings capable of providing comprehensive cleft care (2), an optimum setting with resources abound, all settings (1), any setting with any health professional involved in cleft lip and palate care (1) Resource limited settings: mobile surgical hospital (1), resource-constrained settings, low-resource settings and LMICs (2), outreach setting (2), countries where national protocols need to be established (1) No setting stated (6)

5.4.3 Synthesis of results

This section summarises the charted results in relation to the review questions and objectives outlined in this study. Table 21 outlines themes (characteristics of care pathways) searched within the data set as well as the sub-themes identified throughout the literature, adding structure to the descriptive format on the characteristics of MDT care pathways for the management of patients with orofacial clefts. A narrative summary of each theme with its sub-themes explores the results as they relate to the objectives and review question "What are the characteristics of a basic MDT care pathway that is both sustainable and scalable, compared to an ideal MDT care pathway for the management of patients with orofacial clefts?". Tables 22-25 and Figure 5 support the presentation of results.

Table 21 Themes (characteristics of care pathways) searched within the data set and the sub-themes identified.

Data items/Themes	Sub-themes
MDT cleft care pathway statement of goals	-
Key elements of MDT cleft care	-infrastructure of the cleft care pathway -cleft MDT composition (disciplines and their roles within the cleft MDT) -supporting documents for the delivery of safe, quality cleft care
Cleft care timeline (Steps in the cleft care pathway with time-frames)	-Time points /ages of timeline from start to follow-up -Time-frame for interventions
Facilitating factors to optimising the care pathways	-Financial aid -Support from cleft foundations/organisations with training of local surgeons/local skills development -Audit/quality assurance programmes and research -Electronic Medical Records (EMR)

5.4.3.1 Theme: MDT cleft care pathway statement of goals

The care pathways in this review share the goal of providing surgery and multidisciplinary team care for babies born with a non-syndromic orofacial cleft to ensure that patients achieve maximum function (oral feeding, hearing and speech) and facial aesthetics, ultimately improving psycho-social wellbeing and development (Chauhan 2024; WHSSC 2023; Technical Committee of the European Committee for Standardization (CEN/TC) 2015).

Within the literature, the terms multidisciplinary and interdisciplinary are used interchangeably. In an ideal cleft care pathway, the team of professionals adopt an interdisciplinary working relationship where the various disciplines work together to coordinate the care of a patient. This is unlike a multidisciplinary team of professionals who work independently in evaluating and treating patients with little communication and interaction among the team members. Although the multidisciplinary relationship may be part of a basic cleft care pathway, the goal is integration of information or recommendations when approaching a plan of care for individual cleft patients (Strauss, 1999) (Watted et al. 2020).

5.4.3.2 Theme: Key elements of MDT cleft care (infrastructure, team members and roles)

The key elements of multidisciplinary cleft care were found to include the infrastructure/setting of care delivery, cleft MDT composition (the clinical disciplines and their roles), documents supporting delivery of quality care.

i. *Infrastructure of the Cleft Care Pathways*

The UK's centralised Cleft Service infrastructure is considered by many to represent a paradigm of cleft care with its "hub-and-spoke" model of delivery. The "hubs" are based in the main geographic population centres for cleft MDT clinics and surgery, whereas the "spokes" operate as outreach multidisciplinary clinics closer to patients' homes to reduce travel and inconvenience associated with multiple clinic appointments such as with Speech and Language Therapy, Paediatric Dentistry, Orthodontic treatment (McIntyre 2014).

In the UK, the reorganisation and centralisation of OFC care on a national scale in the early 2000's resulted in the delivery of a high quality standardised, audited and networked cleft service that is well regarded internationally.

This was founded upon the work of the Clinical Standards Advisory Group (CSAG) that identified disparities in the provision of cleft services, clinical protocols and cleft-related outcomes within the UK compared to the centralised model of cleft care based in Scandinavian countries, particularly, Norway.

The CSAG demonstrated that superior aesthetic and functional outcomes were achieved in multidisciplinary cleft units treating high volumes of patients (Bearn et al. 2001;Fell et al. 2022). To counter the UK system's problem of numerous surgeons performing primary cleft repairs on few patients and the lack of multidisciplinary oversight, the CSAG recommended service centralisation to the Government. The result was a move from over 50 hospitals engaging in cleft care to 8-15 UK cleft clinical networks. These cleft clinical networks adhered to a national standard of care with a full range of readily available clinical services including psychological support and minimum numbers treated per surgeon with improved outcomes. Each network served a delineated geographic area, forming a hub-and-spoke model of delivery. The multidisciplinary nature and importance of following a schedule of care is also

prioritised as the UK follows a “modified Oslo protocol”. Recently, introduction of Integrated Care Systems has begun to address current-day disparities in cleft care by enabling services to be more responsive to local population needs.

For a basic CPW, the infrastructure or an institution’s capacity required for hosting a surgical outreach programme may be considered the minimum requirement. Chahine et al’s (2023) updated quality assurance standards for OFC surgical repair outreach programmes in low-resource settings outlines the facilities and equipment required to consider a site appropriate for hosting the surgical programme. This includes adequate size and number of operating rooms, available anaesthesia equipment (monitors and ventilators suitable for use in children < 6 months old), availability of overnight staff and to a post-anaesthesia care unit (PACU), availability of a blood bank, pharmacy, proper sterilisation equipment, laboratory, and imaging facilities and accessibility to an intensive care unit at or in close proximity to the hospital (Berlin et al. 2008; Politis et al. 2011; Chahine et al. 2023). Campbell and Kreshanti (2021) provide details on the different facilities commonly found in low-resource settings appropriate for delivering sustainable and scalable cleft care. A basic cleft care pathway would be appropriate for countries or settings that are considered low-resource in terms of lacking specialists, facilities and equipment but have basic infrastructure such as hospitals, universities, human resources and personnel available. In such cases, the horizontal and diagonal care delivery models are more suitable than the vertical model in terms of sustainability and scalability. The infrastructure of the basic CPW should be able to evolve into a self-sustainable MDT cleft service offering comprehensive cleft care. Appropriate facilities for the basic CPW would therefore be under-funded local healthcare systems or hospital facilities that allow for sponsoring organisations to provide and invest funding, equipment and training to local surgeons, allowing them to treat patients within their communities. Other appropriate facilities include institutions that have the capacity to expand services such as universities, governmental hospitals, private healthcare systems to support an MDT cleft service. Campbell and Kreshanti (2021) describe the most advanced facility in low-resource settings as the stand-alone comprehensive cleft care centre (CCCCs) that treats a high volume of patients, acting as a catalyst for the development of the structure, processes and techniques

that ultimately lead to better quality and outcomes. With CCCCs, surgical capacity and sustainability increase while complications and costs generally decrease. Some notable examples of comprehensive cleft care centres (CCCCs) that have gained global recognition as centres of excellence in low-resource settings include partnerships like Operation Smile's Guwahati Comprehensive Cleft Care Centre in India and the Cleft Care Centre in Bogotá, Colombia. Additionally, the GSR Institute of Craniofacial Surgery in India, in collaboration with Smile Train, and the Cleft and Craniofacial Centre in Indonesia, which began as a partnership with Sahlgrenska University Hospital in Sweden, also exemplify successful initiatives. Another facility in low-resource settings is the mobile surgical hospital (MSH), a modified version of a stand-alone comprehensive cleft care centre (CCCC). The MSH is a mobile subspecialty hospital featuring operating rooms, a full-time team, pre- and postoperative wards, and multidisciplinary services, all housed in expandable tractor-trailers that can travel to patients in need. An example is Mobile Surgery International in Mexico, which provides medical, social, and cleft lip and palate surgeries (Campbell and Kreshanti 2021).

ii. *Cleft MDT composition (the disciplines and their roles within the cleft MDT)*

The members of the cleft MDT may include but not be limited to individuals from the areas of professional practice outlined in Table 22. The specific members of the cleft MDT will be determined by the availability of qualified personnel and by the types of patients served by the team. For example, children with isolated cleft lip will have different needs from those that have cleft affecting both the lip and palate (Padovano et al. 2020).

The core cleft team and key procedures

Essential cleft team are the disciplines recognised by the ACPA: Cleft Surgeon, Orthodontist and Speech and Language Pathologist. This structure has remained unchanged since the first cleft team was established in Philadelphia, USA, in 1938(O'Gara et al. 2023). However, today, the World Cleft Coalition's minimum core standards for comprehensive cleft care recognise that, for the minimum core to function, healthcare professionals in anaesthesiology, dentistry, nursing, paediatrics, psychosocial care, along with overall coordination, must also be provided (Kassam et al. 2020; Operation Smile, 2020). The 2020 Medical Global Standards minimum staffing requirements further include a Post Anaesthesia Care Unit (PACU) Physician, a Surgical Circulating Nurse, Surgical Scrub (Operation Smile, 2020).
As clinical pathways cannot effectively function without management and coordination, as required for ACPA (American Cleft Palate Association) accreditation and as per the NVSCA (Netherlands Association for Clefts of the Lip and Palate and Craniofacial abnormalities) guidelines, both a Team Coordinator and a Case Manager/Social Worker should be included in the core cleft team (Frederick et al. 2022).

Common to all cleft care protocols around the world are surgical repair of the lip and palate procedures. Most protocols also include alveolar bone grafting (if indicated), orthodontics, speech evaluation and therapy (Chauhan 2024). It must be noted that pre-surgical orthopaedic techniques like nasoalveolar moulding (NAM) varies worldwide and is not currently part of the UK's NHS cleft service care pathways. It is however part of the New York University's Naseolaveolar Moulding Protocol and many global cleft care pathways used in low-resource settings. As discussed later

under the cleft care timeline theme, this is because the role of NAM is to support surgeons that are not capable of handling wide cleft repairs initially but may no longer be required as surgical skills progress (Murthy 2019;Shen et al. 2020; ERN CRANIO, 2023; Chauhan 2024). For this reason, the basic CPW includes NAM but as surgeons advance in skills, may not be needed as in the ideal CPW.

The wider cleft team and additional procedures

ACPA-approved cleft teams must also establish access to professionals in social work, dentistry, otolaryngology, audiology, genetics and primary paediatric medical care. These professionals can be considered to be part of the wider team (O'Gara et al. 2023). Chauhan's review (2024) highlighted additional procedures that were found in some, not all protocols. This includes genetic testing, feeding plates/obturators, velar closure for speech development, tympanostomy, pharyngoplasty, interceptive orthodontics, orthognathic surgery, rhinoplasty and secondary operations like scar revision surgeries. The ideal MDT cleft care pathway includes the option for the patient to have additional procedures if necessary. This is outlined in the UK NHS cleft care pathways.

Table 22 Summary of the members of the Cleft Team within the literature and their roles (Sources of data: Chauhan 2024; Chadha and Beale 2023; Frederick et al. 2022; Kassam et al. 2020; Operation Smile, 2020; Watted et al. 2020; ACPA 2018; Hartzell and Kilpatrick 2014)

Member of the Cleft Team	Role
Surgical specialities	
Cleft surgeon (Plastic Surgeon; Oral and Maxillofacial Surgeon)	Improves facial aesthetics with surgical lip repair, rhinoplasty and improves function, feeding, speech and hearing through surgical repair of the palate
Otorhinolaryngologist ("ENT surgeon")	Surgically repairs upper airway obstruction, velopharyngeal insufficiency, middle ear abnormalities, provides hearing aids, including bone-anchored devices
Other members of a cleft surgical team (minimum staffing requirements according to Operation Smile's (2020) Medical Global Standards)	
Post Anaesthesia Care Unit (PACU) Physician	Care and support during each phase of a patient's perioperative care (anaesthetic, surgery, recovery)
Surgical Circulating Nurse	Ensures coordination of activities and patient safety in the operating room, manages documentation, monitors the surgical environment
Surgical Scrub Personnel	Responsible for maintaining the sterile field during operations
PACU Nurse	Responsible for the assessment, evaluation and implementation of care given to patients within the recovery room
Medical specialties	
Paediatrician	Routine child health surveillance manages general medical concerns including growth and development
Clinical Geneticist	Assesses for syndromic aetiologies, determines the risk for familial recurrence, counsels parents and children on the risks of cleft +/- other syndromes being an inherited problem that may occur in future siblings or generations, may offer future pre-natal testing
Anaesthetist; Anaesthesiologist	Checks that patient appropriate for operation, delivers anaesthetic and analgesic medicines
Dental Specialities	
Paediatric dentist	Prevention of dental disease, liaising and managing with other members of the dental team as the patient's dentition evolves from deciduous to permanent
Orthodontist	Improves early dental and skeletal malocclusion with devices and prostheses in preparation for surgical intervention, works closely with SLT to create feeding plates/obturators to maximise the feeding response
Prosthodontist	Works closely with SLP to create feeding plates/obturators to maximise the feeding response, provides adjunctive prostheses to improve overall orofacial aesthetic and function for issues that surgery cannot address, replaces and restores the dentition
Restorative Dentist	Replaces missing teeth in the cleft area, camouflages dental asymmetries, obturates palatal fistulae, supports speech therapists by providing speech prostheses
Allied health professionals	
Fetal sonographer	Able to detect the presence of cleft lip and/or palate ultrasonically in approximately 80% of cases.
Radiographer	For diagnostic medical imaging
Medical Photographer	For medical records used in diagnosis and treatment planning, monitoring growth and audit purposes
Biomedical Technician	Responsibilities include guaranteeing the integrity of hospital infrastructure and systems
Specialist nurse; registered nurse; Clinical Nurse Specialist; "Cleft Nurse"	A continuing role in pre-operative and post-operative visits and liaising with the surgical team Provide counselling and support for parents in the hospital or at home, teach parents and carers how to feed their babies.
Speech and Language Therapists (SLT); speech language pathologist	Monitor and assess speech and language development from birth until the completion of treatment (around 20 years) and provides therapy if needed, counsels the family on communication development expectations and manages feeding concerns by determining a safe, efficient method of feeding
Audiologist	Works closely with the Otolaryngologist to monitor hearing, address failed newborn hearing screens, concurrent middle ear disease and provide assisted hearing devices
Psychologist	Support to patients and their families throughout the care pathway in decision-making, managing expectations around treatments, managing self-concept and handling questions from peers and strangers
General Dental Practitioner (GDP)	Preventative and routine dental care
Registered Dietitian	Ensures a safe and effective feeding regimen and nutrient intake for growth and development and postoperatively
Medical Records assistant/staff	Responsible for organising, updating and storing records
Personnel responsible for team management and coordination	
Team Coordinator	Liases between the cleft team and caregivers, coordinates follow up appointments, team meetings for the professionals to plan next steps in care
Case Manager/Social Worker	Helps the family in planning medical appointments, ensures access to funding resources and all necessary equipment recommended by the team

iii. *Supporting documents for the delivery of safe, quality cleft care*

Throughout this review of cleft care pathways, documents such as standards, guidelines, policies and protocols were encountered within the literature to support the delivery of timely, safe and quality cleft care. Whilst policies set the direction, protocols are a step-by-step approach that must be followed and are unlike guidelines which are designed to assist decision making and standards that define the level of quality that must be achieved and maintained at the best possible level (Picard 2022). As they are not the same, they are highlighted within this paper as supporting documents toward the delivery of quality cleft care.

A main focus of any healthcare pathway is the safety of patients, their family and healthcare providers. Following the COVID-19 pandemic, recommendations for routine safety measures for operative care (pre, peri, post) in cleft care protocols were reviewed by an international working group and published along with suggestions for adaptions during and after the pandemic (Fell et al. 2023).

Another area that has recently developed consensus to management is oral care for children with OFCs. This is critical to reducing the caries burden in those who are already undergoing various treatments for the correction of an orofacial cleft. Early childhood caries is a preventable disease yet has a higher prevalence rate in children with OFCs in both the primary and permanent dentition compared with children without an OFC (Worth et al. 2017). Studies have reported reasons such as difficulty in maintaining oral hygiene due to limited accessibility to the cleft area, crowded dentition and reduced oral clearance by saliva and tongue thus accelerating the incidence of Early Childhood Caries (ECC) in children with CLP. Most recently, guidelines were released by Smile Train and the FDI World Dental Federation for both oral health and non-oral health professionals to facilitate comprehensive oral health care throughout the cleft patient's life.

Additionally, the European Reference Network for Rare Craniofacial Anomalies (ERN CRANIO) has developed comprehensive clinical practice guidelines that support the delivery of safe and high-quality multidisciplinary care for individuals with cleft lip and/or palate across Europe, emphasising standardised approaches and

knowledge sharing to improve outcomes (ERN CRANIO, 2023). Other documents that have been developed to support the delivery of quality care in comprehensive cleft care pathway are outlined in the Table 23 below.

Table 23 Documents supporting safe, quality cleft care.

Aspect of cleft care	Supporting document for the delivery of quality cleft care
Cleft surgery safety measures (Fell et al. 2023)	-Safety and Quality Protocol ((Smile Train 2024c) -Clefts of the Lip and Palate Evidence based Clinical Practise Guideline (ERN CRANIO, 2023) -Surgical (pre-,intra-, post-operative) considerations for Outreach Cleft Programs (Chahine et al. 2023) -Anaesthetic (pre-,intra-, post-operative) considerations for Outreach Cleft Programs (Chahine et al. 2023) -Paediatric (pre-,intra-, post-operative) considerations for Outreach Cleft Programs (Chahine et al. 2023) -2020 Medical Global Standard 4- Patient Selection (Operation Smile, 2020) -2020 Medical Global Standard 5- Medical Patient Management (Operation Smile, 2020) -Surgical Safety Checklist for Cleft Lip and Palate (Smile Train 2024d) -Post-operative Care Discharge Checklist (Smile Train 2024b) -2020 Medical Global Standard 6 Safety (Operating Smile, 2020) -General Essential Emergency Equipment List (World Health Organization (WHO) 2003)
Oral health	-Oral health in comprehensive cleft care (Mossey et al. 2022) -Dental procedures: safety and quality protocol (Oral Health in Comprehensive Cleft Care Task Team 2022) -Dental health standards (WHSSC, 2023)
Quality assurance and quality improvement	-2020 Medical Global Standard 7-Quality (Operation Smile, 2020) -Key performance indicators (WHSSC, 2023) -Antenatal care standards (WHSSC, 2023) -Post natal and infant care standards (WHSSC, 2023) -Care and facilities for children and young people standards (WHSSC, 2023) -Cleft surgery standards (WHSSC, 2023) -ENT and audiology standards (WHSSC, 2023) -Speech and language therapy standards (WHSSC, 2023) -Clinical psychological and counselling services standards (WHSSC, 2023) -Genetic services standard (WHSSC, 2023) -Audit records and post-infant patient/parent satisfaction standards (WHSSC, 2023) -Adults returning to the service standard (WHSSC, 2023)
Members of the team (Example: members; qualifications; minimum staffing requirements)	-2020 Medical Global Standard 2-Team (Operation Smile, 2020) -Clefts of the Lip and Palate Evidence based Clinical Practise Guideline (ERN CRANIO, 2023)
Equipment, supplies and pharmaceuticals required for the members of the team	-2020 Medical Global Standard 3- Equipment, Supplies and Pharmaceuticals (Operation Smile, 2020)

5.4.3.3 Theme: Cleft care timeline (Steps in the cleft care pathway with time-frames)

Today, cleft care pathways begin before birth with early identification via prenatal 2D ultrasound scan as early as 16 weeks and more commonly within the literature during 18-21 weeks in utero (Frederick et al. 2022; WHSSC 2023; NHS England 2013). As of 2016, the World Health Organization (WHO) recommends an ultrasound scan as part of routine antenatal care and should therefore be included in a basic care pathway.

Although the long-term health of OFC patients is an insufficiently studied area, studies suggest that individuals born with an OFC have a higher-than-expected incidence of psychiatric and behavioural diseases, an increased risk for cancer and an increased mortality in general from all major causes of death (Robin et al. 2006). The need for comprehensive and extended follow-up to monitor and manage complications is therefore emphasised (Chadha and Beale, 2023). A lifetime cleft service serves not only to monitor and manage any complications or conditions that may arise throughout a patient's life but also to allow for management of late-presenting patients who have missed out on the care pathway early on in life. According to the Clinical Service Specification for the UK's Cleft Lip and/or Palate service, these patients should be assessed and treated so far as that is clinically possible and appropriate regardless of age, according to clinical need and in an appropriate environment (Welsh Health Specialised Services Committee 2023). The timeline for the ideal CPW therefore extends throughout the patient's life. A basic, sustainable CPW is not initially capable of providing a lifetime service in terms of further management. However, to maintain contact with patients throughout their life for the eventuality that care pathway progresses to address concerns that often develop later in life, patients should be recalled for audit and research purposes. This also prevents loss to follow-up in this population.

Essential procedures are considered those common to all cleft protocols: feeding advice, primary cleft surgical repair (lip; palate), speech and language therapy. The coordination of steps and timing at which primary surgical repair procedures are

performed is essential to eliminating further steps in the treatment plan (Watted et al. 2020).

The literature varies in the different procedures included in care pathways. For example, in UK cleft care pathways, NAM is not usually incorporated. Like Murthy (2019) reports, the role of NAM is to support surgeons that are not capable of handling wide cleft repairs and would often be found in care pathways associated with surgical outreach programs or where surgical skills and knowledge may need improving. Other interventions considered unnecessary include feeding plates, pre-surgical orthognathic procedures, frequent scar review follow-up appointments, non-functional fistula repair, orthodontic interventions in mixed dentition (Murthy, 2019).

In terms of Orthodontic interventions, European centres ranked as having the least favourable outcomes were centres with the longest orthodontic interventions and highest number of interventions of early treatment including hospitalisation for presurgical orthopaedics. This showed that complexity and intensity of treatment protocols did not relate to improved treatment outcomes and concluded that simple protocols can provide better or equally good outcomes with less burden of care (Sallis et al. 2008; Murthy, 2019).

Table 24 Characteristics of the ideal MDT care pathway based on the literature highlighting the recommendations on the approximate timepoint and reasons that an orofacial cleft should be seen by the different disciplines throughout their life

(sources of data: Chauhan, 2024,CLAPA 2024; WHSSC 2023; Dudding et al. 2023; Fowler et al. 2021; Murthy, 2019; Oberoi et al. 2018; NHS England 2013).

Approximate timepoint (age that patient should be seen)	Clinical discipline/speciality	Reason for contact (eg. Telephone call Appointment, Consultation, procedure/surgery/management, review)	Recommendations
Before birth/Antenatal: At 18-21 weeks in utero	Local Obstetric Unit or private ultrasound centre +/- Foetal Medicine specialist	- 2D Ultrasound scan: antenatal diagnosis of OFC, confirmed if necessary, by foetal medicine specialist	Within 24 hours of diagnosis of an OFC, the local obstetric unit contacts the Cleft Team for referral of the family to the CNS allied to their local Cleft Team[2,3].
	Cleft Clinical Nurse Specialist (CNS)	- Provides the first point of contact with the parents provides crucial support and information to families throughout the pregnancy. - Telephone contact: Negotiate face-to-face meeting - Appointment: Provide with printed information, offer contact with a cleft lip and palate association eg. The UK's CLAPA	Within 24 hours of referral, the CNS should contact the family/parents to negotiate an appropriate time and place for a face-to-face visit [2,3]. They will remain as a key contact for the parent(s) throughout the remainder of the pregnancy and until the birth of the baby and beyond [3].
At birth to 8 weeks	Local maternity unit (any discipline)	Following birth, before discharge: - While at local maternity unit, before discharge from birth facility, a neo-natal hearing screen should be done[10].	Local maternity unit should contact for referral to Cleft Team within 24 hours of birth. Hearing screen should be done and made available for Audiology
	CNS	Specialist feeding assessment and management, printed information, offer CLAPA referral .	CNS visit within 24 hours of referral to Cleft Team[2,3]. This CNS visit may be in hospital or following discharge home.
	Cleft MDT	Age 4-6 weeks: - First outpatient appointment - Meet Cleft team before any cleft surgery - appropriate Paediatric surveillance for co-morbidity & syndromes	Clinical Psychology support should be offered at all team clinics and be made available throughout all the time points in the care pathway. If indicated, refer parents to Genetics for counselling[1]
9 weeks-2 years	Cleft Surgeon: OMFS/Plastic Surgery	At 3-6 months: Lip repair At 6-12 months: Palate repair	For a child with a cleft lip, the first surgical procedure is the lip repair, which is typically completed between the age of 3-6 months. If the cleft involves the palate, the hard palate will also be repaired at this time, but the alveolar cleft is typically left until a later age to preserve facial growth.
	Cleft MDT	- Review after primary surgery	A patient with cleft palate, should be referred for audiological assessment and management [1]
	Audiologist	- Audiological assessment and management - At 10 months: hearing test for cleft palate pt and treatment as necessary - Annually up to 3 years of age: hearing assessments	
	Paediatrician	Local paediatric follow up to ensure continued surveillance for co-morbidity, syndromes and appropriate referral to other specialist services	
	Paediatric Dentist	By 6 months of age: consultation	Be seen by the Paediatric Dentist for dental health education/advice by 6 months of age as the deciduous teeth begin to erupt and direct/liaise with appropriate general dental care
	Speech and Language Therapist (SLT)	Age 18 months- formal speech and language assessment and management	Following palate repair, speech development must be monitored closely by the cleft team, particularly the cleft specialist speech therapist[1,3]. At 18 months and again at 3 years, the child will have a speech assessment but the exact timing will depend on the number of words the child has developed to ensure an adequate speech sample can be obtained[3].
3-7 years	At and around age 3 years: Cleft MDT	At pre-school entry/ age 3 years: - Cleft MDT clinic review - ENT and audiology assessment if cleft palate - Formal speech assessment by SLT At age >3 years: - Surgery to revise lip and speech (velo-pharyngeal insufficiency) if necessary.	Later investigation (e.g. nasoendoscopy and videofluoroscopy) for speech problems if necessary and this may be required at any stage in the care pathway [1] Paediatric Dentistry advice and/or intervention if necessary Psychological support should be offered prior to school entry Ensure ongoing routine preventative dental advice and treatment
	At and around age 5 years: Cleft MDT	At age 5-6years: - Full MDT and records - ENT and audiology assessment - Formal speech assessment by SLT - Audit records[3] At this visit, the child is assessed by dental and orthodontic teams, audiology, psychology, clinical photography, and speech and language therapy. The primary aim of the visit is to identify any arising problems but also to record a series of metrics for the national registry database and audit network (eg. CRANE in the UK)	At the age of five, the child will attend the cleft unit for the first of up to four audit clinics [3]
8-14 years	Cleft MDT: Orthodontist, Paediatric Dentist and Surgeon responsible for ABG	Assessment between 7 years of age and before 9 years by Cleft MDT: - if an alveolar defect is present (At age 8 years: Cleft MDT alveolar bone graft assessment) - Paediatric dentistry care if necessary At 10-11 years: Full Cleft MDT and records at 10 years At 11-15 years: Definitive orthodontic treatment	Assessment between 7 years of age and before 9 years by Cleft team. If required, pre-ABG orthodontic care followed by Alveolar Bone Grafting at age 8-11 years, completed before 12 years, timed prior to the eruption of the adult canine tooth [1,2]. Post-op follow-up should be at 6 months. Referral to primary care for routine preventative dental advice and treatment
	Other: speech and hearing	If there is palatal involvement, speech and hearing checked and problems managed	
15-21years	Full MDT clinic (at 15 years)	At 15-16 years: Cleft MDT clinic for review and records, Team assessment for orthognathic surgery if indicated, planning and pre-treatment for skeletalsurgery	Full MDT clinic and records at 15 and 20 years . Orthognathic surgery and associated Orthodontics if indicated .
	Orthodontist (at 16-18 years)	At age 16-18 years: pre-orthognathic orthodontic treatment	
	Oral and Maxillofacial surgeon, Plastic surgeon	At age 18 + years: Orthognathic surgery, septorhinoplasty	
	Full Cleft MDT clinic (at 20 years[1]) (includes the Oral and Maxillofacial Surgeon, Speech and Language Therapist)	At 18-20 years: -for review -completion of post-orthognathic surgery records -speech assessment	The following surgeries may be indicated: -Revisional surgery if indicated (nose, lip) -Speech revision surgery if indicated[1] The MDT service should closely liaise with continuing local care (orthodontic treatment, paediatric and restorative dental care)[1].
	Geneticist	For personal genetic counselling	Genetic referral should be offered[1]
>21 years returning		Continuation of/or return to care from previous period. Adult patients returning for care may require: Speech and Language assessment and therapy, lip and/or nose revisional surgery, speech revision surgery, palatal fistula repair, orthodontics, alveolar bone graft (ABG) surgery if not done previously, Orthognathic surgery, Septorhinoplasty, Clinical Psychology, ENT and hearing assessment, restorative dentistry	Adults can get a referral to the Cleft Unit from their GP or Dentist[2]. If it is deemed necessary, adults may re-enter the cleft service at any time for a consultation about any aspect of their care, including psychosocial support, genetic counselling and specialist dental treatment[2]. Any adult who has missed out on the care pathway should be assessed and treated according to the Clinical Service Specification in so far as that is clinically possible and appropriate regardless of age, according to clinical need and in an appropriate environment.

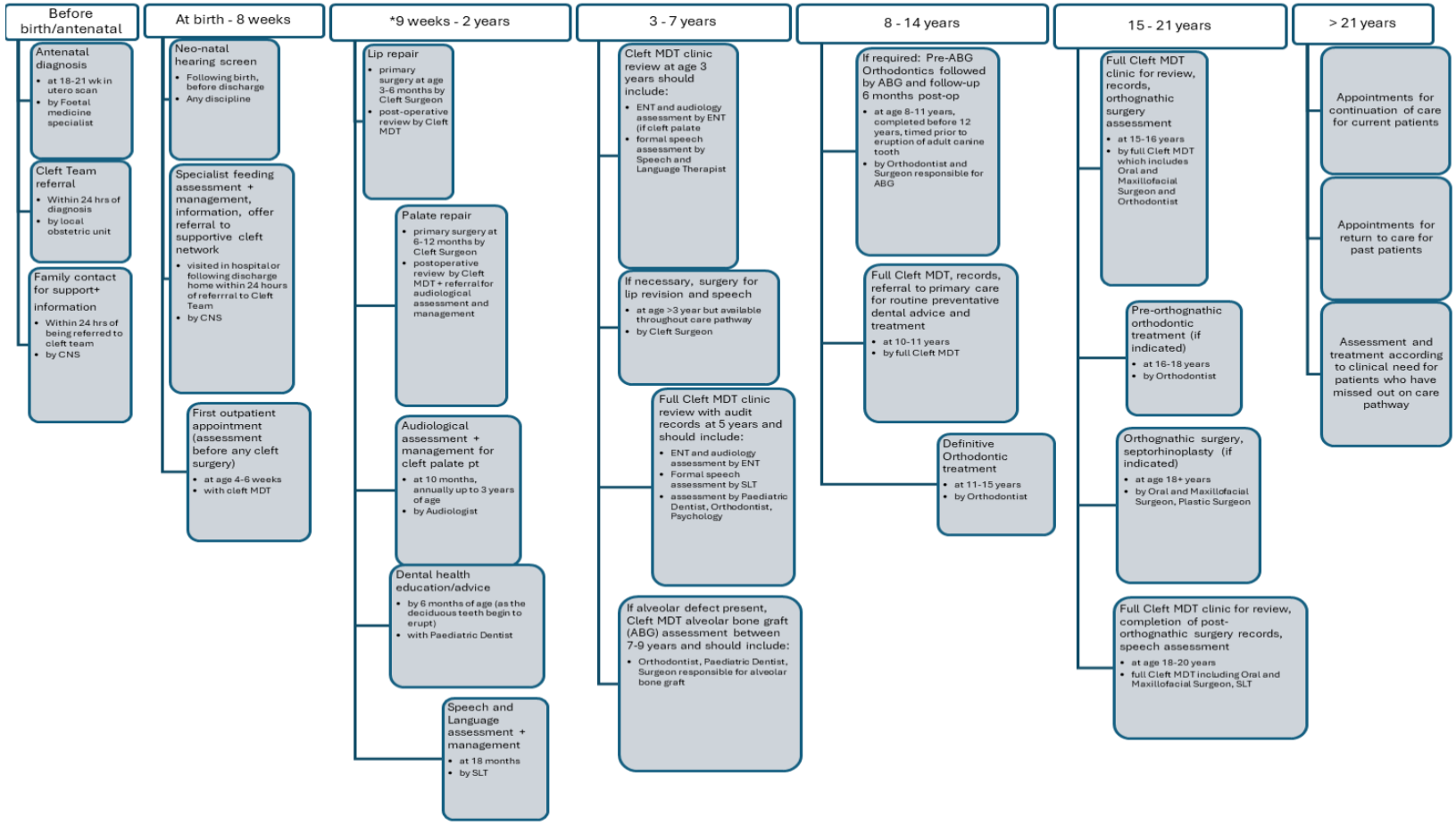

Figure 5 Timeline for the ideal MDT Cleft Care Pathway

Table 25 Characteristics of a basic MDT care pathway based on the literature and highlighting the recommendations on the approximate timepoint and reasons that an orofacial cleft should be seen by the different disciplines throughout their life (sources of data: Campbell and Kreshanti, 2021; Operation Smile, 2020; Oberoi et al. 2018; CEN/TC, 2015; Operation Smile 2015).

Approximate timepoint (age that patient should be seen)	Clinical discipline/speciality	Reason for contact (eg. Telephone call Appointment, Consultation, procedure/surgery/management, review)	Recommendations
Before birth/antenatal		Potential diagnosis with antenatal ultrasound imaging. Once diagnosed with OFC, refer for antenatal counselling and support	
At birth - 8 weeks	Multidisciplinary Orthodontist, plastic surgeon	As a newborn: feeding assessment, medical assessment, genetic counselling, treatment information At 0-3 months: Presurgical orthopaedics	Bilateral clefts with a prominent premaxilla will benefit from presurgical lip taping to bring the premaxilla back for easier lip repair. This treatment is only effective in very young babies, birth to 8 weeks, as later the tissues become less plastic and more difficult to bend [24]
9 weeks - 2 years	Cleft surgeon (Plastic surgeon) Plastic surgeon, otolaryngologist Speech and language therapist (SLT)	At 3-6 months (or after presurgical orthopaedics): primary cleft lip repair At 10-18 months (delayed if airway or medical concerns): Primary cleft palate repair with intralveolar veloplasty, myringotomy, and tubes if needed 3-6 months after palate repair: Recall for speech assessment.	Primary cleft palate repair optimal age range is 10-18 months but should be done early before the child has full speech development so that speech is learned in a normal oral environment and reduce the need for speech therapy[24]. The child should be recalled for speech assessment 3–6 months after palate repair [24].
3 - 7 years	Speech pathologist, plastic surgeon, otolaryngologist, orthodontist	3-4 years Diagnosis of velopharyngeal insufficiency Secondary palate repair lengthening or pharyngoplasty Speech obturator	
8 - 14 years	Plastic surgeon Orthodontist, plastic surgeon, oral surgeon	School-age years Treatment of secondary lip and nasal deformities 7-9 years (mixed dentition) Secondary alveolar bone graft Presurgical orthodontics	
15 – 21 years	Plastic surgeon, oral surgeon	Skeletal maturity LeFort I Definitive open rhinoplasty	
>21 year			

5.4.3.4 Theme: Challenges to implementing an ideal cleft care pathway and facilitating factors as potential solutions to overcoming them

Challenges to progressing a basic MDT cleft care pathway to an ideal one include lack of funding, shortage of trained surgeons and qualified practitioners. Potentials solutions to overcoming them are discussed as facilitating factors to overcoming them. These key characteristics of the basic CPW contribute to its sustainability and scalability, paving the way for its evolution into an ideal CPW.

Facilitating factors

Financial aid

Although all countries have committed to trying to achieve universal health coverage as part of the United Nations' 2030 Agenda for Sustainable Development, the systems in place vary significantly. For example, in developed nations like the UK, health coverage has been universal since the creation of the National Health Service (NHS). However, this model differs greatly from that of high-income yet resource-limited countries like Trinidad and Tobago, where healthcare is provided free of charge but often lacks comprehensive services, such as specialised cleft care. In these settings, it is crucial to invest in human resources, infrastructure, and ongoing operational costs. Meticulous record-keeping is essential for monitoring resource utilisation and performance, highlighting the need for sustained investment. Additional support can come from corporate partners, philanthropic organisations and academic institutions. Cleft-focused organisations, such as Smile Train, also play a crucial role in low-resource settings by funding surgeries and training, as well as providing equipment and comprehensive services. This empowers local doctors to offer free cleft repair surgery and holistic care within their communities. Since 1999, Smile Train has facilitated over one million cleft surgeries worldwide through this collaborative approach (Campbell and Kreshanti 2021).

Support from Cleft Foundations/Organisations with training of local surgeons/local skills development

A focus on skills and training improvement of local surgeons helps to reduce burden of care in that the need for pre-surgical orthopaedics like NAM and even revision surgeries is reduced (Murthy 2019). In response to the shortage of local trained surgeons and qualified practitioners in low-resource settings, several cleft foundations have evolved their support to include educational initiatives, fellowships, competency-based training programs and the use of emerging technologies to demonstrate and increase confidence in procedures. Some foundations that have demonstrated success of this "teach a man to fish" strategy include Operation Smile with their Physicians Training Program in cleft care, the FDI and Smile Train with open online courses for oral health professionals within cleft teams and Global Smile Foundation (GSF). GSF has been instrumental in progressing surgical education and increasing procedural confidence to clinicians. They introduced the first training programme in NAM therapy and their annual MDT cleft care workshops deliver didactic lectures and simulation-based hands-on training in areas of need around the world (Kantar et al., 2019). Achievable through strong partnerships between GSF and healthcare institutions, these workshops have received endorsement from key organisations including the American Cleft Palate Association, the European Association of Plastic Surgeons, the American Society of Plastic Surgeons, European Cleft Organization, and Latin American Craniofacial Association. GSF also promote training of local surgeons in underserved countries through fellowship programs such as the GSF Cleft Surgery Training program (GSF-CSTP) where fellows are directly trained and mentored by experts in the field, developing surgical skills, cultural competence, and communication skills required to provide compassionate care to patients and their families.

Audit, quality assurance programmes and research

Outcomes evaluation and quality assessment are important stepping-stones for sustainable cleft care as they allow continual improvement of care and service development by assessing current practices against international standards. This is well established in the UK with the Cleft Registry and Audit Network (CRANE), managed by the Clinical Effectiveness Unit at the Royal College of Surgeons. It serves as a comprehensive database for recording epidemiological data on children born with orofacial clefts, tracking clinical outcomes across cleft services and monitors individual cleft centre performance against key performance indicators, identifying outliers for remediation and generating national data for quality assurance purposes. For example, key performance indicators, such as palate repair timing (6-12 months), are assessed against established benchmarks and the national average. Centres falling two to three standard deviations below the average are flagged as ‘alerts,’ while those over three standard deviations are marked as ‘alarms.’ Identified outliers undergo thorough investigation and quality improvement processes to ensure services are improved (Chadha and Beale 2023; Dudding et al. 2023). The ideal MDT cleft care pathway would include a comprehensive network like CRANE, while a basic MDT cleft care pathway would incorporate audit and quality assurance programmes that can evolve into such a structured system. Details on the audit records that are collected and the subsequent assessments performed by MDT cleft teams in the UK from birth into adulthood can be found in McIntyre’s first part of a three article series on the management of patients with non-syndromic clefts of the lip and/or palate (McIntyre, 2014a).

Research is crucial for advancing cleft care services, as demonstrated by the restructuring and centralisation of the UK’s cleft service into the hub-and-spoke model. This restructuring was driven by a series of studies (CSAG I) conducted by the Clinical Standards Advisory Group (CSAG), which identified disparities in service delivery, clinical protocols and cleft-related outcomes within cleft services across the UK and produced recommendations for improvement. The 2015 follow-up “Cleft Care UK” study

(CSAG II) found improvements in surgical, occlusal, speech and language, facial proportions and psychological outcomes following centralisation, although dental and hearing outcomes showed no significant change. Additionally, the UK's Cleft Collective, the largest programme of cleft research in the world, conducts cohort studies aimed at addressing key questions, not only relating to cause of OFCs but also to the optimal treatment pathways and long-term impacts on patients and their families (Chadha and Beale 2023; Dudding et al. 2023). For low-resource settings, Campbell and Kreshanti (2021) suggest that the aim of research in the basic CPW is to improve quality of care and advance and optimise knowledge and skills, standards and practices of cleft care in low-resource settings. Data collection should therefore be meticulous and overseen by an institutional review board. Local and international university partnerships and involvement in groups such as the International Confederation of Cleft Lip and Palate and Related Craniofacial Anomalies, can support collaboration and resource sharing for effective research (Campbell and Kreshanti 2021).

Electronic Medical Records (EMR)

The Global Smile Foundation (GSF) uses its own electronic medical record (EMR) system when visiting low-resource settings. It contains documentation from all disciplines involved in care, from screening and clearing for surgery, pre-operative notes detailing treatment plans, postoperative inpatient progress notes to patient follow-up and documentation of complications. An EMR system not only allows consistent patient documentation and longitudinal collection of patient clinical data but also facilitates research, care coordination and patient-follow up (Chahine et al. 2023). During situations like natural disasters and the COVID-19 pandemic, the EMR enabled GSF to easily adapt to challenges, upload notes and discuss and coordinate MDT care through this system and video calls. For a basic CPW, it is essential to implement an EMR system or, at the very least, ensure meticulous medical record-keeping, with copies of all records preserved for future conversion to a digital system (Chahine et al. 2023).

5.5 Discussion

5.5.1 Summary of evidence

This scoping review found 34 sources that met the inclusion criteria from 1259 sources of data. They were published between 2005 and 2024 and covered cleft care for global populations and specific to developed countries (UK, Europe, USA, Canada, New Zealand, Netherlands, Germany, Israel), with cleft associations/organisations linked to 18 out of 34 sources. The scoping review encompassed data on cleft care from diverse settings, including hospital environments, clinics within hospitals, standalone centres, private healthcare systems, resource-limited environments and some sources addressed care across multiple settings.

The aim of this scoping review was to use the information found to suggest characteristics of a care pathway appropriate for introducing basic MDT cleft care that is both sustainable and scalable. Characteristics of care pathways were treated as data items/themes that were searched within the data sources and this allowed sub-themes to be identified, forming the structure for discussing the characteristics of each care pathway. The aim was achieved through investigating two objectives.

5.5.1.1 Context and relevance (objectives)

Data sources containing the themes searched/ characteristics of a care pathway, including a timeline for delivery of care, reported on the UK's NHS Cleft Service. This allowed the characteristics of an ideal MDT cleft care pathway to be clearly defined. The UK's NHS Cleft Service is a near-standardised, audited and networked cleft service on a national scale, considered by many to represent a paradigm of cleft care. It was remodelled after the system of cleft care delivery in Scandinavian countries, particularly Norway, that was associated with comparatively superior outcomes (Chadha and Beale, 2023).

This review encountered data sources such as Campbell and Kreshanti's (2021) review on implementing comprehensive cleft care centres in resource-limited settings and the CEN/TC's 2015 report "Early care services for babies born with cleft lip and/or palate"

aimed at providing an informative document that can be used by countries where national protocols need to be established. However, the timeline suggested included additional procedures and services that a low-resource setting lacking wider members of the MDT may not be able to implement. The characteristics of such a basic, cleft MDT care pathway was not available within the data sources identified in this scoping review. As such, suggestions were instead made for characteristics of a basic MDT cleft care pathway. Implementing potential solutions, referred to as facilitating factors, to overcoming challenges to achieving an ideal MDT cleft care pathway, the basic CPW can be considered sustainable and scalable.

This scoping review approach allowed the research question “What are the characteristics of a basic DT care pathway that is both sustainable and scalable, compared to an ideal MDT care pathway for the management of patients with orofacial clefts?” to be answered and this illustrated in Table 26.

Table 26 How the characteristics identified for an ideal MDT cleft care pathway compare to the suggestions for characteristics of a basic MDT cleft care pathway that is sustainable and scalable

Cleft care pathway characteristic (data items)		Characteristics identified for an ideal MDT cleft care pathway	Suggestions for characteristics of a basic MDT cleft care pathway that is sustainable and scalable
Themes (data items searched within the literature)	**Sub-themes (identified during scoping review of the literature)**		
MDT cleft care pathway statement of goals	-	Share the same statement of goals, delivered through an interdisciplinary approach	Share the same statement of goals, initially delivered through a multidisciplinary approach, with the aim of advancing to an interdisciplinary approach.
Key elements of MDT cleft care	Infrastructure of the cleft care pathway	Centralisation of cleft services. Eg. The UK's hub-and-spoke model of delivery, modelled after the centralised model of cleft care based in Scandinavian countries, particularly Norway	At a minimum, infrastructure required should satisfy the requirements for hosting a surgical outreach programme. Appropriate facilities include under-funded local healthcare systems or hospital facilities that allow for sponsoring organisations to provide financial aid, universities, governmental hospitals, private healthcare systems, a stand-alone comprehensive cleft care centres (CCCCs), mobile surgical hospital.
	Cleft MDT composition (disciplines and their roles within the cleft MDT)	Core and wider members of the cleft team; key procedures (not including NAM) + additional procedures if indicated	A smaller MDT limited to core cleft team members and key procedures: cleft lip surgical repair, cleft palate surgical repair, alveolar bone grafting, orthodontics, speech evaluation and therapy and nasoalveolar moulding (depending on cleft surgeon's expertise) if indicated.
	Supporting documents for the delivery of safe, quality cleft care	Follows and maintains these standards	Ongoing quality improvement to achieve these standards
Cleft care timeline (Steps in the cleft care pathway with time-frames)	Age that timeline starts	Before birth with antenatal detection with the antenatal scan	The timeline of care should begin with the antenatal scan similar to that of the ideal CPW but it is understood that an OFC may go undetected. If detected, it allows the family to be informed and supported and the introduction of the Cleft Nurse Specialist as a member of the team.
	Age that timeline ends	A lifetime cleft service that allows individuals requiring re-treatment or who missed out on the care pathway to receive care if needed	Initially not capable of providing a lifetime service in terms of further management but prevents patient loss to follow-up through recalling for audit and research purposes. This maintains patient contact for the eventual development of the basic CPW to offer management services into adulthood.
	Time-frame for interventions	The timeline has time-frames for performing procedures and are considered key performance indicators that are monitored and improved to ensure the standard is maintained	The timeline should incorporate wider age range/time-phases for primary surgical repair of clefts. This will allow late-presentation patients to still receive surgical repair.
Facilitating factors to optimising the care pathways	Financial aid	Universal Health Coverage which includes a national cleft service	Government support from corporate partners, philanthropic organisations, academic institutions (eg. Universities) and cleft-focused organisations.
	Support from Cleft Foundations with training of local surgeons/local skills development	-	Educational initiatives, fellowships, competency-based training programs, the use of emerging technologies to demonstrate and increase procedure confidence.
	Audit, quality assurance programmes and research	Include a comprehensive network like the UK's Cleft Registry and Audit NEtwork (CRANE) for audit, quality assurance purposes and the recording of epidemiological data on a national scale Has a research group (eg. The Clinical Standards Advisory Group in the UK) dedicated to conducting studies to identify disparities in service delivery, clinical protocols and cleft-related outcome and producing recommendations for improvement.	Incorporate audit and quality assurance programmes that can evolve into such a structured system as CRANE. A basic CPW should focus on meticulous data collection which should be overseen by an institutional review board. Support for research may be gained through collaboration and resource sharing with local and international university partnerships or international research groups.
	Electronic Medical Records (EMR)	Implement an EMR system.	Implement an EMR system or, at the very least, ensure meticulous medical record-keeping, with copies of all records preserved for future conversion to a digital system.

5.5.1.2 Evidence gaps

While the literature presents evidence for an ideal multidisciplinary team (MDT) cleft care pathway, there is a lack of clearly defined, sustainable, and scalable care pathways for implementing basic MDT cleft care in low-resource settings.

5.5.2 Strengths and limitations

As the aim was to use the literature to suggest characteristics for a basic care pathway suitable for introducing cleft MDT care in a high-income yet developing country like Trinidad and Tobago, a scoping review generating in-depth and broad results was deemed appropriate. To ensure that the proposed care pathways were based on evidence-based recommendations, this review was designed to strictly adhere to scoping review guidance such as the JBI methodology and PRISMA. To minimise bias and ensure the integrity of the results, blinded screening for eligibility, independent review of each study by at least two researchers and the use of a third experienced reviewer was done.

However, despite the efforts made to identify relevant sources, including systematically searching multiple electronic databases, forward and backward citation chaining of relevant papers and contacting cleft organisations, some may have gone unidentified. Authors of relevant studies could have been contacted for clarity on present and future work. The exclusion criteria of non-English language studies is considered a limitation as much of the efforts from Foundation-based cleft care in the Latin America and the Caribbean (LAC) region has been in Latin American countries where English is not the primary language, rather than the Caribbean islands. Relevant papers in Spanish or Portuguese reporting on foundation-based cleft care in Latin American countries (such as the countries in the entire continent of South America) that could have been instrumental in developing a basic, sustainable care pathway could have, therefore, been missed. For example, the Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC-USP), commonly known as Centrinho in Bauru, Brazil, is internationally recognised for its comprehensive, multidisciplinary cleft care model

that has influenced practice across Latin America. However, much of the detailed literature describing its model is not available in English, limiting its inclusion in this review despite its relevance (Hospital for Rehabilitation of Craniofacial Anomalies, University of São Paulo (HRAC-USP), 2025). This limitation suggests that future reviews could benefit from incorporating multilingual search strategies or collaboration with native speakers to capture insights from such established programmes in the LAC region, thereby informing the development of cleft care pathways in other low-resource settings.

Other notable limitations include the absence of a quality assessment with an appraisal tool for included sources. Additionally, a care pathway is only a general guide intended to help affected families understand what they can expect at each stage of their child's life. It outlines the "right" timing of procedures considered essential in improving patient quality of life and achieving the best outcomes. However, like every child is unique, so too is their orofacial cleft and care will be tailored to their specific needs. like most studies, the focus of the care pathway is on cleft lip and/or palate. For example, Dudding et al's (2023) describes the cleft MDT care pathway in the UK specific for a patient born with a complete, left-sided unilateral cleft lip and palate, which is not dissimilar to the management for other orofacial cleft subtypes. Finally, the ideal care pathway reflects current evidence-based recommendations which will require timely review and revision guided by advances in technology and research on clinical outcome.

5.6 Conclusions

The evidence synthesised in this structured review explored the characteristics of orofacial cleft care pathways globally. It identified characteristics of an ideal care pathway. This review of the literature also allowed suggestions on the characteristics of a basic MDT cleft care pathway. The basic pathway should allow the introduction of the MDT approach to cleft care that is sustainable and scalable through consideration of the challenges and facilitating factors to implementation of the ideal care pathway. The sustainable characteristics of this care pathway are the facilitating factors identified within the literature that support the progression of the basic, sustainable care pathway to an ideal care pathway designed from standardised care pathways within developed countries. This review is not to suggest a single optimal care pathway for cleft patients but to provide cleft teams in low-resource settings suggestions for the characteristics of a cleft care pathway that introduces comprehensive cleft care and has the potential to progress to the characteristics of an ideal cleft care pathway. Based on these initial suggestions, the next steps would involve further review and appraisal involving stakeholders to develop recommendations. In conclusion, this work supports the United Nation's Sustainable Development Goals, specifically targeting 3.8 and 3.C in achieving access to essential healthcare services and increasing the development of the health workforce in developing countries, especially in SIDS and LDCs, thereby leading to timely management and enhancing function, aesthetic appearance and psychological morale.

CHAPTER 6 OVERALL SUMMARY

The aims and objectives of this thesis were achieved through two pieces of work.

The epidemiological study conducted provides an update on the birth prevalence of the most common craniofacial anomaly, orofacial clefts, within the population of Trinidad and Tobago, which is 0.64 per 1,000 births. However, this study encountered missing data, inconsistently available and ambiguous data, underscoring the absolute imperative of improving the ascertainment and registration of OFCs, since progress and meaningful improvements cannot be implemented without reliable results. It provides evidence that record-keeping needs improvement and optimisation and highlights key areas for focused efforts such as patient history documentation, craniofacial anomaly surveillance and orofacial cleft classification. Although only a limited number of variables were appropriate for analysis, significant predictors of OFCs were still identified (gestational age; birth weight; birth length; maternal age; maternal medical history within normal limits; gravida; para). This study's findings suggest that the likelihood of a birth with an OFC decreases with gestational age, birth weight, birth length and if there is a maternal medical history within normal limits. Also, the likelihood of a birth with an OFC increases with maternal age and number of pregnancies. When analysed together, only maternal medical history within normal limits and gravida remain significant suggesting these are the stronger predictors which might themselves be influencing the other variables. The analysis suggests that a mother with a normal medical history is 91% less likely to give birth to a baby with an OFC. Women with a higher gravida are 74% more likely to give birth to a baby with an OFC. This study also suggests that development is required to establish a basic cleft MDT care pathway that introduces comprehensive cleft care to these individuals as an observational finding was the absence of a standardised multidisciplinary pathway providing comprehensive cleft care.

Finally, the scoping review provides a comprehensive overview of global evidence on cleft care pathways. Countries preparing to implement cleft services can use this

information as a foundation for developing their own initial protocols introducing basic, sustainable and scalable multidisciplinary team cleft care, allowing for gradual advancement toward an ideal care pathway. Most importantly, it must be emphasised that while this work may benefit countries like Trinidad and Tobago, the wider Caribbean region, other Small Island Developing States and low-resource settings, an ideal cleft service is ultimately one that prioritises patient-centred and individualised care. It is a service that recognises that the key outcome extends beyond the technical quality of surgical repair to include the patient's long-term quality of life (QoL). In this regard, a service such as India's "SIRAT-The Cleft Warriors Ensemble" that amalgamates holistic, patient-focused cleft care with multidisciplinary team care aimed at improving functional, aesthetic, psychological and social outcomes for individuals with OFCs (SIRAT, 2024).

CHAPTER 7 FUTURE RESEARCH

Areas identified as needing development to lay the foundation for further epidemiological research in Trinidad and Tobago include optimising the standards of record keeping across all RHAs with national audit and quality improvement projects. Three specific areas requiring improvement were identified as patient history taking, CFA surveillance and the use of an OFC classification system. These projects aim to reduce missing data and achieve standardisation of record keeping across all RHAs.

Once the groundwork has been set, future epidemiological studies on orofacial clefts and craniofacial anomalies will be able to contribute data on the phenotypes and sub-phenotypes of OFCs, clinical features of CFAs and the missing variables encountered in this thesis' epidemiological study. Such studies should be observational and prospective over a 10-year period in design, to increase the dataset with the addition of matching maternal ages in addition to baby gender, birth month and geographic region to further reduce bias with confounding variables with matching to a control group.

Optimising record keeping not only establishes a foundational set for epidemiological studies but also supports collaboration and contribution to an international research database on craniofacial anomalies. This, in turn, has the potential to improve our global understanding of these conditions. It also opens doors to research in areas such as quality of life, burden of care, treatment outcomes, and genetics. The multi-ethnic population of Trinidad and Tobago presents potential for substantial contributions to genome-wide association studies, which could ultimately benefit the global scientific community.

Furthermore, optimising record keeping such as through digitisation, aligns with emerging research on the integration of artificial intelligence (AI) tools within cleft care. Recent systematic and scoping reviews highlight that digitisation facilitates the use of AI in cleft care, particularly in facilitating collection of data, classification of cleft and objective cleft measurements and monitoring systems. For example, AI offers

capabilities in automating data extraction from imaging and clinical records, processing large volumes of cleft care clinical datasets, supporting the development of assisted algorithms and predictive models allowing clinically relevant information that may otherwise go unnoticed to be identified and stored, ultimately improving data availability and consistency for research and clinical audits in cleft care (Dhillon et al., 2021; Shah et al., 2025; Zambrano et al., 2025). Its role in facilitating objective cleft measurements and cleft classification is also noteworthy, with AI enabling automated, standardised assessment of cleft types and anatomical landmarks on clinical images, quantifying cleft dimensions and facial asymmetry to enhance consistency in documentation, treatment planning and prenatal assessment (Dhillon et al., 2021; Baeza-Pagador et al., 2024; Shah et al., 2025). Collectively, these advancements highlight the potential of AI-enabled digitisation to strengthen data quality, monitoring, and treatment planning within cleft care pathways (Dhillon et al., 2021; Baeza-Pagador et al., 2024; Shah et al., 2025; Zambrano et al., 2025).

To pragmatically address the challenges identified in this thesis, a phased strategic plan should be considered for the development of cleft care services in Trinidad and Tobago. In the short term, efforts should focus on optimising surveillance and registration systems, raising professional awareness, and providing targeted training for healthcare workers to improve early identification and referral of OFCs. In the medium term, establishing a pilot multidisciplinary cleft care pathway within selected RHAs will enable the delivery of basic, sustainable, and scalable cleft care using existing healthcare infrastructure while developing interprofessional collaboration for surgical, dental, and speech care. In the long term, the goal should be the creation of a national cleft service aligned with Universal Health Coverage principles, prioritising patient-centred and individualised care while recognising that outcomes extend beyond surgical repair to include the long-term quality of life for individuals with OFCs. This pragmatic approach offers a realistic, actionable roadmap for strengthening cleft care services in Trinidad and Tobago and can serve as a model for other Small Island Developing States facing similar challenges.

Moving forward, collaboration with local stakeholders, including healthcare providers, policymakers, and patient advocacy groups, will be essential to refine these initial suggestions into actionable, context-appropriate recommendations. This will ensure that the development of cleft care services in Trinidad and Tobago remains aligned with local needs, sustainable practices, and global best evidence, paving the way for meaningful improvements in the care and outcomes for individuals with orofacial clefts.

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Zambrano, C.D.B., Jiménez, M.A., Muñoz Rodríguez, A.G. and Hernández Rincón, E.H. 2025**.** Revolutionizing cleft lip and palate management through artificial intelligence: A scoping review. *Oral and Maxillofacial Surgery*, 29, p.79. doi:10.1007/s10006-025-01371-1

Appendix 2: Data collection proforma

Patient demographics:

- Date of birth:
- Gestational age/ weeks of gestation at delivery:
- Sex:M? F?
- Birth weight:
- Race/ethnicity:

Diagnosed craniofacial anomaly and medical hx

- Type of craniofacial anomaly recorded
- Side?
- Presence of other congenital anomalies?
- Presence of syndromes?

Family history

Parental history:

- Family History of craniofacial anomaly
- Parental consanguinity (degree of consanguinity?)
- Maternal age
- Paternal age

Maternal history

Maternal age
Maternal obesity, height, weight.
Marital status
Socioeconomic level
Education level
Nutritional status
Maternal medical history:
Chronic conditions (e.g. migraine, epilepsy, diabetes):?

Pregnancy and sexual history:

- Number of pregnancies
- History of abortion
- History of STIs during pregnancy
- Anaemia complicating pregnancy?
- Excessive vomiting in pregnancy?

Maternal drug history:
Use of prescription (licit) drugs?

- Antiseizure agents (phenytoin, sodium valproate, topiramate, methotrexate)
- Ondansetron for nausea and vomiting
- Diazepam
- Nitrofurantoins
- Corticosteroids

Use of illicit drugs?
Use of multivitamins containing folate during pregnancy? (dose recorded?)
Maternal social history:

- Occupation?
- Smoking history during pregnancy`
- Alcohol use?
- Stress reported?

Other observations

Appendix 3: PRISMA-ScR Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	106
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	107, 108
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	110
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	110
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	111
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	111,112
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	113
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	114
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	115
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	115, 116
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	116
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	116
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	117
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	118-123
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	n/a
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	119-122
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	124-142
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence camavailable), link to the review questions and objectives, and consider the relevance to key groups.	143
Limitations	20	Discuss the limitations of the scoping review process.	146-148
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	159
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	N/A

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

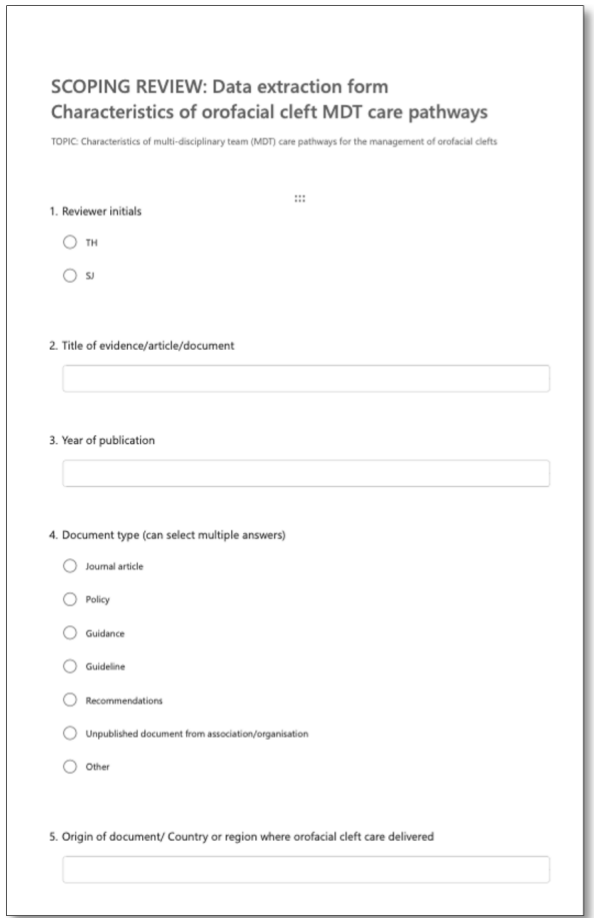
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Appendix 4: Data extraction form used in Scoping Review



SCOPING REVIEW: Data extraction form
Characteristics of orofacial cleft MDT care pathways

TOPIC: Characteristics of multi-disciplinary team (MDT) care pathways for the management of orofacial clefts

1. Reviewer initials

- ○ TH
- ○ SJ

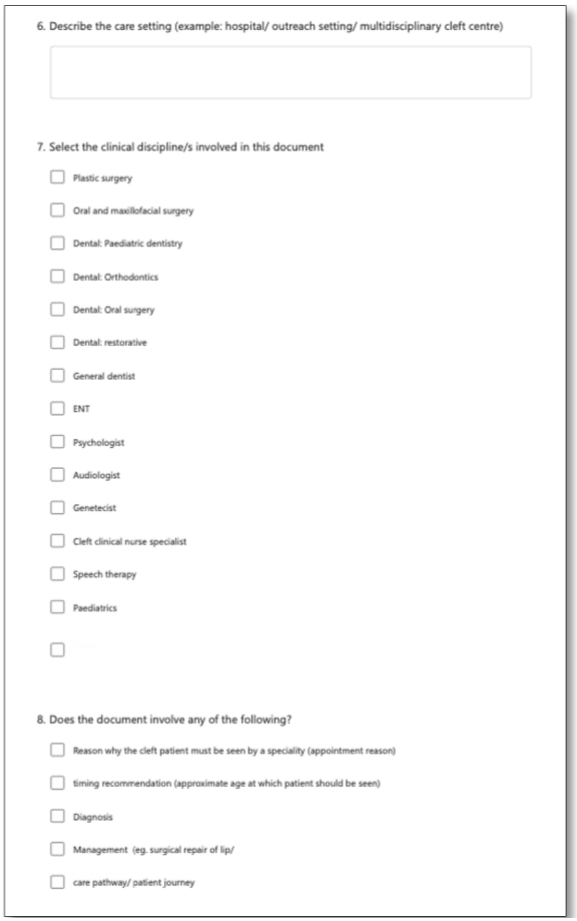
2. Title of evidence/article/document

3. Year of publication

4. Document type (can select multiple answers)

- ○ Journal article
- ○ Policy
- ○ Guidance
- ○ Guideline
- ○ Recommendations
- ○ Unpublished document from association/organisation
- ○ Other

5. Origin of document/ Country or region where orofacial cleft care delivered



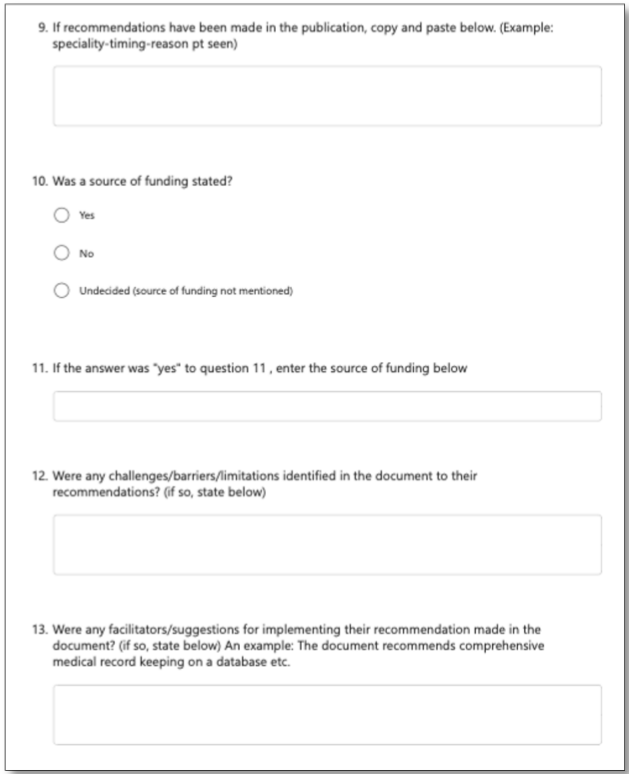
6. Describe the care setting (example: hospital/ outreach setting/ multidisciplinary cleft centre)

7. Select the clinical discipline/s involved in this document

- ☐ Plastic surgery
- ☐ Oral and maxillofacial surgery
- ☐ Dental: Paediatric dentistry
- ☐ Dental: Orthodontics
- ☐ Dental: Oral surgery
- ☐ Dental: restorative
- ☐ General dentist
- ☐ ENT
- ☐ Psychologist
- ☐ Audiologist
- ☐ Genetecist
- ☐ Cleft clinical nurse specialist
- ☐ Speech therapy
- ☐ Paediatrics
- ☐

8. Does the document involve any of the following?

- ☐ Reason why the cleft patient must be seen by a speciality (appointment reason)
- ☐ timing recommendation (approximate age at which patient should be seen)
- ☐ Diagnosis
- ☐ Management (eg. surgical repair of lip/
- ☐ care pathway/ patient journey



9. If recommendations have been made in the publication, copy and paste below. (Example: speciality-timing-reason pt seen)

10. Was a source of funding stated?

- ○ Yes
- ○ No
- ○ Undecided (source of funding not mentioned)

11. If the answer was "yes" to question 11 , enter the source of funding below

12. Were any challenges/barriers/limitations identified in the document to their recommendations? (if so, state below)

13. Were any facilitators/suggestions for implementing their recommendation made in the document? (if so, state below) An example: The document recommends comprehensive medical record keeping on a database etc.

Appendix 5: Glossary of terms

This glossary defines terms to enhance reader interpretation as the author has intended in the context of this work.

A

Agenesis
A condition where all or part of an organ doesn't develop properly during the early stages of growth in the womb. This means that the organ may be missing or not fully formed after birth.

Antenatal; prenatal
Relating to the medical care given to pregnant women before birth occurs.

Aplasia
Aplasia refers to the incomplete development or absence of an organ, tissue, or body part. It occurs when the affected area fails to grow to its normal size or is entirely absent, resulting in functional impairment or physical anomalies.

B

Binge-drinking
More than four alcoholic drinks on any one occasion.

C

Choanal stenosis or atresia
A condition where the back of the nose is blocked or narrowed, which can make it difficult for air to pass through. In choanal atresia, the passage is completely closed off, while in choanal stenosis, it is just narrowed. This can cause breathing problems, especially in babies, since they mainly breathe through their noses. Treatment usually involves surgery to open up the blocked area.

Cleft Registry and Audit Network (CRANE)
A UK-based NHS database which collects information about all children born with cleft lip and/or cleft palate in England, Wales and Northern Ireland.

Coloboma
A condition where a part of the eye, such as the iris, pupil, lens, or retina, is missing some tissue. This can affect how the eye looks and how it functions.

Craniofacial anomalies (or craniofacial abnormalities)
Congenital structural deformities, malformations, or other abnormalities of the cranium and facial bones.

E

Epigenetics
The study of how behaviours and environment can cause changes that affect the way genes work. Epigenetic changes are reversible and do not change the DNA sequence but can change how the body reads a DNA sequence.

Ethnicity
Ethnicity is a broader term than race. It describes the culture of people in a given geographic region. It refers to cultural factors, including nationality, regional culture, ancestry and language.

G

Gestational age
The number of weeks between the first day of the mother's last normal menstrual period and the date of delivery.

H

Hypoplasia
A condition where a part of the body doesn't develop fully, resulting in it being smaller or less complete than normal. This can happen in various tissues or organs, like teeth or muscles.

Hypotonia
A condition where the muscles are weaker than usual, making them feel floppy or limp. This can affect a person's ability to move and control their body, leading to challenges in activities like sitting, standing, or walking.

I

Incidence
Incidence looks at newly diagnosed cases and refers to the number of new births identified as having a craniofacial anomaly during a specified time period.

M

Micrognathia
A condition where the lower jaw is smaller than normal.

N

Nasal sill
The nasal sill is the narrow ridge of tissue that forms the junction between the nasal vestibule (the front part of the nasal cavity) and the skin of the face. It serves as a structural support for the nostrils and plays a role in maintaining the shape and function of the nose.

P

Palpebral fissures
The palpebral fissures are the openings between the upper and lower eyelids. They define the shape and size of the eye's visible area and play a role in protecting the eye, facilitating blinking, and maintaining moisture.

Periconception period
A critical window defined as 14 weeks before and 10 weeks after conception during which gametogenesis, organogenesis and placental development occur. It is a critical window with substantial impact on foetal growth and development (Steegers-Theunissen et al. 2013).

Population attributable fraction
An epidemiologic measure that is the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario.

Prevalence
Prevalence differs from incidence in that it looks at new and pre-existing cases of craniofacial anomalies within a population at a particular point in time.

R
Race
Race is seen as biological, referring to the physical characteristics of a person.

Retrognathia
A condition where the lower jaw is positioned farther back than the upper jaw. This can affect how the teeth fit together and may lead to problems with biting or chewing. In some cases, it can also cause issues with the airway or make the face look different. Treatment options may include braces or surgery, depending on how severe it is.

T
Trimesters
A pregnancy is divided into trimesters: the first trimester (0 to 13 weeks), second trimester (14 to 26 weeks), third trimester (27-40 weeks).