



**This electronic thesis or dissertation has been
downloaded from Explore Bristol Research,
<http://research-information.bristol.ac.uk>**

Author:

Alattar, Batol K S

Title:

**An investigation into interdental arch relationship outcomes of 5-Year-Olds born with a
Unilateral Cleft Lip and Palate using the Modified Huddart Bodenham Index following
the centralisation of cleft services within the United Kingdom**

General rights

Access to the thesis is subject to the Creative Commons Attribution - NonCommercial-No Derivatives 4.0 International Public License. A copy of this may be found at <https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode> This license sets out your rights and the restrictions that apply to your access to the thesis so it is important you read this before proceeding.

Take down policy

Some pages of this thesis may have been removed for copyright restrictions prior to having it been deposited in Explore Bristol Research. However, if you have discovered material within the thesis that you consider to be unlawful e.g. breaches of copyright (either yours or that of a third party) or any other law, including but not limited to those relating to patent, trademark, confidentiality, data protection, obscenity, defamation, libel, then please contact collections-metadata@bristol.ac.uk and include the following information in your message:

- Your contact details
- Bibliographic details for the item, including a URL
- An outline nature of the complaint

Your claim will be investigated and, where appropriate, the item in question will be removed from public view as soon as possible.



**This electronic thesis or dissertation has been
downloaded from Explore Bristol Research,
<http://research-information.bristol.ac.uk>**

Author:

Alattar, Batol K S

Title:

An investigation into interdental arch relationship outcomes of 5-Year-Olds born with a Unilateral Cleft Lip and Palate using the Modified Huddart Bodenham Index following the centralisation of cleft services within the United Kingdom

General rights

Access to the thesis is subject to the Creative Commons Attribution - NonCommercial-No Derivatives 4.0 International Public License. A copy of this may be found at <https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode>. This license sets out your rights and the restrictions that apply to your access to the thesis so it is important you read this before proceeding.

Take down policy

Some pages of this thesis may have been removed for copyright restrictions prior to having it been deposited in Explore Bristol Research. However, if you have discovered material within the thesis that you consider to be unlawful e.g. breaches of copyright (either yours or that of a third party) or any other law, including but not limited to those relating to patent, trademark, confidentiality, data protection, obscenity, defamation, libel, then please contact collections-metadata@bristol.ac.uk and include the following information in your message:

- Your contact details
- Bibliographic details for the item, including a URL
- An outline nature of the complaint

Your claim will be investigated and, where appropriate, the item in question will be removed from public view as soon as possible.

An investigation into interdental arch relationship outcomes of 5-Year-Olds born with a Unilateral Cleft Lip and Palate using the Modified Huddart Bodenham Index following the centralisation of cleft services within the United Kingdom.

Batol Kh Alattar

BSc, BChD, MChD, MOrth (Ed)

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Dental Surgery in Orthodontics, School of Oral and Dental Sciences, Faculty of Health Sciences.

September 2023

Word count: 28,252

Abstract

Aim: To investigate the interdental arch relationship outcomes of 5-year-old children with unilateral cleft lip and palate (UCLP) before and after centralisation of cleft services in the United Kingdom (UK) using the Modified Huddart-Bodenham Index (MHBI).

Design: Retrospective cross-sectional study.

Setting: Evaluation of 3D orthodontic study models of children with a complete UCLP.

Participants: All available 5-year-old orthodontic study models of participants with UCLP from the pre-centralisation (Clinical Standard Advisory Group CSAG n=107) and post-centralisation (Cleft Care UK CCUK n=195) studies.

Outcome measure: Differences between the interdental arch relationship outcomes for the CSAG and CCUK cohorts were assessed using the Modified Huddart-Bodenham Index (MHBI). This index scored the buccal/palatal or labial/palatal relationships of 8 maxillary deciduous teeth with the opposing mandibular dentition. The anterior segment (deciduous central incisors), buccal (deciduous canine, first and second deciduous molar) cleft segment and non-cleft segment scores were calculated along with the sum of the three segments combined to calculate the total arch MHBI scores.

Results: The inter- and intra-examiner reliability had a high level of agreement. Statistically significant differences in the anterior segment, buccal non cleft segment, and total arch MHBI

scores were found between CCUK and CSAG cohorts, with CCUK performing better. There was no difference in the buccal cleft segment scores.

Conclusions: There were improved transverse and anterior interdental arch relationships post centralisation (CCUK) of cleft services in the UK, suggestive of better primary surgical outcomes post CSAG.

Acknowledgement

I am incredibly grateful to my dedicated supervisors, Professor Tony Ireland and Dr Peter Fowler, for their invaluable patience, mentorship, and constant support throughout this research. Their expertise, detailed feedback and constructive criticism have been essential in shaping this dissertation and my overall research experience. I would also like to thank Professor Martyn Sherriff for his invaluable help with the statistics. The time you invested in this research is greatly appreciated.

I am immensely thankful to the Government of Kuwait for fully sponsoring my studies. This sponsorship allowed me to concentrate on conducting my research and enhancing my professional knowledge without any financial concerns.

I want to take this opportunity to express my deepest gratitude to my husband, Omran. Your love, encouragement and constant belief in my abilities helped me achieve my dream. This accomplishment is as much yours as it is mine and thank you for being my pillar of strength.

Lastly, I would like to thank my family and friends for their unwavering love and support. I am extremely thankful to my parents for the time and effort they put into helping me accomplish my goals and reaching where I am today.

Authors' Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements on the University's Regulations and Code of Practice of Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidates own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed:



Date: 28/08/2023

Table of Contents

Abstract	2
Acknowledgement	4
Authors' Declaration	5
List of tables	10
List of figures.....	11
1.0 Introduction:	13
2.0 Review of the literature	15
2.1 Epidemiology.....	15
2.2 Embryonic facial development:	16
2.3 Aetiology of orofacial cleft.....	18
2.3.1 Syndromic orofacial cleft:	19
2.3.2 Non-Syndromic orofacial clefts.....	20
2.4 Classification of orofacial clefts:	23
2.5 Comorbidities associated with OFC:	25
2.6 History of cleft care delivery in the UK:	26
2.6.1 The need for change in the care of OFC in the UK	26
2.6.2 Clinical Standards Advisory Group (CSAG).....	27
2.6.3 Changes made to the cleft care in the UK since the CSAG report:.....	31
2.6.4 Cleft Care UK (CCUK).....	33
2.6.5 Current cleft care pathways in the UK:.....	38

2.7 Transverse interdental arch relationships:	45
2.8 Outcome measures for patients with OFC assessing transverse buccal and anterior interdental arch relationships.....	51
2.8.1 Ideal Qualities of Outcome Measures	51
2.8.2 The GOSLON Yardstick:	53
2.8.3 Measuring overjet:.....	55
2.8.4 The EUROCRAN index	56
2.8.5 The 5-Year-Olds' Index:.....	57
2.8.6 Modified Huddart-Bodenham Index:.....	60
2.9 Comparing CSAG and CCUK interdental arch outcomes using dental study models: ...	65
2.9.1 Comparative 5-Year-Olds' Index outcomes	65
2.9.2 Comparative maxillary arch width dimensions outcomes	66
2.10 Summary of literature review	67
3.0 Research Question, Aims and Objectives:.....	68
3.1 Aims:	68
3.2 Objectives:.....	68
4.0 Materials and Methods:.....	70
4.1 Materials:.....	70
4.2 Permission:	71
4.3 Index used in this study:	72
4.4 Methodology:	75
4.4.1 Scanning and randomisation of sample:	75

4.4.2 Model scoring:	77
4.4.3 Reproducibility	78
4.4.4 Sample size calculation	78
4.4.5 Gender and laterality	79
4.5 Statistical analysis:	79
5.0 Results:.....	81
5.1 Demographic characteristics of the study sample:	81
5.2 Intra- and inter-rater reliability for the MHB index:	82
.....	86
5.4 Transverse and antero-posterior interdental arch relationship outcomes using MHBI:	87
5.4.1 Anterior segment:	87
5.4.2 Buccal cleft segment:	89
5.4.3 Buccal non-cleft segment	90
5.4.4 Total arch MHBI scores	92
6.0 Discussion:.....	94
6.1 Overview:	94
6.2 Reliability of measurement:.....	94
6.3 Missing data:	96
6.4 Study sample demographics:.....	96
6.5 Interpretation of results:	97

6.5.1 Anterior segment scores.....	97
6.5.2 Buccal cleft segment scores and buccal non-cleft segment scores.....	98
6.5.3 Total arch MHBI scores:	99
6.5.4 Laterality:	102
6.5.5 Gender:	102
6.5.6 Hand scanned vs lab scanned digital models:	103
6.6 Study limitations:	104
6.6.1 Sample selection and data loss.....	104
6.6.2 Model measurement :	104
6.6.3 Model artifacts:.....	105
7.0 Implications of the study and future work:.....	107
8.0 Conclusion	109
9.0 References.....	110
Appendices	127
Appendix I – Guidance on using the Modified Huddart- Bodenham Index given to assessors.	127
Appendix II: Screenshot of no ethical approval was needed to conduct this study.	128
Appendix III: Cleft Care data access approval.....	129
Appendix IV: National Institute for Health Research.....	130
Appendix V: Peer review.....	131
Appendix VI: CCUK Resource Research Proposal Form	133

List of tables

Table 1	LAHSAL coding system by the Royal College of Surgeons (RCS).	23
Table 2	Comparison between CCUK and CSAG study cohorts in methods, measures, demographics, and outcomes.	36
Table 3	Summary of current cleft care pathway in the UK.	43
Table 4	5-Year-Olds' index criteria for assessment of UCLP primary surgical outcomes.	57
Table 5	Summary of the articles that compared the MHBI with other indices and their findings.	62
Table 6	Demographic characteristics of the 5-year-olds' patients with UCLP in this study.	81
Table 7	Interpretation of level of agreement using intraclass correlation coefficients.	82
Table 8	Intra-rater agreement using intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for both assessors (BA and PF) for each segment and total arch MHBI scores.	82
Table 9	Intra-rater agreement using intraclass coefficients (ICC) and 95% confidence interval (CI) for hand-scanned versus lab scanned models for BA for each segment and total arch MHBI.	83
Table 10	Inter-rater agreement using intraclass coefficients (ICC) and 95% confidence interval (95% CI) for 1 st cycle and 2 nd cycle of scoring for each segment and total arch MHBI.	84
Table 11	MBHI Median scores and interquartile ranges for the CSAG and CCUK 5-year-olds cohorts, anterior segment, buccal cleft segment, buccal non-cleft segment and total arch scores.	85
Table 12	The results of the ordered logistic regression analysis CSAG vs CCUK for the anterior segment MHBI values along with gender and laterality.	87
Table 13	The results of the ordered logistic regression analysis CSAG vs CCUK for the buccal cleft segment MHBI values along with gender and laterality.	88
Table 14	The results of the ordered logistic regression analysis CSAG vs CCUK for the buccal non-cleft segment MHBI values along with gender and laterality.	90
Table 15	The results of the ordered logistic regression analysis CSAG vs CCUK for the total arch MHBI values along with gender and laterality.	91
Table 16	Estimated Modified Huddart- Bodenham scores for 5-year-olds' index category.	99

List of figures

Figure 1	Palatogenesis in mouse.	17
Figure 2	Representation of the most common types of clefts,	22
Figure 3	Huddart-Bodenham Index segments.	74
Figure 4	Modified Huddart-Bodenham Index scoring guide.	75
Figure 5	Example of digital model with poor anatomical detail preventing correct articulation for MHBI scoring.	77
Figure 6	Example of a digital model where the presence of insufficient anatomical detail prevented scoring individual maxillary teeth accurately.	78
Figure 7	A bar graph showing the non-normal distribution of CSAG and CCUK study cohort total arch MHBI's scores.	87
Figure 8	A float plot showing the frequency of values of the anterior segment MHBI scores for CSAG and CCUK.	89
Figure 9	A float plot showing the frequency of values of the buccal cleft segment MHBI scores for CSAG and CCUK.	91
Figure 10	A float plot showing the frequency of values of the buccal non-cleft segment MHBI scores for CSAG and CCUK.	92
Figure 11	A float plot showing the frequency of values of the total arch MHBI scores for CSAG and CCUK.	94

Glossary

CSAG	Clinical Standards Advisory Group
CCUK	Cleft Care United Kingdom
UCLP	Unilateral Cleft Lip and Palate
CL	Cleft Lip
CP	Cleft Palate
BCLP	Bilateral Cleft Lip and Palate
RCS	Royal College of Surgeons of England
CIG	Cleft Implementation Group
ENT	Ear, Nose and Throat (Otolaryngology)
MDT	Multi-Disciplinary Team
CNS	Clinical Nurse Specialist
PSIO	Pre-surgical Infant Orthopaedics
PNAM	Pre-surgical Naso-Alveolar Moulding
VPI	Velopharyngeal Insufficiency
SABG	Secondary Bone Grafting
HBI	Huddart and Bodenham index
MHBI	Modified Huddart and Bodenham index
WHO	World Health Organisation
A-P	Anteroposterior
OJ	Overjet
NHS	National Health Service

1.0 Introduction:

Transverse buccal and anterior interdental arch relationships refer to the bucco-lingual / labial-palatal relationship of the maxillary posterior and anterior teeth relative to the opposing mandibular teeth. Transverse buccal and anterior interdental arch relationships are an important consideration when assessing the outcome of growth and development of the dentition and underlying skeletal structures.

Unfavourable transverse buccal and anterior interdental arch relationships often occur in patients with orofacial cleft (OFC) and can present orthodontic treatment planning challenges in the correction of these relationships and subsequent retention.

Children with OFC often experience restricted maxillary growth following surgical repair, particularly if the cleft involves the lip, alveolus and palate. This restriction can occur in vertical, anteroposterior, and transverse maxillary dimensions and often becomes more apparent with continued facial growth. Restricted transverse buccal and anterior maxillary dimensions can lead to constricted and distorted upper dental arch forms and unfavourable interdental arch relationships.

The use of interdental arch relationship outcomes at age 5 years offers an opportunity to assess the occlusion following the surgical repair and continued facial growth, and prior to the transition to the permanent dentition and any orthodontic treatment.

Cleft care in the United Kingdom (UK) underwent a fundamental reorganisation following the recommendations of the 1998 Clinical Standards Advisory Group (CSAG). The CSAG findings highlighted the relatively poor outcomes when compared to other European cleft centres, where the number of surgical repairs undertaken per surgeon were considerably higher. As a result, cleft care in the UK was centralised and surgical services restricted to 16 sites. The purpose was to ensure higher volumes of surgical repairs were carried out by each surgeon. Improved outcomes from the centralised service were reported in the follow up Cleft Care UK (CCUK) investigation in 2013.

Previous outcome studies comparing pre (CSAG) and post (CCUK) cleft care centralisation have reported significant improvements including those assessing interdental arch relationship outcomes for children with repaired complete unilateral cleft lip and palate (UCLP) cleft at age 5 years. These have included measures of the anterior-posterior (AP) interdental arch relationship as well as maxillary arch form and width dimensions. Although significant improvements in AP interdental arch relationship were found, the maxillary arch width dimension improvements were relatively small. To date, no studies have investigated the transverse buccal and anterior interdental relationship outcomes using the Modified Huddart-Bodenham Index (MHBI) on dental models from the CSAG and CCUK studies. The MHBI is an index that assesses the severity and frequency of crossbites in the sagittal and transverse dimension to evaluate the amount of constriction within the maxillary arch. The study findings will add to the knowledge of clinically relevant outcomes following centralisation and may assist in the benchmarking of outcomes if future changes occur to surgical services in the UK.

2.0 Review of the literature

This literature review will start with the epidemiology of orofacial clefts (OFC), aetiology, and classification, followed by the comorbidities and quality of life of people with OFC. The current cleft care pathway in the UK will be discussed. Furthermore, the CSAG and CCUK studies will be reviewed, along with a comparison between them. The different interdental arch relationship outcome measures used in assessing complete unilateral cleft lip and palate (UCLP) will also be discussed along with the pros and cons of each outcome measure. Finally, the review will include the studies using the most common interdental arch relationship outcome measures used for children born with a UCLP, along with their reported findings.

2.1 Epidemiology

The prevalence of OFC in the UK is estimated to be 13 per 10,000 live births (CRANE, 2020) and is the most common craniofacial deformity (Gorlin *et al.*, 1971). The incidence of OFC varies considerably across geographic regions and ethnic groups with populations of Amerindian origin reporting the highest incidence of OFC clefts (27 per 10,000), whereas populations of African origin report the lowest incidence (4.2 per 10,000) (WHO, 2001). OFC can exist as a part of other abnormalities associated with a syndrome or can be non-syndromic and occur as an isolated event. Approximately 30% of OFC are associated with other abnormalities or syndromes (Dixon *et al.*, 2011), with a higher proportion of children with cleft palate (CP) associated with a syndrome (WHO, 2003). These syndromes can include Down syndrome, Teacher Collins syndrome and Pierre Robyn syndrome.

OFC represent a spectrum of defects that can extend from a micro-form or submucous versions of cleft limited to the lip or soft palate, to defects that include a complete bilateral cleft that extends from the lip, alveolus, hard and soft palate. Atypical OFCs are often termed Tessier Clefts and represent more extensive forms of facial cleft that can extend to include the orbit and/or cranial structures (Laurice Ann, 2018). These atypical OFCs are very rare and will not be included within this literature review.

According to CRANE (Cleft Registry and Audit Network), cleft palate (CP) (44%) is the most common cleft phenotype in the UK followed by cleft lip (CL) (23.3%), unilateral cleft lip and palate (UCLP) (22.8%) and bilateral cleft lip and palate (BCLP) (9.6%). CRANE is a national clinical audit managed by the Clinical Effectiveness Unit of the Royal College of Surgeons of England (RCS) that was established by the Department of Health in 2000 to collect information about children born with OFC. CRANE also reported that CP occurs more frequently in females (3:2), whereas cleft lip and palate (CLP) is more frequent in males (2:1), and that unilateral clefts on the left side are more common than on the right (2:1) regardless of gender, ethnicity and severity of the defect (Fitzsimons *et al.*, 2023).

2.2 Embryonic facial development:

During normal embryogenesis, facial development begins at around 4 weeks post conception. Neural crest cell migration and proliferation results in the formation of five facial processes: the frontonasal, two maxillary and two mandibular processes. It is the joining and fusion of these five processes that give rise to the facial structure. The development of the mandible and lower lip result from the midline fusion of the paired

mandibular processes very early on around week 5 *in utero*. By week 5 of development, the frontonasal processes also enlarge and give rise to the medial and lateral nasal processes, which surround the nasal placodes. Nasal pits result following the enlargement of the medial and nasal processes. The base of the nasal pits is lined by the oral nasal membrane, which separates it from the primitive oral cavity. At the same time, the maxillary processes start to migrate toward the centre, fusing with lateral nasal process and forming the nasolacrimal duct, the cheek, and the base of the nose. By the end of week 6, the maxillary processes continue to move medially, pushing the lateral nasal processes superiorly, which then allows it to join the medial nasal processes, forming the upper lip, primary palate, and the central portion of the nose. Therefore, upper lip formation is the result of the midline fusion of the maxillary and medial nasal processes (Jiang *et al.*, 2006).

The palate starts to develop around weeks 6-7 *in utero* and is completed around week 10. Embryologically, the palate is divided into the primary and secondary palate. The medial nasal process gives rise to the primary palate, comprising the four maxillary incisors, their alveolus and the premaxilla. The secondary palate develops from the maxillary process by fusion of the two palatine shelves. Initially, the palatine shelves are oriented vertically and are situated on either side of the tongue. As they grow and develop, they elevate above the tongue and fuse in the midline with their counterpart. The oral cavity and nasal cavity are separated by the fusion of the palatine shelves, the nasal septum, and the primary anterior palate (Figure 1) (Bush and Jiang, 2012).

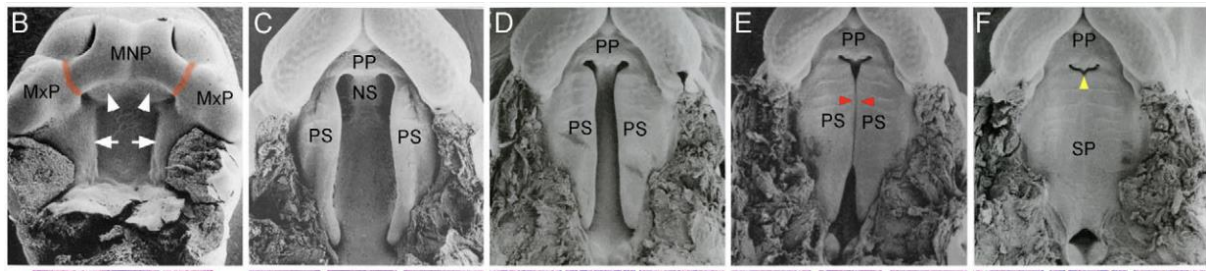


Figure 1: Palatogenesis in mouse. MNP, medial nasal process; MxP, maxillary process; NS, nasal septum; PP, primary palate; PS, palatal shelf; SP, secondary palate (Bush and Jiang, 2012).

Occasionally, failure of fusion or abnormal development of the maxillary processes or nasal processes can occur resulting in anomalies including OFC. The periderm surrounding the medial edge of the palatine shelves must be disrupted for the palatal shelves to adhere and fuse. This disruption will lead the periderm cells to change in shape dramatically, resulting in the apoptosis of their nuclei. The exfoliation of the dead epidermal cells allows the opposing palatine shelves to fuse at the midline. Similar apoptotic mechanisms occur around the medial nasal and maxillary prominences before lip fusion (Lan *et al.*, 2015).

2.3 Aetiology of orofacial cleft

The aetiology of OFC is unknown but appears to be multifactorial, resulting from both genetic and environmental interaction affecting facial development at a specific point during embryogenesis (Cobourne, 2004).

Identifying the main genes involved in OFC could help in early diagnosis, prevention and perhaps the development of adjunctive therapies. However, there remains limited understanding of the genetic aetiology of non-syndromic OFC due to its Mendelian

inheritance pattern, the restricted availability and expenses of genomic tools and the need for large data sets (Dixon *et al.*, 2011). By contrast there has been significant progress in identifying the genes involved in syndromic OFC due to advancements in genomics.

2.3.1 Syndromic orofacial cleft:

Orofacial cleft has been known to be an associated feature of over 300 syndromes (Online Mendelian inheritance in man: <http://www.ncbi.nlm.gov/omim>). Like all syndromes, the aetiology of syndromic CLP can be subdivided into:

- Those resulting from a single gene defect.
- Those resulting from chromosomal structural abnormalities.
- Known teratogens associated with syndromes.
- Those with unknown causes (Cobourne, 2004).

Genes that are strongly associated with several syndromic OFCs include:

- IRF6: mutation in IRF6 gene has been recognised to cause Van Der Woude syndrome (VDW) (Cobourne, 2004). It has been suggested that it works by regulating the interactions between members of TGF β (transforming growth factor- β) (Kondo *et al.*, 2002). However, the exact mechanism of how IRF6 can affect development remains unknown.
- PVRL1: Homozygous loss-of-function mutation in PVRL1 gene has been identified to cause CLP-ectodermal dysplasia syndrome (Suzuki *et al.*, 2000). The findings from

Suzuki *et al.* (2000) suggest that normal PVRL1 gene function plays a vital role in regulating the palatine shelves fusion during palatogenesis.

- COL2A1: mutation in COL2A1 gene have been shown to be associated with type 2 Stickler syndrome. Abnormalities in this gene can affect collagen biosynthesis, which manifests as abnormal skeletal morphogenesis and can appear as isolated CP (Richards *et al.*, 1996).
- Other genes associated with syndromic OFC are SOX9 in Pierre Robin (Benko *et al.*, 2009), FGFR2 in Crouzon, PTCH1 in Gorlin syndrome and TCOF1 in Treacher Collins (Treacher Collins Syndrome Collaborative Group 1996), (Dixon *et al.*, 2011).

2.3.2 Non-Syndromic orofacial clefts

As previously described, non-syndromic orofacial clefts account for 70% of all OFC (Dixon *et al.*, 2011). The aetiology and pathogenesis of non-syndromic OFC are poorly understood due to its multifactorial nature resulting from complex interactions between genetic and environmental factors at a certain point during facial embryogenesis (Cobourne, 2004). Up to 14 genes and loci were identified to be associated with non-syndromic OFC through genome-wide association studies (Lidral and Murray, 2004), including IRF6 (Rahimov *et al.*, 2008), VAX1 (Mangold *et al.*, 2010), MSX1 (van den Boogaard *et al.*, 2000; Jezewski *et al.*, 2003) and ABCA4 (Beaty *et al.*, 2010).

Environmental risk factors have also been found to be important in the aetiology of OFC.

Maternal smoking, alcohol consumption, poor nutrition, viral infection, drugs, and exposure to teratogens at work and in the home during early pregnancy have been investigated.

A strong link between maternal smoking and increased risk of both CLP and CP have been found with a population-attributable risk as high as 20% (Little *et al.*, 2004). However, the relationship between maternal smoking and CLP prevalence might be underestimated, because passive smoking was not considered in most studies. A UK study suggested that the risk of OFC might increase in infants carrying the cleft associated *TGF* mutation if the mothers were smoking cigarettes (Shaw *et al.*, 1996). A recent systematic review and meta-analysis that investigated maternal smoking as an aetiological factor for OFC reported a moderate association (Fell *et al.*, 2021). However, the quality of the studies included in this review were poor (Fell *et al.*, 2021). In the UK, there has been a significant change in smoking behaviour between 2000 to 2018, with the number of smokers reducing by more than a third, due to the implementation of smoking-free legislation. Despite this dramatic change, the predicted effect on OFC incidence was relatively small (from 14.2 per 10,000/year down to 13.5 per 10,000/year) but may have contributed to reducing OFC incidence in the UK (Fell *et al.*, 2021).

Alcohol consumption during pregnancy has also been associated with an increased risk of OFC (DeRoo *et al.*, 2008). However, the role of alcohol in causing OFC is less clear, with some studies finding a positive association (Romitti *et al.*, 1999; Chevrier *et al.*, 2005) but not in others (Meyer *et al.*, 2003; Romitti *et al.*, 2007).

Nutritional intake during pregnancy is thought to impact on the prevalence of OFC, but some of the studies that have investigated the intake of folate supplements to prevent OFC were controversial. While some studies have found a detectable reduction in the incidence

of OFC when folic acid was used in food fortification programme (7% reduction) (Yazdy *et al.*, 2007; Johnson and Little, 2008) others have not (Ray *et al.*, 2003; Lopez-Camelo *et al.*, 2010). In general, when folate was used in food fortification, a reduction in OFC has been seen in the USA (Yazdy *et al.*, 2007) but not in Chile (Lopez-Camelo *et al.*, 2010) or Canada (Ray *et al.*, 2003). A relatively recent study found no association between OFC and high levels of folate receptor autoantibodies in pregnant women (Bille *et al.*, 2010). Although many of the previous studies have suggested folic acid is useful in protecting against OFCs, they have often suffered from data and design limitations. In addition the sample sizes have been small, there have been power limitations and in some cases the folic acid was used in combination with other supplements (Wehby *et al.*, 2010).

Drugs such as diazepam, phenytoin and corticosteroids have been shown to have a positive correlation with OFC (Abrushamchain *et al.*, 1994; Shaw *et al.*, 1995; Park-Wyllie *et al.*, 2000). However, these findings need to be cautiously interpreted due to the risk of publication bias. Other environmental factors that need further investigation with respect to the aetiology of OFC include maternal stress, obesity, ionising radiation, and occupational exposures.

2.4 Classification of orofacial clefts:

Orofacial clefts can be classified as being complete or incomplete based on the severity of the cleft, as well as unilateral or bilateral depending on whether it involves one side or both sides (Figure 2).

CL/P can range from a notching of the upper lip, with or without involvement of the alveolus, to complete unilateral or bilateral lip, alveolus, and hard/soft palate clefts.

Whereas CP can range from a bifid uvula or simple submucous cleft to a complete cleft involving the primary and secondary palate (Couborne, 2004).

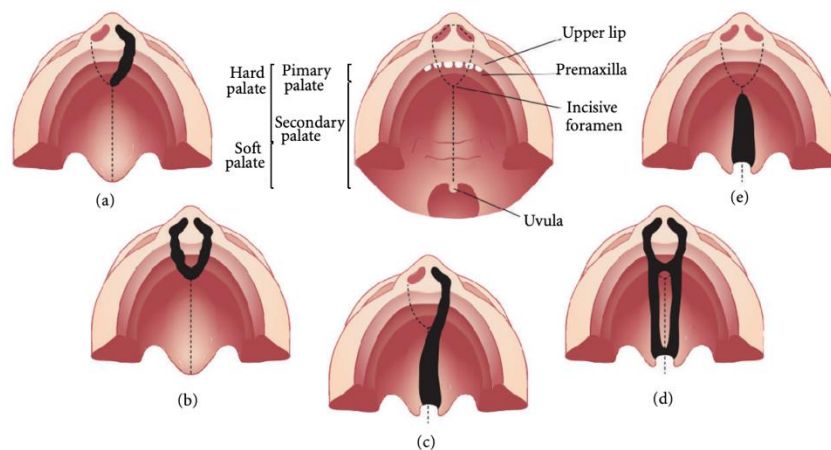


Figure 2: Representation of the most common types of clefts: a. unilateral cleft palate with alveolar involvement; b. bilateral cleft with alveolar involvement; c. unilateral cleft lip associated with cleft palate; d. bilateral cleft lip and palate; e. cleft involving both soft and hard palate (Brito *et al.*, 2012).

Many classifications have been used to describe OFC (Kernahan and Stark, 1958; Schwartz *et al.*, 1993; Koul, 2007), but most use the anatomy of facial embryology, as it is the simplest method. The most common classification used in the UK, which uses anatomy of facial embryology as its base is the 'LAHSAL' classification, as it is easy to use and is sufficient for most purposes. 'LAHSHAL' was first described by Otto Kriens (1989) and was modified based on the recommendation of the Royal College of Surgeons (RCS) by dropping one "H". This made the system simpler to use as it removed the necessity to record bilateral clefts of the hard palate, which is a midline structure (Hodgkinson *et al.*, 2005). Each letter of the LAHSAL code relates to one of the six anatomical sites that can be affected by a cleft (Table 1). The extent of the cleft can be determined by the use of upper- or lower-case letters. For instance, an upper-case letter, *e.g.*, L, indicates a complete cleft lip. In contrast, a lower-case letter, *e.g.*, l, indicates an incomplete cleft lip, and an absence of letters (and replaced with a dot) indicates that there is no cleft affecting that site.

L	A	H	S	A	L
Right Lip	Right Alveolus	Hard palate	Soft palate	Left Alveolus	Left Lip

Table 1: LAHSAL coding system by the Royal College of Surgeons RCS (CRANE Database, 2019).

2.5 Comorbidities associated with OFC:

Orofacial clefts can have a profound impact not only on social interaction but also on the quality of life of children born with such a deformity, which can extend from birth until their twenties and maybe longer. Common comorbidities associated with OFC include problems with feeding, chronic ear infection, speech and language difficulties (Roberts *et al.*, 2012) as well as abnormalities in dental development, which include missing/extra teeth or malpositioned teeth, increased risk of caries and/or Class III malocclusion (Ranta, 1986; McCance *et al.*, 1990; Bokhout *et al.*, 1997).

Rehabilitation for children born with OFC starts soon after birth and can continue until early adulthood. The primary aim of treatment is to achieve as near normal facial appearance as possible, improve function as well as psychosocial wellbeing (Dudding *et al.*, 2023). The treatment undertaken, particularly in the early stages, should ideally have minimal impact upon inherent future facial growth and development. To achieve successful outcomes, a multi-disciplinary, highly specialised treatment from birth to early adulthood is needed, along with a lifetime commitment to oral health maintenance (Colbert *et al.*, 2015).

2.6 History of cleft care delivery in the UK:

2.6.1 The need for change in the care of OFC in the UK

After the Fifth International Congress of Cleft Lip and Palate and Related Craniofacial Anomalies in 1986, orthodontists agreed to carry out an international study to compare treatment outcome in UCLP across Europe. This international multi-centre study included six European centres (Eurocleft), which allowed for assessment and comparisons between primary surgical outcomes, craniofacial form, dental arch relationships and nasolabial appearance to be carried out (Shaw *et al.*, 1992a). The two UK cleft centres which participated in the study reported poor outcomes compared to the other European centres in this study. The consequences of poorly organised care included increased suffering of patients and their families and greater economic costs on health services associated with further need for operations and ancillary care (Shaw *et al.*, 1992b).

Identifying the factors behind the two UK centres poor performance was challenging (Shaw *et al.*, 1992a). Although different treatment programs were used between the units, there was no evidence to suggest which primary surgical technique or other treatments used was better than the other (Shaw *et al.*, 1992b). However, the investigators suggested operator caseloads may have a significant impact on treatment outcome. It was found that the centres where the surgeons had high volume caseloads of UCLP repair, achieved better results, whereas the centres that had more surgeons, but with lesser caseloads per surgeon had the worst quality of treatment (Shaw *et al.*, 1992b).

Other factors that have been associated with poor treatment outcomes include lack of standardisation and centralisation (Sandy *et al.*, 2001). The presence of a high number of cleft surgeons and low caseloads per surgeon also meant that it would take decades to accumulate sufficient numbers of 5 year olds with repaired OFC for an inter-centre comparison to take place (Williams *et al.*, 1996).

2.6.2 Clinical Standards Advisory Group (CSAG)

From the issues mentioned above, it was apparent the cleft care pathway in the UK needed to improve. A research team was commissioned in 1998 by the Clinical Standards Advisory Group (CSAG) committee to perform an audit to report on the care and outcome in every non-syndromic UCLP case at 5 and 12 years of age over a period of two years (Sandy *et al.*, 2001). Patients with UCLP were chosen as it was considered that they best represented cleft care outcomes and that it would be unrealistic to include all types of clefts. Two different age groups were chosen because at 5 years of age, primary surgical outcome could be assessed without the outcome distorted by orthodontic treatment or bone grafting. The 12-year-old group was chosen so that the assessment of success of secondary alveolar bone grafting and facial development could be carried out.

The interdental arch relationship outcomes at 5-years-old were assessed using the 5-Year-Olds' index (Atack *et al.*, 1997) and the 12-year-old interdental arch relationship outcomes were assessed using the GOSLON Yardstick (Williams *et al.*, 2001).

2.6.2.1 The CSAG Study Sample and Method:

Study models (239 out of 326 participants with a mean age of 6.4 years) included in the CSAG report were identified using cleft surgeons' operating lists from April 1982 – December 1984 for 12-year-old data and April 1989 – December 1991 for 5-year-old data (Sandy *et al.*, 1998). Pre-lip repair photographs and/ or dental models were used to confirm the original diagnosis and assess suitability to meet inclusion criteria, which included children born with complete UCLP including a soft tissue band of less than 5mm (Sandy *et al.*, 1998). Cleft care outcomes were evaluated in terms of skeletal relationships and interdental arch relationships, alveolar bone grafting, hearing and speech, oral health and psychological status, and patient satisfaction (Sandy *et al.*, 1998). The patients were recruited by the research team for record collection and the following data were gathered:

- Audiology and tympanometry.
- Speech recording.
- Extra oral photographs
- Dental study models.
- Oral health status.
- Parent and patient satisfaction (12-year-old cohort only).
- Radiographs of alveolar bone graft (12-year-old cohort only).
- Lateral cephalogram (12-year-old cohort only).

Furthermore, recently appointed consultant orthodontists to cleft teams were surveyed to assess their experience and training in cleft care (Sandy *et al.*, 1998).

2.6.2.2 CSAG Results:

Interdental arch and skeletal relationships: The 5-year-old index and the GOSLON index were used to assess the AP interdental arch relationship for the 5-year-old and the 12-year-old cohorts respectively. It was found that 37% of the 5-year-old dental arch models and 39% of the 12-year-old dental arch models were rated as “poor” or “very poor” (Sandy *et al.*, 1998). This indicated that those participants had sufficient interdental arch discrepancies that would likely involve orthognathic and orthodontic treatment to achieve a satisfactory occlusion. This would be undertaken once facial growth had been completed.

Cephalometric radiographs were used to assess the AP skeletal relationship of the older cohort. It was found that the majority (70%) (Sandy *et al.*, 1998) of the cohort had a skeletal class III relationship compared to only 5% of the general population experiencing skeletal class III relationship (Todd and Lader, 1988). A shortcoming of the CSAG study was that no assessment was undertaken to specifically assess transverse interdental arch relationship outcomes.

Quality of alveolar bone graft (ABG) and oral health: The assessment of anterior occlusal radiographs for patients who had secondary alveolar bone grafting (SABG), established that only 58% of the SABG were scored as successful, 30% were seriously deficient and 12% had failed. Fifteen percent of the 12-year-old cohort had not yet been offered a SABG, although this surgery was required by all UCLP patients and ideally should be carried out prior to the age of 12 years. The outcome of the SABG was scored using a modified Bergland index to assess bony infill (Bergland *et al.*, 1986).

Oral health assessments reported 40% percent of the 5-year-old and 20% of the 12-year-old had active caries that required treatment.

Psychosocial status, difficulties attending cleft clinics and parent satisfaction: Almost 20% of the parents of the 5-year-olds and 28% of the parents of the 12-year-olds felt that their child's confidence had been affected by the OFC. Moreover, 36% experienced difficulties in attending cleft clinics and the factors contributed included distance, time off work, arranging care for the siblings, and the child with OFC missing school. Despite the other poor results revealed in the CSAG report, most parents were satisfied with the 'care and attention' received by the cleft team and 56% were satisfied with the treatment and outcome.

Training of orthodontists: Sixty percent of the recently qualified orthodontic consultants felt their training could be improved by provision of more study days along with treatment of more cleft cases.

When the results of the CSAG report were compared with results from other European countries, the cleft care within the UK performed significantly worse in both the interdental arch relationships and secondary alveolar bone grafting (Bearn *et al.*, 2001).

2.6.2.3 CSAG recommendations:

The following recommendations were made by the CSAG committee (Bearn *et al.*, 2001):

- Reduction in cleft units from 57 to 18-15 units to concentrate the resources and expertise, with consideration given to population needs and accessibility.
- The different specialities needed in the cleft team and the necessary standards required in respect of process and treatment outcome should be clearly indicated.
- Trusts undertaking cleft care must have a full range of clinical skills. Furthermore, trusts and commissioners need to work together to provide a plan for centralisation of cleft services.
- Clinicians should agree on a database for all cleft patients which will allow for comparative studies to be undertaken.
- All cleft specialists must train at high-volume cleft centers with high-quality clinical experience. Furthermore, surgical specialties should establish a surgical trainee pathway, given the small number involved in cleft care.
- Improve the completeness of cleft birth recording in the UK.

2.6.3 Changes made to the cleft care in the UK since the CSAG report:

All the CSAG report recommendations were accepted by the UK government and supported by the Cleft Lip and Palate Association (CLAPA), which is a charity that supports people born with CLP and their families in the UK. The Department of Health established the Cleft Implementation Group (CIG) to assist with the execution of the CSAG recommendations (Sandy *et al.*, 2003).

Although the recommendations received widespread support, the implementation was slow. Many factors contributed to this, although devolution within the United Kingdom (UK)

was an early and significant contributing factor (Sandy, 2003). Even though the study was UK-based and the recommendations were made for the whole UK population, the CIG had jurisdiction only in England. Scotland, Wales, and Northern Ireland were free to set their own care protocols (Sandy, 2003).

A further disruption to implementation was the spread of misinformation, misconceptions and occasionally mistruth by some clinicians who felt that their units were under threat (Sandy, 2003). A main CSAG recommendation was to dramatically reduce the number of cleft units to establish high volume cleft centres through centralisation of cleft care. Centralisation had been shown to have a positive impact on cleft care in many European countries (Sandy, 2003).

Despite these barriers to implementation, cleft care in the UK today is significantly different. The cleft care units have been reduced to 16 cleft centres, or managed clinical networks structured on a hub and spoke model for the delivery of cleft care. Each of these centres provide a base for the multidisciplinary cleft team and are the surgical hubs supported by outreach spoke centres where non-surgical care is provided (Sandy *et al.*, 2012). Each multidisciplinary team is led by a clinical director with a supporting manager, and each cleft centre treats at least 80-100 newborns with OFC per year and a consistent surgical protocol was introduced. The multidisciplinary team providing the care comprises a variety of specialists and the clinicians involved must have completed designated Training Interface Group courses and have shown commitment to the care of patients with OFC, as well as maintaining good patient records and outcomes. In addition, outcomes must be audited,

and an annual report must be provided to the commissioners by the cleft centres (Colbert *et al.*, 2015).

2.6.4 Cleft Care UK (CCUK)

Fifteen years after the centralisation, a nationwide multi-centre cross-sectional study known as Cleft Care UK (CCUK) was undertaken to assess the impact of the changes made by the reconfiguration of cleft services (Persson *et al.*, 2015). 268 out of the 359 5-year-old cleft affected children, born between April 2005 and March 2007 and with a non-syndromic UCLP, were included in the study. The study design and measurements were carried out in a similar manner to the original CSAG study to enable valid comparisons to be made (Persson *et al.*, 2015), but with some additional outcome measures. The outcomes recorded were:

- Surgical treatment
- Interdental arch relationship (using the 5-year-old index)
- Facial aesthetics
- Oral health (caries and the presence of oral fistula)
- Audiology and speech
- Somatic growth
- Psychosocial factors
- Health and lifestyle

2.6.4.1 Results:

When interdental arch relationships were compared using the 5-Years-Olds' Index, it was found that more than 50% of children included in the CCUK study had good AP interdental arch relationships and approximately 20% had poor relationships. Like the CSAG study, a potential shortcoming of the CCUK reporting was that no assessment was undertaken to specially evaluate the transverse or vertical interdental arch relationships. As for facial appearance, almost 40% of cleft patients had good facial appearance compared with 32% in CSAG (Al-Ghatam *et al.*, 2015). Three factors were considered to account for these improvements in the facial and dental outcomes, namely:

1. The caseload each surgeon treats every year had increased significantly since the centralisation. Seventeen out of the nineteen surgeons met the aim of treating 40-50 patient with OFC a year. In comparison, in the CSAG study, only one surgeon performed this many repairs.
2. All cleft surgeons had undergone training in a specialised cleft centre.
3. The establishment of an audit culture in the UK, which encouraged the cleft team to share results and allowed for critical and reflective practise to be achieved.

As for oral health and hearing, the results were rather disappointing since there was no difference in outcomes of CCUK compared with CSAG. This was mainly due to the slow and incomplete implementation of paediatric dental services and ENT into the cleft MDT (multidisciplinary team) (Smallridge *et al.*, 2015).

Although the methods used for speech assessment in CCUK were different to those used in the original CSAG report, due to evolution within the speciality, the results of speech in the CCUK cohort were better than those of the CSAG. This enhancement was credited to the development of MDTs within the cleft service (Sell *et al.*, 2015). Nevertheless, a few children with major speech difficulties still existed and the percentage of those children remained the same both before and after centralisation. Unfortunately, not all the speech outcomes measured were shown to improve following centralisation and these included nasal emission, nasal turbulence, hyponasality and lateralisation (Sell *et al.*, 2005).

Poor self-confidence was reported less in the CCUK cohort (8%) compared to the CSAG (19%). Furthermore, centralisation had no effect on families' ability to attend their appointments as suggested by those originally opposed to centralisation (Waylen *et al.*, 2015).

To conclude, although centralisation has been shown to improve most treatment outcomes including anterior-posterior interdental arch relationships in patients with OFC, other outcomes have failed to improve. Further enhancements and monitoring of the current centralisation service are needed to ensure best outcomes for all patients with OFC (Ness *et al.*, 2017). The table below summarises the differences between CSAG and CCUK studies in terms of methods, measures, demographics, and outcomes. Table 2 is a simplified version of the table presented by Ness *et al.*, (2017).

<u>Comparison</u>	CSAG 1998	CCUK 2015
<u>Type of study</u>	Audit carried out by a study team	Research carried out by local teams
<u>Outcome measures</u>		
Appearance	Photographs	Digital images
Dento-alveolar arch relationships	Cast models	Cast models and photographs
Oral health	Calibrated dental examination by orthodontists	Calibrated dental examination by consultant paediatric dentist
Hearing	Pure tone audiometry and otology assessment	Pure tone audiometry, tympanometry and otology assessment
Speech	Speech recordings	Speech recordings
Psychology assessment	Psychosocial questionnaire, 18 items; self-confidence response was yes/no	Modified psychosocial questionnaire, 8 items; self-confidence response was 0–10 (0 = very negative effect; 5 = no difference; 10 = very positive effect)
<u>Demographics</u>		
Year of birth	1989-1991	2005-2007
Eligible	326	359
Recruited	239	268
Mean age (yrs)	6.4	5.5
<u>Outcomes</u>		

Facial appearance (% good or excellent)	32	36
Dento-alveolar relationships (using the 5 Year-Olds' Index) (% good or excellent) <i>(Al-Ghatam et al., 2015)</i>	30	53
Oral health (DMFT=0) % <i>(Smallridge et al., 2015)</i>	45	48
Hearing (none or mild hearing loss in better ear) % <i>(Smallridge et al., 2015)</i>	79	78
Speech (no hypernasality) % <i>(Sell et al., 2015)</i>	82	90
Child's self-confidence not affected (%) <i>(Waylen et al., 2015)</i>	81	92

Table 2: Comparison between CCUK and CSAG study cohorts in outcome considerations, demographics, and outcomes. Modified from (Ness et al., 2017).

2.6.5 Current cleft care pathways in the UK:

Depending on cleft severity, a child born with OFC may need complex long-term treatment. There might be life-long effects not only on the affected individuals but also on their families. The principal aims of OFC cleft treatment is to produce as near normal facial appearance, oral function when eating, swallowing, and speaking as well as hearing.

The management of OFC is best undertaken using an integrated multidisciplinary approach (Cobourne, 2014). A contemporary UK cleft team would usually comprise a cleft surgeon, an orthodontist, a speech therapist, a cleft nurse, an ENT surgeon, a paediatrician, a paediatric dentist, a restorative dentist, a psychologist, an audiologist, a general dental practitioner, and a clinical geneticist (Cobourne, 2014). Orthodontic intervention is usually required at different time points during the first 20 years of the affected child's life, often to facilitate interventions by other specialists (Cash, 2012). The milestones in cleft diagnosis and treatment will now be described.

Pre-birth/ At Birth

The diagnosis of OFC is often, but not exclusively, made during the prenatal screening at around 20 weeks (CRANE, 2021). Such a diagnosis can leave the parents in emotional distress, especially if the diagnosis is not made until the time of birth. Parents can experience very mixed emotions, including shock, anger, grief, guilt and sometimes rejection. It is vital that support is given within the first 24 hours of diagnosis, by either a psychologist or a cleft clinical nurse specialist (CNS) (Dudding *et al.*, 2023). A baby born with OFC can often have difficulties with feeding due to the direct communication between the

oral and nasal cavities. The CNS will provide the parents with advice and support to overcome any such challenge (Young *et al.*, 2001).

Previously, various forms of presurgical infant orthopedic (PSIO) appliances were commonly part of the treatment protocol for individuals with orofacial clefts in the UK. There are different types of PSIO available with different mechanics and different treatment objectives. Advocates believed that PSIO made primary surgery easier by improving arch form, facilitating surgical closure, and therefore improving aesthetics, feeding and speech (Grayson and Cutting, 2001; Grayson *et al.*, 1999; Kozelj, 2000; Larson *et al.*, 1993; Millard *et al.*, 1999). However, many studies including a Randomised Controlled Trial (RCT), systematic reviews and a meta-analysis concluded that PISO did not improve maxillary arch form and dimension and did not prevent maxillary arch collapse (Kuijpers-Jagtman and Prahll-Andersen, 2006; Papadopoulos *et al.*, 2012; Prahll *et al.*, 2001; Severens *et al.*, 1998). Furthermore, PISO did not improve occlusion and arch relationship in children with UCLP. In terms of cost, it was found that the cost of PISO was significantly higher in treatment groups when compared to non PISO group (Kuijpers-Jagtman and Prahll-Andersen, 2006; Papadopoulos *et al.*, 2012; Prahll *et al.*, 2001; Severens *et al.*, 1998) and a more recent systematic review and meta-analysis recommended not including PSIO as an intervention treatment for OFC due to a lack of certainty about its effect on maxillary morphology (Dallaserre *et al.*, 2022).

In recent years, an interest has been raised in a new approach to traditional PSIO known as presurgical nasoalveolar molding (PNAM). This technique has been reported to be successful at improving nasal asymmetry and lip appearance by elongation of the columella

and improving the nasal cartilage (Grayson and Cutting, 2001). However, the use of PNAM remains controversial with some studies reporting beneficial changes while others not (Kornbluth *et al.*, 2018; Shetty *et al.*, 2017).

Currently, PNAM and other forms of PISO are not generally undertaken in the UK.

1st year:

Primary lip and palate repair are carried out within the first 12 month of life. Usually, the lip repair is carried out around 3-6 months and palatal repair around 12 months (Slator *et al.*, 2022).

Early years (18 months – 5 years):

One of the most common complications of palatal repair is velopharyngeal insufficiency (VI), which results from lack of mobility of the soft palate due to scarring or shortness of the soft palate (Sell *et al.*, 1999). VI is usually diagnosed by formal speech and language assessment. Therefore, a speech and language therapist play a vital role in improving speech in cleft's children. In some instances, speech therapy input may not be enough to improve speech if VI is present and a secondary surgery might be needed to re-repair the soft palate (Sell *et al.*, 2015). This is usually carried out around the age of 4 once the VI is diagnosed and before starting school.

Another complication of scarring of the soft palate is otitis media, which is not only due to the distorted anatomy, but also due to the muscle disruption of the soft palate during repair, affecting the Eustachian tube function (Flynn *et al.*, 2009). As a consequence, this can

result in persistent middle ear infections and affect the children's ability to hear, which in turn can affect the development of speech and language (Bluestone, 1985). It is crucial that an audiologist monitors these children around this age to assess if any further interventions are needed, which may include the surgical placement of grommets (ventilation tubes) (NICE, 2008). An additional complication of palatal repair is the development of a palatal fistula, which may require additional palatal surgery with further scarring and disruption of future maxillary growth. The presence of palatal fistula has been found to be as high as 31% in the UK, (Yang *et al.*, 2020), which is higher than in many other countries (17%) (Hardwick *et al.*, 2014).

A dental preventive program for cleft affected children should be established as soon as the first primary tooth erupts. Studies have reported that children with clefts have a higher risk of caries than non-cleft children (Worth *et al.*, 2017). Therefore, prevention in the form of oral hygiene instruction, fluoride varnish, regular checkups and dietary advice should be established early on in a child's life (Smallridge *et al.*, 2015).

It is expected that individuals with OFC will demonstrate delayed eruption of teeth adjacent to the cleft side, hypodontia of the lateral incisors and buccal crossbites (Tannure *et al.*, 2012). However, active orthodontic treatment is not usually carried out in the primary dentition.

School years (6 – 12 years):

Individuals who are affected by OFC can present with a residual maxillary bony defect involving the alveolus, which can leave them with aesthetic and functional problems affecting their occlusion. Secondary alveolar bone grafting (SABG) is usually carried out around the ages of 8-10 years, before the eruption of permanent maxillary canine, and when approximately two thirds of canine root formation has occurred (Martin *et al.*, 2023). The surgical procedure involves placing cancellous bone taken from the iliac crest, into the cleft maxillary alveolar defect. Usually, a period of orthodontic intervention is needed before bone grafting to expand the collapsed maxilla, facilitating surgical access to the cleft site for nasal floor repair and placement of bone (Dudding *et al.*, 2023). This maxillary arch expansion is usually achieved by means of a quadhelix and establishment of more favourable maxillary arch form and transverse dental arch relationships. (Roberts-Harry and Sandy, 1992). It is expected that as permanent teeth start to erupt, anterior and posterior crossbites might develop due to palatal tissue scarring, which also restricts normal maxillary growth in three planes of space, particularly in the lesser segment (cleft side) (McCance *et al.*, 1990). The severity of crossbite reflects the amount of maxillary growth disruption following the primary palatal surgical repair (McCance *et al.*, 1990).

A dental preventive program should continue during this stage of dental development. Permanent molars should be fissure sealed, oral hygiene should be reinforced, and fluoride supplements should be prescribed if appropriate, along with regular dental check-ups (Smallridge *et al.*, 2015).

Teenage Years and Early Adulthood:

Once the patient's full adult dentition is established, a decision must be made whether orthodontic treatment is sufficient to produce a normal occlusion, or a combination of orthodontic treatment and orthognathic surgery is needed. Before making any final decision, a period of monitoring facial development and growth may be needed, since the majority of cleft affected individuals will present with a class III malocclusion due to restrictive maxillary development (Dudding *et al.*, 2023). If orthognathic surgery is to be performed, then presurgical orthodontic treatment is needed to decompensate and align the dental arches. Furthermore, cleft rhinoplasty might be needed in those individuals where the nasal aesthetic is poor (nasal tip asymmetry) on the cleft side (Roberts-Harry and Sandy, 1992).

Repair	Unilateral cleft lip only	Bilateral cleft lip only	Cleft lip and alveolus	Unilateral cleft lip and palate	Bilateral cleft lip and palate	Isolated cleft of secondary palate
Lip adhesion	-	-	-	-	2-4 months	-
Definitive lip repair	3-6 months	4-6 months	3-6 months	3-6 months	6-8 months	-
Hard palate repair (with vomer flap)	-	-	-	With lip repair	Unilateral at each stage of lip repair	-
Complete palate repair +/- grommet placement	-	-	-	9-13 months	9-13 months	9-13 months
Primary rhinoplasty	With definitive lip repair	With definitive lip repair	With definitive lip repair	With definitive lip repair	With definitive lip repair	-
Alveolar bone graft	-	-	8-10 years	8-10 years	8-10 years	-

Table 3: Summary of current cleft care surgical pathway in the UK. Surgery beyond the age range above include orthognathic and rhinoplasty once facial growth has ceased (Dudding *et al.*, 2023).

2.7 Transverse interdental arch relationships:

While the MHBI assesses both anterior and buccal crossbites, this literature review will focus on the transverse interdental arch relationship. A study by Al-Ghatam *et al.*, (2015) have shown that centralisation has a significant effect on the interdental arch relationship in the AP direction, but no study to date has investigated the effect of centralisation on the transverse interdental arch relationships.

Transverse interdental arch relationships refer to the buccolingual relationship of the maxillary buccal teeth relative to the opposing mandibular teeth. Discrepancies in the transverse interdental relationship exist when the maxillary teeth are positioned too buccal or too palatal from the normal relationship. These discrepancies are described as a crossbite and there are three main descriptors of posterior crossbite used to classify the variation of transverse interdental relationships:

- Buccal crossbite: where the buccal cusps of the mandibular teeth occlude buccal to the buccal cusps of the opposing maxillary teeth (Littlewood *et al.*, 2019).
- Scissor/Lingual crossbite: where the buccal cusps of mandibular teeth occlude lingual to the lingual cusps of the opposing maxillary teeth (Littlewood *et al.*, 2019).
- Edge to edge buccal relationship: where the buccal cusps of maxillary and mandibular teeth occlude with each other.

Crossbites can either occur unilaterally or bilaterally, affecting a single tooth or multiple teeth. Crossbites can reflect an underlying transverse skeletal discrepancy, a discrepancy in

tooth position or a combination of the two (Littlewood *et al.*, 2019). In some cases that exhibit more severe transverse interdental arches relationships discrepancies, the constricted maxillary arches can extend to include the anterior dentition.

When crossbites are present, it is important to clinically check for the presence of a mandibular displacement on closure, as this can either simplify or complicate the treatment further. A mandibular displacement can be defined as a mandibular deviation to the right or left and/or anteriorly on closing from initial tooth contact into maximum interdigitation when the mandible is in a retruded position (Littlewood *et al.*, 2019).

There are generally no descriptors used in clinical dentistry to help define or measure the extent or frequency of the crossbite discrepancy other than the above. However, a specific transverse and anterior segment assessment index scoring of individual maxillary tooth position in relation to the opposing tooth has been used in patients with OFC and is known as the Huddart Bodenham Index (Huddart and Bodenham, 1979). One of the most common occlusal features of patients with OFC relates to maxillary arch constriction, resulting in transverse and AP interdental arch discrepancies. The incidence of buccal crossbites in patients with a UCLP has been reported to be as high as 96% (Dahl, 1979). The crossbites and distortions in maxillary arch form are thought to be due to scarring of the palatal tissue following surgical repair, leading to the restriction of the normal transverse growth of the maxilla (Karsten *et al.*, 2017). There are also restrictions in the normal downward and forward maxillary growth, leading to Class 3 skeletal jaw relationships, often resulting in anterior crossbites as well as open bites.

2.7.1 The effect of surgical repair on the transverse and anterior interdental arch relationships

Surgical correction of the cleft lip and palate is required to restore as near to normal aesthetics, function, and speech. However, many studies have confirmed the negative effect of cleft surgery on the normal growth and development of the midface. A study by Mars and Houston (1990), based in Sri Lanka, investigated the impact of surgical repair on patients with OFC and compared the outcomes to patients with OFC who had not undergone surgical repair. They reported that patients with unoperated UCLP and those who had received a CL repair only had normal maxillary growth, with normal maxillary arch dimensions and normal transverse and AP interdental arch relationships. The distortions of the maxillary arch form were limited to the teeth adjacent to the cleft site. In contrast, patients who had an early surgical repair of the palate experienced a high rate of midface retrusion and constricted maxillary dental arch forms. The authors concluded that the maxillary arch constriction for patients with repaired UCLP was due to surgical scarring and not due to any inherent growth deficiency of the maxilla in these children (Mars and Houston, 1990).

The goals of CLP repair include an anatomical closure of the defect to aid function and aesthetics, achieving normal speech outcomes, while limiting any growth restrictions due to surgical scarring. Based on these goals, the following principles are observed when performing surgical repair:

- Defect closure
- Tension-free suturing
- Restructuring of the abnormally positioned soft palate musculature
- Soft palate lengthening

- Limiting stripped or exposed areas of bone and oral/nasal mucosa that result in scarring of the palatal tissues
- Layered closure of the hard and soft palate

However, there is no one universal repair protocol used to carry out surgical repair. There are many different surgical repair techniques used as well as differences in the staging of repair, all of which have variable impacts on maxillary growth. Due to the large number of confounders including surgeon (experience, training, surgical volume) surgical protocol (technique, staging, timing, presurgical procedures) and patient (cleft severity, anatomical deficiencies) it has been difficult to determine the ideal surgical repair.

Cleft Lip repair techniques:

The repair of cleft lip is usually carried out between the age of 3-6 months. There are three main procedures for the correction of a cleft lip, which include the Fisher (used in 53% of cases), Millard (used in 15% of cases), and Tennison (used in 3% of cases) techniques (Fell *et al.*, 2023).

When the influence of lip repair on maxillary growth was investigated, a study by Filho *et al.* (1996) reported that lip repair can significantly affect the growth of the dentofacial complex when compared to a non-operated group with complete UCLP. This finding was also supported by a more recent study by Liu *et al.* (2018) who reported that lip repair in patients with or without operated cleft palate experienced maxillary arch constriction, which tended to worsen with age.

Cleft alveolus repair techniques:

The most common surgery in the UK to repair the cleft of the alveolus is secondary alveolar bone grafting (SABG) and it is usually carried out before the eruption of the permanent canines at approximately 8-10 years old. It utilises cancellous bone taken from the iliac crest. The advantages of carrying out such surgery are to minimise any potential maxillary growth disturbances, to create upper arch integrity and to allow for the development of the dentition adjacent to the cleft side.

Cleft palate repair techniques:

Repairing the soft palate typically takes place when a child is between 10 and 13 months old. While there are various surgical methods for repairing the soft palate, the primary procedures in the UK are intravelar veloplasty (used in 94% of cases) and a combination of relieving incisions with intravelar veloplasty (used in 44% of cases) (Fell *et al.*, 2023).

Utilisation of this technique, as well as modifying it and combining it with other surgical techniques, has been shown to offer not only a better velopharyngeal competency, but also improved middle ear function (Sommerlad, 2003)

When it comes to repairing the hard palate, it is typically done alongside cheiloplasty between 3-6 months of age. In the UK, the most commonly used technique is the vomer flap, which is used in 84% of cases (Fell *et al.*, 2023). This technique has been shown to have reduced interference with maxillary growth due to elimination of dissection on the non-cleft side of the hard palate (Hay *et al.*, 2018).

Controversies of palatal repair:

The ideal surgical repair technique and timing of a surgical closure of the palate has remained controversial. This has led to cleft centres developing different surgical and timing protocols for palatal repair. It is important to note that surgical timing should enable normal speech development and avoid restricting normal maxillofacial growth. Different factors need to be considered to determine the ideal timing for primary palatal cleft repair. These include the cleft type involved, the patient's condition and the ability of the cleft team to manage any morbidities that might be caused during the surgery (Rautio *et al.*, 2017).

Supporters of early palatal repair advocate for the surgery to be carried out before the age of 12 months to aid speech development, since speech begins in children at one year of age. Although delaying palatal repair beyond this age might cause less impairment in maxillofacial growth, speech development tends to be of poor quality (Heliovaara *et al.*, 2022).

In the UK, prior to centralisation the surgical palatal repair technique and timing of staging of repair varied and most surgeons undertaking the repairs had limited surgical volume. Post centralisation studies have reported higher surgeon volume, less variation in surgical palatal repair techniques and the timing of the repair. This probably reflected the introduction of a common cleft surgical training pathway. However, variations were still reported both between different surgeons and by the same surgeon depending upon the individual circumstances of the presenting cleft. A recent study by Ozawa *et al.* (2021), found that the major factor that influenced dental arch relationship following UCLP repair was the

surgeon experience rather than the techniques used for surgical repair or age of patient (Butterworth *et al.*, 2021; Ozawa *et al.*, 2021; Slator *et al.*, 2023).

In summary, the earlier the hard palate repair the greater the amount of maxillary growth restriction, but the better speech outcomes. The later the hard palate repair the less impact of surgical scarring on maxillary growth (and better dental arch and skeletal relationship outcomes), but the speech outcomes are poorer. The actual surgical repair technique appears to have little impact on outcomes, but surgical volume of the surgeon has a major influence on interdental arch relationship and skeletal outcomes. Repairs of the cleft lip and soft palate and the undertaking of SABG surgical repair have limited influence on interdental arch relationship outcomes, while hard palate repair and early alveolar bone grafting (ABG) have a major influence on these relationships.

2.8 Outcome measures for patients with OFC assessing transverse buccal and anterior interdental arch relationships.

2.8.1 Ideal Qualities of Outcome Measures

Both the CSAG and the CCUK used outcome measures to assess surgical outcomes of patients with complete UCLP. Certain ideal qualities are needed for an outcome measure to be widely used. These qualities involve the measure being valid, reliable, cheap, quick, and easy to use. Furthermore, it should not ideally require any special equipment or training and should be non-invasive (Jones *et al.*, 2016).

A reliable measure should be consistent and reproducible. This means that the same results should be obtained every time the measurement is repeated by the same person (intra-examiner) or by different people (inter-examiner).

Assessing an outcome measure's validity gauges how accurately it measures its intended purpose. Validating a new outcome measure is more difficult than testing its reliability because it requires a standard to compare against. If a gold standard is not available, consensus or face validity can be determined by comparing results with expert opinion in the field.

Many outcome measures are available for cleft care assessments. This is due to the different specialities involved in cleft care and the available outcome measures rarely being perfectly valid or reliable. Furthermore, different clefts cannot always be evaluated using the same measurement outcome due to different treatments and confounding complexities present. Most indices found in OFC literature are used to assess UCLP patients. This is because UCLP involves the care of the lip, alveolus and palate defects, meaning that it can indicate the outcome across the whole of cleft care.

The main outcomes used to assess cleft care include cleft surgery repair, facial growth, hearing, speech, nasolabial aesthetics, dental, secondary alveolar bone grafting, orthodontic, quality of life and patient satisfaction outcomes. For this literature review, the outcome measures of interdental arch relationships will be focused on, since there is limited information regarding the outcomes of transverse and AP interdental arch relationship following centralisation. The differences in outcomes between CSAG and CCUK children can

be related to their surgical experiences. For example, in the CSAG study, most surgeons had a low volume of operations, were working in isolation without the support of a MDT and had different protocols. Whereas in the CCUK study following centralisation, the opposite was true.

Assessing the dental arch relationship as early as possible will provide information about the impact of surgical repair on the patient's occlusion, function, and aesthetics, and whether further intervention is needed to overcome the unwanted side effects of the initial surgery.

2.8.2 The GOSLON Yardstick:

The first interdental arch outcome measure that was widely adopted was the Great Ormond Street, London and Oslo, Norway Yardstick, known as the GOSLON Yardstick (Mars *et al.*, 1987). The measurements were made on patient's study models in the adult dentition stage around the age of 12, as the authors considered this is the age at which both skeletal and occlusal problems are most evident, and at which time the definitive orthodontic and surgical treatment are planned.

Although the GOSLON Yardstick assesses the interdental arch relationships, it was developed as a default assessment of the primary cleft surgery outcomes categorising the AP position of the maxilla for patients with UCLP. The Yardstick scoring is indicative of restricted maxillary growth, and its development was based on the features that posed the greatest difficulty for correction with orthodontics and /or surgery. Hence the AP relationship was considered to be of greatest clinical importance, followed by the vertical and finally the transverse relationships. For instance, in the AP dimension, a Class III incisor

relationship was deemed less satisfactory than a Class II division 1 incisor relationship in the early permanent dentition stage. Similarly, a deep overbite and the absence of a crossbite were considered more desirable than a reduced overbite and a unilateral crossbite (Mars *et al.*, 1987).

To develop this Yardstick, four orthodontists ranked 30 sets of study models of patients with UCLP that were selected from The Hospital for Sick Children at Great Ormond Street, and which represented the full range of interdental arch relationship outcomes *i.e.*, excellent to very poor. These models were ranked by severity of discrepancy and anticipated degree of difficulty to correct. Following the ranking it was apparent the cases could be divided into five groups according to Mars *et al.*, (1987):

- Group 1- **Excellent**: desirable outcomes which might need simple orthodontic treatment or no treatment at all.
- Group 2- **Good**: desirable outcomes which might need straightforward orthodontic treatment or no treatment at all.
- Group 3- **Fair**: more complex orthodontic treatment would be required but reasonable results should still be achieved.
- Group 4- **Poor**: borderline orthodontic treatment with surgery possibly needed to achieve full correction of skeletal deformity if present following growth completion.
- Group 5- **Very poor**: the least desirable outcomes with orthognathic surgery needed to correct skeletal malformation.

Representative models from each of the five groups were then chosen as a template model set to offer reference for use when categorising other study models within the above groups.

The Yardstick was then tested on 55 study models retrieved from the Oslo Cleft Lip and Palate Clinic of patients with UCLP, who were in their early permanent dentition stage. Four orthodontists applied the index to the 55 models on 2 separate occasions. Reliability was tested using the Spearman's rank correlation coefficient which was found to be high. Unfortunately, using correlation coefficient statistical test to examine the intra and inter-examiner reliability was not appropriate, as the Yardstick is a categorical scale (Bland and Altman, 1986).

Having said that, many studies have demonstrated its reliability (Mølsted *et al.*, 2005; Hathaway *et al.*, 2011). Furthermore, since the publication of the Yardstick scoring system, its effectiveness has been proved by many studies (Mars *et al.*, 1992; Noverraz *et al.*, 1993; Hathorn *et al.*, 1996). The downside of using the Yardstick remains to be its inability to assess 5-year-old patients with UCLP and to evaluate the vertical and transverse dimensions the same way it does for the AP (Mars *et al.*, 2006).

2.8.3 Measuring overjet:

In 1994, Morris *et al.*, tried to simplify the GOSLON Yardstick index by assessing the most crucial factor when using the Yardstick for scoring study models, which is the overjet (OJ). They reported that measuring the OJ alone gave the same score as the GOSLON Yardstick in 87% of the cases (Morris *et al.*, 1994). The study measured the OJ by measuring the distance

parallel to the functional occlusal plane from the mid incisal edge point of the non-cleft side upper central incisor to the mid incisal edge point of the lower incisor (Morris *et al.*, 1994). The study then calibrated the OJ with the GOSLON Yardstick. For example, if the OJ was greater than 6.5mm this would equate to a GOSLON score of 1. If the OJ score was < -5.8 , this would equate to a GOSLON score of 5. This demonstrated the importance placed by the Yardstick on the AP interdental arch relationship and the lack of weighting for adverse transverse and vertical interdental arch relationships. Despite the simplicity of just measuring the overjet, its validity and reliability has been questioned (Jones *et al.*, 2016), because there is no acknowledgement of the transverse and vertical dimensions. Furthermore, accurate measurement of OJ might not always be possible, such as in cases with an anterior open bite, incisal wear or missing anterior teeth (Jones *et al.*, 2016).

2.8.4 The EUROCRAN index

The EUROCRAN index was created with four interdental dental arch relationship assessment categories (EUROCRAN Index Group, 2007). In addition, a second ranking system, which considers palatal morphology, was also included to aid in more precise discrimination between results. Two versions of the index have been produced, the 5-year-old and the 9-year-old. It has been reported that the EUROCRAN index has acceptable inter and intra examiner reliability scores for dental arch assessment, and moderate scores for palatal morphology assessment (Fudalej *et al.*, 2011; Altalibi *et al.*, 2013)

Despite the potential benefits of this index, it has not gained widespread acceptance due to unproven validity and low reliability scores. Furthermore, it is more complex to learn, more

time-consuming to carry out and it has an element of subjectivity when it comes to assessing the palatal vault (Haque *et al.*, 2015).

2.8.5 The 5-Year-Olds' Index:

Although the GOSLON Yardstick was beneficial in assessing the primary surgery outcomes in the AP dimension, two main issues were identified, namely: Firstly, the surgeons had to wait at least ten years to observe standardised interdental arch relationship outcomes from their treatment. Secondly there was the risk of not directly recording the outcomes of primary surgery as a result of the patient having already received orthodontic treatment or secondary alveolar bone grafting by the time records were taken to measure the outcome using GOSLON at age 12 years (Southall *et al.*, 2012). In 1997, Attack *et al.* developed an index that was based on similar concepts to GOSLON, with similar reliability and reproducibility that could be used at five years of age. This index became known as the 5-Year-Olds' Index (Attack *et al.*, 1997a). Twenty-seven sets of study models were examined at ages 5 and 10. The GOSLON Yardstick was applied to score the models at both ages. Where the Yardstick scores were consistent between ages 5 and 10, two sets of study models were selected to represent the five groups identified by the GOSLON Yardstick. These models were used as reference points when comparing them to the 5-Year-Olds' index. The criteria used for scoring models using the 5-Year-Olds' index is shown in the Table 4:

Groups	General features	Predicted long-term outcome
1	<ul style="list-style-type: none"> • Positive overjet with average inclined or retroclined incisors. • No crossbites/openbites • Good maxillary arch shape and palatal vault anatomy 	Excellent
2	<ul style="list-style-type: none"> • Positive overjet with average inclined or retroclined incisors • Unilateral crossbite/ crossbite tendency • +/- Openbite tendency around cleft site 	Good
3	<ul style="list-style-type: none"> • Edge to edge bite with average inclined or proclined incisors • Reverse overjet with retroclined incisors • +/- Openbite tendency around the cleft side 	Fair
4	<ul style="list-style-type: none"> • Reverse overjet with average inclined or proclined incisors • Unilateral crossbite +/- bilateral crossbite tendency • Openbite tendency around the cleft site 	Poor
5	<ul style="list-style-type: none"> • Reverse overjet with proclined incisors • Bilateral cross bite • Poor maxillary arch form and palatal vault anatomy 	Very poor

Table 4: 5-Year-Olds' index criteria for assessment of UCLP primary surgical outcomes.

Reproduced from Attack *et al.*, 1997.

In order to test the reliability and validity of the 5-Year-Olds' Index, 60 patients were chosen from the Oslo CLP growth archive and Southwest of England audit. The inter and intra-examiner agreement was tested using weighted kappa statistics. This statistical test demonstrated excellent agreement for the intra-examiner reliability and was more variable for the inter-examiner reliability (Attack *et al.*, 1997b). However, a study investigating the predictive validity of dental arch relationships using the 5-Year-Olds' index once the patients reached adulthood reported poor predictive validity for those models graded in groups 4 and 5 (Pegelow *et al.*, 2021). However, the 5-Years-Olds' Index was developed to assess the

outcome of primary surgery rather than predicting the final interdental arch relationship outcomes in adulthood.

The 5-Year-Olds' Index has been well accepted and used in several studies (Johnson *et al.*, 2000; Williams *et al.*, 2001; Flinn *et al.*, 2006). However, there have been a number of criticisms of the index (Mars *et al.*, 2006). For example, the authors of the 5-Year-Old's Index have categorised an edge-to-edge bite within category 3 (fair), while this type of bite is considered normal in the primary dentition of a 5-year-old. However, this point was addressed in a recent modified version of the 5-Year-old index. The authors stated that an edge-to-edge bite with no posterior crossbite should be placed in category 2 instead of category 3 (Mittal *et al.*, 2019).

In 2006, Mars *et al.* carried out a study in which they scored study models of 5-year-olds using the GOSLON Yardstick and 5-Year Olds' Index, followed by an assessment of the same patients at the age of 10 by using the GOSLON Yardstick only. The study concluded that using GOSLON Yardstick for assessing five-year-old patients is more reliable and has a better predictive validity than the use of the 5-Year-Olds' Index. However, a few modifications to the GOSLON Yardstick would be required to be appropriate for testing 5-year-old patients.

In summary both the GOSLON Yardstick and the 5-Year Old's Index are appropriate as outcome measures for AP inter dental arch relationships following primary surgery in children with UCLP. However, both have received similar criticism in terms of using categorical scoring; both requiring a calibration course for competent use; both needing a

degree of professional (orthodontic) judgment, which introduces an element of subjectivity; and finally, the need for reference models when scoring (Mossey *et al.*, 2003).

To address these issues and to introduce more objective outcome assessments the Modified Huddart-Bodenham index (MHBI) has been proposed. The MHBI allows for measurements to be carried out in the primary, mixed and permanent dentitions and as such has greater versatility (Mossey *et al.*, 2003; Gary and Mossey, 2005; Dobbyn *et al.*, 2012). These studies have found the modified Huddart and Bodenham scoring system to be reliable, objective, versatile and more sensitive when compared to the GOSLON Yardstick and the 5-Year Olds' Index (Jones *et al.*, 2016). Furthermore, the MHBI scoring system has been shown to be appropriate for the creation of fully automated scoring software (Martin *et al.*, 2016) and has been validated on plaster models, digital models and photographs obtained from intraoral scanning (Gray and Mossey, 2005; Dobbyn *et al.*, 2012).

2.8.6 Modified Huddart-Bodenham Index:

This index can be used to assess both the transverse and AP interdental arch relations and was first described in 1972 for use in 5-year-old UCLP affected individuals in the primary dentition (Huddart and Bodenham, 1972). The index uses the severity and frequency of crossbite to assess maxillary arch restriction in relation to the opposing dentition and includes both the anterior and buccal segments. Each maxillary tooth (except the lateral incisors) is scored (-3 to +1) according to its buccolingual / labial palatal relationship with the corresponding tooth in the mandible. The maxillary deciduous lateral incisors were not included due to them often being absent or severely displaced. If a scissor bite is present a

positive grade is given, whereas a buccal crossbite is given a negative grade. The higher the positive score, the more desirable the outcome is and vice versa for the negative score. This index has been modified (MHBI) by Mossey *et al.*, (2003) by taking the following points into consideration:

- Premolars should be scored in a similar manner to primary molars.
- If a central incisor is missing, then the other central incisor is used to score it
- If a premolar is missing, then it is scored based on the neighbouring premolar. If both are missing, then the score is given based on the relationship between the midpoint of the ridge, in the site of the missing premolars, with opposing tooth.
- Before age of 6, the permanent molars are not scored, even if erupted. After the age of 6, they should be scored, and if missing, the midpoint should be used in a similar manner to that mentioned previously.

The MHBI scores the occlusion in a similar manner to the original HBI but makes allowance for the presence of permanent teeth as well as providing an increased scoring range for the teeth in the buccal segments. This allows for a greater range of segment scores and total arch scores (Mossey *et al.* 2003).

Previous findings using MHBI:

This index has been shown to have several advantages, including:

- *Objectivity and simplicity.* Not only is it objective and simple to use, but requires no calibration or reference models (Tothill and Mossey, 2007). In

addition, it has been suggested no clinical experience is necessary to use this index efficiently (Mossey *et al.*, 2003).

- *Versatility*. It can be used on the study models of patients of any age and has previously been used for other cleft phenotypes i.e. BCLP/CP, as well as UCLP.
- *Sensitivity*. It is an ordinal scale facilitating parametric statistical analysis (Tothill and Mossey, 2007).
- *Digital recording*. It is possible to use this index on scanned digital images (Martin *et al.*, 2016) and artificial intelligence (AI) has been used to objectively score the models, further improving reliability (Woodsend *et al.*, 2022).

Recently, attempts have been made to develop fully automated dental landmarking and scoring software using the MHBI scoring system (Woodsend *et al.*, 2022). When compared to manual scoring, it was found that both had similar results. However, operator intervention was still required to identify the dental landmarks required when using the MHBI. Furthermore, the software was able to identify the primary and permanent dentition only, but not the mixed dentition and so was not user-friendly. Once these shortcomings using AI have been addressed, it should lead to more accurate and reproducible MHBI scoring. Table 5 shows a summary of the articles that compared the MHBI with other indices and their findings:

Articles	Index evaluated	Criteria evaluated	Results
Mansudprasti <i>et al</i> (2011)	MHBI vs GOSLON Yardstick	Reliability	Using GOSLON Yardstick was faster than MHBI in assessing study models. However, the MHBI provided more specific information about the location of the occlusal discrepancy.
Patel (2011)	MHBI vs EUROCRAN	Reliability and simplicity	Although using EUROCRAN was faster to score the models, MHBI was more reliable, simple, and straightforward.
Tonthill and Mossey (2007)	MHBI	Reliability	MHBI is a useful measurement tool in assessing maxillary arch constriction in all cleft types.
Mossey <i>et al.</i> , (2003)	MHBI vs GOSLON and 5- Year-Olds' index	Reliability and validity	MHBI is more objective, reliable, and simple than the GOSLON and the 5-Year-Olds' index.
Garry and Mossey (2005)	MHBI vs GOSLON Yardstick and 5-Year-Olds' index	Reliability	High degree of correlation existed between MHBI and GOSLON Yardstick. Both GOSLON and 5-Year-Olds' index were subjective and required calibration whilst the MHBI doesn't.
Dobbryn <i>et al.</i> , (2012)	MHBI vs GOSLON Yardstick and 5-Year-Olds' index	Reliability	MHBI was simpler, more objective and did not need calibration. MHBI was more versatile as it can be used to assess all cleft types. MHBI is based on crossbites and does not taken into consideration the vertical discrepancy nor the skeletal bases.

Table 5: Summary of the articles that compared the MHBI index with other indices and their findings (Altalibi *et al.*, 2013).

Although a useful index, the MHBI it is not without drawbacks. For instance, it scores transverse discrepancies higher than AP discrepancies. This is unlike the other indices, which place a greater emphasis on AP, which might be considered more challenging to treat and more reflective of maxillary retrusion. Furthermore, the MHB does not consider either vertical discrepancies or incisor inclinations and so does not attempt to score the underlying skeletal base. Nevertheless, a systematic review by Altalibi *et al.*, (2013) concluded that the MHBI outperformed all the other cleft indices in all of the WHO criteria for an ideal index. Furthermore, they recommended that the MHBI should become the index of choice for assessment of interdental arch relationship outcomes in all cleft phenotypes.

Summary of outcome measures using dental models for patients with OFC:

A comparison of the 5-Year-Olds' Index, GOSLON Yardstick, Modified Huddart-Bodenham Index, EUROCRAN and Overjet was carried out in terms of reliability, validity, and ease of use (Jones *et al.*, 2016). It was found that:

- The GOSLON Yardstick was easier to use and less time-consuming in assessing primary UCLP surgery in the mixed and early permanent dentitions than the 5-Year Olds' index. However, using the 5-Year Olds' index in the primary dentition was recommended since has approved validity and allows earlier audit of primary cleft surgery to be carried out.
- Due to the unproven validity and the low-reliability scores, neither the EUROCRAN nor overjet indices could be recommended as an outcome measure to assess primary surgery outcomes.

- Finally, the Modified Huddart-Bodenham Index scoring system was the most reliable and objective outcome measure for assessing the primary surgery outcomes compared to the other four indices. Furthermore, its validity has been proven in the primary dentition but remains under question when used in the mixed dentition.

Although transverse interdental assessments are used within the 5-Year-Old Index, GOSLON Yardstick and EUROCRAN Index, there is no formal assessment of the transverse interdental relationship, as in the MHBI. This makes the MHBI a unique outcome measure for patients with cleft, and to date this has been overlooked by previous investigators involved in the original CSAG and CCUK studies.

2.9 Comparing CSAG and CCUK interdental arch outcomes using dental study models:

2.9.1 Comparative 5-Year-Olds' Index outcomes

A study conducted by Al-Ghatam *et al.* in 2015 examined the outcomes of interdental arch relationships after centralisation, using the 5-Year-Olds' index. The study found that more than 50% of the CCUK cohort had good or excellent dentoalveolar outcomes (groups 1 and 2), while around 20% had poor outcomes (group 4 and 5). In contrast, less than 25% of CSAG cohort had good outcomes, and over 36% had poor outcomes. This highlighted the significant improvement in interdental arch relationship outcomes since the introduction of centralisation (Al-Ghatam *et al.*, 2015).

2.9.2 Comparative maxillary arch width dimensions outcomes

Although the changes in interdental arch relationships were investigated in the CCUK study, changes in actual maxillary width and form measurements were lacking until a recent study by Molyneaux *et al.* (2022). The Molyneaux study retrospectively investigated the changes in transverse maxillary arch dimension and form between CSAG and CCUK 5-year-old dental models. They reported clinically and statistically significant differences between CSAG and CCUK groups for the intermolar maxillary arch width and for buccal cleft segment, but not the buccal-non cleft segment (Molyneaux *et al.*, 2020). The assessment in that study was undertaken using the 3D scans of the original plaster maxillary models for each CSAG and CCUK patient. Both angular and linear measurements were recorded including intercanine and intermolar width, the canine and second primary molar distance to the midline, the depth of the anterior and posterior palate, and finally, arch length and form (Molyneaux *et al.*, 2020). Unfortunately, neither cleft laterality nor gender differences were investigated. Although the study reported positive improvements for the CCUK model measurements, there were surprisingly small differences reported between the CSAG and CCUK with the mean intermolar distance 1.23 mm wider in the CCUK cohort. This was of limited clinical relevance due to the lack of reference to opposing mandibular arch dimensions. The positive changes reported by Molyneaux *et al.* for CCUK maxillary arch dimensions were not reflective of the improved interarch relationships assessed by the 5-Year-Old-Index using the same models.

To date, no study in the UK has investigated the changes in the interdental arch transverse buccal and anterior relationship following the centralisation of cleft care using the MHBI.

2.10 Summary of literature review

Treatment outcomes of children with UCLP have changed significantly for most outcome measures within the UK since centralisation of cleft care, which followed the recommendations of the CSAG study. Since centralisation, many studies have been undertaken to assess the effect of the changes in cleft care (Al-Ghatam *et al.*, 2015; Smallridge *et al.*, 2015; Sell *et al.*, 2015; Waylen *et al.*, 2015; Molyneaux *et al.*, 2022). However, of those studies, only one has investigated the effect of centralisation on maxillary arch form dimensions (Molyneaux *et al.*, 2022) and none have been undertaken to compare transverse interdental arch relationship outcomes.

3.0 Research Question, Aims and Objectives:

Research question:

What are the transverse and anteroposterior interdental arch outcomes of 5-Year-Olds born with a complete UCLP following the centralisation of cleft services within the UK using the MBH Index?

3.1 Aims:

To determine if the transverse and anteroposterior interdental arch relationships of children with a complete UCLP, as determined by the MHBI, have improved following the centralisation of the cleft care pathways in the UK.

3.2 Objectives:

- The primary objective was to investigate the transverse and anteroposterior interdental arch relationship outcomes of 5-year-old children with UCLP treated before and after the centralisation of cleft services in the UK using the MHB index.
- The secondary objectives were to investigate the influence of gender and cleft laterality on the MHBI assessment of 5-year-old children with UCLP.
- The third objective was to assess the reliability between bench scanning and handheld scanning when assessing models of 5-year-old children with UCLP using the MBH index.

Null Hypothesis:

There is no difference in the transverse interdental arch relationship outcomes of 5-year-old children with complete UCLP treated before and after the centralisation of cleft services in the UK, when assessed with the modified Huddart and Bodenham Index.

4.0 Materials and Methods:

4.1 Materials:

- 5-year-old maxillary and mandibular plaster orthodontic study models from the CSAG study (number = 106)
- 5-year-old maxillary and mandibular plaster orthodontic study models from the CCUK study (number = 199)
- 3Shape R750™ Orthodontic 3D Scanner – 3Shape HQ, 3Shape A/S, Holmens Kanal 7, 1060 Copenhagen, Denmark
- 3Shape TRIOS 3 Move + intra-oral scanner
- OrthoAnalyzer™ 2019 software – ESM Digital Solutions, ESM Digital Solutions Ltd., Unit 4, Broadmeadow Hall, Applewood, Swords, Co. Dublin, K67 Y5F2, Ireland
- Plastic boxes were used to store and transport study models from Bristol to Bath for scanning.
- Customised scoring spreadsheet for MHBI was formulated in Microsoft Excel™ 2021 Microsoft Corporation, Redmond, WA, USA
- Instruction sheet for MHBI was printed on A4 paper as reference when carrying out the assessment.
- All results were entered to Microsoft Excel™ 2021 spreadsheet – Microsoft Corporation, Redmond, WA, USA
- Stata, StataCorp 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.

4.2 Permission:

This research project was submitted to the Research and Ethics Department at the University of Bristol and was classified as a project that required no ethical approval (Appendix II). The sample used in this project were maxillary and mandibular orthodontic study models of five-year-old patients with UCLP used in the CSAG (Sandy *et al.*, 2001) and CCUK (Persson *et al.*, 2015) studies. The research ethics committee required no ethical approval when the CSAG study was carried out as it was considered an audit project. As for the CCUK models, permission to use the required Cleft Care UK data was granted by the Cleft Care Management Group and the CCUK and CSAG study team at University of Bristol NHS Foundation Trust (Appendix III). Data collected by the original CCUK study was carried out with ethical approval (REC reference number: 10/H0107/33, Southwest 5 REC) and consent was obtained prior to model collection.

4.3 Index used in this study:

The Modified Huddart-Bodenham Index (MHBI):

This index divides the maxillary arch into two buccal segments (the cleft and non-cleft buccal segments) and an anterior (labial) segment (Figure 3). Each buccal segment consisted of a deciduous canine and first and second primary molars, whereas the anterior segment consisted of the deciduous central incisors only. The maxillary deciduous lateral incisors were not included due to their frequent absence. A numerical score was determined for each maxillary tooth relative to the opposing mandibular tooth with the models in occlusion as illustrated in Figure 4 (Huddart and Bodenham, 1972), although it was the MHBI (Figure 4) that was used in this study. As described previously, the modified index used the following:

- If a central incisor was missing, then the other central incisor was used to score it.
- If a deciduous molar was missing, then it was scored based on the neighbouring deciduous molar. If both are missing, then the score was given based on the relationship between the midpoint of the missing deciduous molar ridge and the opposing tooth.

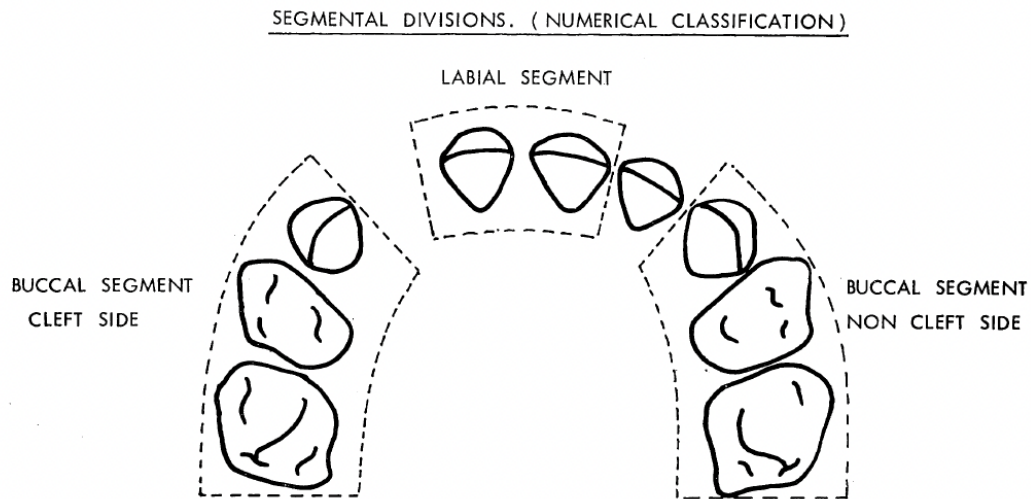


Figure 3: Huddart and Bodenham Index Segments (Huddart and Bodenham, 1972)

Each model had a potential maximum total arch MHBI score ranging from -24 to +8, with a more negative score representing a more severe transverse and AP interdental arch relationship. Using this index normal occlusal relationships were scored 0; an edge-to-edge occlusion was scored -1; a crossbite with contact was scored -2; a crossbite without contact was scored -3; while an increased overjet or buccal occlusion scored +1. Separate segment scores were obtained for anterior, buccal non cleft side and buccal cleft side, with a total arch MHBI score derived from combining the anterior, buccal non-cleft side and buccal cleft side segment scores (Figure 4).

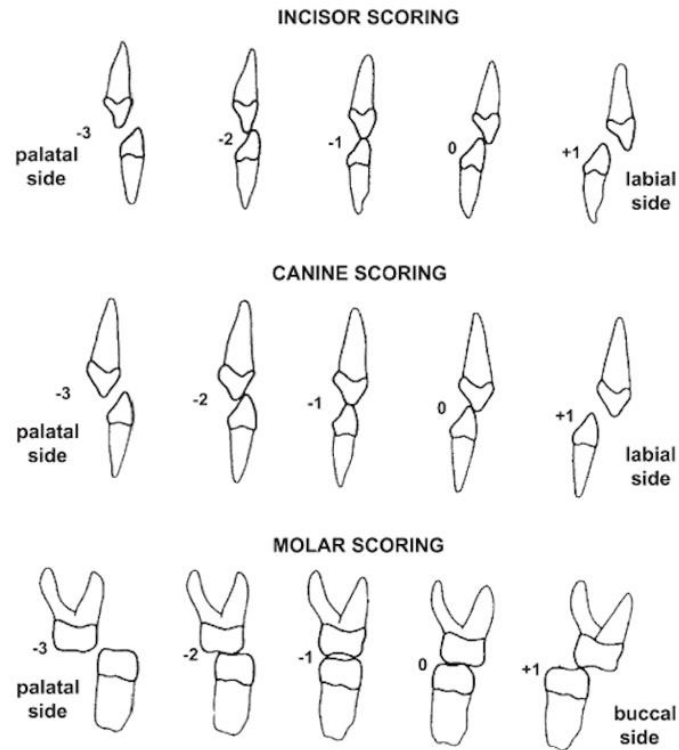


Figure 4: The Modified Huddart and Bodenham Index (MHBI) scoring guide (Mossey *et al.* 2003)

The instruction sheet for assessors used in this study was based on that used by Jones *et al.* (2014). It included model illustrations of the various degrees of crossbites in order to help explain how the scoring system worked as well as clear descriptors of the scoring options.

4.4 Methodology:

4.4.1 Scanning and randomisation of sample:

Maxillary and mandibular plaster orthodontic study models of five-year-old patients with complete UCLP (with a soft tissue band of less than 5mm) were identified from the CCUK and CSAG model archives held at Bristol Dental School. All models were trimmed to a wax bite taken at the time of the impressions to accurately reflect the true interdental arch relationship. All were previously given a unique identifier number specific to each study (CSAG and CCUK) to protect and anonymise patient information. These unique identifier numbers were then used to link new study reference numbers for blinding of the assessors to the origin of the models and to allow for sample randomisation.

A single researcher (BA) scanned and digitally articulated all study models over a four-week period. Models were scanned randomly using 3 Shape R750™ desk top laboratory laser scanner. The scanned models were then checked for correct orientations and accuracy of articulation with the original plaster models. Five of the scanned models had to be rescanned using 3 Shape TRIOS intra-oral scanner due to the inability to accurately capture the correct articulation of the plaster models within the 3 Shape R750™ scanner. The TRIOS intra-oral scanner allowed greater versatility to correctly record the articulation for these five models. To ensure accuracy of the scanning of the models, the 3 Shape R750™ scanner was calibrated weekly to ensure a 0.2mm degree of accuracy using the manufacturer calibration wizard. As for the TRIOS intra-oral scanner, a 2-stage calibration was carried out weekly as per manufacturer guidelines.



Figure 5: Example scanned model with poor anatomical detail preventing correct articulation for MHBI scoring.

Once all models were scanned and calibrated, a dental data manager assigned random study identification numbers to the digital files using a random number generator (<https://www.randomcodegenerator.com/en/generate-codes>). These files were uploaded into the OrthoAnalyzer™ software programme to aid model viewing and scoring. Two scanned models had to be eliminated from the assessment, one due to the poor quality of the original cast model and insufficient capture of anatomical detail to enable transverse and AP interdental arch assessment (Figure 5), while the other was eliminated due to a lack of dentition and difficulties establishing the correct interdental arch relationship (Figure 6).

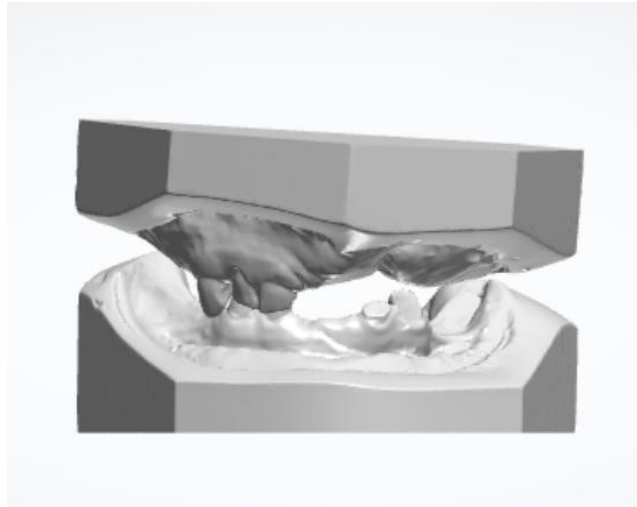


Figure 6: Example of a digital model where the presence of insufficient anatomical detail prevented scoring individual maxillary teeth accurately.

4.4.2 Model scoring:

Prior to scoring, both assessors (BA/PF) undertook a calibration exercise using 15 digital study models of patients with UCLP unrelated to the CCUK and CSAG sample. The assessment was carried out independently using the same MHBI instruction sheet. Once completed, both assessors compared their MHBI scores and where differences were noted, each assessor discussed their interpretation of the scoring criteria to reach a consensus for future scoring.

A customised MS Excel sheet was formulated with all the scanned models randomised by their study reference number for the entry of the MHBI scoring. Scores were entered directly into the MS Excel sheet for each maxillary tooth within each of the anterior, buccal cleft and non-buccal cleft side segments. Automatic summation of the segments and total arch MHBI score was carried out within Excel. Both assessors carried out their assessments

independently, viewing the digital models on the same laptop and using the same digital viewing software (OrthoAnalyzer™) settings. The software allowed for 3D manipulation of the models and magnification as well as the viewing of the occlusal surfaces for tooth identification.

4.4.3 Reproducibility

Once both assessors had completed their scoring of the entire sample, 30 models were randomly chosen for repeat scoring. The repeat assessment was carried out four weeks after the first assessment with scoring entered in a separate Excel file. The repeat scoring sample equalled 10% of the total sample number which allowed for intra- and inter assessor reliability to be tested.

Furthermore, since two different scanners were used, one a laboratory bench top scanner and other a handheld intra oral scanner, a reproducibility assessment within and across the two methods had to be carried out. This was achieved by hand scanning 29 randomised cast models using 3 Shape TRIOS intra-oral scanners. The repeat assessment was carried out two weeks after the initial assessment by one assessor (BA), and data were entered on a separate MS Excel sheet.

4.4.4 Sample size calculation

It was calculated that a total sample size of 140 participants (70 per group) would give a power of 80% with 5% significance level to detect a true difference in transverse dental arch relationship total arch MHBI scores greater than 1.58. The sample size was determined by

ClinCalc.com (Kane, 2018) using total MHBI arch scores differences reported by Mikoya *et al.* (2015) who investigated two groups of five-year-old Japanese children with UCLP. The study investigated 68 participants who were grouped according to two different surgical repair techniques undertaken (Group 1 n=31; Group 2 n=37). They reported significant differences in mean total arch MBHI scores between Group 1 (-6.43 +/-3.34) and Group 2 (-8.01 +/-4.29). Their study concluded that the interdental arch relationship was better for those who had undertaken a two-stage repair (Group 1) than those who had undertaken a one-stage repair (Group 2).

4.4.5 Gender and laterality

Participant demographic data (sex and date of birth) was obtained from the data manager of the CSAG and CCUK studies. This data was collected from clinical notes at the time the respective studies were initiated and recorded on master data spreadsheets along with unique study participant identification coding. Cleft laterality was determined by the main author (BA) after conducting the clinical examination of the scanned study models and was confirmed by an experienced orthodontic consultant (PF). Sex, date of birth and laterality data were entered into a master Excel sheet used in this study.

4.5 Statistical analysis:

The data were analysed using Stata version 16 (Stata Corp, College Station, Texas, USA) with a predetermined level of significance set at $\alpha = 0.05$.

Intra- and inter-rater reliability for the MHBI:

Intraclass correlation coefficients (ICC) were used to assess the levels of inter- and intra-examiner agreement using the MHBI with the laboratory scanned images. In addition, it was used to assess the agreement when the models were hand scanned versus lab scanned. In each case, 30 and 29 models were assessed respectively over two assessments with a four-week period between the 1st and 2nd cycles.

Comparison of interdental arch relationship, CSAG vs CCUK:

Ordered logistic regression was used to test if there was statistical evidence of better outcomes for CCUK when compared to CSAG. The comparison between CCUK and CSAG was divided into 4 scores:

1. Anterior segment scores
2. Buccal cleft segment scores
3. Buccal non-cleft segment scores
4. Total arch MHBI scores

Ordered logistic regression was also used to investigate if there was any effect of gender or laterality in each case.

5.0 Results:

5.1 Demographic characteristics of the study sample:

A total of 344 5-year-olds' orthodontic models with UCLP were retrieved from the CCUK/CSAG record archive located at the University of Bristol dental school. Model identification coding of 35 models could not be accurately determined, while 4 CCUK and 3 CSAG models were found to be incomplete. This resulted in the assessment of 302 models made up of 195 CCUK, and 107 CSAG 5-year-olds' orthodontic study models. The CCUK cohort had missing data relating to gender (n=4) and age (n=6), while the CSAG cohort had missing data relating to age (n=5). Both cohorts had similar distribution for gender, while the mean age of the CSAG cohort was slightly greater at 6.5 years vs 5.6 years for CCUK. The CCUK cohort had a higher proportion of left sided UCLP when compared with CSAG (71.3% vs 62.6%). Table 6 shows the demographics of the study sample.

Characteristics	CCUK	CSAG	Total
Sample size n	195	107	302
Gender n (%)			
Male	132 ^a (67.7%)	74 (69.1%)	206 (68.2%)
Female	59 ^a (30.3%)	33 (30.9%)	92 (30.4%)
Cleft laterality n (%)			
Left	139 (71.3%)	67 (62.6%)	206 (68.2%)
Right	56 (28.7%)	40 (37.4%)	96 (31.8%)
Mean age (yrs)	5.6 ^b	6.5 ^c	

^a Missing data (n=4) ^b Missing data (n=6) ^c Missing data (n=5)

Table 6: Demographic characteristics of the 5-year-old patients with UCLP in this study.

5.2 Intra- and inter-rater reliability for the MHB index:

ICC and 95% confidence interval (95% CI) were used to measure the level of agreement of the MHBI scoring for the anterior segment, the buccal cleft segment, the buccal non-cleft segment, and the total MHBI on 30 randomly selected digital models. This was performed on repeated measurements carried out by the same assessor (intra-rater) and between measurements carried out by two different assessors (inter-rater). Reliability assessment was also carried out on the MHBI scoring of 29 digital models obtained from hand scanner versus lab scanner.

ICC values are interpreted using guidelines set by Shrout and Fleiss (1979) as shown in the table below:

ICC (3,1) value	Level of agreement
<0.20	Poor
0.21 to 0.40	Fair
0.41 to 0.60	Moderate
0.61 to 0.80	Good
0.81 to 1.00	Almost perfect

Table 7: Interpretation of level of agreement using intraclass correlation coefficients set by Shrout and Fleiss (1979)

Using Shrout and Fleiss's interpretation of the level of agreement, 'almost perfect' intra-rater agreement was achieved for MHBI scores of all segments for both assessors (BA and PF), and for the hand-scanned versus lab scanned models for assessor BA (Table 8 and 9).

Measurement	BA (ICC 3,1)	BA (95%CI)	PF (ICC 3,1)	PF (95%CI)
Anterior total	0.975	0.946 to 0.987	0.994	0.986 to 0.996
Buccal cleft total	0.952	0.900 to 0.976	0.987	0.972 to 0.993
Buccal non-cleft total	0.960	0.916 to 0.980	0.974	0.946 to 0.987
Total arch MHBI	0.967	0.931 to 0.984	0.990	0.979 to 0.995

Table 8: Intra-rater agreement using intraclass correlation coefficients (ICC) and 95% confidence intervals (CI) for both assessors (BA and PF) for each segment and total arch MHBI.

Measurement	Agreement (ICC 3,1)	95% CI
Anterior total	0.999	0.997 to 0.994
Buccal cleft total	0.993	0.983 to 0.996
Buccal non-cleft total	0.986	0.969 to 0.993
Total arch MHBI	0.996	0.990 to 0.997

Table 9: Intra-rater agreement using intraclass coefficients (ICC) and 95% confidence interval (CI) for hand-scanned versus lab scanned models for BA for each segment and total arch MHBI.

The ICC and 95% CI between the two examiners for scoring the 1st cycle and both examiners for 2nd cycle are shown in Table 11. The results fall into the almost perfect agreement category for all segments and total arch MHBI score. The table also shows that although the inter-rater agreement was almost perfect for all the segments, the buccal cleft and non-cleft segments had less strong agreement, but still falling within the ‘almost perfect’ category.

Measurement	1 st cycle (ICC 3,1)	95% CI	2 nd cycle (ICC 3,1)	95% CI
Anterior segment	0.954	0.905 to 0.977	0.953	0.903 to 0.977
Buccal cleft segment	0.877	0.757 to 0.939	0.846	0.701 to 0.923
Buccal non-cleft segment	0.870	0.744 to 0.935	0.843	0.695 to 0.921
Total arch MHBI	0.973	0.944 to 0.987	0.970	0.938 to 0.985

Table 10: Inter-rater agreement using intraclass coefficients (ICC) and 95% confidence interval (95% CI) for 1st cycle and 2nd cycle for each segment and total arch MHBI.

5.3 Distribution of the CCUK and CSAG segments and total arch MBHI scores

The frequency of the total arch MBHI scoring is illustrated in Figure 7. The distribution was non normal and for comparative purposes the medians and interquartile range (IQR) were calculated for the anterior segment, buccal cleft segment, buccal non-cleft segment and total arch MBHI scores for both CCUK and CSAG cohorts (Table 7).

Ordered logistic regression was used since the data being tested was ordinal, independent, and non-parametric (Figure 7). Figure 7 demonstrated that although the data for both cohorts are not normally distributed, the CCUK cohort data were closer to being normally distributed than CSAG cohort.

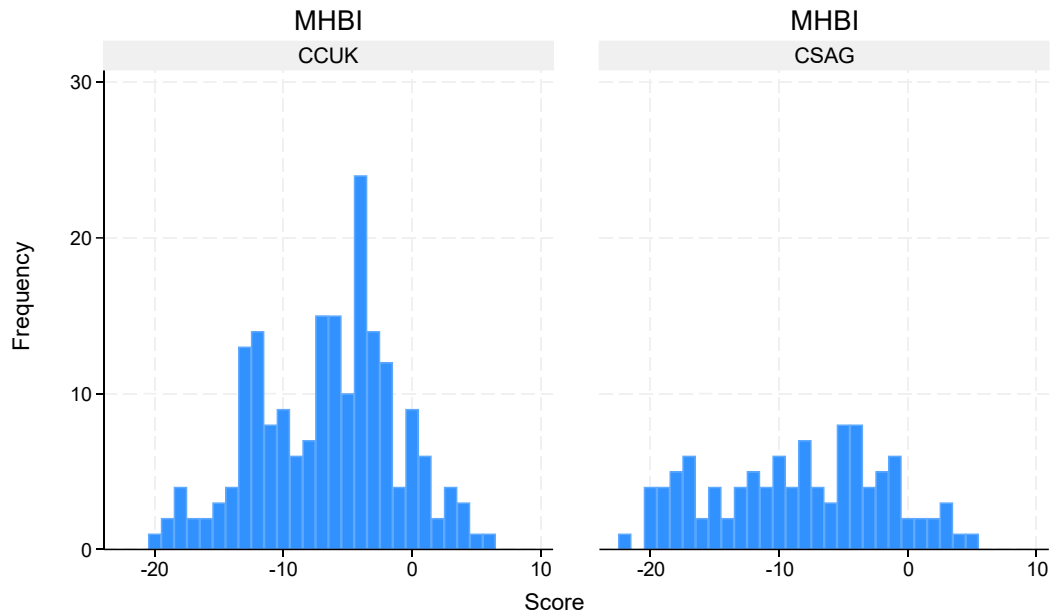


Figure 7: A bar graph showing the non-normal distribution of CSAG and CCUK study cohort total arch MHBI's scores.

	MHBI component	Median MHBI scores (IQR)
CCUK	Anterior	-2 (-6 to 2)
	Buccal Non-Cleft	1 (0 to 1)
	Buccal Cleft	-6 (-7 to -3)
	Total arch MHBI	-6 (-11 to -3)
CSAG	Anterior	-3 (-6 to 2)
	Buccal Non-Cleft	0 (-5 to 1)
	Buccal Cleft	-5 (-7 to -3)
	Total arch MHBI	-8 (-14 to -4)

Table 11: MBHI Median scores and interquartile ranges for the CSAG and CCUK 5-year-olds cohorts, anterior segment, buccal cleft segment, buccal non-cleft segment and total arch scores.

5.4 Transverse and antero-posterior interdental arch relationship outcomes using MHBI:

Ordered logistic regression, p-value, odds ratios and 95% confidence intervals were calculated to evaluate whether the scores differed between CCUK and CSAG for the anterior segment, buccal cleft segment, buccal non-cleft segment and total arch MHBI scores.

Ordered logistic regression was also used to investigate any potential effect of gender and laterality within each segment and for the total arch MHBI scores. The results are illustrated in Tables 12, 13, 14 and 15.

The odds ratios were calculated to evaluate the difference in the total arch MHBI scores between CCUK and CSAG, gender and laterality. Odds ratios were used since it allows for a comparison to be carried out between two groups, one of them being the reference group. In this study, the reference group was the CCUK cohort, hence if odds ratio is > 1 this implies that the CSAG cohort outcomes are more favourable than CCUK, and if it was < 1 then the CSAG have less favourable outcomes than CCUK.

5.4.1 Anterior segment:

The results show that there was a statistically significant difference in scores for the anterior segments between CCUK and CSAG (Table 12). In the case of gender and laterality within the anterior segment, there was no statistically significant effect. The float plot, Figure 8, shows that there were more positive and less negative frequency values for CCUK when compared to CSAG, indicating that the surgical outcomes for the anterior segment following centralisation had improved.

Variable	Odds ratio	Std. err	P-value	95% CI	
CCUK vs.	1	(base)	0.04	0.419	0.990
CSAG	0.644	0.141			
Male vs.	1	(base)	0.71	0.585	1.441
Female	0.919	0.211			
Left vs.	1	(base)	0.48	0.544	1.330
Right side	0.851	0.193			

Table 12: The results of the ordered logistic regression analysis CSAG vs CCUK for the anterior segment MBHI values along with gender and laterality.

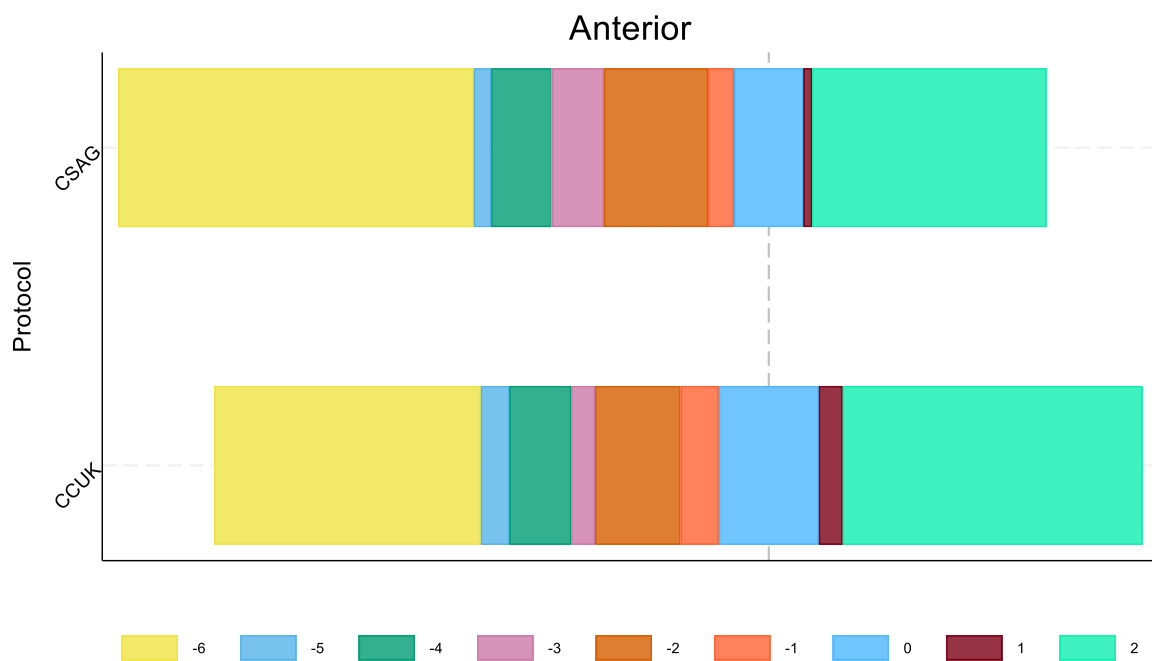


Figure 8: A float plot showing the frequency of values of the anterior segment MBHI scores for CSAG and CCUK.

5.4.2 Buccal cleft segment:

The ordered logistic regression showed that although the CSAG buccal cleft MBHI score was more favourable than the CCUK, and Female scored less favourable than male, neither were significantly different (Table 13). The only statistical difference in the buccal cleft segment MBHI score was seen in cleft laterality, with right-sided cleft having better outcomes than left-sided cleft. Figure 9 shows that the frequency of values of the buccal cleft segment MHBI scores for CSAG and CCUK were similar.

	Odds ratios	Std. err	P-value	95% CI	
CCUK vs.	1	(base)	0.43	0.775	1.794
CSAG	1.179	0.252			
Male vs.	1	(base)	0.06	0.422	1.024
Female	0.657	0.148			
Left vs.	1	(base)	0.04	1.00	2.362
Right side	1.540	0.336			

Table 13: The results of the ordered logistic regression analysis CSAG vs CCUK for the buccal cleft segment MHBI scores along with gender and laterality.

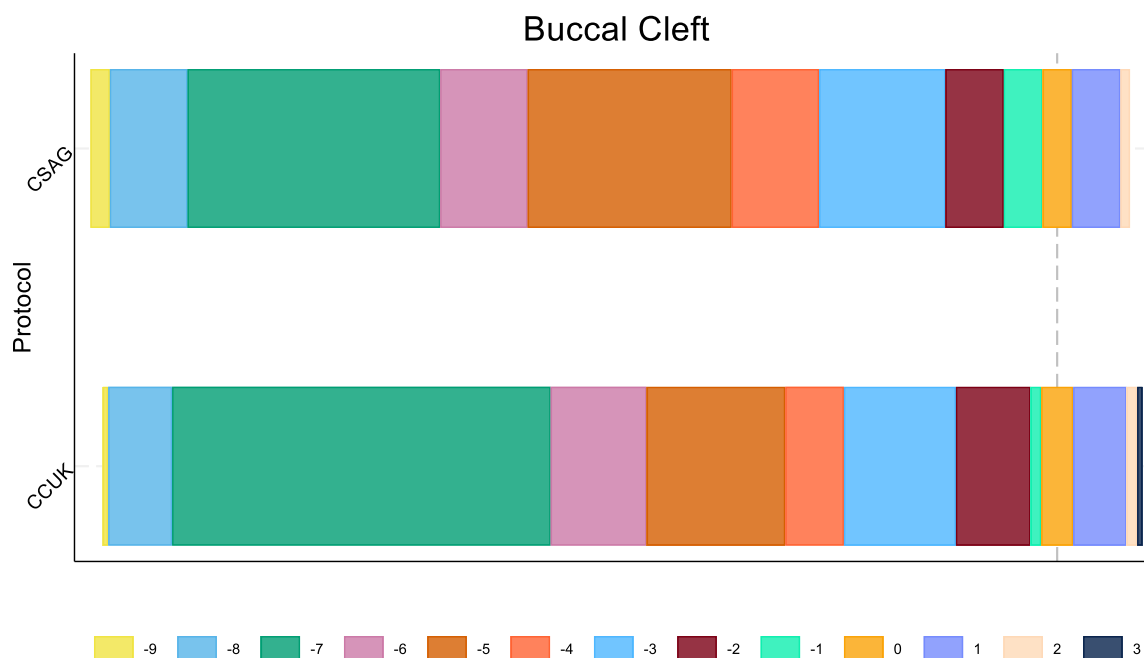


Figure 9: A float plot showing the frequency of values of the buccal cleft segment MHBI scores for CSAG and CCUK.

5.4.3 Buccal non-cleft segment

The ordered logistic regression showed that there was a statistically significant difference for the buccal non-cleft side MHBI scores between the two cohorts, with the scores for CCUK being better than those of CSAG (Table 14). In the case of gender and laterality there was no effect. The float plot Figure 10 shows that the majority of CCUK buccal non-cleft segment MBHI scores were greater than those observed in CSAG.

	Odds ratios	Std. err	P-value	95% CI	
CCUK vs.	1	(base)	0.001	0.306	0.745
CSAG	0.477	0.108			
Male vs.	1	(base)	0.718	0.593	1.432
Female	0.922	0.207			
Left vs.	1	(base)	0.694	0.702	1.698
Right side	1.092	0.245			

Table 14: The results of the ordered logistic regression analysis CSAG vs CCUK for the buccal non-cleft segment MHBI values along with gender and laterality

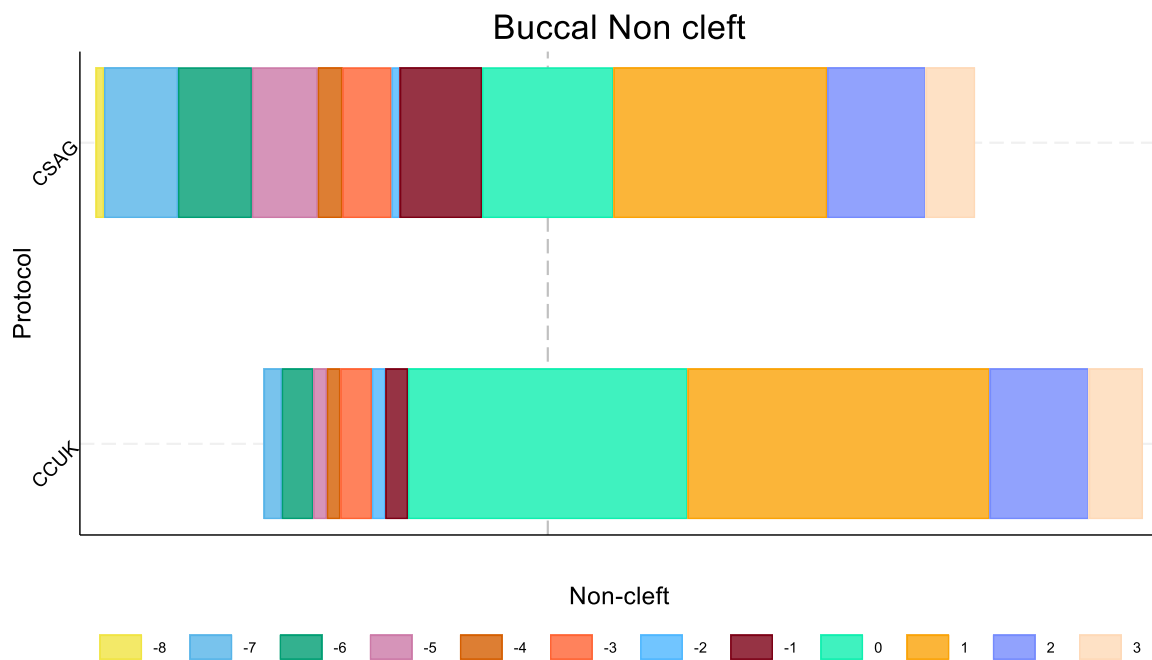


Figure 10: A float plot showing the frequency of values of the buccal non-cleft segment scores for CSAG and CCUK.

5.4.4 Total arch MHBI scores

For the total arch MHBI scores, the ordered logistic regression showed there was a statistically significant difference between CCUK and CSAG, with CCUK showing improved scores when compared with CSAG (Table 15). Furthermore, gender and laterality did not affect total arch MHBI scores. Figure 11 shows the frequency of values of the total arch MHBI scores for CSAG and CCUK with more positive values in the CCUK cohort. This confirms that following centralisation of cleft care in the UK, the interdental arch relationship had improved.

	Odds ratios	Std. err	P-value	95% CI	
CCUK vs.	1	(base)	0.013	0.379	0.890
CSAG	0.581	0.126			
Male vs.	1	(base)	0.121	0.462	1.094
Female	0.711	0.156			
Left vs.	1	(base)	0.823	.680	1.622
Right side	1.050	0.232			

Table 15: The results of the ordered logistic regression analysis CSAG vs CCUK for the total arch MHBI values along with gender and laterality

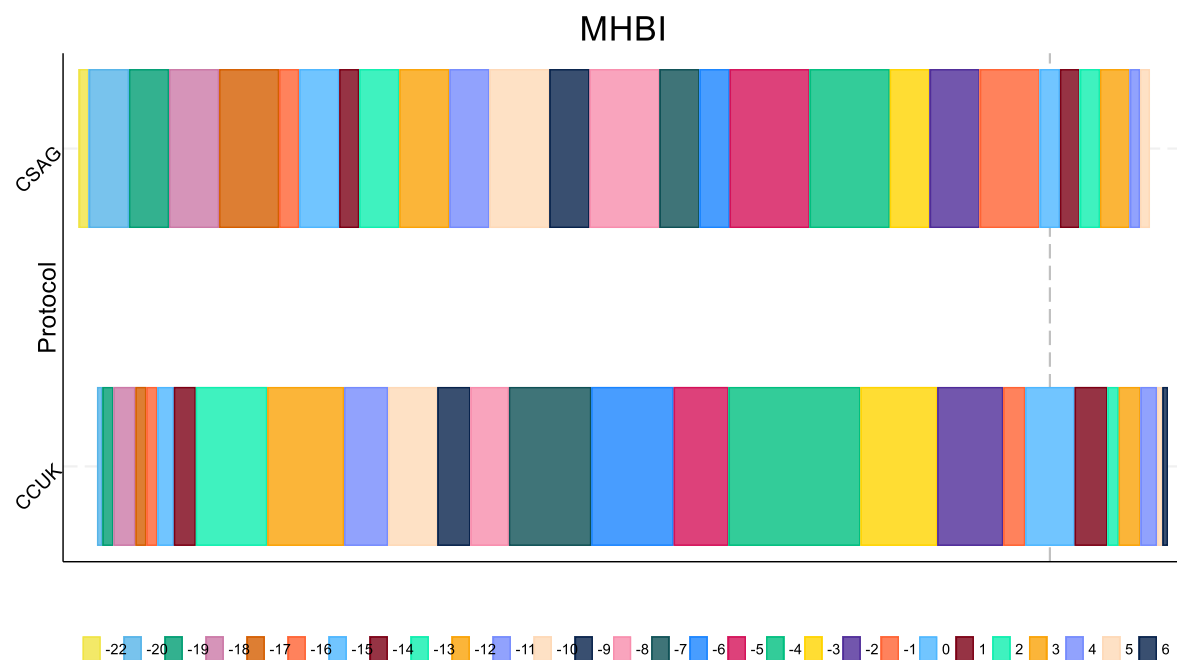


Figure 11: A float plot showing the frequency of values of the total arch MHBI scores for CSAG and CCUK.

6.0 Discussion:

6.1 Overview:

This study aimed to evaluate the interdental arch relationship outcomes of 5-year-old children born with a complete unilateral cleft lip and palate treated before and after the centralisation of cleft services in the UK, when assessed with the Modified Huddart and Bodenham Index.

The study found that there were significant differences in the anterior segment, buccal non-cleft segment, and the total arch MHBI scores with the CCUK models scoring better than the CSAG. No differences were found for the buccal cleft segment scores. Neither gender nor laterality had an impact on the total MHBI scores. Finally, the reliability between the hand-scanned and lab-scanned study models was 'almost perfect'.

6.2 Reliability of measurement:

The inter- and intra-examiner reliability agreement for the anterior segment, buccal cleft segment, buccal non-cleft segment and total arch MHBI scores for CCUK and CSAG were investigated using intraclass correlation coefficient (ICC) and 95% confidence intervals (95%CI). According to Shrout and Fleiss (1979), to obtain an 'almost perfect' reliability value, ICC (3,1) should be >0.8 which indicates that the results are highly reliable and repeatable for inter and intra-examiner testing.

The results indicate that the MHBI has an 'almost perfect' level of inter- and intra-examiner reliability, as evidenced by an ICC of 0.967 (with a 95%CI range of 0.931 to 0.984) and 0.973

(with a 95%CI range of 0.944 to 0.987), respectively. These findings are consistent with a study by Salazar *et al.* (2022), which demonstrated an inter- and intra-rater agreement of 0.950 and 0.965, respectively using the MHBI. Additionally, Martin *et al.* (2016) found that both inter- and intra-examiner reliability were 'excellent' when the MHBI was carried out on digital study models using OrthAnalyzer™ software, with ICC values of 0.975 and 0.979, respectively. The high reliability of the MHBI was also supported by many other studies (Mossey *et al.*, 2003; Garry and Mossey, 2005; Tothill and Mossey, 2007; Manosudprasit *et al.*, 2011; Patel, 2011; Dobbryn *et al.*, 2012) confirming the high objectivity of the index.

A possible reason for the high reliability of the assessment in this study may be because it was conducted using digital models. This enabled 3D manipulation of the models and zooming in on areas that would be more difficult to see with traditional plaster models. Furthermore, the software fixed the articulation of the digital models, reducing the possibility of human error when hand articulating during the assessment.

Although the developers of the MHBI stated that no calibration was needed for this index (Mossey *et al.*, 2003), there were some subjective and calibration elements in the scoring process used in this study. For instance, while the scoring was particularly easy at the extremes of measurement (-3 and +1), it was more difficult at the boundary between -2, -1 and 0. This because if there was lack of vertical contact or the tooth was rotated, this will result in variable occlusal relationships.

6.3 Missing data:

A total of 302 (CCUK= 195, CSAG= 107) study models were recruited for this study. These numbers were significantly less than the original sample numbers for both cohorts (CCUK= 264, CSAG= 239). This large reduction in sample numbers between the original CCUK and CSAG studies and this study was due to missing study models and the presence of study models that could not be assigned to either cohort due to inadequate model coding.

Although proportionally the CSAG had greater loss of data (55.2% vs 26.1%) it was assumed that the loss occurred randomly. However, the size of the data loss may affect the representativeness of the study sample and limit its generalisability.

6.4 Study sample demographics:

Both, CSAG and CCUK studies included children born with non-syndromic complete UCLP at 5-years-old (with a soft tissue band of less than 5mm). The demographics such as gender and mean age of the current study cohort (male CCUK= 67.7%, CSAG= 69.1%; mean age CCUK= 5.6, CSAG= 6.5) were similar to the original CCUK and CSAG study cohorts (male% CCUK= 67.5%, CSAG= 66.5%; mean age CCUK= 5.5, CSAG= 6.4). This indicated that it was unlikely that there was systematic bias associated with the models lost between the original CCUK and CSAG study cohort and that used in this study and that the study data were still representative of the original CCUK and CSAG population.

The mean age (5.6 years) of the CCUK models used in this study were closer to the target age of 5 years compared to CSAG (6.4 years), which also had a wider range of ages. The implications of the age difference relate to potential differences in facial growth and dental

development between the two study samples and the interpretation of results should be done with caution.

As for laterality, left-sided cleft dominated in both study cohorts (CCUK =71.3%, CSAG=62.6%). This finding agreed with the prevalence of cleft laterality documented in the literature (Cohen, 1978; Nagase *et al.*, 2010; WHO, 2002; CRANE, 2021). The current study investigated laterality, which was not previously explored in the original CCUK and CSAG studies but has recently been raised in more recent studies investigating cleft laterality outcomes (Staudt *et al.*, 2021; Chong *et al.*, 2022).

6.5 Interpretation of results:

6.5.1 Anterior segment scores

The presence of UCLP has a significant impact on the anterior segment interdental arch relationship and can present considerable challenges for correction, if discrepancies are present (Salazar *et al.*, 2022).

The current study found a significant difference in MHBI scores for anterior segment between CCUK and CSAG cohorts, with CSAG having worse outcomes. It was observed that a higher number of patients in the CCUK cohort had near normal occlusion with a MHBI anterior segment score of 0 to +1 (normal occlusion). This finding was supported by Al-Ghatam *et al.* (2015), who reported that over 50% of the CCUK cohort had 'good' or 'very good' 5-Year-Old Index gradings. Although the 5-Year-Olds' Index does not divide the interdental arch into anterior and buccal segments, the index places a majority of its grading

on the AP position of the anterior dentition. A 'good' or 'excellent' grading is suggestive of an edge to edge or positive overjet. By comparison, in the CSAG cohort a greater proportion had negative MBHI anterior segment scores, and this was also reflected with only 30% of the CSAG sample graded by Al Ghatam *et al.* (2015) as 'good' or 'excellent' using the 5-Year-Old Index. This further supports the evidence that centralisation of cleft services has resulted in improved outcomes in the anterior segment interdental arch relationship. When compared to other studies that used the MBHI for interdental arch evaluation, it was found that the CCUK's median anterior segment score value was similar to those reported by other recent studies (Karsten *et al.*, 2017; Salazar *et al.*, 2022), while CSAG's anterior segment score compared less favourably.

6.5.2 Buccal cleft segment scores and buccal non-cleft segment scores

Within the buccal segment, there was no significant difference between the buccal cleft sides between the CCUK and CSAG models. However, on the buccal non-cleft side, a significant difference was found with CCUK performing better than CSAG. Possible explanations for these findings may include differences in surgical palatal repair protocols, the surgeons' training and surgeon's case load volume.

As a possible explanation to the improvement in MBHI scores for the CCUK being detected on the non-cleft buccal segment and not the cleft buccal segment, the CSAG cohort commonly underwent primary palatal repair based on the Veau and Wardill-Kilner pushback (VWK) technique at around the age of 12-24 months (Sommerlad *et al.*, 2009). This surgical palatal repair was generally undertaken in one setting with releasing dissections on both the

cleft and non-cleft side of the hard palate, a procedure which can lead to greater maxillary arch collapse (Sommerlad *et al.*, 2009). As for the CCUK cohort, they commonly undertook a primary lip and hard palate repair using the vomer flap technique at 3-5 months, often removing the requirement for releasing dissection on the non-cleft side of the hard palate. This technique has shown to have reduced interference with maxillary growth (Hay *et al.*, 2018).

A more recent retrospective study has found similar findings to this study, where the MHBI scores on the cleft side had greater negative values than the buccal non-cleft side. (Staudt *et al.*, 2021). The study concluded “the more constricted buccal cleft side reflects the difficulty in correcting the more medially positioned lesser maxillary segment” Additionally, cleft side constriction makes orthodontic correction of transverse arch discrepancy more challenging, and stability is questioned.

6.5.3 Total arch MHBI scores:

Overall, the odds ratios of the total arch MHBI scores show that the transverse and AP interdental arch relationships following centralisation had improved from CSAG to CCUK. This is also reflected in the differences in the median scores between the two study cohorts. The median score for CCUK was similar to more recent studies (Mikoya *et al.*, 2015; Karsten *et al.*, 2017), whilst the CSAG median was an outlier. This was reflected in the reduced frequency of anterior and buccal crossbites in the CCUK cohort compared to CSAG. Such improvements could result in reduced orthodontic treatment burden relating to arch preparation to facilitate surgical access for secondary bone grafting. Furthermore, the

likelihood of the need for orthognathic surgery may also be reduced once growth has been completed. It may also have implications for stability of orthodontic correction and potential reduced risk of relapse following transverse orthodontic expansion. (Staudt *et al.*, 2021).

The findings of this study are supported by Al-Ghatam *et al.* (2015), who found similar outcomes when the 5-Year-Olds' index was used. Although the method of assessment of dental arch relationship was different, in a 2012 study, Dobbryn *et al.* found that the MHBI scoring system can be calibrated to the 5-Year-Olds' index categories (Table 16).

Al-Ghatam's study found that approximately 53% of the CCUK cohort had good to excellent dental relationship and 19% poor outcomes compared to only 29% good and 36% poor outcomes for the CSAG. In this study, the frequency of values that scored between -6 and +8 was significantly higher in the CCUK cohort compared to CSAG (Figure 12). However, in the 5-Year-Olds' Index categories 4 and 5, the relationship between the two indices was less predictable, likely due to the differences in what the indices measure (incisor decompensation and lesser segment relapse).

Category	1 (Excellent)	2 (Good)	3 (Fair)	4 (Poor)	5 (V. poor)
Estimated total arch MHBI scores for each 5-year-olds' index category rankings	+8 to -1	-2 to -6	-7 to -10	-11 to -14	-15 to -24

Table 16: Estimated modified Huddart and Bodenham scores for 5-year-olds' index

category. Recreated from (Dobbryn *et al.*, 2012).

Therefore, from Table 16, it could be anticipated that the total arch MHBI median score for CCUK would equate to a 5-Year-Olds' Index ranking of group 2 (good), while the CSAG score would fall into group 3 (fair).

The promising improvements in cleft outcomes following service centralisation are likely due to multiple factors, including changes in:

- Surgical protocol: The Oslo Surgical repair protocol has been adapted for treatment of children born with UCLP. This protocol starts at three months of age, which is when a Millard lip repair and anterior hard palate repair is performed with a single layer Vomer flap. At nine months, hard and soft palate repair is done using a modified von Langenbeck technique. The goal is to balance favourable facial growth with adequate speech development. In addition, by using this protocol improved craniofacial morphology and nasio-labial appearance will be achieved (Fudalej *et al.*, 2015);
- Surgeon's experience: Centralisation has increased the number of patients seen by surgeons annually, as each surgeon is now required to treat at least 40 babies with UCLP per year. A 2014 cross-sectional survey that looked into the number of children who underwent primary cleft surgery for UCLP from April 1, 2009 to March 31, 2010, found that 17 out of the 19 surgeons who performed primary cleft surgery have met the target of operating on 40 patients minimum per year (Scott *et al.*, 2014);

- Surgical training: Surgical training in the UK now follows a more structured pathway via oral and maxillofacial surgery or plastic surgery craniofacial fellowships. This is crucial for gaining experience, as a recent study has shown that surgeons who were still learning find primary cleft surgery more challenging (Rautio *et al.*, 2017).

6.5.4 Laterality:

Regarding laterality, surgical outcomes were better for right sided clefts, but these findings were only limited to the buccal cleft segment. No significance was found for the anterior, buccal non-cleft and the total MHBI scores. The buccal cleft segment score could be a chance finding. Although it is interesting to note that 65% of patients with left-sided clefts required orthognathic surgery, compared to 20% of patients with right-sided clefts (Staudt *et al.*, 2021). On the other hand, Chong *et al.* (2022) reported that left-sided clefts had better outcomes than right-sided clefts due to anatomical differences (Chong *et al.*, 2022). Such controversial findings could be due to the initial cleft morphology and severity as well as the handedness of the orthodontist/surgeon (Staudt *et al.*, 2021). The influence of laterality on surgical outcomes remains unresolved.

6.5.5 Gender:

When gender was investigated in this study, it was found that it did not affect the total arch MHBI scores. This means the interdental arch relationship was similar regardless of gender for both cohorts. A similar finding was reported in a study by Siegenthaler *et al.* (2018), who found that gender did not influence the total arch MHBI scores following early secondary alveolar bone grafting and late secondary alveolar bone grafting using the MBHI.

6.5.6 Hand scanned vs lab scanned digital models:

This study found a high level of reliability using either the hand-scanned or lab-scanned digital models when assessing the MBHI, with the lab scanner being quicker and easier to use and the hand-held scanner being more accurate when having articulation issues. In a study conducted by Jeong *et al.* (2016), the lab scanner was found to be more accurate than the hand scanner, while Zarone *et al.* (2020) found that hand-scanned study models were more accurate than laboratory bench scanners. These contradictory findings could be attributed to various factors, such as differences in accuracy levels between the scanners used, variations in scanning range, field of view and image resolution.

The use of digital models in this study was similar to another study which used the MHBI on digital study models (Martin *et al.*, 2016) and previous investigations have demonstrated good or excellent inter- and intra-rater reliability when comparing cast to digital models (Martin *et al.*, 2016; Asquith and Mclyntre, 2012). Digital models are therefore valid alternatives to plaster models for assessment of interdental arch relationship in 5-years-old patients with complete UCLP.

The CCUK study had a limitation in that they had to take photographs for 15% of the 5-year-old patients when impressions were not possible, and these photographs were not as reliable as cast models (Al-Ghatam *et al.*, 2015). As a result, they had to exclude them from the study, leading to fewer models and a potential for bias. However, using intra-oral scanners could make data collection easier for 5-year-olds since it may reduce discomfort and provide similar information to study models.

6.6 Study limitations:

6.6.1 Sample selection and data loss

It has been acknowledged by both the CSAG and the CCUK studies that their respective study recruitment was limited by the constraints of the retrospective nature of their study design. Approximately 73% of all available patients with UCLP were recruited by CSAG and 74% for the CCUK. While the effect of missing data on their outcomes is unknown, it has been reported that the relatively high recruitment percentage of both the CSAG and the CCUK studies collected were representative samples (Persson *et al.*, 2015).

A large proportion of the models were missing from the CCUK and CSAG archives (29% and 55% respectively). The reason for this is unknown but it is possible that some have been loaned to other researchers and not returned as a complete set or simply misplaced. Nevertheless, the remaining sample sizes were still relatively large and were deemed to be representative of the original archive. A sample size calculation prior to data collection suggested the number of remaining models would be more than sufficient to measure differences using the MHBI. In addition, the gender distribution and mean ages of this sample were similar to the original CSAG and CCUK studies, suggesting that any loss of data occurred randomly.

6.6.2 Model measurement :

In order to minimise researcher bias, one researcher scanned all the study plaster models, with the study model identifying numbers visible on the model bases, allowing the CCUK

and CSAG cohort models to be distinguished. To ensure subsequent anonymity of the models for use in the scoring part of the study, a third party (ST) generated new identifying numbers for both cohorts, which were entered into the OrthoAnalyzer™ software by a fourth party (OM) to prevent the researcher from distinguishing which study models belonged to which cohort when the MHBI scoring was undertaken.

6.6.3 Model artifacts:

Seven models had to be excluded from this study due to the presence of artifacts such as gauze covering the occlusal surfaces of the teeth, damaged plaster models, incomplete sets of study models, or the lack of teeth present. Additionally, 35 models were not included due to a lack of clear coding of the plaster model bases, which further added to the data loss issue in this study.

6.6.4 Lack of potential confounding data:

There were potential confounders that could have influenced the interdental arch relationship outcomes but were not available for assessment in this study. These include the surgical protocol used (staging, timing and surgical technique), the skill and experience of the surgeon, the possible use of pre-surgical lip strapping or PISO devices and the use of any additional surgical procedures relating to fistula repair, speech related surgery or lip revision. In the absence of these potential confounders, it can only be hypothesised that the variations in outcomes are attributed to the centralisation process, but we lack the necessary data to determine which aspect of the change led to the improved outcomes.

Whether it was due to better-trained surgeons, increased utilisation of the vomer flap, or higher surgical volume is still uncertain.

7.0 Implications of the study and future work:

The findings of this study once again confirm that the changes made following the recommendations of the CSAG investigation have positively influenced the outcomes of surgical repair, and so contribute to the ongoing body of evidence.

By improving the transverse and AP dental arch outcomes in 5-year-olds with complete UCLP, the need for orthodontic expansion prior to secondary alveolar bone grafting could be reduced, leading to easier and more stable correction of the transverse and AP interdental arch relationships following orthodontic (and orthognathic) treatment. This would reduce the burden not only on patients but also the NHS cleft service.

A digital record of the CSAG and CCUK models has been created as part of this study and is suitable for use in future audits and research. The digital archive is more robust and more accessible than the original plaster models, which are prone to damage and/or loss.

Future research could investigate the potential confounders previously described *i.e.* surgical protocol (staging, timing and surgical technique), surgeon experience, the use of pre-surgical lip strapping or PISO devices, and any additional surgical procedures relating to fistula repair, speech related surgery or lip revision on the occlusal outcomes.

In terms of the MHBI, a possible further modification would be to include an assessment of vertical occlusal discrepancies. Such a modified index could then easily be used to compare

the digitally archived CSAG and CCUK models at 5 years and the separate 12 years CSAG and CCUK model archive.

8.0 Conclusion

The null hypothesis for this study which states that there is no difference in the transverse interdental arch relationship outcomes of 5-year-old children with complete UCLP treated before and after the centralisation of cleft services in the UK, when assessed with the modified Huddart and Bodenham Index was rejected, as there was a significant difference in the total arch MHBI scores between CCUK and CSAG groups, with the CCUK group performing better in the anterior segment, the buccal non-cleft segment, and the total arch MHBI scores. This confirms that the transverse and AP interdental arch relationship following primary surgery of patients with unilateral cleft lip and palate has improved since cleft care centralisation in the United Kingdom.

The investigation of the secondary objectives found no significant differences in MHBI scores by gender or laterality. In addition, the third study objective found no difference between handheld and bench scanning methods when scoring the digital study models of 5-year-old children with UCLP using the MBHI.

9.0 References

- ABRISHAMCHIAN, A. R., KHOURY, M. J. & CALLE, E. E. 1994. The contribution of maternal epilepsy and its treatment to the etiology of oral clefts: a population based case-control study. *Genet Epidemiol*, 11, 343-51.
- AL-GHATAM, R., JONES, T. E. M., IRELAND, A. J., ATACK, N. E., CHAWLA, O., DEACON, S., ALBERY, L., COBB, A. R. M., CADOGAN, J., LEARY, S., WAYLEN, A., WILLS, A. K., RICHARD, B., BELLA, H., NESS, A. R. & SANDY, J. R. 2015. Structural outcomes in the Cleft Care UK study. Part 2: dento-facial outcomes. *Orthodontics & craniofacial research*, 18 Suppl 2, 14-24.
- ALTALIBI, M., SALTAJI, H., EDWARDS, R., MAJOR, P. W. & FLORES-MIR, C. 2013. Indices to assess malocclusions in patients with cleft lip and palate. *Eur J Orthod*, 35, 772-82.
- ALZAIN, I., BATWA, W., CASH, A. & MURSHID, Z. A. 2017. Presurgical cleft lip and palate orthopedics: an overview. *Clinical, cosmetic and investigational dentistry*, 9, 53-59.
- ASQUITH, J. A. & MCINTYRE, G. T. 2012. Dental arch relationships on three-dimensional digital study models and conventional plaster study models for patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 49, 530-4.
- ATAK, N., HATHORN, I., MARS, M. & SANDY, J. 1997. Study models of 5 year old children as predictors of surgical outcome in unilateral cleft lip and palate. *Eur J Orthod*, 19, 165-70.
- ATAK, N. E., HATHORN, I. S., SEMB, G., DOWELL, T. & SANDY, J. R. 1997. A New Index for Assessing Surgical Outcome in Unilateral Cleft Lip and Palate Subjects Aged Five: Reproducibility and Validity. *Cleft Palate Craniofac J*, 34, 242-246.
- BEARN, D., MILDINHALL, S., MURPHY, T., MURRAY, J. J., SELL, D., SHAW, W. C., WILLIAMS, A. C. & SANDY, J. R. 2001. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 4: outcome comparisons, training, and conclusions. *Cleft Palate Craniofac J*, 38, 38-43.
- BEATY, T. H., MURRAY, J. C., MARAZITA, M. L., MUNGER, R. G., RUCZINSKI, I., HETMANSKI, J. B., LIANG, K. Y., WU, T., MURRAY, T., FALLIN, M. D., REDETT, R. A., RAYMOND, G., SCHWENDER, H., JIN, S. C., COOPER, M. E., DUNNWALD, M., MANSILLA, M. A., LESLIE, E., BULLARD, S., LIDRAL, A. C., MORENO, L. M., MENEZES, R., VIEIRA, A. R., PETRIN, A., WILCOX, A. J., LIE, R. T., JABS, E. W., WU-CHOU, Y. H., CHEN, P. K., WANG, H., YE, X., HUANG, S., YEOW, V., CHONG, S. S., JEE, S. H., SHI, B., CHRISTENSEN, K., MELBYE, M., DOHENY, K. F., PUGH, E. W., LING, H., CASTILLA, E. E., CZEIZEL, A. E., MA, L., FIELD, L. L., BRODY, L., PANGILINAN, F., MILLS, J. L., MOLLOY, A. M., KIRKE, P. N., SCOTT, J. M., ARCOS-BURGOS, M. & SCOTT, A. F. 2010. A genome-wide association study of cleft lip with and without cleft palate identifies risk variants near MAFB and ABCA4. *Nat Genet*, 42, 525-9.

- BELL, A., LO, T. W., BROWN, D., BOWMAN, A. W., SIEBERT, J. P., SIMMONS, D. R., MILLETT, D. T. & AYOUB, A. F. 2014. Three-dimensional assessment of facial appearance following surgical repair of unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 51, 462-71.
- BENKO, S., FANTES, J. A., AMIEL, J., KLEINJAN, D. J., THOMAS, S., RAMSAY, J., JAMSHIDI, N., ESSAFI, A., HEANEY, S., GORDON, C. T., MCBRIDE, D., GOLZIO, C., FISHER, M., PERRY, P., ABADIE, V., AYUSO, C., HOLDER-ESPINASSE, M., KILPATRICK, N., LEES, M. M., PICARD, A., TEMPLE, I. K., THOMAS, P., VAZQUEZ, M. P., VEKEMANS, M., ROEST CROLLIUS, H., HASTIE, N. D., MUNNICH, A., ETCHEVERS, H. C., PELET, A., FARLIE, P. G., FITZPATRICK, D. R. & LYONNET, S. 2009. Highly conserved non-coding elements on either side of SOX9 associated with Pierre Robin sequence. *Nat Genet*, 41, 359-64.
- BILLE, C., PEDERSEN, D. A., ANDERSEN, A. M., MANSILLA, M. A., MURRAY, J. C., CHRISTENSEN, K., BALLARD, J. L., GORMAN, E. B., CABRERA, R. M. & FINNELL, R. H. 2010. Autoantibodies to folate receptor alpha during early pregnancy and risk of oral clefts in Denmark. *Pediatr Res*, 67, 274-9.
- BISHARA, S. E., SIERK, D. L. & HUANG, K. S. 1979. A longitudinal cephalometric study on unilateral cleft lip and palate subjects. *Cleft Palate J*, 16, 59-71.
- BLAND, J. M. & ALTMAN, D. G. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1, 307-10.
- BOKHOUT, B., HOFMAN, F. X., VAN LIMBEEK, J., KRAMER, G. J. & PRAHL-ANDERSEN, B. 1997. Incidence of dental caries in the primary dentition in children with a cleft lip and/or palate. *Caries Res*, 31, 8-12.
- BLUESTONE, C. D. 1985. Current concepts in eustachian tube function as related to otitis media. *Auris Nasus Larynx*, 12 Suppl 1, S1-4.
- BRITO, L. A., MEIRA, J. G. C., KOBAYASHI, G. S. & PASSOS-BUENO, M. R. 2012. Genetics and Management of the Patient with Orofacial Cleft. *Plastic Surgery International*, 2012, 782821.
- BUSH, J. O. & JIANG, R. 2012. Palatogenesis: morphogenetic and molecular mechanisms of secondary palate development. *Development*, 139, 231-43.
- BUTTERWORTH, S., HODGKINSON, E. L., SAINSBURY, D. C. G. & HODGKINSON, P. D. 2021. Surgical Variation Between Consultant Surgeons Performing a Sommerlad Radical Intravelar Veloplasty. *Cleft Palate Craniofac J*, 58, 1490-1499.
- CADOGAN, J., MARSH, C. & WINTER, R. 2009. Parents' views of 4D ultrasound scans following diagnosis of cleft condition. *British Journal of Midwifery*, 17, 374-380.

- CAPELOZZA FILHO, L., NORMANDO, A. D. & DA SILVA FILHO, O. G. 1996. Isolated influences of lip and palate surgery on facial growth: comparison of operated and unoperated male adults with UCLP. *Cleft Palate Craniofac J*, 33, 51-6.
- CHEVRIER, C., PERRET, C., BAHUAU, M., NELVA, A., HERMAN, C., FRANCANNET, C., ROBERT-GNANSIA, E. & CORDIER, S. 2005. Interaction between the ADH1C polymorphism and maternal alcohol intake in the risk of nonsyndromic oral clefts: an evaluation of the contribution of child and maternal genotypes. *Birth Defects Res A Clin Mol Teratol*, 73, 114-22.
- CHIGURUPATI, R., HEGGIE, A. & BONANTHAYA, K. 2010. Cleft lip and palate: an overview. *Oral and Maxillofacial Surgery. Oxford: Wiley-Blackwell*, 945-72.
- CHONG, D. K., SOMASUNDARAM, M., HO, E., DHOOGHE, N. S. & FISHER, D. M. 2022. Comparison of Presurgical Anthropometric Measures of Right and Left Complete Unilateral Cleft Lip and/or Palate. *Plast Reconstr Surg*, 149, 248e-253e.
- COBOURNE, M. T. 2004. The complex genetics of cleft lip and palate. *Eur J Orthod*, 26, 7-16.
- COBOURNE, M.T. and DIBIASE, A.T. (2016). *Handbook of orthodontics*. Edinburgh ; New York: Elsevier.
- COHEN, M. M., JR. 1978. Syndromes with cleft lip and cleft palate. *Cleft Palate J*, 15, 306-28.
- COLBERT, S. D., GREEN, B., BRENNAN, P. A. & MERCER, N. 2015. Contemporary management of cleft lip and palate in the United Kingdom. Have we reached the turning point? *British Journal of Oral and Maxillofacial Surgery*, 53, 594-598.
- COUPLAND, M. A. & COUPLAND, A. I. 1988. Seasonality, incidence, and sex distribution of cleft lip and palate births in Trent Region, 1973-1982. *Cleft Palate J*, 25, 33-7.
- DAHL, E. & HANUSARDÓTTIR, B. 1979. Prevalence of malocclusion in the primary and early mixed dentition in Danish children with complete cleft lip and palate. *Eur J Orthod*, 1, 81-88.
- DALLASERRA, M., PANTOJA, T., SALAZAR, J., ARAYA, I., YANINE, N. & VILLANUEVA, J. 2022. Effectiveness of pre-surgical orthopedics on patients with cleft lip and palate: A systematic review and meta-analysis. *J Stomatol Oral Maxillofac Surg*, 123, e506-e520.
- DEROO, L. A., WILCOX, A. J., DREVON, C. A. & LIE, R. T. 2008. First-trimester maternal alcohol consumption and the risk of infant oral clefts in Norway: a population-based case-control study. *American journal of epidemiology*, 168, 638-646.
- DIXON, M. J., MARAZITA, M. L., BEATY, T. H. & MURRAY, J. C. 2011. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet*, 12, 167-78.

- DOBBYN, L. M., WEIR, J. T., MACFARLANE, T. V. & MOSSEY, P. A. 2012. Calibration of the modified Huddart and Bodenham scoring system against the GOSLON/5-year-olds' index for unilateral cleft lip and palate. *Eur J Orthod*, 34, 762-7.
- DUDDING, T., MARTIN, S. & POPAT, S. 2023. An introduction to the UK care pathway for children born with a cleft of the lip and/or palate. *British Dental Journal*, 234, 943-946.
- ESTACIO SALAZAR, A. R., KODAMA, Y., YUKI, R., OMINATO, R., NAGAI, T., WATANABE, M., YAMADA, A., KOBAYASHI, R., ICHIKAWA, K., NIHARA, J., IIDA, A., ONO, K., SAITO, I. & TAKAGI, R. 2022. Occlusal Evaluation Using Modified Huddart and Bodenham Scoring System Following 2-Stage Palatoplasty With Hotz Plate: A Comparison Among 3 Different Surgical Protocols. *Cleft Palate Craniofac J*, 10556656221093293.
- FELL, M., DAVIES, A., DAVIES, A., CHUMMUN, S., COBB, A. R. M., MOAR, K. & WREN, Y. 2023. Current Surgical Practice for Children Born with a Cleft lip and/or Palate in the United Kingdom. *Cleft Palate Craniofac J*, 60, 679-688.
- FELL, M., RUSSELL, C., MEDINA, J., GILLGRASS, T., CHUMMUN, S., COBB, A. R. M., SANDY, J., WREN, Y., WILLS, A. & LEWIS, S. J. 2021. The impact of changing cigarette smoking habits and smoke-free legislation on orofacial cleft incidence in the United Kingdom: Evidence from two time-series studies. *PLoS One*, 16, e0259820.
- FITZSIMONS, K., HAMILTON, M., VAN DER MEULEN, J., MEDINA, J., WAHEDALLY, M., PARK, M. & RUSSELL, C. 2023. Range and Frequency of Congenital Malformations Among Children With Cleft Lip and/or Palate. *Cleft Palate Craniofac J*, 60, 917-927.
- FLEMING, P. S., MARINHO, V. & JOHAL, A. 2011. Orthodontic measurements on digital study models compared with plaster models: a systematic review. *Orthod Craniofac Res*, 14, 1-16.
- FLINN, W., LONG, R. E., GARATTINI, G. & SEMB, G. 2006. A multicenter outcomes assessment of five-year-old patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 43, 253-8.
- FLYNN, T., MÖLLER, C., JÖNSSON, R. & LOHMANDER, A. 2009. The high prevalence of otitis media with effusion in children with cleft lip and palate as compared to children without clefts. *Int J Pediatr Otorhinolaryngol*, 73, 1441-6.
- FREITAS, J. A., ALMEIDA, A. L., SOARES, S., NEVES, L. T., GARIB, D. G., TRINDADE-SUEDAM, I. K., YAEDÚ, R. Y., LAURIS RDE, C., OLIVEIRA, T. M. & PINTO, J. H. 2013. Rehabilitative treatment of cleft lip and palate: experience of the Hospital for Rehabilitation of Craniofacial Anomalies/USP (HRAC/USP) - Part 4: oral rehabilitation. *J Appl Oral Sci*, 21, 284-92.
- FUDALEJ, P., KATSAROS, C., BONGAARTS, C., DUDKIEWICZ, Z. & KUIJPERS-JAGTMAN, A. M. 2011. Dental arch relationship in children with complete unilateral cleft lip and

- palate following one-stage and three-stage surgical protocols. *Clin Oral Investig*, 15, 503-10.
- FUDALEJ, P. S., WEGRODZKA, E., SEMB, G. & HORTIS-DZIERZBICKA, M. 2015. One-stage (Warsaw) and two-stage (Oslo) repair of unilateral cleft lip and palate: Craniofacial outcomes. *J Craniomaxillofac Surg*, 43, 1224-31.
- GAGGL, A., SCHULTES, G. & KÄRCHER, H. 1999. Aesthetic and Functional Outcome of Surgical and Orthodontic Correction of Bilateral Clefts of Lip, Palate, and Alveolus. *Cleft Palate Craniofac J*, 36, 407-412.
- GRAY, D. & MOSSEY, P. A. 2005. Evaluation of a modified Huddart/Bodenham scoring system for assessment of maxillary arch constriction in unilateral cleft lip and palate subjects. *Eur J Orthod*, 27, 507-511.
- GRAYSON, B. H. & CUTTING, C. B. 2001. Presurgical nasoalveolar orthopedic molding in primary correction of the nose, lip, and alveolus of infants born with unilateral and bilateral clefts. *Cleft Palate Craniofac J*, 38, 193-8.
- GRAYSON, B. H., SANTIAGO, P. E., BRECHT, L. E. & CUTTING, C. B. 1999. Presurgical nasoalveolar molding in infants with cleft lip and palate. *Cleft Palate Craniofac J*, 36, 486-98.
- GREWAL, S. S., PONDURI, S., LEARY, S. D., WREN, Y., THOMPSON, J. M. D., IRELAND, A. J., NESS, A. R. & SANDY, J. R. 2021. Educational Attainment of Children Born with Unilateral Cleft Lip and Palate in the United Kingdom. *Cleft Palate Craniofac J*, 58, 587-596.
- HAMEED, O., AMIN, N., HARIA, P., PATEL, B. & HAY, N. 2019. Orthodontic burden of care for patients with a cleft lip and/or palate. *J Orthod*, 46, 63-67.
- HAQUE, S., ALAM, M. K. & ARSHAD, A. I. 2015. An overview of indices used to measure treatment effectiveness in patients with cleft lip and palate. *Malays J Med Sci*, 22, 4-11.
- HARDWICKE, J. T., LANDINI, G. & RICHARD, B. M. 2014. Fistula incidence after primary cleft palate repair: a systematic review of the literature. *Plast Reconstr Surg*, 134, 618e-627e.
- HATHAWAY, R., DASKALOGIANNAKIS, J., MERCADO, A., RUSSELL, K., LONG, R. E., JR., COHEN, M., SEMB, G. & SHAW, W. 2011. The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 2. Dental arch relationships. *Cleft Palate Craniofac J*, 48, 244-51.
- HATHORN, I., ROBERTS-HARRY, D. & MARS, M. 1996. The Goslon yardstick applied to a consecutive series of patients with unilateral clefts of the lip and palate. *Cleft Palate Craniofac J*, 33, 494-6.

- HATHORN, I. S., ATTACK, N. E., BUTCHER, G., DICKSON, J., DURNING, P., HAMMOND, M., KNIGHT, H., MITCHELL, N., NIXON, F., SHINN, D. & SANDY, J. R. 2006. Centralization of Services: Standard Setting and Outcomes. *Cleft Palate Craniofac J*, 43, 401-405.
- HAY, N., PATEL, B., HARIA, P. & SOMMERLAD, B. 2018. Maxillary Growth in Cleft Lip and Palate Patients, With and Without Vomerine Flap Closure of the Hard Palate at the Time of Lip Repair: A Retrospective Analysis of Prospectively Collected Nonrandomized Data, With 10-Year Cephalometric Outcomes. *Cleft Palate Craniofac J*, 55, 1205-1210.
- HAYASHI, I., SAKUDA, M., TAKIMOTO, K. & MIYAZAKI, T. 1976. Craniofacial growth in complete unilateral cleft lip and palate: a roentgeno-cephalometric study. *Cleft Palate J*, 13, 215-37.
- HEIDBUCHEL, K. L. W. M. & KUIJPERS-JAGTMAN, A. M. 1997. Maxillary and Mandibular Dental-Arch Dimensions and Occlusion in Bilateral Cleft Lip and Palate Patients from 3 to 17 Years of Age. *Cleft Palate Craniofac J*, 34, 21-26.
- HEIDBUCHEL, K. L. W. M., KUIJPERS-JAGTMAN, A. M., VAN'T HOF, M. A., KRAMER, G. J. C. & PRAHL-ANDERSEN, B. 1998. Effects of early treatment on maxillary arch development in BCLP. A study on dental casts between 0 and 4 years of age. *Journal of Cranio-Maxillofacial Surgery*, 26, 140-147.
- HELIÖVAARA, A., KÜSELER, A., SKAARE, P., BELLARDIE, H., MØLSTED, K., KARSTEN, A., MARCUSSON, A., RIZELL, S., BRINCK, E., SÆLE, P., CHALIEN, M. N., MOONEY, J., EYRES, P., SHAW, W. & SEMB, G. 2022. Scandcleft randomized trials of primary surgery for unilateral cleft lip and palate: comparison of dental arch relationships and dental indices at 5, 8, and 10 years. *Eur J Orthod*, 44, 258-267.
- HODGKINSON, P. D., BROWN, S., DUNCAN, D., GRANT, C., MCNAUGHTON, A. M. Y., THOMAS, P. & MATTICK, C. R. 2005. Management of children with cleft lip and palate: a review describing the application of multidisciplinary team working in this condition based upon the experiences of a regional cleft lip and palate centre in the United Kingdom. *Fetal and Maternal Medicine Review*, 16, 1-27.
- HUDDART, A. G. & BODENHAM, R. S. 1972. The evaluation of arch form and occlusion in unilateral cleft palate subjects. *Cleft Palate J*, 9, 194-209.
- JEONG, I.-D., LEE, J.-J., JEON, J.-H., KIM, J.-H., KIM, H.-Y. & KIM, W.-C. 2016. Accuracy of complete-arch model using an intraoral video scanner: An in vitro study. *The Journal of Prosthetic Dentistry*, 115, 755-759.
- EZEWSKI, P. A., VIEIRA, A. R., NISHIMURA, C., LUDWIG, B., JOHNSON, M., O'BRIEN, S. E., DAACK-HIRSCH, S., SCHULTZ, R. E., WEBER, A., NEPOMUCENA, B., ROMITTI, P. A., CHRISTENSEN, K., ORIOLI, I. M., CASTILLA, E. E., MACHIDA, J., NATSUME, N. &

- MURRAY, J. C. 2003. Complete sequencing shows a role for MSX1 in non-syndromic cleft lip and palate. *J Med Genet*, 40, 399-407.
- JIANG, R., BUSH, J. O. & LIDRAL, A. C. 2006. Development of the upper lip: morphogenetic and molecular mechanisms. *Dev Dyn*, 235, 1152-66.
- JOHNSON, C. Y. & LITTLE, J. 2008. Folate intake, markers of folate status and oral clefts: is the evidence converging? *Int J Epidemiol*, 37, 1041-58.
- JOHNSON, N., WILLIAMS, A. C., SINGER, S., SOUTHALL, P., ATTACK, N. & SANDY, J. R. 2000. Dentoalveolar relations in children born with a unilateral cleft lip and palate (UCLP) in Western Australia. *Cleft Palate Craniofac J*, 37, 12-6.
- JONES, T., AL-GHATAM, R., ATTACK, N., DEACON, S., POWER, R., ALBERY, L., IRELAND, T. & SANDY, J. 2014. A review of outcome measures used in cleft care. *J Orthod*, 41, 128-40.
- JONES, T., LEARY, S., ATTACK, N., IRELAND, T. & SANDY, J. 2016. Which index should be used to measure primary surgical outcome for unilateral cleft lip and palate patients? *Eur J Orthod*, 38, 345-352.
- KANE, S. P. 2018. *Clinical tools and calculators for medical professionals - ClinCalc* [Online]. Available: <https://clincalc.com/>. [Accessed 07/08/2023].
- KARSTEN, A., MARCUSSON, A., HURMERINTA, K., HELIÖVAARA, A., KÜSELER, A., SKAARE, P., BELLARDIE, H., RØNNING, E., SHAW, W., MØLSTED, K., SÆLE, P., BRINCK, E., RIZELL, S., NAJAL CHALIER, M., EYRES, P. & SEMB, G. 2017. Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 7. Occlusion in 5 year-olds according to the Huddart and Bodenham index. *J Plast Surg Hand Surg*, 51, 58-63.
- KERNAHAN, D. A. & STARK, R. B. 1958. A new classification for cleft lip and cleft palate. *Plastic and Reconstructive Surgery*, 22, 435-441.
- KHANNA, R., LAKHANPAUL, M. & BULL, P. D. 2008. Surgical management of otitis media with effusion in children: summary of NICE guidance. *Clin Otolaryngol*, 33, 600-5.
- KLASSEN, A. F., TSANGARIS, E., FORREST, C. R., WONG, K. W. Y., PUSIC, A. L., CANO, S. J., SYED, I., DUA, M., KAINTH, S., JOHNSON, J. & GOODACRE, T. 2012. Quality of life of children treated for cleft lip and/or palate: A systematic review. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, 65, 547-557.
- KONDO, S., SCHUTTE, B. C., RICHARDSON, R. J., BJORK, B. C., KNIGHT, A. S., WATANABE, Y., HOWARD, E., DE LIMA, R. L., DAACK-HIRSCH, S., SANDER, A., MCDONALD-MCGINN, D. M., ZACKAI, E. H., LAMMER, E. J., AYLSWORTH, A. S., ARDINGER, H. H., LIDRAL, A. C., POBER, B. R., MORENO, L., ARCOS-BURGOS, M., VALENCIA, C., HOUDAYER, C., BAHUAU, M., MORETTI-FERREIRA, D., RICHIERI-COSTA, A., DIXON, M. J. & MURRAY,

- J. C. 2002. Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. *Nat Genet*, 32, 285-9.
- KOO, T. K. & LI, M. Y. 2016. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med*, 15, 155-63.
- KORNBLUTH, M., CAMPBELL, R. E., DASKALOGIANNAKIS, J., ROSS, E. J., GLICK, P. H., RUSSELL, K. A., DOUCET, J. C., HATHAWAY, R. R., LONG, R. E., JR. & SITZMAN, T. J. 2018. Active Presurgical Infant Orthopedics for Unilateral Cleft Lip and Palate: Intercenter Outcome Comparison of Latham, Modified McNeil, and Nasoalveolar Molding. *Cleft Palate Craniofac J*, 55, 639-648.
- KOUL, R. 2007. Describing cleft lip and palate using a new expression system. *Cleft Palate Craniofac J*, 44, 585-9.
- KOZELJ, V. 2000. The basis for presurgical orthopedic treatment of infants with unilateral complete cleft lip and palate. *Cleft Palate Craniofac J*, 37, 26-32.
- KUANG, W., AARTS, M., KUIJPERS-JAGTMAN, A. M., HE, H. & ONGKOSUWITO, E. M. 2021. Treatment Outcome in Bilateral Cleft lip and Palate Patients Evaluated With the Huddart-Bodenham Scoring System and the Bilateral Cleft lip and Palate Yardstick: A Systematic Review. *Cleft Palate Craniofac J*, 10556656211041883.
- KUIJPERS-JAGTMAN, A. M. & PRAHL-ANDERSEN, B. History of Neonatal Maxillary Orthopedics: Past to Present. 2006.
- LAN, Y., XU, J. & JIANG, R. 2015. Cellular and Molecular Mechanisms of Palatogenesis. *Current topics in developmental biology*, 115, 59-84.
- LARSON, M., SÄLLSTRÖM, K. O., LARSON, O., MCWILLIAM, J. & IDEBERG, M. 1993. Morphologic effect of preoperative maxillofacial orthopedics (T-traction) on the maxilla in unilateral cleft lip and palate patients. *Cleft Palate Craniofac J*, 30, 29-34.
- LARSON, O. & NILSSON, B. 1983. Early bone grafting in complete cleft lip and palate cases following maxillofacial orthopedics. VI. Assessments from photographs and anthropometric measurements. *Scand J Plast Reconstr Surg*, 17, 209-23.
- LAURICE ANN, B. C. 2018. Cleft Beyond the Lip and Palate: A Bilateral Tessier Cleft. 33.
- LEMOES, L. S., REBELLO, I. M., VOGEL, C. J. & BARBOSA, M. C. 2015. Reliability of measurements made on scanned cast models using the 3 Shape R 700 scanner. *Dentomaxillofac Radiol*, 44, 20140337.
- LI, Y., SHI, B., SONG, Q. G., ZUO, H. & ZHENG, Q. 2006. Effects of lip repair on maxillary growth and facial soft tissue development in patients with a complete unilateral cleft of lip, alveolus and palate. *J Craniomaxillofac Surg*, 34, 355-61.

- LIDRAL, A. C. & MURRAY, J. C. 2004. Genetic approaches to identify disease genes for birth defects with cleft lip/palate as a model. *Birth Defects Res A Clin Mol Teratol*, 70, 893-901.
- LITTLE, J., CARDY, A. & MUNGER, R. G. 2004. Tobacco smoking and oral clefts: a meta-analysis. *Bull World Health Organ*, 82, 213-8.
- LITTLEWOOD, S.J., MITCHELL, L., LEWIS, B.R.K., BARBER, S.K. AND JENKINS, F.R. (2019). *An introduction to orthodontics*. Oxford, United Kingdom: Oxford University Press.
- LIU, X. & CHEN, Z. 2018. Effects of Palate Repair on Cranial Base and Maxillary Morphology in Patients With Unilateral Complete Cleft Lip and Palate. *Cleft Palate Craniofac J*, 55, 1367-1374.
- LÓPEZ-CAMELO, J. S., CASTILLA, E. E. & ORIOLI, I. M. 2010. Folic acid flour fortification: impact on the frequencies of 52 congenital anomaly types in three South American countries. *Am J Med Genet A*, 152a, 2444-58.
- MAARSE, W., PISTORIUS, L. R., VAN EETEN, W. K., BREUGEM, C. C., KON, M., VAN DEN BOOGAARD, M. J. & MINK VAN DER MOLEN, A. B. 2011. Prenatal ultrasound screening for orofacial clefts. *Ultrasound Obstet Gynecol*, 38, 434-9.
- MANDAL, E., FILIP, C., ANDERSSON, M. E. & ØGAARD, B. 2019. Eighteen-Year Follow-Up of 160 Consecutive Individuals Born With Unilateral Cleft Lip or Cleft Lip and Alveolus Treated by the Oslo Cleft Lip and Palate Team. *Cleft Palate Craniofac J*, 56, 853-859.
- MANGOLD, E., LUDWIG, K. U., BIRNBAUM, S., BALUARDO, C., FERRIAN, M., HERMS, S., REUTTER, H., DE ASSIS, N. A., CHAWA, T. A., MATTHEISEN, M., STEFFENS, M., BARTH, S., KLUCK, N., PAUL, A., BECKER, J., LAUSTER, C., SCHMIDT, G., BRAUMANN, B., SCHEER, M., REICH, R. H., HEMPRICH, A., PÖTZSCH, S., BLAUMEISER, B., MOEBUS, S., KRAWCZAK, M., SCHREIBER, S., MEITINGER, T., WICHMANN, H.-E., STEEGERS-THEUNISSEN, R. P., KRAMER, F.-J., CICHON, S., PROPPING, P., WIENKER, T. F., KNAPP, M., RUBINI, M., MOSSEY, P. A., HOFFMANN, P. & NÖTHEN, M. M. 2010. Genome-wide association study identifies two susceptibility loci for nonsyndromic cleft lip with or without cleft palate. *Nature Genetics*, 42, 24-26.
- MANOSUDPRASIT, M., WANGSRIMONGKOL, T., KITSAHAWONG, S. & THIENKOSOL, T. 2011. Comparison of the modified Huddart/Bodenham and GOSLON yardstick methods for assessing outcomes following primary surgery for unilateral cleft lip and palate. *J Med Assoc Thai*, 94 Suppl 6, S15-20.
- MARS, M., ASHER-MCDADE, C., BRATTSTRÖM, V., DAHL, E., MCWILLIAM, J., MØLSTED, K., PLINT, D. A., PRAHL-ANDERSEN, B., SEMB, G., SHAW, W. C. & ET AL. 1992. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 3. Dental arch relationships. *Cleft Palate Craniofac J*, 29, 405-8.

- MARS, M., BATRA, P. & WORRELL, E. 2006. Complete unilateral cleft lip and palate: validity of the five-year index and the Goslon yardstick in predicting long-term dental arch relationships. *Cleft Palate Craniofac J*, 43, 557-62.
- MARS, M. & HOUSTON, W. J. B. 1990. A Preliminary Study of Facial Growth and Morphology in Unoperated Male Unilateral Cleft Lip and Palate Subjects over 13 Years of Age. *Cleft Palate Journal*, 27, 7-10.
- MARS, M., PLINT, D. A., HOUSTON, W. J., BERGLAND, O. & SEMB, G. 1987. The Goslon Yardstick: a new system of assessing dental arch relationships in children with unilateral clefts of the lip and palate. *Cleft Palate J*, 24, 314-22.
- MARTIN, C. B., MA, X., MCINTYRE, G. T., WANG, W., LIN, P., CHALMERS, E. V. & MOSSEY, P. A. 2016. The validity and reliability of an automated method of scoring dental arch relationships in unilateral cleft lip and palate using the modified Huddart-Bodenham scoring system. *Eur J Orthod*, 38, 353-8.
- MARTIN, S. V., VAN EEDEN, S. & SWAN, M. C. 2023. The role of primary surgery in the management of orofacial clefting. *Br Dent J*, 234, 859-866.
- MCCANCE, A. M., ROBERTS-HARRY, D., SHERRIFF, M., MARS, M. & HOUSTON, W. J. 1990. A study model analysis of adult unoperated Sri Lankans with unilateral cleft lip and palate. *Cleft Palate J*, 27, 146-54; discussion 174-5.
- MEYER, K. A., WERLER, M. M., HAYES, C. & MITCHELL, A. A. 2003. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study. *Birth Defects Res A Clin Mol Teratol*, 67, 509-14.
- MIKOYA, T., SHIBUKAWA, T., SUSAMI, T., SATO, Y., TENGAN, T., KATASHIMA, H., OYAMA, A., MATSUZAWA, Y., ITO, Y. & FUNAYAMA, E. 2015. Dental arch relationship outcomes in one- and two-stage palatoplasty for Japanese patients with complete unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 52, 277-86.
- MILLARD, D. R., LATHAM, R., HUIFEN, X., SPIRO, S. & MOROVIC, C. 1999. Cleft lip and palate treated by presurgical orthopedics, gingivoperiosteoplasty, and lip adhesion (POPLA) compared with previous lip adhesion method: a preliminary study of serial dental casts. *Plast Reconstr Surg*, 103, 1630-44.
- MILLARD, D. R., JR. & LATHAM, R. A. 1990. Improved primary surgical and dental treatment of clefts. *Plast Reconstr Surg*, 86, 856-71.
- MINK VAN DER MOLEN, A. B., MAARSE, W., PISTORIUS, L., DE VEYE, H. S. & BREUGEM, C. C. 2011. Prenatal screening for orofacial clefts in the Netherlands: a preliminary report on the impact of a national screening system. *Cleft Palate Craniofac J*, 48, 183-9.

- MITTAL, T. K., IRELAND, A. J., ATTACK, N. E., LEARY, S. D., RUSSELL, J. I., DEACON, S. A., NESS, A. R. & SANDY, J. R. 2019. Outcome Measures in UCLP: The Modified 5-Year-Olds'-Index-Development and Reliability. *Cleft Palate Craniofac J*, 56, 248-256.
- MØLSTED, K., BRATTSTRÖM, V., PRAHL-ANDERSEN, B., SHAW, W. C. & SEMB, G. 2005. The Eurocleft Study: Intercenter Study of Treatment Outcome in Patients with Complete Cleft Lip and Palate. Part 3: Dental Arch Relationships. *Cleft Palate Craniofac J*, 42, 78-82.
- MOLYNEAUX, C., SHERRIFF, M., WREN, Y., IRELAND, A. & SANDY, J. 2022. Changes in the Transverse Dimension of the Maxillary Arch of 5-Year-Olds Born With UCLP Since the Introduction of Nationwide Guidance. *Cleft Palate Craniofac J*, 59, 1064-1071.
- MORRIS, T., ROBERTS, C. & SHAW, W. C. 1994. Incisal overjet as an outcome measure in unilateral cleft lip and palate management. *Cleft Palate Craniofac J*, 31, 142-5.
- MOSSEY, P. A., CLARK, J. D. & GRAY, D. 2003. Preliminary investigation of a modified Huddart/Bodenham scoring system for assessment of maxillary arch constriction in unilateral cleft lip and palate subjects. *Eur J Orthod*, 25, 251-257.
- MURRAY, J. J. 2003. Cleft lip and palate services. A review of developments five years after the CSAG report. *International journal of paediatric dentistry*, 13, 395-402.
- NAGASE, Y., NATSUME, N., KATO, T. & HAYAKAWA, T. 2010. Epidemiological Analysis of Cleft Lip and/or Palate by Cleft Pattern. *J Maxillofac Oral Surg*, 9, 389-95.
- NAZER, J., HUBNER, M. E., CATALÁN, J. & CIFUENTES, L. 2001. [Incidence of the cleft lip and palate in the University of Chile Maternity Hospital and in maternity Chilean participating in the Latin American Collaborative Study of Congenital Malformations (ECLAMC)]. *Rev Med Chil*, 129, 285-93
- NESS, A. R., WILLS, A. K., MAHMOUD, O., HALL, A., SELL, D., SMALLRIDGE, J., SOUTHBY, L., STOKES, D., TOMS, S., WAYLEN, A., WREN, Y. & SANDY, J. R. 2017. Centre-level variation in treatment and outcomes and predictors of outcomes in 5-year-old children with non-syndromic unilateral cleft lip treated within a centralized service: the Cleft Care UK study. Part 6: summary and implications. *Orthod Craniofac Res*, 20 Suppl 2, 48-51.
- NOPOULOS, P., BERG, S., VANDEMARK, D., RICHMAN, L., CANADY, J. & ANDREASEN, N. C. 2001. Increased incidence of a midline brain anomaly in patients with nonsyndromic clefts of the lip and/or palate. *J Neuroimaging*, 11, 418-24.
- NOPOULOS, P., LANGBEHN, D. R., CANADY, J., MAGNOTTA, V. & RICHMAN, L. 2007. Abnormal brain structure in children with isolated clefts of the lip or palate. *Arch Pediatr Adolesc Med*, 161, 753-8.

- NOVERRAZ, A. E., KUIJPERS-JAGTMAN, A. M., MARS, M. & VAN'T HOF, M. A. 1993. Timing of hard palate closure and dental arch relationships in unilateral cleft lip and palate patients: a mixed-longitudinal study. *Cleft Palate Craniofac J*, 30, 391-6.
- OZAWA, T. O., DUTKA, J. C. R., GARIB, D., LAURIS, R., ALMEIDA, A. M., BROSCO, T. V. S., LAURIS, J. R. P., DOLCE, C. & PEGORARO-KROOK, M. I. 2021. Influence of surgical technique and timing of primary repair on interarch relationship in UCLP: A randomized clinical trial. *Orthod Craniofac Res*, 24, 288-295.
- OZAWA, T. O., SHAW, W. C., KATSAROS, C., KUIJPERS-JAGTMAN, A. M., HAGBERG, C., RØNNING, E. & SEMB, G. 2011. A new yardstick for rating dental arch relationship in patients with complete bilateral cleft lip and palate. *Cleft Palate Craniofac J*, 48, 167-72.
- PAPADOPOULOS, M. A., KOUMPRIDOU, E. N., VAKALIS, M. L. & PAPAGEORGIOU, S. N. 2012. Effectiveness of pre-surgical infant orthopedic treatment for cleft lip and palate patients: a systematic review and meta-analysis. *Orthod Craniofac Res*, 15, 207-36.
- PARK-WYLLIE, L., MAZZOTTA, P., PASTUSZAK, A., MORETTI, M. E., BEIQUE, L., HUNNISETT, L., FRIESEN, M. H., JACOBSON, S., KASAPINOVIC, S., CHANG, D., DIAV-CITRIN, O., CHITAYAT, D., NULMAN, I., EINARSON, T. R. & KOREN, G. 2000. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*, 62, 385-92.
- PECYNA, P. M., FEENEY-GIACOMA, M. E. & NEIMAN, G. S. 1987. Development of the object permanence concept in cleft lip and palate and noncleft lip and palate infants. *J Commun Disord*, 20, 233-43.
- PEGELOW, M., RIZELL, S., KARSTEN, A., MARK, H., LILJA, J., CHALIEN, M. N., LEMBERGER, M., PETERSON, P., FITZSIMONS, K., DEACON, S., MEDINA, J., CALVERT, M. & MARS, M. 2021. Reliability and Predictive Validity of Dental Arch Relationships Using the 5-Year-Olds' Index and the GOSLON Yardstick to Determine Facial Growth. *Cleft Palate Craniofac J*, 58, 619-627.
- PERSSON, M., BECKER, M. & SVENSSON, H. 2008. General intellectual capacity of young men with cleft lip with or without cleft palate and cleft palate alone. *Scand J Plast Reconstr Surg Hand Surg*, 42, 14-6.
- PERSSON, M., SANDY, J. R., WAYLEN, A., WILLS, A. K., AL-GHATAM, R., IRELAND, A. J., HALL, A. J., HOLLINGWORTH, W., JONES, T., PETERS, T. J., PRESTON, R., SELL, D., SMALLRIDGE, J., WORTHINGTON, H. & NESS, A. R. 2015. A cross-sectional survey of 5-year-old children with non-syndromic unilateral cleft lip and palate: the Cleft Care UK study. Part 1: background and methodology. *Orthod Craniofac Res*, 18 Suppl 2, 1-13.
- PRAHL, C., KUIJPERS-JAGTMAN, A. M., VAN'T HOF, M. A. & PRAHL-ANDERSEN, B. 2001. A randomised prospective clinical trial into the effect of infant orthopaedics on

- maxillary arch dimensions in unilateral cleft lip and palate (Dutchcleft). *Eur J Oral Sci*, 109, 297-305.
- RAHIMOV, F., MARAZITA, M. L., VISEL, A., COOPER, M. E., HITCHLER, M. J., RUBINI, M., DOMANN, F. E., GOVIL, M., CHRISTENSEN, K., BILLE, C., MELBYE, M., JUGESSUR, A., LIE, R. T., WILCOX, A. J., FITZPATRICK, D. R., GREEN, E. D., MOSSEY, P. A., LITTLE, J., STEEGERS-THEUNISSEN, R. P., PENNACCHIO, L. A., SCHUTTE, B. C. & MURRAY, J. C. 2008. Disruption of an AP-2alpha binding site in an IRF6 enhancer is associated with cleft lip. *Nature genetics*, 40, 1341-1347.
- RANTA, R. 1986. A review of tooth formation in children with cleft lip/palate. *Am J Orthod Dentofacial Orthop*, 90, 11-8.
- RAUTIO, J., ANDERSEN, M., BOLUND, S., HUKKI, J., VINDENES, H., DAVENPORT, P., ARCTANDER, K., LARSON, O., BERGGREN, A., ÅBYHOLM, F., WHITBY, D., LEONARD, A., LILJA, J., NEOVIUS, E., ELANDER, A., HELIÖVAARA, A., EYRES, P. & SEMB, G. 2017. Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 2. Surgical results. *J Plast Surg Hand Surg*, 51, 14-20.
- RAY, J. G., MEIER, C., VERMEULEN, M. J., WYATT, P. R. & COLE, D. E. 2003. Association between folic acid food fortification and congenital orofacial clefts. *J Pediatr*, 143, 805-7.
- REISER, E., SKOOG, V., GERDIN, B. & ANDLIN-SOBOCKI, A. 2010. Association between cleft size and crossbite in children with cleft palate and unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 47, 175-81.
- REVINGTON, P. J., MCNAMARA, C., MUKARRAM, S., PERERA, E., SHAH, H. V. & DEACON, S. A. 2010. Alveolar bone grafting: results of a national outcome study. *Ann R Coll Surg Engl*, 92, 643-6.
- RICHARDS, A. J., YATES, J. R., WILLIAMS, R., PAYNE, S. J., POPE, F. M., SCOTT, J. D. & SNEAD, M. P. 1996. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in alpha 1 (XI) collagen. *Hum Mol Genet*, 5, 1339-43.
- ROBERTS, R. M., MATHIAS, J. L. & WHEATON, P. 2012. Cognitive functioning in children and adults with nonsyndromal cleft lip and/or palate: a meta-analysis. *J Pediatr Psychol*, 37, 786-97.
- ROBERTS-HARRY, D. & SANDY, J. R. 1992. Repair of cleft lip and palate: 1. Surgical techniques. *Dent Update*, 19, 418-23.
- ROMITTI, P. A., LIDRAL, A. C., MUNGER, R. G., DAACK-HIRSCH, S., BURNS, T. L. & MURRAY, J. C. 1999. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment

- interactions from a population-based case-control study of orofacial clefts. *Teratology*, 59, 39-50.
- ROMITTI, P. A., SUN, L., HONEIN, M. A., REEFHUIS, J., CORREA, A. & RASMUSSEN, S. A. 2007. Maternal periconceptional alcohol consumption and risk of orofacial clefts. *Am J Epidemiol*, 166, 775-85.
- ROSS, R. B. 1987. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. *Cleft Palate J*, 24, 5-77.
- SANDY, J., RUMSEY, N., PERSSON, M., WAYLEN, A., KILPATRICK, N., IRELAND, T. & NESS, A. 2012. Using service rationalisation to build a research network: lessons from the centralisation of UK services for children with cleft lip and palate. *British Dental Journal*, 212, 553-555.
- SANDY, J. R. 2003. Molecular, clinical and political approaches to the problem of cleft lip and palate. *The Surgeon*, 1, 9-16.
- SCHWARTZ, S., KAPALA, J. T., RAJCHGOT, H. & ROBERTS, G. L. 1993. Accurate and systematic numerical recording system for the identification of various types of lip and maxillary clefts (RPL system). *Cleft Palate Craniofac J*, 30, 330-2.
- SCOTT, J. K., LEARY, S. D., NESS, A. R., SANDY, J. R., PERSSON, M., KILPATRICK, N. & WAYLEN, A. E. 2014. Centralization of services for children born with orofacial clefts in the United kingdom: a cross-sectional survey. *Cleft Palate Craniofac J*, 51, e102-9.
- SCOTT, J. K., LEARY, S. D., NESS, A. R., SANDY, J. R., PERSSON, M., KILPATRICK, N. & WAYLEN, A. E. 2015. Perceptions of team members working in cleft services in the United kingdom: a pilot study. *Cleft Palate Craniofac J*, 52, e1-7.
- SELL, D., MILDINHALL, S., ALBERY, L., WILLS, A. K., SANDY, J. R. & NESS, A. R. 2015. The Cleft Care UK study. Part 4: perceptual speech outcomes. *Orthod Craniofac Res*, 18 Suppl 2, 36-46.
- SEVERENS, J. L., PRAHL, C., KUIJPERS-JAGTMAN, A. M. & PRAHL-ANDERSEN, B. 1998. Short-term cost-effectiveness analysis of presurgical orthopedic treatment in children with complete unilateral cleft lip and palate. *Cleft Palate Craniofac J*, 35, 222-6.
- SHAW, G. M., WASSERMAN, C. R., LAMMER, E. J., O'MALLEY, C. D., MURRAY, J. C., BASART, A. M. & TOLAROVA, M. M. 1996. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. *American journal of human genetics*, 58, 551-561.
- SHAW, G. M., WASSERMAN, C. R., O'MALLEY, C. D., LAMMER, E. J. & FINNELL, R. H. 1995. Orofacial clefts and maternal anticonvulsant use. *Reprod Toxicol*, 9, 97-8.
- SHAW, W. C., DAHL, E., ASHER-MCDADE, C., BRATTSTRÖM, V., MARS, M., MCWILLIAM, J., MØLSTED, K., PLINT, D. A., PRAHL-ANDERSEN, B., ROBERTS, C. & ET AL. 1992. A six-

- center international study of treatment outcome in patients with clefts of the lip and palate: Part 5. General discussion and conclusions. *Cleft Palate Craniofac J*, 29, 413-8.
- SHAW, W.C., ASHER-MCDADE, C., BRATTSTRÖM, V., DAHL, E., MCWILLIAM, J., MØLSTED, K., PLINT, D.A., ORTH, D., PRAHL-ANDERSEN, B., SEMB, G. AND THE, R.P.S. (1992). A Six-Center International Study of Treatment Outcome in Patients with Clefts of the Lip and Palate: Part 1. Principles and Study Design. *The Cleft Palate-Craniofacial Journal*, 29(5), pp.393–397. doi:https://doi.org/10.1597/1545-1569_1992_029_0393_asciso_2.3.co_2.
- SHAW, W. C. & SEMB, G. 1990. Current approaches to the orthodontic management of cleft lip and palate. *Journal of the Royal Society of Medicine*, 83, 30-33.
- SHETTY, V., AGRAWAL, R. K. & SAILER, H. F. 2017. Long-term effect of presurgical nasoalveolar molding on growth of maxillary arch in unilateral cleft lip and palate: randomized controlled trial. *Int J Oral Maxillofac Surg*, 46, 977-987.
- SHROUT, P. E. & FLEISS, J. L. 1979. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*, 86, 420-8.
- SIEGENTHALER, M., BETTELINI, L., BRUDNICKI, A., RACHWALSKI, M. & FUDALEJ, P. S. 2018. Early versus late alveolar bone grafting in unilateral cleft lip and palate: Dental arch relationships in pre-adolescent patients. *Journal of Cranio-Maxillofacial Surgery*, 46, 2052-2057.
- SLATOR, R., PERISANIDOU, L. I., SELL, D., SANDY, J., NESS, A. R. & WILLS, A. K. 2023. Surgical sequence, timing and volume, and variation in dento-facial outcome, speech and secondary surgery in children with unilateral cleft lip and palate: The Cleft Care UK Study. *Orthod Craniofac Res*, 26, 297-309.
- SMALLRIDGE, J., HALL, A. J., CHORBACHI, R., PERFECT, V., PERSSON, M., IRELAND, A. J., WILLS, A. K., NESS, A. R. & SANDY, J. R. 2015. Functional outcomes in the Cleft Care UK study--Part 3: oral health and audiology. *Orthod Craniofac Res*, 18 Suppl 2, 25-35.
- SMARIUS, B., LOOZEN, C., MANTEN, W., BEKKER, M., PISTORIUS, L. & BREUGEM, C. 2017. Accurate diagnosis of prenatal cleft lip/palate by understanding the embryology. *World journal of methodology*, 7, 93-100.
- SOMMERLAD, B. C. 2003. A technique for cleft palate repair. *Plast Reconstr Surg*, 112, 1542-8
- SOUTHALL, P., WALTERS, M. & SINGER, S. 2012. The influence of orthodontic treatment on the Goslon score of unilateral cleft lip and palate patients. *Cleft Palate Craniofac J*, 49, 215-20.
- SPRITZ, R. A. 2001. The genetics and epigenetics of orofacial clefts. *Curr Opin Pediatr*, 13, 556-6

- SUZUKI, K., HU, D., BUSTOS, T., ZLOTOGORA, J., RICHIERI-COSTA, A., HELMS, J. A. & SPRITZ, R. A. 2000. Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. *Nat Genet*, 25, 427-30.
- TANNURE, P. N., OLIVEIRA, C. A., MAIA, L. C., VIEIRA, A. R., GRANJEIRO, J. M. & COSTA MDE, C. 2012. Prevalence of dental anomalies in nonsyndromic individuals with cleft lip and palate: a systematic review and meta-analysis. *Cleft Palate Craniofac J*, 49, 194-200.
- TOTHILL, C. & MOSSEY, P. A. 2007. Assessment of arch constriction in patients with bilateral cleft lip and palate and isolated cleft palate: a pilot study. *Eur J Orthod*, 29, 193-197.
- UZEL, A. & ALPARSLAN, Z. N. 2011. Long-term effects of presurgical infant orthopedics in patients with cleft lip and palate: a systematic review. *Cleft Palate Craniofac J*, 48, 587-95.
- VAN DEN BOOGAARD, M.-J. H., DORLAND, M., BEEMER, F. A. & VAN AMSTEL, H. K. P. 2000. MSX1 mutation is associated with orofacial clefting and tooth agenesis in humans. *Nature Genetics*, 24, 342-343.
- WAYLEN, A., NESS, A. R., WILLS, A. K., PERSSON, M., RUMSEY, N. & SANDY, J. R. 2015. Cleft Care UK study. Part 5: child psychosocial outcomes and satisfaction with cleft services. *Orthod Craniofac Res*, 18 Suppl 2, 47-55.
- WEHBY, G. L. & CASSELL, C. H. 2010. The impact of orofacial clefts on quality of life and healthcare use and costs. *Oral Dis*, 16, 3-10.
- WEHBY, G. L. & MURRAY, J. C. 2010. Folic acid and orofacial clefts: a review of the evidence. *Oral Dis*, 16, 11-9.
- WILCOX, A. J., LIE, R. T., SOLVOLL, K., TAYLOR, J., MCCONNAUGHEY, D. R., ABYHOLM, F., VINDENES, H., VOLLSET, S. E. & DREVON, C. A. 2007. Folic acid supplements and risk of facial clefts: national population based case-control study. *Bmj*, 334, 464.
- WILLIAMS, A. C., BEARN, D., MILDINHALL, S., MURPHY, T., SELL, D., SHAW, W. C., MURRAY, J. J. & SANDY, J. R. 2001. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 2: dentofacial outcomes and patient satisfaction. *Cleft Palate Craniofac J*, 38, 24-9.
- WILLIAMS, A. C., SHAW, W. C., SANDY, J. R. & BRENDAN DEVLIN, H. 1996. The surgical care of cleft lip and palate patients in England and Wales. *British Journal of Plastic Surgery*, 49, 150-155.
- WOODSEND, B., KOUFOUDAKI, E., LIN, P., MCINTYRE, G., EL-ANGBAWI, A., AZIZ, A., SHAW, W., SEMB, G., REESU, G. V. & MOSSEY, P. A. 2022. Development of intra-oral

automated landmark recognition (ALR) for dental and occlusal outcome measurements. *Eur J Orthod*, 44, 43-50.

WORTH, V., PERRY, R., IRELAND, T., WILLS, A. K., SANDY, J. & NESS, A. 2017. Are people with an orofacial cleft at a higher risk of dental caries? A systematic review and meta-analysis. *Br Dent J*, 223, 37-47.

YANG, A. S., RICHARD, B. M., WILLS, A. K., MAHMOUD, O., SANDY, J. R. & NESS, A. R. 2020. Closer to the Truth on National Fistula Prevalence After Unilateral Complete Cleft Lip and Palate Repair? The Cleft Care UK Study. *The Cleft Palate Craniofacial Journal*, 57, 5-13.

YAZDY, M. M., HONEIN, M. A. & XING, J. 2007. Reduction in orofacial clefts following folic acid fortification of the U.S. grain supply. *Birth Defects Res A Clin Mol Teratol*, 79, 16-23.

YOUNG, J. L., O'RIORDAN, M., GOLDSTEIN, J. A. & ROBIN, N. H. 2001. What information do parents of newborns with cleft lip, palate, or both want to know? *Cleft Palate Craniofac J*, 38, 55-8.

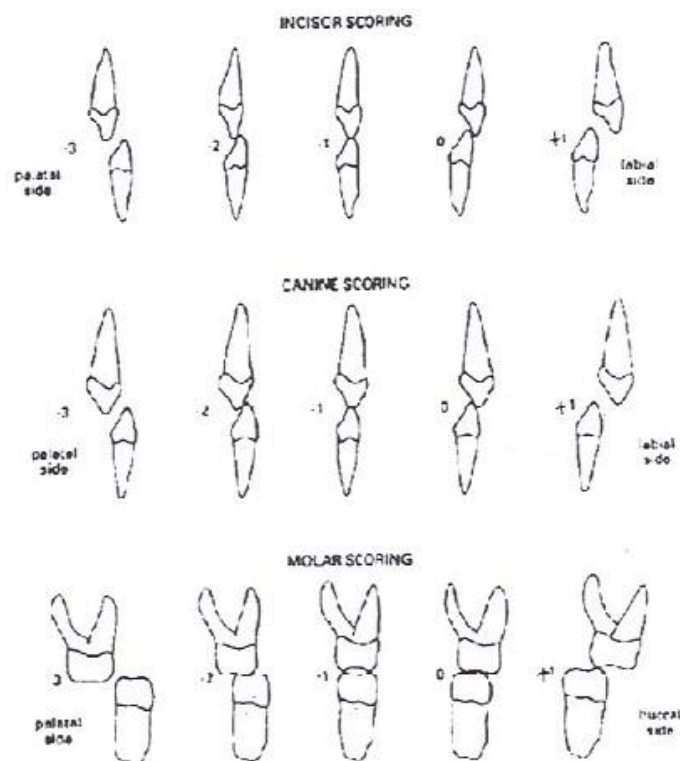
ZARONE, F., RUGGIERO, G., FERRARI, M., MANGANO, F., JODA, T. & SORRENTINO, R. 2020. Accuracy of a chairside intraoral scanner compared with a laboratory scanner for the completely edentulous maxilla: An in vitro 3-dimensional comparative analysis. *J Prosthet Dent*, 124, 761.e1-761.e7.

Appendices

Appendix I – Guidance on using the Modified Huddart- Bodenham Index given to assessors.

Guidance on using the modified Huddart/Bodenham scoring system

This system uses the frequency and severity of crossbite of the dental occlusion to evaluate maxillary arch constriction in the labial and buccal segments. Each maxillary tooth is scored according to its relationship with the corresponding tooth in the mandible. The diagram below shows the scores which should be assigned to each tooth depending on its relationship with its opposing tooth.



Use for 5 year olds

For scoring the models of five year olds, the A's, C's, D's and E's should all be assigned a score. The B's are omitted from the scoring. When one central incisor is missing, the other central incisor should be used to assign the score. If any other teeth are missing then the score should be determined by the mid-point of the maxillary alveolar ridge. The first permanent molars should not be scored even if they are erupted. The sum of all eight individual scores should produce a total score for each model between +8 and -24.

Appendix II: Screenshot of no ethical approval was needed to conduct this study.

Research Ethics Applications

Work Area

Contacts

Help

Dr Batol Alattar (gp20177@bristol.ac.uk)

Previous

Next

Navigate

View as PDF

Documents

Signatures

Save

Share

Collaborators

Completeness Check

Submit

University of Bristol Research Ethics Application

11470

Version: 1.31

Project Title: An investigation into transverse interdental arch outcomes of 5-Year-Olds born with a UCLP following the centralisation of cleft services within the UK.

Further ethics checklist information

Based on your responses to the checklist questions, your research ethics application has qualified for an expedited research ethics checklist review.

This means that a full research ethics application is not required at this stage and your application does not need to go to the full research ethics committee for review.

To ensure that your research ethics checklist ethics application is reviewed the following further information is required.

Please ensure that **all participant facing study documentation** has been provided for review.

Appendix III: Cleft Care data access approval

Sam Leary

To: Batol Alattar; cleftcareuk@uhbw.nhs.uk

Cc: Peter Fowler; Stu Toms; Shirley Jenkins; Vanessa Marshall

  Reply  Reply all  Forward    ...

Thu 17/03/2022 14:58

Batol,

Thank you for the submission of your proposal, we are happy to approve it.

Shirley will add it to our website, and Stu will continue liaising with you regarding models/data.

Thanks,
Sam

Dr Sam Leary
Associate Professor in Applied Statistics
Co-Head of Staff Support and Development, Bristol Dental School

Working hours: Monday to Thursday 8.30am - 4.30pm
(In office Wednesday and/or Thursday)

NIHR Bristol Biomedical Research Centre - Nutrition Theme
(Bristol Dental School, University of Bristol)
Level 3, University Hospitals Bristol Education and Research Centre
Upper Maudlin Street
Bristol, BS2 8AE
E-Mail: S.D.Leary@bristol.ac.uk Tel: 0117 4557460

...

Appendix IV: National Institute for Health Research



**Clinical Research Network
Children's Specialty**

Institute in the Park
Alder Hey Children's NHS Trust
Liverpool
L12 2AP
Tel: 0151 282 4533
Email: csg.crnchildren@nihr.ac.uk
Web: www.crn.nihr.ac.uk

Letter sent via email

Dr Alattar Batol
579 Electricity House, Colston Ave. Bristol.
BS1 4TB

7th April, 2022

Dear Dr Batol,

Re: Transverse interdental arch outcomes of 5-Year-Olds born with a UCLP following changes in cleft services within the United Kingdom

Thank you for submitting your study to the Cleft and Craniofacial Conditions (CCC) CSG for review. Members of the group agree that this is an interesting and relevant area for audit/research which will be of great interest to families and clinicians.

Clinical members were particularly positive about this study, and characterised it as a straightforward and concise study. Members were particularly positive about the opportunity use the complete CSAG and CCUK datasets to answer the important question about surgical outcomes.

Consumer members felt it would be particularly helpful to identify the optimal surgical technique and that this information will be particularly beneficial to patients and families.

Consumer members had some additional questions:

- Members highlighted the importance of this study informing current surgical practice, and were concerned that the CSAG and CCUK data are quite old and may not reflect current surgical practice. Members felt it was important to clarify whether this comparison would enable a discussion that would reflect current practice in the UK.
- Members also felt it would be important to include patient-reported outcome measures in this study. Members were aware that this may not be possible given the study is investigating treatment outcomes before the centralisation of services, and PROMs may not exist from this time. However, they felt it would be important to investigate whether this information could be included to learn if patients were satisfied with the treatment outcomes.

Members recommended that the CSG should support the inclusion of this study in the NIHR CRN portfolio.



Faculty of Health Sciences Research Ethics Committee
PEER REVIEW STATEMENT

Notes to peer reviewer:

- The information you provide on the scientific quality and validity of the project will help the committee make a decision about the ethical acceptability of the study.
- The information and opinions you provide on this form are confidential and will only be made available to the researcher concerned and the Faculty of Health Sciences Research Ethics Committee (FREC).
- Please return this form to the applicant so that they can action any required changes prior to their submission. The peer review form needs to be included with the ethics application by the submission deadline for the ethics application to be valid and ready for review.
- All fields should be completed in full.

Notes to applicant:

- Peer review is mandatory for all studies submitted to the FMDCE for ethical review. This form should be completed by a suitably qualified reviewer of your choice.
- For staff projects, peer review should be by an independent researcher *ie* someone not involved in the project. For student projects, review by a supervisor is sufficient.

1. Project Title:

Transverse interdental arch outcomes of 5-Year-Olds born with a UCLP following changes in cleft services within the United Kingdom

2. Applicant's Name:

~~Batol Alattar~~

3. Please comment on the value of the project in the field being researched

This is an area with little research and is fundamental question when evaluating whether centralization of surgical services has impacted on outcomes for children with cleft lip and palate. I would support this as a clinician with an active role in national evaluation of cleft services.

4. Is the project feasible within the allotted time?

Yes

5. Please comment on the clarity of the aims and objectives of the project

Clear aims and objectives. Could clarify why modified Huddart and Bodenham index gives additional benefit to just measuring the maxillary arch in isolation as previously done Le measuring the change in dental occlusion as a whole between 2 samples?

6. Please explain whether, in your opinion, the methods proposed will meet the aims of the project.

Yes, these seem appropriate for the proposed aims of the project.

7. Where quantitative data analysis is required, please comment on the suitability of the methods of analysis proposed. Where complex analysis is required, should the advice of a departmental statistician be sought?

In view that the main scoring system to be used here is not strictly "normally" distributed due to the construct it might be useful to check the stats testing proposed for identifying difference between 2 groups with a statistician.

8. Where qualitative data analysis is required, please comment on the suitability of the methods of analysis proposed.

NA

9. Are there any areas in your opinion where the study could be improved?

None identified

10. General comments. If you would like to make any other comments on this study, please do so here:

10. Name of Reviewer:

Mr Scott Deacon

11. Position:

Lead Consultant Orthodontist South West Cleft Service
Senior Clinical Lecturer UoB (Honorary)

12. Qualifications:

BDS MSc MFDS MOrth MDTFFd FFMLM FDS(Orth)

13. Contact details, including email address:

Scott.deacon@bristol.ac.uk
01173421158

14. Date of peer review:

30/03/22

Thank you for completing this review.

Appendix VI: CCUK Resource Research Proposal Form

CCUK Resource Research Proposal Form

Collaborator's outline project proposal (using existing CCUK data or collection of new data).

1. Applicants

Principal applicant	Name:	Batol Alattar
	Affiliation:	University of Bristol
	Email:	Gp20177@bristol.ac.uk
	Telephone:	07723030010
	Address:	DDS room, CDH, Bristol Dental Hospital. BS1 2LY
Co-applicants	Names:	Professor Ireland and Dr Fowler

2. Project

Project title (no more than 120 characters with spaces):	An investigation into interdental arch relationship outcomes of 5-Year-Olds born with a Unilateral Cleft Lip and Palate using the Modified Huddart Bodenham Index following the centralisation of cleft services within the United Kingdom.
Start date:	12/2021
End date:	08/2023

3. Funding

Has the project <u>been</u> or will it be peer reviewed?	Yes <input checked="" type="checkbox"/> No
If yes, by what organisation?	Professor Sandy
Has funding been sought?	Yes <input type="checkbox"/> No x

4. What data is being requested?

Dento- facial	
Oral health	
Audiology	
Perceptual speech	
Psychosocial	
Satisfaction	
Centralisation	x
Cropped anonymised images	
Models	x

5. Justification

Please state below the rationale for using CCUK data for this study (including aims and hypotheses) - **limit to half an A4 page.**

- Please see attached [document](#)

6. Scientific outline

Please provide a 1 – [2 page](#) outline of your proposal, highlighting the specific requirements of the project for the CCUK data specified above.

- Please see attached [document](#)

7. Summary for website

Please provide a [250 word](#) summary with keywords for inclusion on the website

- Please see attached [document](#)

8. Agreement

Please sign below to confirm your agreement to the terms and conditions set out in this document and to certify that the details you have provided are correct.

Signature:	Batol Alattar
Date:	21/02/2022
Name (on behalf of applicants)	Batol Alattar

If you are sending this form by email then you should note that in the absence of this signature, the emailing of this proposal constitutes your personal certification that the details are correct.

Please send completed forms to CCUK Study Team (cleftcareuk@uhbw.nhs.uk).

CCUK Study Team
August 2020
Version 1.2