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The correlation between static and dynamic facial dysmorphology in unilateral cleft lip and palate (UCLP)

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Abstract

Objective – The objective of this study was to assess the correlation between static (3D) facial dysmorphology at both rest and maximum smile and dynamic (4D) facial dysmorphology as represented by the frame of maximum asymmetry during a maximum smile in unilateral cleft lip and palate (UCLP). When maximum asymmetry occurs during a maximum smile was also analysed.

Design and setting – This study was designed as a retrospective cross-sectional study utilising quantitative methodology to assess a cohort of patients with a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP). Patients had 4D imaging carried out at Glasgow Dental Hospital and School for audit purposes and as part of their routine care by the local cleft team working under the Managed Clinical Network (MCN) Cleft Care Scotland.

Materials and Methods – Thirty-one (31) patients between the ages of 13 to 17 years old with a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP) had 4D images based on passive stereophotogrammetry captured at 60 frames per second (fps). Each patient was captured performing a maximum smile three times over a three second window. Data processing involved the conformation of a generic mesh containing over 7000 vertices or quasi-landmarks to the facial surface before tracking all the vertices during the facial expression. Partial ordinary Procrustes analysis was utilised to calculate an asymmetry score for each frame during the expression. The rest frame (3D), frame of maximum smile (3D), and frame of maximum asymmetry (4D) were used to determine the correlation between static and dynamic facial dysmorphology.

Results – Asymmetry scores were higher at maximum smile than at rest and maximum asymmetry was most frequently observed during the relaxation phase following a maximum facial expression (N=27/31; 87.1%). Asymmetry scores for maximum smile were less than but comparable to maximum asymmetry scores. Static (3D) asymmetry at rest and maximum smile was strongly correlated to dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile. The strongest correlation was seen with analysis using the frame of maximum smile focussing on the nasolabial region.

Conclusions – The use of 4D imaging combined with mesh conformation and dense correspondence analysis provides a valid objective measure of facial asymmetry. The fact that asymmetry scores for maximum smile were less than but comparable to maximum asymmetry scores highlights that assessment of facial asymmetry at maximum smile is still a valid assessment of facial dysmorphology despite not depicting the full extent of the asymmetry. Static (3D) asymmetry at rest and maximum smile is strongly correlated to; and likely highly predictive of, dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile. The strongest correlation is seen with analysis using the frame of maximum smile focussing on the nasolabial region. Future research could use linear regression modelling to predict dynamic (4D) asymmetry scores using static (3D) images.

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Finally, a huge thank you to my family and friends for their ongoing love and support.

“If I have seen further, it is by standing on the shoulders of Giants” – Isaac Newton.

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List of Abbreviations

Abbreviation	*Explanation*
ABG	Alveolar bone grafting
AC	Aesthetic Component
BASCD	British Association for the Study of Community Dentistry
BCLP	Bilateral cleft lip and palate
BMI	Body Mass Index
BSPA	Baseline Security Product Assessment
BSSO	Bilateral sagittal spilt osteotomy
CAPS-A	Cleft Audit Protocol for Speech-Augmented
CBCT	Cone-beam computerised tomography
CLAP	Cleft lip and palate
CLAPA	The Cleft Lip and Palate Association
CLEFTSiS	Cleft Services in Scotland
CLPED	Cleft lip/palate-ectodermal dysplasia
CPO	Isolated cleft palate
CPU	Central Processing Unit
CRANE	The Cleft Registry and Audit Network
CSAG	Clinical Standards Advisory Group
CSC	Cleft speech characteristics
CT	Computerised tomography
DHC	Dental Health Component
DMFT	Decayed, Missing, Filled Teeth index
ENT	Ear, Nose, and Throat
EUROCRAN	European collaboration on craniofacial anomalies
FIPS	Federal Information Processing Standard
GAS	Glasgow Anterior Stabilisation
GB	Gigabyte
GGC	Greater Glasgow and Clyde
GHz	Gigahertz
GOSLON	Great Ormond Street, London and Oslo, Norway
GPA	Generalised Procrustes analysis
mHB	Modified Huddart Bodenham system
HRQOL	Health-related quality of life
ICD	International Classification of Diseases
IOS	Intraoral scanner
IOTN	Index of Orthodontic Treatment Need
IRF6	Interferon regulatory factor-6
LCD	Liquid-crystal display
MCN	Managed Clinical Network
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MSX1	Drosophila MSH homeobox homolog-I
MTHFR	5,10 Methylenetetrahydrofolate reductase

NATO	North Atlantic Treaty Organization
NCSC	National Cyber Security Centre
NG	Nasogastric tube
NHS	National Health Service
NICE	National Institute of Clinical Excellence
OME	Otitis media with effusion
OMFS	Oral and maxillofacial surgery
PAR	Peer Assessment Rating
PC	Personal Computer
PCA	Principal component analysis
PNAM	Presurgical nasoalveolar moulding
PTA	Pure Tone Average
PVRL1	Poliovirus receptor-related 1
R&I	Research and Innovation
RAM	Random access memory
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised control trial
REC	Research Ethics Committee
SALT	Speech and language therapy
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire
SIMD	Scottish Index of Multiple Deprivation
TB	Terabyte
TBX22	T-box transcription factor
TCS	Treacher Collins syndrome
TGFA	Transforming growth factor-alpha
TGFB3	Transforming growth factor beta-3
TIM	Tiers of Involvement Measure
UCLP	Unilateral cleft lip and palate
UK	United Kingdom
URA	Upper removable appliance
USA	United States of America
USS	Ultrasound scanning
VDWS	Van der Woude syndrome
VPI	Velopharyngeal insufficiency
WHO	World Health Organisation

Author’s Declaration

I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, for any other degree or professional qualification except as specified.

Except where stated otherwise by reference or acknowledgment, the work presented is entirely my own.

Chapter 1 Introduction and Literature Review

1.1. Background

Cleft lip and palate is an umbrella term for a group of the most frequently occurring craniofacial birth defects worldwide (Crockett & Goudy, 2014). Cleft lip and palate (CLAP) conditions are associated with a failed fusion of the palate, alveolus and/or lip during fetal development. It encompasses a selection of conditions ranging from a bifid uvula up to and including a bilateral cleft lip and palate. A selection of the most common types of cleft palate are depicted in Figure 1-1.

Patients with cleft lip and palate require specialist multidisciplinary health and social care input from a diverse range of healthcare providers including but not limited to; a cleft surgeon, consultant anaesthetist or paediatric anaesthetist, consultant in paediatric dentistry, consultant orthodontist, consultant restorative dentist, paediatrician, speech and language therapist, clinical psychologist, a clinical nurse specialist (cleft nurse), ENT (Ear, Nose, and Throat) surgeon, consultant audiologist and consultant geneticist. Unfortunately, despite multidisciplinary input, patients with cleft lip and palate have a higher morbidity and mortality throughout their life when compared to the rest of the unaffected population (Mossey et al., 2009).

Cleft lip and palate can be a severely debilitating condition if left untreated, resulting in problems with speech, feeding, swallowing, hearing and significant psychosocial ramifications. Cleft lip and palate causes a substantial global burden of disease and an additional localised burden to both the child and their parents or carers (Sinno et al., 2012). This burden of disease is not limited to just the health of the individual but also to their quality of life and the subsequent socioeconomic impact of the condition (Wehby & Cassell, 2010). The NHS cost for care of individuals with cleft lip and palate from birth to 10 years of age has been estimated; ranging from approximately £6,137 for cleft palate only up to £17,004 for bilateral cleft lip and palate (Hasanally, 2020).

A child born with cleft lip and palate has an increased healthcare exposure and requirement, both in terms of inpatient care and successive outpatient appointments (Martin et al., 2020). For orthodontic treatment alone they may have to attend over 40 appointments and have protracted treatment over the course of 3 years or more (Hameed et al., 2019). This healthcare responsibility and liability often falls with the child’s parent and carer, resulting in significant time away from work. This often equates to lost income and the additional financial requirement of travelling to the appointments. The long-term effect on the child is often more complex and difficult to quantify. Initially they have significant school absences due to recurring appointments, which may affect academic performance and also lead to difficulties in social situations and low self-esteem (Sousa et al., 2009). Additionally, despite improving surgical techniques, affected individuals are often left with a degree of residual facial asymmetry. This can result in teasing or bullying at school, the feeling of isolation in social situations and difficulty in forming meaningful relationships with their peers.

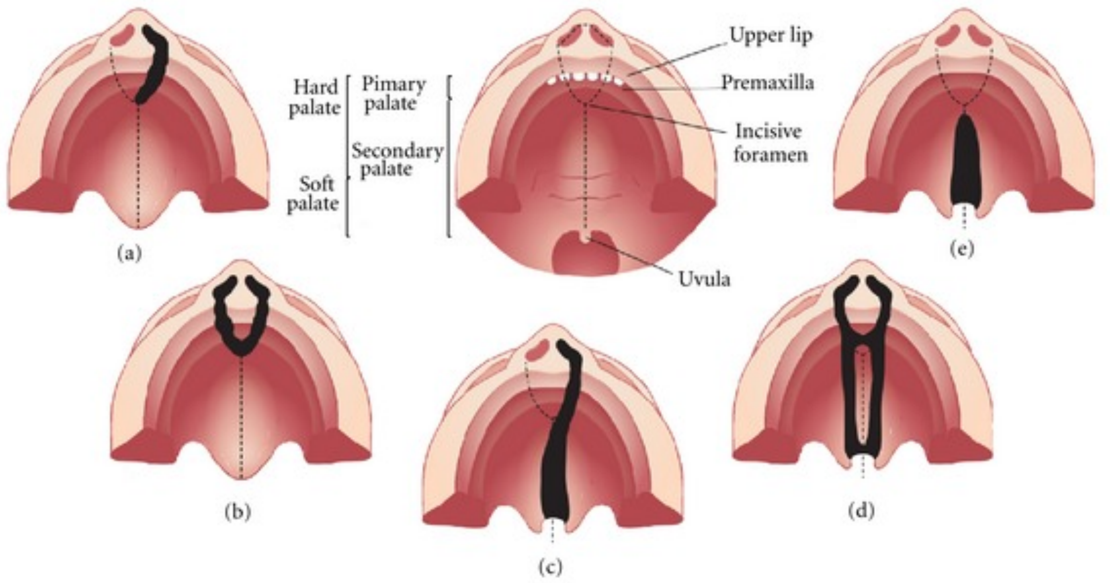


Figure 1-1. Common types of cleft palate. (a) Unilateral cleft lip with alveolar involvement; (b) bilateral cleft lip with alveolar involvement; (c) unilateral cleft lip associated with cleft palate; (d) bilateral cleft lip and palate; (e) cleft palate only (Brito et al., 2012).

Understanding the magnitude of the resulting residual facial asymmetry and how this then effects patients in their daily social interactions will allow us to better shape the future of cleft lip and palate research. The goal being the improvement of the aesthetic outcome for patients and their subsequent health-related quality of life (HRQOL).

1.2. Epidemiology

1.2.1. Prevalence

Cleft lip and palate is one of the most common craniofacial birth defects worldwide with a prevalence of approximately 1 in every 600 to 700 human births (Olasoji et al., 2005). When accounting for the estimation of approximately 15,000 children born every hour globally, a child is born somewhere in the world with cleft lip and palate every 2 and a half minutes, or 220,000 births every year (Mossey, 2003) The prevalence of isolated cleft palate (CPO) is approximately 1 in every 2,500 births compared to approximately 1 in every 1,000 births for cleft lip with or without palatal involvement (Worley et al., 2018).

In the United Kingdom (UK), the Cleft Registry and Audit NEtwork (CRANE) was founded in 2000 and collects data regarding individuals born with cleft lip and palate in England, Wales, and Northern Ireland. Since its inception in the year 2000, 21,865 children have been born with cleft lip and palate in England, Wales, and Northern Ireland (CRANE, 2021). This averages out at around 1,041 children born with cleft every year or an incidence of 15 per every 10,000 live births. The information presented in the CRANE database 2021 annual report indicated that isolated cleft palate (CPO) was the most frequently occurring cleft, equally 44% of all reported cases of orofacial clefting.

CLEFTSiS (Cleft Services in Scotland) was set up in 2000 to collate data regarding patients born with cleft lip and palate in Scotland and it has since been rebranded to Cleft Care Scotland, a national managed clinical network. The vision of Cleft Care Scotland is to ensure the provision of equitable care to individuals born with cleft lip and palate in Scotland. From April 2015 to March 2016, 91 children were born in Scotland with a diagnosis of cleft lip and palate (Cleft Care Scotland, 2016).

The incidence of cleft lip and palate varies worldwide, with cleft lip with or without palatal involvement being higher in Asia and Latin America and comparably lower in Southern Europe and South Africa (Mossey et al., 2009). The prevalence of non-syndromic cleft lip and palate across Europe is depicted in Figure 1-2.

Unfortunately, there are still many parts of the world with sparce, incomplete and limited data on the epidemiology and prevalence of cleft lip and plate including Russia, the Middle East, Eastern Europe, Central Asia and parts of Africa (Shaw, 2004).

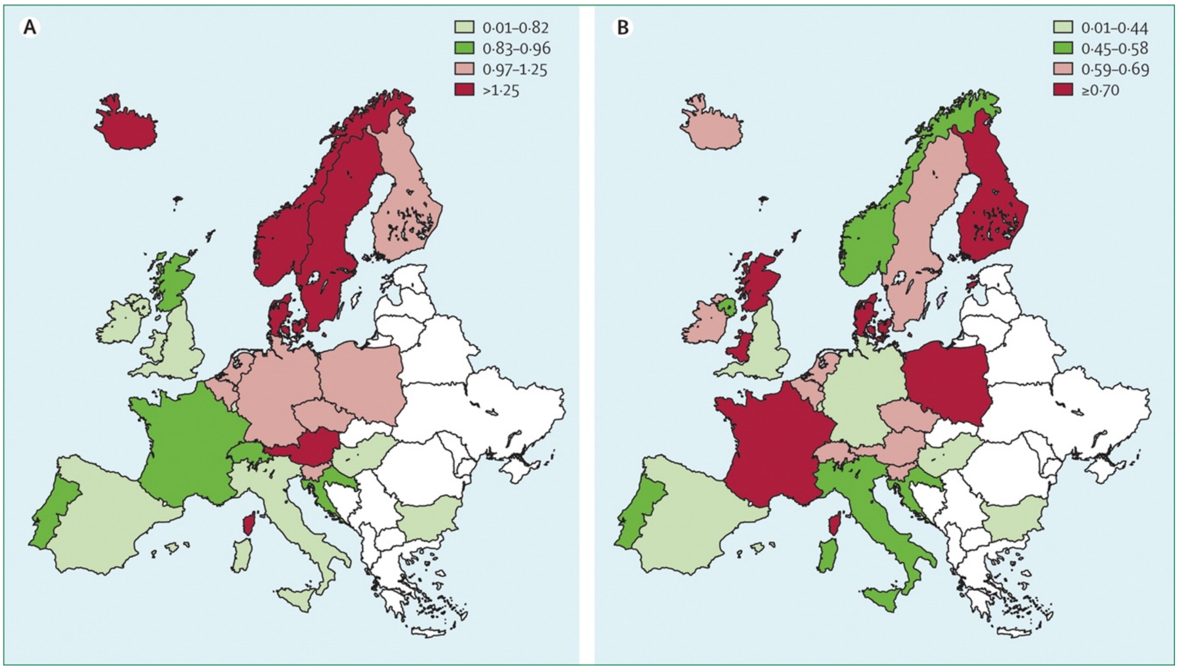


Figure 1-2. European prevalence of non-syndromic cleft lip and palate per 1000 births. (a) Cleft lip with or without cleft palate; (b) Isolated cleft palate (Mossey et al., 2009).

1.2.2. Gender

The prevalence of a child being born with cleft lip and palate has a complex connection and association with the child’s gender. It has been reported that a female is more likely to be born with an isolated cleft palate (CPO) and a male with cleft lip with or without palate (CLAP) (Shaw et al., 1991). Research has further defined this difference as males being twice as likely to have CLAP compared to females, and males having only two thirds of the risk of developing CPO compared to their female counterparts (Freitas et al., 2004; Pool et al., 2021).

The gender disparity in cleft lip and palate has been linked to the differences in embryonic craniofacial development when comparing male and female embryos. Female embryos show slower closure of the secondary palate/palatal shelves, perhaps accounting for their increased probability of CPO and problems with the hard and soft palate (Burdi & Silvey, 1969). When assessing subphenotypes, defects in females have been shown to occur more frequently in the late embryonic period, associated with failed fusion of the secondary palate. Male defects more commonly occur in both the early and late embryonic periods, associated with defects with both the primary and secondary palate (Pool et al., 2021).

Additionally, there is an association between increased incidence of cleft lip and palate with increasing maternal age. With woman over the age of 39 having double the probability of having a child born with cleft lip and palate, irrespective of the child's gender (Shaw et al., 1991).

1.2.3. Laterality

Cleft lip and palate can be either bilateral, unilateral affecting the left side or unilateral affecting the right side. Unilateral cleft lip and palate is the more common form, with 4 unilateral cases for every individual case of bilateral cleft lip and palate (Allam et al., 2014). For unilateral clefting, epidemiological studies have shown that for cleft lip with or without alveolar clefting the left side is affected twice as much as the contralateral right (Mandal et al., 2019; Sivertsen et al., 2008). However, there has been no evidence linking the laterality of the cleft with cleft severity (Carroll & Mossey, 2012).

It has been suggested that cleft laterality likely has a complex aetiology involving both environmental and genetic risk factors, and the prevalence difference between contralateral sides may suggest a aetiological variation in right sided clefts (Gallagher et al., 2018). A common limitation of research on the laterality of clefting tends to be the comparative sparsity of right sided clefts. Developmental laterality variation is also seen in other human developmental traits including brain lateralisation and handedness, this developmental preference may partly explain the difference in clefting prevalence (Gallagher et al., 2018).

1.2.4. Ethnicity

It has been widely reported that the incidence of cleft lip and palate varies based on an individual's ethnicity. The lowest reported prevalence being in individuals of African descent; 1 in 2,500 live births, with 1 in 1000 Europeans affected, and the highest prevalence in individuals of Asian origin; approximately 1 in 500 live births (Dixon et al., 2011).

The incidence of isolated cleft palate tends to remain stable independent of patient ethnicity, however the prevalence of cleft lip with or without palatal involvement varies depending on the patient's race (Worley et al., 2018).

There is likely a complex interaction of both environmental and genetic factors in risk determination for individuals of different ethnic and genetic backgrounds (Croen et al., 1998). However, the ethnic variation in cleft lip and palate prevalence appears to be linked to a genetic differential as opposed to a geographical determinant, as individuals tend to maintain incidence figures of their ethnic origin as opposed to their residing location (Mossey et al., 2009).

1.3. Aetiology

The aetiology of cleft lip and palate is complicated and still not yet fully understood. It can occur as an isolated condition or as part of larger, more intricate genetic syndrome (Dixon et al., 2011). There is thought to be both genetic and environmental factors that influence cleft lip and palate pathophysiology; in addition to a potential elaborate and complicated gene-environment interaction (Romitti et al., 1999; Shaw & Lammer, 1999).

1.3.1. Embryology

1.3.1.1. Normal Development

The formation of the face of an embryo begins in utero around week 4. The development of the lip occurs in conjunction with facial development from week 4 to approximately week 6. The formation of the palate occurs later, beginning around week 6 to 8 and with completion occurring around week 12 (Yoon et al., 2000).

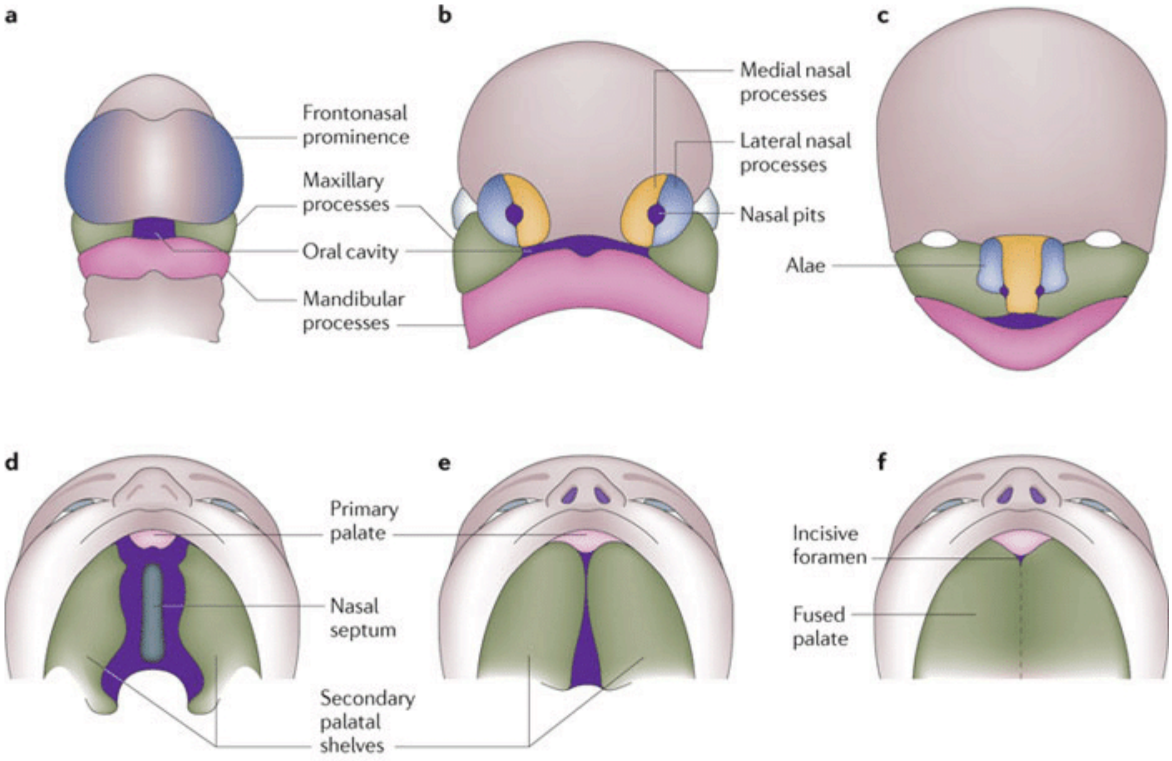


Figure 1-3. Development of the lip and palate. (a) Formation of the frontonasal prominence, maxillary processes, and mandibular processes. (b) Development of the medial and lateral nasal processes and nasal pits. (c) Formation of the upper lip, primary palate, nose, and lower jaw. (d) Formation of the primary palate, nasal septum, and secondary palatal shelves. (e) Downward growth followed by horizontal elevation of the secondary palatal shelves. (f) Fusion of the primary palate with the elevated secondary palatal shelves (Dixon et al., 2011).

The embryonic face develops from the frontonasal prominence (or process) and the first pharyngeal arch (or mandibular arch). The first pharyngeal arch gives rise to a pair of maxillary processes and a pair of mandibular processes. Nasal placodes then form on either side of the frontonasal process and eventually develop to form nasal pits surrounded bilaterally by medial and lateral nasal processes. The mandibular processes fuse to form the lower lip and jaw. The maxillary processes fuse to form the cheeks, the secondary palate and fuse with the medial nasal processes to form the upper lip and philtrum. The medial nasal processes also form the primary palate, part of the nose, associated anterior teeth and alveolar bone in this region. The lateral nasal processes form the alae surrounding the nostrils (Senders et al., 2003). This process is depicted in Figure 1-3(a), Figure 1-3(b) and Figure 1-3(c).

As previously discussed, the medial nasal processes form the intermaxillary segment, its associated structures, and the primary palate. The maxillary processes form the secondary palatal shelves in addition to the other structures listed above. The secondary palatal shelves grow downwards before elevating and fusing horizontally with each other and the primary palate. Fusion also occurs vertically with the nasal septum; completing palatal fusion and separating the embryonic oral and nasal cavities (Diewert & Wang, 1991; Fulton, 1957). This process is depicted in Figure 1-3(d), Figure 1-3(e) and Figure 1-3(f). Gender studies have highlighted differences in male and female craniofacial development, with females showing much later closure and fusion of the palate (Burdi & Silvey, 1969).

1.3.1.2. Abnormal Development in Cleft Lip and Palate

Cleft lip and palate can occur in utero when an embryo does not develop as depicted above and undergoes abnormal development. A cleft lip occurs due to the failed fusion of the maxillary processes with the medial nasal processes; this can occur either unilaterally or bilaterally, in isolation or in conjunction with clefting of the palate (Merritt, 2005; Wantia & Rettinger, 2002). A cleft palate occurs due to the failed fusion of the secondary palatal shelves. A cleft palate can have a range of severities and can also occur either in isolation or in conjunction with clefting of the lip (Merritt, 2005).

1.3.2. Genetic Factors

Despite the complex aetiology of cleft lip and palate it is now understood that genetics plays a major role in an embryo’s susceptibility of developing clefting of the lip and/or palate. However, genetic pathophysiology is complex, and no single gene has been identified as causative. Cleft lip and palate has been described as polygenic as it exhibits a non-Mendelian pattern of inheritance (Marazita & Mooney, 2004).

Clefting of the lip and/or palate can occur in isolation or as a part of a larger genetic syndrome. The genetic aetiology of syndromic clefting is different from that of isolated cleft lip and palate. The development of a cleft lip with or without palatal involvement has been identified as a symptom in over 200 named genetic syndromes. Conversely, clefting of the palate with or without lip involvement has been identified as a symptom in over 400 named genetic syndromes. Syndromic cleft lip and palate accounts for around 5-7% of total clefts (Mossey et al., 2009).

Clefting of the lip and/or palate is a recorded symptom in many syndromes including but not limited to; Treacher Collins syndrome (TCS), Pierre Robin syndrome, hemifacial microsomia, Crouzon syndrome and Apert syndrome (Kohli & Kohli, 2012). Research has been ongoing to identify genes associated with specific orofacial cleft syndromes. X-linked cleft palate has be linked with T-box transcription factor (TBX22), cleft lip/palate-ectodermal dysplasia (CLPED) has been linked with poliovirus receptor-related 1 (PVRL1) and Van der Woude syndrome (VDWS) has been linked with Interferon regulatory factor-6 (IRF6)(Kohli & Kohli, 2012; Wong & Hagg, 2004).

In non-syndromic clefting research has shown a different genetic makeup when compared to that of syndromic cleft lip and palate. The genetic susceptibility of non-syndromic clefting is complex, polygenic, and still not yet fully understood. Multiple different genes have been identified as significant in multiple different studies; with several loci potential having more influence on the phenotype observed (Marazita & Mooney, 2004). There is thought to be genetic loci that are in part causative, loci that can modify the phenotypic appearance and loci that increase the embryos susceptibility to related and known environmental factors. Therefore, highlighting the complex aetiological gene-environment interaction associated with the pathogenesis of cleft lip and palate (Cobourne, 2004).

Genetic loci that have been identified and have shown an association with non-syndromic cleft lip and palate include but are not limited to; transforming growth factor-alpha (TGFA), Drosophila MSH homeobox homolog-I (MSX1), 5,10 Methylenetetrahydrofolate reductase (MTHFR), and transforming growth factor beta-3 (TGFB3) (Kohli & Kohli, 2012; Mossey et al., 2009; Wong & Hagg, 2004). Genetic research into clefting is an ever evolving subject and personalised and precision treatments may be available to treat individuals once their exact genetic cause of clefting is identified. Full genome sequencing of newborns or foetuses may open up new treatment modalities including intrauterine interventions and gene therapy (Kini, 2023).

1.3.3. Environmental Factors

1.3.3.1. Socioeconomic Status & Deprivation

The socioeconomic status of a population is often difficult to quantify and difficult to define; therefore making it difficult to research (P. A. Mossey et al., 2009). Many of the worlds most deprived areas and countries unfortunately lack sufficient resources to accurately record birth defects in their population, making global statistical comparisons challenging to carry out. However, studies in Scotland have shown a positive correlation between low socioeconomic status and an increased risk for cleft lip and palate (Clark et al., 2003). Perhaps reflecting an increase in common environmental risk factors and risk-taking behaving in mothers from lower socioeconomic backgrounds. Associated environmental risks could include maternal smoking, maternal alcohol consumption including binge drinking and poorer nutrition (Clark et al., 2003).

1.3.3.2. Smoking

Maternal cigarette smoking; especially in the first trimester of pregnancy, has been shown to be associated with an increased incidence of cleft lip and palate (Lie et al., 2008). This is understood to be related to hypoxia of the embryo in utero. However, research results have been varied, likely due to the varied genetic makeup of individuals and genetic susceptibility of different embryos. (Cobourne, 2004).

Transforming growth factor alpha (TGFα) has be linked with increased genetic susceptibility to environmental maternal smoking in the causation of orofacial clefts (Shaw et al., 1996). A mother smoking more than or equal to 20 cigarettes per day is thought to have between a 3-11-fold increased risk of having a child with an orofacial cleft. No link has been established between orofacial clefting and paternal smoking and there is limited current evidence on the potential adverse effect of passive smoking.(Shaw et al., 1996)

Following the implementation of smoke-free legislation in England, Wales, and Northern Ireland in 2007, there has been a decline in the prevalence of smoking in the UK by approximately 37%. This public health benefit has translated into an estimated 8% reduction in cleft incidence in England, Wales, and Northern Ireland; a benefit not replicated in data from Scotland (Fell et al., 2021).

1.3.3.3. Alcohol

Maternal alcohol consumption is another recognised risk factor for many conditions, and it is a known and recognised teratogen. Current evidence on the association between cleft lip and palate and maternal alcohol consumption is inconsistent. However, binge drinking (drinking more than or equal to 5 drinks) in the first trimester is thought to increase the risk of both cleft lip with and without palatal involvement and isolated cleft palate (DeRoo et al., 2008; Dixon et al., 2011). This associated risk is further increased if the mothers participate in binge drinking on more than 3 occasions during the first trimester (DeRoo et al., 2008).

1.3.3.4. Drugs & Medications

Several drugs and medications have been linked with cleft lip and palate and their association with potential pathogenesis has been researched. These include but are not limited to, folate antagonists, anticonvulsant drugs, corticosteroids, and retinoids.

Folate antagonists include commonly used medications such as methotrexate, phenytoin, trimethoprim, and carbamazepine. These drugs are known to increase the associated risk of an embryo developing a neural tube defect or an orofacial cleft (Hernández-Díaz et al., 2000). Anticonvulsant drugs such as phenytoin, diazepam and valproic acid have been linked to an increase in cleft lip and palate incidence. This increased risk is associated with maternal epilepsy, the risk is therefore due to the mothers anticonvulsant drug regime during pregnancy (Abrishamchian et al., 1994; Dravet et al., 1992). Corticosteroid use; namely prednisolone, and the use of retinoids (retinoic acid); commonly found in many females daily skin care routine, have also been linked to an increased risk of an embryo developing an orofacial cleft (Abbott et al., 1989; Park-Wyllie et al., 2000).

1.3.3.5. Nutrition

Poor nutrition has been linked with an increased risk of developing orofacial clefts. However, similar to socioeconomic status, nutrition and dietary intake is often very difficult to accurately record and research, especially in more deprived and less affluent areas (Mossey et al., 2009).

Folate deficiency has a well-documented and understood link to an increased risk of neural tube defects and other common birth defects. It has also been thought to be linked with an increased prevalence of orofacial clefting, however it is unethical to conduct research including a group with low folate intake due to the known risk of a potential neural tube defect on the embryo. We could conclude however that since folate supplementation has been shown to reduce the incidence of orofacial clefting, that folate deficiency is indeed a risk factor (G. Wehby & Murray, 2010; Wilcox et al., 2007).

Severe zinc deficiency is widespread in the Philippines and research has previously shown that higher levels of zinc was associated with a lower risk of having a child with cleft lip or palate (Tamura et al., 2005). However, similar research was conducted in the United States of America (USA) and no similar association was observed (Munger et al., 2009; Tamura et al., 2005). Therefore, there is a potential risk of cleft lip and palate with severe zinc deficiency but perhaps not with mild or moderate deficiencies.

The use of multivitamins is now extremely common and many of these over-the-counter medications also include folic acid (folate). Maternal use of multivitamins during the periconceptional period, first trimester and remainder of pregnancy has been identified in being protective in reducing the risk of non-syndromic clefting by as much as 25% (Mossey et al., 2009; Wilcox et al., 2007; Zhou et al., 2020).

1.4. Diagnosis

The diagnosis of cleft lip and palate most commonly occurs either prenatally or shortly after birth. Prenatal ultrasound scanning (USS) of the foetus is now considered a global standard for routine antenatal care (Stoll et al., 2000). Prenatal USS can detect a foetus with an isolated cleft lip, cleft lip with clefting of the palate, and less frequently an isolated cleft palate. Across Europe detection rates vary considerably, but on average 27% of cases of cleft lip with or without palatal involvement and 7% of cases of isolated cleft palate are picked up (Clementi et al., 2000). Detection may be possible as early as 13 to 16 weeks in utero; however, is more common at the 20-week mid pregnancy or ‘anomaly’ scan. It is easier for the USS examiner to visualise a cleft as the embryo continues to increases in size (Clementi et al., 2000).

Isolated cleft palate is more commonly diagnosed and confirmed at or shortly after birth as it is often very difficult to accurately visualise the palate on the prenatal USS. However, the use of 3D-ultrasound imaging is improving the prenatal diagnosis of isolated cleft palate (Bäumler et al., 2011), and it may even be diagnosed on a fetal MRI (Magnetic Resonance Imaging) if it is being used as an adjunct to USS (Zheng et al., 2019).

If a cleft diagnosis is confirmed on an USS it is often possible to offer to carry out amniocentesis, to test for a possible associated inherited genetic syndrome (Stock et al., 2019). However, this may raise difficult discussions around the termination of the pregnancy and therefore patients should fully understand the benefits and potential psychological risks of carrying out further antenatal testing.

In 2020 in England, Wales and Northern Ireland 87% of newborns had their cleft diagnosed either before birth (46%) or at birth (41%), and the accuracy and techniques used for diagnosis is continuing to improve (CRANE, 2021). Early diagnosis of clefting is essential, ideally a cleft should be diagnosed within 24 hours of birth to facilitate an appropriate and timely referral to specialist cleft services (CRANE, 2021). The Royal College of Paediatrics and Child Health (RCPCH) developed a NICE (National Institute of Clinical Excellence) accredited best practice guide for palatal examination and identification of clefting in newborns (RCPCH, 2015). It involves examination of the hard and soft palate as part of a newborns physical examination and has facilitated an improvement in outcomes for timely cleft diagnosis. An early diagnosis can aid expedition and promotion of family counselling, support, advice, and provision of suitable neonatal care. It may also be useful to prepare staff with regards to potentially difficult questions pertaining to termination of pregnancy (Clementi et al., 2000).

1.5. Classification

Many different classifications for cleft lip and palate have been used and suggested over the years with some being more widely recognised and more universally adopted than others. Different classifications often have a discrete focus with some being based on aetiology and others being based on the anatomy or morphology of the cleft. A dichotomous relationship is evident; with simple classifications being easy to understand and adopt but lacking adequate detail to fully describe the intricacies of an individual cleft diagnosis. Complex classifications in contrast are often detailed enough to fully describe the cleft diagnosis but may be too convoluted to be easily read, adopted or understood (Allori et al., 2017; McBride et al., 2016). Basic breakdowns are often seen in the literature with common descriptions such as; syndromic versus non-syndromic, unilateral versus bilateral, complete versus incomplete and cleft lip with and without cleft palate and cleft palate only (Mossey et al., 2009).

1.5.1. The Veau Classification

Victor Veau’s cleft classification initially separated clefting into four discrete morphological forms. Clefts of the soft palate, clefts of the hard and soft palate up to the incisive foramen, clefts of the hard and soft palate extending unilaterally through the alveolus and clefts of the hard and soft palate extending bilaterally through the alveolus. The Veau classification was simple and easy to understand; and therefore readily adopted due to its simplicity, practicality and convenience (Allori et al., 2017; Veau & Borel, 1931).

1.5.2. Kernahan's Classification and the Modified Striped Y

Kernahan's classification was developed by Desmond Kernahan in the USA and is seen as a key classification that has been modified and adapted by many over the years. Its key benefit was its simplicity and its ease of use (Kernahan & Stark, 1958). Kernahan's classification divided clefts around the anatomy of the incisive foramen, the point of differentiation between the primary and secondary palate. He proposed three distinct groups: clefts anterior to incisive foramen occurring in the primary palate, clefts posterior to the incisive foramen occurring in the secondary palate and clefts both anterior and posterior to the incisive foramen occurring in both the primary and secondary palate (Allori et al., 2017; Kernahan & Stark, 1958).

Kernahan further modified his classification with the development of the Striped Y (Kernahan, 1971). This was a diagrammatic representation of cleft classification designed to make classification easier and faster thus allowing it to gain widespread use and acceptance. Kernahan's striped Y is depicted in Figure 1-4. Alternative shading was used to differentiate between complete and incomplete clefting. The incisive foramen is depicted by the small circle at the junction of the limbs of the Y, anterior to the incisive foramen depicts the lip, alveolus, and hard palate anterior to the incisive foramen. Posterior to the incisive foramen represents the sections of the hard and soft palate.

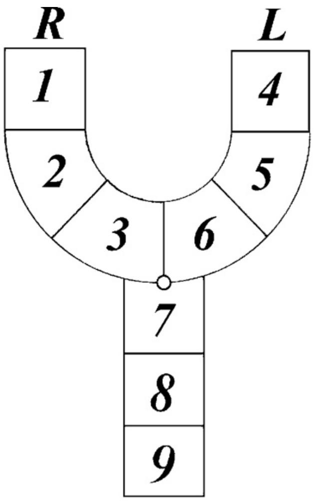


Figure 1-4. Kernahan's Striped Y. A symbolic classification of cleft lip and palate (Kernahan, 1971).

1.5.3. The LAHSHAL Classification

The LAHSHAL classification was originally described by Otto Kriens in 1989. LAHSHAL is a palindrome representing the lip, alveolus, hard palate and soft palate from a patient's right side to left side (Kriens, 1989). The LAHSAL classification is depicted in Figure 1-5. The classification itself is very descriptive and can be used to describe over 12,000 variations of cleft anatomy and subtype. It was developed to be simple, exact, flexible, morphological and graphic (Kriens, 1989). It is also compatible with the ICD-10/11 (International Classification of Diseases – 10th and 11th revisions) coding as well as surgical coding, therefore allowing for efficient computer database coding of cleft cases for more accurate regional, national, and global comparisons. A capital letter in the classification represents a complete cleft, a lowercase letter represents an incomplete cleft, an asterisk (*) represents minimal clefting, a dot represents normal development and a further modification included a plus sign (+) in the position of the right or left lip to represent a Simonart band. A Simonart band is a weblike band of tissue that partially covers the gap between the medial and lateral portions of a cleft lip. For example, "LAHS•••" would represent a right sided complete cleft of the lip, alveolus, and hard and soft palate.

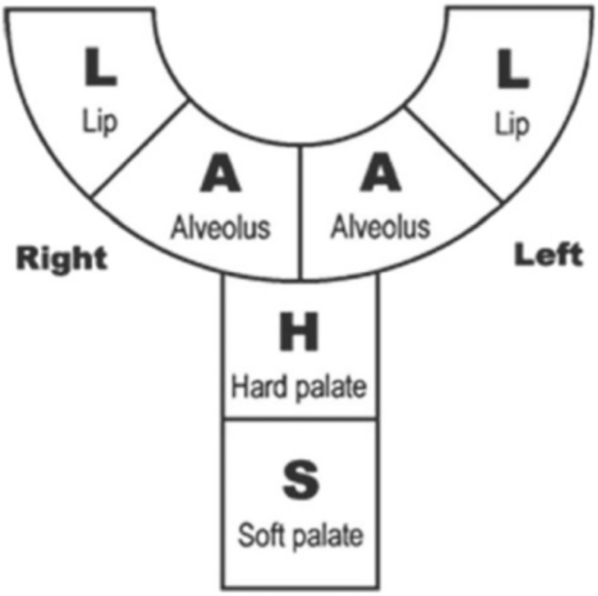


Figure 1-5. The LAHSHAL classification. A coded classification for cleft lip and palate (Kriens, 1989; Zhang et al., 2017).

1.6. Treatment

The treatment of cleft lip and palate is complex and multi-facetted and therefore requires specialist multidisciplinary health and social care input from a diverse range of healthcare providers. As previously discussed, the treatment of cleft lip and palate often involves a cleft surgeon, consultant anaesthetist or paediatric anaesthetist, consultant in paediatric dentistry, consultant orthodontist, consultant restorative dentist, paediatrician, speech and language therapist, clinical psychologist, a clinical nurse specialist (cleft nurse), ENT (Ear, Nose, and Throat) surgeon, consultant audiologist and consultant geneticist. An example of a national care pathway for patients with unilateral cleft lip and palate that has been developed by the managed clinical network (MCN) Cleft Care Scotland is depicted in Figure 1-6. The general treatment timeline for patients with cleft lip and palate will be discussed below; treatment would of course be tailored to each patient depending on their individual diagnosis and its severity.

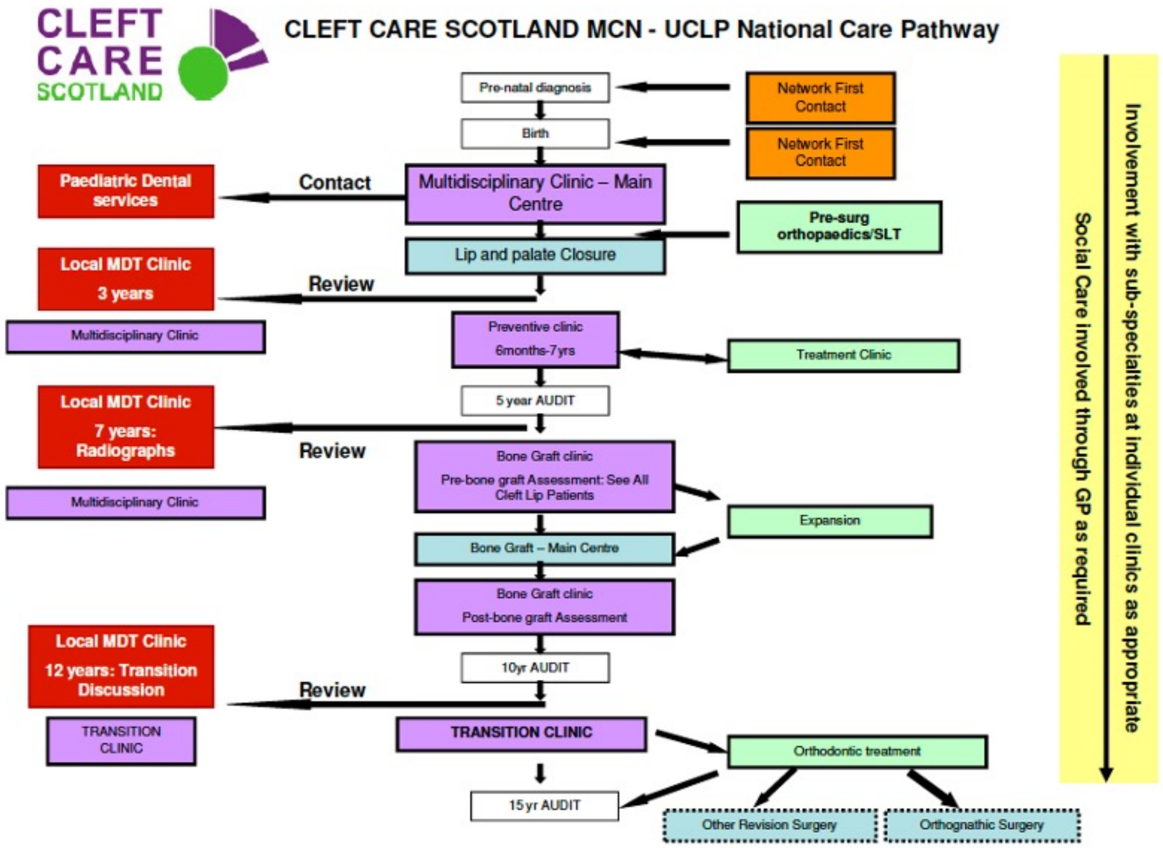


Figure 1-6. Unilateral Cleft Lip and Palate (UCLP) National Care Pathway. Cleft Care Scotland Managed Clinical Network (MCN) (Cleft Care Scotland, 2018).

1.6.1. Antenatal

The care, advice, and planning for treatment of a child with cleft lip and palate begins from their diagnosis. This can be from the prenatal ultrasound (20-week anomaly scan) in the case of cleft lip with or without palatal involvement or at birth for an isolated cleft palate (Clementi et al., 2000; Stoll et al., 2000). The cleft should ideally be diagnosed within the first 24 hours of birth to facilitate a timely onward referral to the cleft team (CRANE, 2021). The cleft centre or team then contact the family to arrange a suitable face-to-face meeting to discuss any concerns and answer any pertinent questions the parents may have. This initial contact and planned discussion is often carried out by the cleft nurse or clinical nurse specialist, who tends to act as the parents primary contact within the wider cleft team (NHS England, 2013). Following the initial contact with the cleft team parents are offered to be put in touch with the UK charity CLAPA (The Cleft Lip and Palate Association) who support people born with a cleft and their families in the UK. CLAPA can provide an extensive amount of support to families including relevant information packs on birth and diagnosis, parent contacts, Facebook groups for parents and access to photo galleries showcasing pre- and post-surgery photos of other children who have been through cleft treatment (CLAPA, 2021b).

1.6.2. Birth to 8 weeks

Following birth, the multidisciplinary care for cleft patients begins. Newborns with a recent cleft diagnosis undergo a specialist feeding assessment, which includes a tailored feeding plan and appropriate management. Follow-up parental support is provided in the use of specialised feeding bottles or a nasogastric tube (NG) tube if required. CLAPA can often support infant feeding as their welcome pack includes specialist feeding bottles and teats, information leaflets as well as everything else mentioned above (CLAPA, 2021b).

After birth the cleft nurse also arranges for the family to meet the rest of the cleft team prior to any major surgical intervention. Early involvement of clinical psychology is usually indicated to provide support and perspective for the family; and psychology involvement can be sought by the patient or family at any time during the cleft pathway. A referral to a consultant geneticist can be completed if indicated or requested by the parents, this can aid in determining if the cleft has occurred in isolation or in the presence of a syndrome as well as determining the risk of the parents having another child with cleft lip and palate. Paediatric routine surveillance can be important to allow regular screening for common co-morbidities and detect any other symptoms of possible syndromes. Genetic counselling can also be sought in conjunction with clinical psychology and clinical genetics to aid parents in understanding genetic diagnosis, inheritance, risk, and management (NHS England, 2013).

Other routine care after birth includes dental health education, a neo-natal hearing test and additional primary care paediatric services which is provided for every child including monitoring of development and vaccinations.

1.6.3.9 weeks to 2 years

9 weeks to 2 years is an important timeframe for cleft patients and their families as it marks the beginning of treatment involving major surgical intervention. It can be an emotional, stressful, and demanding time. Surgical intervention begins with the primary repair of the lip, followed by the primary repair of the palate; both of which will be discussed below.

In addition to the surgical intervention, routine appointments, reviews, and non-surgical treatment is still required. The volume of inpatient and outpatient activity often equates to increased exposure to healthcare staff and parental absence from work; the financial implications of which can cause increased pressure and anxiety. Outpatient appointments can include but are not limited to; ENT assessment and subsequent treatment if required, speech and language therapy assessment and management, paediatric dental review and education, audiology 10 month assessment (if cleft palate) and any necessary treatment and routine child health surveillance (NHS England, 2013).

1.6.3.1. Primary repair of the lip

The primary repair of the cleft lip is normally the first major surgical intervention for patients with cleft lip with or without cleft palate. The surgery is generally carried out between 3 to 6 months old and loosely follows the rule of 10; where the patient is at least 10 weeks old (often translated to 3 months old), weights at least 10 pounds and their haemoglobin level is at least 10g/dL (Wilhelmsen & Musgrave, 1967). The predominant aim of the surgery is to achieve an aesthetic and functional outcome for patients, balanced with a reduced burden on the parents when possible.

In the months preceding the planned surgery the cleft nurse will liaise with the patient's family to arrange a preadmission appointment. This provides the cleft team an opportunity to meet the family, fully consent the parents to the procedure, discuss the plan for the surgery, discuss the risks and benefits of the procedure and carry out any required pre-surgical medical screening. The patient is then admitted either on the day of the surgery or night before and the surgery is completed under general anaesthetic over the period of 1 to 2 hours.

There are a variety of surgical techniques that have been used, modified, and developed for the primary repair of cleft lip including but not limited to; the rotation advancement technique (Millard technique and subsequent modifications), the Fisher subunit method and the Randall-Tennison Triangle technique (Fuller & Shaye, 2020).

Orthopaedic remodelling through taping, lip adhesion or presurgical nasoalveolar moulding (PNAM) was used historically as it was thought to improve surgical outcomes if carried out in advance of surgery (Aslan et al., 2018). However, the evidence for its benefits is debated and often requires significant patient and parent cooperation (Prahl et al., 2003). The charity CLAPA also provide excellent information and resources for parents and families going through primary lip surgery, including surgical information leaflets and pre and post-op photographs of the planned surgery (CLAPA, 2021b).

1.6.3.2. Primary repair of the palate

The primary repair of the cleft palate is normally the second major surgery for cleft lip and palate patients but can be their first major surgery if they have a diagnosis of isolated cleft palate (CPO). The surgery is routinely carried out between 6 to 12 months old with the primary aims being to facilitate speech development, improve function and feeding, allow dental development and facial growth and ensure adequate operation of the velopharyngeal apparatus (Shaw et al., 2019; Shkoukani et al., 2014).

Often there is a fine balance between early surgery to aid the patient in timely speech development in line with their peers, versus delaying surgery to prevent early maxillary restriction and reducing maxillary growth interference. Maximising speech development and function is often seen as more critical and early surgery is generally preferred, while attempting to minimize both the formation of palatal fistulas and maxillary growth restriction (Moores et al., 2016).

Mirroring the pre-surgical planning for primary repair of the cleft lip, a preadmission appointment is arranged prior to the primary repair of the cleft palate. Often the cleft nurse will liaise with the family to arrange this appointment at which the family can be consented, advised of the surgical plan, discuss the risks and benefits and any routine pre-surgical checks can be completed. The patient is admitted either the evening prior to the surgery or on the morning of the surgery. The procedure is completed under general anaesthetic, takes approximately 2 hours and patients can routinely remain in hospital post-operatively for 1 to 3 days.

Echoing the diversity of surgical techniques used for the primary repair of cleft lip, there are a variety of surgical techniques that have been used, modified, and developed for the primary repair of cleft palate; with alternative techniques used based on the diagnosis and complexity of palatal clefting. Techniques include the von Langenbeck technique and subsequent modifications, intravelar veloplasty, the VY pushback palatoplasty (Veau-Wardill-Kilner), two-flap palatoplasty and the Furlow double opposing Z–palatoplasty (Shkoukani et al., 2014; Strong & Buckmiller, 2001).

Orthopaedic remodelling may again be used prior to surgery in an attempt to reduce the cleft width and potentially improve the functional and surgical outcomes (Strong & Buckmiller, 2001). However, its usefulness is again debatable and it significantly increases the burden of care for the patient (Prahl et al., 2003). As the patient grows, further revision surgeries may be needed and are completed as and when required. The cleft charity CLAPA again provide useful information leaflets on the cleft palate repair surgeries and photos both pre and post-surgery (CLAPA, 2021b).

1.6.4.3 to 7 years

Treatment from 3 to 7 years of age may also include surgical intervention; lip revision surgery, further palatal repair and velo-pharyngeal surgery may be carried out if required. Further outpatient input takes the form of care from clinical psychology prior to starting school, continued assistance from speech and language therapy (SALT), paediatric dental review, prevention and treatment, ENT assessment and audiology assessment (if cleft palate) including any required treatment (CLAPA, 2021b; NHS England, 2013).

A complete set of multidisciplinary records are collected for all cleft patients at 5 years of age for national audit purposes and assessment is carried out by the whole cleft team. The Cleft Registry and Audit Network (CRANE) then collates this 5 year audit data from England, Wales and Northern Ireland and publishes its findings and recommendations (CRANE, 2021). The primary aim of this national clinical audit is to improve the care patients receive, monitor outcomes at discrete intervals and allow healthcare professionals to strive to provide the best evidence-based care for their patients. Databasing this key information allows clinicians to monitor multiple clinical and qualitative outcomes for patients with a diagnosis of cleft lip and palate.

1.6.5.8 to 14 years

Between the age of 8 to 14 years old cleft patients continue to have multiple outpatient visits, reviews and treatment as required. Follow-up appointments are arranged with speech and language therapy (SALT),ENT, paediatric dentistry, audiology, clinical psychology and orthodontics (CLAPA, 2021b).

A further set of full multidisciplinary records are collected for all cleft patients at 10 years of age for national audit purposes and again assessment is carried out by the whole cleft team including clinical psychology. This forms the basis for the 10-year-old cleft patient statistics in the Cleft Registry and Audit Network (CRANE) database, shaping clinical recommendations for treatment of patients with cleft lip and palate (CRANE, 2021).

If a patients cleft extends through the alveolar bone further surgery may be required to repair the alveolar defect present prior to eruption of the permanent canine tooth. These patients are assessed prior to surgery at around 7 to 9 years of age by the cleft surgeon, orthodontist and paediatric dentist (NHS England, 2013). The alveolar bone grafting (ABG) surgery will be discussed in more detail below.

Surgical repair of the cleft lip and cleft palate has been shown to reduce maxillary growth. Patients often present with maxillary retrusion as well as reduced maxillary height and width (Antonarakis et al., 2016). Consequentially because of this restricted growth pre-alveolar bone grafting orthodontics may be required. Clinically patients may present with a class III malocclusion or maxillary retrognathia, anterior crossbites or a reverse overjet and posterior crossbites caused by a maxillary deficiency in the transverse dimension (Vig & Mercado, 2015).

Pre-surgical orthodontics may focus on correcting the transverse discrepancy, establishing a broader maxillary arch form, and opening space for ease of surgical access for grafting the alveolar cleft site. Expansion can be completed with the use of a Hyrax-type expander, quad-helix, Haas-type expander, fan-shaped expander or other suitable device (Allareddy et al., 2020). However, posterior crossbites can be accepted pre-alveolar bone graft and instead corrected in the definitive orthodontic phase of treatment. This has the added benefit of reducing a patients total orthodontic treatment time and reducing the likelihood of burning through their cooperation. Anterior crossbites may be corrected with the use of an upper removable appliance (URA) to improve surgical access to the cleft site and correction tends to be stable in the presence of a positive overjet and positive overbite. Retained primary (deciduous) teeth and supernumerary teeth in close proximity to the cleft site are often removed prior to surgery to improve surgical access and ease of surgery (Lilja, 2009). For patients with a diagnosis of bilateral cleft lip and palate pre-surgical orthodontics may involve the stabilisation of the premaxilla with the use of fixed orthodontic appliances, occlusal wafers and arch bars or the Glasgow Anterior Stabilisation (GAS) appliance (Singh et al., 2012; Vuity et al., 2017).

1.6.5.1. Alveolar Bone Grafting (ABG) Surgery

Alveolar bone grafting is normally carried out before the age of 12 years old, with the age range for surgery between 9 to 12 years old. However, the timing of the surgery is generally based on an individual’s dental development rather than their chronological age (Scalzone et al., 2019). As previously discussed, the timing of the surgery tends to be based on the expected eruption time of the permanent canine tooth on the ipsilateral side to the cleft site. The successful eruption of the permanent canine tooth through the bone graft is most successful when the surgery is completed when the canine has undergone half of its root development (El Deeb et al., 1982).

The aim of the surgery is to fuse the maxillary alveolar segments with the utilisation of a graft, provide bony support for the eruption of the teeth, close any fistulas that may be present, improve lip and support and improve facial aesthetics (Cho-Lee et al., 2013).

Pre-admission appointments are utilised to discuss the plan of the surgery, consent the parents or carers, discuss the risks and benefits and carry out any routine pre-surgical checks. Patients are admitted to have the procedure carried out under general anaesthetic, the procedure can take up to 3 hours and following surgery patients may remain as an inpatient in hospital for 1 to 3 days (CLAPA, 2021b).

Autogenic bone grafting is preferred for the repair of the alveolar defect, with the bone being harvested from a secondary surgical site on the same patient. The most common site for an autogenic bone graft is bone harvested from the iliac crest (Dasari et al., 2018). While this may produce scarring at the surgical site it is often preferred to the alternative sites that have been used such as, the mandibular symphysis, tibia and rib (Coots, 2012). Following successful surgery, the patients may undergo a period of post-alveolar bone grafting orthodontics before commencing their definitive orthodontic treatment when indicated.

1.6.6. 15 to 21 years

Between the age of 15 and 21 years of age a cleft patient's definitive orthodontic treatment is completed unless it has already been completed in the preceding years. Delayed definitive orthodontic management may be indicated depending on the underlying malocclusion and propensity for latent adverse growth.

Full multidisciplinary records are again collected for all cleft patients at 15 and 20 years of age for national audit purposes and assessment is repeated by the whole cleft team. The data is stored and aggregated and forms the basis for shaping future cleft care and recommendations (CRANE, 2021).

Genetic counselling can again by accessed by both the patient and the patient's parents on referral. This may be requested to discuss the aetiology of the patient's diagnosis, the risk to the parents of having future children with similar diagnosis or the probability of the patient passing it on to their own children (Lynch & Kimberling, 1981).

Additional repair and revision surgeries may be required or requested for the cleft lip, cleft palate, and nose. Continued outpatient input is also provided by the orthodontic department, paediatric dentistry department, and restorative dentistry department (NHS England, 2013). Depending on the complexity and severity of the underlying malocclusion combined orthodontics and orthognathic surgery may be required to facilitate comprehensive correction. Orthognathic surgery will be discussed in more detail below.

Patients are offered to be discharged from cleft services around 16 to 21 years of age if they are satisfied with all aspects of their care. A discharge appointment is completed; however, they can re-enter the cleft services at any age following appropriate re-referral from their general medical or dental practitioners.

1.6.6.1. Orthognathic Surgery

Patients may seek further treatment involving combined orthodontics and orthognathic surgery if they have ongoing concerns regarding their profile or malocclusion. Cleft lip and palate patients often have maxillary deficiency in all three planes of space; the anteroposterior (AP) dimension, transverse dimension and vertical dimension (Yen et al., 2020). Additional presenting complaints may include, posterior crossbites with or without associated displacements, anterior crossbites with a reverse overjet and functional difficulties in relation to incising or chewing food. Comprehensive correction of a malocclusion by orthognathic surgery is only completed at the cessation of growth to ensure further latent growth would not undo the planned surgical correction.

It would be hoped that with careful planning and appropriate timing of other primary cleft surgeries there would be a diminished requirement for orthognathic surgery. Orthognathic surgery is required for 38% of patients with bilateral cleft lip and palate (BCLP), 30% of patients with unilateral cleft lip and palate (UCLP), 4% of patients with isolated cleft palate (CPO) and less than 2% of patients with cleft lip only (Choi et al., 2021).

Prior to the surgery patients meet with the cleft team and surgeon to discuss their surgical plan and timeline for treatment. Clinical psychology input is desired to manage patients' expectations with the surgery and provide support to individuals entering the orthognathic pathway.

Pre-surgical orthodontics is carried out to decompensate and coordinate the maxillary and mandibular dental arches. This can take up to 18 months and aims to produce an interdigitated and stable occlusion post-surgery (Baik, 2009).

Orthognathic surgery for patients with cleft lip and palate may involve a single jaw surgery; most commonly involving the maxilla (maxillary osteotomy), or double jaw surgery; involving the maxilla and the mandible (bimaxillary osteotomy). The Le Fort I osteotomy is the most common surgical procedure performed on the maxilla and facilitates surgical movement of the upper jaw. The maxilla can be repositioned as a single piece, or a maxillary segmental osteotomy may be performed to split the maxilla into segments to correct more complex malocclusions. Conversely, the bilateral sagittal spilt osteotomy (BSSO) is the most common surgical procedure performed on the mandible. For cleft patients a BSSO may be performed in conjunction with a Le Fort I osteotomy for comprehensive surgical correction (Phillips et al., 2012). Following the surgery post-surgical orthodontics are completed to finish and detail the occlusion as well as allowing for a degree of occlusal settling (Lee, 1994).

1.6.7.>21+ years

Adult cleft patients may still be receiving ongoing treatment past the age of 21 but otherwise they can re-enter the cleft service if they are unsatisfied with their care or require additional support and advice. A suitable re-referral can be completed by their general medical or dental practitioners and patients are often screened by clinical psychology prior to accessing further treatment to discuss their reasons for seeking latent care.

Adult patients returning to care may access services for lip or nose revisional surgery, speech revision surgery, palatal revision surgery, speech and language therapy, orthodontics, alveolar bone grafting if not previously completed, orthognathic surgery, clinical psychology input, hearing assessment and treatment, restorative dentistry treatment and any other routine dental care (CLAPA, 2021b; NHS England, 2013).

1.7. Assessment of Outcomes

Assessing the outcomes of care for cleft lip and palate patients has been a central focus of research globally. The Eurocleft Study was a longitudinal cohort study assessing the outcomes of patients born with unilateral cleft lip and palate (UCLP) in five centres across Northern Europe (Brattström et al., 2005). The primary aims of the study was to assess the burden of care of cleft treatment protocols, assess longitudinal outcomes of care by national centre and to determine patient and parent satisfaction with care when compared to the burden of care required to achieve the overall outcome (Semb, Brattström, Mølsted, Prahl-Andersen, & Shaw, 2005).

The Eurocleft Study was initially initiated by six national centres and five of the six centres agreed to follow up their cleft cohorts longitudinally (Semb, Brattström, Mølsted, Prahl-Andersen, Zuurbier, et al., 2005). The results of the study revealed dramatic variation in both length of treatment and outcomes for cleft patients across Northern Europe. It sparked reformation, redistribution and increased funding to cleft services across Europe (Shaw et al., 2001).

The two United Kingdom (UK) centres involved in the Eurocleft Study came out as having several of the poorest outcomes for cleft patients as well as the most disjointed and unorganised care pathways (Sandy et al., 2001). This led to the Clinical Standards Advisory Group (CSAG) Study being developed to look at the quality of cleft lip and palate care in the UK (Williams et al., 2001). Its primary aim was to assess the standard of care received by patients born with unilateral cleft lip and palate (UCLP) in the UK and the relative training and experience of the health care professionals providing the care (Sandy et al., 2001). UCLP patients were selected as previous research had indicated that the treatment outcomes of patients with UCLP was predictive of outcomes for overall cleft care (Shaw et al., 1992).

The CSAG study indicated that 57 centres were involved in cleft care in the UK, with some centres only treating a few cleft patients per year. They recommended a restructuring and reorganisation of cleft services in a bid to improve outcomes for patients and provide MDT specialised cleft care at dedicated centres. Increased volume of cleft patients together with dedicated specialist training pathways for those involved in cleft care was advised to both improve outcomes and facilitate adequate case numbers to allow statistically adequate national and international comparisons (Bearn et al., 2001). There are currently nine cleft services in the UK which included sixteen cleft centres as depicted in Figure 1-7. The restructuring and provision of a centralised MDT cleft service has improved outcomes for cleft patients in the UK (Ness et al., 2015). A selection of cleft outcomes will be discussed below.

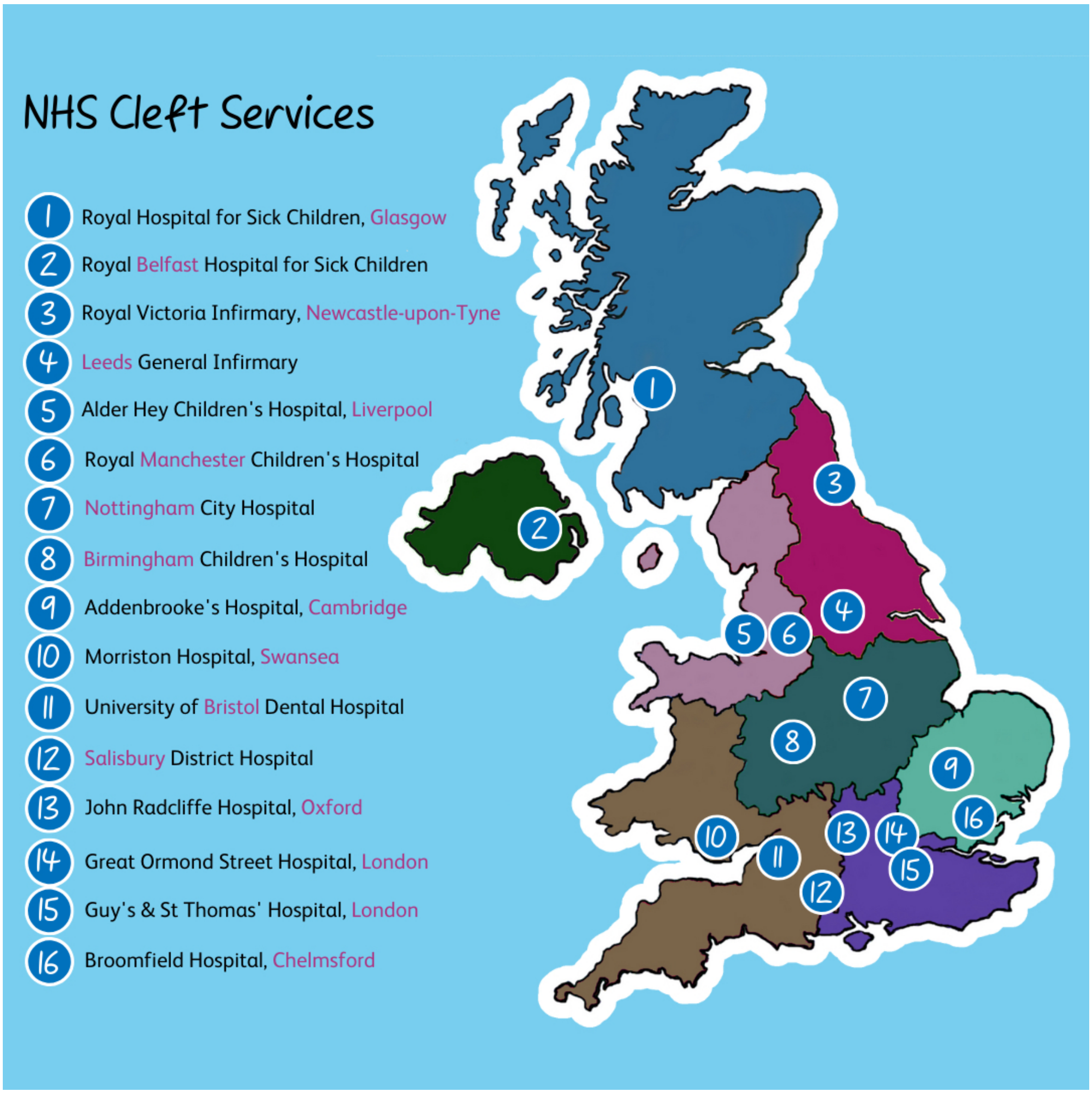


Figure 1-7. NHS Cleft Centres in England, Scotland, Wales, and Northern Ireland (CLAPA, 2021a).

1.7.1. Timely diagnosis and referral

As previously discussed in the diagnosis section, timely diagnosis and referral is essential for early intervention, support, and advice for families with a child born with cleft lip and palate. Measuring and recording the cleft diagnosis as well as when it was diagnosed is an important outcome measure for the timely provision of cleft care. Cleft lip with or without cleft palate can be picked up at the 20 week anomaly scan, but isolated cleft palate is more commonly picked up at birth due to the difficulties in visualising the palate in the 20 week anomaly scan (Clementi et al., 2000).

The gold standard for cleft care that the Cleft Registry and Audit Network (CRANE) aspires to achieve is all (100%) children to have a recorded time of diagnosis, all clefts diagnosed either in utero or within 24 hours of birth, all children to be appropriately referred to cleft services within 24 hours of birth, and all families to receive follow-up contact from the cleft team within 24 hours of receipt of referral (CRANE, 2021). In England, Wales, and Northern Ireland in 2020, 92% of children born with a cleft had a recorded time of diagnosis in their medical notes, 87% were diagnosed within 24 hours of birth, 83% were referred to cleft services within 24 hours of birth and 96% were contacted by the cleft team within 24 hours of receipt of referral (CRANE, 2021).

The timely diagnosis and referral of cleft patients has improved dramatically over the last 10 years in response to the annual auditing from CRANE and the development of the Royal College of Paediatrics and Child Health's (RCPCH) NICE accredited best practice guide for palatal examination and identification of clefting in newborns (RCPCH, 2015).

1.7.2. Gestational age and birth weight

Another important outcome measure that is assessed at birth is the gestational age of a child born with cleft lip and palate and their associated birth weight. Recording of these details is not just important to monitor the link between cleft lip and palate and gestational age but also to accurately monitor future surgical timing. Previous research into the association between cleft lip and palate and gestational age or prematurity has been varied, but the environmental risks factors for both cleft lip and palate and premature births are indistinguishable. The World Health Organisation (WHO) defines a premature birth as any baby that is born alive before 37 weeks of pregnancy (WHO, 2018). There may not be a causative relationship, but perhaps an association with common risks and confounding factors (Shehan et al., 2021). Therefore, data collection on gestational age and birth weight is an important outcome measure that could shape future cleft research.

The benchmark set by the Cleft Registry and Audit Network (CRANE) is that all babies born with cleft lip and palate have their gestational age and birthweight recorded. In 2020 only 52% of babies born with a cleft has their gestational age recorded and 51% had their birth weight recorded (CRANE, 2021). 12% of babies born with a cleft lip and palate in the UK in 2020 were premature, higher than the national average of 8% of annual births. Additionally, when looking at babies born with a cleft diagnosis at full term between 2017 and 2019, 7% were born with a low birth weight (<2,500g) and 8% where born with a high birth weight (≥4000g) (CRANE, 2021).

1.7.3. Child growth

Monitoring child growth of patients born with cleft lip and palate is an important outcome measure that allows comparisons to be drawn between cleft and non-cleft children. Early feeding problems for cleft patients is common as feeding can be an onerous and challenging task. This early malnutrition may become habitual and be maintained long term, leading to reduced growth and failure to thrive. Alternatively, rebound nutrition and catch-up may lead to further growth and increased risk of weight gain and obesity. The research into child growth in cleft patients is limited and varied; further future research into this area would be recommended (Gallego et al., 2021).

In 2020 in England, Wales, and Northern Ireland only 38% of 5-year-old cleft patients had their height and weight recorded, allowing their Body Mass Index (BMI) to be calculated. For 5-year-old cleft patients born between 2011 and 2013, 87% had a healthy BMI (13.0 to 17.5), 2% were underweight (<13.0), 7% were overweight (17.5 to 19.0), and 4% were obese (>19.0) (CRANE, 2021). The link between a diagnosis of cleft lip and palate and a child’s BMI would of course have many confounding factors including maternal environmental risk factors and socioeconomic status.

1.7.4. Dental Health

Monitoring dental health is an important outcome measure for all patients receiving dental treatment. For individuals with a diagnosis of cleft lip and palate this importance is magnified, as research has shown that they have worse dental health and more caries experience; despite often rigorous oral hygiene instruction and intensive intervention (Chopra et al., 2014; Worth et al., 2017). The comparatively high caries experience may be somewhat explained by poor oral hygiene, reluctance to rigorously clean around the cleft site, dental arch crowding, dental malformations or anomalies, and surgical scarring increasing the difficulty of cleansing (Worth et al., 2017).

Historically, dental health was monitored via the British Association for the Study of Community Dentistry (BASCD) criteria for recording dental caries experience. This BASCD was used for landmark UK research trials including the Clinical Standards Advisory Group (CSAG) Study (Williams et al., 2001). The current outcome measure most commonly used is the decayed, missing, filled teeth index (dmft/DMFT). Whereby dmft denotes decayed, missing and filled teeth in the primary dentition and DMFT denotes decayed, missing and filled teeth in the permanent dentition (Worth et al., 2017).

For the Cleft Registry and Audit Network (CRANE) database dmft scores are recorded for the 5-year-old audit and DMFT scores are recorded for the 10-year-old audit and beyond. For audit purposes all children should have a dmft score recorded at 5 years of age, but only 56% had a dmft score recorded between 2017 to 2019 (CRANE, 2021). Results from 5 years olds born between 2011 and 2013 indicated that 38% had at least one caries experience (dmft >0); 5% higher than the national average, and 14% had extensive decay (dmft >5) (CRANE, 2021).

Outcome measures for dental health can also focus on the intervention provided to patients by the cleft service. Two common additional measures of intervention outcome are the treatment index and the care index. The treatment index is a snapshot measurement of dental health at that moment in time relative to previous caries experience, in essence it is a measure of current active carious lesions. A score of 100% would indicate that all caries has been treated and would be the benchmark for excellent intervention. Alternatively, the care index is a measure of early detection and minimally invasive intervention. Essentially, it monitors if caries has been detected early and treated with fillings rather than being treated with more invasive extractions. A gold standard of 100% would indicate timely diagnosis and early minimally invasive intervention. In the CRANE 5-year-old cohort born between 2011-2013, the average treatment index was 76% and the average care index was 70% (CRANE, 2021).

1.7.5. Facial growth

Monitoring facial growth in patients undergoing treatment for cleft lip and palate is important as surgical intervention may be detrimental to midfacial growth. Maxillary restriction may occur following primary repair of the cleft palate, restricting midfacial development, and leading to and increased incidence of class III skeletal malocclusions (Farber et al., 2019). However, the proclivity to utilise the incidence of class III skeletal malocclusions to assess the outcome of surgical treatment for patients with cleft lip and palate may be controversial, as there is well documented global and geographical variations in background class III skeletal prevalence (Alhammadi et al., 2018). Identical surgical treatments could be carried out in two different geographical locations with varying outcomes of class III malocclusions occurring due to the underlying genetic predisposition of the treated population.

The assessment of facial growth can be done by utilising the GOSLON (Great Ormond Street, London and Oslo, Norway) Yardstick that was developed as a clinical tool to quantify the degree of malocclusion present in patients with unilateral cleft lip and palate; an indirect assessment of maxillary growth (Mars et al., 1987). This can be used to index patients in the late mixed and early permanent dentition into 5 discrete categories: Group 1 – excellent outcome or result; Group 2 – good outcome or result: Group 3 – fair outcome or result: Group 4 – poor outcome or result and Group 5 – very poor outcome or result. The GOSLON Yardstick was used for the 12-year-old patient cohort in both the Clinical Standards Advisory Group (CSAG) Study and the Eurocleft Study (Mølsted et al., 2005; Williams et al., 2001). It facilitates the assessment of the antero-posterior (A-P), vertical and transverse relationships of dental study casts as an indirect indicator of surgical outcome.

The 5-year-old index was developed as a modification to the GOSLON Yardstick to facilitate the assessment of surgical outcome at an earlier age (Atack et al., 1997). It involves the assessment of a cleft patient's malocclusion at 5 years of age via either study models or photographs, if the clinician wants to avoid alginate impressions in young children. The index uses the same 5 categories as originally set out by the GOSLON Yardstick from an excellent result in Group 1; depicted in Figure 1.8, to a very poor result in Group 5; depicted in Figure 1.9.

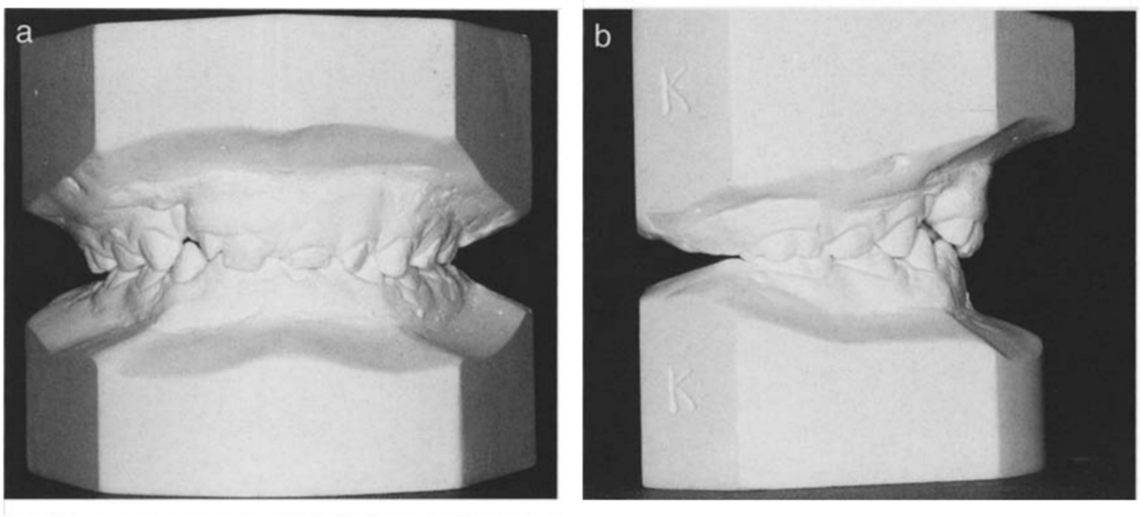


Figure 1-8. 5-year-old index. Example of Group 1 – an excellent result. (a) Antero-posterior (A-P) view (b) Lateral view (Atack et al., 1997).

The earlier use of the 5-year-old index allows the outcome of surgery to be known at an earlier timepoint; allowing surgeons to potentially alter their surgical protocol, and acts as a predictor of future growth potential and treatment requirement. In general terms a score of 1 or 2 in the GOSLON Yardstick or 5-year-old index would indicate either no orthodontic input required or simple orthodontic treatment, a score of 3 would indicate more complex orthodontic treatment and a score of 4 or 5 would indicate the likely need for orthognathic surgery in the future (Mars et al., 1987; Mølsted et al., 2005). Alternative indices that have been used include the EUROCRAN index, Huddart Bodenham system, and the modified Huddart Bodenham (mHB) system (Haque et al., 2015).

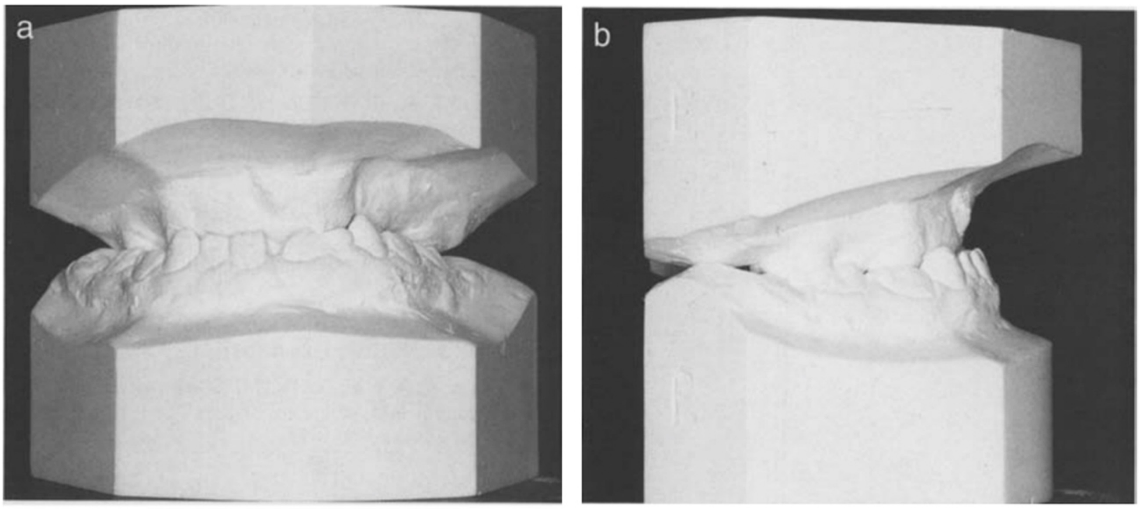


Figure 1-9. 5-year-old index. Example of Group 5 – a very poor result. (a) Antero-posterior (A-P) view (b) Lateral view (Atack et al., 1997).

The Clinical Standards Advisory Group (CSAG) Study also assessed facial growth based on the skeletal relationship depicted on lateral cephalometric radiographs. These radiographs were digitised and the relationship of the maxilla to the mandible was assessed using the anterior cranial base (S-N, Sella – Nasion) as a reference plane. The skeletal relationship between the maxilla and the mandible was depicted as the angle ANB. Results for the 12-year-old cohort showed 70% with a class III skeletal relationship (ANB<2°), 17% with a class I skeletal relationship (ANB 2-4°), and 13% with a class II skeletal relationship (ANB>4°) (Williams et al., 2001). The high percentage of class III skeletal relationships was noted as a poor surgical outcome as the incidence of skeletal III relationships in the general population was only 5%.

As previously discussed, the CSAG Study highlighted the inadequacies in cleft care in the United Kingdom (UK) and the reported facial growth statistics for the 5-year-old index confirmed this conclusion. 29% of patients achieved a good result (Group 1 and 2), 34% achieved a fair result (Group 3), and 37% achieved a poor result (Group 4 and 5) (Williams et al., 2001). This was particularly concerning as 4 out of every 10 patients had a poor surgical outcome, especially as further pubertal growth would likely worsen the class III skeletal relationship and further increase the need for orthognathic treatment.

The Cleft Registry and Audit Network (CRANE) has set the benchmark of all patients to have a recorded 5-year-old index (100%). For patients born with cleft lip and palate between 2011 and 2013, 66% had a recorded 5-year-old index (CRANE, 2021). The annual recording of the 5-year-old index allows for the longitudinal comparison of facial growth outcomes in the UK and international comparisons to be made with other centres globally. The index is strategically timed to assess facial growth potential prior to any definitive orthodontic treatment or alveolar bone grafting surgery. The 5-year-old index scores for children born with cleft lip and palate between 2011 and 2013 in the UK were: 38% with a good outcome (Group 1 and 2), 38% with a fair outcome (Group 3), and 24% with a poor outcome (Group 4 or 5)(CRANE, 2021). This constitutes an improvement from the previously reported outcomes of the CSAG Study and represents an improvement of cleft care following the restructuring of UK cleft services.

1.7.6. Speech

A patient born with clefting of the palate, either in isolation or in the presence of cleft lip, is at a much higher risk of developing difficulties with speech, articulation, and enunciation. This may have a negative impact on their development of literacy, comprehension and meaningful social bonds (Britton et al., 2014). Within the cleft pathway these patients often require tailored input from speech and language therapy (SALT) and may require surgical intervention in the form of primary speech surgery and speech revision surgery. This surgery may be a targeted repair of velopharyngeal insufficiency (VPI), whereby the soft palate fails to create an adequate seal at the back of the throat, leading to potential nasal air emission and hypernasality (Fisher & Sommerlad, 2011).

The restructuring of cleft services after the CSAG Study led to a focus on auditing of outcomes for cleft patients and in turn gave rise to the development of the Cleft Audit Protocol for Speech-Augmented (CAPS-A) as a validated tool to monitor speech outcomes (John et al., 2006). The centralisation of the cleft services and focus on specialist multidisciplinary care has led to detectable improvements in cleft care and speech outcomes (Sell et al., 2015).

The Cleft Audit Protocol for Speech-Augmented (CAPS-A) is used to assess non-syndromic patients with a cleft palate with or without clefting of the lip. The 16 CAPS-A outcome parameters include audible nasal emission, nasal turbulence, hypernasality, hyponasality and 12 incorrect productions of specific sounds called cleft speech characteristics (CSCs). The cleft speech characteristics (CSCs) are further subcategorised into anterior oral CSCs, posterior oral CSCs, non-oral CSCs and passive CSCs (John et al., 2006; Sell et al., 2015).

The recording of the 16 CAPS-A speech outcomes is a requirement for the Cleft Registry and Audit Network (CRANE). For children born between 2011 to 2013, 70% of eligible patients had all 16 CAPS-A speech parameters recorded and a further 2% had some of the speech parameters recorded. At the 5-year-old audit for children born with cleft palate with or without clefting of the lip between 2011 and 2013, almost 18% where found to have had speech revision surgery before the age of 5, 67.5% had speech without the presence of cleft speech characteristics (CSCs), and 60% had been assessed to have speech within the normal range (CRANE, 2021).

1.7.7. Psychology

Patients born with cleft lip and palate often have difficulties with social interaction, forming meaningful bonds with their peers, and low self-esteem and self-worth. The reason for this is often complicated and multifactorial but may include social isolation due to their appearance, communication difficulties due to their speech and hearing difficulties, and other compounded psychological and psychosocial factors (Sousa et al., 2009). Early input from clinical psychology can be beneficial for patients and families to provide support and assistance around birth and diagnosis, treatment, and future expectations. Early introduction to cleft psychology services increases accessibility to care and ensures families know that they can access care at any stage throughout the cleft pathway.

Assessing the outcome and input of clinical psychology can be done via the Tiers of Involvement Measure (TIM) and the Strengths and Difficulties Questionnaire (SDQ). The Tiers of Involvement Measure (TIM) is an audit tool that is used to record the level of involvement of clinical psychology in an individual’s care. Scores range from 0 to 4: 0 meaning a patient has not yet been assessed by a psychologist, 1 whereby a patient has been assessed and no further psychology input is required, 2 where input has been provided on clinic, 3 where further action is required but no appointment with the patient is necessary and 4 where an appointment with clinical psychology is required (CRANE, 2021). The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioural screening tool used for children between the ages of 4 and 16 and may be completed by an individual or their parents. It assesses areas of an individual's behaviour including their emotion, conduct including any behavioural issues, hyperactivity, relationships with peers, and social interaction (Goodman, 1997). Questionnaire responses can be analysed thematically and categorised into 4 bands: 1 – average or close to normal, 2 – slightly raised, 3 – high and 4 – very high. Low scores indicate individuals with behaviour close to that of the general population and no concern from a psychological point of view, high scores indicate a potential behavioural difficulty and may require tailored help and support from clinical psychology services.

For the Cleft Registry and Audit Network (CRANE), all 5-year-olds born with a cleft lip and palate should have audit data collected on their psychological outcomes and this should then be submitted for analysis. For children born between 2011 and 2013, 54% had adequate 5-year-old audit data submitted. The benchmark for excellent care would be for all patients to be screened by clinical psychology before 6 years of age, patients seen by clinical psychology for the 5-year-old audit to have their TIM assessment completed, and SDQ scores to be calculated to compared to population averages. For patients born between 2011 and 2013, 97% were screened by a psychologist before 6 years of age, 93% had a TIM assessment at the 5-year-old audit and 18% of children had high or very high SDQ scores; higher than the population average of 10% (CRANE, 2021).

1.7.8. Audiology

A cleft palate with or without clefting of the lip is commonly associated with hearing difficulties primarily linked with eustachian tube dysfunction. This can give rise to conductive hearing loss, otitis media with effusion (OME); commonly known as glue ear, and middle ear atelectasis (Crowley et al., 2021). Therefore, patients with clefting of the palate are assessed frequently by ENT and audiology throughout the cleft treatment pathway. Treatment may include regular assessments, hearing tests, grommets and/or hearing aids if required.

Audiology outcomes can be assessed using the Pure Tone Average (PTA) assessment tool, which can measure the average hearing threshold of an individual in each ear at varying frequencies at a prescribed snapshot in time (Skuladottir et al., 2015). Research has shown that there is no difference between PTA scores for unilateral cleft lip and palate (UCLP) versus bilateral cleft lip and palate (BCLP), right ear versus left ear; despite the increased prevalence of left sided UCLP, and PTA scores tend to improve with age. Indicating either effective timely intervention or the self-limiting nature of the symptoms (Skuladottir et al., 2015). Assessment of the middle ear can be done by tympanometry and/or otoscopy. Assessment of audiology outcomes by the Cleft Care UK Study has indicated that unfortunately there has been no detectable improvements in outcomes for patients from the original CSAG Study (Smallridge et al., 2015). However, fewer gromets are being placed and hearing aids are being used more frequently.

The Cleft Registry and Audit Network (CRANE) are currently working with clinical networks in both audiology and ENT to determine what data could be collected to appropriately monitor audiology outcomes for patients born with cleft lip and palate (CRANE, 2021).

1.7.9. Qualitative outcomes

Qualitative outcomes and by proxy qualitative research, focuses on analysing and interpreting non-numerical data on an individual or groups subjective perception of outcome. Assessment of qualitative outcomes for cleft patients allows us to better assess a patient’s quality of life (QoL) following treatment, understand holistic aspects of their care, and refer to their combined care outcome. Focusing on perceived patient, parent, and staff outcomes helps facilitate more tailored, high quality care in the NHS (Darzi, 2008).

Patient and parent satisfaction is important in assessing the perceived opinion of a patient’s outcome in relation to both their facial appearance and resulting quality of life. However, qualitative outcomes are notoriously difficult to assess, difficult to adequately quantify, and difficult to compare meaningfully on a national and international scale. Common techniques that are used to collect qualitative data include patient interviews and patient and parent satisfaction questionaries. Questionnaire response rates can however be low and often questionaries are designed for use in the general population, potentially reducing their validity when used in cleft research (Jones et al., 2014).

Research into how patients and parents perceive their cleft care has shown good levels of satisfaction from both parties on the tailored care they have received from the entire cleft team. Dissatisfaction from patients tended to focus on their nasolabial appearance, profile, and speech outcomes. Parental opinion tended to mimic that of their children but additionally highlighted the parental perception of the impact of the treatment of cleft lip and palate on their offspring. They felt that the protracted care had a negative impact on their child's educational performance and academic development (Noar, 1991). Questionnaire based research into the opinion of the whole cleft team on outcome suggested good inter-specialty agreement. The perception was that patients were receiving a high quality of care but could still be left with residual facial asymmetry, altered speech, and negative long term effects on their social and emotional intelligence (Noar, 1992).

The CSAG Study included patient and parent questionnaires for all groups and additional interviews for data collection for the 12-year-old patient cohort. Questionnaires focused on the perception of the care and attention received as well as clinical outcomes like an individual's speech, profile, dental appearance, and nasolabial appearance. Mirroring other research into cleft care, both patients and parents were satisfied with the level of care they had received. However, responses in the 12-year-old cohort did note dissatisfaction with their speech and nasolabial appearance (Williams et al., 2001).

1.7.10. Other outcomes

In orthodontics the Index of Orthodontic Treatment Need (IOTN) is used to assess the eligibility of patients to receive NHS orthodontic treatment based on their degree of malocclusion and dental aesthetics. It includes a Dental Health Component (DHC); scored from 1-no need for treatment to 5-very high need for treatment, and an Aesthetic Component (AC); scored from 1 to 10. Patients born with defects of cleft lip and palate and other craniofacial anomalies have a very high need for treatment (IOTN – 5p) (Brook & Shaw, 1989).

The most common way of assessing the outcome of orthodontic treatment is the Peer Assessment Rating (PAR) (Jones et al., 2014; Richmond et al., 1992). The PAR score is a validated assessment tool that provides a single score summary of all the occlusal anomalies in a patient's malocclusion. The measurements are taken using a PAR ruler and comparisons are made between pre-treatment and post-treatment dental study models. An improvement in PAR score would indicate an improvement in malocclusion and reflect a good outcome following orthodontic treatment (Richmond et al., 1992). The use of PAR scores in assessing orthodontic outcomes in patients born with cleft lip and palate facilitates meaningful comparisons to be made with the general population as a non-cleft control. However, due to the complexity of both the malocclusion and orthodontic treatment in cleft patients, minimal PAR score improvements may be observed. Scoring of a patient's post-treatment dental study models may indicate that the malocclusion is 'worse or no different' when compared to the pre-treatment models (Furness et al., 2021).

Assessing the outcome following Alveolar Bone Grafting (ABG) surgery can also be carried out to monitor treatment outcomes for patients born with cleft lip and palate. The Clinical Standards Advisory Group (CSAG) Study utilised a modified Bergland index to assess ABG surgical outcomes and found that 15% of 12-year-olds had still not received alveolar bone grafting and only 58% of grafts were deemed successful (Bergland et al., 1986; Williams et al., 2001). Most modern research studies now use the Kindelan bone-fill index to assess the surgical outcome based on comparisons of pre- and post-treatment radiographs. Commonly an anterior occlusal radiograph is taken at least 3 months post-surgery and the degree of post-operative bony infill is assessed. It is graded from 1 to 4; Grade 1 - >75% bony fill, Grade 2 – 50-75% bony fill, Grade 3-<50% bony fill, and Grade 4 – no complete bony bridge (Kindelan et al., 1997; Kindelan & Roberts-Harry, 1999). Grades 1 and 2 would indicate successful surgical intervention, grade 3 would indicate partial failure and grade 4 would suggest total failure. Research by Revington et al. (2010) indicated that there has been improvement in UK ABG surgical outcomes since the CSAG study and reorganisation of surgical services; with a success rate of up to 85%. However, as a different outcome measure was used in the original CSAG Study it can be difficult to draw meaningful comparisons (Revington et al., 2010; Williams et al., 2001).

Mirroring audiology outcomes, the Cleft Registry and Audit Network (CRANE) are currently working with clinical networks in orthodontics and oral and maxillofacial surgery (OMFS) to potentially collect data on the outcome measures in relation to orthodontic care and alveolar bone grafting (ABG) surgery (CRANE, 2021).

1.7.11. Facial Asymmetry

Facial symmetry tends to correspond with attractiveness and good facial symmetry and balance is often seen as a prerequisite for acceptable facial aesthetics and beauty. Lateral facial asymmetries may have minimal to no impact on a persons perceived beauty but attractiveness diminishes as an obvious asymmetry approaches the midline of the face (Springer et al., 2007). Research has shown that when viewing a face, an observers gaze tends to be drawn towards an individual’s eyes, nose and mouth (Mertens et al., 1993). The most frequently observed facial region on initial gaze positively correlates with the most frequently affected region in patients born with cleft lip and palate. However, perfect symmetry does not necessarily equate to facial aesthetic perfection. Highly attractive faces may be symmetrically and systemically different than an average symmetrical face (Perrett et al., 1994). Understanding the relationship between facial asymmetry and facial attractiveness can help shape future care and treatment protocols in patients born with cleft lip and palate.

Increased attractiveness as a by-product of facial symmetry has been shown to derive a greater social acceptance, improved social skills, and increased likeability (Goldman & Lewis, 1977). Conversely, patients born with cleft lip and palate may develop a social stigma related to their facial asymmetry. They may be socially deprived at an early age, be subject to bullying and teasing, and be less desirable as a potential future mate (Meyer-Marcotty et al., 2011). Psychologically, individuals may present with less self-esteem and a lower self-worth than their peers; potentially arising from their lack of popularity at school, discrimination based on their appearance, and lack of social support (Sousa et al., 2009).

Patients born with cleft lip and palate have a congenital birth defect that can affect the soft tissue facial morphology as well as the underlying hard tissue that provides support and structure to the face. A diagnosis of unilateral cleft lip and palate (UCLP) equates to increased asymmetry on the ipsilateral side of the cleft and even following surgery a degree of residual asymmetry is often present. In the general population the chin tends to be the area of most notable facial asymmetry, but for cleft patients the asymmetry is more concentrated in the nasolabial region (Kuijpers et al., 2015). Research more commonly involves patients with unilateral cleft lip and palate (UCLP) as opposed to bilateral cleft lip and palate (BCLP) as BCLP is a more symmetrical defect (Bugaighis et al., 2014). Analysis of facial asymmetry in UCLP allows more meaningful comparisons of facial dysmorphology between the affected and unaffected sides.

Facial symmetry and consequently facial attractiveness have a significant determination on an individual’s quality of life. The assessment of facial asymmetry will be discussed in detail in the following section.

1.8. Assessment of Facial Asymmetry

1.8.1. Clinical Examination

Clinical examination of a patient with cleft lip and palate includes evaluation of many different aspects of an individual by various healthcare professionals but tends to include a clinical assessment of facial asymmetry. Clinical examination of facial proportions is carried out systematically in all three planes of space: antero-posterior (A-P), vertical, and transverse. Clinicians tend to assess the underlying skeletal pattern of the patient in the A-P dimension, their vertical growth pattern, their facial symmetry and balance in the transverse dimension, and assess their maxilla and mandible for deficiency or excess. Observations are carried out via frontal inspection, inspection in profile, and further inspection via birds-eye view or worms-eye view to better visualise any asymmetries around the midline.

An evaluation of facial asymmetry is commonly done via the observation of differences bilaterally around an imagined facial midline. This can be useful in detecting obvious facial asymmetries but may not detect more subtle discrepancies. Difficulties can also arise in a patient with pan-facial asymmetry whereby an obvious midline would be challenging to imagine or construct. An alternative method is to divide the face in frontal view into vertical fifths as depicted in Figure 1-10. The imaginary lines are constructed through the medial and lateral canthi, with the chin and nose centred in the central fifth, and the interpupillary distance approximately equal to the width of the mouth (Proffit et al., 2018).

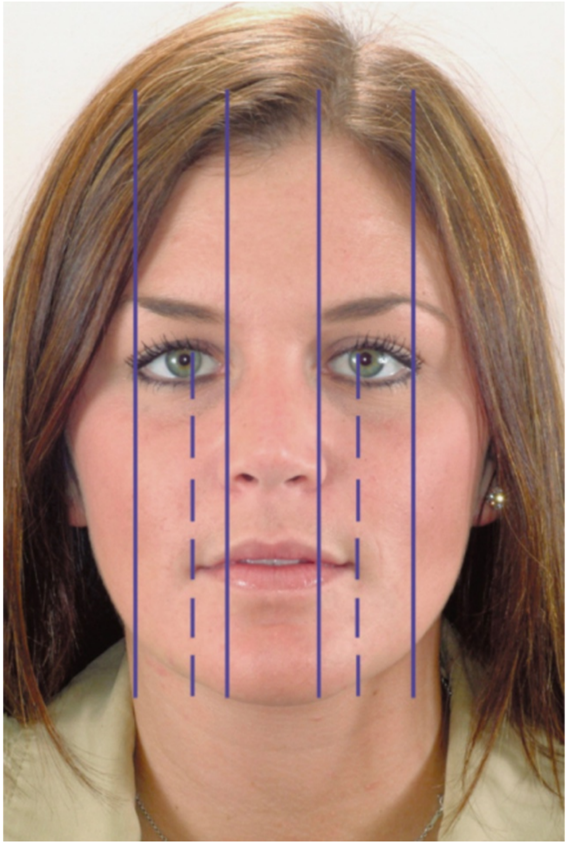


Figure 1-10. Facial proportions, symmetry, and vertical fifths in the frontal plane. The face can be divided into central, medial, and lateral fifths via vertical lines through the medial and lateral canthi. The nose and chin should be contained within the central fifth and the interpupillary distance should be equal to the width of the mouth (Proffit et al., 2018).

The main limitation of a clinical exanimation of facial asymmetry is its reliance on the subjective perception of the observer. Without clinical records the clinical interpretation is also non-reproducible and non-specific. It tends to assess the face in a static position and therefore the fluidity of motion during dynamic social interaction is not assessed. The risk is that the clinician focusses on the broader evaluation of certain key facial features like the chin point, nasal tip, or interpupillary line and may miss more subtle facial asymmetrical points. It also produces data that lacks sufficient validity and reproducibility to be used to make statistical comparisons and draw meaningful conclusions from.

1.8.2. Radiology

Facial asymmetry has also been observed and researched via the use of ionising radiation, most commonly with lateral cephalograms but also via computerised tomography (CT) and cone-beam computerised tomography (CBCT).

A longitudinal growth study by Sadowksy et al. (1973) looked at serial lateral cephalograms from 75 patients with unilateral cleft lip and palate (UCLP) compared to non-cleft controls. They analysed patients' soft tissue profile as a marker of facial dysmorphology and by proxy facial asymmetry. Patients born with UCLP tended to initially have thinner upper lips and a less convex facial profile with detectable midfacial flattening (Sadowsky et al., 1973). Early European comparisons utilising lateral cephalograms on 5-year-olds with UCLP between Oslo, Norway and Manchester, UK showed worse outcomes in the UK cohort. Patients born with UCLP in the UK were more likely to have maxillary retrognathia with upper lip retrusion significantly behind the esthetic plane (Mackay et al., 1994). The esthetic plane or E plane is an imaginary line from the tip of the nose to the tip of the chin initially described by Ricketts (1960). An ideal aesthetic facial profile is thought to have the lower lip positioned approximately 2mm behind the E plane and the upper lip 4mm behind (Ricketts, 1960).

108 cleft infants with a mean age of 22-months-old with UCLP were compared to unilateral cleft lip controls using infant cephalometry in the lateral, axial, and frontal projections. This assessment of infant facial dysmorphology showed the primary differences being localised to the maxillary complex, but this research involved a significant radiation dose to young children (Hermann et al., 2000).

Research by Bearn et al. (2002) looked at lateral cephalograms of 182 patients between 12 to 14 years of age with UCLP to analyse their soft tissue profile. Analysis included evaluation of their soft tissue ANB, nasolabial angle, and facial convexity. The primary outcome measures for UK participants were unfortunately worse than previously studied populations (Bearn et al., 2002). Analysis of soft tissue thickness of patients born with UCLP and BCLP using lateral cephalograms has shown cleft patients tend to have thicker soft tissues over stomion and rhinion and thinner soft tissues over subnasale (Erdur et al., 2019).

The use of lateral cephalograms in orthodontic diagnosis and treatment planning is common, but their use in the assessment of facial asymmetry has several limitations. Firstly, they use ionising radiation, and a small dose is imparted on each patient. Lateral cephalograms also only assess facial morphology in profile and lack frontal observation of potential asymmetry and distortion associated with the vermillion border and columella. Methodological errors may also cause capture errors associated with patient head angulation, rotation, and head tilt; this may lead to an inaccurate radiograph or increased difficulty in landmark identification. The reproducibility, validity, and accuracy of landmark identification may also be questioned especially when identifying soft tissue points. Observations of facial asymmetry for patients with UCLP in profile may also result in superimposition of the cleft side with the contralateral unaffected side and the validity of assessing a three-dimensional (3D) deformity in 2D has been disputed (Bearn et al., 2002). Finally, the lateral cephalogram is a static 2D image and lacks assessment of facial dysmorphology in 3D and during dynamic facial animation.

Computerised tomography (CT) and cone-beam computerised tomography (CBCT) are commonly used in research to assess hard tissue structures and can be used in cleft lip and palate to assess alveolar bone grafting (Dado et al., 1997). They are not recommended in assessing facial asymmetry due to their proportionally higher radiation dose and poor soft tissue resolution and contrast. The equipment is also expensive to procure and maintain. While they offer assessment in 3D over 2D lateral cephalograms this benefit is outweighed by the poor soft tissue visualisation and image artefacts.

1.8.3. Anthropometry

Anthropometry is the study and measurement of the human body and was originally developed as a tool to assess human development in anthropology. It can involve measurements of distance, size, height, length, and angulation. Anthropometry can either be direct; with measurements taken directly on a patients face as seen in Figure 1-11 (a) and (b), or indirect; with measurements taken from clinical records including photographs, radiographs, and study models as seen in Figure 1-11 (c), (d), and (e).

Figure 1-11. Facial measurements for anthropometric analysis. (a) With the use of bow callipers. (b) With the use of straight callipers. (c - e) Commonly used anthropometric measurements (Proffit et al., 2018).

1.8.3.1. Direct

Direct anthropometry was originally carried out via direct measurements on the non-living dry human skull. For skeletal dimension measurements on living individuals, landmarks can be identified using soft tissue points that overly the previously established hard tissue landmarks (Proffit et al., 2018). Accurately carrying out direct anthropometric measurements requires training, calibration, and practice. Additionally, it can be time consuming and laborious for the examiner and the examinee; especially if the subject is a young child.

Large research studies have been carried out using direct anthropometry on healthy North American Caucasians. Farkas et al. (1981) analysed data from 308 Caucasian participants of equal gender spread taken from a larger anthropometric study that included 1312 Caucasian children from 13 distinct age cohorts. He concluded that facial asymmetry is common; even in healthy individuals, and the degree of facial asymmetry detected is independent of a patient's age and gender (Farkas & Cheung, 1981). Farkas is seen as one of the pioneers of direct anthropometry of the head and neck region and has written a book on the subject (Farkas, 1994). He details the appropriate technique to carry out measurements, the advantages and limitations of the technique, the potential sources of error, and lists craniofacial norms for varying ethnic populations. Farkas was also one of the first to apply direct anthropometry to children born with cleft lip and palate (Farkas, 1990). Direct anthropometric measurements of patients born with cleft lip and palate pre- and post-primary repair surgery showed a significant reduction in facial asymmetry post-surgery. However, residual dysmorphology was common and discrepancies of the nasal floor width and columella length were seen (Farkas et al., 1993).

1.8.3.2. Indirect

Indirect anthropometry as previously described is indirect measurements of distances and angles taken from a patient's clinical records; including but not limited to patients' photographs, radiographs, and study models. The benefit of indirect measurements is that the measurement can be repeated and validated, and multiple observers can complete the measurements to ensure adequate reproducibility. Conversely, the accuracy of the measurements depends on the quality of the clinical records. Poor study model definition and clinical photographs that are out of focus or dimly lit may reduce the accuracy of landmark identification and subsequent measurements.

A previous retrospective analysis of two primary cleft lip repair techniques included 33 patients with UCLP between the ages of 4 and 5 years of age and carried out direct and subsequent indirect anthropometric analysis of the participants' clinical photographs. The anthropometric measurements included nasal tip deviation, nasal protrusion, nasal height and length, nasolabial angle, and alar and nostril length (Horswell & Pospisil, 1995). Indirect anthropometry can also be carried out on 3D images as well as 2D clinical photographs. Preoperative 3D stereophotogrammetry was used to capture 26 consecutive patients with unrepaired UCLP and indirect measurements were taken of 26 linear and angular measurements (Tse et al., 2014). The benefit of utilising 3D is that more surface information is available and landmark identification should be easier when each landmark can be viewed from multiple angles. There is also a reduced chance of measurements being influenced by 2D capture angulation errors and parallax errors. Indirect anthropometry has also been carried out via the use of automated computer assisted software (Hurwitz et al., 1999).

Despite the clear benefits of direct and indirect anthropometry several key limitations are also evident. The measurements rely on the precision of the observer accurately identifying salient landmarks, which can be increasingly difficult to locate by indirect means as the quality of the clinical record decreases. Assessment of facial asymmetry also focusses on identifiable landmarks in 2D and 3D; the rich surface information of the whole face is lost, and no assessment is carried out during facial animation. Previous research into the precision and reliability of craniofacial anthropometry showed that intra- and inter-observer reliability, reproducibility, and validity is questionable. Measurement errors are common and anthropometric measurements of less than 10cm are of high risk of a significant capture error and therefore reduced reliability and validity (Jamison & Ward, 1993). Unfortunately, the most valuable anthropometric measurements of patients with cleft lip and palate are taken from the nasolabial region and all measurements tend to be less than 10cm.

1.8.4. 2D Imaging

Assessment of facial asymmetry using two-dimensional imaging (2D) is the current most common form of assessment used in research and international comparisons. 2D imaging can include clinical photographs, radiographs, and clinical videos. The accuracy of the assessment often relies on the quality of the clinical record and measurement accuracy is prone to error based on patient position, head rotation, facial expression, parallax errors and image distortion and processing errors. 2D imaging can also function as part of the assessment of facial asymmetry within the previously discussed clinical examination, radiological examination, and indirect anthropometric measurements.

The most widely accepted 2D assessment of facial asymmetry in patients with a unilateral cleft lip and palate is the Asher-McDade Aesthetic Index, which has been shown to be a reliable and valid assessment tool and has been adopted and utilised by large research studies including the Clinical Standards Advisory Group (CSAG) Study and the Eurocleft Study (Brattström et al., 2005; Williams et al., 2001). It involves the assessment of the nasolabial region while masking the patients background facial features. This anonymises the patient and conceals other facial features that may induce observation bias on the subjective assessment, such as a patient’s hair, eyes, and general facial attractiveness. The cropping of the clinical photographs to show the nasolabial region is shown in Figure 1-12. However, Figure 1-12 depicts a patient with bilateral cleft lip and palate (BCLP) and we will be focussing on unilateral cleft lip and palate (UCLP) for this study. The assessment involves the subjective rating of 2D clinical photographs by a panel of examiners. The nasolabial region is ranked on an ordinal scale and the examiners assess nasal form, nasal symmetry or deviation, nasal profile, and the vermillion border (Asher-McDade et al., 1991). This standardised assessment facilitates broader comparisons of treatment outcomes to be made between different centres and countries; however, it still involves subjective assessments of static 2D images.

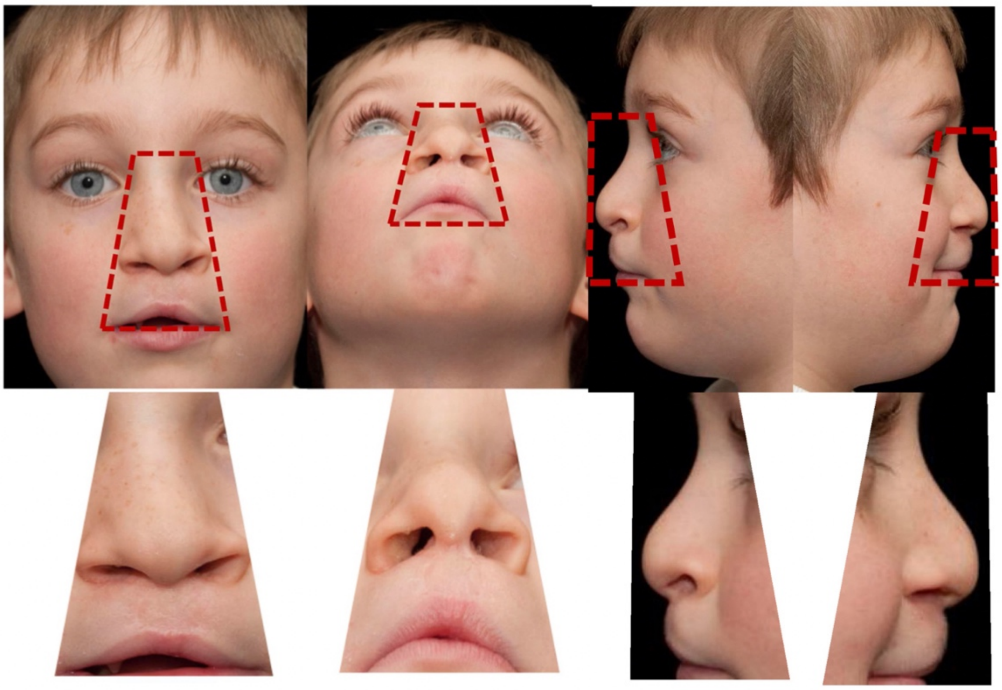


Figure 1-12. Cropped clinical photographs to show the nasolabial region. These images can be used in the assessment of facial asymmetry via the Asher-McDade Aesthetic Index adapted for use in patients with a bilateral cleft lip and palate (Thomson et al., 2021).

The Eurocleft study adopted the Asher-McDade Aesthetic Index and used frontal and profile clinical photographs of the nasolabial region of patients with UCLP from 9 to 17 years of age (Brattström et al., 2005). As previously discussed, they obscured the background features to focus on the nasolabial region and subjective assessments were completed by a panel of 4 examiners. A Likert scale was used to assess nasal form, nasal symmetry or deviation, nasal profile, and the vermillion border. Unfortunately, there was low inter-examiner agreement in the assessment and there was significant variability in the quality of the clinical photographs including the capture angulation and tilt. In addition, a subset of the profile photographs was captured from the non-cleft side, potentially introducing a degree of inconsistency and bias to the ratings. Overall, the authors advised that the comparative results should be interpreted with caution.

The Clinical Standards Advisory Group (CSAG) Study assessed the nasolabial appearance of 200 5-year-olds and 191 12-year-olds with UCLP via the Asher-McDade Aesthetic Index. Standardised clinical photographs with background masking to highlight the nasolabial region were assessed by a panel of 3 judges. Subjective assessments were made via a 5-point Likert scale and inter- and intra-rater reliability was good due to a more standardised clinical photograph capture methodology compared to the Eurocleft study (Williams et al., 2001). Unfortunately, only 31% of 5-year-olds and 20% of 12-year-olds were perceived to have had a good or very good lip appearance outcome, and for the 12-year-old cohort, 42% of children were deemed to have had a poor or very poor nasal appearance. The assessment was still limited by the subjective assessment of 2D static images. Interestingly, patients tended to report a high level of satisfaction with their nasolabial appearance (Williams et al., 2001). This may be partially explained by their inability to liken their own personal outcome with a comparable peer with the same diagnosis. Therefore, they draw comparisons of their post-surgical appearance with their own perceived memory of their pre-surgical disfigurement.

The assessment of facial asymmetry in cleft lip and palate utilising 2D imaging can also assess facial animation via the use of video recordings. Morrant and Shaw (1996) described a technique for using standardised video recordings to assess the outcome of cleft surgery. They assessed the nasolabial region of 30 patients with UCLP between the age of 11 to 14 years old. This involved subjective assessments of 2D animation by a panel of examiners, but unfortunately had inherent risk of inter- and intra-rater variability.

Clinical photographs and video recordings can be used in conjunction for the assessment of facial asymmetry in cleft lip and palate, to facilitate the assessment of both static and dynamic facial dysmorphology. Research by Trotman et al (2007) utilised 2D photographs and videos to carry out subjective evaluation of patients prior to potential lip revision surgery. The final decision regarding lip revision surgery is often determined by the subjective clinical assessment of the surgeon and may vary depending on the surgeon’s confidence, skill, competence, and willingness to perform the surgery. This study had an expert panel of 8 plastic surgeons and showed poor inter-rater reliability and agreement, highlighting the need for more objective measures of assessment (Trotman et al., 2007).

Further attempts have been made to link subjective and objective assessment measures. Bearn et al. (2002) carried out retrospective analysis of the soft tissue profile of 175 patients with UCLP between 12 to 14 years of age. They compared the subjective evaluation of an expert panel assessment with 7 objective angular measurements. The subjective and objective outcome measures showed good association and this further highlighted the need to move towards more objective measures of facial asymmetry to facilitate broader comparisons and eliminate subjectivity and bias Bearn et al., 2002).

Unfortunately, despite the breadth and depth of research utilising 2D imaging in the assessment of facial asymmetry in cleft lip and palate it is not without its limitations. 2D imaging in the form of clinical photographs is static and only becomes dynamic when video recordings are used. The assessment is commonly subjective and prone to observer bias and poor inter- and intra-rater reproducibility and reliability. Adequate expert panel calibration is difficult and ensuring sufficient validity is challenging. As previously discussed, assessment relies on high quality clinical records and may be influenced by errors in image quality and angulation. Accurate landmark identification on poor quality records may be seen and observers may focus on confounding landmarks or variables when assessing the nasolabial region unless background masking is provided. Finally, the assessment is carried out in 2D and 2D assessment has been shown to underestimate the dynamic facial dysmorphology of an animated 3D object (Gross et al., 1996). Assessment in 2D does not consider the direction or velocity of landmark displacement during animation or allow for the assessment of asymmetry in all 3 planes of space.

1.8.5. 3D Imaging

The assessment of facial asymmetry using three-dimensional imaging (3D) is becoming more widely used in clinical research. 3D imaging can be in the form of images produced from ionising radiation, such as computerised tomography (CT), cone-beam computerised tomography (CBCT), and magnetic resonance imaging (MRI), or non-ionising three-dimensional imaging (3D). Non-ionising 3D imaging is increasing in popularity with different hardware and software being developed to capture the images. 3D image acquisition may be captured via various scanners, cameras, and technologies; including but not limited to laser scanning, structured light-based scanning, and 3D stereophotogrammetry. 3D imaging provides the benefit of full-face capture and assessment in all 3 planes of space. Assessment of facial asymmetry, rating of facial features, and landmark identification can be performed from multiple angles and viewpoints, eliminating the potential positional or parallax errors commonly seen in 2D image analysis. The assessment of facial asymmetry on 3D imaging can be accomplished via either subjective or objective methodology. However, there is currently no internationally agreed methodology for assessment and as such it is difficult to combine research results due to the significant heterogeneity in the outcome measures used (Thierens et al., 2018).

1.8.5.1. Ionising radiation

As previously discussed, the use of computerised tomography (CT) and cone-beam computerised tomography (CBCT) is common in the assessment of hard tissues in cleft lip and palate patients. It is a useful research tool in the longitudinal assessment of alveolar bone grafts (Dado et al., 1997). The soft tissues of patients can also be observed on CBCT imaging but with poorer contrast and resolution. The poor surface texture definition coupled with image artefacts and a proportionally higher dose of ionising radiation means CBCT's are seldom used in the assessment of facial asymmetry in isolation.

Fisher et al. (1999) utilised CBCT's in the assessment of 12 patients with unrepaired UCLP aged 3 months old. The images were used to analyse the primary cleft lip nasal deformity prior to surgical intervention. Unfortunately, this study had a low sample size, a proportionally high radiation dose, and the poor soft tissue resolution may have obscured the surface landmark identification accuracy (Fisher et al., 1999).

1.8.5.2. Laser scanning

Non-ionising 3D imaging in the form of laser scanning uses a low-level laser light to construct a three-dimensional image. The laser tracks across the face and the beam scatters over the surface before being collected and converted into a 3D image using the X, Y, and Z coordinates via trigonometry (Thierens et al., 2018). Laser scanning of the face tends to have a longer capture time when compared to 3D stereophotogrammetry and as such may not be suitable for use in younger patients who would struggle to sit still for prolonged periods. Lasers have been reported to potentially cause retinal damage if used inappropriately, however, eye-safe lasers can be utilised (Djordjevic et al., 2014). The main advantage of laser scanning over alternative methods is its affordability and portability as a capture tool.

Duffy et al. (2000) used laser scanning to construct a 3D image of 39 patients with cleft lip and palate and 25 unaffected controls between the ages of 8 to 11. They used anthropometric landmarks to analyse linear facial measurements and carry out distance mapping. Their objective assessment methodology concluded that laser scanning is effective in the assessment of facial dysmorphology and patients with cleft lip and palate have significant differences in their nasal base width, vermillion thickness, and intraocular width compared to unaffected controls (Duffy et al., 2000).

Kishi et al. (2012) carried out analysis of the philtral dimple and changes in philtral morphology during development using 3D images acquired via laser scanning. They analysed and compared 15 patients with UCLP with 55 adult and 75 child controls. They employed landmark based objective analysis of linear and angular facial measurements and concluded that patients with UCLP have altered and deformed philtral morphology (Kishi et al., 2012).

Djordjevic et al. (2014) used laser scanning to assess facial asymmetry and shape in 12 5-year-old patients with UCLP and 35 age-matched unaffected controls. Their objective assessment of facial dysmorphology was independent of landmark analysis and they did not utilise linear or angular measurements. Facial asymmetry was calculated via superimposition of the 3D image with its own mirror image. A completely symmetrical face would superimpose perfectly and as such facial asymmetry was calculated via the average distance between the two facial surfaces. They concluded that laser scanning can be effective in young patients provided they are briefed prior to capture and are cooperative during the capture window (Djordjevic et al., 2014).

3D imaging with laser scanning is used less frequently than 3D stereophotogrammetry due to its prolonged capture time and potential retinal damage if used inappropriately. However, with the development of eye-safe lasers and ever improving capture times these limitations are becoming less relevant. Laser scanning may be seen as a more affordable and portable method to introduce 3D imaging to a service. Subjective and objective assessment methodology can be used and the limitations of landmark based analysis may be overcome via superimposition of the scan with its own mirror image (Djordjevic et al., 2014).

1.8.5.3. Structured light-based scanning

Structured light-based scanning, when used in the assessment of facial asymmetry, involves the projection of white light onto the surface of a face. The light may be in the form of an alternating or phase-shifted pattern of horizontal stripes, vertical stripes, dots, or a meshed grid (Thierens et al., 2018). The light pattern is distorted by the surface texture of the face and the light deformation pattern is then recorded by a camera and the 3D image is calculated and produced. Similar to laser-based scanning the comparative capture time for structured light-based imaging is longer than 3D stereophotogrammetry and therefore it may not be suitable for facial analysis of younger children with short attention spans or poor cooperation.

Bilwatsch et al. (2006) used structured light-based scanning in the form of phase-shifted fringe patterns to construct 3D images of 22 patients with UCLP at 10 years of age who had undergone primary lip repair via the Tennison-Randall technique. Facial asymmetry of the nasolabial region was assessed via objective linear, angular, and volumetric measurements following landmark identification and determination of a plane of symmetry via superimposition. They concluded that following primary lip repair, patients with UCLP still had significant residual facial asymmetry present (Bilwatsch et al., 2006). However, the objective measurements were based on landmark identification and measured in relation to an imaginary line of symmetry and therefore their accuracy and reproducibility are questionable.

Meyer-Marcotty et al. (2010) assessed the impact of facial asymmetry in visual perception using 3D images constructed using structured light-based scanning in the form of a phased vertical stripe pattern. They carried out objective and subjective assessment of facial asymmetry in 18 adult patients with UCLP compared to 18 unaffected controls. Subjective assessment was done via the rating of facial appearance and facial asymmetry by a panel of 30 lay assessors. Objective assessment was landmark independent and involved superimposition of the 3D scan with its own mirror image and facial asymmetry was calculated based on the distance between the two facial surfaces. They concluded that patients born with UCLP had objectively increased soft tissue asymmetry especially concentrated in the midface and subjectively cleft patients were viewed more negatively in terms of facial appearance (Meyer-Marcotty et al., 2010).

1.8.5.4. Stereophotogrammetry

3D stereophotogrammetry is the most commonly used method of 3D image capture and provides a broader field of capture in a single exposure. The principle of 3D stereophotogrammetry uses 2 or more cameras to take synchronous images of the face from different angles. The images are then stitched together to form a complete 3D image (Thierens et al., 2018). 3D stereophotogrammetry provides an accurate representation of the subject’s surface facial geometry as well as colour and texture data, thus providing a geometrically accurate rendering of the face (Heike et al., 2010). It allows for a faster and safer image acquisition compared to the previously discussed methods and therefore lends itself to imaging of younger patients.

Ayoub et al. (2011) used 3D stereophotogrammetry to assess the lip morphology of 21 Scottish Caucasian 3-year-old children with UCLP following primary surgical repair compared to 96 unaffected controls. 3D image capture was carried out via a di3D (Dimensional Imaging, Ltd.) stereophotogrammetry system and participants faces were captured both at rest and at maximum smile. Objective assessment was carried out by the identification of 4 facial landmarks by a single operator followed by the analysis of linear and angular measurements. 3D images were mirrored and superimposed using Procrustes analysis to create a homogenous sample for analysis. This study identified that patients with UCLP still had residual facial dysmorphology present post-surgical repair. Compared to controls, patients with UCLP had a flatter upper lip and an increased philtrum width (Ayoub et al., 2011). A potential limitation with this study; common to many research studies in cleft lip and palate, was the difficulty in recruiting large numbers of age-matched patients with UCLP given its prevalence. The comparison also relied on accurate landmark identification and subsequent linear and angular measurements, not fully assessing the asymmetry and shape of the whole face.

Bell et al. (2014) used 3D stereophotogrammetry to objectively assess postsurgical facial dysmorphology in unilateral cleft lip (UCL) and unilateral cleft lip and palate (UCLP) compared to non-cleft controls. They captured 3D images of 10-year-old children using a di3D (Dimensional Imaging, Ltd.) stereophotogrammetry system. 51 patients with UCLP, 44 with UCL, and 68 non-cleft controls were analysed. Images were captured at rest and at maximum smile and landmark-based analysis was used in conjunction with facial curve analysis. They also concluded that residual facial asymmetry remains following surgical repair, with the highest asymmetry associated with the contour of the upper lip of cleft patients (Bell et al., 2014). The assessment of facial asymmetry using facial curve analysis allowed for a more comprehensive analysis of facial shape and residual deformity, but still relied on accurate landmark identification.

Dadáková et al. (2016) used 3D stereophotogrammetry to assess facial morphology in pre-school children with cleft lip and palate. 3D images were captured of children between the ages of 2.5 to 5 years old using a Vectra 3D scanner (Canfield Scientific, Inc., Fairfield, NJ, USA). A total of 40 patients with UCL, 22 with UCLP, 10 with BCLP, and 60 non-cleft controls were included in the study. 3D images were captured at rest and facial shape analysis and variability was analysed using generalised Procrustes analysis (GPA) and principal component analysis (PCA). They concluded that patients with a more severe cleft diagnosis; UCLP and BCLP, reflected more significant facial shape dysmorphology (Dadáková et al., 2016). The key benefit of this study was the use of full facial shape analysis over more rudimentary landmark-based analysis.

It facilitated a more in-depth analysis of the entire face; however, facial asymmetry was still not assessed during facial animation as this was a static assessment not a dynamic one.

1.8.5.5. Alternative methods and limitations

An alternative method for 3D capture of the nasolabial region in patients with cleft lip and palate is the use of an intraoral scanner (IOS). Ayoub et al. (2021) validated the use of an IOS by capturing the nasolabial region of 18 patients with UCLP. Subjective evaluation by 5 experts and 5 lay representatives positively correlated with the objective assessment of lip asymmetry and residual scarring (Ayoub et al., 2021). The use of an intraoral scanner could therefore be seen as a cost effective and valid objective assessment tool that could be used in the assessment of facial asymmetry in cleft lip and palate.

There are several limitations of using 3D imaging in the assessment of facial asymmetry in cleft lip and palate. Most notably the assessment is in 3D rather than 4D; it is the static assessment of facial dysmorphology and does not account for dynamic asymmetry during facial animation and facial expressions. Facial asymmetry has been shown to be greater at maximum smile, therefore assessing dynamic facial motion is key (Al Rudainy et al., 2019). There is also a wide range of assessment methodologies used and therefore it is difficult to combine and meaningfully interpret the results. Many techniques rely on landmark identification and tracking and do not fully utilise the data rich surface of the entire face. Several assessment methodologies use subjective evaluation techniques that may lack sufficient reproducibility and validity. Widely used objective measurements are needed to inhibit observer bias and improve validity. The 3D capture equipment is also expensive to procure and maintain, from which we may conclude that 3D imaging is likely to be more common in wealthier countries and international comparisons with poorer socioeconomic regions may not be possible. Low-income regions are more likely to use 2D image capture methodology that has proven validity for subjective and objective assessment. 3D image processing and analysis is also very data intensive and requires complex statistical analysis, implementation on a wider scale without expert input may be challenging. A review of methodology used in the assessment of facial asymmetry in cleft lip and palate concluded that there was significant variation in research study designs and an internationally accepted objective assessment tool was required (Al-Omari et al., 2005).

1.8.6. 4D Imaging

Assessment of facial asymmetry in cleft lip and palate using 4D imaging is the logical next step following assessment in 3D. The dynamic assessment of facial motion and animation better mimics the facial movements of cleft patients on a day-to-day basis during social interaction. Static assessment in 2D and 3D fails to adequately assess the intricate asymmetries that may be present during facial expression. 4D imaging is in essence a dynamic 3D image of the face that is tracked throughout a given facial movement. The most common form of 4D imaging is the use of 4D stereophotogrammetry, to capture multiple 3D images of a patient every second depending on the fps of the capture system. It has been long understood that dynamic capture was required to fully assess the facial asymmetry present in patients with cleft lip and palate; early research used 2D video recordings for this purpose but the evaluation was often subjective and the video recordings were at risk of image capture error, positioning error, and parallax errors (Trotman et al., 2007). There is currently a dearth of research of 4D imaging in cleft lip and palate, but this is steadily improving as access to 4D imaging is increasing. The barriers to incorporating 4D imaging into the routine assessment for facial asymmetry include the expense in procuring the 4D imaging hardware and software, data storage issues given the volume of data collected, and the difficulty in processing and meaningfully analysing the data given its mass and complexity.

Early research by Trotman et al. from the United States of America carried out objective assessment of facial dysmorphology in cleft lip and palate using 4D images captured by a video-based tracking system (Motion Analysis; Motion Analysis Corporation, Santa Rosa, CA) at a rate of 60-fps (frames per second) (Trotman et al., 2000, 2005, 2007). Retro-reflective facial markers were placed on identifiable facial landmarks and tracked throughout several maximum facial expressions. The initial study used 30 4mm facial markers to track 4 facial expressions: maximum smile, cheek puff, lip purse, and grimace (Trotman et al., 2000). Subsequent studies improved the precision of the assessment by using 38 2mm facial markers to track 5 facial expressions: maximum smile, cheek puff, lip purse, grimace, and mouth opening (Trotman et al., 2005, 2007).

The initial study looked at the objective assessment of nasolabial displacement during facial movement of 4 patients with UCLP and 5 patients with BCLP compared to 50 non-cleft controls. They adjusted for patient head movements with modified Procrustes fit methodology and found a difference in the magnitude and symmetry of nasolabial movements between cleft patients and non-cleft controls (Trotman et al., 2000). This study was limited by its use of landmark-based tracking as it did not utilise the data-rich surface texture and morphology of the full face. It also had a low sample size and relied on accurate landmark identification and placement of retro-reflective markers. Placement of markers on the facial surface is also prone to positional error and potential slippage during facial animation; the markers being present on the face may also inhibit or alter full facial movement.

Further research on the visual and statistical modelling of facial movements in patients with cleft lip and palate analysed 12 patients with unilateral cleft lip and 4 patients with bilateral cleft lip compared to 8 non-cleft controls. Despite the previously discussed issues with landmark-based tracking, low sample size, and non-homogenous cleft sample, they demonstrated a suitable approach to objective 4D analysis of facial asymmetry (Trotman et al., 2005). Further objective assessment of functional outcomes of cleft lip surgery focussing on the analysis of nasolabial movement included 31 patients with repaired cleft lip and palate planned for revision surgery, 32 patients with repaired cleft lip and palate not planned for revision surgery, and 37 non-cleft controls. They found that patients with cleft lip and palate had restricted upper lip movement when compared to non-cleft controls and greater restriction was seen in BCLP compared to UCLP (Trotman et al., 2007). This study had a much-improved sample size, but analysis was still restricted by landmark identification and tracking.

Mishima et al. (2009) used 4D imaging of 2 17 year-old patients with BCLP compared to 6 healthy non-cleft controls captured using a 3D video (OGIS

Research Institute Co. Ltd, Osaka, Japan) system at a rate of 30-fps. This capture system had half the number of frames as the 60-fps capture system from the Motion Analysis Corporation and as such comparatively only half of the data of facial motion was recorded. They analysed lip motion before and after lip repair by assessing lip movement during phonation (Mishima et al., 2009). As this movement was not a maximum expression it may lack adequate reproducibility for future studies. The analysis was carried out on landmark-based analysis and the use of Bézier curves to assess the entire motion of lip movement. The results should be interpreted with caution due to the above-mentioned limitations coupled with the low sample size, low fps of image capture, and non-reproducible facial movement.

Further research by Trotman et al. (2010, 2013) again utilised objective methodology for facial assessment via the video-based tracking system (Motion Analysis; Motion Analysis Corporation, Santa Rosa, CA) at a rate of 60-fps. A study looking at the objective assessment of the effect of lip revision surgery on the restriction of circumoral movements in patients with repaired cleft lip and palate used 38 3mm retro-reflective facial markers for analysis. The study included the assessment of 34 patients with repaired cleft lip and palate planned for revision surgery, 32 patients with repaired cleft lip and palate not planned for revision surgery, and 37 age and sex-matched non-cleft controls. Analysis was carried out on 6 facial expressions: maximum smile, cheek puff, lip purse, grimace, mouth opening, and natural smile. They concluded that lip revision surgery did not unduly restrict facial movements; and that the potential post-op scarring restriction was less than the potential benefit the surgery conveys to facial symmetry (Trotman et al., 2010).

When assessing facial soft tissue dysmorphology before and after primary lip repair in infants under 6-months-old a similar 4D landmark-based analysis was used (Trotman et al., 2013). 15 infants with unrepaired cleft lip and palate were compared to 15 non-cleft infant controls before and after primary lip repair. 12 3mm retro-reflective facial markers were used, less than previous studies due to the relatively smaller face of infants. Facial dysmorphology was assessed during spontaneous facial movements, the response to the patient’s mothers voice, and the response to tasting both salt and sugar. They concluded that primary lip repair reduced hypermobility of the lip and improved upper lip symmetry (Trotman et al., 2013). These analyses were again limited by their reliance on landmark identification and landmark-based motion tracking. 4D imaging of infants is also limited by their cooperation with capture and placement of facial markers coupled with the non-reproducibility of their spontaneous facial movements.

Hallac et al. (2017) used 4D video stereophotogrammetry to assess dynamic facial asymmetry in patients with repaired cleft lip and palate using objective methodology. Dynamic images were captured of 12 patients with UCLP and 11 non-cleft controls between the ages of 8 to 11 using a di4D (Dimensional Imaging, Ltd.) stereophotogrammetry system at 50-fps. 13 landmarks were identified and tracked during two facial expressions: a voluntary smile and a lip pucker. They concluded that patients with repaired UCLP had residual asymmetry present in both the magnitude and path of facial motion (Hallac et al., 2017). This study had a lower frame rate than previous studies, a small sample size, a non-homogenous cleft sample with a wide age range, and non-maximal facial expressions that may not be reproducible. The amount of data collected in this study was huge with the capture system collecting approximately 10GB of data per second. Unfortunately, due to processing restraints large amounts of this data was discarded and analysis was based on landmark tracking; the limitations of which have been previously discussed.

Gattani et al. (2020) used 4D imaging to assess dynamic facial asymmetry in patients with repaired UCLP. They assessed 25 patients aged between 8 to 10 years old with surgically managed UCLP and compared them to 75 age and sex-matched non-cleft controls. 4D images were captured by a 4D video stereophotogrammetry device (Dimensional Imaging, Ltd.) at a rate of 60-fps. Facial asymmetry was analysed during maximum smile due to its reported high reproducibility. During image processing a generic facial mesh containing over 7000 vertices or quasi-landmarks was conformed to each patients face at rest and each point was tracked during the maximum smile (Gattani et al., 2020). Asymmetry scores were calculated by creating a mirror image of each patient and superimposing the initial image on its own mirror image. Best fit was calculated using partially ordinary Procrustes analysis based on translation and rotation. Asymmetry scores were determined based on the distance between each vertex with its own mirror image; perfect symmetry would produce an asymmetry score of zero. They assessed facial asymmetry of the nasolabial region so asymmetry in other regions of the face would not dilute or inflate asymmetry scores of the area of interest. This study described an innovative objective assessment tool for the analysis of dynamic facial asymmetry in cleft lip and palate. The use of the generic mesh allows all the data-rich surface morphology and shape of the face to be used in analysis and removed the limitations of landmark-based tracking.

Further research from the University of Texas Southwestern Medical Centre used a 4D video capture system, di4D (Dimensional Imaging, Ltd.) stereophotogrammetry system at 50-fps (Seaward et al., 2022; Zhao et al., 2021). They utilised a dense facial mesh containing 884 landmarks with automated mesh tracking software. This allowed for a more complete analysis of facial asymmetry when compared to landmark-based assessment. Initial analysis was carried out to compare 10 patients between the ages of 4 to 15 years old with unilateral cleft lip (UCL) with 12 age and sex-matched non-cleft controls. The dynamic assessment was carried out during maximum smile and average distance displacements were calculated for multiple key regions of interest. They concluded that there was increased facial asymmetry in the UCL group during maximum smile (Zhao et al., 2021). This study was limited by its low number of cleft patients and analysis of specific regions of interest rather than full facial assessment and utilisation of their entire data-rich facial mesh. The subsequent study utilised the same software and analysed 13 patients with repaired UCL compared to 13 controls during maximum smile. This study was unique as they assessed the magnitude and direction of vector movement during facial animation. They concluded that the differences in vector direction was greater than the detectable difference in vector magnitude and that patients with UCL had greater vector distance discrepancies especially around their oral commissures compared to the non-cleft controls (Seaward et al., 2022). This study was again limited by its low number of cleft patients and focus on specific regions of interest.

4D imaging therefore provides a more detailed and complete assessment of dynamic facial dysmorphology in cleft lip and palate. Facial asymmetry is not a constant throughout facial motion or social interaction and asymmetry tends to be higher during facial expression (Al Rudainy et al., 2019). Research in 4D imaging for cleft lip and palate remains sparce due to the expense and expertise required to capture, process, and analyse the vast quantities of data. Access to computers capable of processing 4D imaging may increase in the future based on Moore’s Law, which states that the number of transistors in a dense integrated circuit doubles approximately every 2 years while the cost of the computer reduces. More powerful computers at a more affordable price may open future possibilities for 4D imaging research. Current research highlights the need for internationally accepted methodology for the analysis and interpretation of 4D data in cleft lip and palate to allow global comparisons to be made. While current access to 4D imaging remains rare and onerous it would be advantageous to know if there is a correlation between static (3D) and dynamic (4D) facial dysmorphology in cleft lip and palate. Would it therefore be possible to predict dynamic (4D) facial dysmorphology from static (3D) data capture where 4D imaging is inaccessible. Alternatively, would it further highlight the inadequacies of static assessment and highlight the need to transition to 4D imaging.

1.9. Research Rationale and Justification

The primary focus and justification of this study is to provide an enhanced insight into the assessment of facial asymmetry in unilateral cleft lip and palate and ultimately improve the quality of care and outcomes for patients born with all forms of cleft. Understanding the correlation between static (3D) and dynamic (4D) facial dysmorphology will aid clinicians’ decisions on the need or requirement for 4D imaging. The conclusions about objective methodology to assess facial dysmorphology may help inform future surgical decisions on lip revision surgery for residual facial asymmetry.

1.10. Research Aims and Hypothesis

1.10.1. Research Aims

1. Assess the correlation between static (3D) asymmetry at rest and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP).
2. Assess the correlation between static (3D) asymmetry at maximum smile and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP).
3. Assess when maximum asymmetry occurs in patients with unilateral cleft lip and palate (UCLP) during a maximum smile.

1.10.2. Null Hypothesis

1. Static (3D) asymmetry at rest is not predictive of dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP). $H_{0:}$ r=0.
2. Static (3D) asymmetry at maximum smile is not predictive of dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP). $H_{0:}$ r=0.

1.10.3. Alternative Hypothesis

1. Static (3D) asymmetry at rest is predictive of dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP). $H_{1:}$ $r \neq 0$.
2. Static (3D) asymmetry at maximum smile is predictive of dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP). $H_{1:}$ $r \neq 0$.

Chapter 2 Subjects and Methodology

2.1. Study Design

This study was designed as a retrospective cross-sectional study utilising quantitative methodology to assess a cohort of patients with a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP). Patients with UCLP were selected as it allows for the assessment of facial dysmorphology by comparing the cleft side with the unaffected contralateral side. Bilateral cleft lip and palate (BCLP) is a more symmetrical defect and therefore it is more difficult to assess the effect of clefting on the symmetry and morphology of the face (Bugaighis et al., 2014).

Patients had 4D imaging carried out at Glasgow Dental Hospital and School for audit purposes and as part of their routine care by the local cleft team working under the Managed Clinical Network (MCN) Cleft Care Scotland.

2.2. Ethical approval

Ethical approval was obtained from the Research Ethics Committee (REC) of South-East Scotland (REC Reference - 22/SS/0090), and NHS Research and Innovation (R&I) approval was obtained from the Greater Glasgow and Clyde (GGC) Health Board (R&I Reference - GN220D246).

2.3. Sample Size Calculation

The sample size for this study was calculated via the following formula (Hulley et al., 2013):-

$$\text{Total sample size } (N) = [(Z\alpha + Z\beta)/C]^2 + 3$$

Where: -

$Z\alpha$ = *the standard normal deviate for* α.

$Z\beta$ = *the standard normal deviate for* β.

r = *expected correlation coefficient.*

$C = 0.5 \times 1n\,[(1+r)/(1-r)]$.

The level of significance or probability of making a type I error (α) was set at 0.05; indicating that we have a 5% chance of getting a false positive or rejecting the null hypothesis when it is actually true. The probability of making a type II error (β) was set at 0.20; indicating that we have a 20% chance of getting a false negative or failing to reject the null hypothesis when it is actually false. Therefore, the power of the study ($1-\beta$) is 0.80, indicating that we have an 80% chance of correctly rejecting the null hypothesis when the alternative hypothesis is actually true.

As no previous research has been done on the correlation between static (3D) and dynamic (4D) facial dysmorphology in unilateral cleft lip and palate (UCLP) there is therefore no estimation of the expected correlation coefficient in the literature. Given that we are comparing the static (3D) facial asymmetry of participants with their own dynamic (4D) facial asymmetry we hypothesised a moderate ($0.5 < r < 0.7$) to strong ($r > 0.7$) correlation coefficient. The thresholds we will use to determine the strength of the relationship are: $r < 0.3$ – none or very weak, $0.3 < r < 0.5$ – weak, $0.5 < r < 0.7$ – moderate, and $r > 0.7$ – strong (Moore et al., 2013); these thresholds are shown in Table 2-1. Assuming a correlation (r) ≥ 0.5 a sample size of 29 participants would ensure our study was adequately powered at 0.80 (80%) and the results statistically significant.

Table 2-1. Correlation (r) - Strength of Relationship Thresholds.

Correlation (r)	Strength of Relationship
$r < 0.3$	None or very weak
$0.3 < r < 0.5$	Weak
$0.5 < r < 0.7$	Moderate
$r > 0.7$	Strong

Note. r = correlation coefficient. Values adapted from the basic practice of statistics (Moore et al., 2013).

2.4. Subject Selection Process

Subjects were recruited from a retrospective review of the data of patients who attended Glasgow Dental Hospital and School for the capture of 4D images. Patients were selected based on the adherence to the following inclusion/exclusion criteria.

2.4.1. Inclusion criteria

- 4D images collected and available for analysis.
- Diagnosis of non-syndromic unilateral cleft lip and palate (UCLP).
- Primary repair of cleft completed.
- Patients between 13 to 17 years old.

2.4.2. Exclusion criteria

- 4D images not collected or corrupted and unable to be analysed.
- Diagnosis of syndromic unilateral cleft lip and palate (UCLP).
- Any other cleft diagnosis.
- Unrepaired cleft.
- Patients out with the defined age range.
- Failure to meet inclusion criteria.

Image capture was completed at Glasgow Dental Hospital and School and all suitable 4D images were analysed to ensure they were not corrupted and free of any image defects or artefacts.

Participants with a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP) were selected, as patients with syndromic unilateral cleft lip and palate (UCLP) may exhibit additional facial characteristics indicative of increased facial asymmetry that could influence and confound the results (Wilson-Nagrani et al., 2018). As previously discussed, patients with UCLP were included to facilitate adequate comparisons between the ipsilateral cleft side with the contralateral side (Bugaighis et al., 2014). A prerequisite for inclusion was that the primary repair of the cleft was completed, this was to ensure a homogenous sample as an unrepaired cleft would exhibit much higher levels of facial asymmetry and act as a significant outlier which could influence the outcome (Al-Rudainy et al., 2018). The age range of 13 to 17 years old was selected to again ensure a homogenous sample and to target patients post-primary repair but prior to any orthognathic surgery.

2.5. Materials

2.5.1. Hardware

2.5.1.1. PC Specifications

Data capture, processing and analysis utilised a PC running on a 6-core Intel i7 CPU (Intel i7-4930K at 3.40GHz) with 32 GB of RAM using a 64-bit version of Windows 10 Enterprise.

Peripherals included a standard keyboard and mouse, a liquid-crystal display (LCD) monitor, a suitable storage medium and the 4d capture system.

2.5.1.2. Storage Medium

4D images were stored, built, and processed on a 1 TB iStorage Diskashur Pro2 hard drive. This storage medium ensured patients' data was secure as the drive was password protected and is encrypted to FIPS 140-2 Level 2/3, NCSC CPA, NLNCSA BSPA and NATO Restricted level.

1 TB of storage was required to handle the large volume of data produced by the 4D image capture process. 1TB equates to 1,000 GB of data storage capacity which is required as the 4D imaging system captures data at approximately 10 GB per second. When we then factor in that for each patient multiple facial expressions are captured, each facial expression is captured 3 times, and each facial expression is approximately 3 seconds long we end up with a vast quantity of data produced.

2.5.1.3. 4D Imaging System

4D images were captured using a Di4D facial performance imaging system (Dimensional Imaging, Ltd. Hillington Park, Glasgow, Scotland) based on passive stereophotogrammetry; this system is shown in Figure 2-1. Passive stereophotogrammetry involves the capture of an object or surface with multiple synchronised cameras that produce stereo images that are combined and constructed into a 3-dimensional surface image.

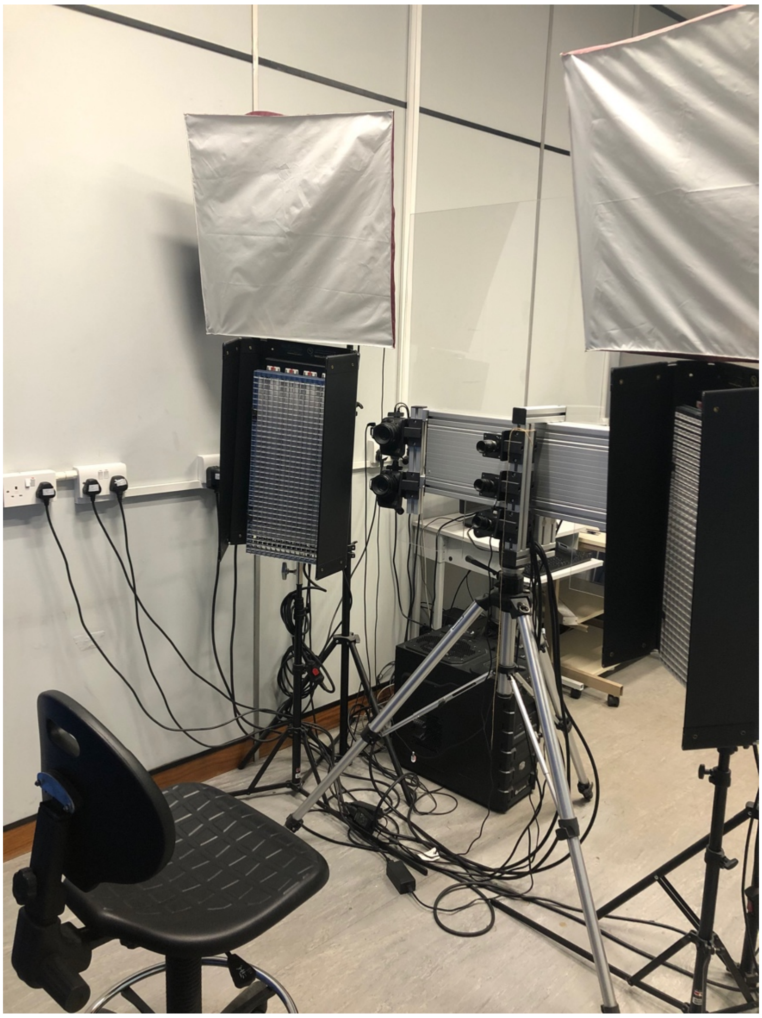


Figure 2-1. The Di4D facial performance imaging system.

Our 4D imaging system consists of 3 pods of synchronised cameras that are arranged and programmed to capture a subject simultaneously. The 2 outer pods each contain a grey-scale or monochrome camera (Model aVA 1600- 65km/ kc; resolution 1600x1200 pixels, Kodak sensor model KAI-02050; Basler, Germany) that is used for 4D facial reconstruction, and the central pod contains a colour camera that is used to produce surface detail including texture and colour. Participants were illuminated with a lighting system consisting of a set of 2 light sources (Diva-Lite 401 series; Kino Flo Corporation, Burbank, CA, USA) producing a daylight quality soft light source ideal for facial capture.

The 4D imaging system captures 4D facial data at a rate of 60-fps, which generates 60 3D facial images per second during facial animation. Each facial animation takes on average 3 seconds, which translates into approximately 180 3D images per capture, multiplied by the number of captures, per facial expression, and per patient. The 4D imaging system allows us to analyse colour 4D facial performance data that is captured and produced in high resolution and high fidelity. The use of passive stereophotogrammetry allows us to automatically track facial landmarks throughout facial expressions without the need for participants to have facial markers, make-up, or structured light projected onto their face. The process of automatic facial landmark tracking in 4D imaging has been previously validated (Al-Anezi et al., 2013).

2.5.2. Software

The Di4D facial performance imaging system (Dimensional Imaging, Ltd. Hillington Park, Glasgow, Scotland) was used in conjunction with specialised software packages including Di4D Capture, Di3D View, and Di4D View.

The Di4D Capture software is the control panel and user interface of the 4D imaging system that allows us to calibrate the system, capture the 4D images, and build the raw data into 4D image sequences. The Di3D View software facilitates landmark placement and mesh conformation, while the Di4D View software facilitates image manipulation via translation, magnification, rotation, superimposition, and automatic mesh tracking. Further detail of this process will be discussed during data processing.

2.6. Data Capture

2.6.1. Consent

Prior to data capture patients were consented to having 4D imaging carried out. The process for image acquisition was explained and informed written consent was obtained. All participants included in this study consented to their 4D images being used for the purpose of research.

2.6.2. Calibration

The Di4D facial performance imaging system was calibrated prior to each session of 4D data capture to ensure the accuracy of the images being collected. The calibration process was carried out in line with the manufacturer's instructions and the local standard operating procedure. Calibration utilised the calibration board or target depicted in Figure 2-2. The calibration board was positioned in front of the imaging system and parallel to it at 95cm. Imaging of the calibration board was then completed with the flash from the lighting system switched on. The boards angulation was subsequently altered, and further imaging was carried out to view the board from 9 separate positions of gaze. The Di4D Capture software then automatically calibrated the system and determined the focal length and orientation of the cameras.

Figure 2-2. The Dimensional Imaging Calibration Board used for system calibration.

2.6.3. Image capture protocol

4D imaging was carried out at Glasgow Dental Hospital and School for audit purposes as part of patients' routine care by the local cleft team. The 4D images were already captured prior to this study using the following protocol. For 4D image acquisition the Di4D facial performance imaging system (Dimensional Imaging, Ltd. Hillington Park, Glasgow, Scotland) was controlled using the Di4D Capture software. Following system calibration, a new imaging session could begin by adding a new subject to the system linked to the participants unique identification number. All 4D images were captured with the lighting system illuminated at maximal intensity.

Participants were seated in front of the 4D imaging system parallel to the cameras at a set distance of 95cm. A neutral blue backdrop was used to allow the cameras to focus solely on the participant. Participants were asked to remove their glasses, facial jewellery, and piercings to facilitate a standardised facial capture without unnecessary interference. Patients were provided a hairnet to prevent their hair from covering their face and interfering with data capture. This ensured an accurate capture of facial morphology without participants hair encroaching on the facial field of view.

Each participant was captured performing a series of 4 maximal facial expressions: maximum smile, cheek puff, lip purse, and grimace. They each had the opportunity to practice performing the facial expressions prior to the 4D image capture. Facial expressions were first demonstrated by the operator and the participant practised based on set timings and rhythm. They were instructed to keep their back teeth together and head still during 4D image acquisition. The facial expressions were performed with the patient starting at rest, slowly progressing to a maximal facial expression then relaxing and returning to a state of rest. Every facial expression was captured over a period of 3 to 5 seconds at a rate of 60-fps; meaning a minimum of 180 3D images were captured per expression.

Each expression was then repeated and captured 3 times to ensure the best image was produced. The best facial expression was then selected by a single independent reviewer who assessed the facial expressions with respect to duration, interference, head movement, and quality of image. The selection of the best facial expression was however subjective, and the reliability of the selection was not calculated. Future studies could utilise two independent assessors or a defined objective measurement of the best facial expression. The 4D images were then processed and built from the raw data before being appropriately saved and stored.

Maximum facial expressions were used for this study as they are more reproducible and standardised when compared to spontaneous facial movements or expressions. To assess the correlation between static and dynamic facial dysmorphology in this study we analysed each participants maximal smile, as it has been shown to be one of the most reproducible facial expressions (Johnston et al., 2003).

2.6.4. Data Building

Each participants data was processed in a standard sequence starting with the building of the raw data files. The Di4D facial performance imaging system initially saves the 4D images as compressed raw data. This raw data was then reviewed and assessed for quality of capture as well as absence of artefacts and interference. Following review, the raw data was then decompressed and built into the 4D imaging sequence using the Di4D capture software. This process could take up to 60 minutes per facial expression and exponentially increased the data quantity.

2.6.5. Generic Mesh Conformation Process

Following data building the next stage of data processing is the conformation of the generic mesh. The generic mesh: shown in Figure 2-3, contains over 7000 vertices or quasi-landmarks which are mathematically generated and systematically spaced to cover the entire surface of the mesh. Each vertex occupies a fixed point with known coordinates in all 3 planes of space (x, y and z). The generic mesh itself takes on the shape of an average face with easily recognisable facial attributes and common morphological features. The generic mesh is stored as a .obj file and opened in the Di3D View software together with the first frame of facial expression for each participant.

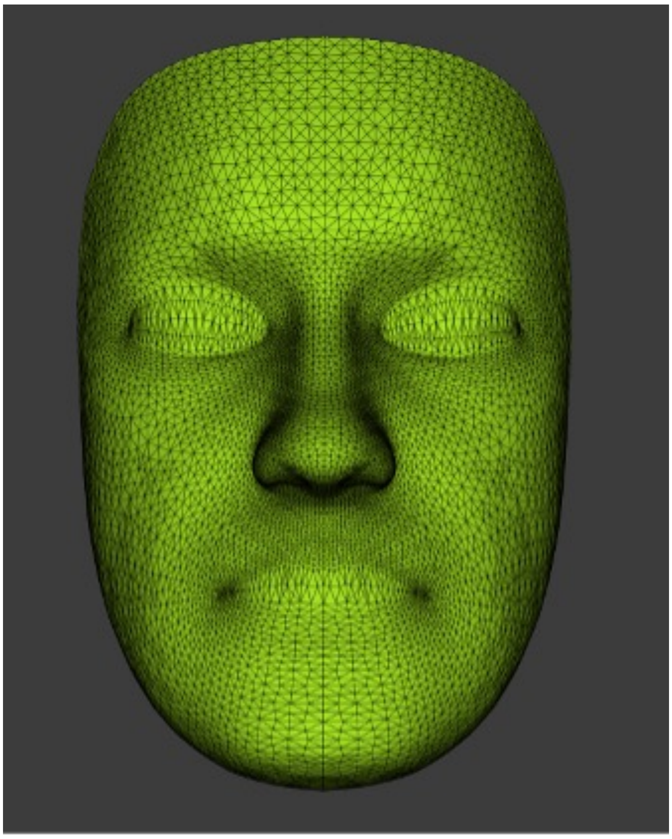


Figure 2-3. The generic mesh.

The generic mesh then undergoes an elastic deformation process and is snapped onto the surface of the first frame of each participant's face. This elastic deformation is the conformation process, whereby the generic mesh mimics the surface morphology of each participant. A unique conformed mesh is produced for the first frame of facial expression for each participant.

The mesh confirmation process initially requires the manual identification and labelling of 30 pre-determined facial landmarks which are depicted in Figure 2-4. These landmarks were based on previous studies that have included the generic mesh and mesh conformation process in their methodological design (Al-Rudainy et al., 2018; Al Rudainy et al., 2019; Gattani et al., 2020).

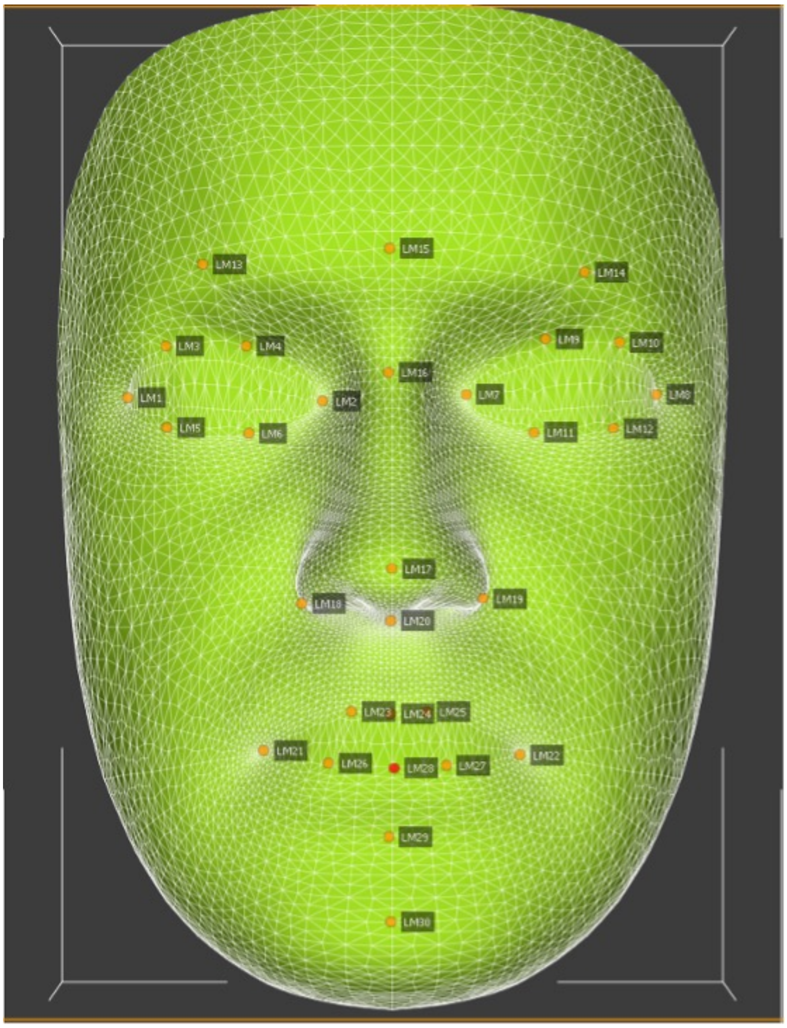


Figure 2-4. The generic mesh with facial landmarks.

The selected landmarks were distributed evenly around the generic mesh with increased landmark density around specific facial features of interest such as the mouth, eyes, and nose. Each landmark was fixed at a specific point on the generic mesh in 3-dimensions. A comprehensive list of all facial landmark used in the mesh conformation process are recorded in Table 2-2. The facial landmarks extend from right to left lateral canthus or exocanthion and from glabella to pogonion. Crucially, these landmarks were used solely in the generic mesh conformation process and were not used in the assessment of facial asymmetry in this study.

Table 2-2. Landmarks used in the generic mesh conformation process.

Landmark Number(s)	Landmark Position
1 and 8	Lateral canthus (exocanthion)
2 and 7	Medial canthus (endocanthion)
3, 4, 9 and 10	Superior medial and lateral blepharon points
5, 6, 11 and 12	Inferior medial and lateral blepharon points
13 and 14	Superciliary points
15	Glabella
16	Nasion
17	Pronasale
18 and 19	Alar base
20	Subnasale
21 and 22	Cheilion
23 and 25	Crista Philtri
24	Labrale superious
26 and 27	Points lateral to labrale inferious
28	Labrale inferious
29	Sublabiale
30	Pogonion

Note. The above landmarks were used in the generic mesh conformation process and not in the assessment of facial asymmetry.

Assessment of the reproducibility of the landmark identification was carried out to ensure accurate landmark digitisation and adequate intra-examiner reliability. 10% of the participants were randomly selected and reassessed by the same independent operator 1 week after the initial assessment. This method has been previously investigated and validated (Al-Anezi et al., 2013).

Following the identification of the facial landmarks on the generic mesh the corresponding landmarks are also identified on the first frame of the facial expression of each participant. The corresponding landmarks on the generic mesh and the first frame of facial animation can be viewed adjacent to each other in the Di3D software and this is shown in Figure 2-5.

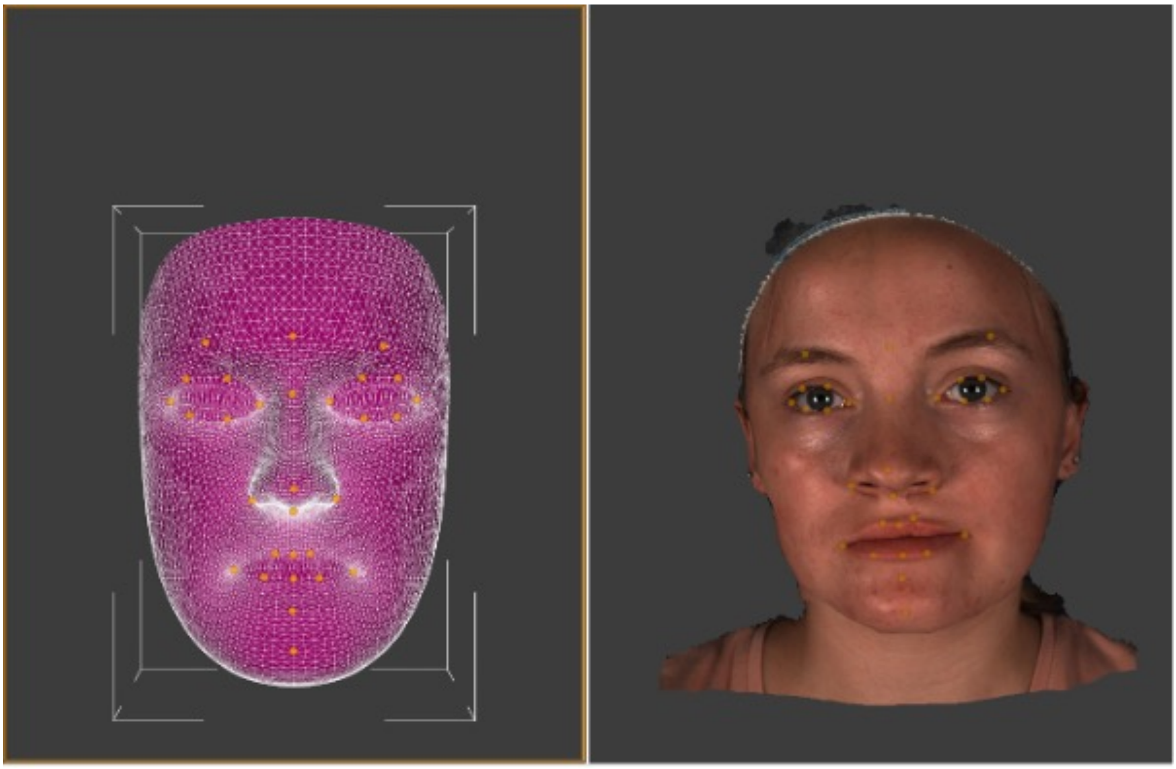


Figure 2-5. Corresponding landmarks on generic mesh and first frame of facial animation.

The Dimensional Imaging software is then able to orientate the generic mesh to the 3D image of the participant using the coordinated landmarks and snap or transfer the shape of the generic mesh onto the surface of the face.

This elastic deformation and transfer of the generic mesh then produces a unique conformed mesh for each participant, an example of a unique conformed mesh is depicted in Figure 2-6. Each unique mesh was saved from the Di3D View software to allow it to be imported into other software packages.

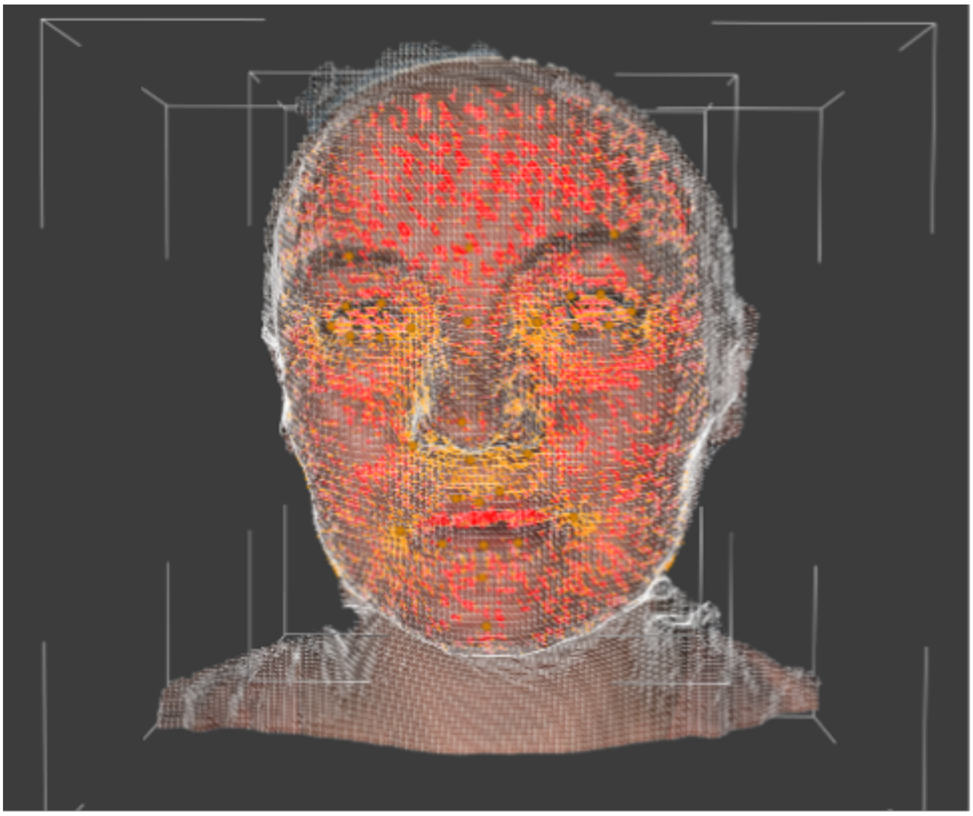


Figure 2-6. Conformed generic mesh.

2.6.6. Mesh Tracking

Following the generic mesh conformation process subsequent mesh tracking could take place. The 4D image sequence was loaded into the Di4D View software which facilitates image manipulation via translation, magnification, rotation, superimposition, and automatic mesh tracking.

The first frame of facial expression was selected in the 4D image sequence, and the unique conformed mesh was then imported to the Di4D View software. The 7000+ vertices or quasi-landmarks could then be identified and referenced in 3-dimensions on the facial surface of the participant. These vertices could then be automatically tracked throughout each participants facial expression. The density and distribution of these 7000+ vertices or quasi-landmarks are depicted in Figure 2-7. The 4D tracked mesh data could then be saved and exported for data analysis.

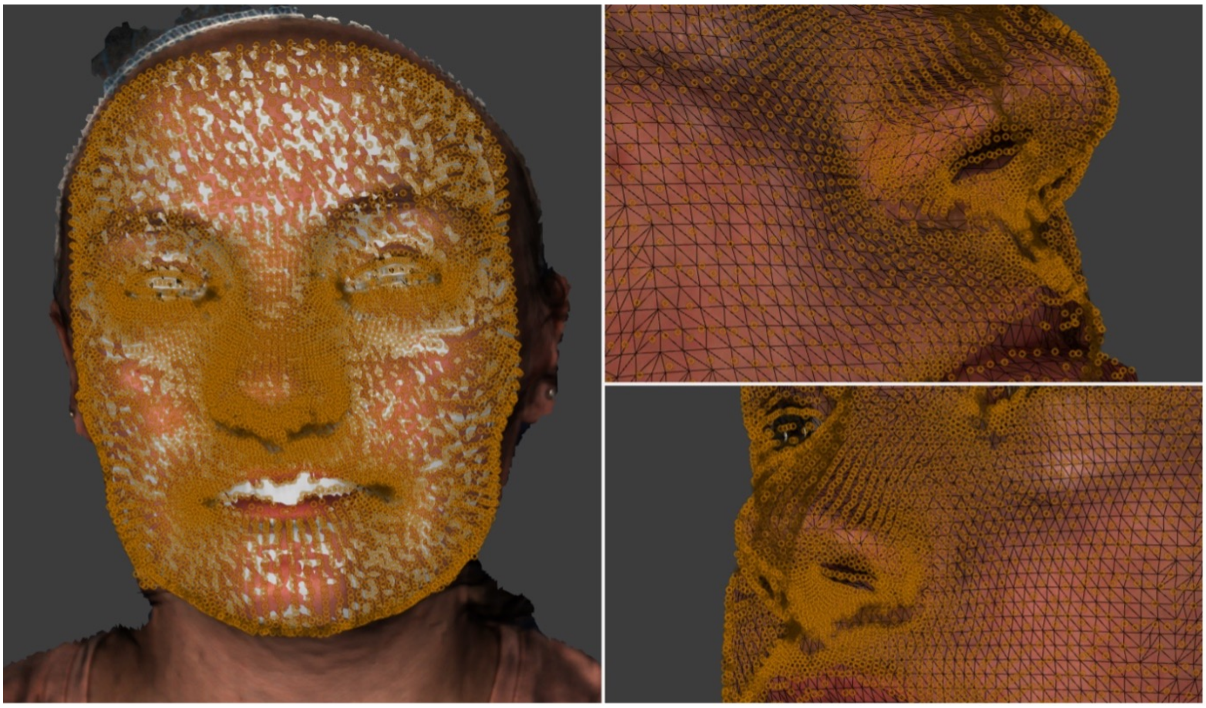


Figure 2-7. Over 7000 vertices or quasi-landmarks on first frame of facial animation. Each vertex is automatically tracked during the motion of facial expression.

2.7. Data Analysis

2.7.1. Assessment of Facial Asymmetry

Following the processing of the data and the tracking of mesh, the data was then analysed to facilitate the assessment of facial asymmetry and facial dysmorphology. Each participant’s 4D image was initially reflected on an arbitrary mathematical reference plane which acted as a mirror to create a mirror image. Facial asymmetry was then calculated using partial ordinary Procrustes analysis.

2.7.2. Partial Ordinary Procrustes Analysis

Partial ordinary Procrustes analysis is a form of shape analysis that uses statistical analysis to determine the overall shape difference between two objects using Procrustes superimposition. Each participant’s original image was superimposed on its own mirror image until optimal superimposition was achieved. Optimal superimposition is determined by the position of the images in which the sum of the squared distances between them is minimised.

Partial ordinary Procrustes analysis involves the translation and rotation of the images to align the mirror image with its own original image in the best possible fit. The uniform scaling or magnification of the images is not carried out to preserve the size of the images. Partial ordinary Procrustes analysis with reflection facilitates image size preservation while allowing translation, rotation, and reflection of the image. The aim of the analysis is to minimise a measure of shape difference in a position of optimal superimposition known as the Procrustes distance.

2.7.3. Asymmetry Scores

Following superimposition, the asymmetry scores for each participant were then calculated by Dr Xiangyang Ju, head of image processing at NHS greater Glasgow and Clyde. The asymmetry score is based on the Procrustes distance, or the sum of the squared Euclidean distances between the conformed mesh and its own mirror image. Distance measurements were taken between all 7000+ vertices or quasi-landmarks and their own corresponding mirror points. In perfect symmetry the image would superimpose with its own mirror image exactly due to their identical shape. Therefore, the sum of the squared distances between the images would be 0. As facial asymmetry increases the Procrustes distance and corresponding asymmetry score also increases.

Full facial asymmetry scores while useful may dilute the analysis of facial dysmorphology in the nasolabial region in patients with unilateral cleft lip and palate. Therefore, a regional facial asymmetry score for each patient was calculated for the nasolabial region as described by Asher-McDade et al. (1991). This ensured that background features that would influence the asymmetry score were removed from the analysis and the asymmetry of the nasolabial region was assessed in isolation.

Asymmetry scores were recorded for each patient at rest and at maximum smile to act as a measure of static facial dysmorphology (3D); as 3D images can be captured at rest and at maximum smile without the use of 4D imaging. Each frame of facial expression was then analysed, and the maximum asymmetry score was recorded to act as a measure of dynamic facial dysmorphology (4D). The exact frame in which the maximum asymmetry score was expressed was also recorded, to determine when the greatest degree of asymmetry is seen during the facial expression.

The frame of maximum smile was identified by a single independent assessor based on the following criteria: the frame of maximum muscle contraction prior to relaxation, with the maximum movement of the commissures resulting in the broadest smile. The rest frame was also identified by the same independent assessor, identified as the frame prior to any muscular contraction.

2.8. Statistical Methodology

2.8.1. Assessment of Normality

To determine if the data was normally distributed the calculated asymmetry scores were assessed for normality using both graphical and numerical methods. The data was presented and visualised graphically on both histograms and Q-Q (Quantile-Quantile) probability plots. The statistical tests that were selected to be used to assess the normality of the data were the Shapiro-Wilk test and the Kolmogorov-Smirnov test. If there was a conflict of normality outcome between the two statistical tests then the Shapiro-Wilk test result was used; as it has been shown to be more powerful in detecting non-normal distributions in smaller sample sizes (Mishra et al., 2019).

For both statistical tests used the null hypothesis was that the data was normally distributed, and the alternative hypothesis was that the data was not normally distributed. If $P>0.05$ we can accept the null hypothesis and assume a normal distribution as there is no evidence to suggest a non-normal distribution. If $P<0.05$ then we can reject the null hypothesis and conclude that the data is not normally distributed. If the data was normally distributed, then a parametric test was used based on the mean of the data, and if the data has a non-normal distribution, then a non-parametric test was used based on the median of the data.

2.8.2. Descriptive Statistics

If the data was normally distributed, then the asymmetry scores were described using the mean as a measure of central tendency and the standard deviation as a measure of dispersion. If the data was non-normally distributed, then the asymmetry scores were described using the median as a measure of central tendency and the interquartile range as a measure of dispersion. Measures of frequency were used to describe when the greatest degree of asymmetry is seen during a maximum smile.

2.8.3. Correlation

To assess the correlation between static and dynamic facial dysmorphology in unilateral cleft lip and palate (UCLP) one of the following statistical tests were used. If the data was normally distributed, then a parametric test was used. The parametric test that was used was Pearson's correlation coefficient (r), which is a bivariate analysis of linear correlation. A two-tailed test of statistical significance was carried out and results were reported at the 0.05 significance level. If the data was non-normally distributed, then a non-parametric test was used. The non-parametric test that was used was the Kendall rank correlation coefficient (τ, tau), which is a measure of rank correlation used to measure the ordinal association between the variables. A two-tailed test of statistical significance was carried out based on an approximate normality assumption and results were reported at the 0.05 significance level. Kendall's rank correlation was selected over Spearman's rank correlation coefficient as the non-parametric test as it has been shown to be more robust and more efficient (Croux & Dehon, 2010). Both Kendall's rank correlation and Spearman's rank correlation coefficient can be used to assess a suspected monotonic relationship, but Kendall's is preferred when there is a smaller sample size or outliers present (Croux & Dehon, 2010).

The assessment of correlation was used to determine if a statistically significant linear relationship exists between static and dynamic facial dysmorphology, as well as determining both the strength and direction of the relationship. If the data was normally distributed, the coefficient of determination (r^2); the effect size explained by the variable, and the coefficient of alienation ($1-r^2$); the effect size not explained by the variable, were expressed.

Chapter 3 Results

3.1. Participant baseline characteristics

A total of 31 participants were included in this retrospective cross-sectional study and the baseline characteristics of all participants are recorded in Table 3-1.

All patients had 4D images captured at Glasgow Dental Hospital and School and all participants had a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP). Primary repair of all clefts was completed, and all participants were aged between 13 to 17 years of age. The mean age of participants was 14.61 with a standard deviation of ± 1.453.

64% (n=20) of participants were male and 35.5% (n=11) of participants were female. With regards to the laterality of the UCLP defect, left-sided clefting was more common making up 61.3% (n=19) of the sample compared to only 38.7% (n=12) right-sided clefting.

Table 3-1. Participant Baseline Characteristics.

Baseline Characteristic	Total (n=31)
Age (Mean ± SD, Range)	14.61 ± 1.453, 13-17
Gender – Female (n, %)	11, 35.5%
Gender – Male (n, %)	20, 64.5%
Laterality – Left (n, %)	19, 61.3%
Laterality – Right (n, %)	12, 38.7%

3.2. Assessment of Normality

To determine if the data was normally distributed the calculated asymmetry scores were assessed for normality using both graphical and numerical methods. The data will be presented and visualised graphically on both histograms and Q-Q (Quantile-Quantile) probability plots. The statistical tests that were selected to be used to assess the normality of the data were the Shapiro-Wilk test and the Kolmogorov-Smirnov test, the results of these tests will be presented in tables below.

3.2.1. Full Face

Full face asymmetry scores for the rest frame, frame of maximum smile, and frame of maximum asymmetry were assessed for normality and the results are depicted below.

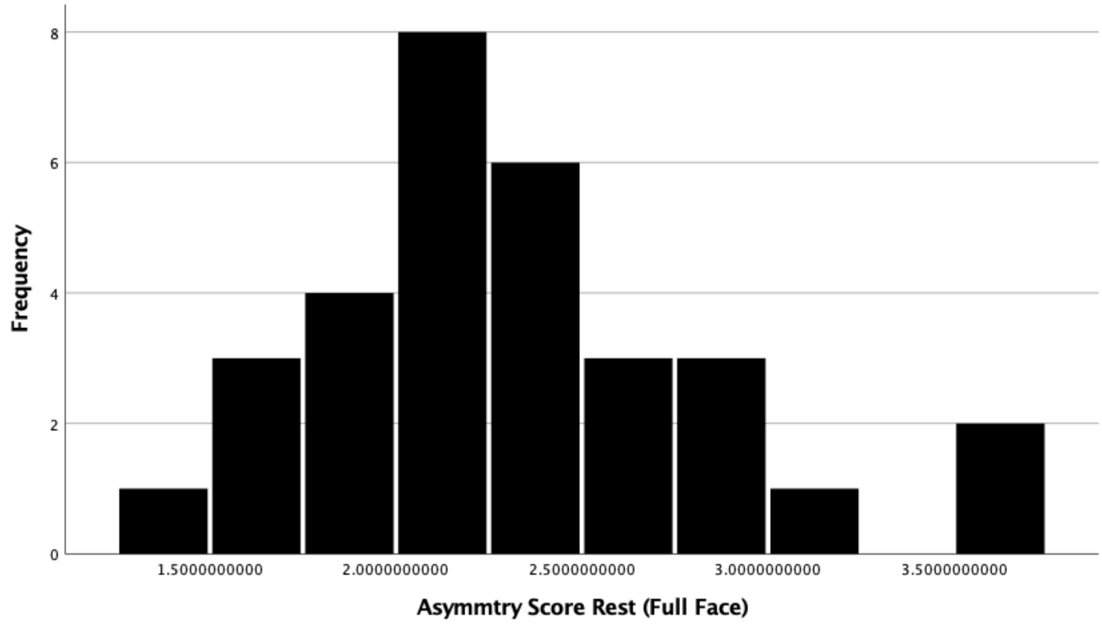


Figure 3-1. Histogram showing Asymmetry Scores at Rest (Full Face).

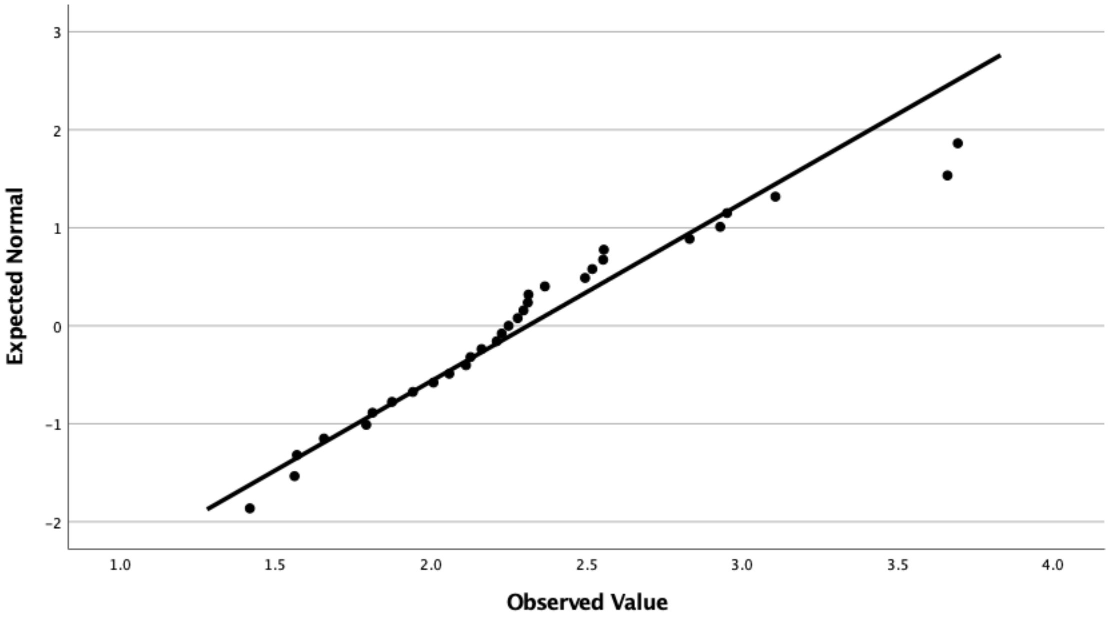


Figure 3-2. Q-Q Probability Plot showing Asymmetry Scores at Rest (Full Face).

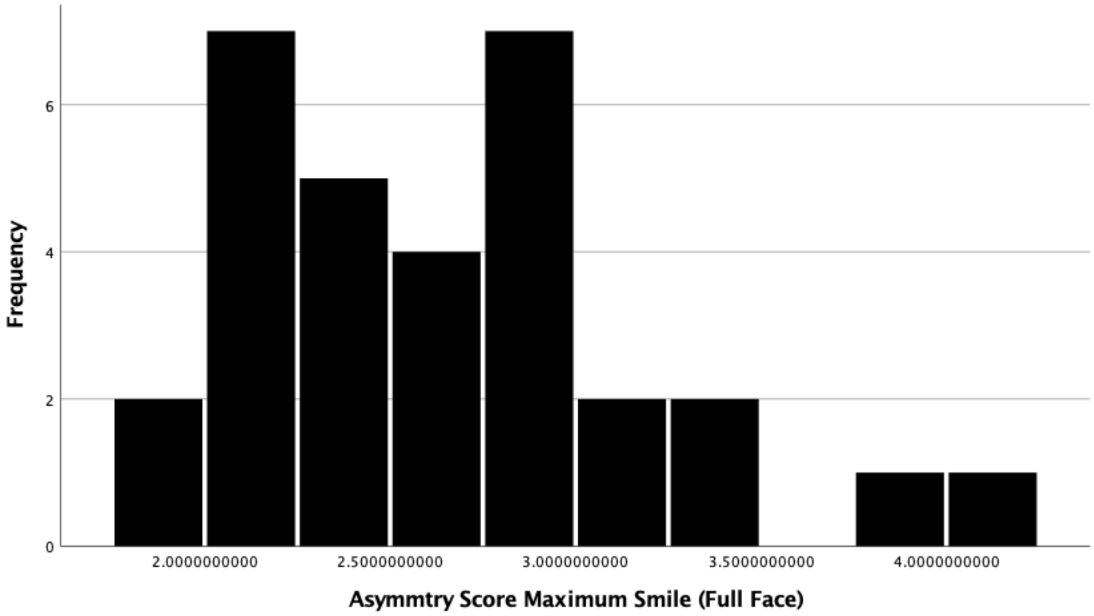


Figure 3-3. Histogram showing Asymmetry Scores at Maximum Smile (Full Face).

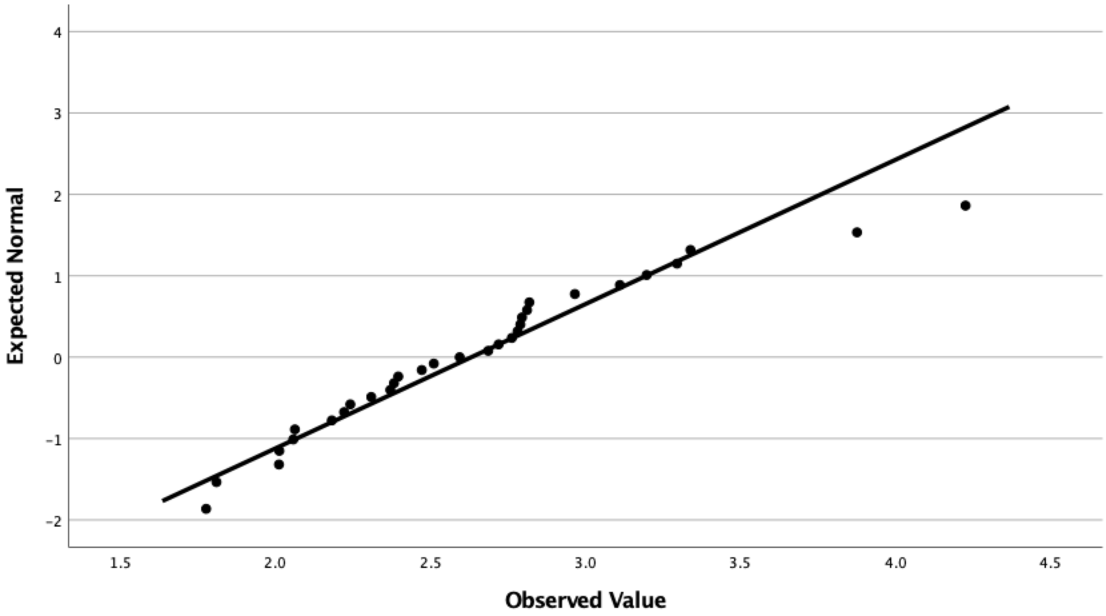


Figure 3-4. Q-Q Probability Plot showing Asymmetry Scores at Maximum Smile (Full Face).

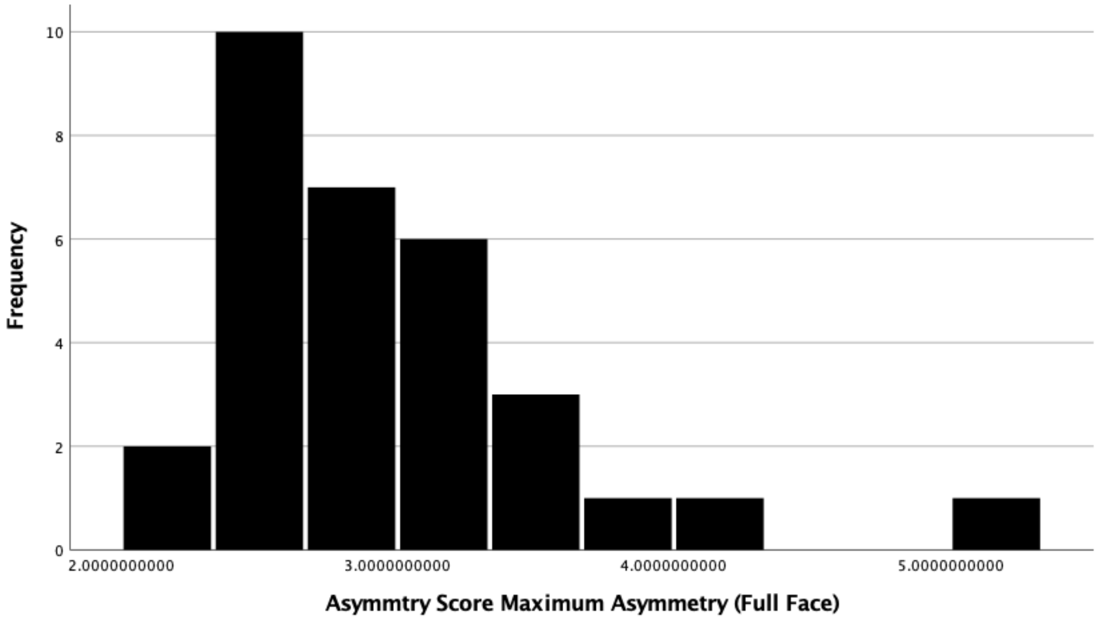


Figure 3-5. Histogram showing Asymmetry Scores at Maximum Asymmetry (Full Face).

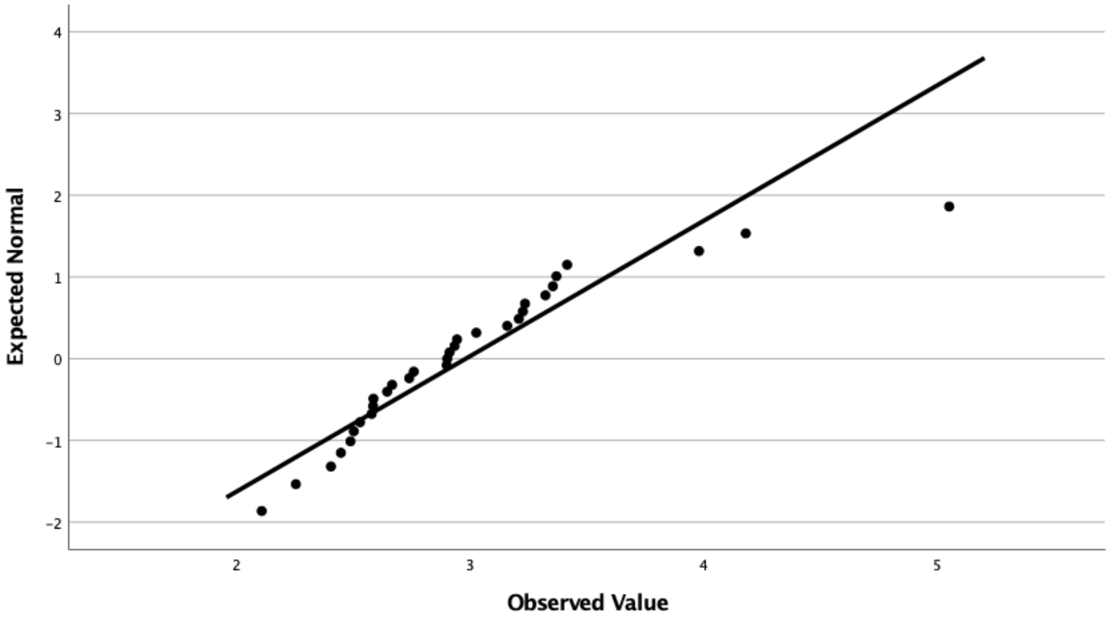
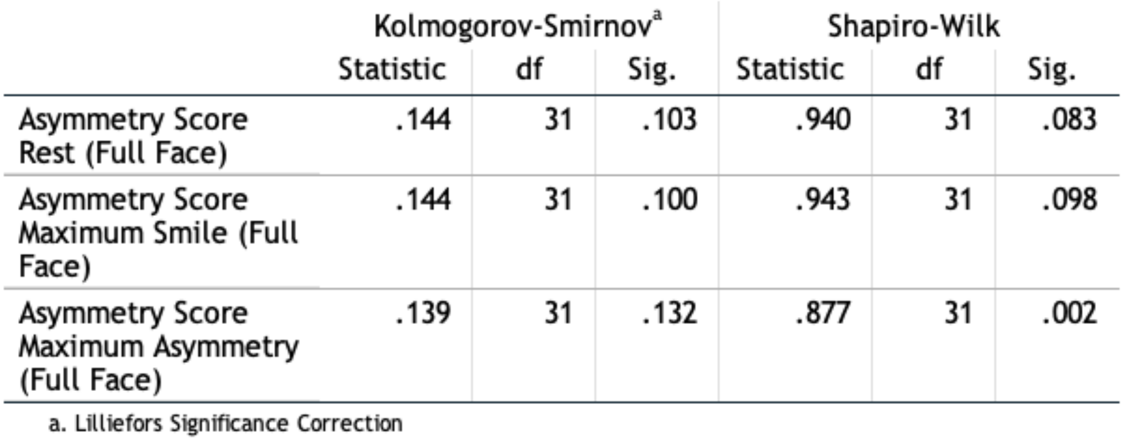


Figure 3-6. Q-Q Probability Plot showing Asymmetry Scores at Maximum Asymmetry (Full Face).

Table 3-2. Results of Normality tests for Full Face Asymmetry Scores.



	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Asymmetry Score Rest (Full Face)	.144	31	.103	.940	31	.083
Asymmetry Score Maximum Smile (Full Face)	.144	31	.100	.943	31	.098
Asymmetry Score Maximum Asymmetry (Full Face)	.139	31	.132	.877	31	.002

a. Lilliefors Significance Correction

For both statistical tests used the null hypothesis was that the data was normally distributed, and the alternative hypothesis was that the data was not normally distributed. As P>0.05 for both the Kolmogorov-Smirnov test and the Shapiro-Wilk test we can accept the null hypothesis and assume a normal distribution as there is no evidence to suggest a non-normal distribution. As the data is normally distributed, then a parametric test will be used based on the mean of the data.

3.2.2. Nasolabial Region

Nasolabial region asymmetry scores for the rest frame, frame of maximum smile, and frame of maximum asymmetry were assessed for normality and the results are depicted below.

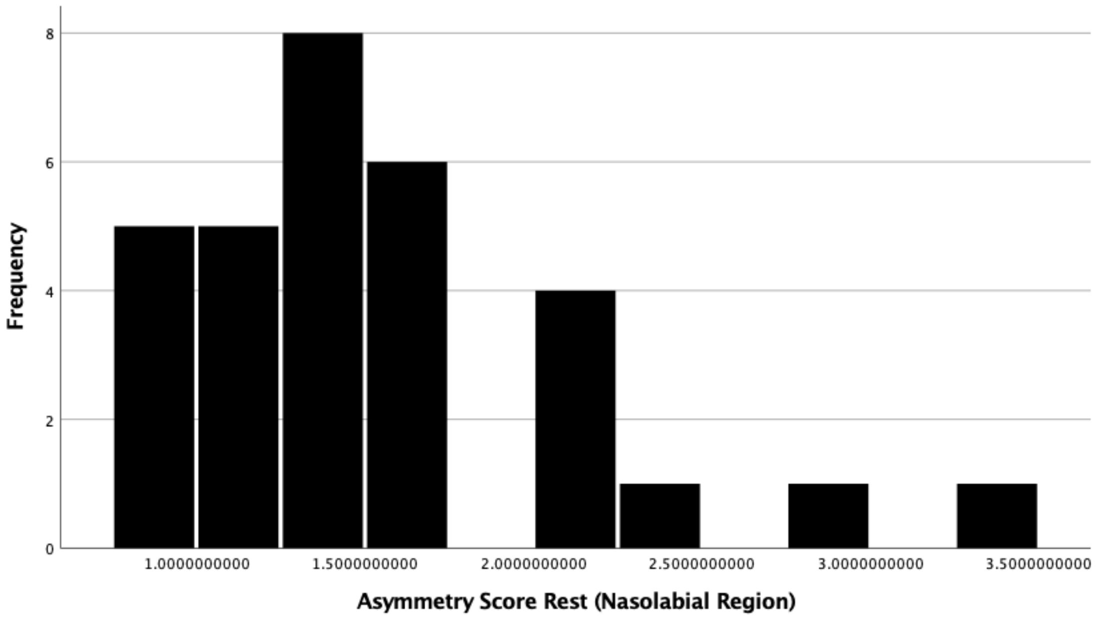


Figure 3-7. Histogram showing Asymmetry Scores at Rest (Nasolabial Region).

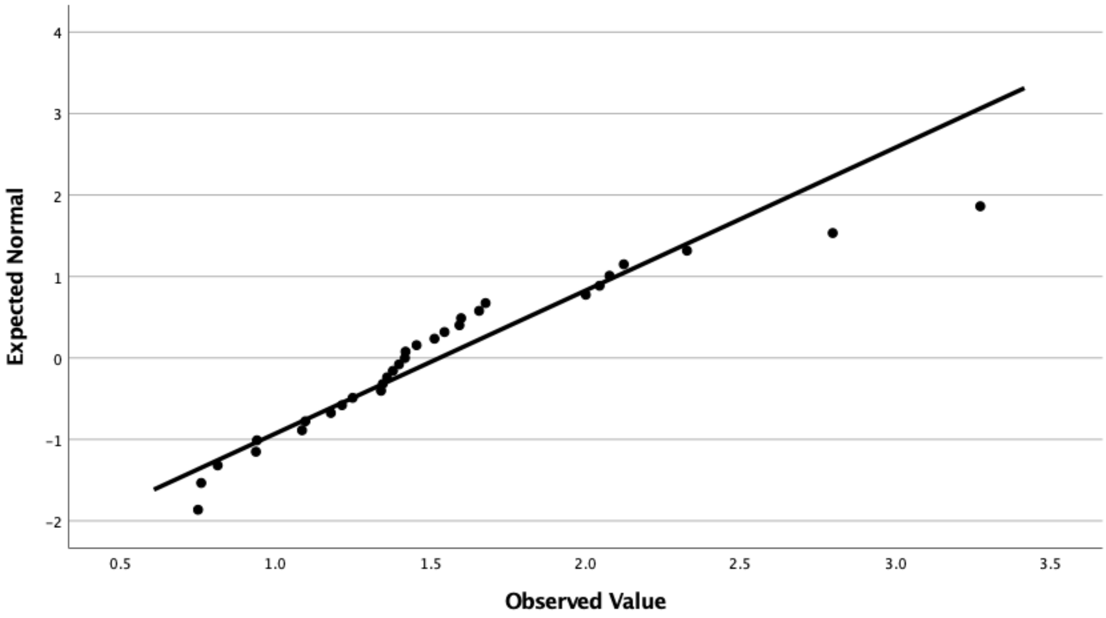


Figure 3-8. Q-Q Probability Plot showing Asymmetry Scores at Rest (Nasolabial Region).

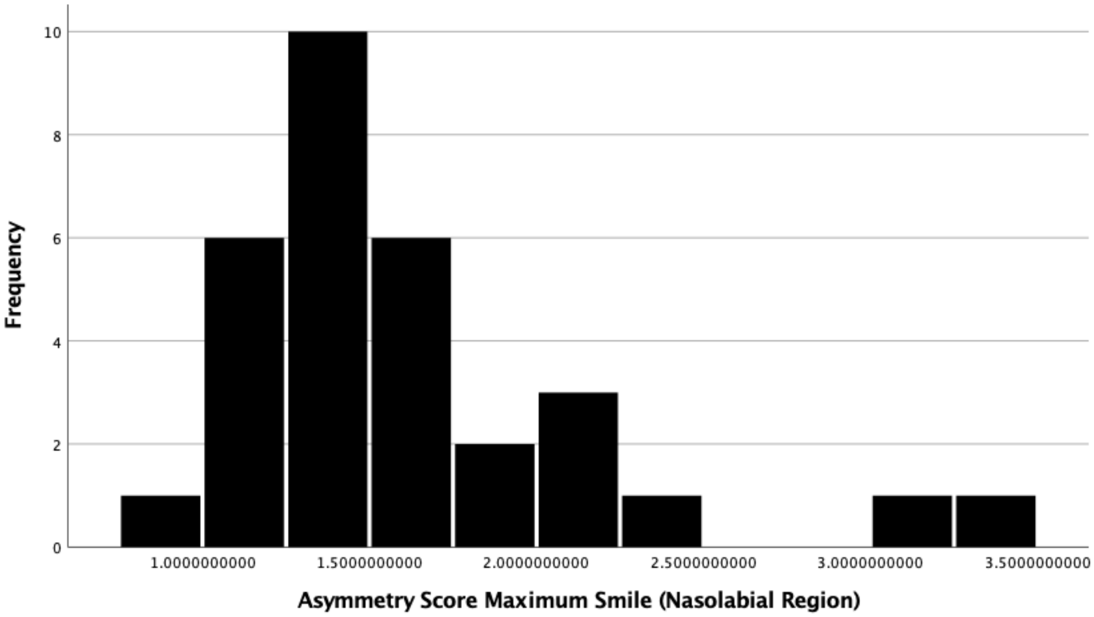


Figure 3-9. Histogram showing Asymmetry Scores at Maximum Smile (Nasolabial Region).

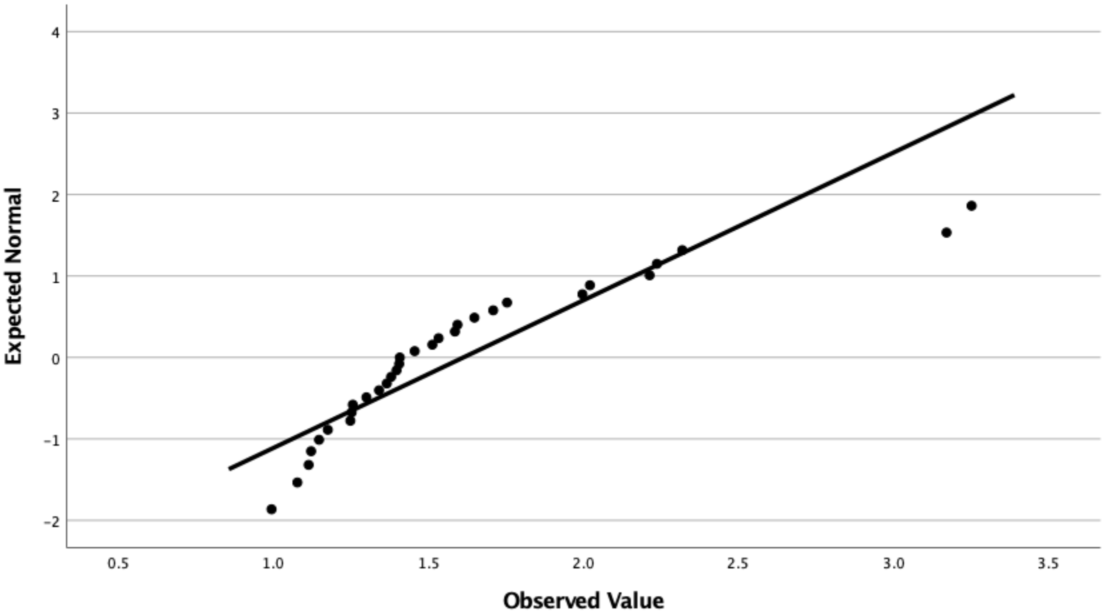


Figure 3-10. Q-Q Probability Plot showing Asymmetry Scores at Maximum Smile (Nasolabial Region).

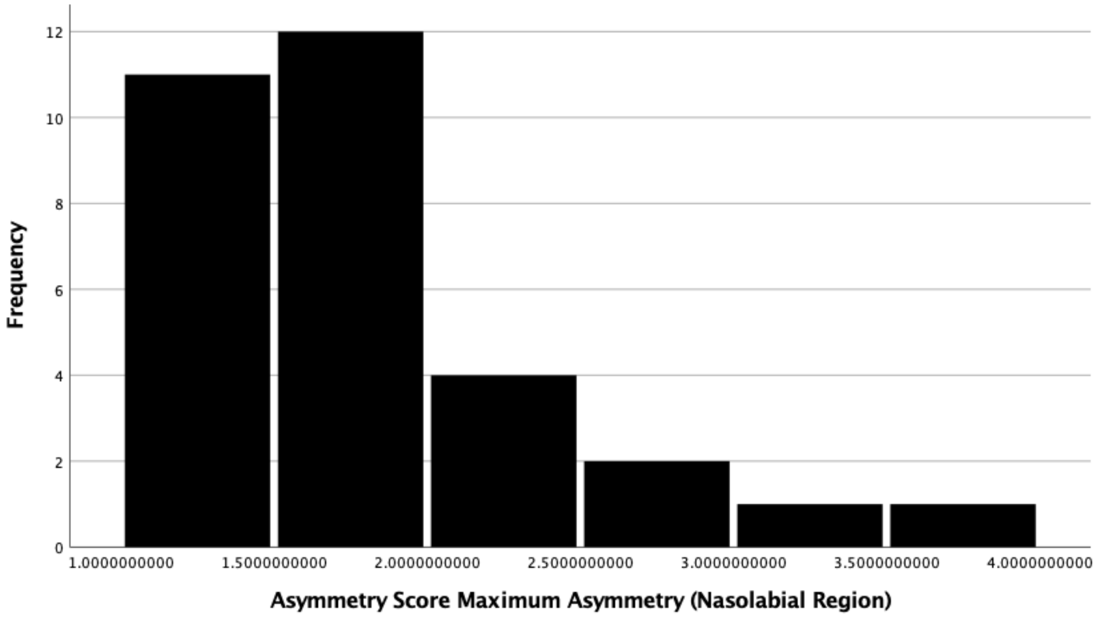


Figure 3-11. Histogram showing Asymmetry Scores at Maximum Asymmetry (Nasolabial Region).

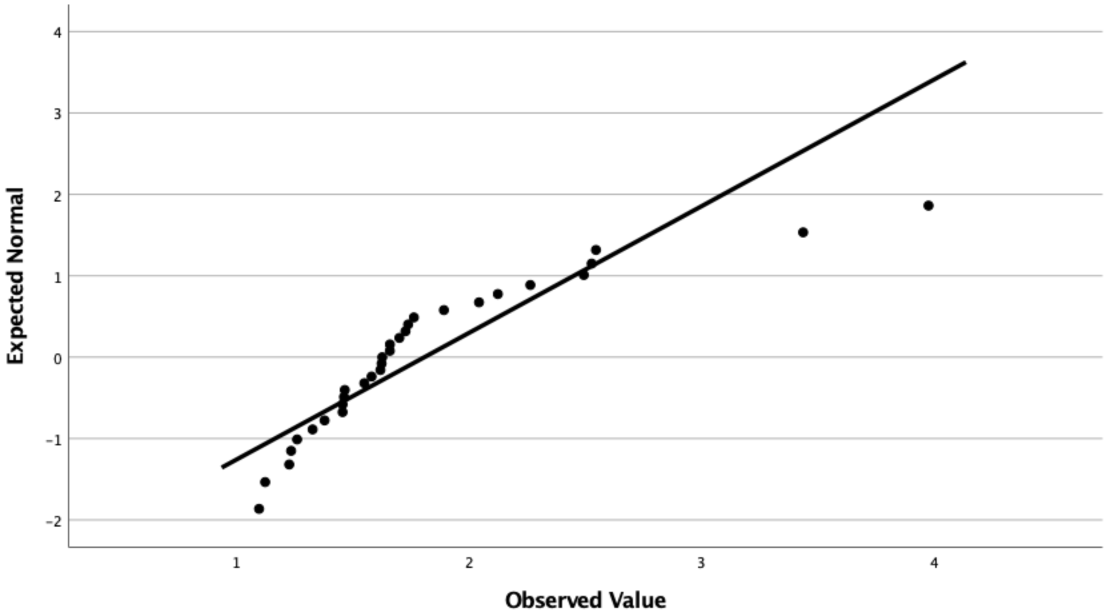
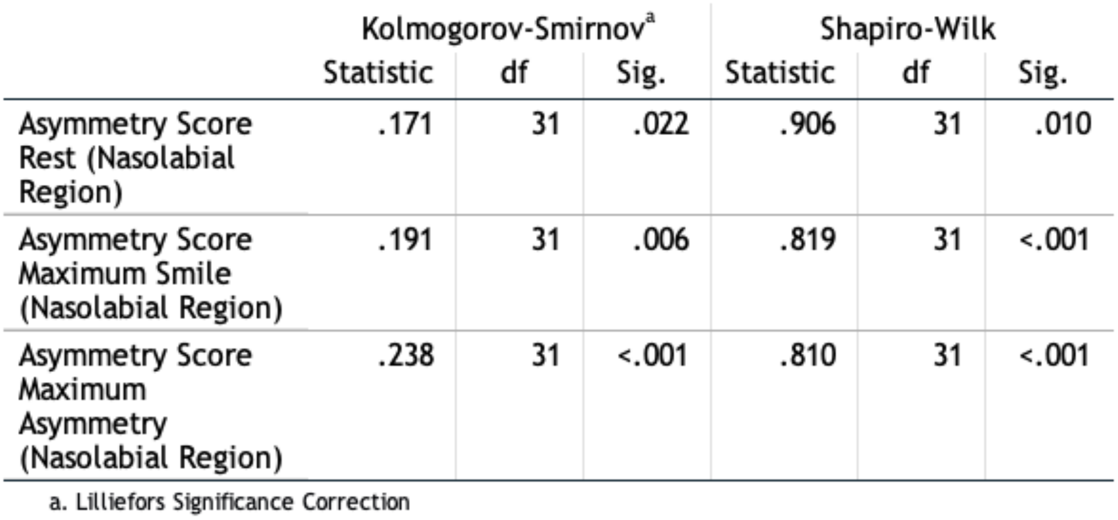


Figure 3-12. Q-Q Probability Plot showing Asymmetry Scores at Maximum Asymmetry (Nasolabial Region).

Table 3-3. Results of Normality tests for Nasolabial Region Asymmetry Scores.



	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Asymmetry Score Rest (Nasolabial Region)	.171	31	.022	.906	31	.010
Asymmetry Score Maximum Smile (Nasolabial Region)	.191	31	.006	.819	31	<.001
Asymmetry Score Maximum Asymmetry (Nasolabial Region)	.238	31	<.001	.810	31	<.001

a. Lilliefors Significance Correction

For both statistical tests used the null hypothesis was that the data was normally distributed, and the alternative hypothesis was that the data was not normally distributed. As P>0.05 for both the Kolmogorov-Smirnov test and the Shapiro-Wilk test we can accept the null hypothesis and assume a normal distribution as there is no evidence to suggest a non-normal distribution. As the data is normally distributed, then a parametric test will be used based on the mean of the data.

3.2.3. Upper Lip

Upper lip asymmetry scores for the rest frame, frame of maximum smile, and frame of maximum asymmetry were assessed for normality and the results are depicted below.

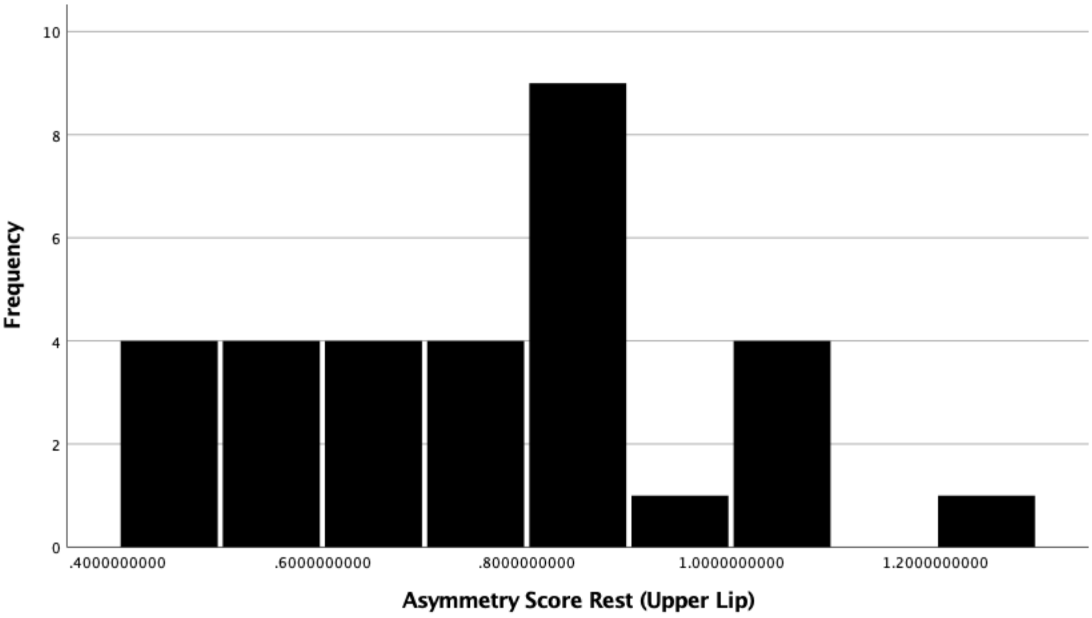


Figure 3-13. Histogram showing Asymmetry Scores at Rest (Upper Lip).

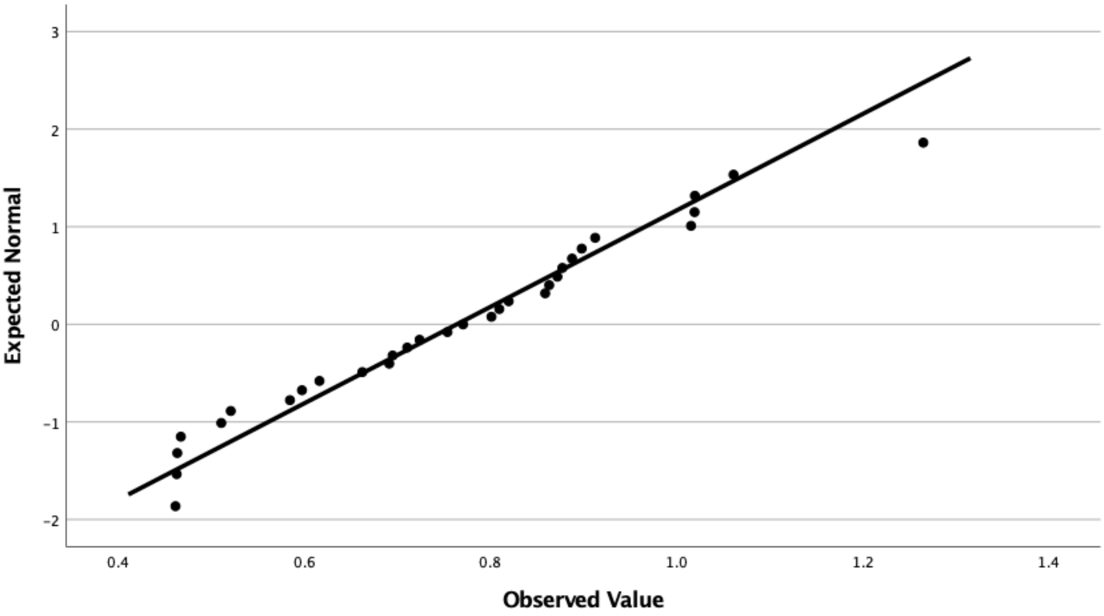


Figure 3-14. Q-Q Probability Plot showing Asymmetry Scores at Rest (Upper Lip).

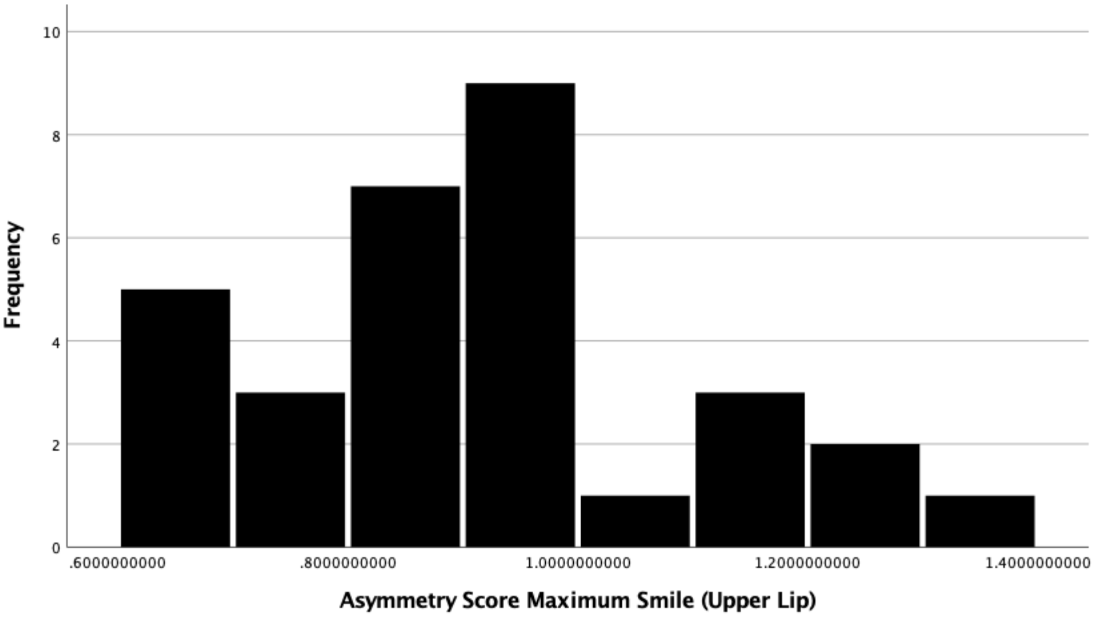


Figure 3-15. Histogram showing Asymmetry Scores at Maximum Smile (Upper Lip).

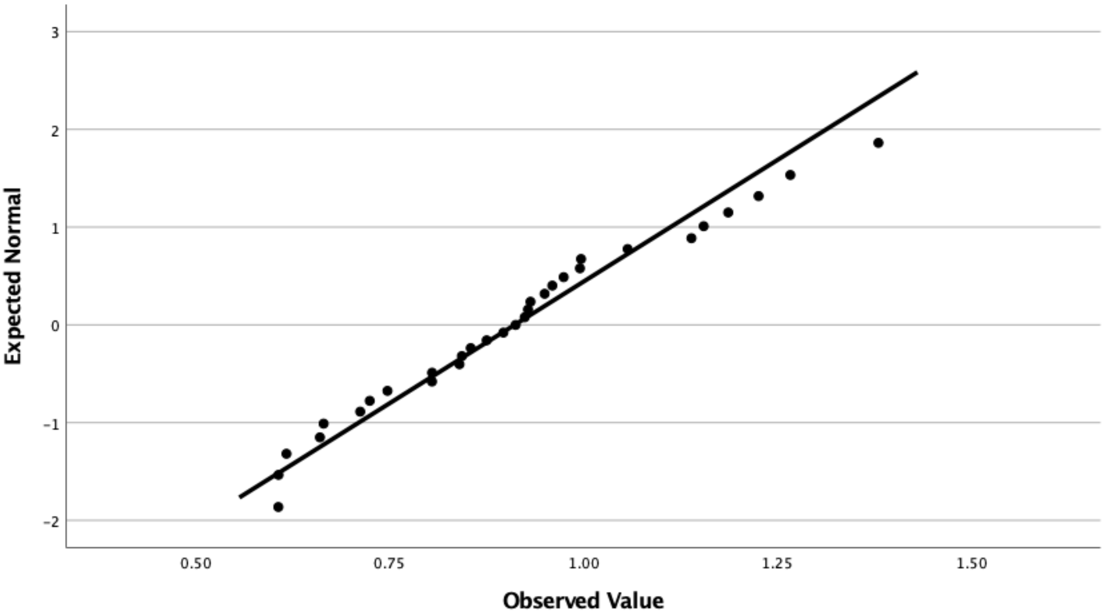


Figure 3-16. Q-Q Probability Plot showing Asymmetry Scores at Maximum Smile (Upper Lip).

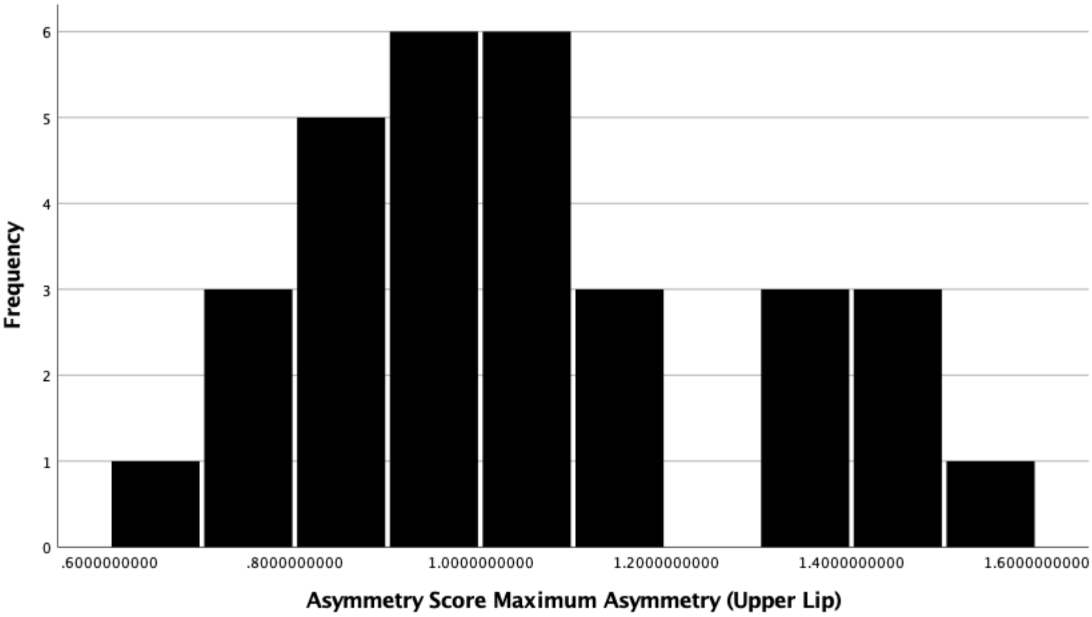


Figure 3-17. Histogram showing Asymmetry Scores at Maximum Asymmetry (Upper Lip).

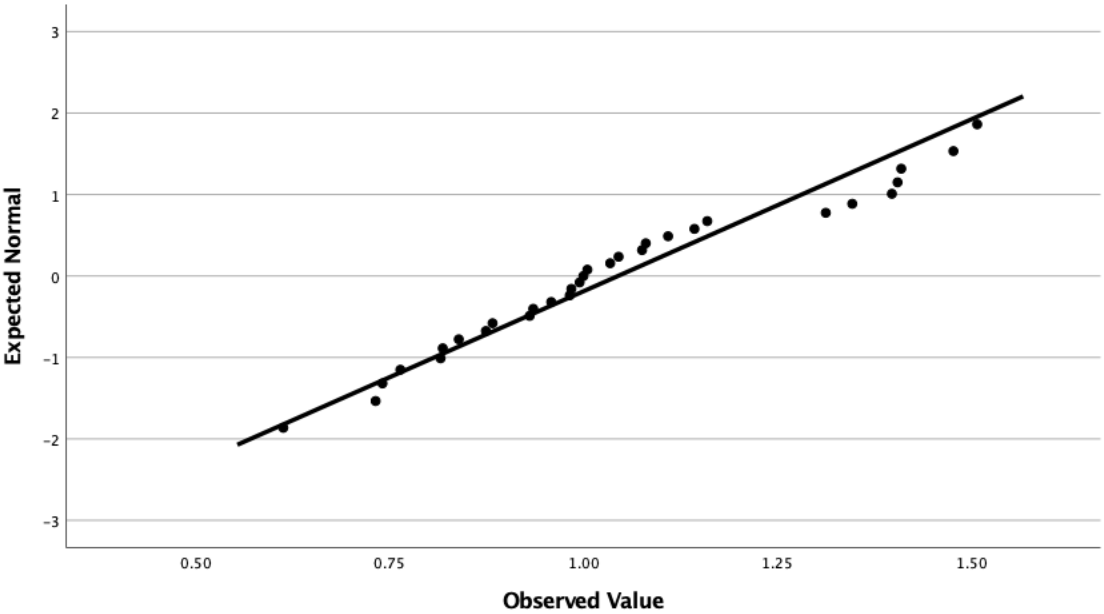
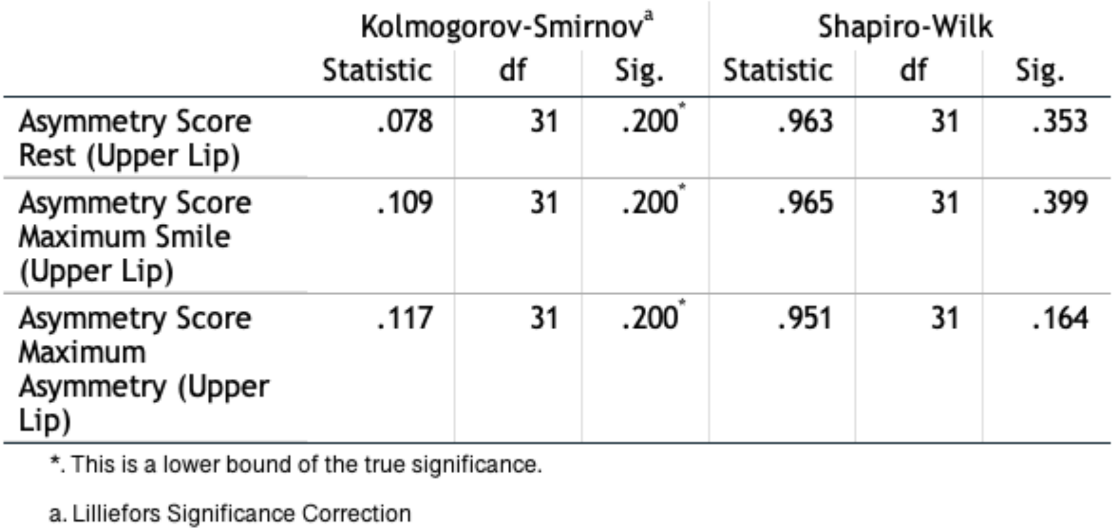


Figure 3-18. Q-Q Probability Plot showing Asymmetry Scores at Maximum Asymmetry (Upper Lip).

Table 3-4. Results of Normality tests for Upper Lip Asymmetry Scores.



	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Asymmetry Score Rest (Upper Lip)	.078	31	.200*	.963	31	.353
Asymmetry Score Maximum Smile (Upper Lip)	.109	31	.200*	.965	31	.399
Asymmetry Score Maximum Asymmetry (Upper Lip)	.117	31	.200*	.951	31	.164

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

For both statistical tests used the null hypothesis was that the data was normally distributed, and the alternative hypothesis was that the data was not normally distributed. As P>0.05 for both the Kolmogorov-Smirnov test and the Shapiro-Wilk test we can accept the null hypothesis and assume a normal distribution as there is no evidence to suggest a non-normal distribution. As the data is normally distributed, then a parametric test will be used based on the mean of the data.

3.2.4. Cheek

Cheek asymmetry scores for the rest frame, frame of maximum smile, and frame of maximum asymmetry were assessed for normality and the results are depicted below.

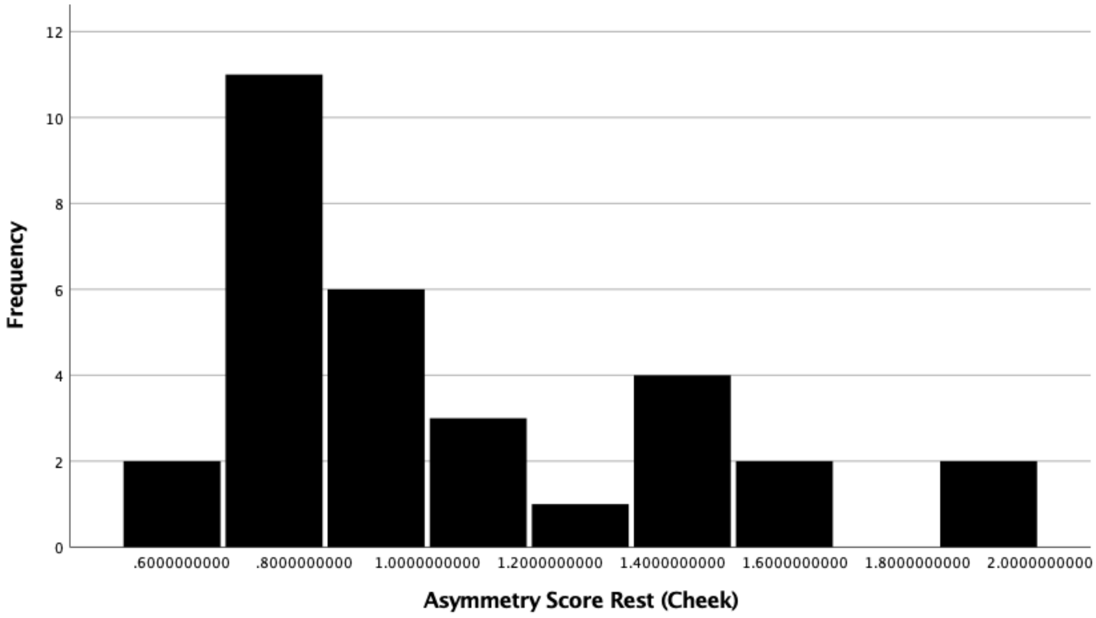


Figure 3-19. Histogram showing Asymmetry Scores at Rest (Cheek).

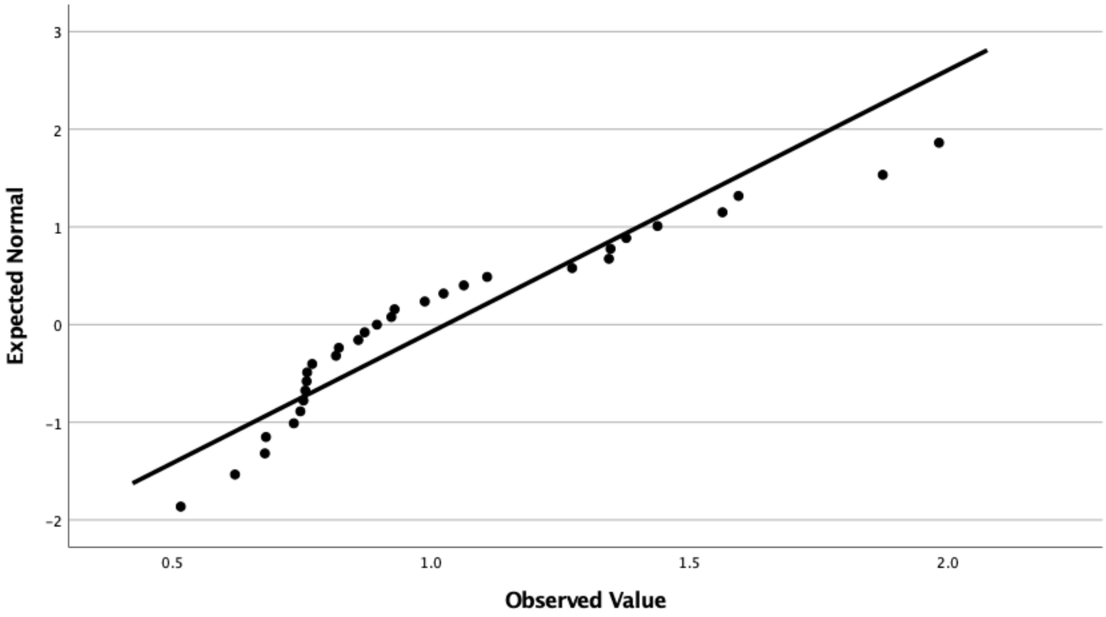


Figure 3-20. Q-Q Probability Plot showing Asymmetry Scores at Rest (Cheek).

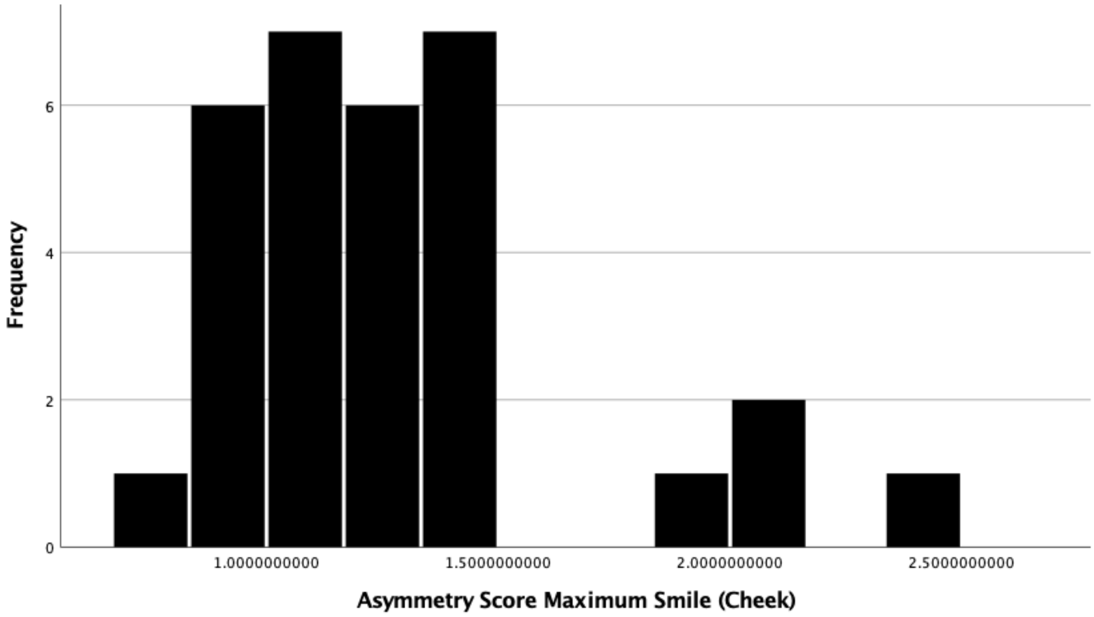


Figure 3-21. Histogram showing Asymmetry Scores at Maximum Smile (Cheek).

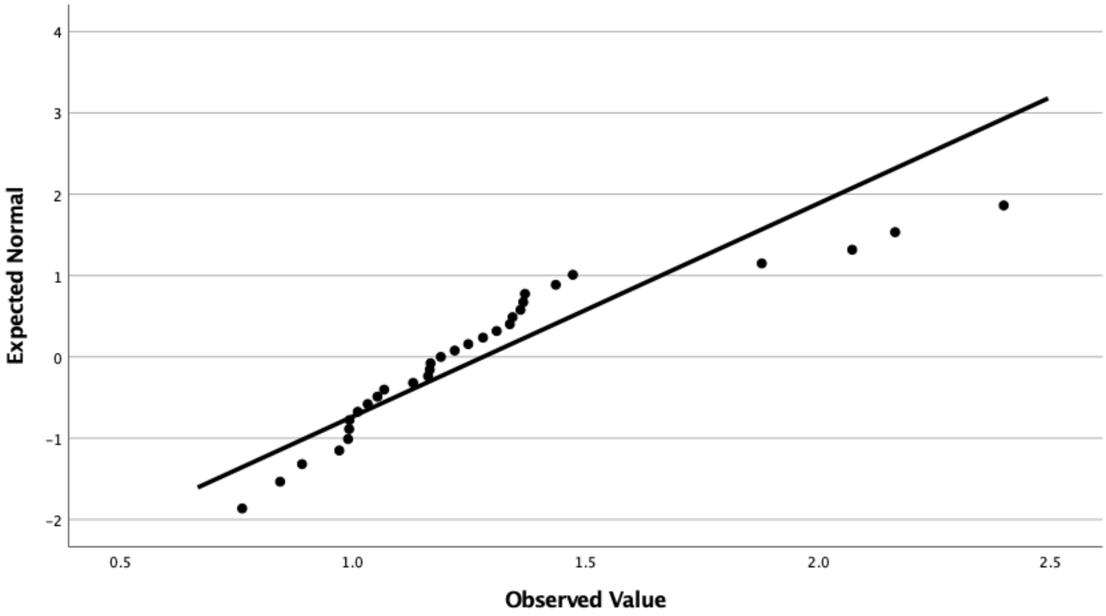


Figure 3-22. Q-Q Probability Plot showing Asymmetry Scores at Maximum Smile (Cheek).

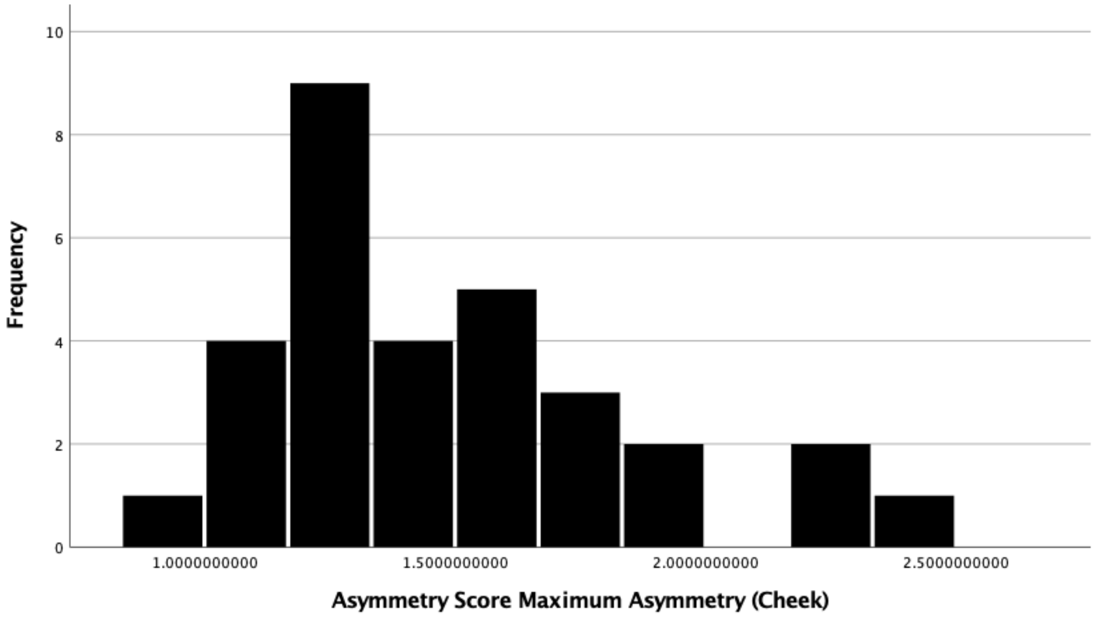


Figure 3-23. Histogram showing Asymmetry Scores at Maximum Asymmetry (Cheek).

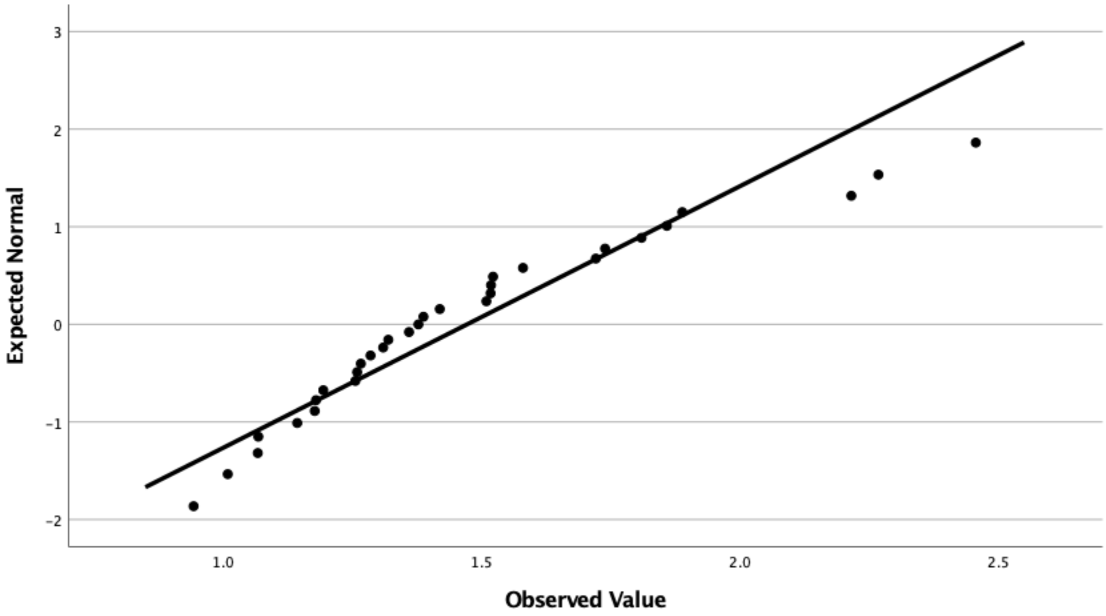
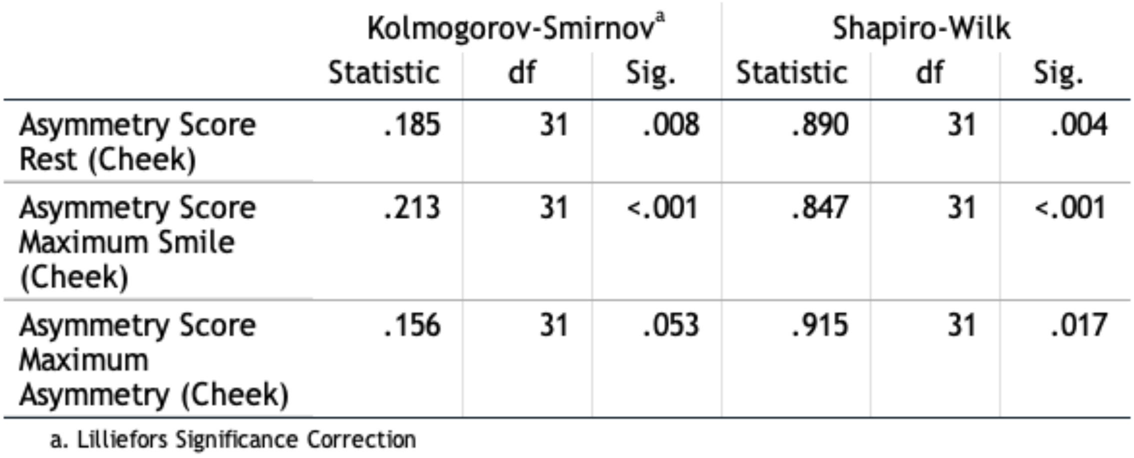


Figure 3-24. Q-Q Probability Plot showing Asymmetry Scores at Maximum Asymmetry (Cheek).

Table 3-5. Results of Normality tests for Cheek Asymmetry Scores.



	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Asymmetry Score Rest (Cheek)	.185	31	.008	.890	31	.004
Asymmetry Score Maximum Smile (Cheek)	.213	31	<.001	.847	31	<.001
Asymmetry Score Maximum Asymmetry (Cheek)	.156	31	.053	.915	31	.017

a. Lilliefors Significance Correction

For both statistical tests used the null hypothesis was that the data was normally distributed, and the alternative hypothesis was that the data was not normally distributed. As P>0.05 for both the Kolmogorov-Smirnov test and the Shapiro-Wilk test we can accept the null hypothesis and assume a normal distribution as there is no evidence to suggest a non-normal distribution. As the data is normally distributed, then a parametric test will be used based on the mean of the data.

3.3. Asymmetry Scores

Asymmetry scores were calculated for the rest frame, frame of maximum smile, and frame of maximum asymmetry for each patient’s full face, nasolabial region, upper lip, and cheek. Asymmetry scores will be presented using descriptive statistics based on measures of central tendency and measures of dispersion. As the asymmetry scores are normally distributed the mean will be used as the measure of central tendency and standard deviation (SD) will be used as the measure of dispersion.

3.3.1. Full Face

Table 3-6. Descriptive Statistics for Full Face Asymmetry Scores.

	N	Minimum	Maximum	Mean	Std. Deviation
Asymmetry Score Rest (Full Face)	31	1.42	3.69	2.31	.55
Asymmetry Score Maximum Smile (Full Face)	31	1.78	4.23	2.63	.56
Asymmetry Score Maximum Asymmetry (Full Face)	31	2.11	5.05	2.98	.60

3.3.2. Nasolabial Region

Table 3-7. Descriptive Statistics for Nasolabial Region Asymmetry Scores.

	N	Minimum	Maximum	Mean	Std. Deviation
Asymmetry Score Rest (Nasolabial Region)	31	.75	3.27	1.53	.57
Asymmetry Score Maximum Smile (Nasolabial Region)	31	.99	3.25	1.61	.55
Asymmetry Score Maximum Asymmetry (Nasolabial Region)	31	1.10	3.97	1.81	.64

3.3.3. Upper Lip

Table 3-8. Descriptive Statistics for Upper Lip Asymmetry Scores.

	N	Minimum	Maximum	Mean	Std. Deviation
Asymmetry Score Rest (Upper Lip)	31	.46	1.27	.76	.20
Asymmetry Score Maximum Smile (Upper Lip)	31	.61	1.38	.91	.20
Asymmetry Score Maximum Asymmetry (Upper Lip)	31	.61	1.51	1.04	.24

3.3.4. Cheek

Table 3-9. Descriptive Statistics for Cheek Asymmetry Scores.

	N	Minimum	Maximum	Mean	Std. Deviation
Asymmetry Score Rest (Cheek)	31	.52	1.98	1.03	.37
Asymmetry Score Maximum Smile (Cheek)	31	.76	2.40	1.28	.38
Asymmetry Score Maximum Asymmetry (Cheek)	31	.94	2.46	1.47	.37

3.4. Correlation

As the asymmetry scores were normally distributed a parametric test was selected to assess the correlation. The parametric test that was used was Pearson's correlation coefficient (r), which is a bivariate analysis of linear correlation. A two-tailed test of statistical significance was carried out and results were reported at the 0.05 significance level.

The assessment of correlation was used to determine if a statistically significant linear relationship exists between static and dynamic facial dysmorphology, as well as determining both the strength and direction of the relationship. As the data was normally distributed, the coefficient of determination (r^2); the effect size explained by the variable, and the coefficient of alienation ($1-r^2$); the effect size not explained by the variable, will also be presented.

The aims of this study regarding correlation were to assess the correlation between static (3D) asymmetry at rest and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile; as well as assessing the correlation between static (3D) asymmetry at maximum smile and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP).

Scatterplots will be used to graphically display the correlational data for full face, nasolabial region, upper lip, and cheek asymmetry scores.

3.4.1. Full Face

3.4.1.1. Correlation between static (3D) asymmetry at rest and dynamic (4D) asymmetry (Full Face)

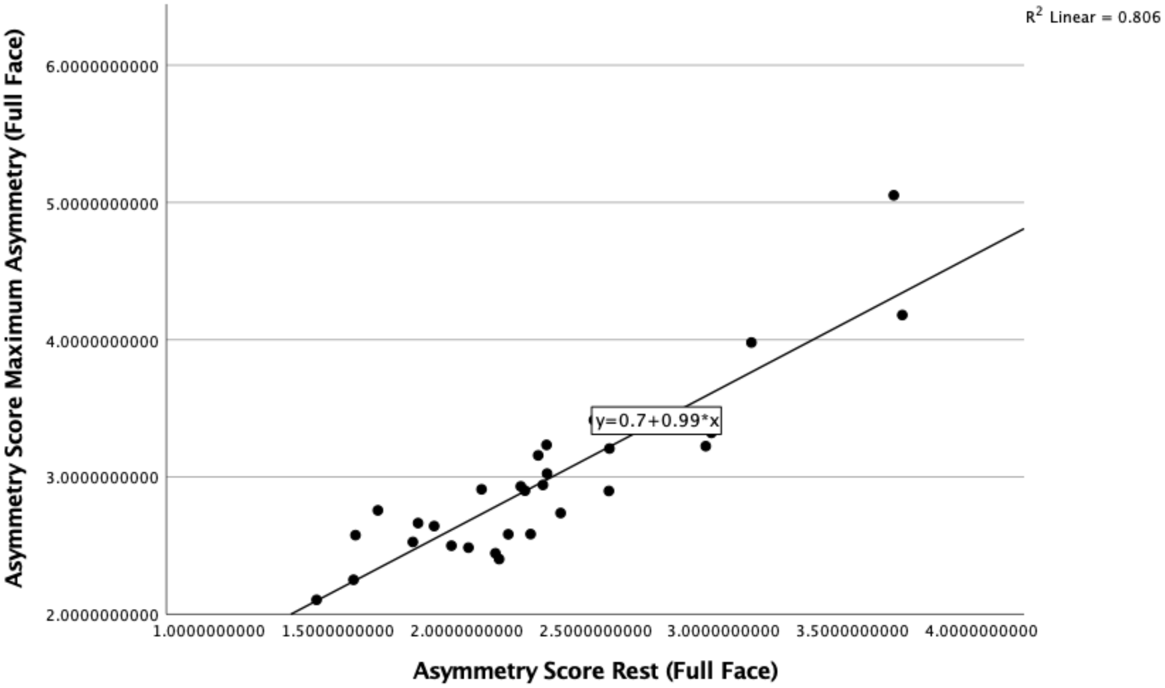


Figure 3-25. Scatterplot showing the correlation between asymmetry scores at rest (3D) and maximum asymmetry scores (4D) (Full Face).

Table 3-10. Correlation results of static (3D) asymmetry at rest and dynamic (4D) asymmetry (Full Face).

		Asym Rest (Full Face)	Asym Max Asym (Full Face)
Asymmetry Score Rest (Full Face)	Pearson Correlation		.898**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Full Face)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson's correlation coefficient (r) was conducted to calculate the relationship between full-face static (3D) asymmetry at rest and full-face dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-10 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-25. Full-face 3D asymmetry at rest was strongly positively correlated to full-face 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; $r\ (31) = .898$, $p<.001$. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.806$ (80.6%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.194$ (19.4%), were calculated. These findings indicated that full-face asymmetry at rest (3D) accounted for 80.6% of the variance in full-face dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.1.2. Correlation between static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Full Face)

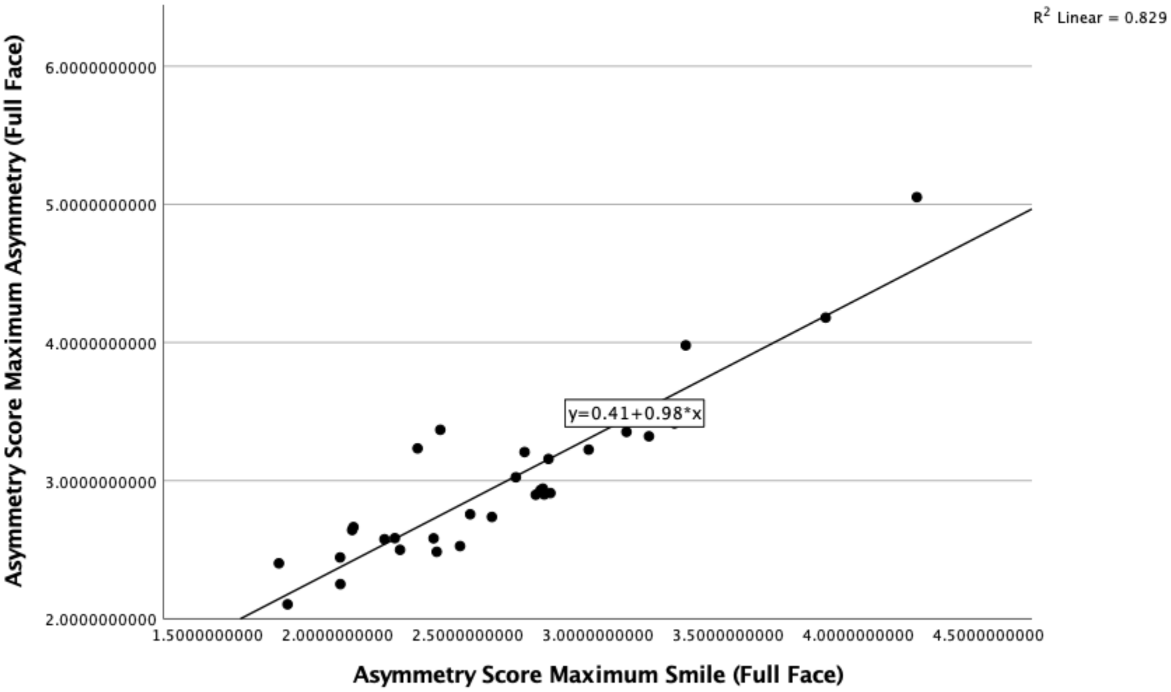
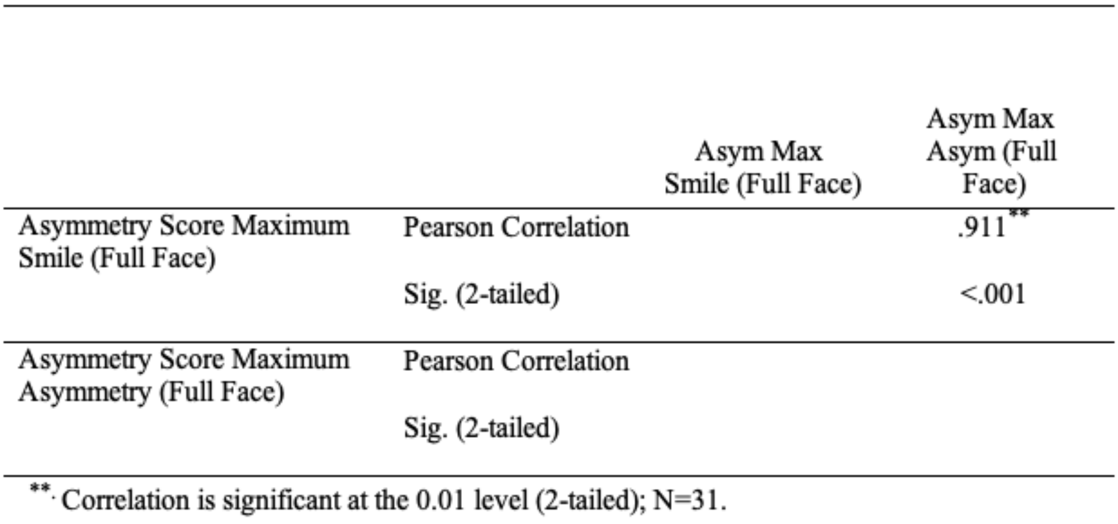


Figure 3-26. Scatterplot showing the correlation between asymmetry scores at maximum smile (3D) and maximum asymmetry scores (4D) (Full Face).

Table 3-11. Correlation results of static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Full Face).



		Asym Max Smile (Full Face)	Asym Max Asym (Full Face)
Asymmetry Score Maximum Smile (Full Face)	Pearson Correlation		.911**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Full Face)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson’s correlation coefficient (r) was conducted to calculate the relationship between full-face static (3D) asymmetry at maximum smile and full-face dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-11 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-26. Full-face 3D asymmetry at maximum smile was strongly positively correlated to full-face 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .911, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.829$ (82.9%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.171$ (17.1%), were calculated. These findings indicated that full-face asymmetry at maximum smile (3D) accounted for 82.9% of the variance in full-face dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.2. Nasolabial Region

3.4.2.1. Correlation between static (3D) asymmetry at rest and dynamic (4D) asymmetry (Nasolabial Region)

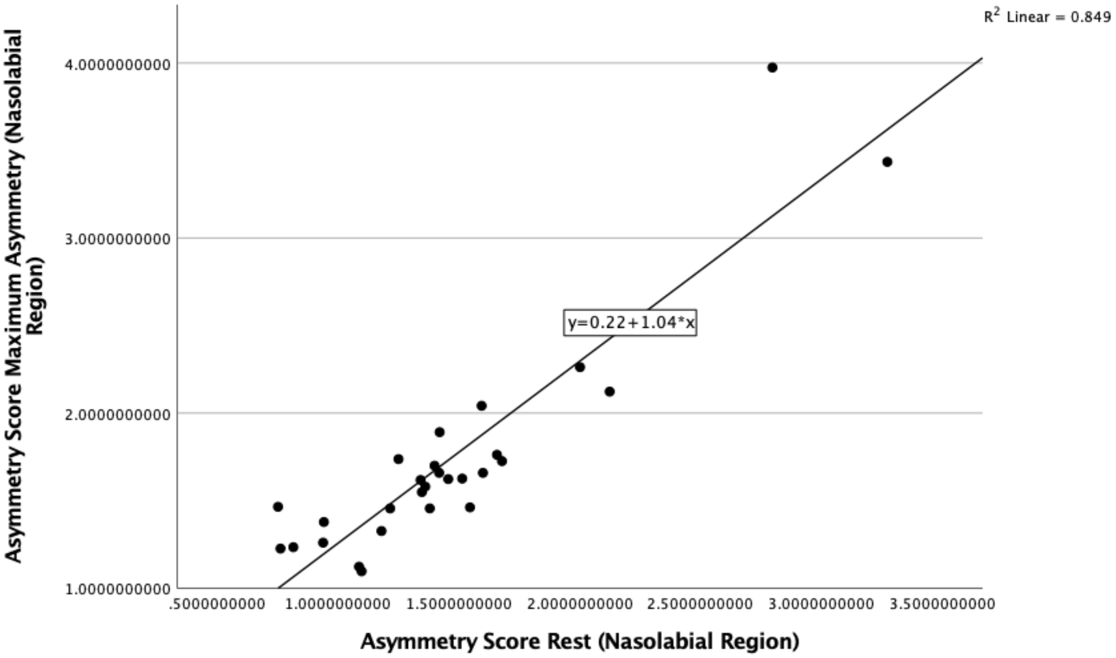
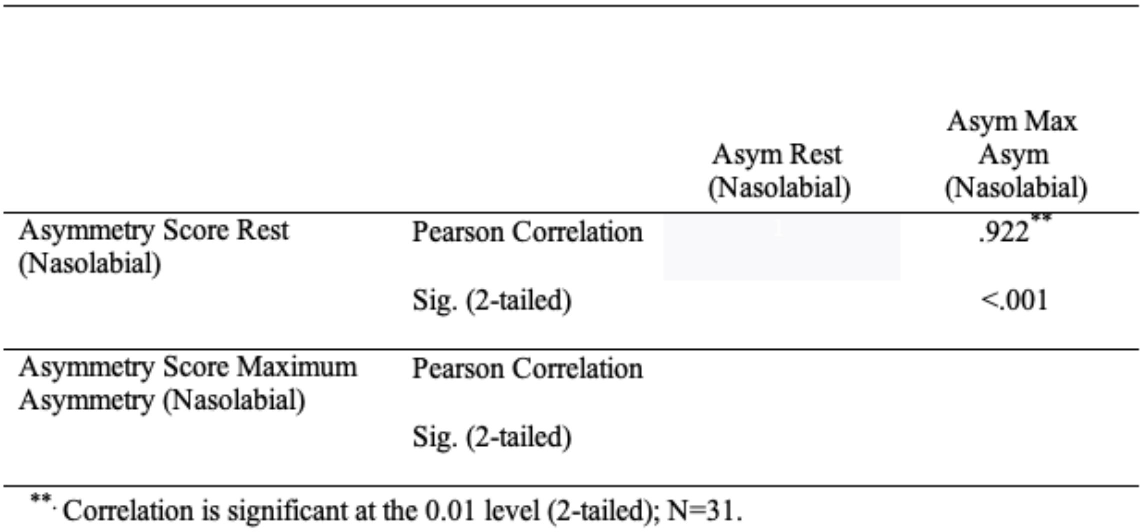


Figure 3-27. Scatterplot showing the correlation between asymmetry scores at rest (3D) and maximum asymmetry scores (4D) (Nasolabial Region).

Table 3-12. Correlation results of static (3D) asymmetry at rest and dynamic (4D) asymmetry (Nasolabial Region).



		Asym Rest (Nasolabial)	Asym Max Asym (Nasolabial)
Asymmetry Score Rest (Nasolabial)	Pearson Correlation		.922**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Nasolabial)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson's correlation coefficient (r) was conducted to calculate the relationship between the nasolabial region static (3D) asymmetry at rest and the nasolabial region dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-12 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-27. Nasolabial region 3D asymmetry at rest was strongly positively correlated to nasolabial region 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .922, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.849$ (84.9%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.151$ (15.1%), were calculated. These findings indicated that nasolabial region asymmetry at rest (3D) accounted for 84.9% of the variance in nasolabial region dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.2.2. Correlation between static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Nasolabial Region)

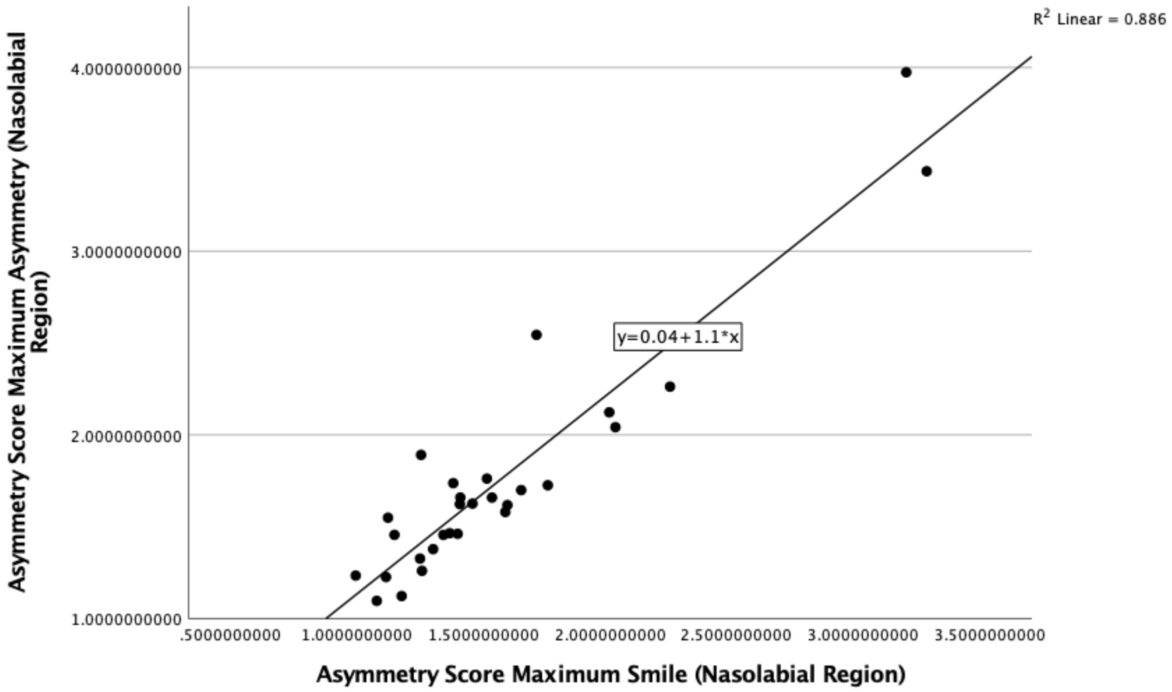
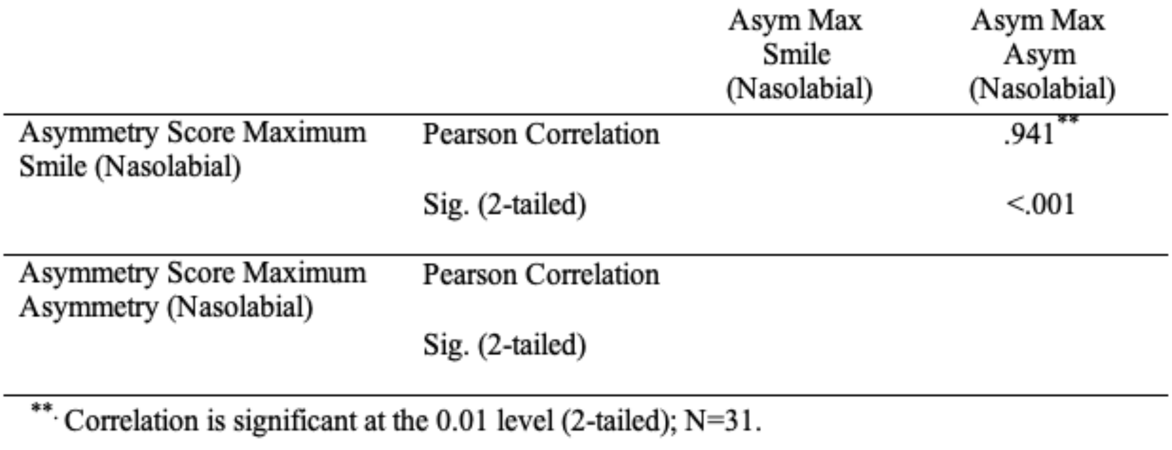


Figure 3-28. Scatterplot showing the correlation between asymmetry scores at maximum smile (3D) and maximum asymmetry scores (4D) (Nasolabial Region).

Table 3-13. Correlation results of static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Nasolabial Region).



		Asym Max Smile (Nasolabial)	Asym Max Asym (Nasolabial)
Asymmetry Score Maximum Smile (Nasolabial)	Pearson Correlation		.941**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Nasolabial)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson’s correlation coefficient (r) was conducted to calculate the relationship between the nasolabial region static (3D) asymmetry at maximum smile and the nasolabial region dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-13 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-28. Nasolabial region 3D asymmetry at maximum smile was strongly positively correlated to nasolabial region 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .941, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.886$ (88.6%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.114$ (11.4%), were calculated. These findings indicated that nasolabial region asymmetry at maximum smile (3D) accounted for 88.6% of the variance in nasolabial region dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.3. Upper Lip

3.4.3.1. Correlation between static (3D) asymmetry at rest and dynamic (4D) asymmetry (Upper Lip)

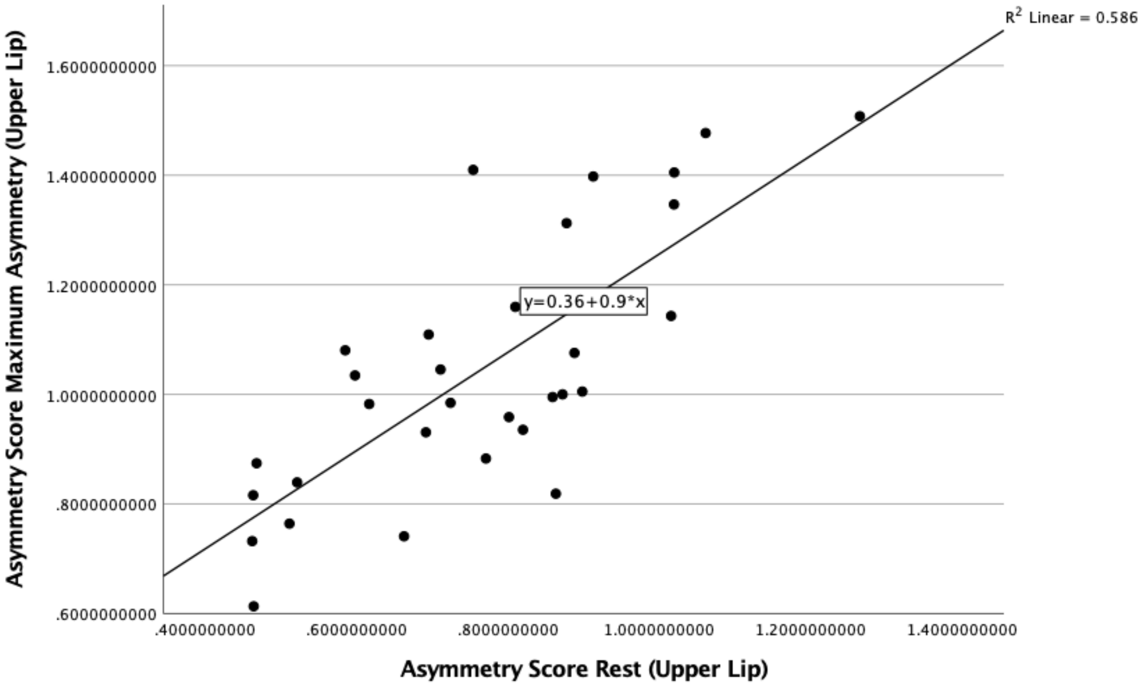
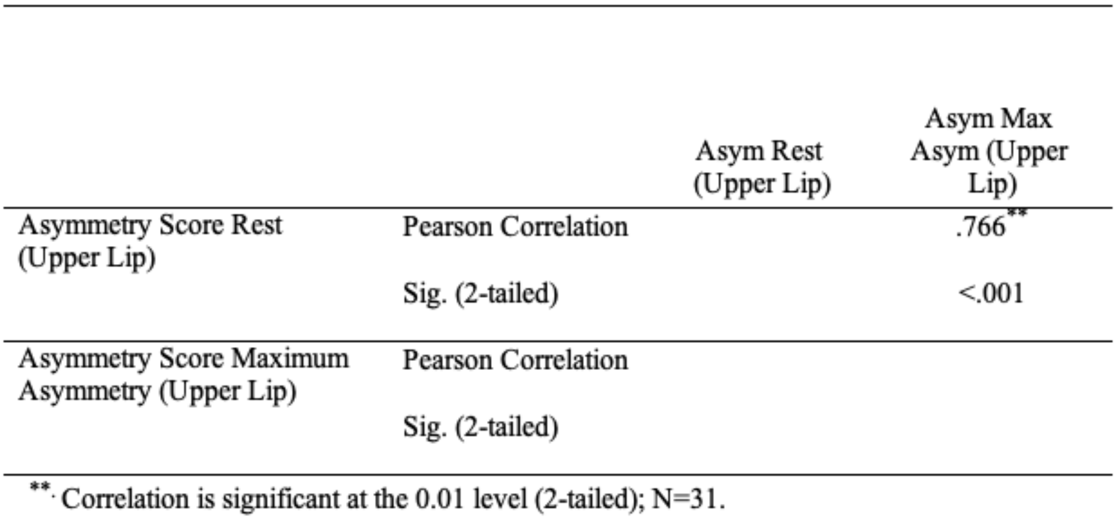


Figure 3-29. Scatterplot showing the correlation between asymmetry scores at rest (3D) and maximum asymmetry scores (4D) (Upper Lip).

Table 3-14. Correlation results of static (3D) asymmetry at rest and dynamic (4D) asymmetry (Upper Lip).



		Asym Rest (Upper Lip)	Asym Max Asym (Upper Lip)
Asymmetry Score Rest (Upper Lip)	Pearson Correlation		.766**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Upper Lip)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson's correlation coefficient (r) was conducted to calculate the relationship between the upper lip static (3D) asymmetry at rest and the upper lip dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-14 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-29. Upper lip 3D asymmetry at rest was strongly positively correlated to upper lip 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .766, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.586$ (58.6%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.414$ (41.4%), were calculated. These findings indicated that upper lip asymmetry at rest (3D) accounted for 58.6% of the variance in upper lip dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.3.2. Correlation between static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Upper Lip)

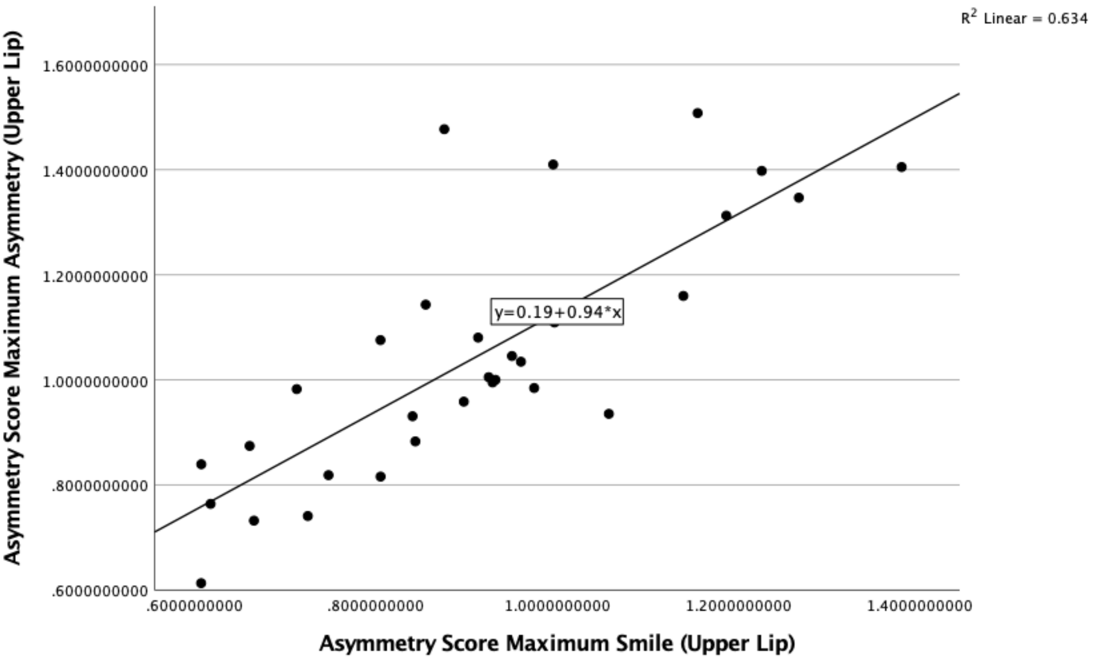
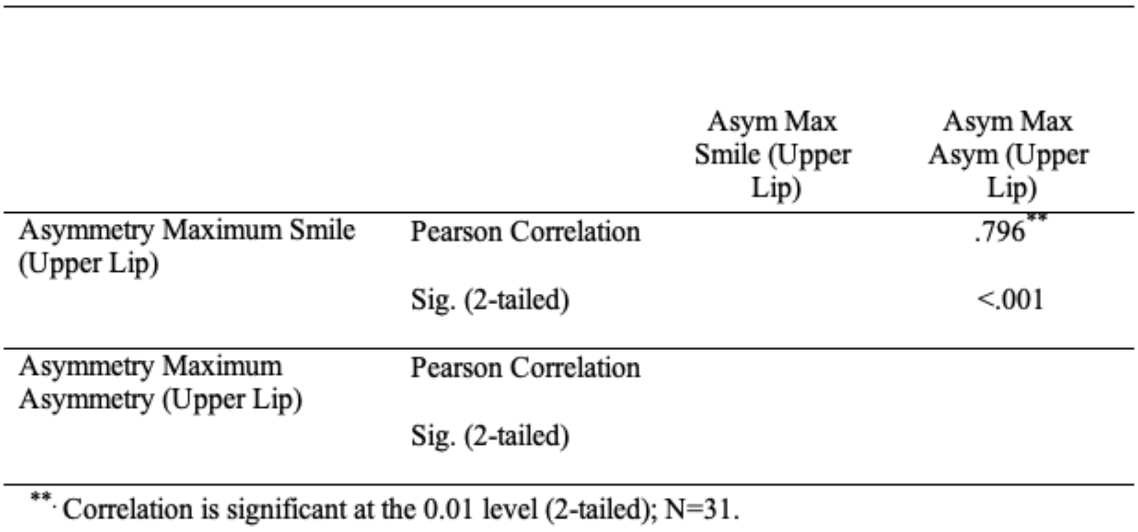


Figure 3-30. Scatterplot showing the correlation between asymmetry scores at maximum smile (3D) and maximum asymmetry scores (4D) (Upper Lip).

Table 3-15. Correlation results of static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Upper Lip).



		Asym Max Smile (Upper Lip)	Asym Max Asym (Upper Lip)
Asymmetry Maximum Smile (Upper Lip)	Pearson Correlation		.796**
	Sig. (2-tailed)		<.001
Asymmetry Maximum Asymmetry (Upper Lip)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson’s correlation coefficient (r) was conducted to calculate the relationship between the upper lip static (3D) asymmetry at maximum smile and the upper lip dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-15 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-30. Upper lip 3D asymmetry at maximum smile was strongly positively correlated to upper lip 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .796, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.634$ (63.4%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.366$ (36.6%), were calculated. These findings indicated that upper lip asymmetry at maximum smile (3D) accounted for 63.4% of the variance in upper lip dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.4. Cheek

3.4.4.1. Correlation between static (3D) asymmetry at rest and dynamic (4D) asymmetry (Cheek)

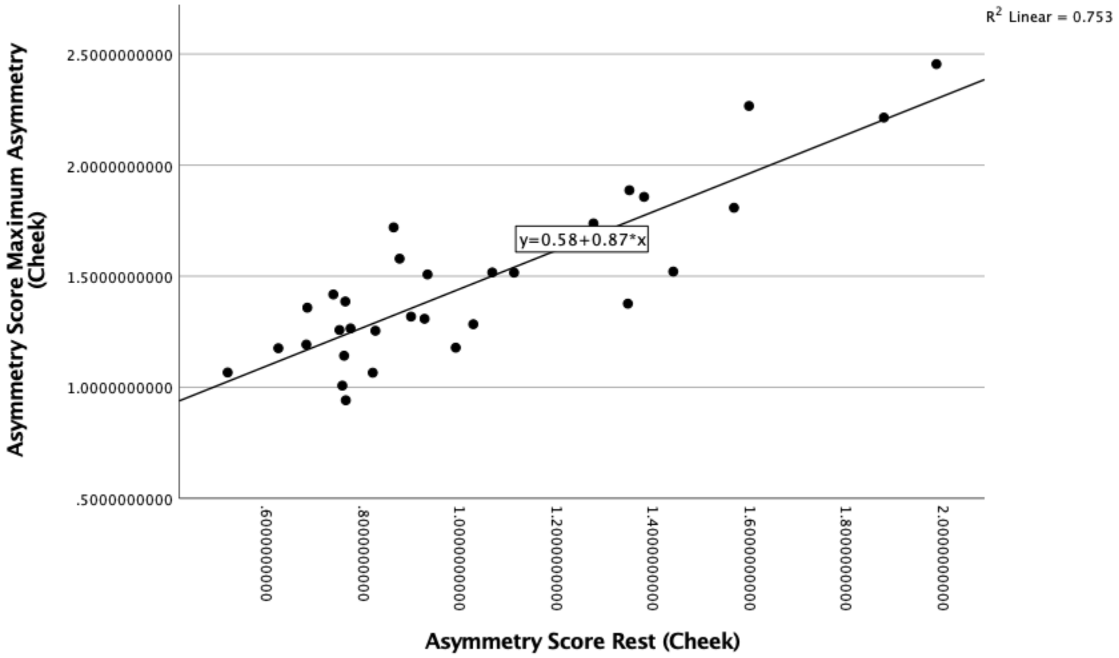
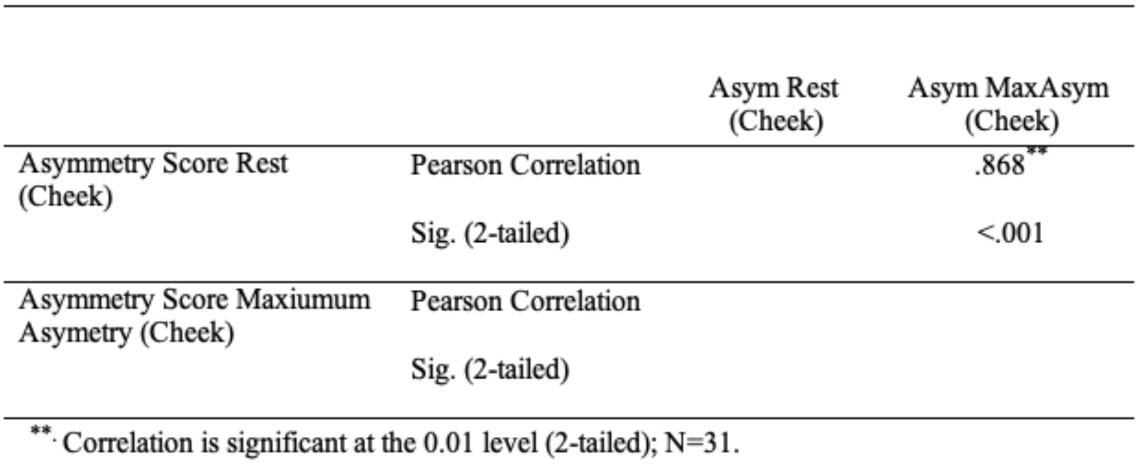


Figure 3-31. Scatterplot showing the correlation between asymmetry scores at rest (3D) and maximum asymmetry scores (4D) (Cheek).

Table 3-16. Correlation results of static (3D) asymmetry at rest and dynamic (4D) asymmetry (Cheek).



		Asym Rest (Cheek)	Asym MaxAsym (Cheek)
Asymmetry Score Rest (Cheek)	Pearson Correlation		.868**
	Sig. (2-tailed)		<.001
Asymmetry Score Maxiumum Asymetry (Cheek)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson's correlation coefficient (r) was conducted to calculate the relationship between the cheek static (3D) asymmetry at rest and the cheek dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-16 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-31. Cheek 3D asymmetry at rest was strongly positively correlated to cheek 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .868, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.753$ (75.3%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.247$ (24.7%), were calculated. These findings indicated that cheek asymmetry at rest (3D) accounted for 75.3% of the variance in cheek dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.4.4.2. Correlation between static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Cheek)

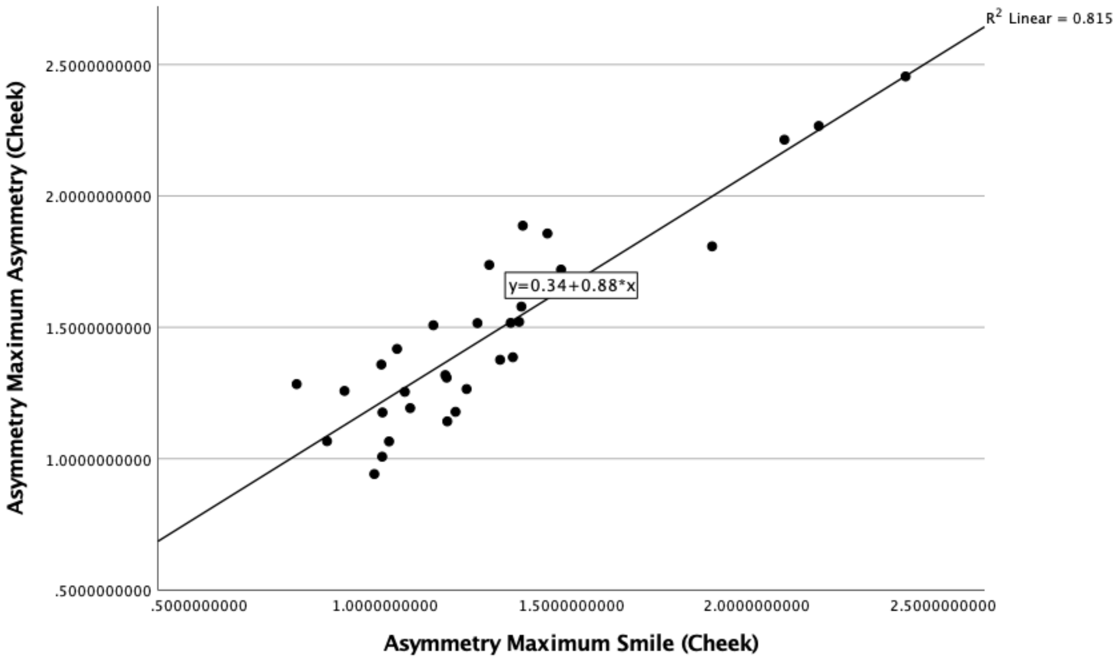


Figure 3-32. Scatterplot showing the correlation between asymmetry scores at maximum smile (3D) and maximum asymmetry scores (4D) (Cheek).

Table 3-17. Correlation results of static (3D) asymmetry at maximum smile and dynamic (4D) asymmetry (Cheek).

		Asym MaxSmile (Cheek)	Asym MaxAsym (Cheek)
Asymmetry Score Maximum Smile (Cheek)	Pearson Correlation		.903**
	Sig. (2-tailed)		<.001
Asymmetry Score Maximum Asymmetry (Cheek)	Pearson Correlation		
	Sig. (2-tailed)		

**. Correlation is significant at the 0.01 level (2-tailed); N=31.

A Pearson’s correlation coefficient (r) was conducted to calculate the relationship between the cheek static (3D) asymmetry at maximum smile and the cheek dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile. The results are shown in Table 3-17 and a scatterplot showing the relationship between the two variables is depicted in Figure 3-32. Cheek 3D asymmetry at maximum smile was strongly positively correlated to cheek 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = .903, p<.001. The strength of the correlation was determined by the strength of relationship thresholds set out in Table 2-1.

The coefficient of determination (r^2); $r^2 = 0.815$ (81.5%), and the coefficient of alienation ($1-r^2$); $1-r^2 = 0.185$ (18.5%), were calculated. These findings indicated that cheek asymmetry at maximum smile (3D) accounted for 81.5% of the variance in cheek dynamic (4D) asymmetry represented by the frame of maximum asymmetry during a maximum smile.

3.5. When does maximum asymmetry occur?

A further aim of this study was to assess when maximum asymmetry occurs in patients with unilateral cleft lip and palate (UCLP) during a maximum smile. Measures of frequency will be used to describe when the greatest degree of asymmetry is seen.

No patients exhibited maximum asymmetry at rest (N=0; 0%), four patients exhibited maximum asymmetry during muscular contraction in the build-up to a maximum smile (N=4; 12.9%), no patients exhibited maximum asymmetry at maximum smile (N=0; 0%), and 27 patients exhibited maximum asymmetry during the relaxation phase post-maximum smile (N=27; 87.1%).

Chapter 4 Discussion and Conclusions

4.1. Discussion

The rationale of this study was to provide a unique and novel assessment of the 4-dimensional (4D) facial asymmetry in a cohort of age-matched patients with a diagnosis of unilateral cleft lip and palate (UCLP). Enhancing our understanding of the relationship between static facial dysmorphology in 3-dimenisions (3D) and dynamic facial dysmorphology in 4-dimenisions (4D) will provide greater understanding and interpretation of the residual facial deformity present in patients with UCLP. The ultimate goal in innovative 4D assessment is to improve the standard of care for patients and ensure adequate surgical outcomes for those entering the cleft pathway. By determining the correlation between static (3D) and dynamic (4D) facial dysmorphology we can shape future cleft record taking by determining whether 4D imaging should be a standard requirement or whether it is surplus to our needs. The need for a suitable objective assessment technique for facial asymmetry in cleft care has been well documented, and an appropriate objective tool may help shape future surgical decisions in care (Trotman et al., 2007).

The research questions we wanted to answer focussed on the correlation between static and dynamic facial asymmetry. Firstly, is there a strong correlation between static (3D) asymmetry at rest and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP)? If the rest frame is strongly correlated with the frame of maximum asymmetry, then could a single 3D image of a patient at rest suffice to predict their dynamic facial asymmetry? Secondly, is there a strong correlation between static (3D) asymmetry at maximum smile and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile in patients with unilateral cleft lip and palate (UCLP)? If the frame of maximum smile is not correlated with the frame of maximum asymmetry, then it would highlight the need for 4D imaging in a comprehensive assessment of facial dysmorphology. Conversely, a strong correlation may indicate that we could predict dynamic facial asymmetry from a single 3D image of patients at maximum smile. Finally, we wanted to determine at what point, during a maximum smile, the greatest asymmetry would most likely be seen. Determining if it is at rest, at maximum smile, on the lead up to maximum smile, or during the relaxation phase could aid in determining the requirement for 4D imaging but also the aetiology of the facial asymmetry.

4.2. Study Design and Subject Selection

This study was designed as a retrospective cross-sectional study utilising quantitative methodology. Retrospective methodology was employed due to the prevalence of a cleft lip and palate diagnosis in the population and the subsequent low incidence of a non-syndromic unilateral cleft lip and palate (UCLP) diagnosis. As previously discussed, cleft lip and palate is seen in approximately 1 in every 700 live births globally, and around 90 children are born with a diagnosis of cleft lip and palate in Scotland each year (Cleft Care Scotland, 2016; Olasoji et al., 2005). Additionally, only 22% of those born with cleft lip and palate will have a diagnosis of unilateral cleft lip and palate (UCLP) (CRANE, 2021). Due to the low prevalence, retrospective analysis is required to achieve an adequately sized cohort of patients for analysis. Even with retrospective data collection, getting sufficient patient numbers in a specific age cohort can take several years. Prospective methodology, while eliminating potential inherent biases, would likely have yielded low numbers during recruitment, and have incurred significantly increased costs in terms of time, resources, and money. The quality of evidence around treatment for cleft lip and palate remains low and, as with any rare condition, recruiting enough patients for a randomised control trial (RCT) is challenging.

For subject selection we analysed facial asymmetry in patients with unilateral cleft lip and palate (UCLP) for several reasons. Firstly, it has been shown that treatment outcomes for patients with UCLP were predictive of outcomes for overall cleft care, independent of specific diagnosis (Shaw et al., 1992). Secondly, bilateral cleft lip and palate (BCLP) is a symmetrical defect and the effect of clefting on facial appearance is difficult to quantify without an unaffected side to allow for direct comparison (Bugaighis et al., 2014). This comparison is facilitated by UCLP via mirroring of the cleft side with the unaffected contralateral side.

Inclusion criteria detailed patients with non-syndromic unilateral cleft lip and palate (UCLP) for the study. This is due to the supplementary facial features that can be indicative of syndromic unilateral cleft lip and palate (UCLP) patients. These features which may increase facial asymmetry but not be directly related to the actual cleft could confound and alter the results (Wilson-Nagrani et al., 2018). The age range of 13 to 17 years old was selected to ensure a homogenous sample for analysis and to recruit patients at the same stage of the surgical journey.

4.3. Maximum Smile

For this study we analysed facial asymmetry of unilateral cleft lip and palate (UCLP) patients during a maximum smile, utilising both the frame of maximum smile and the frame of maximum asymmetry during the maximum smile. Maximum smile was selected for analysis due to its reported high level of reproducibility, reliability, and patient acceptance in performing the expression (Gattani et al., 2020). Each patient was imaged performing four discrete facial expressions, maximum smile, cheek puff, lip purse, and grimace. The other expressions could potentially be analysed in future studies.

It is important to assess facial asymmetry during maximum facial expressions for patients as it more accurately represents their day-to-day appearance during social interaction. Facial asymmetry has also been shown to be increased at maximum smile when compared to an image at rest (Al Rudainy et al., 2019; Zhao et al., 2021).

Maximum facial expressions were selected as they have been shown to be more readily reproducible and valid compared to spontaneous facial movements (Trotman et al., 2013). Spontaneous facial movements and recorded reactions to stimuli vary greatly between individuals and vary in the same individual on separate occasions.

The frame of maximum smile was identified by a single independent assessor to improve reliability and reproducibility. This was a subjective method for the identification of the frame of maximum smile based on predetermined criteria. An objective tool could be devised to determine the frame of maximum smile; however, such a tool would require validation to ensure adequate agreement and correlation to expert examiner observations. Mathematical determination of a maximum smile may be further complicated by individual subject variation. Frame identification would rely on landmark-based analysis which may not be an accurate enough discriminator. Alternatively, the reliability and reproducibility of the identification of the frame of maximum smile could be improved by utilizing two independent assessors who would repeat their frame selections following a suitable washout period. This would allow the intra- and interobserver reliability to be calculated.

4.4. Assessment of Asymmetry

For this study the assessment of facial asymmetry was carried out on 4D images produced by a Di4D facial performance imaging system (Dimensional Imaging, Ltd. Hillington Park, Glasgow, Scotland) based on passive stereophotogrammetry. When determining how to assess facial asymmetry it is important to understand the advantages and limitations of the various options available. Facial asymmetry assessment can be either subjective or objective; subjective analysis infers the risk of observer bias and poor reproducibility while in objective analysis it may be difficult to agree on a standard outcome for statistical comparisons. Objective measures, however, can be reproducible, reliable, and valid, when studied robustly. The final decision regarding lip revision surgery is often determined by the subjective clinical assessment of the surgeon, which has shown poor inter-rater reliability and agreement, highlighting the need for more objective measures of assessment (Trotman et al., 2007). A review of assessment techniques used for facial asymmetry in cleft lip and palate research concluded that there was significant variation in study designs and an internationally accepted objective assessment tool was required

(Al-Omari et al., 2005). For this study we therefore selected an objective assessment method for analysis.

Simple facial asymmetry assessments are carried out every day during clinical examinations, either by observing differences between the left and right sides of the face, around an imagined mid-facial plane, or by dividing the face into vertical fifths on frontal inspection as shown in Figure 1-10 (Proffit et al., 2018). These subjective observations are, however, non-specific, non-reproducible, and not reliable.

The assessment of facial asymmetry utilising 2D imaging is common in research and can include the use of clinical photographs, radiographs, and clinical videos. The Asher-McDade Aesthetic Index uses masked 2D images for assessment and has been utilised in respected national and international cleft lip and palate research studies including the Clinical Standards Advisory Group (CSAG) Study and the Eurocleft Study (Brattström et al., 2005; Williams et al., 2001). While the facial asymmetry assessment in these studies was subjective, they used an ordinal Likert scale to improve inter- and intra-examiner reproducibility. Indirect assessment techniques using 2D images are only as reliable as the quality of the records or photographs used in the assessment. Their reliability can depend on the lighting, focus, image artefacts, and parallax errors in landmark identification if using objective landmark-based analysis. In addition, much like static 3D images, 2D images do not assess a patient’s dynamic asymmetry in motion. Three-dimensional imaging removes the potential for landmark identification errors due to imaging faults or parallax errors but is still based on static rather than dynamic assessments. Due to these documented issues with 2D and 3D imaging we opted to use dynamic 4D imaging for this study.

Four-dimensional imaging excels where 2D and 3D imaging fails by adequately assessing the dynamic asymmetries that are present during social interaction and facial expression. It therefore provides a more detailed and complete assessment of dynamic facial dysmorphology in cleft lip and palate. Facial asymmetry is not a constant throughout facial motion or social interaction and asymmetry tends to be greater during facial expressions (Al Rudainy et al., 2019). This highlights the importance of assessing a patient’s asymmetry during dynamic facial movements, so as to not underestimate their given asymmetry.

Once we have selected the type of image we plan to use, we must then decide how to analyse the image. Will it be a subjective or objective assessment and will it be based on identifiable landmarks or an alternative form of analysis? Landmark based analysis relies on accurate landmark identification and subsequent linear and angular measurements, and therefore it does not fully assess the asymmetry and shape of the whole face. Alternatively, facial curves can be utilised, and studies have used Bézier curves to track the motion of the upper lip (Mishima et al., 2009). Curve-based assessments analyse more of the facial surface so are an improvement on landmark-based analysis, but they still do not analyse the entirety of the dense surface texture of the face. Other studies have attempted to analyse the magnitude and direction of vector movement during facial animation, but these studies, again, do not use the entire surface of the face (Seaward et al., 2022). By utilising a generic mesh that can be conformed to the surface of the face we can calculate an asymmetry score by first creating a mirror image of the conformed mesh and superimposing it on itself via partial ordinary Procrustes analysis. This technique allows for an objective facial asymmetry score to be produced based on the entire surface of the face in a process that has been previously validated (Al-Rudainy et al., 2018; Al Rudainy et al., 2019; Gattani et al., 2020). Therefore, for this study we opted to calculate asymmetry scores with the use of a mesh conformation process.

The final component to consider is how much of the face to assess when analysing facial asymmetry in a unilateral cleft lip and palate cohort. Assessment of full facial asymmetry has the advantage of providing a complete assessment of the face, but asymmetry scores may be diluted or confounded by asymmetry present elsewhere on the face not related to the cleft. Asymmetry of the Asher-McDade region isolates the cleft site and is viewed as a valid area of assessment in the literature (Asher-McDade et al., 1991 Brattström et al., 2005; Williams et al., 2001). Further breaking down the Asher-McDade region into the upper lip and cheek may provide useful insight into the primary component of the asymmetry. For this study our primary focus was the Asher-McDade region (nasolabial region), but we also carried out analysis for the full face, upper lip, and cheek. We calculated total non-directional asymmetry score, and future research could further analyse directional asymmetry in the three planes of space (x,y, and z).

4.5. Discussion of Results

4.5.1. Participant baseline characteristics

Thirty-one participants were included in this retrospective cross-sectional study and the baseline characteristics of all participants are recorded in Table 3-1. Based on our sample size calculation our study was adequately powered for all calculated correlation coefficients at 0.80 (80%). The weakest correlation was seen between upper lip 3D asymmetry at rest and upper lip 4D asymmetry represented by the frame of maximum asymmetry during a maximum smile; r (31) = 0.766, p<0.001.

All participants had a diagnosis of non-syndromic unilateral cleft lip and palate (UCLP) to ensure a homogenous sample. Patients with syndromic unilateral cleft lip and palate were excluded as they may exhibit additional facial features related to their syndrome but not specifically to the cleft that could increase and confound asymmetry scores (Wilson-Nagrani et al., 2018). Unilateral cleft lip and palate (UCLP) was selected to facilitate comparisons between the affected and unaffected sides. As previously discussed, bilateral cleft lip and palate (BCLP) is a more symmetrical defect and therefore it is more difficult to assess the effect of clefting on the symmetry and morphology of the face (Bugaighis et al., 2014). Four-dimensional images that had been previously captured for participants between the ages of 13 and 17 years were selected, with a mean age of 14.61 and a standard deviation of ± 1.453. This was to ensure a comparable sample and to ensure patients were at an equivalent stage of the cleft surgical journey.

A greater proportion of study participants were male (64% (n=20)) rather than female (35.5% (n=11)). This is consistent with other research in cleft lip and palate (CLAP) that a female is more likely to be born with an isolated cleft palate (CPO) and a male with cleft lip with or without cleft palate (CLAP) (Noorollahian et al., 2015; G. M. Shaw et al., 1991). This gender differentiation is likely multifactorial but may be partially explained by differences in male and female embryonic craniofacial development (Burdi & Silvey, 1969).

Cleft laterality in our UCLP cohort favoured left-sided clefting (61.3% (n=19)) compared to right-sided clefting (38.7% (n=12)). This further supports previous epidemiological studies that have shown that left-sided clefting is twice as common as the contralateral side (Mandal et al., 2019; Sivertsen et al., 2008). Cleft laterality is however independent of cleft severity (Carroll & Mossey, 2012). This left-sided cleft laterality preferencing is likely due to a complex gene-environment interaction and may suggest a separate aetiology for right-sided clefting (Gallagher et al., 2018).

4.5.2. Assessment of Normality

The calculated asymmetry scores were assessed for normality using both graphical and numerical methods. The data is presented above on both histograms and Q-Q (Quantile-Quantile) probability plots. The Shapiro-Wilk test and the Kolmogorov-Smirnov test were used to determine if the data is normally distributed. Asymmetry scores at rest, maximum smile, and maximum asymmetry were normally distributed for the assessment of the full-face, nasolabial region, upper lip, and cheek. As all the asymmetry scores were normally distributed, a parametric test in the form of Pearson’s correlation coefficient (r) was utilised.

Under conditions where the distribution of data displays normality, parametric tests are more efficient and more powerful (Vickers, 2005; Zimmerman & Zumbo, 1990). Therefore, we can be reassured regarding the power of this study.

4.5.3. Asymmetry Scores

The distribution of calculated asymmetry scores showed that patients exhibited greatest symmetry at rest for every region analysed; full-face, nasolabial region, upper lip, and cheek. This is often a patient's natural facial pose and a commonly practised position with minimal muscular contraction. Therefore, it is no surprise that patients at rest demonstrated the lowest overall asymmetry scores. This is supportive of other research into the asymmetry of UCLP at rest compared to maximal facial expressions (Gattani et al., 2020; Trotman et al., 2005).

Asymmetry scores were highest for full-facial analysis compared to regional analysis of the nasolabial region, upper lip, or cheek. This is independent of which frame is analysed, rest frame, frame of maximal smile, or frame of maximum asymmetry. This is to be expected as more of the face is analysed and any asymmetries in other parts of the face not related to the cleft will tend to increase the score. The post-treatment goal should never be something unachievable like full-face perfect symmetry, but rather an improvement on the pre-treatment asymmetry observed. Full facial asymmetry scores will tend to be higher as no face is perfectly symmetrical, whether someone has a diagnosis of UCLP or not (Springer et al., 2007).

The degree of facial dysmorphology, as depicted by the asymmetry scores, increased during maximal smile compared to the rest frame. This corroborates the findings of previous studies of increased facial asymmetry during maximum facial expressions (Al Rudainy et al., 2019; Zhao et al., 2021). Previous research has shown that maximum asymmetry most frequently occurs during the relaxation phase after maximal facial expressions (Gattani et al., 2020). However, asymmetry scores for maximum smile were less than, but almost comparable to maximum asymmetry scores. This highlights that assessment of facial asymmetry at maximum smile is still a valid assessment of facial dysmorphology, despite not depicting the full extent of the asymmetry.

The nasolabial region is of particular interest in the assessment of asymmetry scores, as it is an accepted and recognisable area of interest that has been analysed in well-respected national and international trials (Brattström et al., 2005; Williams et al., 2001). Further breakdown of this region into the upper lip and cheek may provide insight into the location and potential cause of the asymmetry but may not capture the full extent of the asymmetry.

4.5.4. Correlation

The Pearson's correlation coefficients' (r) calculated for all regions; full face, nasolabial region, upper lip, and cheek, when comparing 3D facial dysmorphology at both rest and maximum smile with 4D facial dysmorphology as represented by the frame of maximum asymmetry, were all strongly positive. The correlation (r) strength of relationship thresholds are depicted in table 2-1 and are adapted from the basic practice of statistics (Moore et al., 2013). All Pearson's correlation coefficients' (r) were greater than 0.7 (>0.7) and therefore showed strong positive correlation.

The correlation between static (3D) asymmetry at maximum smile and the dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile was higher than the correlation between static (3D) asymmetry at rest and the dynamic (4D) facial asymmetry for all regions of the face. Therefore, the assessment of facial dysmorphology using the maximum smile frame rather than rest frame better represents the true extent of the facial asymmetry present. This further supports the premise that the assessment of facial asymmetry using the frame of maximum smile is a valid assessment despite not depicting the full extent of the asymmetry (Al Rudainy et al., 2019; Zhao et al., 2021).

The strongest correlation between static (3D) and dynamic (4D) facial dysmorphology was seen in the nasolabial region for both the rest frame and the frame of maximum smile. The nasolabial region is an area of particular interest in cleft lip and palate research and was described in the Asher-McDade Aesthetic Index as well as being the focus of large national and international studies (Asher-McDade et al., 1991; Brattström et al., 2005; Williams et al., 2001). The single strongest correlation was found in the nasolabial region between maximum smile frame (3D) and the 4D asymmetry, represented by the frame of maximum asymmetry during a maximum smile; r (31) = 0.941, p<0.001. Therefore, if we are to attempt to predict the true extent of 4D facial dysmorphology from 3D images we should focus on the nasolabial region and the frame of maximum smile.

The Pearson's correlation coefficients' (r) were higher for both the full-face assessment and the nasolabial region assessment compared to the upper lip and cheek, independent of what frame was used for the correlation. This highlights that breaking down the nasolabial region further into the upper lip and cheek may help isolate the location of the asymmetry but will not be useful in aiding the prediction of dynamic (4D) facial dysmorphology from static (3D) images.

Due to the strong correlation between static and dynamic facial dysmorphology in UCLP we could, in theory, use linear regression modelling to predict a patients 4D asymmetry score using static 3D images. If we are to use linear regression modelling based on static 3D images, asymmetry scores for the maximum smile, frame focussing on the nasolabial region, would be highly predictive of dynamic asymmetry in the absence of 4D imaging technology.

The highest coefficient of determination was found between maximum smile (3D) and the frame of maximum asymmetry (4D), for the nasolabial region; (r2); r2 = 0.886 (88.6%). This indicates that nasolabial region asymmetry at maximum smile (3D) accounts for 88.6% of the variance in nasolabial region dynamic (4D) asymmetry. This further confirms the validity of using the frame of maximum smile for assessment in the absence of 4D imaging and the potential use of the nasolabial region's frame of maximum smile to predict 4D asymmetry using linear regression modelling.

Based on the strong correlations observed we could conclude that we can calculate 4D facial dysmorphology from 3D images with a high degree of accuracy. However, we may not be able to pinpoint specific movements related to muscles, or muscle groups, that might be targeted for corrective surgery. Facial asymmetry scores can be used pre- and post-operatively to assess treatment outcomes, but if asymmetry is measured at maximum smile, the true asymmetry is not being recorded and is therefore being underrepresented. Linear regression modelling could supplement the assessment to predict the dynamic asymmetry score.

As static (3D) facial dysmorphology at rest and maximum smile is highly correlated to dynamic (4D) facial dysmorphology, as represented by the frame of maximum asymmetry during maximum smile, we can reject the null hypothesis and accept the alternative hypothesis that 3D asymmetry is predictive of 4D asymmetry.

4.5.5. When does maximum asymmetry occur?

Most patients exhibited the greatest degree of facial asymmetry during the relaxation phase after maximal facial expression (N=27; 87.1%). This supports other research findings that suggested asymmetry is increased during muscular relaxation compared to any other time during a facial expression (Gattani et al., 2020).

4.6. Potential Limitations

As with any study involving rare diseases or conditions, research into cleft lip and palate (CLAP) is often limited by the availability of an adequate sample size. This is further complicated due to the requirement for each participant to be within a narrow age range and to have the same diagnosis. A cleft diagnosis is also often required in the absence of a syndrome, further reducing potential participants. In this study patients with non-syndromic unilateral cleft lip and palate (UCLP) were selected, and despite challenges with recruitment our study was adequately powered. Research into rare conditions is often more challenging due to difficulties in recruitment, more complex designs of clinical studies, and less funding for research than more well-known conditions with higher prevalence (Griggs et al., 2009).

Another potential limitation was that the 4D images that were used for analysis were assessed retrospectively. A prospective study may have been more reliable, but it would not have been feasible to attain an adequate sample size with prospective patient recruitment within an appropriate time frame. Prospective recruitment would have required us to greatly widen the age range for our cohort and patients would then have had their 4D images captured at different stages of their surgical pathway and at different stages of growth and development.

The generalisability of this study may be limited by hardware, software, and personnel requirements needed to capture 4D images and calculate asymmetry scores. Other cleft units may not have access to 4D or even 3D imaging and it requires a significant volume of data storage to appropriately store the 4D images. If other units have access to 3D imaging, then perhaps linear regression modelling could be utilised in the future to predict dynamic asymmetry scores in the absence of 4D technology. Data processing is also a complex task often requiring an expert in digital image acquisition and processing.

As previously discussed, it is beyond the scope of this study to make assumptions around the complex aetiology of cleft lip and palate (CLAP) that often involves a labyrinth of gene-environment interactions.

This study also analysed asymmetry scores as a summative non-directional score. The benefit of this method is that we can define the entirety of the asymmetry with a single score, but we do not know how this asymmetry relates to the three planes of space. Directional asymmetry scores (x, y, z) may provide additional information as to the underlying cause of the asymmetry and be more suggestive of potential surgical interventions required (Gattani et al., 2020).

This study also only assessed the correlation between static (3D) and dynamic (4D) facial dysmorphology in unilateral cleft lip and palate (UCLP) during maximum smile. Alternative facial expressions like cheek puff, lip purse, and grimace could also be assessed, as these facial expressions in 3D may be even more predictive of 4D facial dysmorphology.

4.7. Recommendations for future research

Future studies should consider other facial expressions including cheek puff, lip purse, and grimace to assess the correlation between static (3D) and dynamic (4D) facial dysmorphology in alternative facial expressions.

Other studies could further assess the directional correlation of the inherent asymmetry in the 3 planes of space (x, y, z). This may allow greater understanding into the asymmetry and guide future surgical decisions.

Pre- and post-surgical outcomes could also be analysed in 4D and a longitudinal assessment of patients in different age categories could be completed. This would allow us to assess how dynamic facial asymmetry changes over time with both growth and surgical intervention.

Further research is needed to establish how accurately we can predict dynamic (4D) facial asymmetry using linear regression modelling. This would likely require a further age-matched cohort of non-syndromic unilateral cleft lip and palate (UCLP) patients. 3D asymmetry scores for the nasolabial region at maximum smile could then be calculated and used to predict 4D asymmetry scores, before checking the accuracy of the prediction model.

4.8. Conclusions

The assessment of facial dysmorphology in cleft care is an important measure and audit tool to assess the quality of care provided and the potential requirements for further surgical revision. Current asymmetry assessment is often subjective, non-reproducible, and fails to allow adequate comparisons of pre- and post-op surgical outcomes. This highlights the importance of developing an objective tool to assess facial dysmorphology in the treatment of cleft lip and palate (CLAP).

The use of 4D imaging combined with mesh conformation and dense correspondence analysis provides a valid objective measure of facial asymmetry but is costly to procure and requires an expert in data analysis to interpret.

Asymmetry scores were higher at maximum smile than rest and the greatest degree of asymmetry was observed most frequently during the relaxation phase after a maximum facial expression. Asymmetry scores at maximum smile were less than but comparable to maximum asymmetry scores, highlighting the validity of the assessment of facial asymmetry at maximum smile. However, assessment of facial asymmetry at maximum smile while valid will still underrepresent the true extent of the asymmetry.

Static (3D) asymmetry at rest and maximum smile is strongly correlated to; and likely highly predictive of, dynamic (4D) facial asymmetry represented by the frame of maximum asymmetry during a maximum smile. The strongest correlation is seen with analysis using the frame of maximum smile focussing on the nasolabial region. Future research could use linear regression modelling to predict dynamic (4D) asymmetry scores using static (3D) images.

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