PhD Thesis

The Influence of Breathing Disorders on Face Shape: A Three-Dimensional Study

A thesis submitted in accordance with the conditions governing candidates for the degree of Philosophiae Doctor in Cardiff University

by

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DECLARATION

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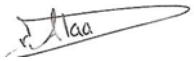
Signed  (candidate) Date 20/12/2013

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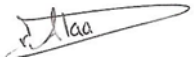
Signed  (candidate) Date 20/12/2013

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ABSTRACT

Breathing disorders can potentially influence craniofacial development through interactions between the respiratory flow and genetic and environmental factors. It has been suggested that certain medical conditions such as persistent rhinitis and renal insufficiency may have an influence on face shape. The effects of these conditions are likely to be subtle; otherwise they would appear as an obvious visible facial feature. The use of three-dimensional imaging provides the opportunity to acquire accurate and high resolution facial data to explore the influence of medical condition on facial morphology. Therefore, the aim of the present study is to investigate the influence of breathing disorders (asthma, atopy, allergic rhinitis and sleep disordered breathing) on face shape in children.

The study sample, comprising of 4784 British Caucasian children of which 2922 (61.1%) were diagnosed with a breathing disorder, was selected from the Avon Longitudinal Study of Parents and Children (ALSPAC), which had been conducted to investigate the genetic and environmental determinants of development, health and disease. Three-dimensional surface laser scans were conducted on the children when they were 15 years old. A total of 21 reproducible facial landmarks (x, y, z co-ordinates) were identified. Average facial shells were constructed for each of the different disease groups and compared to facial shells of healthy asymptomatic children. Face-shape variables (angular and linear measurements) were analysed with respect to the different breathing disorders by employing a variety of statistical methods, including t-tests, chi-square tests, principal component analysis, binary logistic regression and analysis of variance (ANOVA).

The results reveal that individual breathing disorders have varying influences on facial features, including increased anterior lower face height, a more retrognathic mandible and reduced nose width and prominence. The study also shows that the early removal of adenoids and tonsils can have a significant effect on obstructive breathing, resulting in the restoration of the facial morphology to its normal shape. This was particularly evident in children with normal BMIs. Surprisingly, no significant differences in face shape were detected in children with multiple diseases (combinations of asthma, allergic rhinitis, atopy and sleep-disordered breathing) when compared to healthy children. This may indicate the multifactorial, complex character of this spectrum of diseases.

The findings provide evidence of small but potentially real associations between breathing disorders and face shape. This was largely attributable to the use of high-resolution and reproducible three-dimensional facial imaging alongside a large study sample. They also provide the scientific community with a detailed and effective methodology for static facial modelling that could have clinical relevance for early diagnosis of breathing disorders. Furthermore, this research has demonstrated that the ALSPAC patient archive offers a valuable resource to clinicians and the scientific community for investigating associations between various breathing disorders and face shape.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ALSPAC	Avon Longitudinal Study of Parents and Children
ANB	A point, Nasion, B point
ANOVA	Analysis of variance
BMI	Body Mass Index
C3D	Computerized Stereophotogrammetry
CBCT	Cone Beam Computed Tomography
CT	Computerised Tomography
DNA	Deoxyribonucleic acid
ENT	Ear, nose and throat
FDA	Food and Drug Administration
GHR	Hormone Receptor Gene
IgE	Immunoglobulin E
MRI	Magnetic Resonance Imaging
NHP	Natural head posture
NMRI	Nuclear Magnetic Resonance Imaging
OSA	Obstructive Sleep Apnoea
PCA	Principle Component Analysis
SD	Standard Deviation
SDB	Sleep-disordered breathing
SNP	Single Nucleotide Polymorphism
TMJ	Temporomandibular joint
VOCs	Volatile organic compounds
VVD	Vivid Three-Dimensional Scanner Element File

Introduction

0.1 Introduction

Orthodontic treatment is not only concerned with improving tooth alignment but also facial aesthetics. A thorough facial examination can improve diagnosis, treatment planning, treatment outcome and avoid adverse effects on facial aesthetics. The practice of orthodontics continues to embrace new innovations and technologies in relation to the appreciation and incorporation of facial proportions (i.e. in the sagittal, vertical and transverse dimensions) (Sarver, 1998; Ackerman *et al.*, 1999).

New technologies have enabled the mapping and quantifying of facial morphologies, beginning with Bolton-Broadbent's cephalometer (Broadbent, 1981) to the present three-dimensional hard and soft tissue imaging systems (Hajeer, 2004; Mah & Hatcher, 2004; Kau *et al.*, 2005a). Cephalometrics was the traditional method used by orthodontists to assess hard and soft tissue changes due to facial growth and orthodontic treatment. Cephalometric analysis requires invasive radiation however, modern three-dimensional surface imaging devices capture the face without adverse effects quickly and efficiently (Harrison *et al.*, 2004; Aldridge *et al.*, 2005; Kau *et al.*, 2006).

Cephalometric methods present a number of problems such as being a two-dimensional representation of a three-dimensional individual and landmark identification of hard and soft tissues on radiographs can be challenging (Björk, 1969). Many clinicians and researchers claim that precise landmarking is crucial and is a major source of errors (Baumrind & Frantz, 1971a, 1971b). Therefore, cephalometric methods are limited in their ability to comprehensively describe the three-dimensional characteristics of the

face, as the lateral projection of the profile does not give a representation of orientation and depth. Instead, the facial surface exhibits all the characteristics of three-dimensional morphology (form and structure), where distinct facial features and landmarks have their spatial position (x, y, z co-ordinates), which inevitably alter with movement in space (Farkas, 1994) (i.e. landmark nasion is an estimate on a lateral projection and varies if the subject is positioned differently in the cephalostat).

Thus, it becomes obvious that three-dimensional imaging has a role to play in determining how the face develops in the three planes of space. Three-dimensional imaging techniques have already been employed to create databases for normative populations (Yamada *et al.*, 2002), analyse growth changes (Nute & Moss, 2000), and also to assess clinical outcomes for surgical (McCance *et al.*, 1992; Ayoub *et al.*, 1996; McCance *et al.*, 1997; Ayoub *et al.*, 1998; Ji *et al.*, 2002; Khambay *et al.*, 2002; Marmulla *et al.*, 2003) and non-surgical treatments (McDonagh *et al.*, 2001; Ismail & Moss, 2002; Moss *et al.*, 2003) in the head and neck regions.

Of interest to orthodontists is the environmental influence on craniofacial morphology. Evidence suggests that altered muscular function can influence craniofacial morphology (Linder-Aronson, 1979; Tourne, 1990). Breathing disorders have been of interest to orthodontists for decades, as restricted nasal breathing tends to result in facial changes. The change from nasal to mouth-breathing induces functional adaptations that include an increase in the total face height (Linder-Aronson, 1970; Hannuksela, 1981; Bresolin *et al.*, 1983; Trask *et al.*, 1987), which is mostly reflected in an increase in the

lower face height (Linder-Aronson, 1970; Hannuksela, 1981; Bresolin *et al.*, 1983; Tarvonen & Koski, 1987). Facial retrognathism has also been reported (Linder-Aronson, 1970; Bresolin *et al.*, 1983; Sassouni *et al.*, 1985).

Thus, three-dimensional imaging techniques can aid in determining the influences of heritable and environmental factors on facial shape. For example, a comprehensive database of three-dimensional facial changes in a growing individual could also be constructed. This database would permit a better understanding of soft tissue facial form and topography, the mechanisms of facial growth and the investigation of the effects of medical conditions on face shape.

This study utilises three-dimensional technology to assess the influence of a number of medical conditions characterised by breathing disturbance on a large cohort of 15-year-old children, with the aim to identify any associations between these conditions and face shape.

0.2 Organisation and Structure of the Thesis

This thesis is organised into three distinct parts with Chapters 1 to 4 forming the literature review, Chapters 5 to 7 describing the methodologies used and Chapters 8 to 14 reporting on the individual medical conditions. Specifically:

- Chapter 1 describes the fundamental concepts of craniofacial growth, defining the stages of growth and introducing the growth theories.
- Chapter 2 focuses on the role of genetics on craniofacial morphology and discusses the various genes that have been associated with face formation.

- Chapter 3 discusses the influence of environmental parameters on the development of the face. The effect of masticatory muscles, abnormal sucking habits and breathing patterns is summarised.
- Chapter 4 introduces three-dimensional surface technologies and the roles they play on the study of craniofacial growth.
- Chapter 5 summarises the aims and objectives of the study. The participants are described in detail and the research challenges faced are highlighted.
- Chapter 6 contains the experimental section of the thesis. In this chapter, detailed methodology on the three-dimensional imaging software can be found. Image capture, calibration, and normalisation, as well as data analysis and statistical associations are explained.
- Chapter 7 presents an initial study that was performed to assess the reproducibility of facial soft tissue landmarks using laser-scan three-dimensional imaging technology and to ensure that the researcher was able to accurately define facial landmarks and place them manually.
- Chapter 8 explores a potential effect of asthma on face shape.
- Chapter 9 investigates the possibility of any links between atopy and face shape.
- Chapter 10 discusses the effect of allergic rhinitis on face shape.
- Chapter 11 analyses the changes in the shape of the face of children suffering from sleep disordered breathing.

- Chapter 12 extends the findings of Chapter 11 to incorporate changes in the shape of the face of children who are suffering from sleep disordered breathing but have had adenotonsillectomy.
- Chapter 13 incorporates data from children suffering from multiple diseases (asthma, allergic rhinitis, atopy and sleep disordered breathing) and relates it to face shape.
- Chapter 14 summarises the findings of the study and provides suggestions for future research.

0.3 Publications Drawn from the Thesis

Four publications have been drawn from the thesis; three papers and one book chapter.

Papers

Al Ali A, Richmond S, Popat H, Toma A M, Playle R, Pickles T, Zhurov A I, Marshall D, Rosin L P and Henderson J, 2012. The influence of asthma on face shape: A three-dimensional study. *European Journal of Orthodontics,* published online 04 October 2012, doi: 10.1093/ejo/cjs067 (see Appendix 2)

Al Ali A, Richmond S, Popat H, Toma A M, Playle R, Pickles T, Zhurov A I, Marshall D, Rosin P L, Henderson J 2013 A three-dimensional analysis of the effect of atopy on face shape. *The European Journal of Orthodontics,* Published Online First: 28 January 2013. doi: 2010.1093/ejo/cjs2107 (see Appendix 3)

In press

Al Ali A, Richmond S, Popat H, Playle R, Pickles T, Zhurov A I, Marshall D, Rosin P L and Bonuck K 2013 The influence of snoring, mouth-breathing and apnoea on facial morphology in late childhood: A three-dimensional study. *BMJ Open*

Book chapter

Richmond S, Al Ali A, Beldie L, Chong Y T, Cronin A, Djordjevic J, Drage N A, Evans D M, Jones D, Lu Y, Marshall D, Middleton J, Parker G, Paternoster L, Playle R A, Popat H, Rosin P L, Sidorov K, Toma A M, Walker B, Wilson C, Zhurov A I, 2012. Detailing Patient Specific Modeling to Aid Clinical Decision-Making. In: *Patient-Specific Computational Modeling* (Calvo B and Peña E, eds.). Springer 5: 105-131

Chapter 1

Craniofacial Growth

1.1 Introduction

The phenomenon of human craniofacial development includes both pattern (the maintenance of the configuration of the face over time) and growth (the geometric changes in size and shape of craniofacial structures). These concepts, of which every orthodontist should be aware, suggest that genetic inheritance should be considered as the main factor influencing the growing tissue. Sicher (1947) added that genetic control was active mainly upon the connective tissue lying inside joints. Later, with the introduction of new diagnostic methods, the importance of functional aspects has become more evident.

As the thesis focuses on the environmental influence on craniofacial morphology, this chapter is conducted by outlining the concepts of normal craniofacial growth and development.

1.2 Definition and Concepts of Growth

Growth has been defined as an increase in size and number (Houston *et al.*, 1992). However, occasionally increase will be in neither size nor number but in complexity, in which case the term development is used. In this case, development has to take into account the direction of growth, encompassing the shape and surface changes of part of the face. For example, the face not only changes in magnitude, it also appears to grow in a “downward and forward” direction in relation to the base of the skull (Proffit *et al.*, 2007).

Growth is initiated by growth hormone released from the pituitary gland, and the extent and timing of growth is under genetic and environmental control. Interaction between different tissues within the craniofacial complex show

how genetics can influence growth and development. One example of this is the change in development of the muscles that attach to the mandible and bony areas. Genetic alterations in muscle development and function translate into changes in the forces on areas of bone where muscle attach, which in turn leads to the modification of skeletal areas such as the coronoid process and gonial angle of the mandible (Proffit *et al.*, 2007).

1.3 Stages of Growth

It is important to understand how craniofacial growth is influenced and controlled in order to understand the environmental influence on craniofacial morphology. For better understanding, craniofacial growth can be described in two phases, pre- and post-natal.

1.3.1 Pre-Natal Growth

The pre-natal period is defined as the time from conception of the foetus to the birth of the baby and normally last for 38 weeks. A series of complex molecular processes interact with one another to create vital organs and physical characteristics that are distinctively human. However, the upper third of the head bearing the cranium is given priority, as it accommodates an important organ, the brain. As a result, the lower two-thirds of the face is proportionally smaller than the cranium at birth (Figure 1.1). The proportions at this stage are approximately 60% for the cranium and 40% for the face (Ranly, 2000).

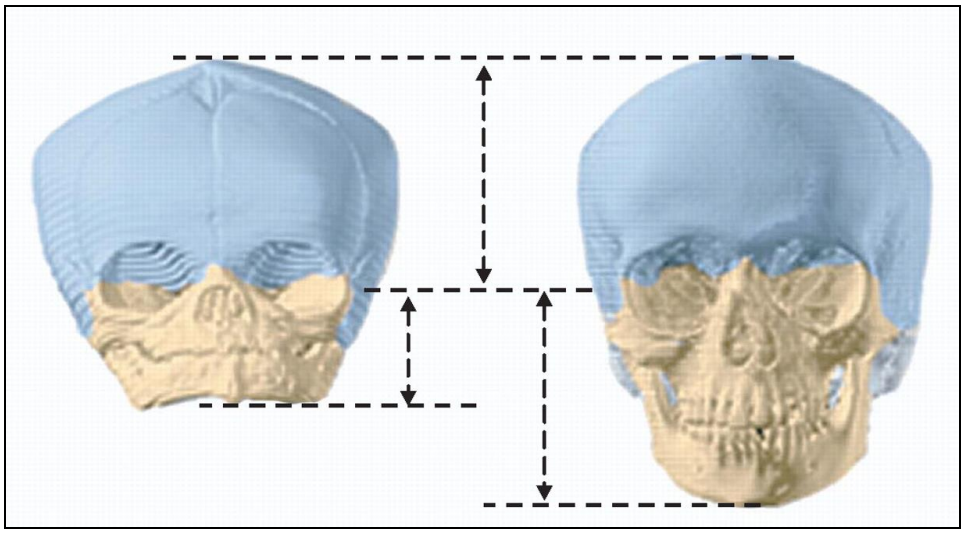


Figure 1.1: Illustration of neonatal skull compared to an adult skull

1.3.2 Post-Natal Growth

After birth, the constraints of the womb are lifted from the face and the individual is then subjected to genetically programmed growth and also the effect of the general environment. These processes alter the external form and facial bones.

1.4 Growth Theories

According to Mateus *et al.* (2008) “Studies on craniofacial embryology and growth have enabled the understanding and treatment of congenital and acquired facial deformities". Various theories have tried to explain facial growth. However, the exact determinants of the growth of the face remain unclear and continue to be subject of intensive research. A number of theories have attempted to explain the determinants of craniofacial growth:

- Sutural Theory (Sicher, 1947).
- Cartilaginous Theory (Scott, 1953).
- The Functional Matrix Theory (Moss, 1962).

- Servo System Theory of Craniofacial Growth (Petrovic, 1972).

1.4.1 Sutural Theory

Weinmann and Sicher (1947) believed that the translation of the maxilla was as a result of pressure created by growth at the sutures which the authors consider as growth centres. For this statement to be true, growth at sutures would have to occur independently, rather than under the environmental control and, furthermore, we would be unable to control growth at these sites. However, evidence suggests this theory is incorrect in that the sutural tissues do not appear to have any innate growth potential in transplantation experiments. Furthermore, growth at the sutures does respond to environmental factors such as rapid maxillary expansion and maxillary restraint with headgear.

1.4.2 Cartilaginous Theory

In response the failure of suture theory, cartilaginous theory argues that sutures are merely permissive, secondary, and compensatory sites of bone formation and growth. According to Scott (1953), who developed the theory, the essential primary elements directing craniofacial skeletal growth are the cartilages found within the cranial base and, in particular, the anterior extension of the chondrocranium, the nasal septal cartilage, which drives the midface downwards and forward from the prenatal stage through to around three to four years of age. In addition, Scott argued that the cranial base synchondroses had a longer-lasting effect on craniofacial growth, with the spheno-ethmoidal synchondrosis impacting until at least seven years of age and the spheno-occipital synchondrosis until puberty. Furthermore, he

posited that the cartilage of the mandibular condyles also directly determine the growth of the mandible as they push the mandible downward and forward.

Transplantation experiments demonstrate that not all cartilage act the same (Koski & Ronning, 1969). Thus, the nasal cartilage when transplanted to a new location or culture continues to grow as epiphyseal plate cartilage (Copray, 1986) indicating that it has innate growth potential. However, little or no growth was observed when mandibular condyle was transplanted (Koski & Ronning, 1969).

Studies by Gilhuus-Moe (1969) and Lund (1974) demonstrated that after a fracture of the mandibular condyle in a child, in 75% of cases the condyle regenerates with no adverse effect on growth.

1.4.3 The Functional Matrix Theory

In contrast Moss (1997a) believed that neither the cartilage of the mandibular condyle nor the nasal septum cartilage are determinants of jaw growth. Instead, he theorized that growth of the face occurs as a response to functional needs and is mediated by soft tissue in which the jaws are embedded. In simple terms, he argued that the soft tissues grow, and both bone and cartilage react. He believed that all genetic control is in the soft tissue. For example, the orbit grows as a result of growth of the eyes, while the cranium increases in size by pressure exerted during growth of the brain which separates the cranial bones at sutures while new bone passively fills in at these sites.

He also theorized that the major determinant of growth in the maxilla and mandible is the enlargement of the nasal and oral cavities as a result of functional needs (Moss, 1997b). Growth of the mandibular is impaired by ankylosis and soft tissue scarring which supports the functional matrix theory.

1.4.4 Servo System Theory

Petrovic (1972) developed the fourth theory of craniofacial growth, the servo system theory in order to attempt to understand the complexity of the various factors influencing craniofacial growth, including primary cartilage, the muscles of mastication, the tongue, sutures, growth and sex hormones, and neural proprioception. He showed how the growth of the mandibular condyle is very responsive to extrinsic systemic factors and local biomechanical and functional factors, because of the nature of secondary cartilage (Petrovic, 1972; Stutzmann & Petrovic, 1979). In simple terms, two factors characterise the theory: first, the hormonally regulated growth of the midface and anterior cranial base; and second, the rate limiting effect of this midfacial growth on the growth of the mandible. Although Petrovic acknowledged that the growth of the mandibular condyle and sutures can be influenced by systemic hormones, their growth is to a greater extent compensatory and adaptive to the presence of extrinsic factors, including local function as well as the growth of other areas of the craniofacial complex.

Servo system theory has a number of elements that impact on craniofacial morphology. First, the cartilaginous cranial base and nasal septum influenced principally by the intrinsic cell-tissue related properties common to all primary cartilages and extrinsically by the endocrine system drive midface growth

downward and forward. In addition, the maxillary dental arch develops in a slightly more anterior position, which means that there is a minute discrepancy between the upper and lower dental arches. The next step is that the occlusal discrepancy is recognised by the proprioceptors within the periodontal regions and temporomandibular joint which activate the lateral pterygoid and masseter muscles. Thirdly, these jaw protruding muscles then impact directly on the cartilage of the mandibular condyle and indirectly through the vascular supply to the temporomandibular joint, stimulating it to grow. The final step is that the muscle function and responsiveness of condylar cartilage is influenced both directly and indirectly by hormonal factors. This cycle will only stop when the midface-upper dental arch growth halts and the appropriate extrinsic, hormonal, and functional factors are no longer supportive.

1.5 Conclusion

In summary, growth of the cranial vault is largely determined by growth of the underlying brain. Expansion of the brain results in tension across the cranial sutures which lead to bone deposition at these sites. The maxilla and mandible both undergo complex patterns of remodelling during growth. They are displaced in a downward and forwards direction in relation to the cranial base and influenced by a combination of the soft tissue matrix and cartilage.

Chapter 2

The Role of Genetics on Craniofacial Morphology

2.1 Introduction

The general craniofacial morphology is largely genetically determined and partly attributable to environmental factors (Carson, 2006; Smith *et al.*, 2007; Smith, 2009; von Cramon-Taubadel, 2011). Johannsdottir *et al.* (2005) argued that the inheritability of craniofacial morphology is high in twins. However, the genetic basis of normal variation in the face shape is poorly understood. Some visible human facial features such as eye and hair colour can be inferred from a DNA sample (Liu *et al.*, 2010; Branicki *et al.*, 2011; Walsh *et al.*, 2011). One of the problems associated with the investigation of the heredity influence on face shape is the complex nature of multifactorial inheritance. Thus, cephalometric analysis using lines and angles has been traditionally used to offer quantitative information of limited values in heritability studies (Watnick, 1972). The problem is summed up by Margolis *et al.* (1968) who stated that

> A small area of the skull surface may be under pure genetic control or environmental control or a combination of both, but unless a small area is considered, multiple, and possibly independent mechanisms may be operating, which may nullify each other and therefore make recognition or study impossible.

2.2 Genetic Involvement in Craniofacial Morphology

The majority of early genetic studies have implications for the dental/orthodontic profession. Miura *et al.* (1991) determined that the heritable morphological features are also predominately found in the cranial base, but other heritable features are also noted in relation to the form of the dental arch, mandible and naso-maxillary complex. Meanwhile, Johannsdottir *et al.* (2005) demonstrated heritability features most predominantly affect the

lower jaw positioning; however, they noted other features were also heritable, including posterior and anterior facial height and cranial base dimensions.

More recent genetic studies have been able to associate specific genetic structures with craniofacial morphology. Zhou *et al.* (2005) assessed the correlation between the height of the mandible in the Chinese population and their genetic influence. By screening growth hormone receptor gene (GHR), they identified six specific single nucleotide polymorphism (SNP) markers. From the SNP markers, they found that the specific CC I526L polymorphism within the Chinese sample was responsible for the variations in mandible ramus height. They concluded that the CC genotype was responsible for a longer mandible ramus compared to those with an AA genotype who displayed a shorter mandible. Coussens and van Daal (2005) conducted a study to analyse high-frequency SNPs in order to ascertain an association with craniofacial variation in non-pathologic human populations (Caucasian, Asian, Australian Aboriginal and African-American populations). They found that eight common SNPs potentially make up part of the genetic background which regulates craniofacial shape. The findings are a starting point in the identification of a set of SNPs that can be genotyped to determine both normal and disease craniofacial phenotypes.

Boehringer *et al.* (2011) studied 11 SNP variations in order to evaluate the association between bizygomatic distance and nose width (Figure 2.1) in two control groups: Netherlands (n=2497) and Germany (n=529). The two most important results were the identification of nose width as associated with SNP re1258763 closest to the GREM2 gene among the Germanic group

whilst the group from the Netherlands demonstrated bizygomatic distance as associated with SNP rs987525 in close proximity to a different gene, CCDC26.

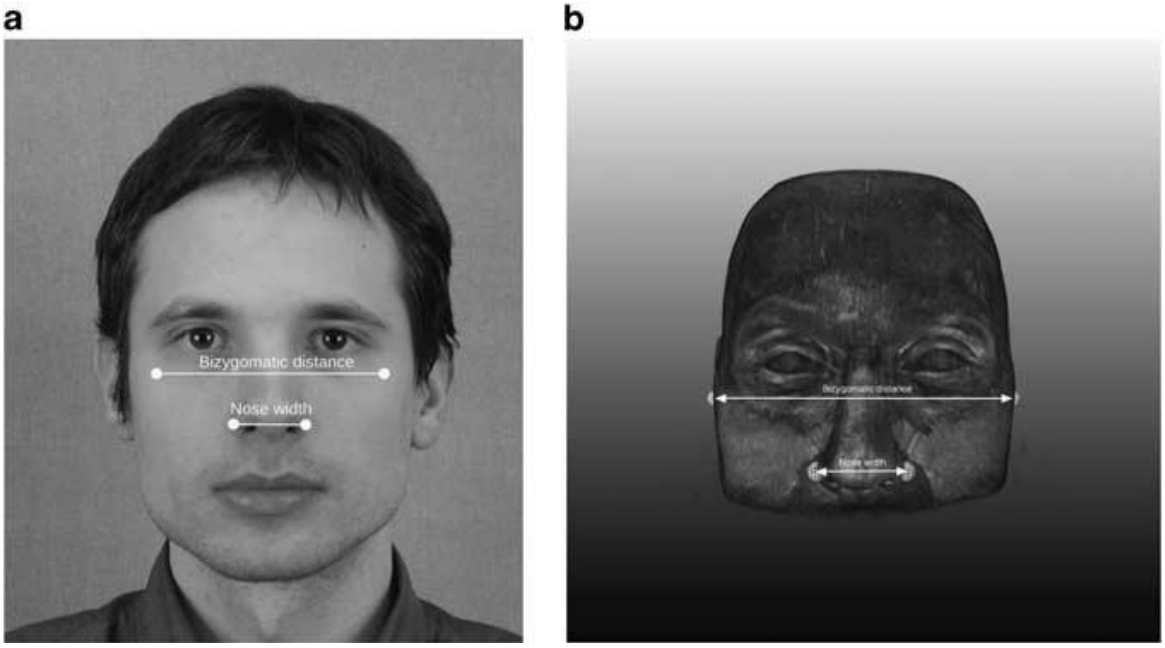


Figure 2.1: The bizygomatic distance and the nose width as defined in the two-dimensional photos (a) and the three-dimensional MRI (b)
Source: Boehringer *et al.,* (2011).

In a large-scale study (n= 2185) of 15 year olds the Avon Longitudinal Study of Parents and Children (ALSPAC) aimed to identify genetic variants associated with normal facial variation using genome-wide analysis for the facial distances and 14 principal components generated from the landmark locations on three-dimensional high-resolution images. The results determined SNP rs7559271 of the PAX3 gene was a key genetic factor in relation to the projection of the nasal bridge (mid-endocanthion to nasion). The findings showed that common variants within the PAX3 gene influence normal craniofacial development (Paternoster *et al.*, 2012b).

Liu *et al.* (2012) identified five independent genetic loci associated with different facial phenotypes, suggesting the involvement of five candidate genes (PRDM16, PAX3, TP63, C5orf50, and COL17A1) in the determination of the human face. PAX3 was discovered to influence the position of the nasion. Nose width was also found to be controlled by the rs4648379 SNP of gene PRM16. The study also identified the following three SNPS and genes responsible for the distance between people's eyes: SNP rs6555969 at gene C5orf50, SNP rs805722 at gene COL17A1, and SNP 17447439 at gene TP63. Overall, the study provides novel and confirmatory links between common DNA variants and normal variation in human facial morphology.

2.3 Conclusion

In conclusion, studies demonstrate a genetic association and control of facial morphology. However, further genetic studies are needed in order to identify predictive genetic markers, which could achieve the accuracy needed for practical applications such as medical diagnosis and future forensics.

Chapter 3

Environmental Influences on Facial Structure during Development

3.1 Introduction

The early phase of life in organisms is characterized by the presence of responses to environmental stimuli. This is important in generating a range of phenotypes suitable for different environments. Thus, development depends on both genes and environment, at each phase of development the organism may be sensitive to a particular environmental factor that impacts on subsequent stages of development.

Three main hypotheses have been developed to explain craniofacial changes due to environmental influence: one focuses on dietary changes and alterations in masticatory activity; the second focuses on the effects of abnormal sucking habits; and the third focuses on the increase in allergies and other factors that might cause airway obstruction and affect normal breathing.

3.2 Masticatory Muscle Influence on Craniofacial Growth

The first hypothesis contends that muscle influences the growth of the bone as a tissue affecting the vascular supply of bone and as a force element (Herring, 1993). Furthermore, it is argued that the muscle is affected by diet. Thus, experiments on animals were undertaken to test the influence of masticatory muscles on craniofacial growth by reducing the load applied on the skull during mastication by feeding the animals with a soft diet. These experiments were undertaken mainly on small animals such as rats (Watt & Williams, 1951; Moore, 1965; Beecher & Corruccini, 1981a; Bouvier & Hylander, 1984; Kiliaridis, 1986; McFadden *et al.*, 1986; Yamada & Kimmel, 1991), and primates (Beecher & Corruccini, 1981b).

The decreased functional demand on the animals because of the soft diet caused structural changes in the masticatory muscles in terms of muscle fibre types and smaller size of the fibres (Kiliaridis *et al.*, 1988). The low biting forces measured in animals with reduced function can be explained by these changes in the masticatory muscles (Kiliaridis & Shyu, 1988). Katsaros *et al.* (1994) conducted a morphometric study which found reduced functional demands; a narrower sutural space and a more parallel orientation of bony surfaces of the facial sutures in rats. Reduced functional demands also caused changes in the size and dimension of the alveolar processes including height and thickness of alveolar bone (Engström *et al.*, 1986; Bresin *et al.*, 1994), and produced radiographically observed morphologic changes which includes an upward rotation of the upper viscerocranium and reduced growth of the angle of the mandible (Avis, 1961; Kiliaridis *et al.*, 1985; Atchley & Hall, 1991). The effect of the muscle function on the maxilla was also tested in rats and found a reduced transverse palatal width (Watt & Williams, 1951; Moore, 1965).

An experimental study undertaken by Mateus *et al.* (2008) concluded that the lack of muscle activity in half of the face results in deviation of facial structure in developing rabbits. This supports the functional matrix theory (Moss, 1962; Moss & Salentijn, 1969), whereby differential forces in each half of the face may produce facial asymmetry. Several studies have been conducted to investigate the effect of functional alterations on the temporomandibular joint in growing animals, by changing the consistency of the diet (Bouvier & Hylander, 1984). Significant differences were found in the condylar length

between groups, with a smaller condyle in the soft diet group. The results of this study indicate that a low masticatory function produces decreased condylar growth.

Studies on humans show that individuals with advanced stages of dental wear and an increased level of masticatory muscle activity are characterized by a short lower face, a small intermaxillary angle, and a small gonial angle compared to normal control groups (Krogstad & Dahl, 1985; Waltimo *et al.*, 1994; Kiliaridis *et al.*, 1995). Similar results were found in wrestlers who are characterized by well-developed dental arches, a short lower face, small intermaxillary angle, and decreased gonial angle of the mandible (Kiliaridis & Persson, 1992). This is explained by the effect of the occlusal forces generated by their well-trained masticatory muscles.

Weak masticatory muscles could be a cause of jaw deformity. Kiliaridis *et al.* (1994) used ultrasonography in adults with jaw deformities and found the thickness of the masseter muscle was less than in the control group; furthermore, thin masseter muscles were associated with a long anterior face (Kiliaridis *et al.*, 1994). However, the findings cannot exclude the possibility that the weakness of the masseter muscle was caused by the existing jaw deformity and the unfavourable functional condition.

Different methods have been used to determine the relationship between facial morphology and the functional capacity of the subjects' masticatory apparatus, such as computer tomography (Hannam & Wood, 1989), ultrasonography (Kiliaridis & Kalebo, 1991; Bakke *et al.*, 1992), magnetic resonance imaging (van Spronsen *et al.*, 1991), and recording the maximal

bite force (Ringqvist, 1973; Ingervall & Helkimo, 1978; Proffit *et al.*, 1983). A common finding in all these studies is that individuals with strong or thick mandibular elevator muscles have a small gonial angle, small lower facial height, wider transversal head dimension and a rectangular shape of the face.

However, in a study conducted by Proffit *et al.* (1983) no statistical differences in bite force could be detected between long face children and normal children; nevertheless, the bite force of adults with long face was comparable to that of the long face children and much lower than that of normal face adults (Proffit *et al.*, 1983). One possible explanation is that the long face subjects were more homogeneous, with thin muscles and low bite force, and the normal face subjects varied in the thickness of the muscles and the bite force level. This means that subjects with weak masticatory muscles could belong to either long or normal face group, whereas it is hard to find individual with strong masticatory muscles in the long face group. The findings by Ingervall and Helkimo (1978) support this explanation: individuals with strong masticatory muscles had a homogeneous facial morphology compared to individuals with weak masticatory muscles, who showed a wide variation.

Thus, it may be concluded that the masticatory muscles could influence the craniofacial growth of an individual in the presence of increased muscle activity but not necessarily when this activity is reduced.

3.3 The Influence of Abnormal Sucking Habits on Face Shape

Several studies have investigated the effect of early sucking activity on the growth of craniofacial complex. It is clear that breast feeding and bottle feeding involve different muscles, leading to different effects on the growth of maxilla and dental arches (Turgeon-O'Brien *et al.*, 1996). Evidence shows the effects of prolonged dummy or finger sucking on dentofacial relationship in growing individuals. Both thumb and dummy sucking are associated with reduced maxillary arch width and increased palatal depth (Warren *et al.*, 2001; Aznar *et al.*, 2006).

Katz *et al.* (2004) investigated the relationship between non-nutritive sucking habits, facial morphology and dental occlusion in 330 Brazilian children. They found an association between sucking habits and malocclusion, including anterior open bite and posterior cross bite. In the permanent dentition anterior open bite is usually due to reduced alveolar growth (Larsson & Ronnerman, 1981) and normally associated with tongue-thrust swallowing. A spontaneous correction will occur when the habit ceases (Larsson & Ronnerman, 1981). The alveolar bone will accelerate in growth and the upper and lower incisors will erupt until an incisal contact is established.

Sustained musical pursuits, such as violin and viola (Kovero *et al.*, 1997), playing a wind instrument, and opera singing (Brattström *et al.*, 1991), were found to have a significant effect on facial morphology. The dentofacial morphology in children playing wind instruments was studied by Brattström *et al.* (1989) who found a smaller anterior facial height as compared with the control group. This was explained by the possibility of the modified pattern of

orofacial muscle activity. Facial muscle hyperactivity and respiratory hyperfunction in professional opera singers has been found to influence the dentofacial morphology resulting in a reduced facial height (Brattström *et al.*, 1991). Long term violin and viola playing has an effect on dentofacial morphology, according to the study undertaken by Kovero *et al.* (1997) who found the effect was manifested as smaller facial heights and greater length of the mandibular body in the violin and viola player than in the control group. Professional violin players usually start playing at early age and are subjected to a continuous pressure which is known to influence bone morphology (Kovero *et al.*, 1997).

3.4 The Influence of Respiratory Pattern on Craniofacial Growth

Normal craniofacial development and proper occlusion depend on various factors. Genetic factors have an important influence on the constitution of the facial and occlusal pattern of an individual (Fairchild, 1968). It is also believed that functions of the stomatognathic apparatus play an important role in craniofacial and occlusal development (Nowak & Warren, 2000).

Normal respiratory activity influences the development of craniofacial structures (Cooper, 1989; Yamada *et al.*, 1997) by adequately interacting with mastication and swallowing which favour harmonious growth (Moss, 1962). The presence of any obstacle in the respiratory system, for example, in the nasal or pharyngeal regions, causes respiratory obstruction and forces the patient to breathe through the mouth (Straub, 1944). Mouth-breathing leads to a change in posture to compensate for the decrease in nasal airflow and to allow respiration (Josell, 1995). This results in a lower position of the

mandible, and a lower or an anterior position of the tongue, usually associated with lower orofacial muscles tonicity (Valera *et al.*, 2003). This will cause abnormality and disharmony in the growth and development of orofacial structures, including narrowing of the maxilla, lower development of the mandible, protrusion of the upper incisors and also alteration of the head in relation to the neck (Rubin, 1980).

If Moss's functional matrix concept (Moss-Salentijn, 1997) is considered, then nasal breathing is fundamentally vital for normal growth and proper development of the whole craniofacial complex. Kilic and Oktay (2008) have observed that the continuous airflow passing through the nasal passage and nasopharinx during unobstructed breathing produces a constant stimulus for both the lateral growth of maxilla as well as for lowering of the palatal vault.

3.4.1 Clinical Studies of Respiratory Obstruction

The relationship between nasal obstruction and facial growth is controversial. Most of this controversy relates to studies and reports published prior to the mid-twentieth century which were based on clinical research that would not meet the present criteria for scientific studies.

The classic clinical example of the possible relationship between craniofacial growth and airway obstruction is a patient described as having adenoid face (Johnson, 1943; Ricketts, 1968; Linder-Aronson, 1970; Moore, 1972; Peltomäki, 2007; Stellzig-Eisenhauer & Meyer-Marcotty, 2010). These patients usually present with a mouth open posture, a small nose, poorly developed nostrils, short upper lip, proclined upper incisors, narrow V-shaped maxillary arch, high palatal vault, and a Class II malocclusion (Figure 3.1).

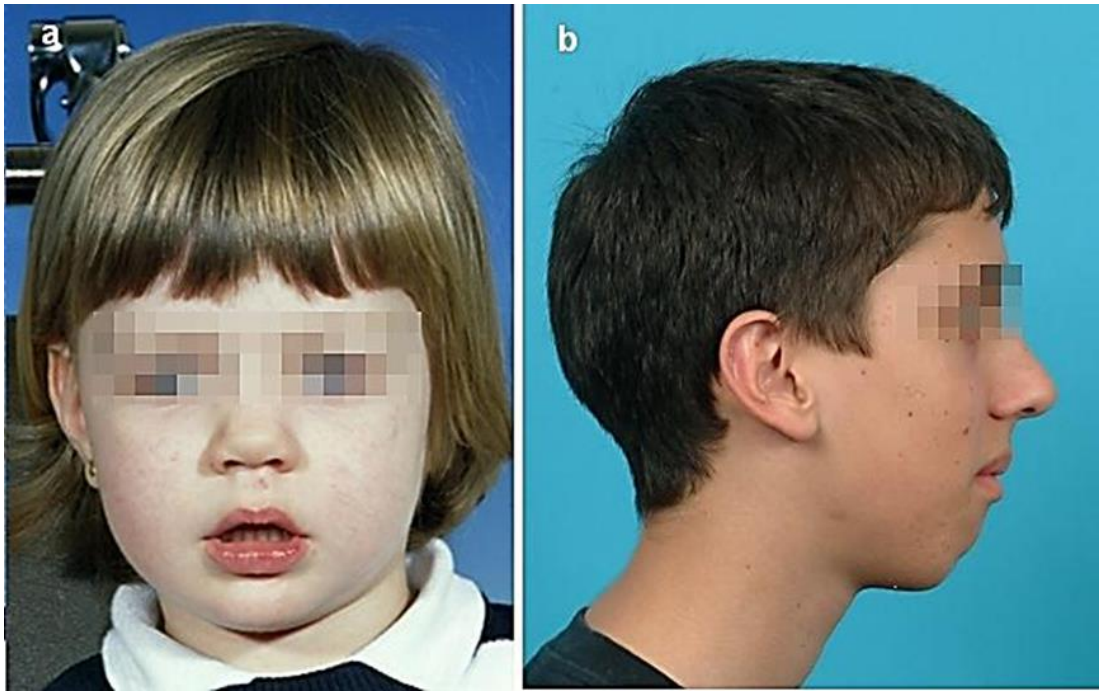


Figure 3.1: a) Patient with “adenoid faces” (open lip posture, mouth breathing), b) Patient with “long face syndrome” (excessively increased vertical dimension).

Source: Stellzig-Eisenhauer & Meyer-Marcotty (2010)

Clinical studies, however, have shown that obstructed respiratory function can be found in patients with a variety of facial characteristics. Howard (1932) reviewed 500 patients with tonsil problems. He classified 159 patients as being mouth breathers, 59% of which presented with normal occlusion, 14% with Class II malocclusion and 27% with either Class I or Class III malocclusions. Leech (1960) studied 500 patients with upper respiratory problems of which 19% were classified as mouth breathers. More than 60% of the mouth-breathing patients were Class I, 25% were Class II, and 10% were Class III. Meanwhile, maxillary alteration occurring in the transverse direction can be seen in mouth breathers. This, leads to a narrow face and palate (Harvold *et al.*, 1981), and is usually associated with cross bite (Linder-Aronson, 1970; Bresolin *et al.*, 1983; Oulis *et al.*, 1994). In addition,

maxillary alteration in the anteroposterior direction leads to maxillary retrusion (Linder-Aronson, 1970).

Retrospective studies of medical histories have also provided information about the relationship between craniofacial morphology and airway problems. Quick and Gundlach (1978) divided 113 orthodontic patients into two groups: 62 with a high mandibular plane angle (the average was 38 degree to the sella-nasion plane), and 51 with a low mandibular plane angle (the average was 26 degree to the sella-nasion). Each patient was given a medical questionnaire and the analysis of the data showed that nasopharyngeal impairment was present in 63% of the high angle group (long-faced patients) but only 23% in the low angle group. Cephalometric analysis of the two groups showed that the nasopharyngeal cavity was smaller in the long faced patients, so that even minor adenoid enlargement could result in upper respiratory obstruction symptoms.

Furthermore, Linder-Aronson and Backström (1960) evaluated 115 children to compare dental occlusion between mouth and nose breathers and investigated the influence of nasal resistance on facial dimensions. They concluded that children with long, narrow jaws had greater nasal resistance. The palatal height was greater in habitual mouth breathers; however, no direct correlation was shown between mouth-breathing and malocclusion.

Linder-Aronson (1970) also compared children requiring adenoidectomy with a control group of similar age. He evaluated the prevalence of a typical adenoid face and identified the correlation between airway obstruction due to adenoid enlargement and dentofacial relationships. Eighty-one children were

examined before and after adenoidectomy and were compared with 81 control subjects of similar age group. Twenty-five percent of the patients undergoing adenoidectomy were judged as having adenoid faces, and characterized as having a narrow, long face with lips apart at rest, with 4% of the control group being classified as having these characteristics.

In a later study, Linder-Aronson (1974) examined patients who had undergone adenoidectomy one year post-operatively to establish if removing the hindrance to nasal airway resulted in a return to normal facial growth. Twenty-seven children, who converted to nose breathing, were compared with nose breathing control subjects. Significant changes had occurred one year after adenoidectomy, in dental arch width, and the angle between the mandibular and nasal planes which indicates a shortening of facial height. The author contended that a corrected balance between the pressure exerted by the lips and tongue resulted in the correction in growth.

Dunn *et al.* (1973) evaluated frontal and lateral cephalometric radiographs from 33 monozygotic twins aged from seven to twelve years in order to investigate the relationship of the nasopharyngeal airway size and the morphology of the mandible. They found an association between nasopharyngeal obstruction and mandibular morphology, with decreased nasopharyngeal airway size; the gonial angle (the angle formed by articulare, gonion and menton) tended to increase along with bigonal width (from gonion to gonion). These findings support the opinion that environmental and functional factors are important in craniofacial morphology.

Woodside and Linder-Aronson (1979) studied 120 lateral radiographs of boys aged six to ten years of age and found a relationship between airway obstruction and increased facial height. Figure 3.2 illustrates cephalometric characteristics in a patient with long face syndrome.

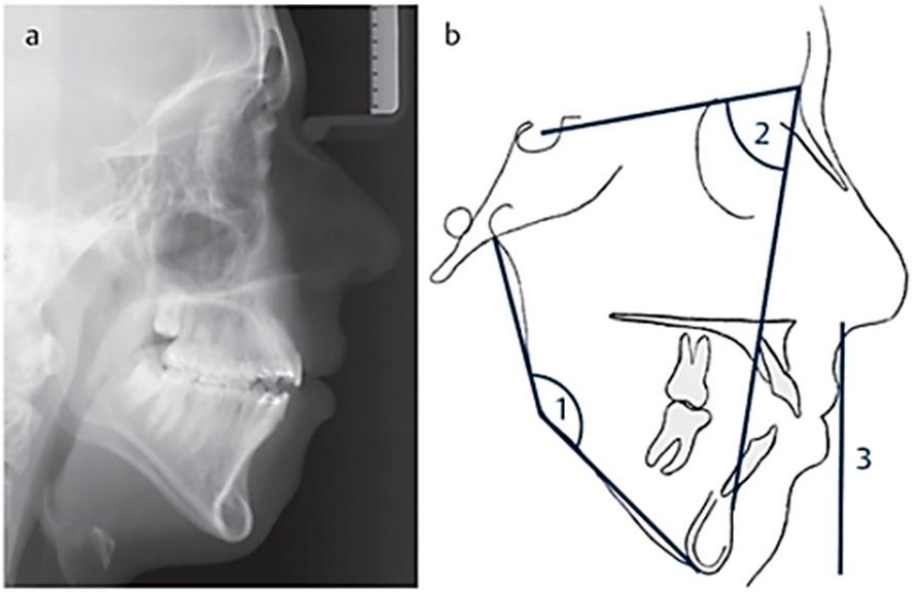


Figure 3.2: Patient with “long face syndrome”

Note: a) Lateral Cephalogram, b) Cephalometric Variations: 1) Increased Angle of the Mandible, 2) Retrognathic Mandible, 3) Increased Lower Facial Height

Source: Stellzig-Eisenhauer & Meyer-Marcotty (2010)

Although most studies support an association between facial development and nasal airway obstruction, the orthodontic relevance of nasal obstruction and its effect on facial growth continues to be debated. Koski and Lähdemäki (1975) studied 15 lateral head radiographs of children with obstructing adenoids indicating a smaller gonial angle. However, Handelman and Osborne (1976) were unable to show a relationship between mandibular plane angle and airway obstruction when evaluating children aged 9 months to 18 years of age.

A recent study by conducted Souki *et al.* (2012) investigated cephalometric differences in mouth-breathing children in the primary and mixed dentition. The sample consisted of a matched sample (sex and age) of 126 mouth and nose breathers. Mouth-breathing was confirmed after clinical and endoscopic ENT examination performed by a multidisciplinary team. The results showed that mouth breathers in the mixed dentition have a smaller mandible than nose breathers. In the primary dentition group, mouth breathers had a longer lower anterior facial height. Despite the strong association between mouth breathers and facial morphology, the results were based on a cross-sectional methodology, and the authors appreciated the need for further longitudinal studies to investigate morphological changes in the mandible.

In all these studies, the different sample selection criteria and diagnostic methodology contributes to conflicting results. Although studies show a relationship between nasal obstruction and facial growth, the limitations of cephalometric analyses need to be considered; these previous reports are based on two-dimensional measurements from lateral skull radiographs of three-dimensional objects. Cephalometric analyses also have measurement errors and inherent problems with landmark identification. A wide variety of cephalometric measures were used, which prevents any comparative data to make any firm conclusions.

3.4.2 Experimental Studies of Respiratory Obstruction

Any relationship between airway obstruction and craniofacial growth could be established by experimental studies. Harvold's studies on monkeys with obstructive nasal airway show that the nose is an important area for normal

craniofacial growth (Harvold, 1975). Furthermore, in his previous research, Harvold *et al.* (1973) studied nine pairs of rhesus monkeys to evaluate nasal obstruction and facial growth. In the experiment, silicone plugs were inserted into the nasal opening of one of each pair; the other animal served as a control. The experimental animals gradually moved from a pattern of nasal to oral respiration. The first changes were functional in nature, by altering their patterns of neuromuscular activity in order to accomplish oral breathing; and learning to posture their mandible with a downward and backward opening rotation. Morphological changes gradually followed the change in the posture. Soft tissue changes occurred first. Notching of the upper lip and grooving of the tongue were seen and also changes in the mandibular shape developed, especially at the gonial region and at the chin. The tongue become long and thin, and an anterior open bite developed.

Harvold (1979) assessed 13 experimental young monkeys against 13 controls and found that the distance from nasion to chin increased significantly in the mouth-breathing groups, and also there was an increased distance from nasion to the hard palate. This indicates that the lowering of the mandible was followed by a displacement of the maxilla in a downward direction. Thus, the gonial angle increased and the lower border of the mandible became steeper.

Yamada *et al.* (1997) investigated the influence of artificial nasal respiratory obstruction on craniofacial growth in young Macaca fuscata monkeys. Nasal obstruction was created by injecting dental impression material into the nasopharyngeal region. A sample of 11 monkeys was used and divided into

an experimental and a control group. A downward and backward rotation of the mandible was seen in the experimental group with nasopharyngeal obstruction, and a divergent gonial angle, resulting in an anterior open bite and spaced dental arch at the lower anterior segment.

Evidence and data from animal's experimental studies should be extrapolated with caution. There are differences in the anatomy of the maxilla, mandible, tempromandibular joint, oropharyngeal passage and location of facial muscles in monkeys and humans (Miller *et al.*, 1982). So muscular adaptations and postural response are not necessarily the same. On the other hand, total nasal obstruction as produced in monkeys, is extremely rare in humans. Therefore, different morphological changes would be expected.

3.5 Conclusion

In summary, various studies, each with a different emphasis, have been conducted in order to determine the association between respiratory obstruction and craniofacial morphology. The earlier studies provided interesting findings but raised difficult questions, highlighting a potential relationship between airway obstruction and craniofacial morphology. This potential relationship should encourage further research.

Chapter 4

Three Dimensional Surface Technologies

4.1 Introduction

Three-dimensional imaging has evolved greatly since the 1980's and has many applications in orthodontics as well as maxillofacial surgery. Traditionally, lateral cephalometric radiographs have been widely used to describe the growth and morphology of the craniofacial structures, which provides direct measurement of bony skeletal dimensions. Unfortunately the inherent limitations of cephalometric analysis and ethical issues associated with ionizing radiation make contemporary studies of facial changes difficult. The major limitation in cephalometry is error in landmark identification of hard and soft tissues on radiographs (Leonardi *et al.*, 2008), other factors quality of images, projection errors which arise due to the fact that it produces a two-dimensional representation of a three-dimensional structure (Kumar *et al.*, 2007), and so, even with a precise head positioning landmarks are still magnified and not all measurements are possible. To overcome these limitations, alternative forms of imaging have been developed.

The introduction of three-dimensional imaging systems is non-invasive and allows quicker and comprehensive evaluation of the facial soft tissues (Hajeer *et al.*, 2004; Kau *et al.*, 2005a). This section focuses on imaging devices that have been used to capture facial morphology, exploring their advantages and disadvantages.

4.2 Computer Tomography

A CT scan is a computerised tomography scan which uses x-rays and a computer to create detailed images of the face or the body. There has been a gradual evolution to produce different generations of CT based on the

organization of the individual parts of the device and the physical motion of the beam in capturing the data.

4.2.1 Cone Beam Computed Tomography

The x-ray source for Cone Beam Computed Tomography (CBCT) is a low energy fixed anode tube similar to that used in dental panoramic machines. It uses a cone-shaped x-ray beam with a special image intensifier and a solid-state sensor or an amorphous silicon plate for capturing the image (Mah & Hatcher, 2004). CBCT devices image patients using one rotation sweep of the patient, similar to that of panoramic radiography, lasting between 10 to 70 seconds (Scarfe *et al.*, 2006). Image data can be collected for a limited regional area of interest, complete dental or maxillofacial volume.

In CBCT, the projection is orthogonal, indicating that the x-ray beams are approximately parallel to one another. Furthermore, because the object is very close to the sensor, there is very little distortion, unlike panoramic radiographs, which always has some projection error because the anatomic region of interest is some distance away and is projected onto the film. In addition, the effect from CBCT is handled by the computer software, resulting in one to one measurements. To ensure that this error correction is functioning as well as other operational systems, a water phantom is used to calibrate the device daily.

The maxillo-mandibular volume acquired with CBCT devices can include image information for both arches and other views, such as panoramic or occlusal. The volume can be reformatted in a process termed secondary reconstruction and viewed from various perspectives by using the

accompanying software. The costs, efficiency, and benefits of this are very favourable, because one imaging session provides multiple views. This must be taken into account when prescribing radiographic images. For example, in treatment planning for a patient requiring dental implants in both arches, panoramic and CT examinations of the maxilla and mandible could be prescribed.

The advantages of CBCT are that the systems have been designed for imaging hard tissues of the maxillofacial region and are capable of providing sub-millimetre resolution in images of high diagnostic quality (0.4mm to as low as 0.125mm). The short scanning times (10-70 seconds) is an advantage as motion artefacts due to subject movement are reduced. Furthermore, the radiation dosage is reportedly up to 15 times lower than those of conventional CT scans (Scarfe *et al.*, 2006). The value of CBCT imaging has been reported in implant planning (Kobayashi *et al.*, 2004) surgical assessment of pathology, Temporomandibular joint (TMJ) assessment (Honda *et al.*, 2004) and pre- and post-operative assessment of craniofacial fractures (Scarfe *et al.*, 2006). In orthodontics, CBCT imaging is useful in the assessment of growth and development (Sukovic, 2003), assessment of root resorption (Ericson & Kurol, 2000), impacted canines (Rossini *et al.*, 2012) and hyperplastic growth or condylar shape anomalies (Proffit *et al.*, 2007).

However, CBCT cannot map exactly the muscle structures and their attachment and it does not capture the true colour texture of skin (Kau *et al.*, 2005a). These intricate structures would have to be imaged using conventional magnetic resonance imaging (MRI) technology, which does not

expose the patient to radiation. Hence, three-dimensional CBCT is probably not suitable for growth studies which analyse facial soft tissue; three-dimensional devices like stereophotogrammetry and laser scanning are still the state of art in capturing soft tissue texture.

There have been recent advances in CBCT technology, with more to come. In general, the advances have increased the speed of image acquisition and improved resolution.

4.2.2 Conventional Three-Dimensional Computer Tomography Scanning

Dr Hounsfield in England introduced computed tomography (CT) in 1969, with the first commercial CT scanner being introduced in 1972. CT is a valuable diagnostic tool for preventive medicine or screening for disease (Frush *et al.*, 2003). For imaging and data recording, CT uses a fan-shaped x-ray beam from its source arranged in a 360° array around the patient. Medical CT devices image patients in a series of axial plane slices that are captured either as stacked slices or from a continuous spiral motion over the axial plane. The CT scan produces a three-dimensional reconstruction based on soft tissue and bone. The volumetric data set comprises a three-dimensional block of smaller cuboids structures, known as voxels; each representing a specific degree of x-ray absorption. The size of these voxels determines the resolution of the image. In conventional CT, the voxels are rectangular cubes where the longest dimension of the voxel is the axial slice thickness and is determined by the slice pitch, a function of gantry motion. Although CT voxel surfaces can be as small as 0.625mm^2, their depth is

usually in the order of 1-2mm, with an error measured between 0.85% and 3.09% (Seeram, 1997).

CT completely eliminates the superimposition of images of structures outside the area of interest (Webber *et al.*, 1997), and also, because of the inherent high-contrast resolution of CT, differences between tissues that differ in physical density by less than 1% can be distinguished. Data from a single CT imaging procedure consists of either multiple contiguous or one helical scan that can be viewed as images in the axial, coronal, or sagital planes, depending on the diagnostic task. This is referred to as multiplanar reformatted imaging.

However, there are a number of limitations of the system. First, they require a dedicated facility and are very expensive. Second, CT is regarded as a moderate to high radiation diagnostic technique. Depending on the tissue being imaged the effective dose from a three-dimensional CT can be three to twenty times higher than conventional orthopantomograph (OPG). Although CT represents only 5% of all x-ray imaging, it accounts for 40% to 67% of all medical radiation (Frush *et al.*, 2003). The estimated lifetime cancer mortality risks attributable to the radiation exposure from a CT scan in a one year old are 0.18% (abdominal) and 0.07% (head); an order magnitude higher than for adults (Brenner *et al.*, 2001). However, if these statistics are extrapolated to the current number of CT scans, the additional rise in cancer mortality could be 1.5% to 2% (Brenner *et al.*, 2001). Furthermore, certain conditions can require children to be exposed to multiple CT scans. Overall, radiation exposure to the patient, especially in dentistry, has limited usage for complex

craniofacial problems and is only suitable for specialized diagnostic information.

4.2.3 CT-Assisted Three-Dimensional Imaging

CT-assisted three-dimensional imaging and modelling of the skull structures were introduced in the mid-1980s for use in maxillofacial surgery (McCance *et al.*, 1992). The patient is exposed to high radiation dose using this technique, thus it is not suitable for long-term assessment and for longitudinal studies e.g. following orthognathic surgery. It has limited resolution of the facial soft tissues due to the minimum 5mm slice spacing and the presence of artefacts created by metal subjects such as dental restorations and fixed orthodontic appliances, due to reduced x-ray penetration.

Xia *et al.* (2000) developed a system for reconstructing three-dimensional soft and hard tissues from sequential CT slices using a surface rendering technique (a process of generating an image from a model by means of computer programs) followed by the extraction of facial features from three-dimensional soft tissues. This technique has a few disadvantages. The accuracy of the constructed three-dimensional soft tissue model is affected by the long capture time and the reproducibility of landmark identification was not performed in order to evaluate the accuracy and validity of facial mapping.

4.3 Photogrammetry

Photogrammetry is the science of obtaining measurements of photographs, and building reconstructions in two or three dimensions.

4.3.1 Facial Plaster Casts

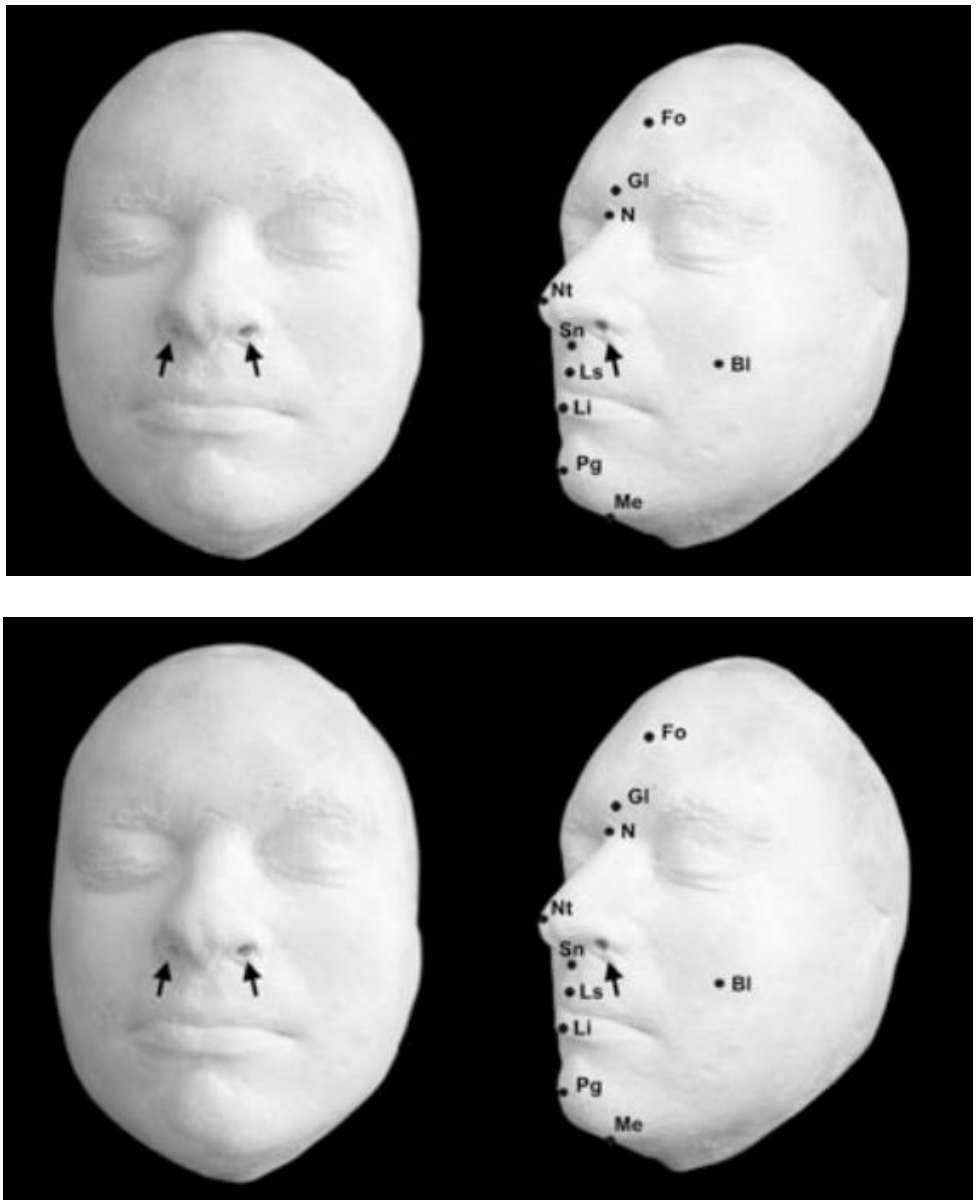


Figure 4.1: Facial plaster cast of a face

Note: The arrows show the opening for nasal respiration. The measuring points for evaluating the accuracy of the facial casts are shown in the right hand figure.

Source: Holberg *et al.* (2006)

The subject must remain absolutely still while the facial plaster cast sets in order to obtain the same facial expression. The disadvantage of this technique is that the plaster contracts on setting. Holberg *et al.* (2006) evaluated the accuracy of facial plaster casts and their suitability for three-dimensional analysis. Significant differences were found between the plaster cast and the facial surface (between 0.95 and 3.55mm), particularly in the area of the lips, the cheeks, the roof of the nose, and in the lower facial area (Figure 4.1).

4.3.2 Morphanalysis

Morphanalysis is a method of obtaining three-dimensional records using photographs, radiograph and study cast of a patient. A grid system is required on which to transfer the three-dimensional coordinates of the images (radiographs and photographs) on two planes on a centimetre scale. This is then used to map the common points on both to create x, y and z coordinates. Rabey (1971) described the accuracy, analytical and statistical validity of morphanalysis for orthognathic surgery. However, the disadvantages are that the equipment is extremely complicated and expensive. The technique is impractical and time consuming for everyday use.

4.3.3 Stereophotogrammetry

Hajeer defined photogrammetry as “the science or art of obtaining reliable measurements by means of photographs” (2002). This technique provides an accurate evaluation of the face and may utilize more than one stereo-pair views to produce three-dimensional coordinates of features of the face

(Hajeer *et al.*, 2002). Photographs with fast shutter speed are taken from each side of the face simultaneously to reduce any inaccuracy due to movement. Contemporary digital stereophotogrammetry was introduced with the use of complex algorithms that can be processed to convert simple photographs into three-dimensional measurements of facial changes. Ras *et al.* (1996) used the stereophotogrammetry system for the analysis of patients with cleft lip and palate by producing three-dimensional coordinates of any chosen facial landmark.

4.4 Structured Light Techniques

The structured light technique is another broad category of system used for capturing three-dimensional information based on triangulation principles. A projector shines a pattern of 'structured' light (that may be composed of elliptical patterns, random texture maps, etc.) onto a targeted surface to be scanned. When the light illuminates the surface, the light pattern distorts and bends. A system of cameras at a known distance captures the reflected and distorted pattern under an angle and translates the information into three-dimensional co-ordinates.

4.4.1 C3D imaging system

C3D imaging is based on the use of stereo-pairs of digital cameras and special textured illumination. The subject sits in the cephalostat of the x-ray machine with two video cameras on either side of the subject and a central light source. Each camera is used to capture half of the face. The slide which is computer controlled illuminates the subject with a texture pattern. The images are then matched by the C3D software to recover the triangulated

distances to each surface point captured by the cameras. To capture the subject's skin texture, a third digital camera is added. C3D then will provide the clinician with a lifelike three-dimensional model of the patient's head that can be rotated, enlarged and measured in three dimensions as required for diagnosis, treatment planning and surgical outcome analysis. The advantage of this technique is that it provides quick capture times (30 milliseconds) and makes the system appropriate for imaging infants, children and adults.

4.4.2 Moiré Topography

This imaging technique uses grid projections during exposure, resulting in standardized contour lines of the face. Motoyoshi *et al.* (1992) studied two-dimensional coordinates of hundreds of grid points on photographs of the human face captured with an image scanner and calculated their three-dimensional coordinates with a computer. They found that the accuracy of this system is high enough for the measurement of the human face with a mean error and standard deviation 0.04± 0.24mm for the x axis, 0.03± 0.16mm for the y axis and 0.08± 0.23mm for the z axis.

4.4.3 Stereolithography

This technique is used to surgically guide simple positioning of orthodontic mini-implants (Kim *et al.*, 2008), and is based on CT scans that enable the representation of complex three-dimensional anatomic structures. The main shortcomings of this technique are patient exposure to radiation during the CT scan and no production of soft tissue in machine-readable form (Ayoub *et al.*, 1996).

4.4.4 Three-Dimensional Cephalometry

It is a method of abstracting three-dimensional coordinate data from two radiographs based on manual techniques (Grayson *et al.*, 1988). The disadvantages of this procedure are patient exposure to radiation, lack of tissue contour assessment, errors in locating the same landmarks in two radiographs and the time-consuming nature of the procedure.

4.4.5 3DMD Face System

This system uses several cameras positioned at different angulations to capture the light pattern that is projected onto the subject. It combines structured light and stereophotogrammetry. The manufacturer's accuracy of the 3DMD face system is less than 0.5mm and the clinical accuracy is 1.5% of the observed variance (Aldridge *et al.*, 2005).

4.5 Three-Dimensional Laser Scanning

Laser scanning is one of the most commonly used techniques in acquiring three-dimensional data from objects in the engineering industry (Blais, 2004). The validity and reliability of the laser scanning are such that it is able to detect minute microscopic defects in the automotive and aerospace industries.

The word laser originally was in the upper-case, an acronym derived from Light Amplification by Stimulated Emission of Radiation, which utilizes optical principles where the distance of the object is computed by means of a directional light source and detector. As the laser beam is projected onto the physical object, a detector captures the scattered beam; hence the distance

between the detector and the object can be calculated by geometric principles. This can be translated into simple x, y, z coordinates.

Laser scanning techniques provide a non-invasive method for capturing the maxillofacial region in three dimensions (McCance *et al.*, 1992; Moss *et al.*, 1994). The three-dimensional laser-scan imaging system measures over 20,000 points over the surface of the face in 8 to 10 seconds and technique is repeatable, non-invasive and non-hazardous (Moss *et al.*, 1987; Linney *et al.*, 1989). Measurements and calibration are stable so that when superimposed profiles are identical with a precision of 0.5mm (Moss *et al.*, 1987). However the disadvantages of this technique include:

- The speed of the method, which generally takes 8 to 10 seconds to scan the face, increasing the chances of distorting the images.
- The need for the patient's eyes to be closed during scanning for protection purposes, which may bring into question the identity of captured image.
- The inability to capture the soft tissue surface texture, which results in difficulties in identification of landmarks that are independent of surface colour. (Hajeer *et al.*, 2002)

Although white-light laser approaches (e.g. Supplied by ARIUS3D) are now capable of imaging surface texture colour, the disadvantages still persist. The combination of laser scan and a CT scan can produce an accurate three-dimensional picture of the face and jaws upon which interactive surgery can be simulated (Moss *et al.*, 1987).

4.5.1 Minolta Vivid 700

Minolta Vivid 700 (Minolta USA, Ramsey, NJ) is a three-dimensional surface scanner which uses a horizontal stripe of laser light to scan the object from top to bottom. According to Kusnoto and Evans (2002), the object to scanner distance is about 0.6-2.5m and the scanning time is 0.6 seconds. It is a Class 1 laser with a wavelength of 690nm at 25mW. By triangulating distances between the reflecting laser beam and the scanned surface, the surface laser scanner can detect the object's length, width and the depth. The reliability of generating three-dimensional object's reconstruction was assessed by Kusnoto and Evans (2002). They used a calibrated cylinder, a dental study model and a plaster facial model to assess the accuracy and reproducibility. Tests were conducted on different distances between the object and the scanner. Kusnoto and Evans found that in the calibrated cylinder tests, spatial distance measurements were accurate to 0.3mm (+/-0.1mm) and 0.5mm (+/-0.1mm) in the horizontal and vertical dimension respectively. In the facial model test, the accuracy was 1.9mm +/- 0.8mm. However in the study model test, molar width was accurate to 0.2mm (+/- 0.1mm, $p>0.05$), and palatal vault depth could be measured to 0.7mm (+/-0.2mm, $p>0.05$).

The laser surface scanner generates accurate three-dimensional data. The availability of a light-weight, user-friendly surface laser scanner in orthodontics makes it possible to analyse growth, soft tissue changes, treatment simulation, appliance designs, and treatment effects in three-dimensions. Three-dimensional computerized data from a laser scanner can also be transformed by using a computer-aided manufacturing and

stereolithography technique to produce orthodontic appliances such as splints, computerized wire bending, e-models, and surgical simulation models (Kusnoto & Evans, 2002).

4.5.2 Minolta Vivid VI900

Minolta released a VI-900 optical laser scanner in 2001, which is an improved version of the VI-700 series. The camera had a reported manufacturing accuracy of 0.1mm. Each camera emits an eye safe Class I laser (FDA) λ=690nm at 30mW with an object to scanner distance of 600 to 2500mm. It collects 307,000 data points with output data of 640×480 pixels for three-dimensional red, green and blue colour (Kau *et al.*, 2005b; Kau *et al.*, 2005c).

The Minolta VI-900 has been used in a host of applications. Kau *et al.* (2004) studied the feasibility of measuring three-dimensional facial soft-tissue morphology in 11-year old children and adults. They found that the laser scanning system enables the facial morphology to be captured from left to right providing a comprehensive picture of the face. Small differences between scans can occur, but the mean ± SD differences are small (<0.3mm). The Minolta was found to be accurate to 0.56mm ± 0.25mm, and the error in computerized registration of left and right scans was 0.13mm ± 0.18mm (Kau *et al.*, 2003). In a further study, Kau *et al.* (2005b) measured the facial morphology of 38 adults with a mean age of 24.5 years in three dimensions. The soft tissue changes were analysed at baseline (T1) and week 1 (T2). Results showed that the mean differences of the merged composite faces superimposed at T1 and T2 was 0.35mm ± 0.09mm for

females and the reproducibility error was 0.7mm when a tolerance of 90% was superimposed on the aligned faces: the reliability of image capture has been reported extensively (Kusnoto & Evans, 2002; Kovacs et al., 2006). The results are in lign with other tests Therefore, the three-dimensional images may be used as an accurate representation of facial morphology. Twins were also examined using a Minolta Vivid 900 three-dimensional optical laser scanner (Kau *et al.*, 2005c). The results showed that changes in height and weight correlated with changes in facial morphology and the three-dimensional data obtained allows magnitude and direction of facial growth to be better appreciated.

4.5.3 Optical Surface Scanning

Optical surface scanning was first tested in 1981 to produce a non-invasive three-dimensional image of the face. The system was modified, improved and retested (Arridge *et al.*, 1985; Moss *et al.*, 1987; Aung *et al.*, 1995). In addition, the system has been developed to scan models of teeth (Stern & Moss, 1994). In 1996, a hand-held camera, which can be used for many scanning parts of the body, was designed to make the system mobile (McCallum *et al.*, 1996). The recent introduction of a probe that records the three-dimensional co-ordinates of any point means that many of the hard tissue points used by Farkas (1994) can now be recorded. Many scanners, which take instant pictures, have the problem of scarcity of data at the periphery of the scan which makes joining two scans difficult and not very accurate (Moss, 2006). In contrast, the hand-held scanners overcome this problem and can collect over 120,000 points around the head. This meets

the criteria of having sufficient data from the surfaces for the analysis of changes in facial morphology, growth and especially of surface shape changes.

4.6 Three-Dimensional Magnetic Resonance Images

Three-dimensional magnetic resonance imaging (MRI), or nuclear magnetic resonance imaging (NMRI), is primarily a medical imaging technique most commonly used in radiology to visualize detailed internal structure of the body. It was described by Hansen and Packard at Stanford University and Purcell, Torrey and Pound at Harvard University in 1949.

It was initially a two-dimensional imaging technique; however, with advances in technology, three-dimensional imaging is now possible. It has about 10,000 times the strength of a magnetic field of the earth (Sadowsky *et al.*, 1988) and patient is placed in a large cylindrical electromagnet of strength 0.2-3.0 tesla. The MRI provides a superior contrast to CT between the different soft tissues of the body, making it especially useful in temporomandibular joints, management of tumours of the head and neck region and for imaging the brain in neurological imaging. It is also versatile, non-invasive with non-ionizing radiation (Patel *et al.*, 2006). However, the accuracy of the data is not sufficient, as it does not differentiate between air and bone (Moss, 2006). Furthermore, the presence of metallic prosthesis (e.g. cardiac pacemakers), orthodontic bands, bonded retainers and metallic implants may be contraindicated to MRI scanning as these objects produce artefacts in the image.

4.7 Three-Dimensional Ultrasound

This imaging technique was introduced to capture three-dimensional data. It delivers a reflection picture, which is then transformed into digital information (Hell, 1995). Ultrasonography waves do not visualize bone or pass through the air, which acts as an absolute barrier during both emission and reflection. Therefore, a specific contact probe is required to generate a three-dimensional database. The disadvantage of the technique is that it is time consuming hence needs a cooperative patient as well as a skilful operator. Movements of the head during acquisition introduce errors and distortions.

4.8 Three-Dimensional Studies of Facial Morphology

The use of three-dimensional measurements may improve the understanding of the craniofacial form and the developing face. Three-dimensional studies have analysed facial morphology and are able to distinguish between individuals of different gender, age, ethnicity and race (Moss *et al.*, 1987; Kau *et al.*, 2005a; Toma *et al.*, 2008; Richmond *et al.*, 2009). Recent studies have used the dense surface models to analyse three-dimensional facial morphology and to discriminate between normal and syndromic faces (e.g. Noonans syndrome) and to explore phenotype and genotype associations (Hammond *et al.*, 2004; Hammond *et al.*, 2005). The results of the studies demonstrated the use of face shape models to assist clinical training through visualization, to support clinical diagnosis of affected individuals through pattern recognition and to enable the objective comparison of individuals sharing other phenotypic or genotypic properties associations (Hammond *et al.*, 2005).

Knowledge of normal ranges of facial morphological features is essential for evaluating dysmorphic features, as the recognition of syndromes can be made from a combination of minor variations and malformations, rather than the presence of major malformations such as cleft lip and palate. Hammond and Suttie (2012) reported the progress over the past decade in three-dimensional imaging and face shape analysis. Illustrative examples were given using a collection of 1107 three-dimensional facial scans of individuals with a number of genetic conditions involving facial dysmorphism and healthy controls. They concluded that techniques for analysing three-dimensional face surfaces have matured considerably. For example, cheap, portable and compact devices have encouraged data capturing. As a result, three-dimensional photogrammetric cameras are widely used by orthodontists, maxillofacial and plastic surgeons, for treatment planning and for post-treatment evaluation, and can assist with clinical genetic studies. Thus, multiple three-dimensional linear measurements, following normalization of facial images, can be combined to determine a craniofacial index of dysmorphology to give an average profile for each syndrome against which an individual can be compared (Ward *et al.*, 1998).

Three-dimensional landmark studies have provided discriminating features in a series of studies of female-male and schizophrenia-control face shape differences, using a principle component analysis (PCA) to reduce the number of three-dimensional facial landmarks to a smaller set of principle components (Hennessy *et al.*, 2004; Buckley *et al.*, 2005).

A recent study by Weinberg *et al.* (2009) investigated face shape differences of 80 unaffected parents of 80 offspring with clefts against 80 controls. The authors identified 16 soft tissue landmarks on three-dimensional images. A geometric morphometric approach was utilized to scale and superimpose landmark coordinates. The results of the study indicated that significant face shape differences were present in the unaffected parents compared with the controls. They concluded that the quantitative assessment of facial morphology in cleft families may enhance knowledge of the root causes of clefts.

The average face surface of a collection of three-dimensional faces has been used in three-dimensional studies to highlight significant topographical facial differences. For example, Djordjevic *et al.* (2012) assessed facial shape and asymmetry of 5-year-old children with repaired unilateral cleft lip and/or palate. Surface-based average faces were constructed in the group of healthy children males and females separately. The individual faces of children with clefts were then compared with the average male and female faces of healthy children, by superimposing them on the mid-endocanthion point. The superimpositions highlighted the differences between facial soft tissues of children with repaired cleft and their non-cleft peers.

4.9 Conclusion

In summary, three-dimensional models of facial morphology are impacting on studies of craniofacial morphology and development. Three-dimensional soft tissue landmark and average face models have shown a good level of

accuracy in analysing facial morphology. Table 4.1 outlines the advantages and disadvantages of the various systems.

Table 4.1: Advantages and disadvantages of three-dimensional models

Device	Advantages	Disadvantages
Direct contact	Inexpensive set-up costs Quick landmark point capture	Poor resolution Geometric shape only Pseudo three-dimensional image
Photogrammetry	Cheap and easy to set up	Magnification errors Tedious work to map surfaces Pseudo three-dimensional image
Radiation	Reasonable resolution Good correlation to hard tissues	Radiation dosage not feasible for multiple exposures Expensive equipment Long scan time
Computer-aided structured light	Rapid capture Non-invasive	Technique sensitive Varying resolution quality
Lasers	High resolution Quick capture Non-invasive Contour topology and surfaces	Expensive equipment Technique sensitive
Video-imaging	Multiple motion capture Speech and animation capture	Low resolution Processing capabilities required

Chapter 5

Study Design

5.1 Research Aims

The study will utilise the data collected for the Avon Longitudinal Study of Parents and Children (ALSPAC) identifying breathing disorders and comparing their facial morphologies to a healthy group. Following the definition by Esteller *et al.* (2011), a subject was classified as having a breathing disorder if their breathing was affected by impediments to the free flow of air through the nose.

The aims of the study are:

- To investigate if asthma influences face shape.
- To investigate if atopy (a predisposition toward developing certain allergic hypersensitivity) influences face shape.
- To investigate if allergic rhinitis influences face shape.
- To investigate if sleep disordered breathing influences face shape.
- To investigate if early removal of adenoids and tonsils in children with a history of sleep disordered breathing (SDB) will normalise face shape.
- To investigate if multiple breathing disorders influence face shape.

For this purpose, facial imaging techniques are used to investigate face shape in children with breathing disorders compared to healthy children. The associations between asthma and face shape are described in Chapter 8. Chapter 9 presents links between atopy and face shape, while a description of the links between allergic rhinitis and face shape can be found in Chapter 10. Changes in the shape of the face of children suffering from sleep disordered breathing without (Chapter 11) and with (Chapter 12)

adenotonsillectomy are also discussed. In Chapter 13, the effect of multiple diseases (asthma, allergic rhinitis, atopy and sleep disordered breathing) on face shape in children is presented. A detailed methodology is presented in Chapters 6, although a brief explanation of the methodology relevant to each disease is also included in every chapter.

5.2 Study Sample

The children involved in this study were recruited from ALSPAC, a geographically based cohort study of children that is broadly representative of the UK population. The ALSPAC study was designed to explore how an individual's genotype is influenced by environmental factors impacting on health, behaviour and development of children (Golding *et al.*, 2001). The initial ALSPAC sample consisted of 14541 pregnancies with this number of pregnant women enrolled in the ALSPAC study with an estimated date of delivery between April 1991 and December 1992. Out of the initial 14541 pregnancies, all but 69 had known birth outcomes. Of the 14472 pregnancies, 195 were twins, three were triplets and one was a quadruplet pregnancy; meaning that there were a total of 14676 foetuses in the initial ALSPAC sample. Of the 14676 foetuses, 14062 were live births and 13988 were alive at 1 year. Detailed information from before birth to late puberty has been collected through self-administered questionnaires, data extraction from medical notes, linkage to routine information systems and research clinics. This unique dataset facilitates the exploration of accumulative genetic and environmental impacts over the life course of an individual or groups of individuals (Golding *et al.*, 2001).

The following records were taken for each subject enrolled in the study: age, gender, body weight and height. Body weight was measured using Tanita scales to the nearest 0.1kg. Height was measured to the nearest 0.1cm using a Harpenden stadiometer (Lawlor *et al.*, 2010). Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

The cohort was recalled in 2006 and 2007 when the children were 15 years old. A total of 9985 participants expressed an interest in taking part in the clinical assessments and three-dimensional facial scanning was performed on those who attended.[1] A total of 5253 facial images were collected for this study. The focus of this research was on breathing disorders that were not secondary to congenital complications, therefore images taken from children with congenital abnormalities or conditions associated with poor growth that could affect their breathing were excluded. The diagnoses were based on initial infant data and parent-reported comments. Conditions excluded were malabsorption syndromes (e.g. coeliac disease); genetic disorders (e.g. Prader-Willi syndrome, Down's syndrome and congenital adrenal hyperplasia); complications such as cleft palate; heart or kidney conditions; and cancer. Diagnoses based on the parent-reported comments were verified by consensus by a panel of experts comprising of a senior paediatrician, a paediatric pulmonologist and a paediatric orthopaedist. Images from non-Caucasian participants, children with obvious facial dysmorphology and poor-quality images were also excluded. The final study sample consisted of 4784 British Caucasian 15-year old children (2254 males

[1] The researcher was not involved in capturing the facial scans but contributed to the construction of average-face shells and performed the analyses, data processing and interpretation of the facial images.

and 2530 females) and included 2922 (61.1%) children with a breathing disorder and 1862 (38.9%) healthy children, based on the definition described in Chapter 5.1 (Esteller *et al.*, 2011). A flow diagram of the selection process is given in Figure 5.1.

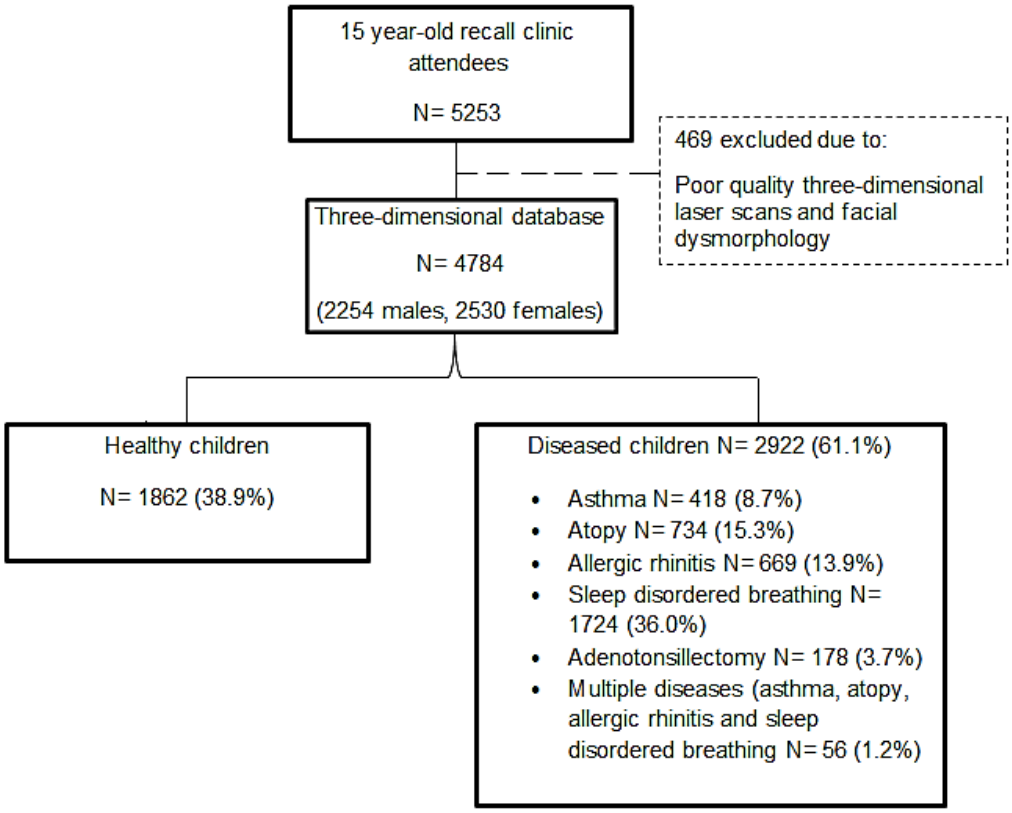


Figure 5.1: Flow chart showing the selection of a study sample used in the present study. The participants were recruited from a 15 year follow-up clinic of the Avon Longitudinal Study of Parents and Children. The percentages of children with the different breathing disorders are given relative to the total number of facial scans (4784).
* Note: these figures include children with a combination of diseases, see Appendix 1

5.3 Study Design

The study design was based on cross-sectional analysis of three-dimensional facial images in relation to the genetic, environmental and medical data of

15-year old children selected from the ALSPAC cohort. This approach enabled the advantages of a cross-sectional study, in which correlations could be made between multiple variables at a single time point, to be combined with longitudinal data from a large study population, thereby increasing the statistical power of the interpretations. A study on childhood asthma by Cornish *et al.* (2014), that was also based on the ALSPAC cohort, found that only 26 (18%) of 141 participants were diagnosed with asthma before the age of nine. Therefore, by collecting facial images from children at 15 years of age, the sample used in the present study was able to include those who developed late onset disease. Various other potentially confounding factors were also taken into consideration; for example, by selecting British Caucasian children, the influences of racial characteristics could be avoided.

The majority of facial development in females is complete at 15 years of age; however substantial facial growth remains in males, particularly in forward and downward growth of the mandible. A chi-square test is undertaken for each breathing disorder in order to determine if there were any significant differences in facial parameters between male and female subjects. In the event of no significant differences being found, the male and female parameters were assessed together; if a significant difference was identified the genders were analysed separately.

5.3.1 The ALSPAC Research Design

The advantages and limitations of the ALSPAC research design were taken into consideration in the present study design. Detailed environmental and

medical data, including diet and lifestyle, attitudes and behaviour, social and environmental features, medication and symptoms, were collected from parents, the children and medical practitioners at specified time-points during the course of the study. Response rates >80% were achieved (Golding *et al*., 2001). The questionnaires were primarily based on parental-reports collected from the early stages of pregnancy until the children were 15 years old, and included nine clinical assessments between the ages of 7 and 15 years (Golding *et al*., 2001). This ensured that the research was not biased by prior knowledge of future outcomes. The questionnaires were designed and piloted to rule out potential ambiguities. The cohort population was considered sufficiently large to ensure that the sample size was suitable for robust statistical analysis and to avoid spurious results (Golding *et al*., 2001).

The validity of the ALSAPC design has been validated in multiple studies for diverse conditions, including those involving breathing disorders. For example, the ALSPAC population study was included in the NIAID/NHLBI/MeDALL joint workshop which assessed over 130 birth cohorts focusing on asthma and allergy (Bousquet *et al.*, 2014). It was also part of a meta-analysis investigating risk *loci* for atopic dermatitis (Paternoster *et al.*, 2012a). Cornish *et al*. (2014) confirmed there was close agreement between GP data and the parental reports of GP-based diagnoses of asthma. In addition, the ASLPAC resource has been utilised, either alone or in combination with other birth cohort studies, to identify wheezing phenotypes (Savenije *et al.*, 2011) and polymorphisms associated with childhood asthma (Savenije *et al.*, 2014).

5.3.2 Limitations of the ALSPAC Research Design

Some of the limitations of the ALSPAC research design are associated with its single geographical area which reduces its ethnic diversity (Fraser *et al.*, 2013). However, as the present study focuses on British Caucasian children at 15 years of age, ethnicity had minimal impact on the interpretations. Golding *et al*. (2001) argued that by "being based in one geographic area, linkage to medical and educational records is relatively simple and hands-on assessments of children and parents using local facilities have the advantage of high quality control".

Face shape is determined by multiple factors, both genetic and environmental, some of which have greater influence than others. The aim of the present study is to identify specific traits in face shape attributable to breathing disorders. It is anticipated that any measured differences attributed to breathing disorders would be small; therefore, a large sample size was employed in order to determine small differences. Under such circumstances, standard statistical methods to evaluate p-values are not always the most appropriate, and confidence intervals should be used to verify the reliability of the data (Gardner & Altman, 1986). Therefore, in order to determine whether or not the measured differences in this study reflected real trends, the following strategies were adopted to enhance the power and precision of the statistical analyses: a large study sample was selected from a validated longitudinal birth cohort (ALSPAC) (Golding *et al.*, 2001); the accuracy and reproducibility of advanced three-dimensional imaging was utilised (Kusnoto & Evans, 2002; Kovacs *et al.*, 2006); and the interpretations were based on

95% confidence intervals (95% CI) as oppose to p-values (Gardner & Altman, 1986).

5.4 Ethical Considerations

Ethical approval to utilise three-dimensional images of children acquired during the ASPAC study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees prior to the commencement of the present study (Appendices 4 and 5).

5.5 Research Challenges

Because of the inherent faults in technology and the possible distortion of light, none of the available three-dimensional systems are accurate over the full field of view. Also, all systems must take into account potential patient movement and alterations of facial expression between the multiple scanning views required to construct a three-dimensional model of the face (Mah & Bumann, 2001; Mah, 2002). However, the continuous improvements in technology and software mean that clinicians and researchers are closer to realistic three-dimensional imaging. The following sections highlight the approach of the research to minimise any technological distortion.

5.5.1 Validity and Reliability of Capturing Technique

Careful attention was given to ensure the standardisation of image capture. The laser scanning system used in this study is described in detail in Chapter 4.5.1. It include two high-resolution cameras (Minolta VIVID 900 Optical Digitizers) operating as a stereo-pair (Figure 6.1). The accuracy and reproducibility of the Minolta VIVID series of digital optimisers for three-

dimensional imaging has been reported extensively (Kusnoto & Evans, 2002; Kovacs *et al.*, 2006) and its reliability in clinical applications has been demonstrated by Kusnoto and Evans (2002). A comprehensive overview of the methodology used in this research is described in Chapter 6.

5.5.2 Image Registration

As described in Chapter 6, quality of registration of the right and left facial scans for all subjects was determined using average distance between shells and percentage of overlap between the right and left shells. The facial scan was evaluated as having good quality when the average distance between right and left facial scan is 0.3mm and below and is therefore suitable for merging (Kau & Richmond, 2008). Generally, 70–100% overlap of the right and left facial shells with a tolerance level set at 0.5mm indicates facial shells is considered suitable for merging and any non-suitable scans were excluded from the study (Toma *et al.*, 2008; Kau & Richmond, 2010).

5.5.3 Reproducibility of Facial Posture

A strict protocol for capturing facial soft tissue morphology was applied in this study. Natural Head Posture (NHP) was adopted in the examinations as it has been shown to be clinically reproducible (Solow & Tallgren, 1971; Chiu & Clark, 1991; Lundstrom *et al.*, 1995). The children sat on an adjustable stool and were asked to look at a “Bristol Red Glass Heart” hung from the ceiling to simulate NHP. NHP was confirmed prior to image capture by an orthodontic examiner experienced in using this technique in clinical examinations. Children were also instructed to swallow hard and to keep their jaws relaxed just before the scans were taken. If a subject moved between

scans, the procedure was repeated. Kau *et al.* (2005b) showed that subjects could adopt the same facial posture at different times. Indeed, the analyses of colour differences between facial maps also showed that a high level of soft tissue reproducibility was achieved.

5.5.4 Reproducibility of Soft Tissue Land Marking

Chapter 7 covers the reproducibility of soft tissue land marking in depth. The 21 facial landmarks, as defined by Farkas (1994), were manually identified on the facial scans by one operator. The majority of the landmarks with the x, y and z coordinates were reliable to less than 1mm error.

5.5.5 The Use of Average Faces and Superimposition Methods

The reliability of average faces is discussed in Chapter 6. In this study, the superimposition method known as the "best fit" is used. This method is mathematically derived and essentially matches closely related triangular vertices of two similar surface shells and approximates them to one another. The resultant errors in distances corresponding to two surfaces are averaged and the shells are fitted together. The errors due to superimposition technique are about 0.2-0.5mm (Kau & Richmond, 2010). However with iterative averaging in the local normal direction to a template method, the error can be evaluated to be less than 0.1mm for 20-30 facial shells and effectively vanishes with increasing the number of shells (Kau & Richmond, 2010).

5.6 Summary

The choice of participants together with the methodology described above provides useful insights on how to best analyse face shape. Upon successful

visualisation, the potential associations between four breathing disorders (asthma, allergic rhinitis, atopy and sleep disordered breathing) and face shape are investigated.

Chapter 6

Methodology

6.1 Introduction

Three-dimensional imaging technology allows reconstruction of facial geometry. Three-dimensional data can be mathematically and statistically analysed which allows assessment of relationships of anatomical structures. This chapter describes the methodology used to obtain the three-dimensional images of the subjects used in this study.

6.2 Three Dimensional Imaging System

Three-dimensional facial imaging was carried out in a dedicated scanning room with neutral blue walls and no windows at the Bristol Dental Hospital. The laser scanning system consisted of a pair of high resolution Konica Minolta Vivid (VI900) cameras (Figure 6.1) which have a reported manufacturing accuracy of 0.1mm (Kau *et al.*, 2003). Two Bowen's tri lamps with a wavelength varying between 400–800nm were used to ensure consistent lighting.

6.2.1 Set-up for Image Capture

The system was set-up to ensure that facial images were captured in a standardized way and the subjects were positioned to ensure the reproducibility of the facial postures (Figure 6.2). This is described detail in Section 5.5.3. Variations in height between the children were compensated for by adjusting the height of the stool so that their eye-level was parallel with the "Bristol Red Glass Heart" hung from the ceiling. Natural Head Posture (NHP) was adopted as this has been shown to be clinically reproducible (Chiu & Clark, 1991; Kau *et al.*, 2005b). The cameras were placed at a distance of 1350mm from the subjects. All subjects were asked to swallow

hard, keep their jaw in a relaxed position and remain still during the scan procedure. The total scan time was approximately 0.8 seconds.

Figure 6.1: Konica Minolta Vivid (VI910) cameras

The scanners were controlled by a multi-scan software and the data coordinates of the right and left scans were saved in a vivid (vvd) file format. The data files contained coordinates which were transformed into a data mesh to generate a three-dimensional representation. Rapidform® 2006

(INUS Technology Inc., Seoul, South Korea) software programme was used for processing and analysis.

Figure 6.2: Three-dimensional image capturing

6.2.2 Camera Calibration

To ensure that the cameras were able to function together and compute the full face of the three-dimensional images, a process known as camera calibration was carried out for each scanning session. A calibration cube of known fixed dimension and coloured surfaces was placed in the area were the subject's head would be. At least three surfaces of the cube need to be visible on both camera screens to accurately capture the three-dimensional data. In order to ensure a standardised positioning, the cube was fixed to a tripod, which was placed on a fixed marking on the floor. The three-dimensional scanning was carried out without moving or adjusting the laser scanners.

6.2.3 The Software

A multi-scan software (Cebas Computer GmBH, Eppelheim, Germany) was used to control the Minolta Vivid VI900 and files of the data coordinates were saved in a vvd file format following (Kau *et al.*, 2004). The data coordinates were then transferred to a commercially available reverse modelling software package, Rapidform® 2006 (INUS Technology Inc., Seoul, South Korea). Rapidform® 2006 is designed to convert data from the three-dimensional scanning devices into good quality data for interpretation and analysis in various three-dimensional studies.

6.2.4 Scanning the Subjects

The subjects were scanned using the standardised procedure described in Chapter 6.2.1 and 5.5.3. The subjects were asked to sit upright on the self-adjustable stool with their feet flat on the floor in the NHP and their eyes focused on a “Bristol red Glass Heart” hung from the ceiling directly ahead. The subjects were observed closely during the scanning procedures to exclude any unsuitable scans due to subject movement. Each subject was scanned twice to ensure that the best scans were obtained with minimal error.

6.2.5 Data Processing

For each scanned subject, right and left three-dimensional facial images were produced using a multi-scan software (Figure 6.3). The data was then automatically converted to point cloud measurements, then triangulated to

generate three-dimensional polygon meshes and finally saved in vvd file format in the appropriate file.

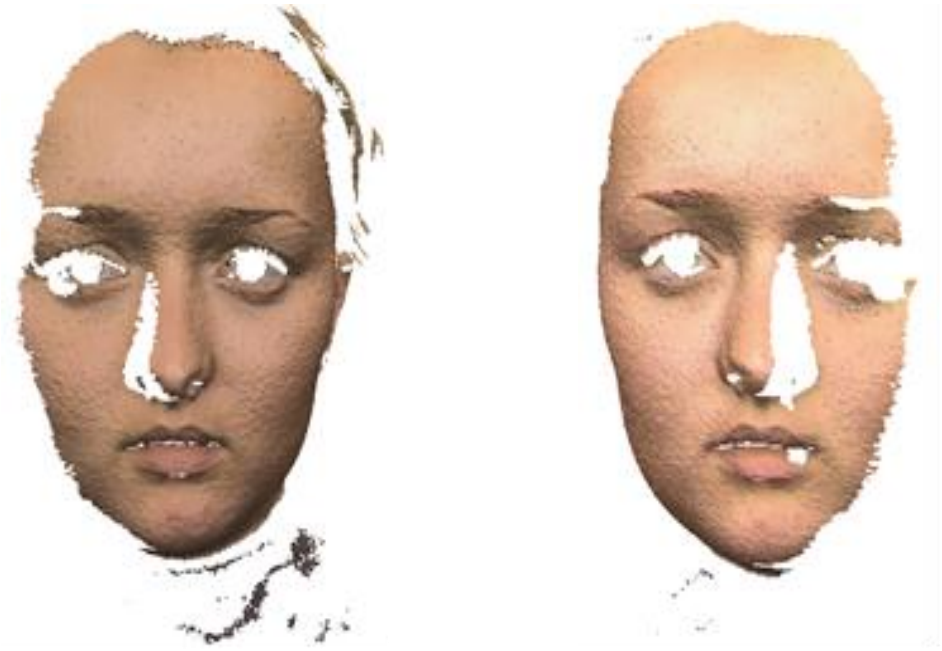


Figure 6.3: Raw scans of each facial half

A locally developed sub-routine prepared in Rapidform® 2006 software was then used to process and analyse the data. Sub-routines were added to the user menu within the Rapidform® 2006 and presented in a form of a dialog box that was easy to use and allowed various actions to be performed. The raw data of the three-dimensional meshes for the right and left scanned facial images were imported into the Rapidform® 2006 software (Figure 6.4).

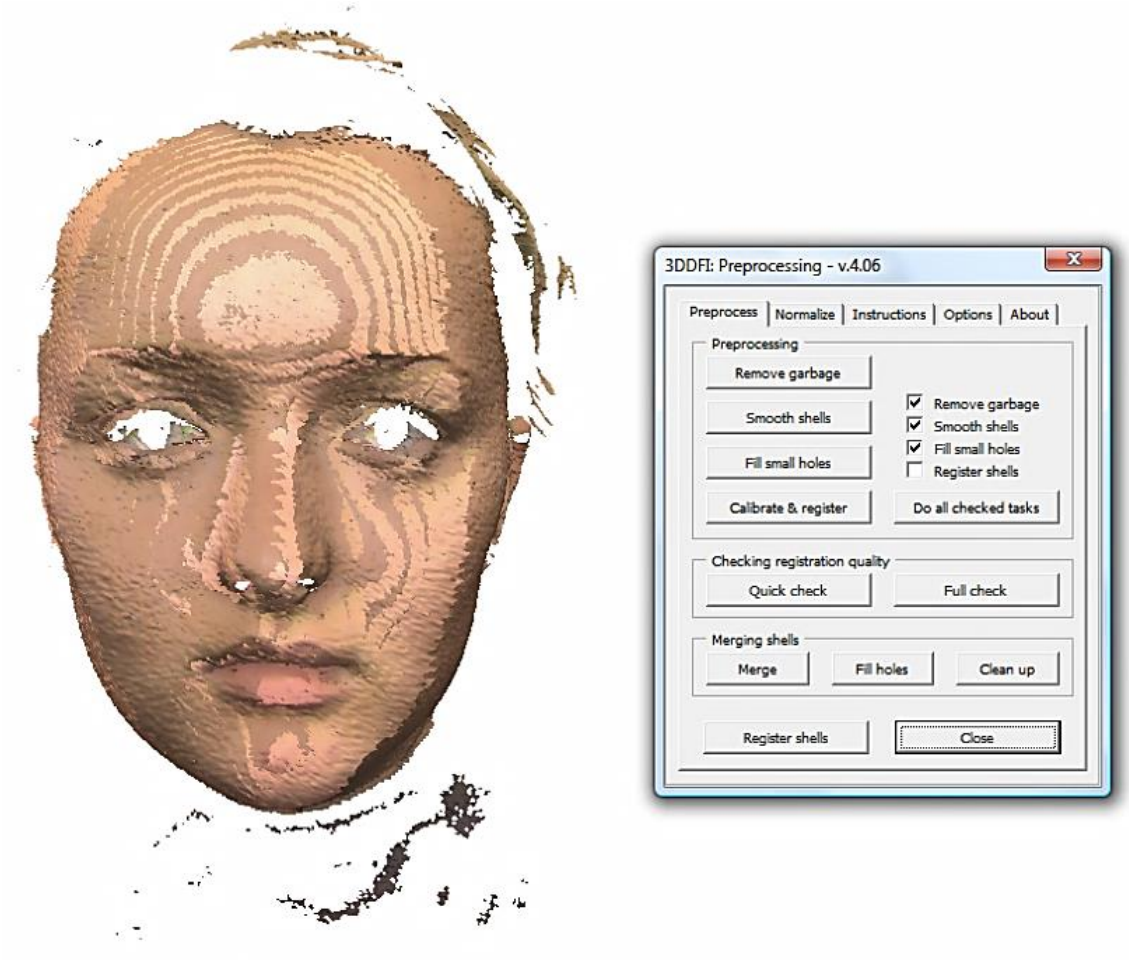


Figure 6.4: Raw scans were imported into Rapidform® 2006 in VVD file format in order to be processed and merged

Figure 6.5: Face after removal of garbage

A number of procedures were then carried out:

- **Removal of garbage**: A sub-routine developed in the department (Zhurov *et al.*, 2005) was used to remove all unwanted data such as hair, ears and neck (Figure 6.5).
- **Smoothing the images**: Facial images were then minimally smoothened to ensure that volume and shape of each facial image was not changed (Figure 6.6).

Figure 6.6: Face after smoothing the surface

- **Filling the holes**: Small holes and any defects in the facial mesh were filled. Such voids were usually associated with the highly reflective eyeballs and the eyebrows which do not form a coherent surface for light reflection (Figure 6.7).

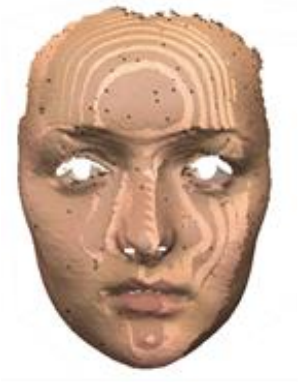


Figure 6.7: Face after filling small holes

- **Calibration and registration**: The iterative closest point (ICP) algorithm, which is based on how much the two facial shells overlap, was used to align the right and left facial scans (Figure 6.8).

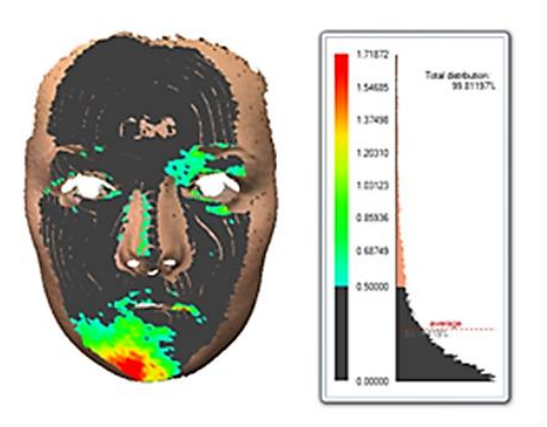


Figure 6.8: Calibration and checking registration quality

- **Checking registration quality**: The aligned shells were checked for registration quality and only those with acceptable tolerance of 0.5mm (at least 70% overlapping of the area of the right and left shells) were included in the study.

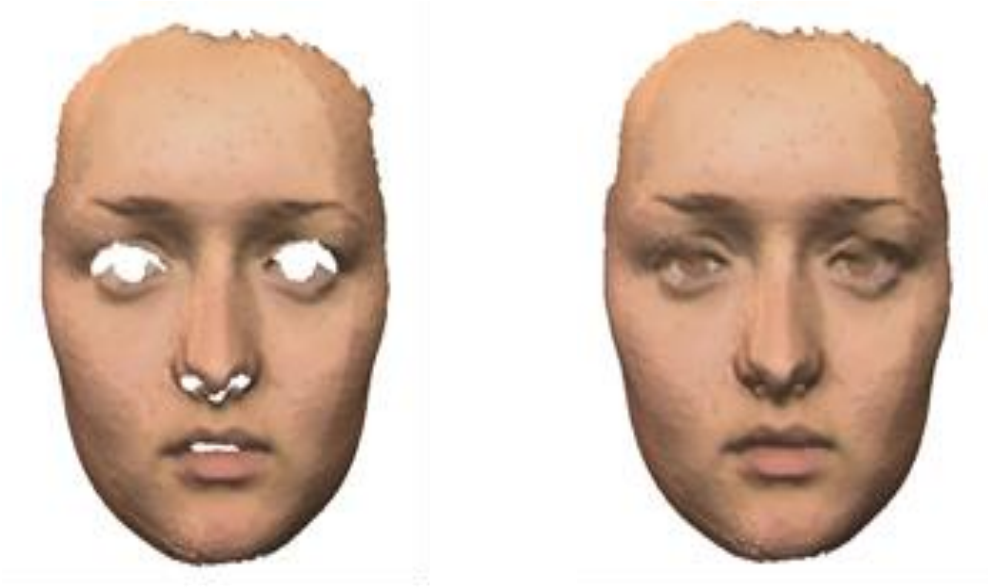


Figure 6.9: Two halves of the face are merged, large holes in the nostrils, eyes, and lips are filled in

- **Merging the shells**: the two facial shells were merged to become one face for each subject. Finally, the three-dimensional facial images finally checked for any defects to refine the images (Figure 6.9).

6.3 Quality of Registration

The quality of the registration of right and left facial scans for all 4784 subjects was determined using average distance between shells and percentage of overlap between the right and left shells. A facial scan is considered very good when the average distance between right and left facial scan is 0.3mm and below and consequently is considered to be the most suitable for merging (Kau & Richmond, 2008). A 70% to 100% overlap of the right and left facial shells with a tolerance level set at 0.5mm indicates the facial shells are also good for merging.

6.4 Reliability of the three-dimensional Imaging System

There have been a number of studies on the accuracy, validity and reproducibility of the Minolta Vivid V1 700 and 900. Kau *et al.* (2003) concluded that the portable Minolta Vivid 900 optical laser scanning cameras are valid and reliable for the measurement and evaluation of facial morphology in field studies. The laser scanning system has reported manufacturing accuracy of 0.1mm. The technique used in our study had recorded the three-dimensional nature of the face non-invasively and without hazardous, as would have been the case using a high radiation dose such as CT imaging (Nakajima *et al.*, 2005).

It is essential that the subjects remain very still during the scanning process in order to obtain a facial image of acceptable tolerance of less than 0.5mm (with left and right scan overlap percentage of at least 70%). Any movement during the scanning procedure would cause a gap between the right and left facial shells which would result in it being difficult to merge and process them, which was the main reason behind those facial scans with poor quality. A high compliance was shown by the 15-year old subjects recruited for the study, as the scan quality was found to be 88% “good quality”, 8% “fair quality” and only 4% “poor quality”. These results are similar to previous finding conducted by Toma *et al.* (2009), Toma *et al.* (2012) and Kau *et al.* (2004). Although minor muscular responses were noticed in the eyelid region and area near the lips, these only caused minor image distortions and were able to be processed without affecting the overall shape and volume of the scanned image.

6.5 Normalization of the Facial Images

The three-dimensional facial shells were oriented in the three planes of space using a locally developed sub-routine in Rapidform® 2006 software. This sub-routine was utilized to automatically standardize the three-dimensional facial images within the reference framework by orienting each three-dimensional facial shell in the three planes of space (x, y, and z) using three reference planes: sagittal (y-z plane), coronal (x-y plane), and transverse (x-z plane) (see Figure 6.10). These planes were referenced to the point between the inner corners of the eyes (mid-endocanthion, men), as research has shown this is the most reliable facial landmark (Toma *et al.*, 2009; Zhurov *et al.*, 2010).

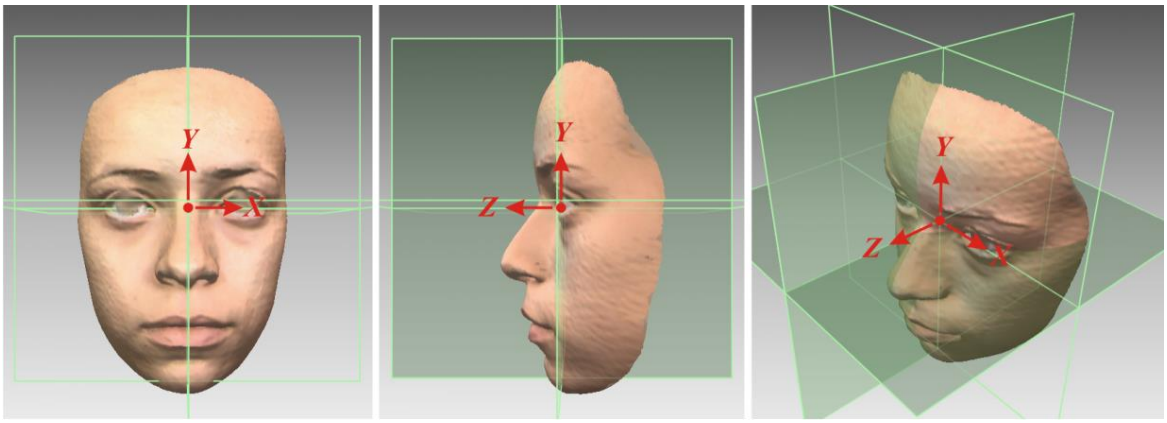


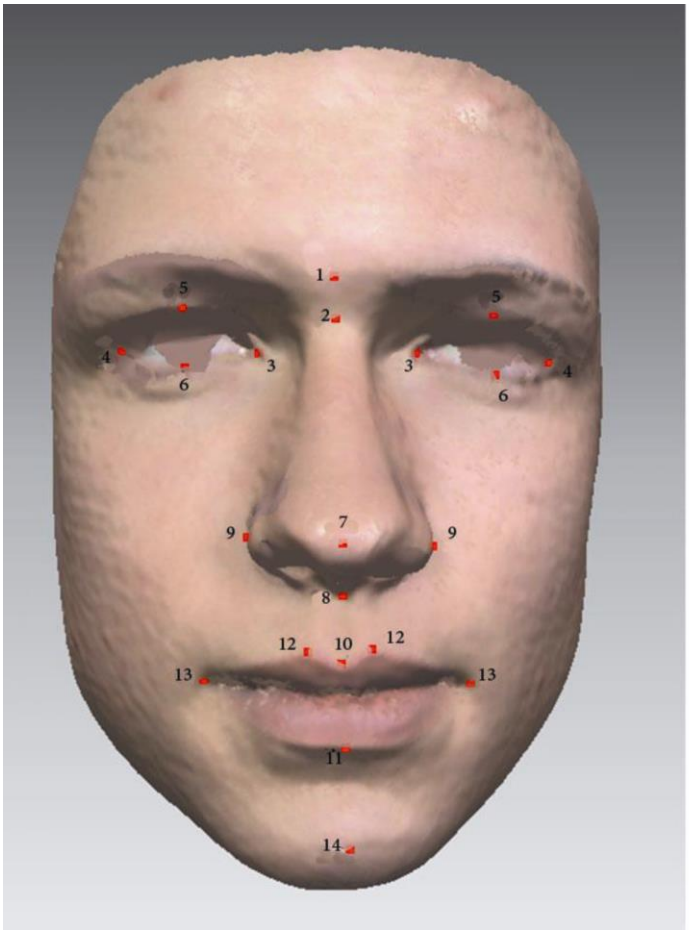
Figure 6.10: Normalization of facial shells to natural head posture

Note: The x-axis (horizontal); y-axis (vertical); z-axis (depth of field); the coronal, sagittal, and transverse planes were taken as the xy, yz, and xz planes, respectively (Toma *et al.,* 2012)

The sagittal plane was referenced to this point running through the mid-line of the face, the coronal plane was established as the average NHP, and the transverse plane was established across the inner canthi points (Toma *et al.*, 2009).

6.6 Identifying Soft Tissue Landmarks

Twenty-one facial soft tissue landmarks (Figure 6.11, Table 6.1) were manually identified on each facial image (Figure 6.12) (Toma *et al.*, 2009; Toma *et al.*, 2012) and the x, y and z co-ordinates were recorded. The reproducibility of these landmarks in the three dimensions has been reported previously generally with an error of less than 1mm for both intra- and inter-examiner assessments (Toma *et al.*, 2009).



Landmarks:

- 1 Glabella (g)
- 2 Nasion (n)
- 3 Endocanthion (en) L/R
- 4 Exocanthion (ex) L/R
- 5 Palpebrale superius (ps) L/R
- 6 Palpebrale inferius (pi) L/R
- 7 Pronasale (prn)
- 8 Subnasale (sn)
- 9 Alare (al) L/R
- 10 Labiale superius (ls)
- 11 Labiale inferius (li)
- 12 Crista philtri (cph) L/R
- 13 Cheilion (ch) L/R
- 14 Pogonion (pg)

Total = 21 Landmarks

Figure 6.11: Facial soft tissue landmarks

Table 6.1: Facial soft tissue landmarks (points)

Facial Region	Landmark Name	Abbr.	Definition
Eyes	Endocanthion(R)	en	Inner commissure of the right eye fissure
	Endocanthion(L)	en	Inner commissure of the left eye fissure
	Exocanthion (R)	ex	Outer commissure of the right eye fissure
	Exocanthion (L)	ex	Outer commissure of the left eye fissure
	Palpebrale superius (R)	ps	Superior mid-portion of the free margin of upper Rt eyelid
	Palpebrale superius (L)	ps	Superior mid-portion of the free margin of upper Lt eyelid
	Palpebrale inferius (R)	pi	Inferior mid-portion of the free margin of upper Rt eyelid
	Palpebrale inferius (L)	pi	Inferior mid-portion of the free margin of upper Lt eyelid
Forehead	Glabella	g	Most prominent midline point between the eyebrows
Nose	Nasion	n	Deepest point of nasal bridge
	Pronasale	prn	Most protruded point of the apex nasi, identified in lateral view of the rest position of the head.
	Subnasale	sn	Midpoint of angle at columella base where lower border of nose and surface of upper lip meet.
	Alare (R)	al	Most lateral point on right alar contour.
	Alare (L)	al	Most lateral point on left alar contour.
Lips & Mouth	Labiale superius	ls	Mid-point of the upper vermilion line
	Labiale inferius	li	Mid-point of the lower vermilion line
	Crista philtri (R)	cph	Point on right elevated margin of the philtrum just above the vermilion line
	Crista philtri (L)	cph	Point on left elevated margin of the philtrum just above the vermilion line
	Cheilion (R)	ch	Point located at right labial commissure.
	Cheilion (L)	ch	Point located at left labial commissure.
Chin	Pogonion	pg	Most anterior mid-point of the chin.

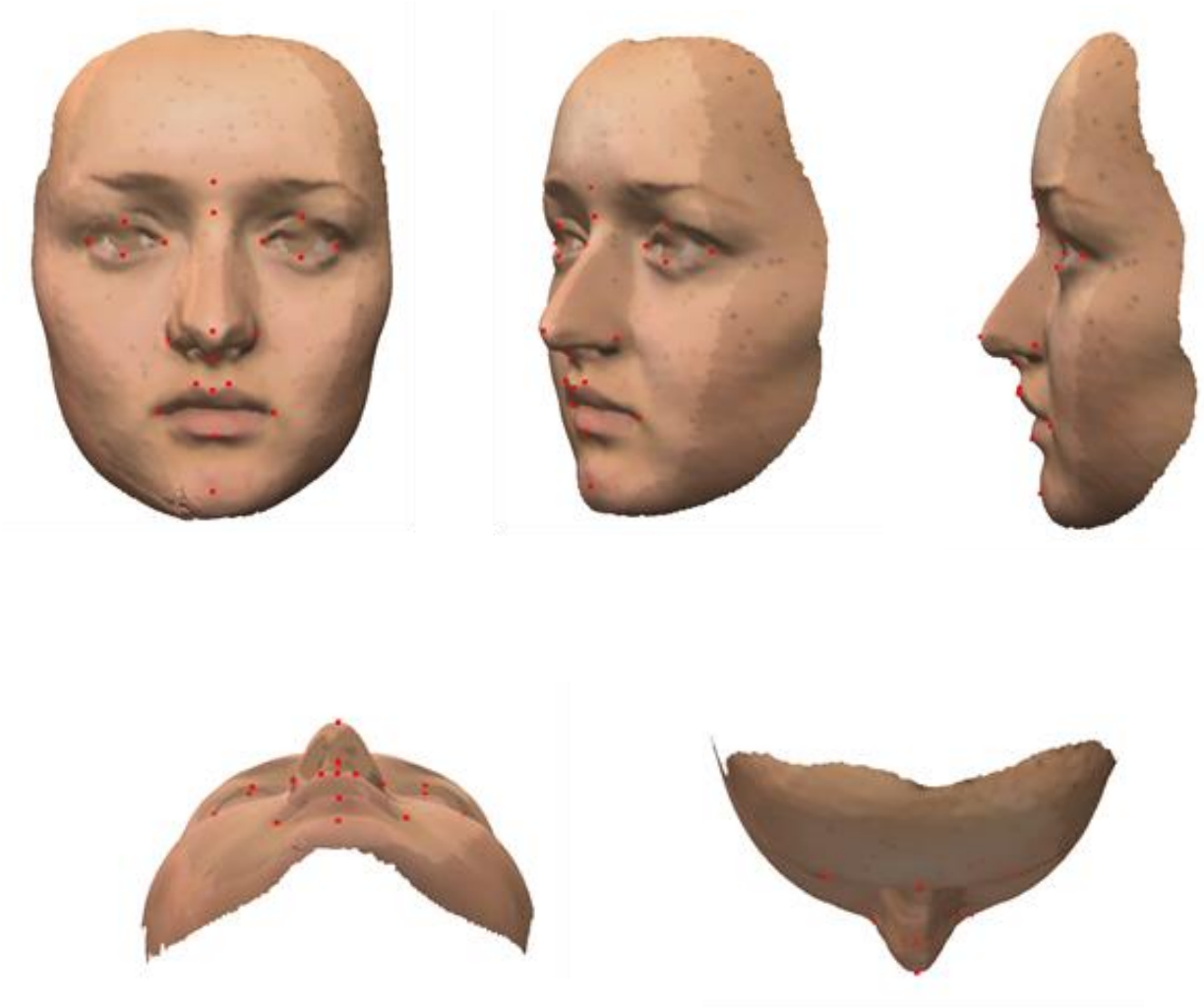


Figure 6.12: Three-dimensional position of each landmark was checked rotating the three-dimensional model of the face on the computer screen

Note: Several viewing positions were particularly important for the correct placement of landmarks.

6.7 Averaging Face Construction and Superimposition

The literature described the use of three-dimensional average faces to compare treatment changes among extraction with non-extraction cohorts (Ismail *et al.*, 2002) and to detect growth changes among children (Kau & Richmond, 2008).

Basically there are four methods of calculating an average shell which are: averaging in cylindrical radical direction; averaging in spherical radical direction; averaging in z-direction and local normal direction to a template (Kau & Richmond, 2010). In this study, the average shell was calculated using both averaging in spherical radical direction and local normal direction to a template. A four-iteration averaging procedure as described in Kau *et al.* (2005a) was used to produce the average face as follows:

- Pre-aligned normalized images for each group were loaded into Rapidform® and were aligned on the common frame of reference.
- The images were averaged in the radial direction of a sphere (iteration 1). The averaging was performed along the radial rays (straight lines from the centre of the sphere) to produce a mesh of averaged point positions (a point cloud). The point cloud was then triangulated to obtain an average facial shell, which was further improved by removing garbage to eliminate any errors and smoothing the shell to remove any sharp edges.
- The final average faces were obtained by three iterations of averaging on a pre-aligned template. The average face resulted from the first iteration was used as the template for further averaging (Kau & Richmond, 2010). This procedure was repeated three times (the average at the previous step was used as the template for the next step). The third-iteration average may be treated as true average for the selected method.

Orthodontists have widely used superimposition methods which are usually done on stable structures. However, it is difficult to determine a stable structure in a growing child. Different studies use different methods. Hajeer *et al.* (2002) identified anthropometric landmarks to line faces before using a procrustes best-fit method for analysing soft tissue changes. The superimposition technique used in this study is known as best-fit algorithm based on Zhurov *et al.* (2010). The best-fit algorithm is mathematically derived and essentially matches closely related triangular vertices of two similar surface shells and approximates them to one another. The resultant errors in distances corresponding to the two surfaces are averaged and shells are fitted together. Toma *et al.* (2008) found that mid-endocanthon is the statistically most reliable point and is therefore most suitable as the common origin.

Within each superimposition of average faces there is variability in the antero-posterior, vertical and transverse dimensions. For this reason, positive and negative changes are produced. Colour maps are an ideal method by which to illustrate this using a tolerance level of 0.25mm to highlight significant topographical facial differences. A tolerance of 0.25mm was used because it represents the mean of reproducibility error previously obtained from the validation investigations and takes into account mathematical and clinical error (Zhurov *et al.*, 2010).

6.8 Statistical Methodology

Various statistical tests have been used to test the research hypothesis that 'breathing disorders are significantly related to face shape measurements of 15-year old Caucasians. The methods used are given in more detail in each of the following chapters. Significant effects were defined in terms of statistical significance, p-values were taken to be significant if they fell below 0.05. Confidence intervals for differences that excluded zero were also deemed significant at the same level.

Multiple statistical tests such as t-test, Chi square, ANOVA, and logistic regression are used to compare the mean face shape measurements between the groups. The normality of face shape measurements was checked using frequency distribution histograms (symmetrical bell-shaped).

6.9 Impact of Tolerance Acceptance on Interpretation of Results

A tolerance of 0.5mm was considered acceptable to ensure consistency in the registration of facial scans and to increase the opportunity in finding small differences between breathing-disorder and control groups. Previous studies have demonstrated that by maintaining consistency in landmarking, employing a sufficiently large sample size and by using three-dimensional scanning, statistically significant phenotype-genotype associations between facial dimensions can be achieved ($p<10^{-8}$), even with relatively large registration and landmarking errors. Paternoster *et al.* (2012b) and Fatemifar *et al.* (2013) have demonstrated that this approach can be successful when applied to analysing face width (inner and exocanthi: *HMGA2*), mid-endocanthion point to nasion and glabella (*PAX3, AJUBA),* and subnasale to

alae (*ADK, VCL, AP3M1*). Although automatic landmarking has the potential to improve precision, some automatic landmarking algorithms currently show errors up to 4mm for some landmarks (Creusot *et al.*, 2013; Liang *et al.*, 2013). In the present study, potentially real differences were expected to be small relative to the sensitivity of the data measurements; therefore, the interpretations were based on 95% confidence intervals (95% CI) as opposed to p-values so that observed trends are considered valid (Gardner & Altman, 1986).

Chapter 7

Reproducibility of Facial Soft Tissue Landmarks

7.1 Introduction

Prior to commencing the research a reliability study was performed to assess the reproducibility of facial soft tissue landmarks using laser-scan three-dimensional imaging technology. This ensured that the researcher was able to accurately define facial landmarks and place them manually, as highlighted by Farkas (1994). Facial landmarks were assessed in 30 British Caucasian children aged 15 years who had been selected from the ALSPAC cohort. They included 15 males and 15 females, all of whom were subsequently included in the final analysis.

7.2 Methods

Twenty-one facial landmarks were placed manually on the three-dimensional facial images and the x, y, and z coordinates for each landmark were recorded by two examiners. The reproducibility of the identification of landmarks at 2-week intervals was assessed for the researcher (intra-examiner). In addition, the reproducibility of landmarks was assessed for two examiners (inter-examiner). Using Bland-Altman plots (Bland & Altman, 1986), both intra- and inter-examiner assessment evaluated the reproducibility of landmarks in three dimensions for the sample divided by gender.

The errors in landmark identification were expressed as a distance between two points (incorporating differences in x, y, and z) and broken down further for errors along each axis. The errors were categorized as: <0.5mm, <1mm, <1.5mm, and ≥1.5mm.

7.3 Statistical Analysis

Bland-Altman plots were used to illustrate the level of agreement between readings taken for each three-dimensional-coordinate (x, y, and z) of the 21 facial landmarks. These plots were conducted for both intra- and inter-examiner reproducibility assessments. For each Bland-Altman plot, the difference between readings for each landmark-coordinate was calculated and plotted against the average of the readings for that particular coordinate.

7.4 Results

The following classification was used to define reproducibility of the landmarks:

- The coordinates with differences between readings for all subjects of less than 0.5mm are classified as ‘very good’ coordinates.
- The coordinates with differences between readings for some subjects of 0.5mm or more but less than 1mm are considered as being ‘good reproducible’ coordinates.
- The coordinates with differences between readings for some subjects of 1mm or more but less than 1.5mm are considered as having ‘fair reproducibility’.
- The coordinates with differences between readings for some subjects of equal or greater than 1.5mm, considered as having ‘Poor reproducibility’.

Table 7.1 shows the results obtained for the intra- and inter-examiner reproducibility assessment for the total sample of 30 subjects. Numbers and percentages were given for the three-dimensional-coordinates showing the

reproducibility at the four levels (<0.5mm, <1mm, < 1.5mm, and ≥1.5mm). The majority of coordinates were reproducible to less than 1mm (intra-examiner 77%, and inter-examiner 78%). The highest reproducibility (<0.5mm) coordinates totalled 38% for the intra-examiner and 33% for the inter-examiner. The poorest reproducibility (≥1.5mm) coordinates constitute 1.5% for intra-examiner and 3.9% for inter-examiner.

Table 7.1: Reproducibility of landmarks identification (total sample)

Method of Assessment	**Intra-examiner (n= 30)**				**Inter-examiner (n= 30)**			
Reproducibility level (mm)	<0.5	<1	<1.5	≥1.5	<0.5	<1	<1.5	≥1.5
Number of coordinates	48	49	27	2	42	57	22	5
Percentages	38.0	38.8	21.4	1.5	33.0	45.0	17.4	3.9

Total number of coordinates=126

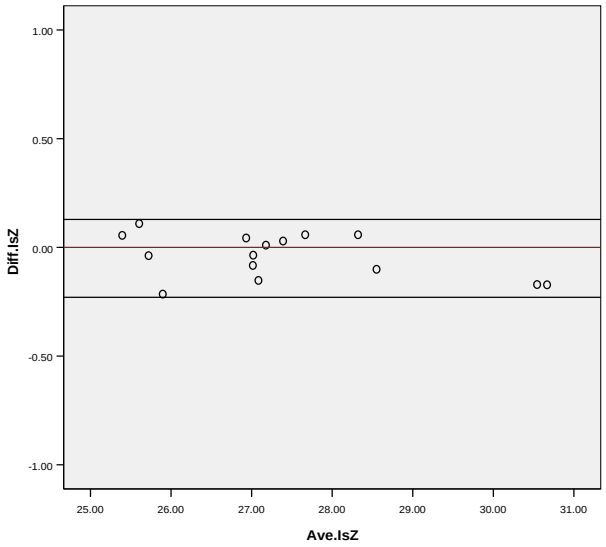
Examples are shown in Figure 7.1 for coordinates of selected landmarks to illustrate the very good, good, fair, and poor levels of agreement between readings taken for the coordinates on different occasions.

Figure 7.1a shows an example of a Bland-Altman plot obtained to assess the reproducibility of the landmark Labiale superius (ls) in the z-plane of the 15 males involved in the intra-examiner reproducibility assessment. The vertical axis of this plot shows the difference between the readings, whereas the horizontal axis shows the average of the readings. The (zero) line refers to subjects where the difference between the readings is equal to zero (highest reproducibility). The two black lines refer to the maximum differences exhibited between the readings. This plot shows the coordinate (labiale superius, z) has very good reproducibility, as the difference between readings for all subjects was less than 0.5mm.

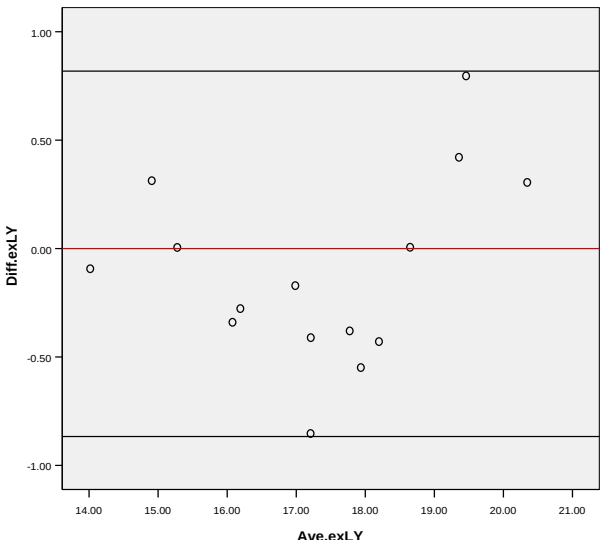
Figure 7.1b shows the Band-Altman plot obtained to assess the reproducibility of the landmark Exocanthion/Left in the y-plane for the 15 males involved in the inter-examiner reproducibility assessment. This plot shows the coordinate (Exocanthion/Left, y) has a good reproducibility, as the difference between readings for some subjects is 0.5mm or greater but is still less than 1mm.

Figure 7.1c shows the Bland-Altman plot obtained to assess the reproducibility of the landmark Endocanthion/Right in the y-plane for the 15 males involved in the inter-examiner reproducibility assessment. This plot shows the coordinate (Endocanthion /Right, y) has fair reproducibility, as the difference between readings for three subjects exceeds 1mm, but is still less than 1.5mm.

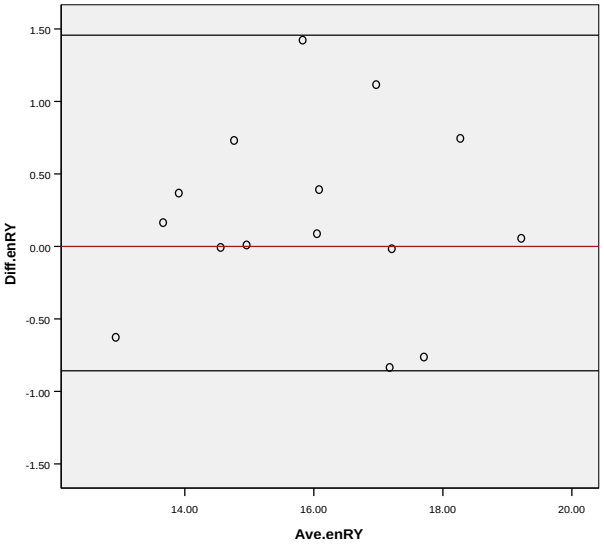
Figure 7.1d shows the Band-Altman plot obtained to assess the reproducibility of the landmark Alare/Left in the z-plane for the 15 males involved in the inter-examiner reproducibility assessment. This plot shows the coordinate (Alare/Left, z) has poor reproducibility, as the difference between readings for some subjects exceeds 1.5mm; however, the majority of the differences are within 0.5mm.



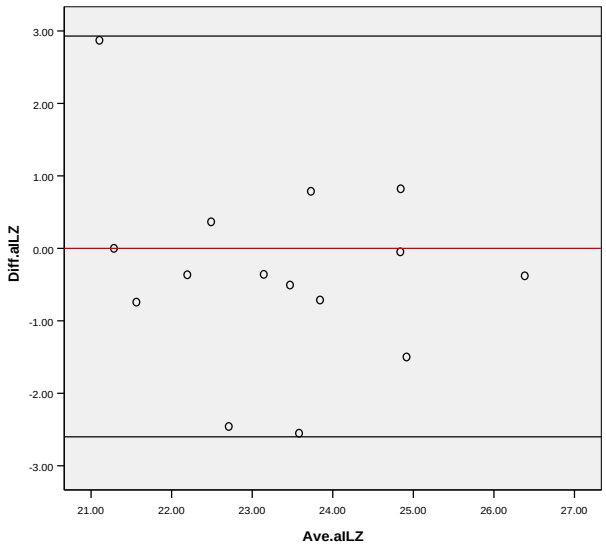
(a) Very good reliability (< 0.5 mm)



(b) Good reliability (< 1 mm)



c) Fair reliability (< 1.5 mm)



d) Poor reliability (> 1.5 mm)

Figure 7.1: Reproducibility of landmarks' identification (bland-altman plots)

Table 7.2: Reproducibility of landmarks' identification for both intra- and inter-examiner assessment

Intra-examiner								**Inter-examiner**							
Female (n=15)				**Male (n=15)**				**Female (n=15)**				**Male (n=15)**			
<0.5 mm	**<1 mm**	**<1.5 mm**	**≥1.5 mm**	**<0.5 mm**	**<1 mm**	**<1.5 mm**	**≥1.5 mm**	**<0.5 mm**	**<1 mm**	**<1.5 mm**	**≥1.5 mm**	**<0.5 mm**	**<1 mm**	**<1.5 mm**	**≥1.5 mm**
n=27	n=26	n=9	n=1	n=21	n=23	n=18	n=1	n=26	n=29	n=7	n=1	n=16	n=28	n=15	n=4
gX	gY	exRX	chRZ	Gz	gX	gY	alLZ	gX	gY	exRX	pgY	gZ	gX	nY	enRX
Gz	nY	exLX		Nx	enLY	nY		gZ	nY	exRZ		nZ	gY	enLZ	enRZ
nX	enLY	piRY		Nz	enLZ	enLX		nX	enLX	alRZ		piLY	nX	exRY	exLX
Nz	enRX	alLZ		psRy	enRX	enRY		nZ	enLZ	cphLX		piLZ	exLX	psRY	exLZ
enLX	enRY	alRZ		piLy	enRZ	exLX		enLY	enRX	cphRX		piRZ	enLY	psRZ	
enLZ	exLY	chLX		piLz	exLY	exLZ		enRY	enRZ	chLX		prnX	enRY	piLX	
enRZ	exLZ	chLZ		piRz	exRY	exRX		psLZ	exLX	ckLZ		prnZ	exLY	piRY	
psLY	exRY	chRY		Prnx	exRZ	psRX		psRX	exLY			alLX	exRX	snY	
psLZ	exRZ	pgY		Prnz	psLX	piLX		psRZ	exLZ			alRX	exRZ	snZ	
psRZ	psLX			snZ	psLY	piRX		piLY	exRY			IsX	psLX	alLZ	
piLZ	psRX			alLX	psLZ	piRY		piLZ	psLX			IsY	psLY	alRZ	
piRZ	psRY			alLX	psRZ	alRY		piRY	psLY			IsZ	psLZ	liY	
prnZ	piLX			IsY	prnY	alRZ		piRZ	psRY			cphLZ	psRX	cphLX	

snZ	piLY			IsZ	snX	cpLX		prnZ	piLX			cphRZ	piRX	cphRX	
alLX	piRX			liX	snY	chLY		snX	piRX			chRY	prnY	pgY	
alRX	prnX			liY	alLY	chRX		alLX	prnX			pgZ	snX		
alRY	prnY			liZ	IsX	chRY		Ally	prnY				alLY		
IsX	snX			cpLy	cpLZ	pgY		alLZ	snY				alRY		
IsY	snY			cphRy	cphRx			alRX	snZ				liX		
IsZ	Ally			cphRZ	chLX			alRY	lsX				liZ		
liY	liX			pgZ	chLZ			lsY	liX				cpLY		
liZ	cphLX				chRZ			lsZ	liY				cpRY		
cphLY	cphRX				pgX			cphLY	liZ				chLX		
cphLZ	chLY							cphLZ	cphRY				chLY		
cphRY	chRX							cphRZ	chLY				chLZ		
cphRZ	pgX							pgZ	chRX				chRX		
pgZ									chRY				chRZ		
									chRZ				pgX		
									pgX						

Table 7.2 first shows that the majority of the x, y, and z coordinates have "Good Reliability <1mm" (26 coordinates among females and 23 among males for intra-examiner reliability; 29 coordinates among females and 28 among males for inter-examiner reliability); followed by a group of coordinates with "Very Good Reliability <0.5mm" (27 coordinates among females and 21 among males for intra-examiner reliability; 26 coordinates among females and 16 among males for inter-examiner reliability); followed by coordinates with "Fair reliability <1.5mm" (9 coordinates among females and 18 among males for the intra-examiner reliability; 7 coordinates among females and 15 among males for the inter-examiner reliability); then, only a few coordinates were having "Poor Reliability ≥1.5mm" (1 coordinate in females and 1 in males for intra-examiner reliability; 1 coordinate in females and 4 in males for inter-examiner reliability). One hundred and twenty six coordinates (x, y, and z) were investigated for reliability for the 21 landmarks that were placed on the three-dimensional facial images.

Poorer reliability was more evident in the inter-examiner reliability assessment (5 coordinates) than in the intra-examiner reliability assessment (2 coordinates), and in males (4 coordinates) more than females (one coordinate) especially in points related to the eyes.

Table 7.3 ranks the landmarks from the most reproducible to the least reproducible for both intra- and inter-examiner reproducibility assessments. Each landmark was assessed according to the differences in readings taken on different occasions for the x, y, and z coordinates, using the following equation:

$$D= \sqrt{(\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2}$$

Where D is total distance, Δx is the difference in the x-axis, Δy is the difference in the y-axis and Δz is the difference in the z-axis.

Table 7.3: Ranking of facial soft tissue landmarks in respect to their reproducibility assessment in three planes of space (x, y and z)

Intra-examiner (n=30)				Inter-examiner (n=30)			
Rank	**Landmark**	**Average**	**SD**	**Rank**	**Landmark**	**Average**	**SD**
1	ls	0.48	0.22	1	ls	0.43	0.18
2	li	0.49	0.24	2	g	0.53	0.29
3	cphR	0.56	0.32	3	piR	0.54	0.37
4	prn	0.59	0.31	4	n	0.55	0.29
5	cphL	0.62	0.44	5	alL	0.57	0.38
6	piL	0.66	0.33	6	prn	0.61	0.27
7	n	0.66	0.39	7	piL	0.67	0.36
8	sn	0.66	0.32	8	cphL	0.68	0.48
9	g	0.67	0.4	9	cphR	0.68	0.34
10	enR	0.72	0.46	10	psR	0.7	0.41
11	psL	0.74	0.37	11	psL	0.75	0.43
12	enL	0.74	0.47	12	enL	0.77	0.68
13	psR	0.75	0.32	13	chR	0.79	0.35
14	piR	0.77	0.43	14	li	0.81	0.62
15	chL	0.88	0.5	15	alR	0.84	0.5
16	pg	0.88	0.51	16	sn	0.88	0.48
17	alL	0.94	0.72	17	exR	0.91	0.53
18	alR	0.96	0.56	18	enR	0.94	0.74
19	exL	1.05	0.61	19	chL	0.96	0.47
20	exR	1.06	0.64	20	exL	0.98	0.64
21	chR	1.11	0.74	21	pg	0.99	0.84

For each landmark, an average and standard deviation were calculated for the total sample (30 subjects) for both intra- and inter-examiner assessments. Generally, the accuracy of the different landmark identifications ranged from 0.43mm to 1.11mm. Eighteen landmarks were reproducible to less than 1mm for both intra- and inter- examiner assessments. The landmark Labiale superius (ls) was the most reproducible landmark (<0.5mm) for both intra- and inter-examiner assessments. The landmark cheilion Right (chR) was the least reproducible landmark for the intra-examiner assessment, followed by exocanthion Right and Left (exR, exL).

7.5 Discussion

Radiographs and photographs have been employed in previous studies for assessing the reliability of soft tissue landmarks. Two main shortcomings in the two methods are apparent: the risk of radiographic analysis, and the poor definition of three-dimensional structure on two-dimensional films. Both methods supply unreal data derived from the two-dimensional projection of facial landmarks.

The reproducibility of different soft tissue landmarks identified on the three-dimensional facial images of our sample was investigated. The reliability assessment results showed a variation between the landmarks placed on the face in relation to the:

- Method of reliability assessment (intra- and inter-examiner).
- Position of the landmarks on the face.

- Three planes of space (x, y, and z) identifying the exact position for each particular landmark on the face.
- Sex of the individual.

Generally, the results show that the majority of the x, y, and z coordinates have “Good reliability” (<±1mm), followed by a group of coordinates with “Very Good reliability” (<±0.5mm), and some coordinates showing “Fair reliability” (<±1.5), then a few coordinates showing “Poor reliability” (>±1.5mm). These finding are similar to previous studies by Gwilliam *et al.* (2006), Baik *et al.* (2007), Toma *et al.* (2009), Toma *et al.* (2012).

These results indicated that some landmarks were more reliable than others, suggesting that the reliability of each landmark might have an impact on the results. This would influence the sample size required in order to detect differences between breathing-disorder and control groups. Those coordinates with “poor reliability” were noticed more in the inter-examiner reliability assessment and in males more than females, especially in relation to landmarks identifying the eyes. The reason for the poor reliability is that even if the images were considered of good quality, the facial surface for some individuals might not have been completely captured, with voids evident in certain areas, particularly around the hairline, ears and eyes. In the case of the eyes, such voids were usually associated with highly reflective eyeballs and the laser absorbent eyebrows.

Soft tissue landmarks with relatively poor reproducibility in the y- axis were mainly due to the difficulty of placing those points accurately with the patient in a NHP in lateral profile. This requires good manipulation skills in order to

move the image to the correct position and also a strong clinical knowledge of NHP. As a result the points can be placed either too high or too low on the vertical axis. Consequently, in the x- and z- axes, the reliability was much better.

Other coordinates that showed variation from high to moderate reliability between females and males was primarily due to differences in soft tissue facial features between males and females. For example, points identifying the lips and mouth area of the face were easier to place for females than for males, due to relatively well-defined borders or edges exhibited in those regions of the females' face such as the philtrum.

7.6 Conclusion

Three-dimensional analysis of facial morphology is reliant upon manual landmarking or surface-based analysis of the three-dimensional surface imaging. Therefore, landmark identification must be within the limits of clinical acceptability. The study shows that the reproducibility of three-dimensional soft tissue landmarks varies depending upon both the assessor placing the landmark and the landmark being placed. Different facial landmarks have different degrees of reproducibility. Landmarks placed on gently curving slopes have a lower degree of reproducibility than those with well-defined borders. The majority of the x, y, and z coordinates taken for the 21 facial landmarks in the study were reproducible to less than 1mm, which is deemed to be clinically acceptable. The landmarks with up to 1mm reliability are the main ones throughout the study and are those which describe the main anterior-posterior, vertical and transverse relationships in facial shape

analysis. Those landmarks outside this range (for example, landmarks identifying the eyes) are included in the face shape analysis but significant findings related to those landmarks are cross-referenced to ensure their reliability.

Chapter 8

Asthma

8.1 Introduction

Asthma is a chronic disorder, characterised by the interaction of a number of asthma-related genes with numerous environmental factors. Asthma in children and young adults is more commonly associated with allergies (atopic asthma); however, asthma which occurs later in life is less obviously allergic and is more common in smokers. Asthma also occurs in industrial areas in response to inhaled proteins such as bakers' flour or particular chemicals (Cookson, 1999). The main characteristics of asthma include airway inflammation, intermittent airway obstruction, and bronchial hypersensitivity, not all of which are necessarily present in all patients to the same degree.

8.1.1 Definition of Asthma

The definition of asthma has been changed in line with the increased understanding of the immunological mechanisms of the disorder. A recent definition was published by the National Heart, Lung and Blood Institute (National Heart Lung and Blood Institute, 1995):

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cell, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial responsiveness to a variety of stimuli.

8.1.2 The Prevalence of Asthma

Asthma has a large geographical spread but ethnic susceptibility varies from 0.5% to 10% (Woolcock *et al.*, 1987; Turkeltaub & Gergen, 1991; Platts-Mills & Carter, 1997), due to the variation in the rates of self-reported asthma across

ethnic groups. In 2001, among persons reporting non-Hispanic blacks were most likely to report having asthma (with 8.5%), followed by non-Hispanic whites (at 7.2%), and other race non-Hispanics and Hispanics (both at 5.9 %) (Rhodes *et al.*, 2003).

Countries may also be classified based on their asthma rates into low incidence countries (Africa and Asia), medium incidence countries (USA, Canada, European countries and United Kingdom) and high incidence countries (New Zealand and Australia) (Anonymous, 1996).

During the period of most rapid somatic growth after infancy, the prevalence of asthma changes, it is reported that the prevalence of asthma is higher in males less than 15 years of age than in females of the same age range, and higher in females over 15 years of age than males in the same age range (To *et al.*, 1996; Krishnan *et al.*, 2001; Schatz & Camargo, 2003).

Differences in the prevalence and severity of asthma have been found between urban and rural areas. A rural life style is associated with a low prevalence of asthma. Exposure to farm animals and drinking unpasteurised milk provides protection for farmers' children (Riedler *et al.*, 2001). Studies have concluded that an environment rich in microbial organisms is beneficial in providing an infant resistance to asthma (Strachan, 1989). Keeley *et al.* (1991) found that in Zimbabwe exercise-induced asthma was associated with urban residency and high living standards. In addition, the offspring of Tokelauans who had migrated to New Zealand had an increased prevalence of asthma when compared to their relatives who remained in Tokelau (Waite *et al.*, 1980). In Japan, Cookson and Moffatt (1997) found that the prevalence of asthma has increased since the

population moved away from well-ventilated houses to Western-style buildings and a recent study assessing children in a city in former West Germany (Munich) and two cities in former East Germany (Halle and Leipzich) has shown that the prevalence of asthma was significantly higher in children in the former West Germany (von Mutius *et al.*, 1994). Thus, the prevalence of asthma appears to be subject to aspects of Westernization: the available data suggest an increase in asthma in the Western world since 1970 (Robertson *et al.*, 1991; Ninan & Russell, 1992; Peat *et al.*, 1994). It is unlikely that within such a short period of time, genetic make-up has contributed to the increased prevalence of asthma. Instead the situation can be explained in terms of the environment with increasing exposure to indoor or outdoor pollution, smoking and occupation or the reduction of many infectious diseases as a result of immunisation programs and high living standards (Newman-Taylor, 1995).

8.1.3 Asthmatic Phenotypes

Phenotype is defined as “the visible characteristics of an organism resulting from the interaction between its genetic makeup and the environment” (Encarta, 1999). A phenotype can vary dependent on interactions with environment. Thus, phenotypes can be defined by clinical or physiological criteria or by environmental triggers such environmental allergens.

However, instead of being a single disease asthma is a collection of different phenotypes. These phenotypes are categorised under ‘Asthma’ because they meet the simple criteria for the diagnosis of this disease. Asthma has been traditionally diagnosed on exhibiting appropriate symptoms such as wheezing, chest tightness or shortness of breath associated with airway obstruction and a

reversible airflow restriction. Clinicians recognise different phenotypes of asthma; however, biomarkers for the different phenotypes have not yet been identified.

Defining the phenotype properly is an important issue in genetic studies. Epidemiological and genetic studies assess asthma phenotypes by means of questionnaire data, bronchial hyperresponsiveness or reported doctors' diagnosis of asthma (Panhuysen *et al.*, 1998; Howard *et al.*, 1999). In large-scale studies, questionnaires are frequently used (Mensinga *et al.*, 1990). However, according to de Marco *et al.* (1998) there is a possibility of overestimating or underestimating the prevalence of asthma. Furthermore, there might be a misclassification with other obstructive lung disease which leads to a diagnostic bias (Martinez *et al.*, 1995). In addition, the variable age at onset and variable progression during lifetime, especially in adults, make the definition more difficult. Due to these problems and the lack of a properly defined asthma phenotype, researchers have shifted to measurable biological markers such as total immunoglobulin E, specific IgE against common allergen, bronchial hyperresponsiveness, eosinophilia, lung function and peak flow variability (Martinez, 1997).

Studies suggest that identification of the phenotype of an asthmatic patient can assist in the management of the disease. Therefore, a better way is required to improve our understanding of the underlying pathology and genetics that contributes to a particular asthma phenotype.

The following sections highlight the different categories that are used to describe asthma phenotypes.

8.1.3.1 Allergic Asthma

Allergic asthma is one of the most common asthma phenotypes, especially in childhood asthma, but is also frequently found in adults. Individuals exhibiting this phenotype usually experience their first symptoms in childhood with the interactions between genes and environment affecting the development of the innate and the adaptive immune systems and allergic sensation (Nicolaï, 2001). Triggering the early phase of the response occurs when an atopic individual encounters an allergen, and is characterized by the release of both preformed and newly synthesized mediators, such as leukotrienes, prostaglandins, histamine and cytokines. In turn, these produce bronchoconstriction and oedema. The late phase is characterized by the activation of lymphocytes and other inflammatory cells.

8.1.3.2 Aspirin-Sensitive Asthma

Asthma which is induced by aspirin and other nonsteroidal anti-inflammatory drugs is referred to aspirin-sensitive asthma and is the most easily identified phenotype due to the specificity of the trigger. The prevalence of aspirin sensitive asthma is likely to be in the 10-20% range of adult asthmatic individuals (Szczeklik & Sanak, 2006).

8.1.3.3 Glucocorticoid-Resistant Asthma: Resistant Inflammation

About 10% of asthma patients demonstrate poor response to glucocorticoid therapy, which is used to target sources of airflow limitation, increase mucus secretion and remodel airways. Individuals experience frequent exacerbations and continual symptoms limiting activity and quality of life (Wenzel, 2006). Decreased glucocorticoid receptors or the diminished capacity of the

glucocorticoid receptor to bind with DNA could induce glucocorticoid-resistant asthma.

8.1.3.4. Occupational Asthma

Occupational asthma may account for up to 15% of adult-onset asthma (Mapp *et al.*, 2005). It results from:

- The development of immunologically mediated sensitisation to the causal agent usually of high molecular weight, through the development of IgE antibodies
- The development of an immunologically mediated response to low molecular weight triggers without the formation of IgE antibodies
- The development of a non-immunological, rapid onset response following exposure to high concentrations of work place irritant chemicals (Mapp *et al.*, 2005)

Occupational asthma can recede if the patient discontinues exposure to the offending agent; however, once the process is established, the immunological phenotype can continue independently of exposure (Mapp *et al.*, 2005).

8.1.3.5 Asthma Defined by Age of Onset

The patient's age at which asthma is developed also differentiates phenotypes. Thus, simply by asking when a patient developed the symptoms of asthma can identify features specific to their disease. Patients with an early onset asthma, defined as onset before 12 years of age, are shown to have a greater likelihood of allergic sensation than patients with late onset (Miranda *et al.*, 2004). Also, patients with early onset asthma are more likely to have a family history of asthma. Generally, early onset asthma is a more homogeneous disease than late

onset asthma which is more likely associated with a mix of allergic, infectious and other environmental factors.

8.1.3.6 Asthma Occurrence through Lifespan

Although asthma can occur at any age, studies have shown that most patients with asthma experience their first symptoms before the age of five. Children with a family history of atopy and/or asthma have the highest risk of developing asthma. In addition, susceptibility in the child to develop asthma is strongly associated with the maternal history (Aberg, 1993; Litonjua *et al.*, 1998). Evidence also suggests that viral infections associated with wheezing can develop subsequent wheezing, bronchial reactivity, asthma and reduced pulmonary function (Bradley *et al.*, 2005; Fjærli *et al.*, 2005; Gern *et al.*, 2006).

Furthermore, research shows that air pollution can trigger symptoms in susceptible children. However, its contribution to the pathogenesis of childhood respiratory disorder such as asthma is still unclear. Many studies investigate traffic-related pollutants by analysing the prevalence of asthma in children living near main roads. The research finds an association between traffic-related pollution and asthma, allergy and respiratory infections, with reports of a higher prevalence of wheeze in children in association with traffic flow or proximity of residence to roads (Wjst *et al.*, 1993; Duhme *et al.*, 1996; Brauer *et al.*, 2007). Although this link is an important area of study, there is also an increased concern about exposure to air pollutants in the indoor environment such as tobacco smoke, nitrogen dioxide and formaldehyde and volatile organic compounds (VOCs) which are emitted from a broad range of sources such as cleaning agents, furnishings, paints, cosmetics, aerosol sprays and pesticides.

The present data on the health effect of this chemical mix is not yet firmly established but there is evidence to suggest that these exposures may be associated with wheeze in young children (Diez *et al.*, 2000; Rumchev *et al.*, 2004; Sherriff *et al.*, 2005).

Henderson *et al.* (2008) found an association between maternal exposure to household chemicals during pregnancy and different wheeze phenotypes in children when they were seven years old. Although studies by Henderson were able to show that the cumulative exposure to chemicals had an adverse effect on the wheezing pattern of a child, it was not possible to be sure that the observed effect was due to utero exposure or due to postnatal exposure.

Overall, the origins of childhood asthma are a complex interaction between genetics, environmental exposures, and immune and pulmonary system development.

8.1.4 Genetics of Asthma

Allergic disorders have long been known to run in families (Cooke & Veer, 1916) and family studies show evidence that genetic influences play an important role in the pathogenesis of asthma (Cooke & Veer, 1916; Schwartz, 1952; Ober & Yao, 2011). However, these studies failed to observe heritability in order to analyse the pattern of inheritance. During the 1980s, a new statistical method, 'segregation', was used to analyse the pattern of inheritance by observing how the trait is distributed in families, through comparing the number of affected individuals with the expected numbers under different genetic models that include dominant, recessive, mixed models and models with environmental influences (Khoury *et al.*, 1993).

Since the late 1980s, molecular genetics has been extensively developed, and is now widely used to identify genes that may cause asthma. It is hypothesised that different genes are responsible for causing this disease and therefore different approaches are used to detect the genes involved in asthma. Thus, genetic linkage is used to define the inheritance of genetic markers to establish linkage between a marker and the disease (Khoury *et al.*, 1993).

One approach is the candidate-gene which is a method that compares the phenotypes between cases with disease and controls, either within or between families (Manian, 1997) in order to investigate the association between regions of genes whose function may be relevant to the disease. In this context, chromosomal regions that may contain genes which contribute to asthma or associated phenotype have been identified by many genetic studies. For example, linkage for high levels of total IgE has been found on chromosome 5q (Meyers *et al.*, 1994; Doull *et al.*, 1996; Noguchi *et al.*, 1997), chromosome 11q (Cookson *et al.*, 1989; Moffatt *et al.*, 1992; Collée *et al.*, 1993) and chromosome 12q (Barnes *et al.*, 1996). Bronchial hyper-responsiveness, which is another asthma phenotype, has been shown to have linkage to chromosome 5q (Hall *et al.*, 1995; Postma *et al.*, 1995).

The genome-wide search positional cloning is a powerful method which could ultimately identify unique genes influencing the development of asthma and its related phenotypes. Positioning cloning is a process of identifying disease gene by finding the genetic region co-inherited with disease. This is achieved by studying genes that are likely to play a role in asthma and is based on existing knowledge on the pathophysiology of the disease. Four genome-wide screens

have contributed to a better understanding of the genes associated with asthma and related phenotypes. These studies have investigated different populations: Western Australia; the United Kingdom; the United States and families from the Netherlands (Daniels *et al.*, 1996; Ober *et al.*, 1998; Wiesch *et al.*, 1999). The outcome of these genome-wide screens provides evidence of linkage in more than one population involving the following chromosomes: 5q, 6p, 11q, 12q and 13q. Furthermore, five asthma gene complexes have been identified by positional cloning, including ADAM33, GRPA, DPP10, PHF11 and SPINK5 (Van Eerdewegh et al., 2002; Zhang et al., 2003; Laitinen et al., 2004). However, the mode of inheritance is still unknown, as is the identity of the genes which lead to the susceptibility of asthma.

The asthma study sample analysed in this study was recruited from the ALSPAC birth population cohort. As prospective data had been collected from parents during pregnancy, its validity for determining genetic effects on human phenotypes was justified (Pembrey, 2004). Furthermore, the ALSPAC data has been cross-validated against other large cohort samples, for example, the Rotterdam Study Cohort (Hofman 2009), and with genotype-phenotype data. In addition, the ALSAPC study has been identified as a model study for a proposed human phenome scan database, to complement genome scan databases (Freimer & Sabatti, 2003).

In summary, despite significant research efforts, the specific genes contributing to the development of asthma have not yet established. The complexity of genetic studies on a particularly complex disease such as asthma arises from different challenges by reason of phenocopies (identical phenotypes can be

attributable to different constellations of genes), the large number of genes involved, and the unknown mode of inheritance.

8.1.5 The Influence of Asthma on Face Shape

Patients with chronic asthma symptoms can show an increased resistance of the lower airways with gas-trapping in the chest (Chaves *et al.*, 2010). The altered mechanics of breathing associated with these changes can lead to the shortening of the cervical respiratory muscles, which, in turn, can alter head and cervical spine posture (Hruska, 1997; Lopes *et al.*, 2007). This may cause dysregulation in the growth and development of the orofacial structures, including a narrowing of the maxilla and a lower development of the mandible (Bresolin *et al.*, 1984; Solow & Sandham, 2002). The effects of atopy on face shape are also associated with mouth breathing. This occurs when environmental irritations cause swelling of the nasopharyngeal mucous membranes. As with asthma, mouth breathing can lead to an increase in face length (Tourne, 1990) and skeletal Class II facial profile (Jefferson, 2010).

8.2 Purpose

The aim in this chapter is to investigate differences in face shape in 15-year-old children taking part in a longitudinal follow-up study that were reported as having asthma at 7½ years of age and healthy children drawn from the same population.

8.3 Subjects and Methods

8.3.1 Sample

The children analysed in the present study were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) and had been diagnosed with asthma by their GP between the ages of 0 and 91 months. The diagnoses

were ascertained through postal questionnaires (see Appendix 6) sent to the parents or primary caregivers when the child was aged 7.5 years (Henderson *et al.*, 2008). The reliability of parent-reported diagnoses has been confirmed by Cornish *et al*. (2014). The cohort was recalled when the children were 15 years old and three-dimensional facial scanning was performed. Although body weight, height and BMI data were collected, a follow-up questionnaire regarding the presence of asthma or medication was not carried out. This was pre-determined by the ALSPAC study plan and therefore beyond the control of this study. It was acknowledged that repeat measurements and assessments associated with medical histories and treatment regimens would have benefited this research.

8.3.2 Facial Imaging

Three-dimensional facial images of the subjects were captured as described in detail in Chapter 5, using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), with a reported manufacturing accuracy of 0.1mm (Kau *et al.*, 2003). Three-dimensional facial images were processed and normalized within a reference framework. Twenty-one facial soft tissue landmarks were manually identified on each facial image (Toma *et al.*, 2009; Toma *et al.*, 2012) and the x, y and z co-ordinates were recorded.

The following soft tissue measurements were evaluated: exR-exL (inter-eye distance), al-al (nose width), n-pg (total facial height), Is-pg (lower face height), Is-men (mid face height), exR-pg-exL (mid face angle), s-sn-pg (face convexity), n-pr-sn (nose prominence), and prn-sn-Is (philtrum depth). The facial measurements included in the analysis were those which describe the main

anterior-posterior, vertical and transverse relationships in facial shape analysis. For example, the inter-eye distance and nose width allow transverse analysis. The face height (total, lower and mid) allows for vertical relationships to be studied. Finally, the mid-face angle, facial convexity, nose prominence and philtrum depth relate to anterior-posterior facial features. The facial measurements included in the analysis were the most common measurements reported that might be influenced by different modes of breathing (Bresolin *et al.*, 1983; Wenzel *et al.*, 1985; Kerr *et al.*, 1989; Harari *et al.*, 2010).

Average faces were superimposed on the mid-endocanthion point (men). Differences in morphology were presented using colour maps, with a tolerance level of 0.25mm to highlight significant topographical facial differences.

8.3.3 Statistical Analysis

The differences in weight, height, BMI and facial measurements between asthmatic and healthy children split by gender were estimated by t-test. This was carried out for male and female groups separately as evidence suggests that both gender and asthma prevalence can influence facial growth (Wenzel *et al.*, 1985; Kynyk *et al.*, 2011). In addition, Crouse and Laine-Alava (1999) indicate gender differences on nasal airflow rate and nasal cross sectional area. Average facial shells were created for the asthmatic and healthy females and males using a previously validated method (Kau & Richmond, 2010; Zhurov *et al.*, 2010).

8.4 Results

A total of 5253 children attended the clinic at age 15 years. Of this sample, participants were excluded from analysis due to: poor quality facial scans, non-Caucasian and obvious facial dysmorphology. The sample therefore represented

variation population-sample of 4784 Caucasian children, of whom 418 children were reported to have asthma at age 7½ years of age (Tagiyeva *et al.*, 2010). A total of 1862 participants (828 male, 1034 female) were selected for the healthy study sample, based on parent-responses to the study questionnaire and the criteria defined by Esteller *et al.* (2011).

Table 8.1: A summary of the statistics for height, weight and body mass index, and results of multiple independent samples t-tests

Facial Parameter	Male			Female		
	Asthmatic (N=233) Mean (SD)	Healthy (N=828) Mean (SD)	Mean difference (95%CI)	Asthmatic (N=185) Mean (SD)	Healthy (N=1034) Mean (SD)	Mean difference (95%CI)
Height (cm)	172.3 (7.71)	174.3 (7.39)	2.27 (1.36 to 3.42)	164.0 (5.84)	164.4 (6.01)	0.49 (-0.31 to 1.50)
Weight (kg)	61.8 (10.83)	64.1 (11.17)	2.39 (0.80 to 4.08)	61.2 (11.77)	58.5 (10.48)	-2.80 (-4.25 to -1.04)
(BMI)	20.7 (3.07)	20.5 (3.32)	0.21 (-0.23 to 0.66)	22.7 (3.84)	21.8 (3.51)	-1.01 (-1.65 to -0.57)

The means of weight (kg), height (cm) and BMI for males and females for both asthmatic and healthy children are shown in Table 8.1. The mean BMI was increased in asthmatic females when compared to healthy females and also to both asthmatic and healthy males. There was no significant difference in BMI between asthmatic and healthy males.

The summary data for the facial measurements used in this study are presented in Table 8.2. When comparing asthmatics with healthy children, there were no statistically significant differences in any of the nine facial measurements in males. In contrast, three of the nine facial measurements differed in females; nose width, mid-face height and mid-face angle. Females with an asthma history had on average 0.5mm wider nose compared with healthy females. The mid-face

height of asthmatic females measured from Is to men was on average 0.4mm shorter than healthy females and the mid-face angle of healthy females was more acute when compared to asthmatic females (51.2° compared to 51.7°).

Table 8.2: A summary of the statistics for facial measurements, and results of multiple independent samples t-tests

Facial Parameter	Male			Female		
	Asthmatic (N=233) Mean (SD)	Healthy (N=828) Mean (SD)	Mean difference (95%CI)	Asthmatic (N=185) Mean (SD)	Healthy (N=1034) Mean (SD)	Mean difference (95%CI)
Eyes Distance (mm) (exR-exL)	88.4 (4.27)	88.5 (4.07)	-0.10 (-0.65 to 0.46)	87.0 (3.60)	86.8 (3.96)	-0.45 (-0.96 to 1.92)
Nose width (mm) (al –al)	34.7 (2.86)	35.3 (2.51)	0.42 (-0.91 to 0.60)	32.7 (2.39)	32.0 (2.24)	0.51 (-0.71 to -0.04)
Total face height (mm) (pg-n)	104.3 (6.05)	104.2 (6.15)	-0.52 (-0.28 to 1.37)	98.9 (4.79)	99.1 (5.16)	0.13 (-0.65 to 0.88)
Lower-face (mm) (ls-pg)	37.5 (3.53)	37.9 (3.80)	0.37 (-1.28 to 0.91)	35.6 (2.93)	35.7 (3.12)	0.04 (-0.39 to 0.54)
Mid-face (mm) (ls-men)	63.8 (3.55)	64.7 (3.39)	0.48 (-0.01 to 0.92)	58.9 (2.93)	59.3 (2.96)	0.44 (0.04 to 0.93)
Mid-face (angle) (exR-pg-exL)	49.8º (2.70)	49.3º (2.71)	-0.23 (-0.65 to 0.10)	51.7º (2.71)	51.2º (2.65)	-0.41 (-0.81 to -0.02)
Face convexity (n-sn-pg)	180.4º (1.51)	180.4º (1.83)	0.09 (-0.15 to 0.33)	180.5º (1.53)	180.4º (1.64)	-0.07 (-0.30 to 0.18)
Nose prominence (n-prn-sn)	179.8º (3.17)	180.0º (2.76)	0.21 (-0.25 to 0.65)	180.2º (2.73)	179º.1 (4.63)	-0.06 (-0.53 to 0.41)
Philtrum depth (Prn-sn-ls)	127.5º (9.38)	127.4º (8.97)	-0.13 (-1.35 to 1.12)	127.7º (8.89)	126.9º (8.39)	-0.84 (-2.12 to 0.42)

The superimposition of average facial shells of asthmatic and healthy males showed no morphological differences whereas superimposing average asthmatic and healthy females facial shells confirmed the landmark measurements of a wider inter-ala distance. Differences of 0.4 to 0.5mm were recorded in the nose width (Figure 8.1).

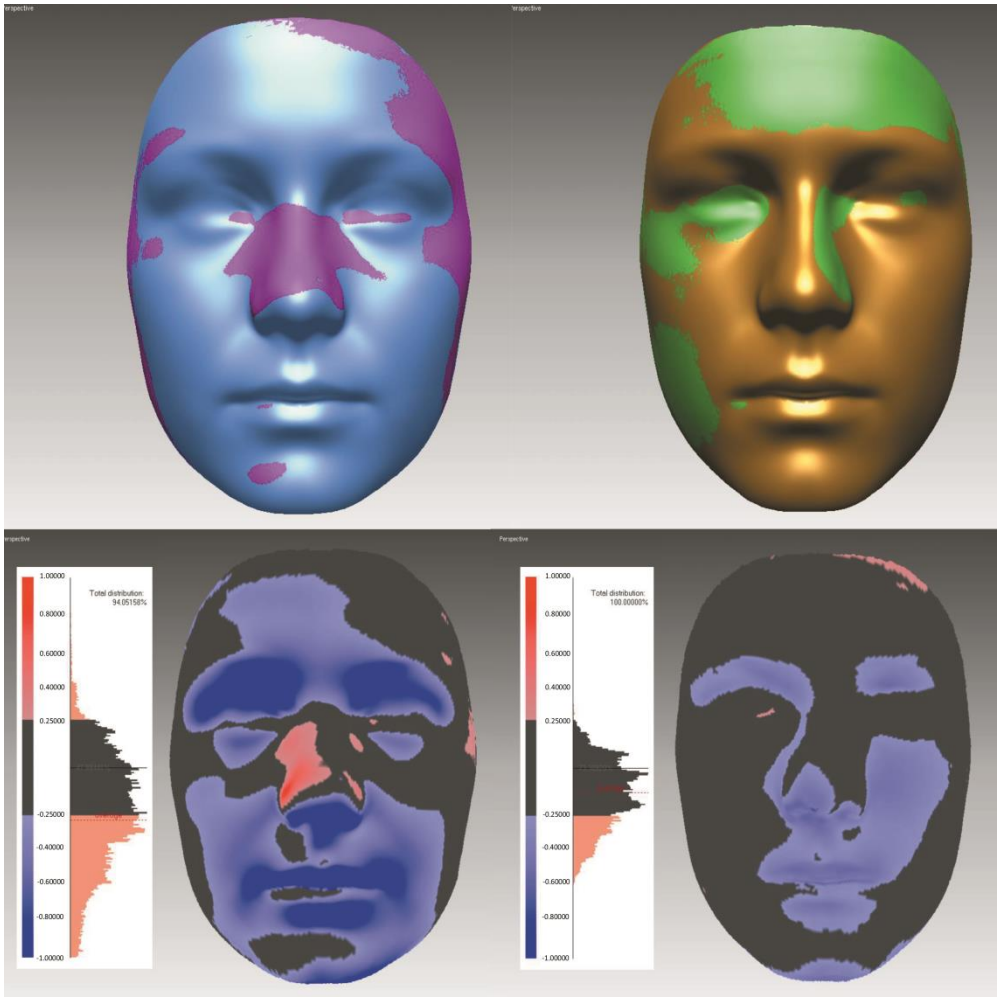


Figure 8.1: Superimposition of asthmatic (purple colour) and healthy (blue colour) average facial shells for females (left hand side) and males (right hand side) (green represents asthmatic males and the brown represents healthy males)

Note: The black area in the colour maps represents no difference in the asthmatic and healthy (0mm). The red areas are those prominent features in the asthmatic face – prominent and wider nose (0.4 to 0.9mm). The blue area indicates less prominent features in the asthmatic group (0.1 to 0.4mm).

8.5 Discussion

To understand the relevance of the results the underlying mechanisms of facial growth in the context of asthma should be considered. Moss (1997a) theorised that growth of the face occurs as a response to functional needs and is mediated by soft tissue in which the jaws are embedded. In simple terms, the soft tissues grow, and both bone and cartilage react. For example, the orbit grows as a result

of growth of the eyes and the cranium increases in size as a result of growth of the brain, which separates the cranial bones at the sutures while new bone passively fills in at these sites (Moss, 1997a). Nasal breathing encourages an increase in size of the nasal cavity in all directions with the floor of the nose developing in a downward and forward direction. Therefore the presence of any respiratory problems may affect normal craniofacial growth, which depends on normal physiological nasal breathing (Vig *et al.*, 1981; Solow *et al.*, 1984; Fricke *et al.*, 1993). Thus, it is argued that mouth-breathing in children results from pharyngeal obstruction (Oulis *et al.*, 1994), affecting the position of the craniofacial muscles and the mandible, leading to occlusal and skeletal alterations (Subtelny, 1954).

Suppression of growth secondary to asthmatic conditions has been suggested (Nelson & Drash, 1959; Falliers *et al.*, 1961; Russell, 1993; Doull, 2004). Studies suggest that growth retardation in asthmatic children may occur for a number of other reasons, including malnutrition (Snyder *et al.*, 1967; Murray *et al.*, 1976), chronic infection (Snyder *et al.*, 1967; Hauspie *et al.*, 1977), steroid therapy (Falliers *et al.*, 1961; Morris, 1975; Murray *et al.*, 1976; McCowan *et al.*, 1998; Price *et al.*, 2002), diminishing lung function (McNicol & Williams, 1973; Hauspie *et al.*, 1977), hypoxia (Murray *et al.*, 1976) and long-term stress (Hauspie *et al.*, 1977).

Several clinical studies support the theory of a relationship between head posture in breathing difficulties and craniofacial morphology (Solow & Tallgren, 1976; Thompson, 1978; Wenzel *et al.*, 1985). Wenzel *et al.* (1985) studied the craniofacial morphology in children with asthma from lateral skull radiographs of

a small sample of 50 asthmatic children with differing ages (6-16 years old) compared with 50 control children and concluded that small differences were found in craniofacial morphology between asthmatic children and controls. The severely affected children tended to have a greater change in morphology and were more likely to develop a retrognathic jaw associated with extension of the head.

Similarly, Bresolin *et al*. (1983) found that the upper facial height as well as maxillary and mandibular inclinations were increased in 30 mouth breathers and allergic children aged 6 to 12 years compared to 15 control children. In addition, they found that the mouth-breathing group was associated with retrognathism of the upper and lower jaws.

The studies by Wenzel *et al.* (1985) and Bresolin *et al*. (1983) were longitudinal, double blind, controlled studies. Both analysed data on children of both sexes and for similar age ranges (6–16 years and 6–12 years, respectively). In addition, their data was acquired using a variety of techniques. These approaches established the robustness of their data; however, their study samples were relatively small (100 and 45, respectively). In contrast, the sample in the present study comprised of 2922 children with breathing disorders and 1862 healthy children (Fig. 5.1). Furthermore, data was available from pre-birth until the age of 15 years at recall. Bresolin *et al.* (1983) evaluated dentofacial development in the mouth breathers with an allergy, whereas the children in this study were diagnosed as wheezing at the age of 7½ years. Moreover, the use of the three-dimensional imaging in this study provided improved accuracy and precision in the recording of face shape compared to anthropometry, cephalometry and

photography (Kau *et al.*, 2004; Kau *et al.*, 2005b). The conflicting findings between previous studies and the present study may be explained by differences in sample size, diagnoses and methods of recruitment and assessment, including age at recruitment.

The results show statistically significant differences in the facial measurements in asthmatic females compared to healthy females. In contrast, no significant differences were identified in asthmatic males. Previous epidemiologic studies of asthma have shown differences in asthma prevalence and severity related to age and gender; for example, the likelihood of developing asthma is approximately 10.5% greater in females than in males, with a significant increase in the severity of asthma in females after puberty (de Marco *et al.*, 2000; Kynyk *et al.*, 2011). This could explain why face shape differences between the asthmatic and non-asthmatic groups were greater for female groups than males. Although statistical significance was implied for some facial measurements in the female group, the linear differences were small; therefore their clinical significance requires further investigation. Research is continuing to explore the potential influences of female sex hormones, which have been associated with both asthma and craniofacial growth, increased bronchial hyper-responsiveness and altered perception of airflow obstruction (Kynyk *et al.*, 2011).

We found a slightly increased nasal width (al-al) in asthmatic females and presume that the size of the nasal airway is related to body size in general as BMI values of asthmatic females were slightly larger than males in this study. However, previous studies in children and young adults indicate that BMI has an effect on airflow rate and nasal airway size (Laine-Alava & Minkkinen, 1997;

Crouse & Laine-Alava, 1999). Laine-Alava and Minkkinen (1997) found that the values for airflow rate tended to rise with the increasing BMI, indicating that subjects with larger body size need higher air volumes. Therefore, asthmatic females showed an increased nasal cross sectional area.

The other significant finding in this study was shorter mid-face height in asthmatic females. The lack of detection of any facial differences in males may be explained by significant facial variation as a result of achieving different stages of facial growth as a result of pubertal changes which may mask any underlying condition effect.

Cephalometric investigations on longitudinal samples identify a pubertal spurt in craniofacial growth that is characterized by wide individual variations in onset, duration and rate (Nanda, 1955; Hunter, 1966; Ekstrom, 1982). Generally puberty starts in females approximately two years before males and is shorter in duration. The mean peak height velocity occurs at around 12 years of age in females and 14 in males. This could explain why males showed no morphological differences between the asthmatic and healthy groups as facial measurements were analysed at the age of 15 years old which coincides with male's pubertal growth spurts. This would suggest that time plays a crucial role in the assessment of the influence of medical conditions such as asthma on face shape and the best timing for an assessment would be around 7-10 years old as males and females have similar growth rates (Figure 8.2). The cohort is continuing to be followed and probably at 20 plus years of age (when facial growth has ceased and patients will have been on steroids the longest) may be the most appropriate time to assess the differences.

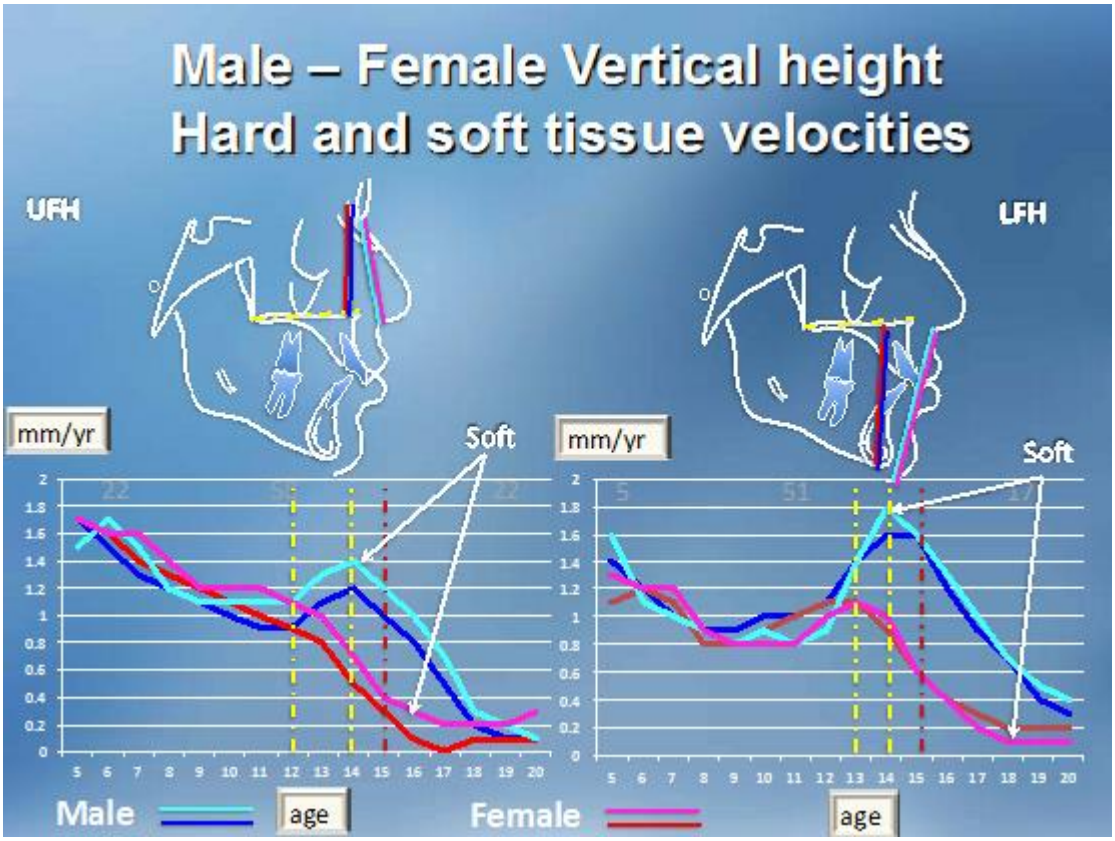


Figure 8.2: Soft and hard tissue velocities in relation to upper and lower face height

Note: Both males and females show similar steady growth velocities (1 to 1.2 mm/year) from 7 to 11 years of age.

Source: Bhatia & Leighton, (1993).

8.6 Limitations

One of the limitations of the study is that the severity of asthma and the type of medication (i.e. inhaler or oral steroid) were not recorded. However, previous research indicates they these factors may only have small influences on craniofacial growth and shape (Hauspie *et al.*, 1977; Russell, 1993; Price *et al.*, 2002; Doull, 2004). The loss to the follow-up group was 34% which is considered acceptable for a longitudinal study of this size (Fewtrell *et al.*, 2008). However, the composition of this group is unknown and therefore potentially asthmatic children may have been lost to the study. In addition, the study only recorded three-dimensional facial shape at 15 years; therefore it is unknown at what age or

when the differences in face shape developed. As stated previously, differences in facial shape resulting from breathing disorders can be subtle in relation to other genetic and environmental factors. As such, they can be smaller than the resolution of the measurements. In order to reduce these effects, a large study sample was recruited from the ALSPAC cohort and advanced three-dimensional imaging technologies were utilised to enhance the reproducibility and accuracy of the findings. Furthermore, 95% confidence intervals (95% CI) were applied to identify valid patterns and trends in the data (Gardner & Altman, 1986).

Despite these limitations, the results of the study are based on a population cohort of UK children that is broadly representative of the general population. In addition the imaging method is valid and therefore the methods are transferrable to other population groups (Kau *et al.*, 2005b).

8.7 Conclusion

The research method provides a framework for the investigation of medical conditions and environmental factors that can influence child's health and development using three-dimensional facial imaging.

The study found:

- Statistically significant differences between asthmatic and healthy females; inter ala width was 0.5mm wider and the face height was 0.4mm smaller in asthmatic females.
- There were no statistical differences in facial measurements for asthmatic and healthy males.

- Three-dimensional facial imaging has sufficient resolution to detect small differences in facial morphologies and can be used to explore genetic and environmental effects on face shape.

Chapter 9

Atopy

9.1 Introduction

The term ‘Atopy’ is poorly defined in the literature, but is generally accepted as referring to groups of allergic conditions which are commonly seen to cluster in family groups. It includes hay fever (allergic rhinitis), eczema, and a variety of other specific and non-specific allergic states (Asher, 2011). In recent literature, atopy has been defined as the tendency to develop immunoglobulin E (IgE) antibodies to commonly encountered environmental allergens (Jarvis & Burney, 1998; Mouthuy *et al.*, 2011). In common clinical practice, the IgE is detected by skin prick testing, although in complex cases, serum levels can be used (Postma *et al.*, 2011).

9.1.1 The Prevalence of Atopy

The prevalence of atopy is hard to estimate, as it is almost certainly under-diagnosed. Downs *et al.* (2001) pointed out that it is now more confidently diagnosed and reported and therefore the apparent incidence is increasing, but this may simply be as a result of improved diagnosis. An overview of the literature highlights that atopy is currently diagnosed in the region of 85-88% in 8-11 year olds of the general population (increasing from about 70% two decades ago) (Downs *et al.*, 2001). This age group represents the peak incidence, as prevalence drops to about 11-15% by the age of 20 years (Anstatt *et al.*, 2003).

9.1.2 Signs and Symptoms of Atopy

The signs and symptoms depend upon the particular manifestation of atopy encountered. Classically, the patient will usually have a positive history of asthma, allergic rhinitis, eczema or hay fever and occasionally urticaria and this is also likely to be found in close relatives. If asthma is the primary manifestation,

the patient as a child will usually exhibit nocturnal wheezing, wheezing during exercise or excessive wheezing when they have a chest infection. This can vary from trivial to life threatening. The majority of cases will subside by adulthood.

9.1.3 The Diagnosis

Diagnosis is generally made on clinical suspicion, a positive family history and various pathophysiological tests including the demonstration of skin reactivity, specific and total levels of IgE greater than 120 IU/ml being considered diagnostic (Bodner *et al.*, 2000).

Development of atopic responses has been linked to several genes and gene products (Steinke *et al.*, 2008). Thus, atopic diseases represent a complex gene and environmental interaction in which environmental antigens interact with the immune system, producing atopic (IgE) responses (Peden, 2000).

9.1.4 The Influence of Atopy on Face Shape

The relevance of atopy in facial growth is that environmental stimuli and irritations may cause chronic swelling of the nasopharyngeal mucous membranes in atopic individuals. Obstruction of the nasal airway due to atopic allergy can therefore be associated with mouth-breathing and facial anomalies, including malocclusions such as increased overjet, a higher palatal plane, narrowing of both upper and lower arches and proclination of incisors (Ricketts, 1968; Linder-Aronson, 1970, 1974; Koski & Lähdemäki, 1975; Faria *et al.*, 2002; Jefferson, 2010).

The effect of atopy on craniofacial structures (determined cephalometrically) was studied in one hundred 11-year-old school children and indicated a backward rotation of the mandibular body and an anterior lowering of the nasal floor in the

moderate and severe nasal allergy groups. Differences were more pronounced in children exhibiting atopy and enlarged adenoids (Hannuksela, 1981).

Cephalometric analysis was also undertaken for 30 chronically allergic mouth-breathing subjects and 15 nonallergic nose breathers ranging in age from 6 to 12 years (Bresolin *et al.*, 1983). The findings revealed that the upper anterior facial height and the total anterior facial height were significantly larger in the mouth breathers. In addition, the maxilla and mandible were more retrognathic in mouth breathers, while the maxillary intermolar width was narrower in the mouth breathers and was associated with a higher prevalence of posterior cross-bite.

9.2 Purpose

The aim of this chapter is to investigate the influence of atopy on face shape using three-dimensional laser scan imaging technology and to assess the null hypothesis that there is no difference in facial shape in atopic and healthy Caucasian children.

9.3 Subjects and Methods

9.3.1 Sample

As indicated previously, the children involved in this study were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) (see Chapter 5). The same study sample was also employed to investigate allergic rhinitis (Section 10.3.1). All children were invited to attend a clinic at 7½ years of age, where skin-prick tests were performed in relation to a panel of six allergens (house dust mite, cat, mixed grass, mixed nuts, peanut and milk) with positive (1% histamine solution) and negative (diluent) controls (Henderson *et al.*, 2008). Skin tests were carried out on the anterior surface of the left arm using new disposable sterile

lancets for each allergen tested. The skin was pricked through a drop of allergen solutions which were blotted off after five minutes and the results were read after a further ten minutes (Henderson *et al.*, 2008). The maximum wheal diameter was measured and a second measurement performed at 90º to the first and the mean wheal diameter was calculated. Atopy was defined in the tests as a positive skin-prick test to the allergens with a weal diameter ≥1mm with negative diluents (Henderson *et al.*, 2008).

The cohort was recalled when the children were 15 years of age where three-dimensional laser facial scans were taken. Body weight and height were also measured for all children. The final sample in this study consisted of 734 atopic and 1862 healthy children.

9.3.2 Facial Imaging

As described in Chapter 6, three-dimensional facial images of the children were captured using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), with a reported manufacturing accuracy of 0.1mm (Kau *et al.*, 2003) and the same process followed as in Chapter 8 but on this occasion in relation to atopic children.

9.3.3 Statistical Analysis

A chi-square test was used to examine the association of atopy with gender. To compare the facial features of atopic and healthy children, independent t-test, 95% confidence intervals of the differences in the facial measurements were used.

9.4 Results

The sample consisted of 2596 Caucasian children with no obvious facial dysmorphology, of whom 734 were recorded as atopic at age 7½ years (Henderson *et al.*, 2008). Despite differences in growth rates between males and females, atopy was not found to be significantly associated with gender (p=0.275), with the proportion of males and females with atopy at 15.4% and 13.8%, respectively. The mean BMI of the sample was within the range (21.2 kg/m²; reported normal range 17 kg/m² to 22.3 kg/m²) (Cole *et al.*, 1995, 1998) with no significant differences between the atopic and the healthy group (mean difference (95% CI) in BMI: 0.47(-1.06 to 0.69); p=0.735)

Table 9.1: Summary of the statistics of three-dimensional co-ordinates

	Atopic (n=734)		Healthy (n=1862)		Mean Difference	95% CI
	Mean	SD	Mean	SD		
Eyes distance (mm) (exR-exL)	87.4	3.97	87.6	4.03	0.07	-0.26 to 0.38
Nose width (mm) (al-al)	33.8	2.86	33.7	2.59	-0.19	-0.40 to 0.03
Mid-face (mm) (ls-men)	62.0	4.22	61.4	3.93	-0.44	-0.79 to -0.12
Mid-face (mm) (sn-men)	48.5	3.69	48.1	3.33	-0.43	-0.71 to -0.13
Mid-face (mm) (n-sn)	52.6	3.94	52.2	3.83	-0.40	-0.65 to -0.02
Total face height (mm) (pg-g)	114.2	6.38	113.5	6.13	-0.63	-1.08 to -0.05
Total face height (mm) (pg-men)	94.1	5.85	93.4	5.64	-0.61	-1.03 to -0.11
Face convexity (angle) (n-sn-pg)	162.0	5.51	162.4	5.49	0.43	-0.05 to 0.83

Generally, the measurements describing transverse distances and the anterior-posterior features in atopic children did not differ significantly from the healthy group (Table 9.1). However, all the measurements that describe vertical relationships showed significant differences between the two groups. Both total

anterior face height (pg-g, pg-men) and mid-face height (ls-men, sn-men, n-sn) were longer (0.6mm and 0.4mm respectively) in atopic children when compared to healthy children.

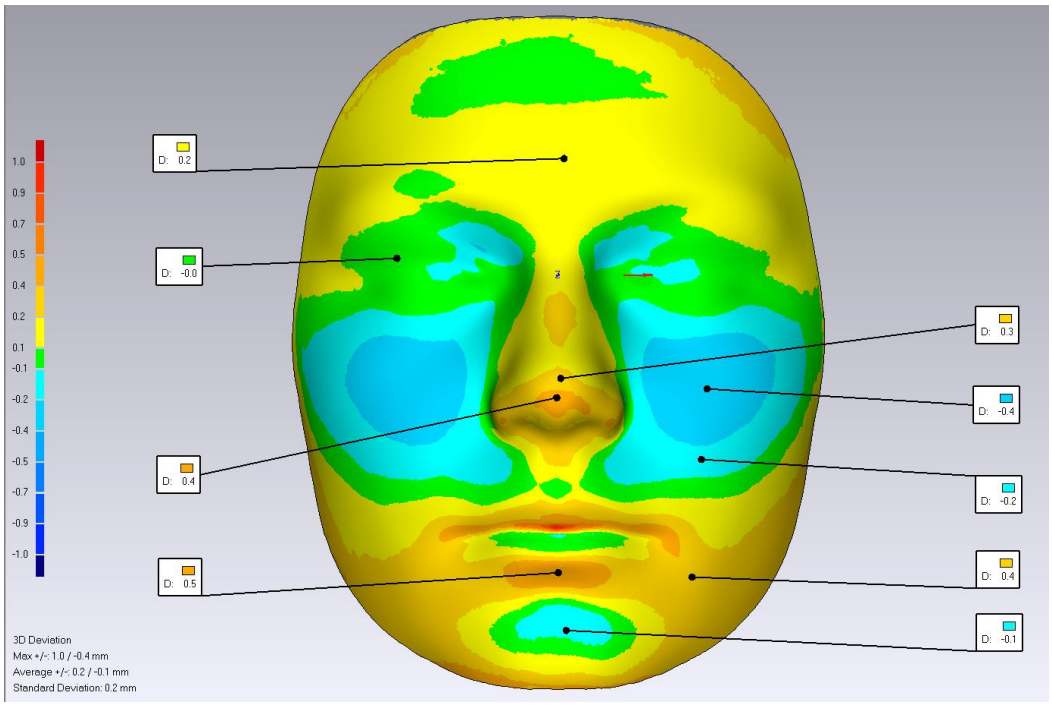


Figure 9.1: Superimposition of atopic and healthy facial shells

Note: Green represents no difference in the atopy and healthy groups (0mm). The blue area indicates less prominent cheeks and chin point in the atopic group (0.1 to 0.4mm); the deeper blue representing greater facial retrusion when compared to the atopic group (>0.4mm). The yellow areas are those prominent features in the atopic face – prominent forehead, nose, lower lip and wider forehead, nose and lower jaw (0.1 to 0.5mm).

The superimposition of average facial shells of atopic and healthy children showed a significant morphological difference between the groups in the z direction. The direction of the differences for the average facial shells for the atopy and healthy groups are shown in three presentations of colour deviation maps (Figure 9.1). The cheeks and chin are less prominent in the atopic group and the atopic children showed an increased nose width (0.49mm) when compared to healthy children.

9.5 Discussion

This study is the first to investigate the influence of atopy on face shape in a large cohort of 15-year-old children using three-dimensional facial imaging. Currently available three-dimensional soft tissue imaging technologies allow clinicians to evaluate facial differences as a result of medical and surgical interventions. The three-dimensional laser scanning system has the advantage of being quick, non-invasive and easy to use, unlike other three-dimensional hard tissue imaging systems such as Cone Beam Computed Tomography (CBCT) and Magnetic Resonance Imaging (MRI) which are both expensive, time-consuming, while CBCT presents a radiation risk (Kau *et al.*, 2007). The present study confirms that a laser scanner can be used in large-scale population studies and is able to detect small facial differences (0.6mm) in atopic children who had longer faces when compared to non-atopic children.

While craniofacial morphology is primarily determined by inherited features (Carlson, 2005), environmental stimuli also markedly influence the growth of the bones, as for instance in patients with partially or totally obstructed nasal airways (Dunn *et al.*, 1973; Kilic & Oktay, 2008). Atopic conditions are associated with the chronic swelling of the nasopharyngeal membrane which can affect normal breathing (Hannuksela, 1981). The mode of breathing and its effect on craniofacial growth has been a controversial issue within orthodontics for decades. It has been described that obstructed nasal breathing leads to mouth-breathing and the so called ‘adenoidal face’ (long face syndrome) with an increased anterior face height (Subtelny, 1954; Linder-Aronson, 1970; Bresolin *et al.*, 1983; Chaves *et al.*, 2010). This craniofacial development has been

explained by changes in the muscular balance. Mouth-breathing leads to a lower tongue position in the oral cavity which will alter the force balance from the cheeks and tongue. In turn, this may be associated with an increased anterior face height, a steep mandibular plane angle resulting in a retrognathic mandible. In addition incompetent lips, a narrow upper dental arch, retroclined mandibular incisors are also seen in children with reported mouth-breathing compared with healthy controls (Solow & Kreiborg, 1977; Linder-Aronson, 1979; McNamara, 1981; Solow *et al.*, 1984).

The findings in Chapter 8 show shorter mid-face height in asthmatic females (0.4mm) compared to healthy children. The conflict with results in this chapter could be explained by the fact that the relationship between atopy and asthma is not straightforward (Carroll *et al.*, 2006). The available epidemiological evidence suggests that the proportion of asthma cases that are attributed to atopy is less than one half indicating that the importance of atopy as a cause of asthma in individuals may have been over emphasised (Pearce *et al.*, 1999).

Although the observed differences (0.4–0.6mm in the vertical plane) were smaller than the errors associated with the measurements, interpretations were based on 95% confidence intervals (95% CI), ensuring that valid trends could be identified (Gardner & Altman, 1986). In addition, the strategies adopted in the study design involved a large study sample recruited from the ALSPAC cohort and three-dimensional scanning technologies with high reproducibility (Kusnoto & Evans, 2002; Kovacs *et al.*, 2006). Support for the reliability of these technologies in identifying associations between facial parameters and genetic influences was demonstrated by Fatemifar *et al*. (2013).

The findings of the present study are consistent with the proposed possible contribution of environmental stimuli such as atopic allergic conditions and breathing difficulty on craniofacial growth and morphology.

9.6 Limitations

The diagnosis of atopy was undertaken when the patients were aged 7½ years, but the facial imaging was done when they were aged 15 years and it is not known if the severity of atopy was the same over the period, However, studies suggest that severity of atopy (in this case early-onset atopy) does not change significantly over time (Peat *et al.*, 1990).

9.7 Conclusion

The results of this study indicate that face shape differences were present in atopic children compared with matched group. The major features included increased mid-face height and total anterior face height. The research methodology provides a framework for the investigation of environmental factors that can influence craniofacial development using a three-dimensional facial imaging.

Chapter 10

Allergic Rhinitis

10.1 Introduction

Rhinitis is described in a number of ways including allergic, non-allergic, seasonal and perennial. By definition, the condition is the “acute or chronic, intermittent or persistent presence of one or more nasal symptoms including runny nose (nasal discharge), itching, sneezing, and stuffy nose due to nasal congestion” and it affects 30% of the UK population (Sin & Togias, 2011). Rhinitis can be a normal response to certain stimuli. On occasions, symptoms can become so persistent that the individual seeks medical advice, thereby medicalising what may be a normal condition. This makes estimates of the prevalence very unreliable, as some individuals will tolerate a high degree of symptomatology while others will expect to have the most minor conditions treated. In essence, there is a blurred boundary between health and disease (Ozdoganoglu & Songu, 2012). Like atopy, this condition appears to have a peak incidence in childhood with a lower incidence in adult life. Researchers such as Lee *et al.* (2003) have observed that the incidence may actually remain the same but the smaller nasal passages in the child may become more easily obstructed and therefore become more clinically obvious. The non-allergic forms are actually a number of heterogeneous conditions, most of which are associated with irritants. These have been termed ‘rhinopathies’. However, the allergic forms of rhinitis are by far the most common.

Consideration of the pathophysiology shows that there is a sensitisation of the T and B lymphocytes in the nasal mucosa and a subsequent production of IgE which circulates in the peripheral blood and attaches itself to mast cells throughout the body. Nasal exposure to the specific allergen triggers an allergic

cascade of inflammatory mediators secondary to mast cell rupture, which is responsible for the manifestation of the allergic symptoms. The inflammatory reaction causes localised oedema in the nasal mucosa which, together with the nasal discharge, can severely reduce airflow through the nasopharynx. The nasal mucosa becomes 'primed' by this reaction and subsequent exposure tends to be of greater severity for the same degree of stimulus. Certain patients become severely hyper-responsive to airborne allergens and can be quite badly disabled by this condition (Westergaard *et al.*, 2005).

10.1.1 Diagnosis

The diagnosis of allergic rhinitis is not always easy, especially in children, due to variations in symptoms during the year and the non-recognition of symptoms by patients. Furthermore, the symptoms are shared by several diseases from wide-ranging aetiology making diagnosis harder.

Diagnosis can be made by the demonstration of high levels of serum IgE to specific antigens or by a nasal allergen challenge. However, in practical terms, it is usually diagnosed by a response to anti-allergic treatment without resorting to complex and relatively expensive tests. An analysis of family history of atopy, chronicity or recurrence of symptoms and the presence of family history of allergy (dermatitis, eczema, asthma, food hypersensitivity, chronic otitis, sinusitis or chronic cough) helps to understand the allergic etiology. It is also useful to question the environmental characteristics of the place where the child lives. Knowledge of the triggers of symptoms is crucial in the diagnosis of rhinitis. Infectious rhinitis in children is caused by a long list of viruses or bacteria, and can be a frequent complication after a viral process. Symptoms of infectious

rhinitis are nasal symptoms such as sneezing and nasal congestions (preceded by other symptoms by 1-2 days), sore throat; mild "scratchy" sensation, eye burning, dry non-productive cough (40-60% of patients) and low grade fever and are often mistaken for allergic rhinitis. In contrast, allergic rhinitis symptoms are nasal discharge, sneezing, itching and nasal blockage (Crystal-Peters *et al.*, 2002).

The immunological mechanism of allergic rhinitis is very similar to atopy. The release of chemical mediators (histamine, leukotrienes, etc.) originating in the activation of mast cells, sensitized with allergen-specific IgE, is responsible for the patient's symptoms. Allergic disease has two distinct stages: a) awareness (genetic predisposition), and b) the presence of symptoms (host-environment interaction).

In the first stage, there must be a susceptible host to induce an immune response to allergens to generate a genetic basis to produce IgE, and able to sensitize the mast cell. In the second stage, activation occurs that triggers the inflammatory process in two stages: immediate (dependent of chemical mediators and cytokines) within minutes of contact and late-dependent cellular infiltrate (eosinophils, neutrophils, mast cells).

This activation of the system generates interactions with neurogenic vascular symptoms. Therefore, the microscopy of the nasal mucosa of patients with allergic rhinitis displayed infiltration of the inflammatory cells (mast cells, basophils, eosinophils, neutrophils and T lymphocytes). These cells play a critical role because they are the source of chemical mediators that modulate the

inflammatory process and consequently the symptoms. The main chemical mediators that play a central role in triggering symptoms are:

- Histamine is the main mediator in the immediate phase of allergic reaction after the antigen challenge. Histamine acts on H1 receptors of various cells and causes the main symptoms of rhinitis.
- Leukotrienes are formed from arachidonic acid by the lipoxygenase pathway, released mainly by mast cells in the early phase and by eosinophils and neutrophils in the late phase. Leukotrienes cause blockage and increased secretion, but not sneezing.
- Cytokines are released by T cells during the late phase reaction and are important in maintaining the chronic inflammation.

10.1.2 The Influence of Allergic Rhinitis on Face Shape

Relatively little quantitative research has been conducted on the craniofacial morphometric anomalies that may be directly related to the pathogenesis of allergic rhinitis in childhood. However, it has been known for many years that dysfunctional airways in childhood associated with an inability to breathe through the nose, lead to mouth-breathing, which can detrimentally influence craniofacial growth, resulting in facial anomalies in adolescence and adulthood. Mouth-breathing has been associated with maldevelopment of the jaw, including a retrognathic maxilla and/or mandible (Bresolin *et al.*, 1983; Wenzel *et al.*, 1985; Solow & Sandham, 2002). Mouth breathers may develop a long narrow face called the ‘long face syndrome’ (Fields *et al.*, 1984). Dental occlusion may also be affected by mouth breathing (Deb & Bandyopadhyay, 2007). Children whose mouth-breathing is untreated may develop narrow jaws, high palatal vaults,

dental malocclusion, gummy smiles, and other facial features such as long, narrow faces and a skeletal Class II facial profile (Jefferson, 2010).

10.2 Purpose

This chapter seeks to verify the hypothesis that allergic children show no facial shape differences when compared to healthy children drawn from the same population.

10.3 Subjects and Methods

10.3.1 Sample

As described in the study design (Section 5.3), the study population was recruited from the ALSPAC cohort, which provided detailed environmental, medical and genetic information (Golding *et al.*, 2001). The same study sample was used as that used in the atopy investigation (Section 9.3.1). In addition to acquiring facial scans from the children at 15 years of age, supporting information relating to allergic rhinitis was obtained from a skin-prick test performed when the children were 11 years old (Henderson *et al.*, 2008), and from parental questionnaires completed throughout the study period. The following questions were asked: “In the past 12 months, has the child had a problem with sneezing or a runny or blocked nose when he/ she did not have a cold or the flu?”; “Has the child ever had hay fever?”, (Questionnaire at 128 months).

10.3.2 Facial Imaging

Three-dimensional facial images were taken using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), with a reported manufacturing accuracy of 0.1mm (Kau *et al.*, 2003). A locally developed algorithm implemented as a macro in Rapidform® 2006 software (Kau

et al., 2004; Zhurov *et al.*, 2005; Toma *et al.*, 2008; Kau & Richmond, 2010) was used to process, register and merge the right and left facial scans of each individual. Twenty-one reproducible soft tissue landmarks with an error of less than 1mm (Toma *et al.*, 2009) were manually identified on each facial shell using Rapidform® 2006 software (Toma *et al.*, 2009; Toma *et al.*, 2012).

Average faces of allergic and healthy children were superimposed on the mid-endocanthion point (men) as this point has shown to be the most reliable facial landmark (Toma *et al.*, 2009). Differences in morphology were explored using colour maps, with a tolerance level of 0.25mm to identify topographical facial differences.

10.4 Statistical Analysis

Three-dimensional soft tissue measurements were analysed to assess anterior-posterior, vertical and transverse relationships in face shape (Table 10.1). The facial measurements included in the analysis were those described in literature to be the most common measurements which might be influenced by different modes of breathing (Bresolin *et al.*, 1983; Wenzel *et al.*, 1985; Kerr *et al.*, 1989; Harari *et al.*, 2010).

Table 10.1: Soft tissue parameters

Transverse Relationship	Vertical Relationship	Anterior-Posterior Relationship
exR-exL (inter-eye distance)	pg-n (total facial height)	n-prn-sn (nose prominence)
al-al (nose width)	Is-men (mid-face height)	prn-sn-ls (philtrum depth)
	exR-pg-exL (mid-face angle)	s-sn-pg (face convexity)
	Is-pg (lower face height)	

A chi-square test was used to examine the association of allergic rhinitis with gender. An independent sample t-test was used to compare BMI in allergic rhinitis groups and 95% confidence intervals to assess the difference in facial measurements between the allergic rhinitis and healthy children.

10.5 Results

Based on the results of the parental questionnaires and skin-prick tests carried out on the children when they were 11 years old, 669 children were diagnosed as having allergic rhinitis. Analysis of the supporting data indicated that BMI was not significantly associated with allergic rhinitis [mean difference (95% CI): 0.04 (-0.3 to 0.5); p=0.813]. Despite differences in growth rates, the proportion of males to females with allergic rhinitis was 14.1% vs. 13.7%, indicating that allergic rhinitis was not significantly associated with gender (p=0.139).

In general, measurements relating to the transverse distances in children with allergic rhinitis did not differ significantly from those in the healthy group (Table 10.2). In contrast, there were significant differences relating to the vertical distances between children with allergic rhinitis and children in the healthy group: the mean differences in the total anterior facial height (pg-n) and lower facial height (Is-pg) were 0.57mm and 0.39mm longer, respectively, in the children with allergic rhinitis. The 95% CI values were -1.08 to -0.03 and -0.79 to -0.07, respectively (Table 10.2). In addition, the angle (n-sn-pg) which describes the anterior-posterior relationship was 0.5º greater in children with allergic rhinitis (95% CI: 0.03 to 0.97; Table 10.2), indicating a more retrognathic mandible.

Table 10.2: Results of the multiple independent samples t-tests

Facial Parameter	Allergic rhinitis n=669		Healthy n=1862		Mean difference	95% CI for Mean difference
	Mean	SD	Mean	SD		
Eyes Distance (mm) (exR-exL)	87.3	3.95	87.4	4.11	0.12	-0.20 to 0.43
Nose width (mm) (al-al)	33.7	2.76	33.6	2.70	0.13	-0.34 to 0.10
Total anterior face height (mm) (pg-n)	102.2	6.27	101.7	6.23	-0.57	-1.08 to -0.03
Lower-face (mm) (ls-pg)	37.0	3.65	36.7	3.61	-0.39	-0.79 to -0.07
Mid-face (mm) (ls-men)	61.7	4.02	61.5	3.98	-0.10	-0.46 to 0.20
Mid-face (angle) (exR-pg-exL)	49.3	2.69	49.5	2.64	0.23	-0.01 to 0.46
Face convexity (angle) (n-sn-pg)	162.0	5.50	162.6	5.68	0.50	0.03 to 0.97
Nose prominence (angle) (n-prn-sn)	100.4	4.69	100.8	4.67	0.35	-0.06 to 0.71
Philtrum depth (angle) (Prn-sn-ls)	127.3	8.79	127.2	8.20	-0.05	-0.76 to 0.68

Meanwhile, the superimposition of average facial shells of allergic and healthy children showed a larger nose, less prominent chin and flatter cheeks and forehead in allergic children (Figure 10.1).

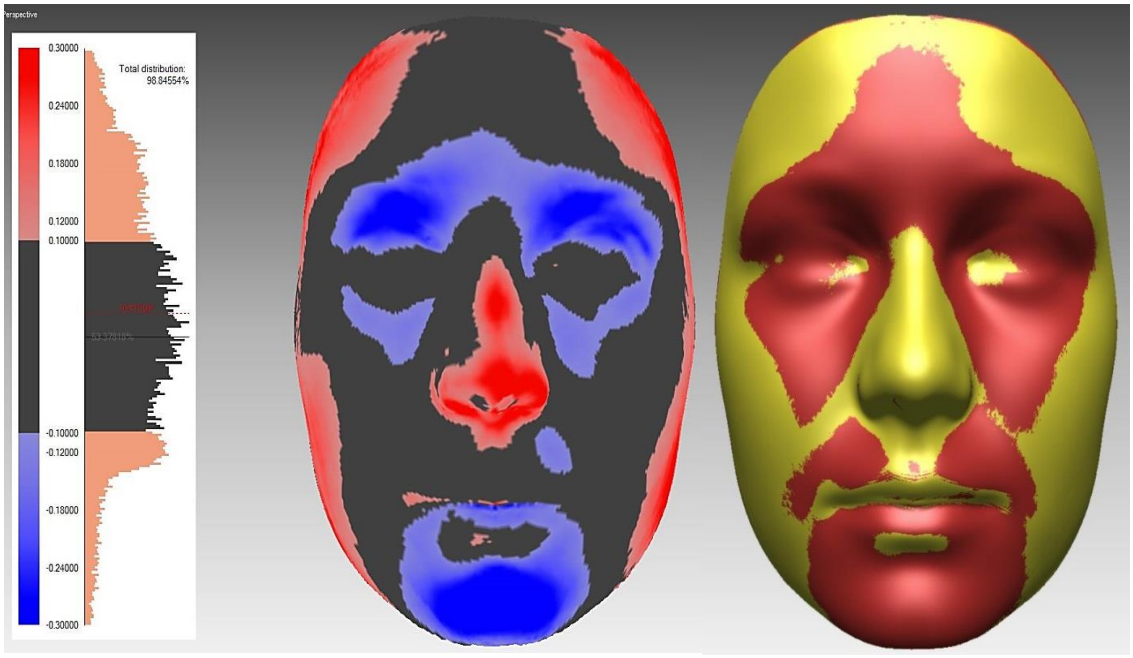


Figure 10.1: Superimposition of allergic and healthy average facial shells

Note: Left: The black area in the colour maps represents no difference between the allergic and healthy (0mm). The red areas are those prominent features in the allergic face (0.1 to 0.3mm)**.** The blue represents greater facial retrusion in the allergic group (0.1 to 0.3mm). Right: allergic (yellow) and healthy (red).

10.6 Discussion

One of the purposes of this study was to clarify the issue of whether or not nasal obstruction due to allergic diseases influences face shape. Previous studies have been inconclusive, primarily due to small sample sizes and poor study design (Miller, 1949; Marks, 1965; Harari *et al.*, 2010). To overcome these problems, the study investigated a large cohort of 15-year-old children using advanced three-dimensional imaging technologies reported to have high reproducibility (Kusnoto & Evans, 2002). This technique enabled average facial shells to be constructed for the different breathing-disorder and healthy groups. As such the surface topographies could be compared between the groups, beyond those from standard landmark measurements, and data could be compiled for a spectrum of facial parameters.

The findings with respect to allergic rhinitis were that the main effects of allergic rhinitis were a less prominent mandible and an increased total and lower face height. The findings support the evidence that mouth-breathing associated with breathing disorders have a tendency towards abnormal skeletal growth pattern including an increased lower face height (Hannuksela, 1981; Sassouni *et al.*, 1985; Tourne, 1990). In addition, a greater tendency towards Class II malocclusion in the Angle's classification was found in the mouth breathers group (Sassouni *et al.*, 1985; Tourne, 1990).

The explanation for these results is that the altered mechanics of breathing associated with increased resistance of the inflamed airways can lead to altering the posture of the head and cervical spine, and facial growth retardation (Doull, 2004; Lopes *et al.*, 2007; Chaves *et al.*, 2010). These processes may be

associated with the stunted development of the mandible (Bresolin *et al.*, 1983; Wenzel *et al.*, 1985; Solow & Sandham, 2002). Individuals with complete nasal blockage develop mouth-breathing patterns due to an oedematous nasal mucous membrane that is secondary to chronic allergic rhinitis. This might adversely affect craniofacial morphology which could result in a series of changes in the musculoskeletal structures of the face including elongated facial pattern, a steep mandibular plane and a Class II malocclusion due to retrognathic mandible (Bresolin *et al.*, 1984; Solow & Sandham, 2002; Chaves *et al.*, 2010). The continuous airflow passing through the nasal passage and nasopharynx during unobstructed breathing produces a constant stimulus for both the lateral growth of maxilla as well as for lowering of the palatal vault (Kilic & Oktay, 2008).

10.7 Limitations

Although results reveal an association between mouth-breathing in allergic rhinitis and modification in craniofacial growth and morphology, further research is required to understand how much nasal obstruction has to occur before an effect on facial growth is observable. Furthermore, research is needed to investigate if this is a reversible condition and whether there is a time-dependent relationship. However, investigating these questions requires the fundamental premise of being able to define nasal obstruction, its position and severity (Vig, 1998).

10.8 Conclusion

This study demonstrates that three-dimensional facial imaging has sufficient resolution to detect very small differences in face shape, and can be used to explore environmental effects on face shape, including the effects of allergic

rhinitis. Statistically significant differences between the allergic and healthy children were detected. Allergic rhinitis children were associated with an increased face height and reduced mandibular prominence. Paediatricians and paediatric dentists should take note of chronic nasal obstruction associated with allergy during the critical growth period in children to prevent abnormal dentofacial development and malocclusions.

Chapter 11

Sleep Disordered Breathing

11.1 Introduction

Sleep-disordered breathing (SDB) including obstructive sleep apnoea (OSA) is highly prevalent among the general population. The most common symptoms are primary snoring, mouth-breathing, and repetitive periods of cessation in breathing during sleep, termed apnoeas, or reductions in the amplitude of a breath, known as hypopneas. These events are associated with fragmented sleep, declines in oxygen saturation, sympathetic nervous system activation, and elevation of the heart rate (Panossian & Daley, 2013).

SDB is becoming increasingly recognized as a major cause of sleep-related morbidity and mortality. SDB is a subtle disorder of early childhood, and may have serious consequences for long-term health, especially among children with macroglossia and retrognathia (Gregg *et al.*, 2000; Defabjanis, 2003). The health-related consequences of SDB include daytime somnolence, cognitive dysfunction, impaired work performance, and reduction in the quality of life (Punjabi, 2008; Jennum *et al.*, 2013). Individuals with major depressive disorders often experience OSA (Cheng *et al.*, 2013). Meanwhile, OSA has been associated with the development of systemic hypertension (Nieto *et al.*, 2000; Peppard *et al.*, 2000), adverse cardiovascular events (Budhiraja & Quan, 2005; Peker *et al.*, 2006; Mirrakhimov & Mirrakhimov, 2013), and abnormalities in glucose metabolism (Sanders & Givelber, 2003; Punjabi & Polotsky, 2005).

11.1.1 Prevalence

According to Panossian and Daley (2013) approximately 30% of people report having OSA and a further 10% have a persistent, potentially diagnosable disorder that meets the diagnostic criteria based on polysomnography, with the

highest prevalence among patients with neurologic disorders or a history of strokes. In addition, the prevalence of OSA is reported to be about 0.7-4.0% among 2-18 year olds (Gislason & Benediktsdottir, 1995; Lofstrand-Tidestrom *et al.*, 1999). However, there are few investigations concerning the prevalence of SDB in children, despite the fact that snoring has been reported in 10% of preschool children (Teculescu *et al.*, 1992; Ali *et al.*, 1993; Ali *et al.*, 1994), while other studies have reported that the prevalence of parent-reported snoring to be 7.5% for 2-18 years old (Lumeng & Chervin, 2008). Furthermore, the prevalence of mouth-breathing in young children ranges from 3% to more than 50% (Abreu *et al.*, 2008; Huang *et al.*, 2009; Felcar *et al.*, 2010).

The prevalence of SDB symptoms is reported by Bonuck *et al.* (2011) who conducted the first study on the natural history of snoring, mouth-breathing, and apnoea in a population-based cohort across a key 6-year period in the development of SDB symptoms. The prevalence of “Always” snoring (range = 3.6-7.7%) and “habitually” snoring (range = 9.6-21.2%), the prevalence of apnoea (“Always”) 1% to 2%, and “Always” mouth-breathing ranged from 2.1% to 7.6% (Bonuck *et al.*, 2011)

11.1.2 Diagnosis

The diagnosis of SDB is frequently based on clinical suspicion and reports of loud snoring, breathing pauses witnessed during sleep, poor sleep quality, and excessive daytime somnolence (Lavie, 2003). A comprehensive sleep history, a physical examination with detailed evaluation of the head and neck, and judicious use of sleep-specific questionnaires, should ideally guide the decision to pursue diagnostic testing (Shelgikar & Chervin, 2013). Meanwhile, OSA may be

diagnosed by observing the complete cessation of airflow through the airways for a minimum of 10 seconds. Diagnosis requires ≥ 5 episodes of apnoea or hypopnoea per hour (Panossian & Daley, 2013). The gold standard diagnostic test for OSA is the overnight polysomnogram, involving the recording of multiple physiologic signals during sleep, including electroencephalogram, electromyogram, electrooculogram, oronasal airflow and oxyhemoglobin saturation levels.

11.1.3 Causes of SDB in Children

The current view is that adenotonsillar hypertrophy is the major cause of SDB in otherwise healthy children (Marcus, 2000; Benninger & Walner, 2007; Li & Lee, 2009). Most children between 2 and 5 years of age exhibiting symptoms of SDB have a hypertrophy of the lymphatic tissues in the adenoid and tonsils (Halbower & Marcus, 2003). At this age, children are often exposed to bacterial and viral infections associated with upper respiratory diseases, resulting in the physiological hypertrophy in the lymphoid tissue as a part of the immune defence (Brandtzaeg, 1988; Ying, 1988). Adenotonsillar hypertrophy is associated with nasal obstruction, resulting in breathing problems, and leading to disturbed patterns of sleeping, eating, swallowing and speaking (Kawashima *et al.*, 2002). Consequently, the primary therapy for children with SDB is adenotonsillectomy (Friedman *et al.*, 2013).

11.1.4 Risk Factors for SDB in Children

It is possible that obesity is a risk factor of SDB. Rudnick *et al.* (2007) reported that children with SDB who undergo adenotonsillectomy are more likely to be obese than children seen in a general paediatric clinic, and that African-American

children who are obese are more likely to have SDB. In addition, Verhulst *et al.* (2008) reviewed the literature on the prevalence, anatomical correlates, and treatment of SDB in obese children. They concluded that obese children are at a higher risk of developing SDB, and suggest that in such children, both adiposity and upper airway factors, such as adenotonsillar hypertrophy, moderated the severity of SDB. In a direct response to this review, Kohler and van den Heuvel (2008) have argued:

> We believe, however, that the available studies do not support a straightforward association of overweight or obesity with increased prevalence of SDB. Rather, the available data is clearly equivocal mainly due to methodological differences between the previous studies.

Kohler and van den Heuvel examined other factors that may moderate the relationship between overweight or obesity and prevalence of SDB in children, particularly ethnicity and age. In a more recent case-controlled study, Tripuraneni *et al.* (2013) concluded that the degree of obesity does not linearly predict the severity of OSA in children; however, obese children may have worse symptoms of OSA (diagnosed by polysomnography) than normal-weight children.

11.1.5 Craniofacial Anomalies Associated with SDB

The idea that nasal obstruction and associated mouth-breathing affects craniofacial development and morphology continues to be controversial (Harari *et al.*, 2010). A number of craniofacial anomalies including maxillary and mandibular retrognathia, enlarged tongue, soft palate, adenotonsillar hypertrophy, and an inferiorly positioned hyoid bone may be associated with decreased posterior airway space and restriction of the upper airway, promoting apnoeas and hypopnoeas during sleep (Cakirer *et al.*, 2001). Cessation of airflow may develop

during OSA because of anatomic obstruction of the upper airway related to obesity, and excessive tissue bulk in the pharynx (Panossian & Daley, 2013).

The evidence to support the existence of facial anomalies associated with SDB in children is limited and conflicting. Some studies have reported an absence of evidence for an association between face shape and children with SDB (Kawashima *et al.*, 2002) but others disagree. For instance, Linder-Aronson (1974) evaluated children who had adenoid hyperplasia and concluded that nasal obstruction may alter facial growth, and coined the term "long or adenoidal face". He found that children with large adenoids usually have longer and narrow faces, lower tongue position, anterior open bite, narrow upper jaw and steep mandibles, with a more backward position. Linder-Aronson *et al.* (1993) hypothesized that adenotonsillar hyptertrophy in children induces mouth-breathing, disrupting the balance of labial, lingual and cheek muscles, resulting in facial anomalies. Furthermore, Tomer and Harvold (1982) and Vickers (1998) suggested that nasal obstruction causes changes in muscular function, conditioning dentofacial anomalies. In addition, children with enlarged adenoids and tonsils may have a larger anterior total and lower facial heights, a more retrognathic mandible, proclined upper incisors, retroclined lower incisors and a large overjet (Behlfelt, 1990). Other facial anomalies that may potentially be associated with SDB include increased anterior face height, incompetent lip posture, increased mandibular plane angle and V-shaped maxillary arch (Schlenker *et al.*, 2000), while nasal obstruction associated with mouth-breathing may lead to a downward and backward rotation of the mandible associated with increased anterior face height (Harari *et al.*, 2010).

A recent systematic review and meta-analysis, comparing healthy controls versus children with OSA and primary snoring, matched for gender provided limited statistical support for an association between OSA and cephalometric measurements in children aged 0 to 18 years (Katyal *et al.*, 2013). The meta-analysis used data extracted from randomized controlled trials, case-control, and cohort studies, with relatively small aggregated samples. The maximum sample sizes were 87 cases with OSA and 113 healthy controls. Compared to the controls, children with OSA and primary snoring were found to exhibit (a) a significantly increased mandibular plane angle to the cranial base (ANB angle); and (b) a significantly reduced upper airway saggital width. However, the increased ANB angle of less than 2^{o} was considered to be of marginal clinical significance. It was concluded that "larger well controlled trials are required to address the relationship of craniofacial morphology to paediatric sleep-disordered breathing" (Katyal *et al.*, 2013). This provided a direction and rationale for the current research. Although environmental and genetic influences on facial shape can be subtle, their effects have potential diagnostic value.

11.2 Purpose

One of the purposes of this study is to determine the extent to which SDB (symptomized by snoring, mouth-breathing, or OSA) is statistically related to face shape measurements among children in late childhood (15 years of age). Based on the literature, we hypothesize that the following face shape measures might be associated with SDB: (a) increased face height; (b) smaller nose prominence; (c) smaller mandibular prominence; and (d) smaller maxillary prominence.

11.3 Materials and Methods

11.3.1 Subjects

The children who participated in this study were Caucasian representatives of the UK population. They were recruited from the ALSPAC (Golding *et al.*, 2001). All children identified as having (a) congenital abnormalities; (b) diagnoses associated with poor growth; or (c) adenotonsillectomy were excluded from the original cohort, because of the focus on cases of SDB, not secondary to congenital or other medical complications. The total sample size used was 3586 (1693 males and 1893 females).

SDB was assessed through parental reports of SDB's hallmark symptoms (snoring, apnoea and mouth-breathing) when each child was 6, 18, 30, 42, 57, 69 or 81 months of age. Based on the criteria defined by Freeman and Bonuck (2012), the questionnaires included the following three questions:

Mouth-breathing: ''Does the child breathe through their mouth rather than their nose?''. At 57 months or older, the parents were asked to provide separate responses for mouth-breathing when the children were awake and asleep; however, only the latter response was used in the analyses.

Snoring: ''Does the child snore for more than a few minutes at a time?''

Apnoea: ''When asleep, does the child appear to stop breathing or hold their breath for several seconds at a time?''

Responses were categorised on an ordinal scale ranging from always to never or rarely/never. As objective sleep evaluations and clinical examination data were unavailable, the SDB measurements employed in this research were not diagnostic. However, the reliability of similar or identical SDB-associated

parameters based on ALSPAC data or from polysomnogram (PSG) sleep laboratories, have been validated in multiple studies. Some of these had been based on parental reports of all three SDB symptoms (snoring, mouth-breathing and apnoea) (Chervin *et al.*, 2000; Franco *et al.*, 2000; Li *et al.*, 2006; Chervin *et al.*, 2007); whereas others were only based on snoring and apnoea (Bruni *et al.*, 1996; Ferreira *et al.*, 2009). Furthermore, it has been suggested that epidemiological studies of SDB symptoms may be more effective in predicting treatment responses and have greater clinical relevance than PSG results, due to the availability of baseline SDB symptoms (Chervin *et al.*, 2007).

Based on the cluster analysis of SDB symptoms by Freeman and Bonuck (2012), SDB can be classified into the following five categories (four SDB categories and one healthy category) according to the severity of the symptoms reported by the parents during childhood:

- asymptomatic (healthy)
- early snoring, with peak symptoms at 6 months
- early snoring, with peak symptoms at 18 months
- late snoring and mouth-breathing, but remains asymptomatic until 4 years old
- severe and sustained symptoms of SDB throughout childhood

Gender, BMI (kg/m^2) and facial scan data were recorded for each child at 15 years old following the same process described in Chapter 8 with surface-based average faces were constructed separately for those with SDB (1724) and healthy children (1862). The average face of children with SDB was compared with the average face of healthy children, by superimposing them on the mid-

endocanthion point using a best-fit registration (Kau & Richmond, 2010; Zhurov *et al.*, 2010). Colour maps were used with a tolerance level of 0.25mm to highlight significant topographical facial differences.

11.3.2 Statistical Analysis

SDB was treated as binary for some analyses (SDB status) and categroised into severity groups for more detailed exploration (SDB groups). The steps undertaken were: a chi-square test was used to examine the association of SDB status with gender. Second, an independent sample t-test was used to compare BMI in SDB status and ANOVA was then used for SDB groups. Third, factor analysis was used to reduce the 17 facial angles and measurements into a smaller number of facial dimensions. Logistic regression was then used to examine the relationship between the facial dimensions and SDB status. Finally, SDB groups were plotted in box plots and tested for significances using one way ANOVA.

11.4 Results

11.4.1 Demographic Summary

The total sample consisted of 3586 children at age 15 (52.8% females; 47.2% males) and included 1724 children with SDB symptoms and 1862 children who were asymptomatic. The demographics of the study sample, based on the categories defined above by Freeman and Bonuck (2012) are summarised in Table 11.1. This shows that the proportion of children in each of the SDB categories, from the lowest to the highest degree of severity, were 15.6%, 9.9%, 16.2% and 5.3%, respectively; with 52.8% categorised as healthy. The proportion of males to females with SDB were 24.10% vs. 23.9%, indicating that SDB was

not significantly associated with gender (p=0.282). In contrast, BMI was significantly different between children with SDB and healthy children (mean difference (95% CI) in BMI: 1.97 (-2.51 to -0.86), p=0.012). The BMI in children with SDB was 23.14 kg/m² compared to 21.15 kg/m² in healthy children; however, BMI did not differ between the SDB groups (ANOVA p=0.100).

Table 11.1: Demographic summary of the sample

	Percentage
Gender: Female	52.8% (1893/3586)
Status	
Asymptomatic (healthy)	52.8% (1862)
Early snoring, peak symptoms at 6 months	15.6% (599)
Early snoring, peak symptoms at 18 months	9.9% (354)
Late snoring and mouth breathing	16.2% (580)
Severe and sustained symptoms of SDB	5.3% (191)

11.4.2 Comparison of Face Shape Measurements

The descriptive statistics (means, standard deviations and 95% CI) for the 17 face shape measurements are presented in Table 11.2. Significant mean differences in facial measurements in those with SDB were: an increased total face height (ls-pg); a decrease in nose prominence (prn-sn); a decrease in nose width (alL-alR) and an increase in mandible angle (g-men-pg), indicating a retrognathic mandible in those with SBD.

Table 11.2: Descriptive statistics for face shape measurements

Dimension		Non SDB		SDB			
		Mean	SD	Mean	SD	ΔM*	95%CI of the mean difference
1	Total face height (pg-men)	93.50	5.63	93.75	5.56	0.25	(-0.61 to 0.11)
	Total face height (pg-g)	113.46	6.12	113.80	6.10	0.33	(-0.73 to 0.06)
	Total face height (pg-n)	101.46	6.17	101.85	6.22	0.39	(-0.80 to 0.01)
	Lower face height (Is-pg)	36.54	3.52	36.83	3.60	0.28	(-0.52 to -0.05)
	Total face height (Ii-men)	74.73	4.69	74.97	4.74	0.24	(-0.55 to 0.06)
	Mid face height (Is-men)	61.69	4.00	61.66	3.96	0.03	(-0.23 to 0.29)
	Mid face angle (exR-pg-exL)	49.67	2.60	49.41	2.68	0.26	(-0.08 to 0.43)
2	Outer eyes distance(exR-exL)	87.68	3.91	87.33	4.11	0.34	(-0.08 to 0.60)
	Inter eyes distance (enL-enR)	34.31	2.86	34.16	2.91	0.14	(-0.04 to 0.33)
	Nose width (alL-alR)	33.64	2.70	33.50	2.72	0.72	(-0.10 to -0.25)
3	Nose prominence (prn-sn)	19.79	1.87	19.66	1.87	0.12	(0.00 to 0.24)
	Mid face height (n-sn)	52.34	3.82	52.34	3.84	0.00	(-0.24 to 0.25)
	Mid face height (sn-men)	48.30	3.49	48.11	3.41	0.18	(-0.03 to 0.41)
	Maxilla angle (n-sn-pg)	162.45	5.69	162.32	5.63	0.13	(-0.23 to 0.50)
	Philtrum angle (prn-sn-Is)	127.12	8.78	127.35	8.85	0.22	(-0.80 to 0.35)
4	Nose angle (n-prn-sn)	100.56	4.57	100.88	4.76	0.31	(-0.01 to 0.62)
5	Mandible angle(g-men-pg)	133.42	6.72	134.29	6.60	0.86	(-1.30 to -0.42)

*mean difference

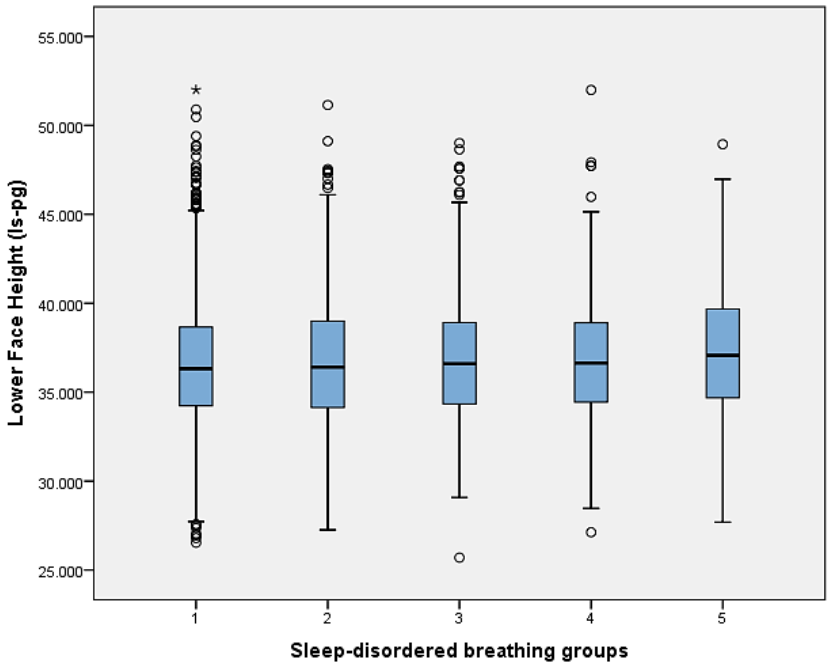


Figure 11.1: Mean ± 95% CI of lower face height (Is-pg) and 5 levels of SDB severity

Systematic relationships between lower face height, nose width, and mandible angle (mean ± 95% CI) with respect to the five levels of SDB severity are illustrated in Figures 11.1, 11.2 and 11.3. Lower face height and mandible angle were consistently higher and nose width was consistently lower for those who experienced severe and sustained symptoms of SDB throughout childhood. ANOVA results for the lower face height, mandible angle and nose width are p=0.006, p<0.001 and p=0.004 respectively, with respect to the five levels of SDB groups.

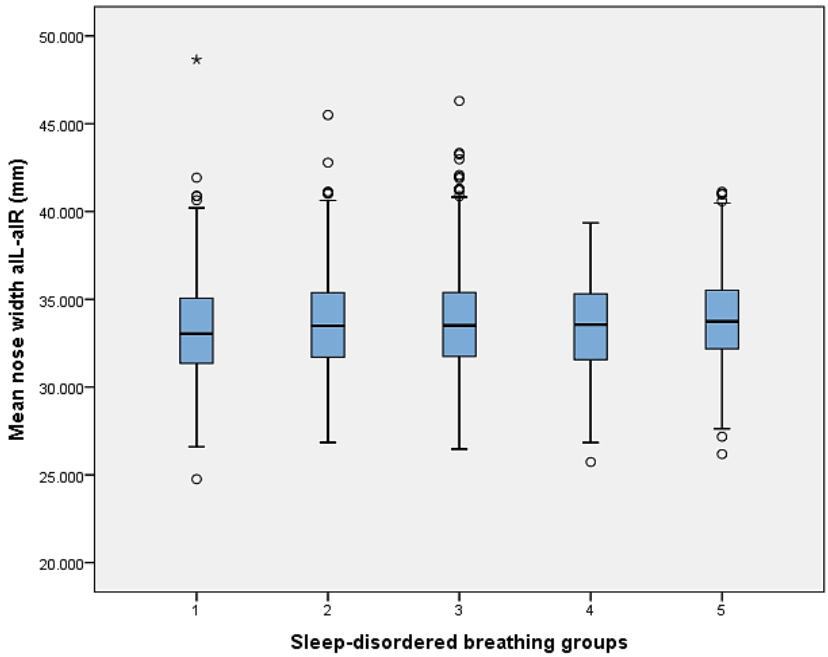


Figure 11.2: Mean ± 95% CI of nose width (alL-alR) and 5 levels of SDB severity

In each Figure: 1 = Asymptomatic healthy; 2 = Children with early snoring, peak symptoms at 6 months; 3 = Children with early snoring, peak symptoms at 18 months; 4 = Children with late snoring and mouth breathing, but remained asymptomatic until 4 years; and 5 = Children with severe and sustained symptoms of SDB throughout childhood.

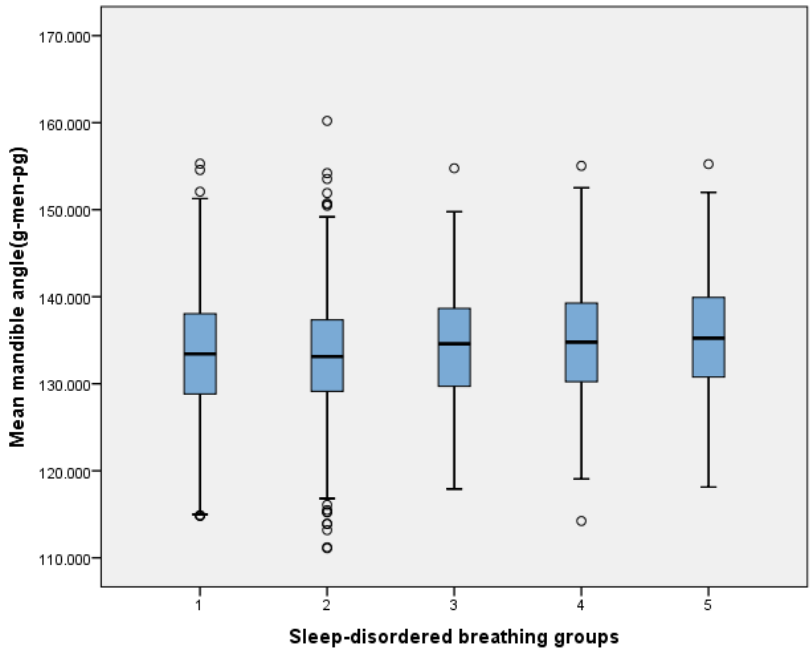


Figure 11.3: Mean ± 95% CI of mandible angle (g-men-pg) and 5 levels of SDB severity

11.4.3 Five Dimensions of Face Shape Measurements

Table11.3: Face shape dimensions extracted by factor analysis

	Percentage of Variance Explained	
	%	Cumulative
Factor 1 (D_1) Total Face Height (pg-men) Total Face Height (pg-g) Total Face Height (pg-n) Lower Face Height (Is-pg) Total Face Height (li-men) Mid Face Height (Is-men) Mid Face Height Angle (exR-pg-exL)	32.6	32.6
Factor 2 (D_2) Outer Eyes Distance (exR-exL) Inter Eyes Distance (enL-enR) Nose Width (alL-alR)	12.9	45.6
Factor 3 (D_3) Nose Prominence (prn-sn) Mid Face Height (n-sn) Mid Face Height (sn-men)	12.7	58.3
Factor 4 (D_4) Maxilla Angle (n-sn-pg) Philtrum Angle (prn-sn-Is) Nose Angle (n-prn-sn)	11.2	69.5
Factor 5 (D_5) Mandible Angle (g-men-pg)	9.5	79.0

Factor solutions collectively explaining 79% of the variance, with consistently strong factor loadings (>0.5), were used to classify the 17 face shape measurents into 5 dimensions (D_1 to D_5) (Table 11.3). D_1 represented face height which explained 32.6% of the variance. D_2 represented eyes distance with nose width which explained 12.9% of the variance. D_3 represented nose prominence with maxilla height (12.7% of the variance). D_4 was the maxilla angle, nose with philtrum angle (11.2% of the variance), and D_5 was the mandible angle (9.5% of the variance).

11.4.4 Association of SDB and Facial Dimensions

Because SDB status was associated with BMI, a logistic regression was used to examine the relationships between the facial dimensions and SDB status adjusted for BMI. A binary logistic regression model was constructed using the factor scores for the five dimensions extracted by factor analysis as the predictor variables to predict the prevalence of SDB (Table 11.4). Four dimensions were significantly associated with SDB. The odds of the children exhibiting symptoms of SBD increased significantly with respect to D_5—Mandible angle (OR 1.11, 95% CI 1.04, 1.19)—and D_1—Face height (OR 1.09, 95% CI 1.02, 1.16). In contrast, an increase in D_2—Eyes distance with Nose width (OR 0.90, 95% CI 0.84, 0.97)—and an increase in D_3—Nose prominence with Mid-face height (OR 0.93, 95% CI 0.86, 0.99)—was associated with a reduced odds of SDB. The dimensions D_4—Maxilla angle, Nose with Philtrum angle—was not significantly associated with SDB. An increase in the BMI was associated with increased odds of SDB (OR 1.03, 95% CI 1.01, 1.05).

Table 11.4: Binary logistic regression model to predict the prevalence of SDB using five face shape dimensions and BMI

Predictor	Odds ratio	p-value	95% CI	
D_1 Face height	1.09	0.011	1.02	1.16
D_2 Eyes Distance with Nose Width	0.90	0.005	0.84	0.97
D_3 Nose Prominence with Mid-face Height	0.93	0.028	0.86	0.99
D_4 Maxilla Angle, Nose with Philtrum Angle	1.05	0.162	0.98	1.12
D_5 Mandible angle	1.11	0.001	1.04	1.19
BMI	1.03	0.003	1.01	1.05

11.4.5 Superimposition of Average Faces

Superimposed surface-based average faces of SDB and healthy children are presented in Figure 11.4, while the colour maps in Figure 11.5 show the morphological differences between the groups. As the figures illustrate, healthy children tended to have slightly bigger noses, more prominent mandible, cheeks and forehead than SDB children.

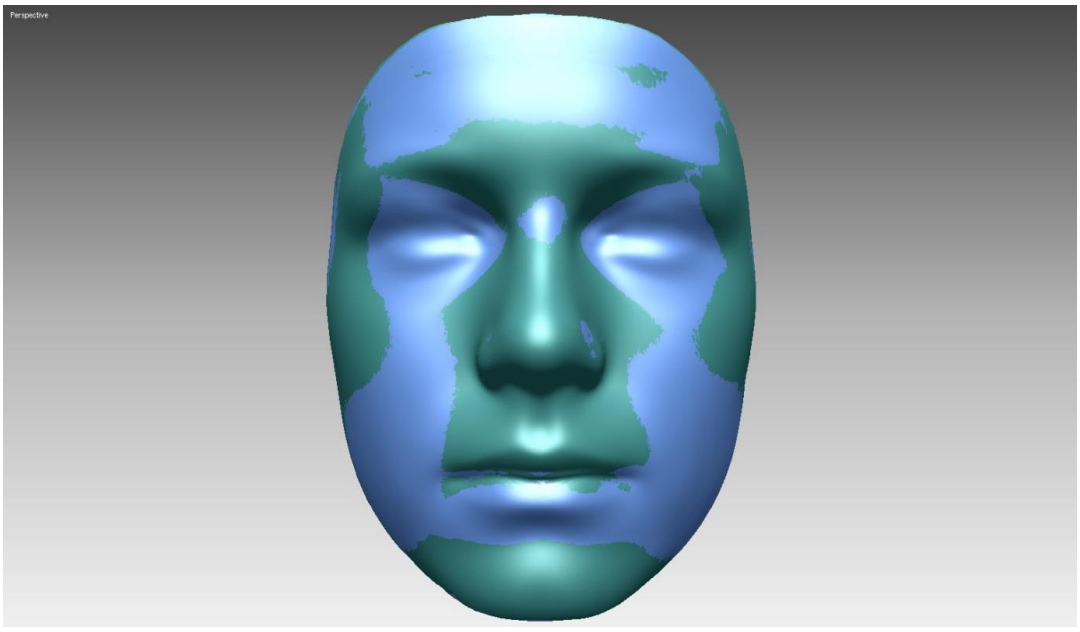


Figure11.4: Superimposition of average facial shells of SDB (blue) and healthy children (green)

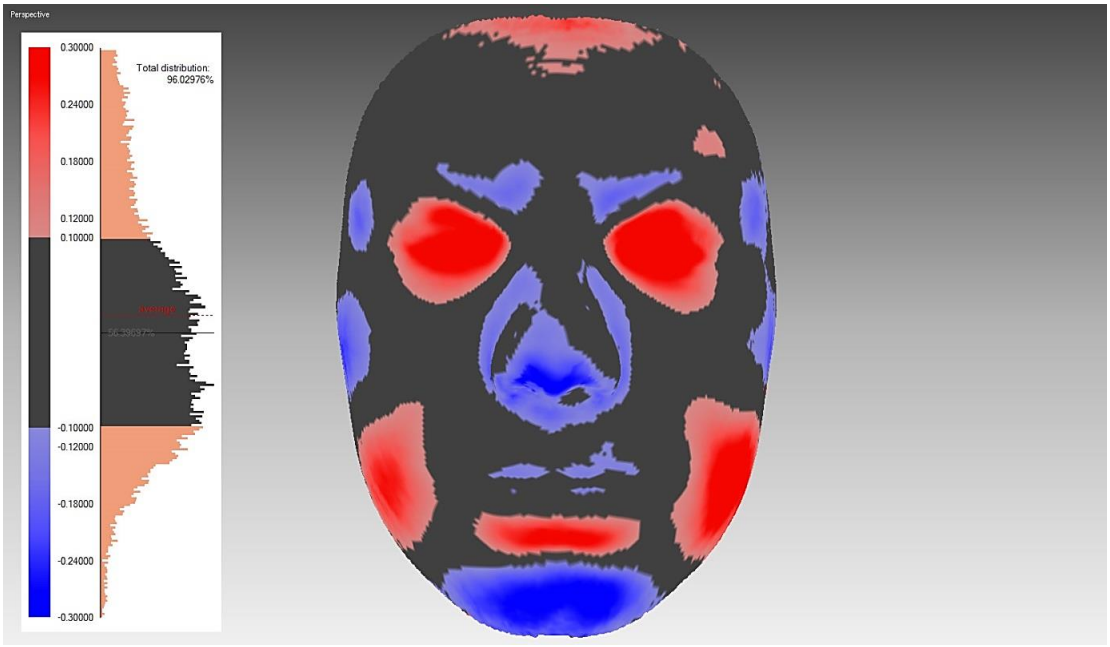


Figure 11.5: Colour maps and histogram plots to assess facial differences between SDB and healthy Children

Note: The black areas represent no difference in the SDB and non-SDB children (0mm). The blue areas represent less prominent nose and chin in the SDB groups (0.1-0.4mm). The red areas are those prominent features in the SDB face (0.1-0.4mm)**.**

11.5 Discussion

Previous analyses of the variability in facial anomalies associated with the development of SDB among children (age 0 to 18 years) provide inconsistent and conflicting results. Consequently, the idea that nasal obstruction and associated mouth-breathing influencing craniofacial development and morphology are related to SDB in children is controversial (Harari *et al.*, 2010). Misleading conclusions may have been drawn in previous studies because the sample sizes were too small, providing insufficient statistical power, and the cases with SDB and the asymptomatic controls were not necessarily equivalent with respect to their demographic and other attributes (e.g., equal proportions of cases and controls by gender, age, obesity, and clinical history). If the study groups were not demographically equivalent, then the differences between the

face shape variables could potentially be confounded by factors other than SDB. In accordance with the design of an effective study (Machin & Cambell, 2005) a large sample size (1693 males and 1893 females), all of whom were the same age (15 years old), was used in order to provide sufficient statistical power, ensure that the SDB and healthy children were demographically equivalent, and control for confounding variables (BMI and gender). Despite this, large studies can find differences that although statistically significant may not be clinically relevant; therefore, care should be taken when interpreting the results. Furthermore, none of the children in this study had their tonsils and/or adenoids removed, while the possible confounding effect of obesity was ascertained, which may be a confounding factor leading to conflicting observations in previous studies. However, the findings support Verhulst *et al.* (2008) who concluded that obese children are at a higher risk of developing SDB.

Using factor analysis, the 17 facial measurements obtained by use of a three-dimensional facial scan were found to be able to be reduced to five dimensions of face shape. Consistent outcomes were established using binary logistic regression and concluded that among children with SDB, relative to healthy children, the mandible was retrognathic, the face height measurements were significantly higher, and the nose prominence and nose width dimensions were consistently lower. These findings support previous studies. The mandible among the SDB children was found to be significantly less prominent and in a posterior position relative to the maxilla, supporting previous evidence that the prevalence of retrognathic mandible in mouth-breathing children is higher than in nasal breathing children (Lessa *et al.*, 2005). In addition, increased total and lower face

height has previously been reported among children with SDB (Finkelstein *et al.*, 2000; Kawashima *et al.*, 2002; Zettergren-Wijk *et al.*, 2006; Pirila-Parkkinen *et al.*, 2010). Furthermore, nasal obstruction associated with mouth-breathing is assumed to lead to a downward and backward rotation of the mandible and to an increase in anterior face height (Linder-Aronson *et al.*, 1993; Cakirer *et al.*, 2001; Harari *et al.*, 2010; Al Ali *et al.*, 2013). In relation to the study's findings on nose prominence, Zettergren-Wijk *et al.* (2006) reported that the nose was less pronounced in a small sample of children (10 boys and 7 girls) with OSA when compared with controls. It is suggested that nose prominence could reflect a comparatively short anterior cranial base. In contrast, we found no statistical evidence to determine a significant difference between SDB and healthy children with respect to maxillary prognathism, consistent with the findings of Zettergren-Wijk *et al.* (2006). Overall, correlations between SDB severity and face shape were indicated in this study, which supports finding of Wenzel *et al.* (1985) who found a more retrognathic mandible in association with increasing severity of breathing disorders.

11.6 Limitations

The limitation of this study is that SDB was assessed through parental reports of SDB's hallmark symptoms (snoring, apnoea and mouth-breathing). Although polysomnogram (PSG) is considered the 'gold standard' for assessing SDB, the time, expense, possible selection bias of those undergoing PSG, and possible methodological changes over time rendered it unfeasible for epidemiological purposes in a large longitudinal cohort study. However, the five patterns of symptoms of SDB defined in this study were assumed to be reliable, because

they are correlated with the outcomes of polysmonogram examination (Chervin *et al.*, 2007; Freeman & Bonuck, 2012). The interpretations could be further reinforced by performing a follow-up analysis. In line with other childhood breathing disorders, the craniofacial effects can only be definitively assessed when the majority of facial growth has been completed. Therefore, these findings can be verified by collating data from a subsequent examination; it is intended to recall the ALSPAC cohort at 24–25 years of age.

11.7 Conclusion

Consistent evidence is provided using binary logistic regression and three-dimensional average faces superimposition to confirm the hypothesis that SDB (snoring, apnoea and mouth-breathing) among a cohort of 15 year old children was associated with (a) an increase in face height; (b) a decrease in nose prominence; (c) a decrease in nose width; and (d) a retrognathic mandible. There was, however, no statistical evidence to determine if the prevalence and severity of SDB was associated with an increase or decrease in the angle of the maxilla. However, evidence was found to indicate an association between increased BMI and the prevalence of SDB symptoms.

Because SDB has serious consequences for long-term health and quality of life, early diagnosis of SDB is essential. Healthcare professionals can play an important role in the early diagnosis of SDB, recognizing distinct facial morphologies of long face, reduced nose prominence and a retrognathic mandible and referring these children to specialists for further assessment of SDB clinical symptoms.

This is the largest cohort study to date that has investigated the associations between facial variations and sleep breathing disorders. The findings of this research were shown to be valid and may therefore merit further investigation.

Chapter 12

Changes in Face Shape after Adenotonsillectomy in Young Children with Sleep Disordered Breathing

12.1 Introduction

Sleep disordered breathing (SDB) has become recognized as a variety of mouth-breathing, snoring and apnea that disturbs nocturnal respiration and sleep architecture (Beebe, 2006; Mitchell & Kelly, 2006; Owens, 2009). The most common cause of SDB in children is adenotonsiller hypertrophy. Adenoid enlargement has long been considered the main cause of upper airway obstruction in children (Weider *et al.*, 2003) and the severity of SDB is associated with the size of the hypertrophic adenoids (Jain & Sahni, 2002). However, in contrast, the size of tonsils does not demonstrate a similar correlation (Agren *et al.*, 1998; Jain & Sahni, 2002). Adenoidectomy and tonsillectomy can be curative in 80% of cases (Rosen, 2003; Chan *et al.*, 2004); however, recent data suggests lower success rates than previously believed, particularly in children who are less than 7 years and/or obese (Bhattacharjee *et al.*, 2010).

Individuals with a nasal obstruction of long duration have shown a significant effect on face shape including an increased lower face height (Hannuksela, 1981; Bresolin *et al.*, 1983). Linder-Aronson (1970), in his landmark study, established the relationship between the presence of adenoid tissue and the following craniofacial features: increased facial height; low tongue position; narrow dental arches; tendency to cross bite; retrusion of maxilla and mandible; and retroclination of maxillary and mandibular incisors. Comparable changes in the craniofacial structure have been described in a group of children with enlarged adenoids and tonsils (Koski & Lähdemäki, 1975; Adamidis & Spyropoulos, 1983; Tarvonen & Koski, 1987; Behlfelt, 1990; Peltomäki, 2007).

Esteller *et al.* (2011) analysed dentofacial morphology of 30 children diagnosed with a sleep-related breathing disorder compared to a control group of 30 healthy children. The ages of both groups were between 3 and 13 years. Although this was a prospective study involving a relatively small sample size, the data had been compiled using a variety of diagnostic techniques, including facial analysis *via* clinical examinations, analysis of dental plaster models and cephalometric analysis. Three of the parameters were found to be significantly different between the two groups: vertical growth of the face, narrow palate and dental malocclusions, with p-values of 0.023, 0.024 and 0.02, respectively. These findings suggested that children with sleep-related breathing disorders develop dentofacial abnormalities caused by upper respiratory obstruction. As such, the authors proposed that these characteristics may be used for determining indications of adenotonsillectomy.

This research studies the influence of SDB with adenotonsillar hypertrophy on face shape of 15 years old children from the ALSPAC cohort, using three-dimensional laser scanning (in Chapter 11). The results show that children with SDB have a longer face height and a more retrognathic mandible when compared to healthy children of same age group.

12.1.1 Consequences after Adenotonsillectomy

Previous studies (Linder-Aronson, 1974; Hultcrantz *et al.*, 1991; Oulis *et al.*, 1994; Trotman *et al.*, 1997) show that the removal of the respiratory obstruction with consequent normalization of respiration results in a tendency towards normalization of the dentofacial morphology. However, total and complete

normalization was not observed in any of the studies, with greater normalization in children who had adenoids and tonsils removed early in life.

The study by Linder-Aronson (1974) was carried out on children ≥8 years old and based on 46 variables. Significant differences were observed in several dentofacial characteristics within one year of the initial examination in the children who underwent adenoidectomy. In contrast, Hultcrantz *et al.* (1991) obtained data from children <6 years old, and was therefore able to conclude that normalisation was greater in children who had adenoids and tonsils removed early in life. The findings by Oulis *et al. (*1994) and Trotman *et al.* (1997) had been carried out on relatively larger sample sizes (120 and 207 children, respectively). These authors also concluded that measurements of cephalometric characteristics provide valuable diagnostic criteria in the evaluation of children with upper airway obstruction.

In a later study, Linder-Aronson (1975) demonstrated varying degrees of recovery during the five years after adenoidectomy in the mandibular plane angle, maxillary arch width and retroclinaltion of maxillary and mandibular incisors. Also, accelerated mandibular growth and closure of mandibular plane angle are reported (Linder-Aronson *et al.*, 1986; Woodside *et al.*, 1991). However, anterior face height in adenoid children was found to be unaffected and it remained longer five years after adenoidectomy when compared to healthy controls, and the growth of mandibular ramus of adenoidectomy patients was found to be greater than that in the controls (Kerr *et al.*, 1989).

12.2 Purpose

The present work offers the first data obtained through three-dimensional soft tissue facial analysis from a study comparing children with a history of SDB and had early removal of adenoids and tonsils with a group of healthy children. It has been suggested that the removal of adenoids and tonsils 'normalises' dentofacial morphology. To test this hypothesis more conclusively would require a longitudinal study of children with and without tonsil and adenoid removal. Since only cross-sectional data at age 15 are available in this study, then a comparison that yields no difference at this age between the groups would suggest (but not prove) that this normalisation may have occurred. Therefore the objective was to compare the facial shape of adenotonsillectomy and healthy children.

12.3 Subjects and Methods

12.3.1 Sample

Children were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC) as described in Chapter 5. Sleep disordered breathing was assessed via pre-existing questionnaires developed by ALSPAC for SDB symptoms (snoring, mouth-breathing and apnoea) when the child was 6, 18, 30, 42, 57, 69 and 81 months of age (Freeman & Bonuck, 2012). Children who had adenoids and tonsils removed were identified from the 57, 69 and 81 month questionnaires.

12.3.2 Facial Imaging

As described in Chapter 6, three-dimensional facial images were obtained using two Konica Minolta Vivid 900 laser cameras (Kau & Richmond, 2008; Kau & Richmond, 2010). The reliability of image capture has been proved to be suitable

for clinical application (Kau *et al.*, 2005b; Kau *et al.*, 2006; Toma *et al.*, 2009; Huang *et al.*, 2011).

An in-house-developed sub-routine was utilized to standardize automatically the three-dimensional facial images within the reference framework by orienting each three-dimensional facial shell in the three planes of space (x, y, and z) using three reference planes: sagittal plane (y-z), coronal plane (x-y), and transverse plane (x-z). These planes were referenced to the mid-intercanthal point (men), as previous research has shown it is the most reliable facial landmark (Toma *et al.*, 2009; Zhurov *et al.*, 2010).

Twenty-one facial soft tissue landmarks were manually identified on each facial image (Toma *et al.*, 2009; Toma *et al.*, 2012) and the x, y and z co-ordinates recorded. Facial analysis was performed based on landmark and three-dimensional average faces to highlight facial differences of children who had early removal of adenoids and tonsils against healthy children. The facial measurements included in the analysis were the most common measurements reported to be influenced by different modes of breathing (Bresolin *et al.*, 1983; Wenzel *et al.*, 1985; Kerr *et al.*, 1989; Yoon *et al.*, 2004; Weinberg *et al.*, 2009; Harari *et al.*, 2010; Al Ali *et al.*, 2012).

12.3.3 Statistical Analysis

Descriptive statistics were performed. A Chi square test was used to examine the association of adenotonsillectomy children with gender. An independent t-test was used to compare BMI in the examined groups. Factor analysis was used to reduce the 17 facial angles and measurements obtained from the facial scans into a smaller number of facial dimensions. Each dimension represents a

mutually exclusive cluster of correlated face shape variables classified by strong factor loadings (>0.5). A t-test and binary logistic regression were used to examine the differences in facial measurements between adenotonsillectomy and healthy children.

12.4 Results

The total sample consisted of 2040 children, of which 54.3% were females. 178 children had a history of SDB symptoms and also had adenotonsillectomy and 1862 were healthy children.

There was a significant difference between males and females with adenotonsillectomy. The proportion of males with adenotonsillectomy was higher than for females (5.0% vs 3.6%, p=0.003). BMI was significantly different between adenotonsillectomy in females (mean difference (95% CI) in BMI: 3.85(-3.98 to -1.85); p=0.034) but no difference in males (0.64(-1.32 to 1.66), p=0.079). Adenotonsillectomy females had a higher BMI (25.31 kg/m^2) than healthy females (21.43 kg/m^2).

Factor solutions collectively explained 84.9% of the variance, with consistently strong factor loadings (>0.5), were used to classify the 17 face shape measurements into 6 dimensions (D_1 to D_6) (Table 12.1). D_1 represents face height, explaining 32.4% of the variance. D_2 represents eyes distance with nose width, explaining 13.0% of the variance. D_3 represents philtrum angle, explaining 12.8% of the variance. D_4 is the mandible angle, explaining 9.6%. D_5 represents the nose prominence, explaining 8.7%, and D_6 is the maxilla angle with nose angle, explaining 8.3% of the variance.

Table 12.1: Face shape dimensions extracted by factor analysis

	Percentage of Variance Explained	
	%	Cumulative
Factor 1 (D_1) Total Face Height (pg-men) Total Face Height (pg-n) Total Face Height (li-men) Total Face Height (pg-g) Mid Face Height (Is-men) Mid Face Height (sn-men) Mid Face Height (n-sn) Lower Face Height (Is-pg) Mid Face Height Angle (exR-pg-exL)	32.4	32.4
Factor 2 (D_2) Outer Eyes Distance (exR-exL) Inter Eyes Distance (enL-enR Nose Width (alL-alR)	13.0	45.5
Factor 3 (D_3) Philtrum Angle (prn-sn-Is)	12.8	58.3
Factor 4 (D_4) Mandible Angle (g-men-pg)	9.6	67.9
Factor 5 (D_5) Nose Prominence (prn-sn)	8.7	76.6
Factor 6 (D_6) Maxilla Angle (n-sn-pg) Nose Angle (n-prn-sn)	8.3	84.9

Binary logistic regression models, adjusted for gender and BMI were constructed to predict adenotonsillectomy (see Table 12.2) using the factor scores for the six dimensions extracted by factor analysis as the predictor variables. Only one dimension (D_1) representing face heights was significantly associated with adenotonsillectomy. The odds of adenotonsillectomy children increased significantly with respect to D_1—Face height (OR 1.34, 95% CI 1.12, 1.60). An increase in the BMI was associated with increased odds of adenotonsillectomy (OR 1.07, 95% CI 0.89, 1.24).

Table 12.2: Binary logistic regression model to predict adenotonsillectomy using six face shape dimensions, gender and BMI

Predictor	Odds ratio	p-values	95% CI	
D_1 Face Height	1.34	0.001	1.12	1.60
D_2 Eyes Distance with Nose Width	0.87	0.101	0.73	1.03
D_3 Philtrum Angle	1.01	0.876	0.86	1.19
D_4 Mandible Angle	1.03	0.731	0.87	1.22
D_5 Nose Prominence	1.26	0.112	1.05	1.52
D_6 Maxilla Angle with Nose Angle	1.03	0.723	0.88	1.21
Gender	0.59	0.019	0.37	0.86
BMI	1.07	0.004	0.89	1.24

Table 12.3: Facial measurements for adenotonsillectomy and healthy children

	Males			Females		
	Adenotonsillectomy n=103	Healthy n=828	Difference in Mean (95%CI)	Adenotonsillectomy n=75	Healthy n=1034	Difference in Mean (95%CI)
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Total Face Height (pg-men)	97.54 (5.71)	96.65 (5.36)	0.88 (-0.19 to 0.21)	93.04 (4.69)	90.80 (4.30)	2.24 (-3.26 to -1.21)
Total Face Height (pg-n)	105.55 (6.68)	104.55 (6.02)	0.99 (-2.23 to 0.24)	101.55 (5.17)	98.80 (4.93)	2.75 (-3.92 to -1.57)
Total Face Height (li-men)	78.28 (4.57)	77.38 (4.29)	0.90 (-1.78 to 0.02)	74.32 (4.19)	72.46 (3.73)	1.85 (-2.74 to -0.96)
Total Face Height (pg-g)	117.27 (6.78)	116.01 (6.19)	1.26 (-2.53 to 0.01)	114.23 (5.26)	111.28 (5.16)	2.94 (-4.17 to -1.72)
Mid Face Height (Is-men)	64.55 (3.78)	64.35 (3.39)	0.20 (-0.90 to 0.50)	60.52 (3.32)	59.41 (2.93)	1.10 (-1.81 to -0.40)
Mid Face Height (sn-men)	50.26 (3.64)	50.16 (3.31)	0.09 (-0.77 to 0.58)	47.08 (3.17)	46.70 (2.79)	0.38 (-1.04 to -0.28)
Mid Face Height (n-sn)	53.94 (4.42)	53.55 (3.87)	0.39 (-1.19 to 0.40)	52.15 (3.62)	51.32 (3.46)	0.83 (-1.66 to -0.01)
Lower Face Height (Is-pg)	38.39 (3.99)	37.74 (3.72)	0.64 (-1.41 to 0.11)	36.79 (3.56)	35.51 (2.97)	1.27 (-1.98 to -0.56)
Mid Face Height Angle (exR-pg-exL)	48.21 (2.89)	48.77 (2.57)	0.56 (-1.09 to 0.03)	49.47 (2.39)	50.44 (2.37)	0.96 (0.40 to 1.53)

The summary data for the nine facial measurements of D_1 are presented in Table 12.3. To compare face shape of adenotonsillectomy and healthy children, 95% confidence intervals of the differences in the facial measurements were used. When comparing adenotonsillectomy and healthy children, there were no

statistically significant differences in any of the 9 facial measurements in males. In contrast, all of the 9 facial measurements were statistically significant in females. Females with adenotonsillectomy had an increased in the total, mid and lower anterior face heights with the maximum mean differences of 3mm when compared to healthy females.

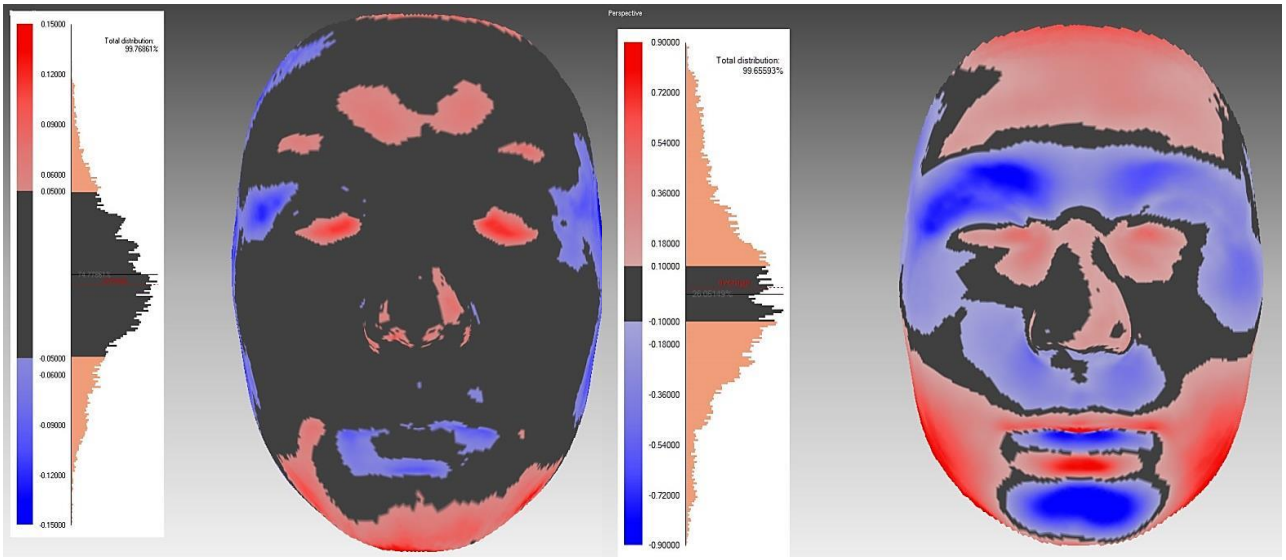


Figure 12.1: Superimposition of adenotonsillectomy and healthy average facial shells (males on left hand side, females on right hand side)

Note: The black area in the colour maps represents no difference between the adenotonsillectomy and healthy (0mm). The red areas are those prominent features in the adenotonsillectomy face – (0.1 to 0.3mm)**.** The blue representing less prominent facial features in the adenotonsillectomy children (0.1 to 0.9mm).

Superimposition of average facial shells of adenotonsillectomy and healthy children showed morphological differences between the groups in the z direction (Figure 12.1). The direction of the differences for the average facial shells is shown in the colour deviation maps for males on the left hand side and females on the right hand side. Adenotonsillectomy females tend to have less prominent chin, and eyebrows when compared to healthy females.

12.5 Discussion

Comparisons between the mean values of selected angular and linear measurements have provided useful information in early studies on facial morphology, including SDB. For example, the five-year follow up studies of Linder-Aronson (1975) and Woodside *et al.* (1991), which compared the cephalometric variables of 38 children following adenoidectomy with matched normal controls, demonstrated a trend towards normalisation with no significant differences between the two groups five years after surgery. The changes were found to be more significant in boys than in girls during the five-year follow-up period, indicating a difference between genders (Woodside *et al.,* 1991).

The use of three-dimensional facial scans and superimposition of average face shells was able to provide data with greater detail and give a better visual presentation of face-shape differences between the various groups (Zhurov *et al.*, 2010).

In the present study, the facial differences between adenotonsillectomy and the healthy children show trends towards normality, especially in males. Thus, males with a history of SDB symptoms but with an adenotonsillectomy in early life, become less long or adenoid face. This was consistent with the findings of Woodside *et al.* (1991). Consequently, a changed mode of breathing appears to influence normal craniofacial growth and development. This finding supports Peltomäki (2007) who reported after adenoidectomy a change in head and tongue position, accelerated mandibular growth and closure of the mandibular plane angle. However, adenotonsillectomy in females showed facial differences including long anterior face height, when compared with healthy females. Bonuck

et al. (2011) suggested that once SDB develops, treatment by adenotonsillectomy may not fully eliminate SDB, especially in the context of obesity. This is in consistent with the findings that adenotonsillectomy females have a higher BMI than healthy females; in contrast, BMI was not significantly different between adenotonsillectomy and healthy males.

A number of other studies have also investigated the above relationships in SDB children post-adenotonsillectomy. When maxillary and mandibular growth and the direction of maxillary growth were studied in adenoidectomic children, it was found that the amount of mandibular growth was higher in adenoidectomic children relative to healthy children (Woodside *et al.*, 1991). The difference was more apparent in males than females. In another study of adenoidectomy SDB individuals, anterior facial height was unchanged but growth of the mandibular ramus and condylar process of adenoidectomy patients was increased compared to normal asymptomatic people (Kerr *et al.*, 1989).

It thus becomes apparent that a more complex mechanism operates and contributes to changes in facial morphology in SDB individuals post adenotonsillectomy. It is suggested that in addition to the changes in head and tongue position and balance of muscles, this mechanism may involve epigenetic effects (Peltomäki, 2007). These effects could be relevant to the growth hormone signalling pathway, a more complex process whose exact dissection and understanding requires further investigation.

12.6 Conclusions

The following conclusions are drawn from the study:

- A higher BMI was recorded in SDB females who had undergone adenotonsillectomy.
- No significant difference was detected for any facial measurements in SDB males who had undergone adenotonsillectomy than healthy males.
- Statistically significant differences were recorded for nine facial measurements in SDB females who had had adenotonsillectomy compared to healthy females.
- In SDB females that have had adenotonsillectomy, higher total, mid and lower anterior face heights were documented compared to healthy females.

Chapter 13

Children with Multiple Diseases

13.1 Introduction

Associations between individual breathing disorders and face shape have been reported in multiple studies and have been identified in this research. These have been discussed in detail in the previous chapters. Therefore, it was of interest to investigate whether or not similar associations could be identified in children with multiple diseases involving asthma (Section 8.1), atopy (Section 9.1), allergy (Section 10.1) and SDB (Section 11.1). For this purpose, 56 children selected from the ALSPAC cohort with recorded asthma, atopy, allergy and SDB were compared to 1862 healthy children. However, these diagnoses were based on earlier assessments and parental reports, and had not been confirmed when the children were 15 years old when the facial scans were performed.

13.2 Subjects and Methodology

13.2.1 Sample

As previously described, children were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC). Asthmatic individuals were identified at 7½ years of age, when parents were asked to complete postal questionnaires that covered a range of health outcomes, including asthma symptoms and whether a doctor had ever diagnosed asthma in their children (Henderson *et al.*, 2008). Atopic children were identified when invited to attend a clinic at 7½ years of age, where skin-prick tests were performed to a panel of six allergens (house dust mite, cat, mixed grass, mixed nuts, peanut and milk) and a positive (1% histamine solution) and negative (diluent) controls (Henderson *et al.*, 2008). The detailed procedure is described in Chapter 9. Allergic rhinitis was detected by skin-prick tests to allergens on children at 11 years of age; the tests were carried

out on the anterior surface of the left arm using new disposable sterile lancets for each allergen tested (Henderson *et al.*, 2008). SDB was assessed via pre-existing questionnaires developed by ALSPAC for SDB symptoms (snoring, mouth-breathing and apnoea) when the child was 6, 18, 30, 42, 57, 69 and 81 months of age (Freeman & Bonuck, 2012). The cohort was recalled when the children were 15 years old, when three-dimensional laser facial scans were performed along with measurements for body weight, height and BMI. However, the health status, in respect to breathing disorders was not confirmed at this age.

13.2.2 Facial Imaging

Three-dimensional facial images of the children were captured using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), Detailed methodology of facial imaging can be found in Chapter 6. Data analysis was conducted (for methodology, see Chapter 8) comparing facial imaging of children with these multiple diseases to healthy children.

The average face of children with multiple diseases was compared with the average face of healthy children, by superimposing them on the mid-endocanthion point using a best-fit registration (Kau & Richmond, 2010; Zhurov *et al.*, 2010). A colour map was used to illustrate positive and negative changes between the study groups.

13.2.3 Statistical Analysis

A chi-squared test was performed in order to examine the association of these multiple diseases with gender. An independent sample t-test was used to compare BMI in children with multiple diseases and healthy children. Factor analysis was employed to reduce the 17 facial angles and measurements into a

smaller number of facial dimensions. Finally, logistic regression was applied in order to investigate the relationship between facial dimensions and the diagnosed groups.

13.3 Results

The total sample consisted of 1918 children, 55.2% of which were females. 56 of the children were diagnosed with multiple diseases and the remainder were healthy children.

No difference was found for the BMI in the children suffering from multiple diseases compared to healthy children (mean difference (95% CI) in BMI: 0.60(-1.56 to 0.35); p=0.874). No gender association was detected: 1.8% of the sample were males and diagnosed with multiple diseases and 1.0% were females and diagnosed with multiple diseases, generating a p value of 0.601.

Factor solutions collectively explained 79.4% of the variance, with consistently strong factor loadings (> 0.5), used to classify the 17 face shape measurements into 5 dimensions (D_1 to D_5) (Table 13. 1). D_1 represents facial height; explaining 32.2% of the variance. D_2 represents the distance between the eyes distance, nose width and maxilla angle, explaining 13.0% of the variance. D_3 represents the nose angle and philtrum angle, explaining 12.9% of the variance. D_4 is the mandible angle, explaining 11.0% of the variance, and D_5 is the nose prominence, which explains 9.1% of the variance.

None of the dimensions were significantly associated with multiple diseases. When differences in the facial dimensions were examined in relation to children

with multiple diseases, it was found that there are no significant differences between children with multiple diseases and healthy children.

Table 13.1: Face shape dimensions extracted by factor analysis

	Percentage of Variance Explained	
	%	Cumulative
Factor 1 (D_1) Total Face Height (pg-men) Total Face Height (pg-g) Total Face Height (pg-n) Lower Face Height (Is-pg) Total Face Height (li-men) Mid Face Height (sn-men) Mid Face Height (n-sn) Mid Face Height (Is-men) Mid Face Height Angle (exR-pg-exL)	32.2	32.2
Factor 2 (D_2) Outer Eyes Distance (exR-exL) Inter Eyes Distance (enL-enR) Nose Width (alL-alR) Maxilla Angle (n-sn-pg)	13.0	46.2
Factor 3 (D_3) Philtrum Angle (prn-sn-Is) Nose Angle (n-prn-sn)	12.9	59.1
Factor 4 (D_4) Mandible Angle (g-men-pg)	11.0	70.2
Factor 5 (D_5) Nose Prominence (prn-sn)	9.1	79.4

Table 13.2: Binary logistic regression model to predict multiple diseases using five face shape dimensions

Predictor	**Odds ratio**	**p-value**	**95% CI**	
D_1 Face Height	1.18	0.212	0.90	1.54
D_2 Eyes Distance, Nose Width, Maxilla Angle	0.85	0.271	0.65	1.12
D_3 Philtrum Angle, Nose Angle	1.07	0.593	0.82	1.41
D_4 Mandible Angle	0.98	0.928	0.75	1.30
D_5 Nose Prominence	0.93	0.647	0.71	1.23

A binary logistic regression model was constructed using the principal component scores for the five dimensions extracted by factor analysis as the predictor variables to predict children with multiple diseases. None of the dimensions were significantly associated with children of multiple diseases (see Table 13.2).

The superimposition of average facial shells of children with multiple diseases and healthy children (Figure 13.1) showed no significant morphological differences between the groups, as seen in the colour map in Figure 13.2.

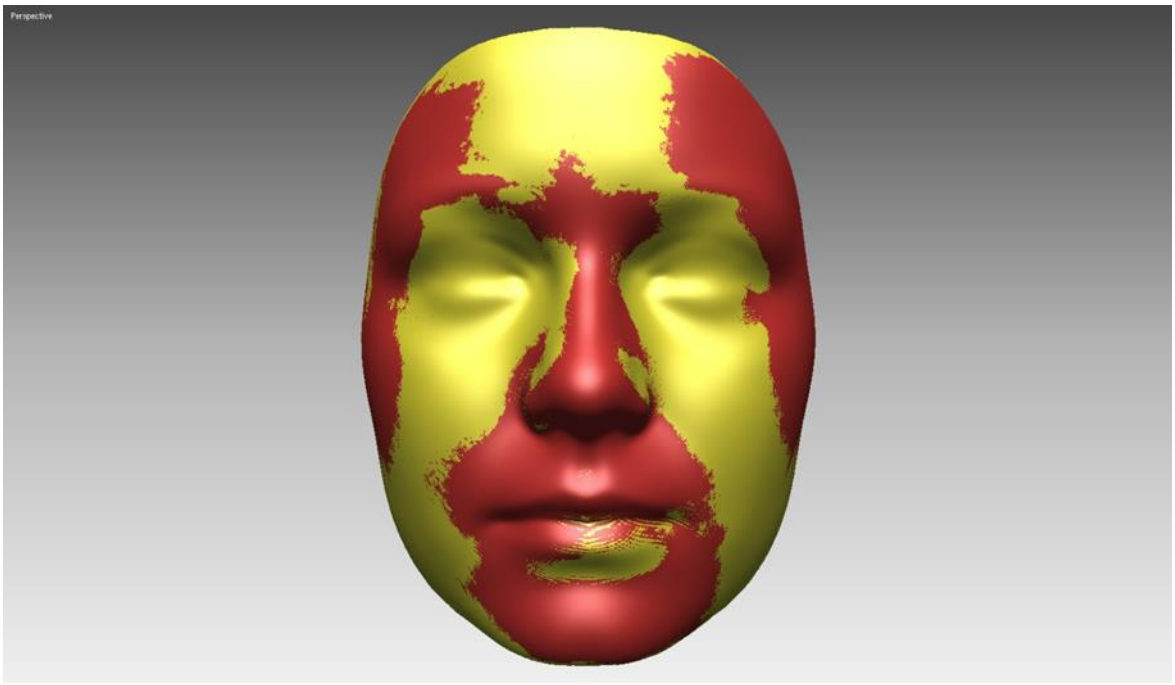


Figure 13.1: Superimposition of average facial shells of children with multiple diseases (yellow) and healthy children (red)

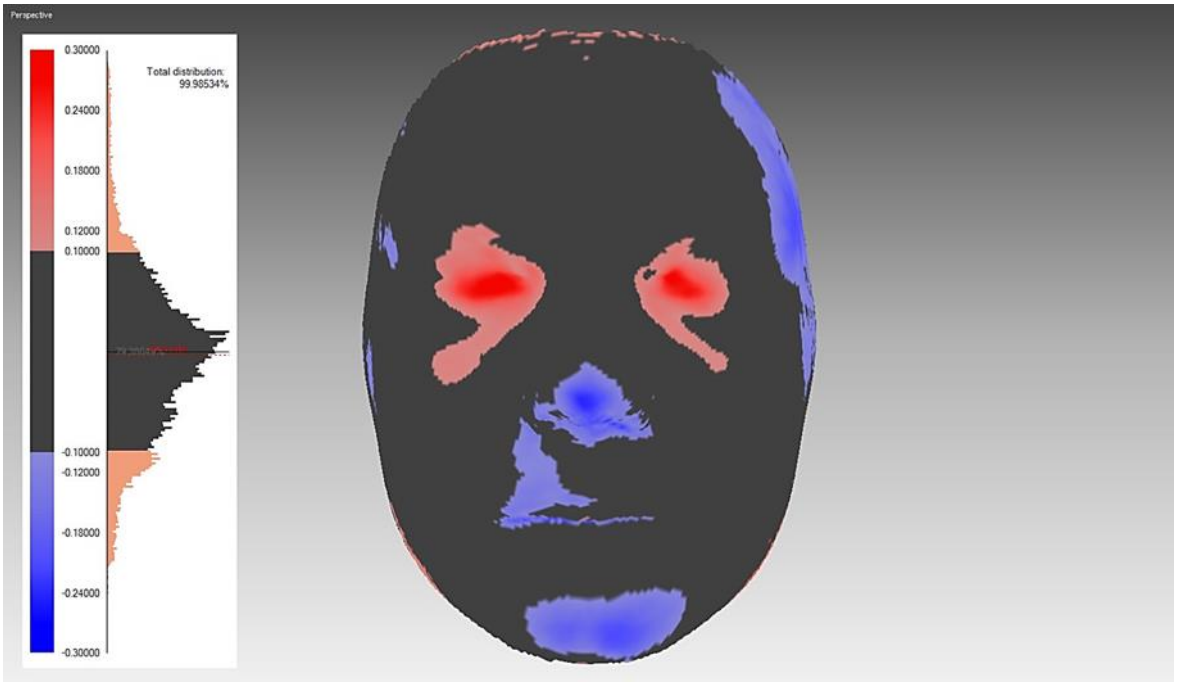


Figure 13.2: Colour maps and histogram plots to assess facial differences between children with multiple diseases and healthy children

Note: The black areas represent no difference in the diseased and healthy children (0mm). The blue areas represent less prominent features in children with multiple diseases (0.1-0.2mm), while the red areas are those prominent features in the faces of children with multiple diseases (0.1-0.3mm)**.**

13.4 Discussion

The detailed analysis compared children with multiple diseases to healthy children. Particular care was taken during the facial data acquisition and analysis to ensure that good images were obtained. In order to avoid gender bias, both males and females participants were included. From the previous data on children with individual breathing conditions, it was expected that a more significant association between facial shape and children with multiple conditions would be found.

However, no such association could be detected. A number of reasons are possible in explaining this lack of association. All these disorders are multifactorial conditions that are heavily influenced by an individual's genetic

predisposition, as well as environmental factors. It is possible that the way of action and function of these factors is contradictory or even antagonistic, such that the effect of one breathing disorder on face shape could be counteracted by another disorder. It is also likely that the association between facial shape and breathing disorders is mild, so that only in some cases can this relationship be validated. In order for firm conclusions to be drawn on the relationship between complex diseases and breathing disorders, this study could be replicated using a larger number of diseased and healthy participants and potentially more detailed diagnosis of the medical conditions, and its severity with more detailed information about treatment intervention and management. In this case, it might be possible to detect the impact of complex breathing disorders on face shape.

13.5 Limitations

A limitation of the study was that the severity of the medical conditions and the supporting medication were not recorded. Nevertheless, in such a large sample it was expected that there would be a broad range of severity and medication. Despite this, differences were not found. Although this information may have been available in the children's medical records, obtaining access to these records was not possible. In addition, the diagnoses of multiple breathing disorders were based on earlier assessments and parental reports, and were not confirmed at 15 years when the facial imaging was performed.

13.6 Conclusions

The study on children suffering from multiple diseases draws the following conclusions. No statistically significant difference was found in the BMI between children with multiple diseases and healthy children. Furthermore, there was no

gender association with children suffering from multiple diseases. In addition, no statistically significant association could be drawn for the facial shape measurements that were examined in children suffering from multiple diseases and the healthy children. The small number of children with multiple diseases (56) may be a reason why no differences were found between children with multiple diseases and healthy children.

Chapter 14

Conclusion

14.1 Conclusion

This thesis employs various methodological and analytical approaches to gather and analyse data on a cohort of children containing individuals with breathing disorders and healthy individuals, in order to address the effect of breathing disorders on face shape. Great emphasis was placed on efficiently capturing, analysing and interpreting facial images in the clinical context, in order to provide healthcare professionals who manage the relevant patient groups with information on diagnosis, treatment planning and outcome assessment. However, the methods presented in this work are not only of value to clinicians, but can be more widely applied to researchers on breathing disorders, other medical conditions and facial morphogenesis.

The thesis is organised in three parts: Chapters 1 to 4 contain the literature review that explains the fundamental concepts behind craniofacial growth, the influence of genetic and environmental factors and the three-dimensional imaging technologies applied to study cranial growth. The second part (Chapter 5 to 7) is concerned with the methodological and experimental approaches used. Chapters 5 and 6 discuss the methodology and aims and objectives of the study. Chapter 7 focuses on using laser scan three-dimensional imaging technology to obtain consistent and reproducible facial soft tissue landmarks. The methodology and troubleshooting described in the chapter is very useful in both a clinical and an experimental setting, as it allows medics and researchers to use three-dimensional facial imaging as a potential detection and prognosis method for a number of disorders and diseases that are known to impact on facial shape. If the effect on face shape can be easily and reliably detected, then clinicians can more

accurately diagnose and advise patients on the most appropriate course of treatment.

In part three, Chapters 8 to 13 apply the methodology of three-dimensional imaging acquisition and analysis to children suffering from asthma, atopy, allergic rhinitis and sleep disordered breathing (SDB). The most reliable measurements of facial shape were applied to all individuals and accurate statistical methods were used to objectively determine the statistical significance of the associations between altered facial characteristics and certain breathing disorders. Special emphasis was also placed on children's gender and their BMI. The findings show that the model was sufficiently sensitive to identify differences in facial shape for almost all disorders and to provide a relationship between these changes and the individual's BMI and gender.

A useful application of the three-dimensional facial imaging methodology could be the adoption of such facial scanning and analysis for the early diagnosis of breathing disorders. This study has successfully identified specific relationships between distinct facial characteristics and asthma, atopy, allergic rhinitis and SDB. Three-dimensional facial imaging scanning could be used in the clinic to identify differences in the facial measurements of children with any of the above breathing disorders. Subsequent to this identification, children with specific facial characteristics, such as a long face or a retrognathic mandible, could be referred for further assessment of potential, underlying breathing disorders. Based on the distinct facial measurements, this methodology allows not only the screening of children with breathing difficulties but it also builds up the understanding of the environmental effect on face shape.

For example, a clear effect on facial shape was detected in children with SDB, irrespective of whether or not they have had undergone adenotonsillectomy. From the data, it became obvious that once SDB develops, treatment by adenotonsillectomy cannot always reliably dispose of it, notably when obesity is a factor.

The three-dimensional facial imaging methodology also permitted the accurate and reproducible determination of soft tissue landmarks. It highlights the significance of correct placing of the landmarks and shows that there is some variability in the reproducibility of certain facial tissue landmarks. Thus, careful consideration should be given when landmarks are placed on curving slopes as opposed to clearly obvious borders. This study successfully manages to reproduce the x, y and z coordinates of 21 facial landmarks to less than 1mm, generating an accuracy of identification of 0.48 to 1.11mm. Also, by using the average facial shells over 4500 surface points (rather than a handful of landmarks) that make up the topography of the face are used. This emphasises the robustness of the methodological work and further illustrates the significance of the associations detected between breathing disorders and facial shape.

14.2 Limitations

Facial variation can be affected by multiple factors and the associations between face shape and breathing disorders can be subtle in relation to other environmental and genetic effects. Strategies were adopted in the study design to address these limitations (Section 5.3), including enrolling a large study population from the ALSPAC cohort and utilising advanced three-dimensional scanning with high reproducibility. In addition, the interpretations were based on

95% confidence intervals (95% CI) rather than p-values in order to identify traits and patterns with potential diagnostic value, as oppose to simple hypothesis testing (Gardner & Altman, 1986).

Although it was possible to define the age, gender and ethnicity of the sample population, environmental factors (such as exposure to tobacco smoke) present a greater challenge and could not be controlled by the research protocol. Therefore, several factors were unknown at the time of study.

Much of the information derived from the ALSPAC data was based on parental records. However, the validity of self-reporting has been confirmed in similar studies (Cornish *et al*., 2014). Furthermore, the ALSPAC study has been cross-validated with other large cohort samples such as the Rotterdam Study Cohort (Hofman *et al.*, 2009) and the results cross-referenced against genotype-phenotype data. Nevertheless, it was acknowledged that the research would have benefitted from repeat questionnaires and further follow-up data.

14.3 Future Research

This study clearly demonstrates the effect of breathing disorders on face shape. It points the direction by which these relationships can be detected and provides the clinical community with a new tool that can be used to enhance knowledge about the environmental influence on facial shape using a novel unique technology. Although this method shows clear associations between breathing disorders and facial shape, some associations were relatively mild and the relationship was not always straightforward. It is worth extending this study to a cohort group containing different age groups of children and incorporating

additional breathing disorders, more information about the severity of the disorders and the type of medication taken.

Regarding the lack of effect of multiple breathing disorders on face shape, the complex character of these diseases needs to be investigated. It remains possible that these associations are very subtle and in order to detect them, a larger cohort group requires to be studied. This group should include children with the complex spectrum of diseases across various age groups and both genders.

It is also worth investigating the possibility that three-dimensional facial imaging methodology can be applied to detect changes in facial landmarks in patients suffering from other diseases that are known to have an impact on face shape. This application could potentially lead to the transfer of this technology to the clinic for use as a diagnostic tool.

Furthermore, it is interesting to investigate if these facial differences affect the dentition i.e. are cross bites and anterior open bites (AOB) found in the longer faced patients? This could be achieved by using three-dimensional technology which allows a detailed visualization of the dental occlusion as previously described by Schutyser *et al.* (2005) .

Finally, it would be exciting to construct an average face template for children with long faces, short face heights and normal face heights, and then to identify which medical conditions are associated with each average face height template. This ambitious objective could potentially lead to new discoveries on the effect of

distinct and, as yet, unknown disorders and diseases, on the shape and characteristics of the human face.

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Appendices

Appendix 1: Children with a combination of varying diseases

	Frequency	Percept
Asthma and Atopy	42	0.8%
Asthma and Allergic rhinitis	14	0.3%
Asthma and Sleep disordered breathing	116	2.4%
Atopy and Allergic rhinitis	123	2.6%
Atopy and Sleep disordered breathing	150	3.1%
Allergic rhinitis and Sleep disordered breathing	152	3.1%
Asthma, Atopy and Allergic rhinitis	35	0.7%
Asthma, Atopy and Sleep disordered breathing	52	1.1%
Atopy, Allergic rhinitis and Sleep disordered breathing	117	2.4%

Appendix 2

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The influence of asthma on face shape: a three-dimensional study

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SUMMARY Respiratory activity may have an influence on craniofacial development and interact with genetic and environmental factors. It has been suggested that certain medical conditions such as asthma have an influence on face shape. The aim of the study is to investigate whether facial shape is different in individuals diagnosed as having asthma compared with controls. Study design included observational longitudinal cohort study. Asthma was defined as reported wheezing diagnosed at age 7 years and 6 months. The cohort was followed to 15 years of age as part of the Avon Longitudinal Study of Parents and Children. A total of 418 asthmatics and 3010 controls were identified. Three-dimensional laser surface facial scans were obtained. Twenty-one reproducible facial landmarks (x, y, z co-ordinates) were identified. Average facial shells were created for asthmatic and non-asthmatic males and females to explore surface differences. The inter-ala distance was 0.4 mm wider (95% CI) and mid-face height was 0.4 mm (95% CI) shorter in asthmatic females when compared with non-asthmatic females. No facial differences were detected in male subjects. Small but statistically significant differences were detected in mid-face height and inter-ala width between asthmatic and non-asthmatic females. No differences were detected in males. The lack of detection of any facial differences in males may be explained by significant facial variation as a result of achieving different stages of facial growth due to pubertal changes, which may mask any underlying condition effect.

Introduction

The development of an individual's facial shape and form depends on the interactions of genetic factors with environmental factors, including the intensity and duration of the latter (Peng *et al.*, 2005; Paternoster *et al.*, 2012). Altered mechanics of breathing may influence the development of craniofacial structures (Cooper, 1989; Yamada *et al.*, 1997) and interfere with normal mastication and swallowing, which favour harmonious facial growth (Moss, 1962). Nasopharyngeal obstruction often results in the mouth-breathing (Straub, 1994), leading to a change in head posture to compensate for the decrease in nasal airflow (Josell, 1995), which can result in disharmony in the growth and development of orofacial structures (Rubin, 1980).

Numerous systemic medical conditions can influence facial shape, such as type 1 diabetes (El-Bialy *et al.*, 2000), growth hormone deficiency (Kjellberg *et al.*, 2000; Van Erum *et al.*, 1998) and asthma (Mattar *et al.*, 2004; Richmond *et al.*, 2009). Reduced somatic growth, which can accompany chronic asthma, is also associated with changes in facial structures in children (Kjellberg *et al.*, 2000; Pirinen *et al.*, 1994).

Asthma is a chronic disorder, characterized by the interaction of a number of asthma-related genes with environmental factors. The main characteristics include airway

inflammation, intermittent airway obstruction and bronchial hypersensitivity, of which not all are necessarily present in patients to the same degree (Kiley *et al*., 2007). During the period of most rapid somatic growth after infancy, the prevalence of asthma changes. It has been reported that the prevalence of asthma is higher in boys under 15 years of age than girls of the same age and higher in females 15 years of age and above (To *et al*., 1996; Krishman *et al*., 2001; Schatz *et al*., 2003).

Patients with chronic asthma symptoms can present with an increased resistance of the lower airways with gas-trapping in the chest (Chaves *et al*., 2010). The altered mechanics of breathing associated with these changes can lead to shortening of the cervical respiratory muscles, which could alter head and cervical spine posture (Hruska, 1997; Lopes *et al*., 2007). This may cause dysregulation in the growth and development of the orofacial structures, including narrowing of the maxilla and lower development of the mandible (Bresolin *et al*., 1984; Solow and Sandham, 2002).

The aim of this study is to investigate differences in facial features in 15-year-old children taking part in a longitudinal follow-up study that were reported as having asthma at 7.5 years of age and a control group drawn from the same population.

Appendices

Subjects and Methods

Sample

The children involved in this study were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC). The study was designed to explore how an individual's genotype is influenced by environmental factors impacting on health, behaviour, and development of children (Golding *et al*., 2001). The initial ALSPAC sample consisted of 14 541 pregnancies. This was the number of pregnant women enrolled in the ALSPAC study with an estimated date of delivery between April 1991 and December 1992. Out of the initial 14 541 pregnancies, all but 69 had known birth outcome. Of these 14 472 pregnancies, 195 were twins, 3 were triplets, and 1 was a quadruplet pregnancy, meaning that there were 14 676 foetuses in the initial ALSPAC sample. Of these 14 676 foetuses, 14 062 were live births, and 13 988 were alive at 1 year.

Mothers were asked to complete postal questionnaires that covered a range of health outcomes, including asthma symptoms and whether a doctor had ever diagnosed asthma in their children at 7.5 years of age (Henderson *et al*., 2008).

The cohort was re-called when the children were 15 years of age. Invitations were sent to 9985 participants who reported that they were interested to take part in the clinics. Of these, 418 asthmatics (185 females, 233 males) and 3010 controls (1636 females, 1374 males) were included in the study. Body weight and height was measured. The BMI was calculated as follows: BMI = weight(kg)/(height(cm)/100)^2. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees prior to the commencement of the study.

Facial imaging

Three-dimensional facial images of the subjects were captured using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), with a reported manufacturing accuracy of 0.1 mm (Kau *et al*., 2003). The scanners were controlled with Multi-scan software (Cebas Computer GmBH, Eppelheim, Germany), and right and left facial scans were saved in a vivid file format. Rapidform 2006 (INUS Technology, Seoul, Korea) was used to process and analyse the facial scans in the manner described in the following paragraphs. The right and left facial scans of each participant were registered and merged using a locally developed subroutine using Rapidform software. Three-dimensional facial images were normalized within a reference framework using three planes: sagittal (Y-Z plane), coronal (X-Y plane), and transverse (X-Z plane), as shown in Figure 1. The origin of the co-ordinate system was the point between the inner corners of the eyes (mid-endocanthion) (men),which, as previous research has shown, is the most stable facial landmark (Toma *et al*., 2009; Zhurov *et al*., 2010).

Twenty-one facial soft tissue landmarks (Figure 2, Table 1) were manually identified on each facial image (Toma *et al*., 2009, 2011), and the x, y and z co-ordinates were recorded. The reproducibility of these landmarks in the three dimensions has been reported previously, generally with an error of less than 1 mm for both intra- and inter-examiner assessments (Toma *et al*., 2009).

Soft tissue parameters were evaluated as follows: exR-exL (inter-eye distance), al-al (nose width), n-pg (total facel height), Is-pg (lower face height), Is-men (mid-face height), exR-pg-exL (mid-face angle), s-sn-pg (face convexity), n-pr-sn (nose prominence), and prn-sn-Is (philtrum depth). The 9 facial parameters included in the analysis were those that describe the main anterior-posterior, vertical and transverse relationships in facial shape analysis. For example, the inter-eye distance and nose width allow transverse analysis. The face height (total, lower and mid) allows for vertical relationships to be studied. Finally, the mid-face angle, facial convexity, nose prominence, and philtrum depth relate to anterior-posterior facial features.

Statistical analysis

The differences in weight, height, and BMI of both genders were estimated by *t*-test. The analysis of the data was carried

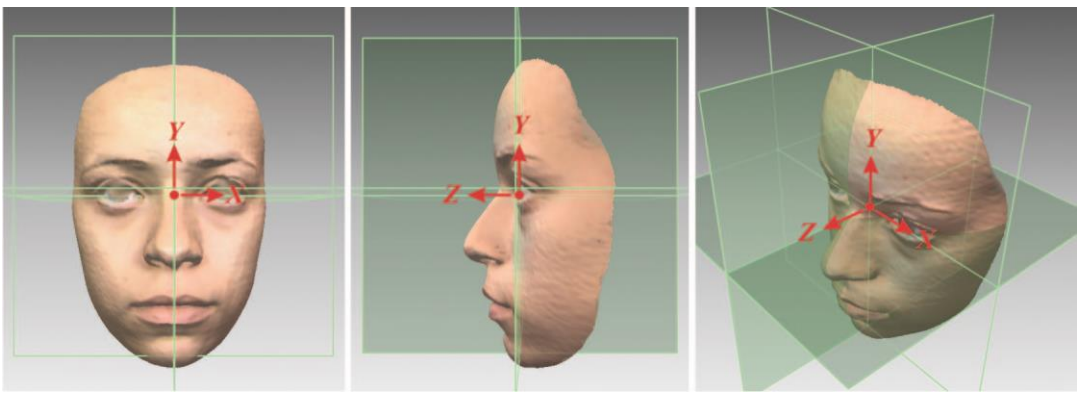

Figure 1 Normalization of facial shells to natural head posture.

Appendices

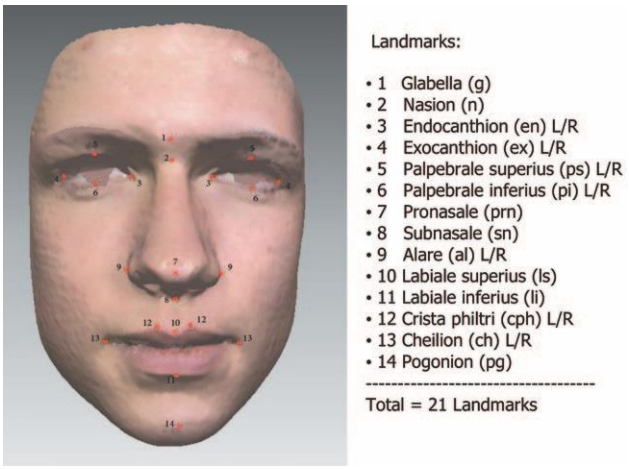

Figure 2 Facial soft tissue landmarks.

out using 95% CIs of the difference in facial parameters were used to examine the magnitude of the differences between the asthmatic and control groups. This was carried out for male and female groups separately as evidence suggests that both gender and asthma prevalence can influence facial growth (Kynyk *et al.*, 2011; Wenzel *et al.*, 1985). Crouse and Laine-Alava (1999) have indicated gender differences on nasal airflow rate and nasal cross-sectional area. Average facial shells were created for the asthmatic and non-asthmatic females and males using a previously validated method (Kau and Richmond, 2010; Zhurov *et al.*, 2010).

Average faces were superimposed on the mid-endocanthion point (men). Differences in morphology were presented using colour maps, with a tolerance level of 0.25 mm to highlight significant topographical facial differences.

Results

A total of 5253 children attended the clinic at 15 years of age. Of this sample, 506 participants were excluded from analysis for the following reasons: not having their facial images recorded at the time of attending the clinic, poor quality facial scans, non Caucasian, and obvious facial dysmorphology. The sample therefore represented variation population-sample of 4747 Caucasian children (2514 females and 2233 males), of whom 418 children were reported to have asthma at 7.5 years of age (Henderson *et al.*, 2010).

The means of weight (kg), height (cm), and BMI for males and females of both asthmatic and non-asthmatic are shown (Table 2). In asthmatic females the mean BMI was greater than non-asthmatic males and females as well as asthmatic males. There was no significant difference in BMI between asthmatic and non-asthmatic males.

The summary data for the nine facial parameters used in this study are presented (Table 3). To compare the facial features of asthmatics and non-asthmatics, 95% CIs of the differences in the measured facial parameters were used. When comparing asthmatics with non-asthmatics, there were no statistically significant differences in any of the 9 facial parameters in males. In contrast, three of the nine facial parameters differed in females; nose width, mid-face height, and mid-face angle. Females with an asthma history had on average a 0.4 mm wider nose compared with non-asthmatic females but could be as much as 0.7 mm. The mid-face height of asthmatic females measured from Is-men was on average 0.4 mm shorter than non-asthmatics but could be as much as 0.9 mm. And the mid-face angle of female non-asthmatics was more acute when compared with asthmatics (51.3 degree versus 51.7 degree).

Superimposition of average facial shells of asthmatic and non-asthmatic males showed no morphological differences. Whereas, superimposition of average asthmatic and non-asthmatic females facial shells confirmed the landmark measurements of a wider inter-ala distance. Differences of 0.4–0.5 mm were recorded in the nose width (Figure 3).

Discussion

This study is the first to investigate facial morphology of adolescents suffering from asthma in a large cohort of 15-year-old children using 3D facial imaging. Our findings suggest that there are small differences between the faces of asthmatic and non-asthmatic individuals; this was predominantly for females.

To understand the relevance of the results the underly- ing mechanisms of facial growth in the context of asthma should be considered. Moss (1997) theorizes that growth of the face occurs as a response to functional needs and is mediated by soft tissue in which the jaws are embedded. In simple terms, the soft tissues grow, and both bone and cartilage react. For example, the orbit grows as a result of growth of the eyes. The cranium increases in size as a result of growth of the brain, which separates the cranial bones at the sutures while new bone passively fills in at these sites (Moss, 1997). Nasal breathing encourages an increase in size of the nasal cavity in all directions with the floor of the nose developing in a downward and forward direction. Therefore the presence of any respiratory problems may affect normal craniofacial growth. Normal craniofacial growth seems to depend on normal physiological nasal breathing (Fricke *et al.*, 1993; Solow *et al.*, 1984; Vig *et al.*, 1981). It has been argued that mouth-breathing in children results from pharyngeal obstruction (Oulis *et al.*, 1994), affecting the position of the craniofacial muscles and the mandible, leading to occlusal and skeletal alterations (Subtelny, 1975).

Suppression of growth secondary to asthmatic condi- tions has been suggested (Nelson and Drash, 1959; Falliers

Appendices

Table 1 Facial soft tissue landmarks (points).

Facial Region	Landmark name	Abbr.	Definition
Eyes	Endocanthion(R)	En	Inner commissure of the right eye fissure
	Endocanthion(L)	En	Inner commissure of the left eye fissure
	Exocanthion (R)	Ex	Outer commissure of the right eye fissure
	Exocanthion (L)	Ex	Outer commissure of the left eye fissure
	Palpebrale superius (R)	Ps	Superior mid-portion of the free margin of upper Rt eyelid
	Palpebrale superius (L)	Ps	Superior mid-portion of the free margin of upper Lt eyelid
	Palpebrale inferius (R)	Pi	Inferior mid-portion of the free margin of upper Rt eyelid
	Palpebrale inferius (L)	Pi	Inferior mid-portion of the free margin of upper Lt eyelid
Forehead	Glabella	G	Most prominent midline point between the eyebrows
Nose	Nasion	N	Deepest point of nasal bridge
	Pronasale	Prn	Most protruded point of the apex nasi,identified in lateral view of the rest position of the head.
	Subnasale	Sn	Mid-point of angle at columella base where lower border of nose and surface of upper lip meet.
	Alare (R)	Al	Most lateral point on right alar contour.
	Alare (L)	Al	Most lateral point on left alar contour.
Lips and Mouth	Labiale superius	Ls	Mid-point of the upper vermilion line
	Labiale inferius	Li	Mid-point of the lower vermilion line
	Crista philtri (R)	Cph	Point on right elevated margin of the philtrum just above the vermilion line
	Crista philtri (L)	Cph	Point on left elevated margin of the philtrum just above the vermilion line
	Cheilion (R)	Ch	Point located at right labial commissure.
	Cheilion (L)	Ch	Point located at left labial commissure.
Chin	Pogonion	Pg	Most anterior mid-point of the chin.

et al., 1961; Russell, 1993; Doull, 2004). Some studies have suggested that growth retardation in asthmatic children may occur for a number of reasons, including malnutrition (Snyder *et al*., 1967; Murray *et al*., 1976), chronic infection (Snyder *et al*., 1967; Hauspie *et al*., 1977), steroid therapy (Murray *et al*., 1976; Falliers *et al*., 1961; Morris, 1975; McCowan, 1998; Price, 2002), diminishing lung function (McNicol and Williams, 1973; Hauspie *et al*., 1977), hypoxia (Murray *et al*., 1976), and long-term stress (Hauspie *et al*., 1977).

Several clinical studies have supported the theory of a relationship between head posture in breathing difficulties and craniofacial morphology (Solow and Tallgren, 1976; Thompson, 1978; Wenzel *et al*., 1985). Wenzel (1985) studied the craniofacial morphology in children with asthma from lateral skull radiographs of a small sample of 50 asthmatic children with differing ages (6–16 years of age) compared with 50 control children and concluded that small differences were found in craniofacial morphology between asthmatic children and controls. The severely affected children tended to have a greater change in morphology and more likely to develop a retrognathic jaw associated with extension of the head.

Asthma or 'variable airflow obstruction' refers to episodic breathing difficulties that sometimes result in dysfunction, severe disability, and even death (Cecil *et al*., 1940). Asthma is recognized from a pattern of one or more characteristic symptoms, including cough, wheeze, chest tightness and dyspnoea, and is better confirmed by evidence of variable or reversible airflow obstruction accompanying symptoms. Bresolin *et al*. (1983) found that the upper face height as well as maxillary and mandibular inclinations were increased in 30 mouth breathers and allergic children aged 6–12 years compared with 15 control children. In addition, they found that the mouth-breathing group was associated with retrognathism of the upper and lower jaws. The conflicting findings between the previous studies and the present study can be explained by diagnosis, age of children, sample size, and methods of recruitment and assessment.

The present study investigated children diagnosed as wheezing at 7.5 years of age, while Bresolin *et al*. evaluated dentofacial development in the mouth breather with allergy. Moreover, the use of the three-dimensional imaging

Table 2 Mean values for height, weight and BMI.

Facial Parameter	Asthmatic control difference in mean					
Male (n = 233)	(n = 1374)	(95%CI)	Female (n = 186)	(n = 1636)	(95%CI)	
Height (cm)	172.39 (7.711)	174.78 (7.493)	2.39 (1.36–3.42)	164.06 (5.840)	164.66 (6.011)	0.59 (−0.31−1.50)
Weight (kg)	61.87 (10.832)	64.31 (12.173)	2.44 (0.80–4.08)	61.29 (11.774)	58.64 (10.484)	−2.64 (−4.25−1.04)
BMI	20.76 (3.077)	20.97 (3.329)	0.21 (−0.23–0.66)	22.71 (3.841)	21.60 (3.513)	−1.11 (−1.65−0.57)

Appendices

Table 3 Descriptive statistics of facial parameters and a test between asthmatic and non-asthmatic groups.

Facial parameter	Asthmatic control difference in mean (SD)					
Male (*n* =233)	(*n* = 1374)	(95%CI)	Female (*n* = 186)	(*n* = 1636)	(95%CI)	
Eyes distance (mm) (exR-exL)	88.4 (4.27)	88.3 (4.04)	−0.09 (−0.65–0.46)	87.0 (3.60)	86.6 (3.96)	−0.4 (−0.96–1.94)
Nose width (mm) (al-al)	34.7 (2.86)	35.0 (2.51)	0.25 (−0.91–0.60)	32.7 (2.39)	32.2 (2.24)	0.4 (−0.72−0.03)
Total face height (mm) (pg-n)	104.3 (6.05)	104.8 (6.15)	−0.54 (−0.28–1.37)	98.9 (4.79)	99.0 (5.16)	0.12 (−0.65−0.89)
Lower face (mm) (ls-pg)	37.5 (3.53)	37.9 (3.80)	0.38 (−1.29–0.90)	35.6 (2.93)	35.6 (3.12)	0.07 (−0.39−0.54)
Mid-face (mm) (ls-men)	63.8 (3.55)	64.3 (3.39)	0.45 (−0.01–0.92)	58.9 (2.93)	59.4 (2.96)	0.49 (0.04−0.93)
Mid-face (angle) (exR-pg-exL)	49.8º (2.70)	49.5º (2.71)	−0.27 (−0.65–0.10)	51.7º (2.71)	51.3º (2.65)	−0.41 (−0.81−0.02)
Face convexity (n-sn-pg)	180.4º (1.51)	180.4º (1.83)	0.09 (−0.15–0.33)	180.5º(1.53)	180.4º (1.64)	−0.06 (−0.31−0.19)
Nose prominence (n-prn-sn)	179.8º (3.17)	180.0º (2.76)	0.20 (−0.25–0.65)	180.2º (2.73)	179º (4.63)	−0.06 (−0.53−0.40)
Philtrum depth (Prn-sn-ls)	127.5º (9.38)	127.3º (8.97)	−0.11 (−1.35–1.12)	127.7º (8.89)	126.9º (8.39)	−0.84 (−2.12−0.42)

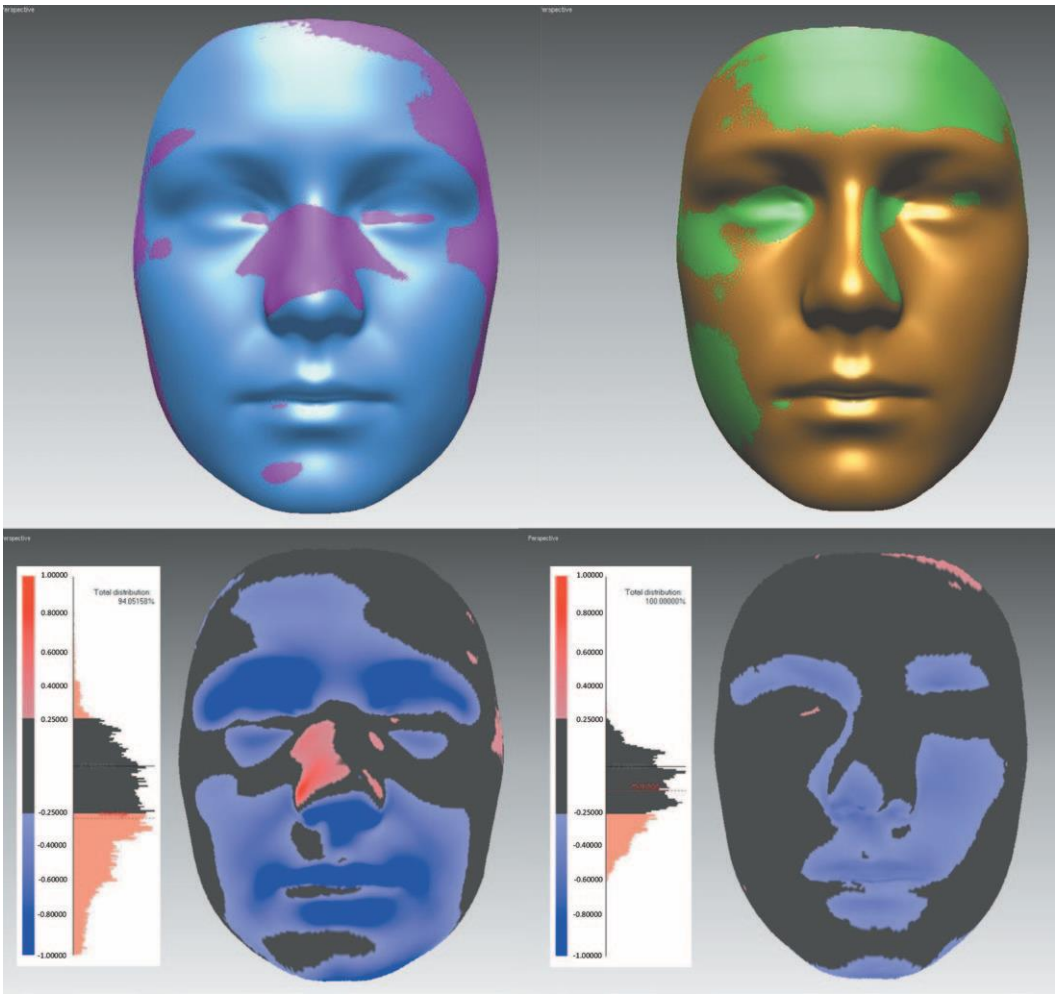

Figure 3 Superimposition of asthmatic and non-asthmatic females average facial shells (left) and males (right).

technique has provided more accurate and precise analysis of facial morphology, than using anthropometry, cephalom- etry, and photography (Kau *et al*., 2004, 2005).

Epidemiologic studies of asthma show differences in asthma prevalence and severity related to age and gender. The likelihood of developing asthma is about 10.5 per cent greater in women than men, with a significant increase in the severity of asthma in women after puberty (de Marco *et al*., 2000; McCallister *et al*., 2011). This could explain why females showed greater facial morphological

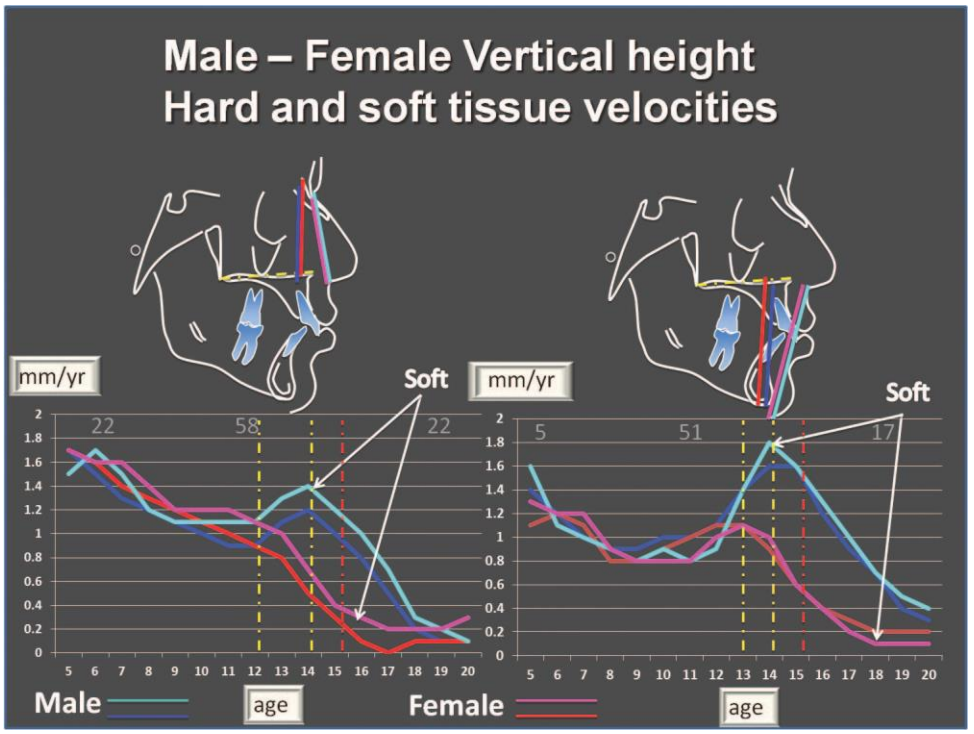

Figure 4 Soft and hard tissue velocities in relation to upper and lower face height. Both males and females show similar steady growth velocities (1–1.2 mm/year) from 7 to 11 years of age. Taken from Bhatia SN, Leighton BC A manual of facial growth. Oxford Medical Publications, 1993.

differences between the asthmatics and control groups when compared with males. It should be noted however that although statistical significance was inferred for some facial parameters in the female group, the linear differences were small. Therefore their clinical significance will require further investigation. Researchers continue to explore the potential influence of the female sex hormones, hormonal influences that are associated with both asthma and craniofacial growth, increased bronchial hyperresponsiveness, and altered perception of airflow obstruction (Kynyk *et al*., 2011).

We found a slightly increased nasal width (al-al) in asthmatic females and might presume that size of nasal airway is related to body size in general, as BMI values of asthmatic females were slightly larger than males in this study. However, previous studies in children and young adults have indicated that BMI has an effect on airflow rate and nasal airway size (Laine-Alava and Minkkinen, 1997; Crouse Uand Laine-Alava MT 1999). Laine-Alava and Minkkinen, 1997 found that the values for airflow rate tended to increase with the increasing BMI, indicating that subjects with larger body size need higher air volumes. Therefore, asthmatic females showed an increased nasal cross-sectional area.

The other positive finding was the shorter mid-face height in asthmatic females. The design of the study was observational longitudinal, as such the analysis was facilitated to find association and not test for hypothesis. Therefore, albeit a positive association was found but with asthmatic females with a reduced mid-face height, the clinical and potential statistical significance is likely to be minimal.

We were not able to detect any facial differences in asthmatic and non-asthmatic males. This may be explained by wide facial variation due to individuals reaching different stages in puberty which may mask any underlying condition effect.

Cephalometric investigations on longitudinal samples have identified a pubertal spurt in craniofacial growth that is characterized by wide individual variations in onset, duration, and rate (Ekström, 1982; Hunter, 1966; Nanda, 1955). Generally, puberty starts in females approximately 2 years before males and is shorter in duration. The mean peak height velocity occurs at around the age 12 years in females and 14 years in males. In a 15 year old population most of the facial growth will be completed in females but there would be still be significant growth potential in males. Therefore timing of assessment of the influence of medical conditions may be better conducted between 7 to 10 years of age when there are similar growth rates in males and females (Figure 4) or at 20 years of age or greater when facial growth has significantly reduced.

One of the limitations of the study is that the severity of asthma and the type of medication (i.e. inhaler or oral steroid) was not recorded. However, if these factors influence craniofacial growth and shape, they are likely to have small effects (Doull, 2004; Hauspie *et al*., 1977; Price

et al., 2002; Russell, 1993). The loss to follow-up for the study group was 34 per cent, which is acceptable for a longitudinal study of this size (Fewtrell *et al*., 2008). Another limitation is that co-morbidity (e.g. allergic rhinitis) was not considered. However this could be investigated retrospectively in the 15-year-old cohort to address this. Lastly as the study only recorded 3D facial shape at 15 years, there is no indication as to when the differences in facial morphology developed.

Despite these limitations, the results of the study are based on a population cohort of UK children that is broadly representative of the general population. In addition the imaging method is valid, and therefore, the methods are transferrable to other population groups (Kau *et al*., 2005).

Conclusion

The research method provides a framework for the investigation of medical conditions and environmental factors that can influence child's health and development using a three-dimensional facial imaging.

The study found;

1. Statistically significant differences found between asthmatic and non-asthmatic females; inter-ala width was 0.4 mm wider and the face height was 0.4 mm smaller in asthmatic females.
2. There were no statistical differences in facial parameters for asthmatic and non-asthmatic males.
3. Three-dimensional facial imaging has sufficient resolution to detect small differences in facial morphologies and can be used to explore genetic and environmental effects on facial morphology.

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We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interview- ers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

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Appendix 3

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A three-dimensional analysis of the effect of atopy on face shape

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SUMMARY Three-dimensional (3D) imaging technology has been widely used to analyse facial morphology and has revealed an influence of some medical conditions on craniofacial growth and morphology. The aim of the study is to investigate whether craniofacial morphology is different in atopic Caucasian children compared with controls.

Study design included observational longitudinal cohort study. Atopy was diagnosed via skin-prick tests performed at 7.5 years of age. The cohort was followed to 15 years of age as part of the Avon Longitudinal Study of Parents and Children (ALSPAC). A total of 734 atopic and 2829 controls were identified. 3D laser surface facial scans were obtained at 15 years of age. Twenty-one reproducible facial landmarks (x, y, z co-ordinates) were identified on each facial scan. Inter-landmark distances and average facial shells for atopic and non-atopic children were compared with explore differences in face shape between the groups.

Both total anterior face height (pg–g, pg–men) and mid-face height (Is–men, sn–men, n–sn) were longer (0.6 and 0.4 mm respectively) in atopic children when compared with non-atopic children. No facial differ- ences were detected in the transverse and antero-posterior relationships.

Small but statistically significant differences were detected in the total and mid-face height between atopic and non-atopic children. No differences were detected in the transverse and antero-posterior relationships.

Introduction

Atopy is the tendency to develop immunoglobulin E (IgE) antibodies to commonly encountered environmental allergens (Jarvis and Burney, 1998). The most common clinical manifestations of atopy are asthma, allergic rhinitis, and atopic dermatitis (Burney *et al.*, 1989). Development of atopic responses has been linked to several genes and gene products (Steinke *et al.*, 2008). Thus, atopic diseases represent a complex gene and environmental interaction in which environmental antigens interact with the immune system, producing atopic (IgE) responses (Peden, 2000). In epidemiological studies, skin prick testing provides an expedi- ent test for atopy (Oryszczyn, 1991; Cookson *et al.*, 1989; Zimmerman, 1988), and/or elevated total serum IgE level (Cookson *et al.*, 1989; Stempel, 1980).

Coca and Cooke (1923) introduced the term 'atopy', which mainly indicates people with asthma, fever, eczema, urtricaria, and the food allergies. The author gave another definition of the atopy: 'it is the abnormal condition of immunology and it would cause inflammation of organs in the body'. The combination of mast cells and basophils are used to differentiate atopy from non-atopy. The author stated that atopy is the genetic predisposition that would produce mast cells and may

cause eosinophilia. The term atopy represents the group of diseases that mainly develops in allergic conditions.

The relevance of atopy in facial growth is that environmental stimuli and irritations may cause chronic swelling of the nasopharyngeal mucous membranes in atopic individuals. Obstruction of the nasal airway due to atopic allergy can therefore be associated with mouth breathing and facial anomalies, including malocclusions such as increased overjet, a higher palatal plane, narrowing of both upper and lower arches, and proclination of incisors (Jefferson, 2010; Faria, 2002; Koski and Lähdemäki, 1975; Linder-Aronson, 1974, 1970; Ricketts, 1968). The switch from nasal to oronasal breathing results in functional adaptation including an increase in total face height and vertical development of the lower anterior face (Tourne, 1990).

A retrospective cephalometric comparative study of 55 paediatric patients who suffered from nasal obstruction and 61 controls indicated that naso-respiratory obstruction was associated with mouth breathing. In the children with nasal obstruction there was a higher tendency for a backward rotation of the mandible associated with an increase in anterior face height by 3 degree (SD 5) of the mandibular plane angle (Harari *et al.*, 2010).

Appendices

The influence of asthma on face shape has been reported previously in a large sample indicating that the mid-face height was 0.4 mm (95% CI) shorter in asthmatic when compared with non-asthmatic females (Al Ali *et al.*, 2012).

The effect of atopy on craniofacial structures (determined cephalometrically) was studied in 100 11-year-old school children and indicated a backward rotation of the mandibular body and an anterior lowering of the nasal floor in the moderate and severe nasal allergy groups. Differences were more pronounced in children presenting with atopy and enlarged adenoids (Hannuksela, 1981).

Cephalometric analysis was undertaken for 30 chroni- cally allergic mouth-breathing subjects and 15 nonaller- gic nose breathers (Bresolin and co-workers in 1983) and revealed that the upper anterior face height and the total anterior face height were significantly larger in the mouth breathers. The maxilla and mandible were more retrognathic in mouth breathers. Maxillary intermolar width was narrower in the mouth breathers and was associated with a higher prevalence of posterior crossbite.

Three-dimensional (3D) analyses of facial surface anatomy are fundamental in determining deviations from normal facial morphology. 3D imaging technologies have provided both reliable and accurate data capture for facial analysis (Kau and Richmond, 2010; Kau *et al.*, 2005; Kevin and Oleh, 1996, Toma *et al.*, 2009, 2011; Kau *et al.*, 2005). Quantitative analysis of facial morphology is of vital importance in determining facial discrepancies in individuals with craniofacial deformities (Kevin and Oleh, 1996). Two-dimensional techniques such as cephalometry and photographs are of limited value in describing the complex 3D topography of the facial surface.

The aim of the present study is to investigate the influ- ence of atopy on craniofacial morphology using 3D laser scan imaging technology and to assess the null hypothesis that there is no difference in face shape in atopic and non- atopic Caucasian children.

Subjects and Methods

Sample

The children involved in this study were recruited from the Avon Longitudinal Study of Parents and Children (ALSPAC), which was designed to explore genetic and environmental factors impacting on health, behaviour, and development of children (Golding *et al.*, 2001). Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees prior to the commencement of the study.

All children were invited to attend a clinic at 7.5 years of age, where skin-prick tests were performed to a panel of six allergens (house dust mite, cat, mixed grass, mixed nuts, peanut, and milk) and a positive (1 % histamine solution) and negative (diluent) controls (Henderson *et al.*, 2008).

Skin tests were carried out on the anterior surface of the left arm using new disposable sterile lancets for each allergen tested. The skin was pricked through a drop of allergen solutions, which were blotted off after five minutes, and the test were read after a further 10 minutes (Henderson *et al.*, 2008). The maximum weal diameter was measured and a second measurement performed at 90 degree to the first, and the mean weal diameter was calculated. Atopy was defined as a positive skin-prick test to the above allergens (weal diameter $\geq$1 mm with as negative diluents response, Henderson *et al.*, 2008).

The cohort was re-called when the children were 15 years of age where 3D laser facial scans were acquired. Body weight and height were also measured for all children. The final sample in this study consisted of 734 atopic and 2829 non-atopic control group children.

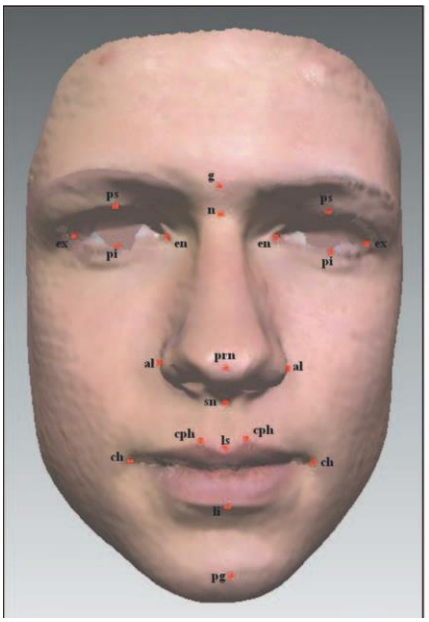
Facial imaging

3D facial images of the children were captured using a pair of high-resolution Vivid 900 laser scanners (Konica Minolta Sensing Europe, Milton Keynes, UK), with a reported manufacturing accuracy of 0.1 mm (Kau *et al.*, 2003). The scanners were controlled with Multi-scan software (Cebas Computer GmBH, Eppelheim, Germany). Rapidform 2006 (INUS Technology, Seoul, Korea) was used to process and analyse the facial scans. The right and left facial scans of each child were registered and merged using a locally developed subroutine for above mentioned software. Quality of registration of right and left facial scans for all subjects was determined using average distance between shells and percentage of overlap between the right and left shells. The facial scan was evaluated as having good quality when the average distance between right and left facial scan is 0.3 mm and below and is the most suitable for merging (Kau and Richmond, 2008). Generally, 70–100 per cent overlap of the right and left facial shells with a tolerance level set at 0.5 mm indicates facial shells suitable for merging, and any non-suitable scans were excluded from the sample of the study (Toma *et al.*, 2008; Kau and Richmond, 2010).

Twenty-one facial soft tissue landmarks (Figure 1) were manually identified on each facial image (Toma *et al.*, 2011, 2009), and the x, y and z co-ordinates were recorded. Landmarks reproducibility in the three dimensions has been reported previously with an error of less than 1 mm for both intra- and inter-examiner assessments (Toma *et al.*, 2009).

Antero-posterior, vertical and transverse relationships in face shape analysis were determined using the following soft tissue parameters: exR–exL (inter-eye distance) and al–al (nose width) allows transverse analysis, pg–g, pg–men (total face height), sn–men, Is–men, n–sn (mid-face height) allows vertical relationship analysis, s–sn–pg (face convexity) relate to antero-posterior features. The statistical analysis used 95% confidence intervals (CIs) of the difference in facial parameters between the atopic and non-atopic group.

Appendices



Glabella (g): Most prominent midline point between the eyebrows
Nasion (n): Deepest point of nasal bridge
Endocanthion (en) L/R: Inner commissure of the left and right eye fissure
Exocanthion(ex) L/R: Outer commissure of the left and right eye fissure
Palpebrale superius (ps) L/R: Superior mid-portion of the free margin of upper left and right eyelid
Palpebrale inferius (pi) L/R: Inferior mid-portion of the free margin of upper left and right eyelid
Pronasale (prn): Most protruded point of the apex nasi
Subnasale (sn): Midpoint of angle at columella base
Alare (al) L/R: Most lateral point on left and right alar contour
Labiale superius (ls): Mid-point of the upper vermilion line
Labiale inferius (li) L/R: Mid-point of the lower vermilion line
Crista philtri (cph) L/R: Point on right elevated margin of the philtrum just above the vermilion line
Cheilion (ch) L/R: Point located at left and right labial commissure
Pogonion (pg) L/R: Most anterior mid-point of the chin

Figure 1 Facial soft tissue landmarks.

The facial parameters included in the analysis were the most common parameters reported that might be influenced by different modes of breathing (Harari *et al.*, 2010; Kerr *et al.*, 1989; Wenzel *et al.*, 1985; Bresolin *et al.*, 1983).

Average facial shells were created for atopic and non- atopic children using a previously validated method (Kau and Richmond, 2010; Zhurov *et al.*, 2010). Average faces were superimposed on the mid-endocanthion point. Differences in morphology were presented using colour maps, with a tolerance level of 0.1 mm to highlight significant topographical facial differences.

Body weight was measured using Tanita scales to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using Harpenden stadiometer (Lawlor *et al.*, 2010). Body mass index (BMI) was then calculated as weight (kg) divided by the square of height (m^2).

Statistical analysis

To compare the facial features of atopic and non-atopic children, independent *t*-test, 95% CI of the differences in the measured facial parameters were used.

Results

The sample represented 3563 Caucasian children (1692 male/ 1871 female) with no obvious facial dysmorphology. Of the 3563 ALSPAC children, 734 children (411 male/ 323 female) were recorded as atopic at age 7.5 years (Henderson *et al.*, 2008). Mean BMI of the study sample was within the range (21.2 kg/m^2; reported normal range 17–24.2 kg/m^2, Cole *et al.*, 1998; Cole *et al.*, 1995) with no significant differences between the atopic and the non-atopic group.

Generally, the parameters describing transverse dis- tances and the antero-posterior features in atopic children did not differ significantly from the non-atopic group (Table 1). However, all the parameters that describe ver- tical relationships showed significant differences between the atopic and non-atopic children. Both total anterior face height (pg–g, pg–men) and mid-face height (Is–men, sn–men, n–sn) were longer (0.6 and 0.4 mm, respectively) in atopic children when compared with non-atopic children. Superimposition of average facial shells of atopic and non-atopic children showed a significant morphological difference between the groups in the z direction. The direction of the differences for the average facial shells for the atopy and non-atopic groups are shown in three presentations of colour deviation maps (Figure 2). The cheeks and chin are less prominent in the atopic group, and the atopic children showed an increased nose width (0.49 mm) compared with non-atopic children.

Discussion

This study is the first to investigate the influence of atopy on facial morphology in a large cohort of 15-year-old children using 3D facial imaging. Currently available 3D soft tissue imaging technologies allow clinicians to evaluate facial differences as a result of medical and surgical interventions. The 3D laser scanning system has the advantage of being quick, non-invasive, and easy to use unlike other 3D hard tissue imaging systems, such as Cone Beam Computed Tomography (CBCT) and Magnetic Resonance

Appendices

Table 1 Summary of the statistics of 3D co-ordinates.

	Atopic (n = 734)		Non-atopic (n = 2829)		Mean difference	95% confidence interval
	Mean	Standard deviation(SD)	Mean	SD		
Eyes Distance (mm, exR–exL)	87.4	3.97	87.5	4.05	0.06	−0.26–0.39
Nose width (mm, al–al)	33.8	2.86	33.6	2.68	−0.18	−0.40–0.03
Mid-face (mm, ls–men)	62.0	4.22	61.6	3.95	−0.45	−0.79–−0.11
Mid-face (mm, sn–men)	48.5	3.69	48.0	3.43	−0.42	−0.71–−0.13
Mid-face (mm, n–sn)	52.6	3.94	52.3	3.83	−0.34	−0.65–−0.03
Total face height (mm, pg–g)	114.2	6.38	113.6	6.23	−0.60	−1.09–−0.07
Total face height (mm, pg–men)	94.1	5.85	93.6	5.66	−0.60	−1.03–−0.11
Face convexity (angle, n–sn–pg)	162.0	5.51	162.5	5.64	0.41	−0.04–0.86

Imaging (MRI), which are both expensive, time-consuming, and with CBCT presenting a radiation risk (Kau *et al.*, 2007).

The present study revealed that laser scanner can be used in large-scale population studies and is able to detect small facial differences (0.6 mm) in atopic chil- dren who had longer faces when compared with non- atopic children.

While craniofacial morphology is primarily determined by heredity (David and Carlson, 2005), environmental stimuli also markedly influence the growth of the bones, as for instance in patients with partially or totally obstructed nasal airways (Kiliç & Oktay, 2008; Dunn *et al.*, 1973). Atopic conditions are associated with chronic swelling of the nasopharyngeal membrane that can affect normal breathing (Hannuksela, 1981). The mode of breathing and its effect on craniofacial growth has been a controversial issue within orthodontics for decades. It has been described that obstructed nasal breathing leads to mouth breathing and the so called 'adenoidal face' (long face syndrome) with an increased anterior face height (Chaves *et al.*, 2010; Bresolin *et al.*, 1983; Linder-Aronson, 1970; Subtelny, 1954). This craniofacial development has been explained by changes in the muscular balance. Mouth breathing leads to a lower tongue position in the oral cavity that will alter the force balance from the cheeks and tongue, which may be associated with an increased anterior face height, a steep mandibular plane angle resulting in a retrognathic mandible. In addition, incompetent lips, a narrow upper dental arch, retroclined mandibular incisors are also seen, in children

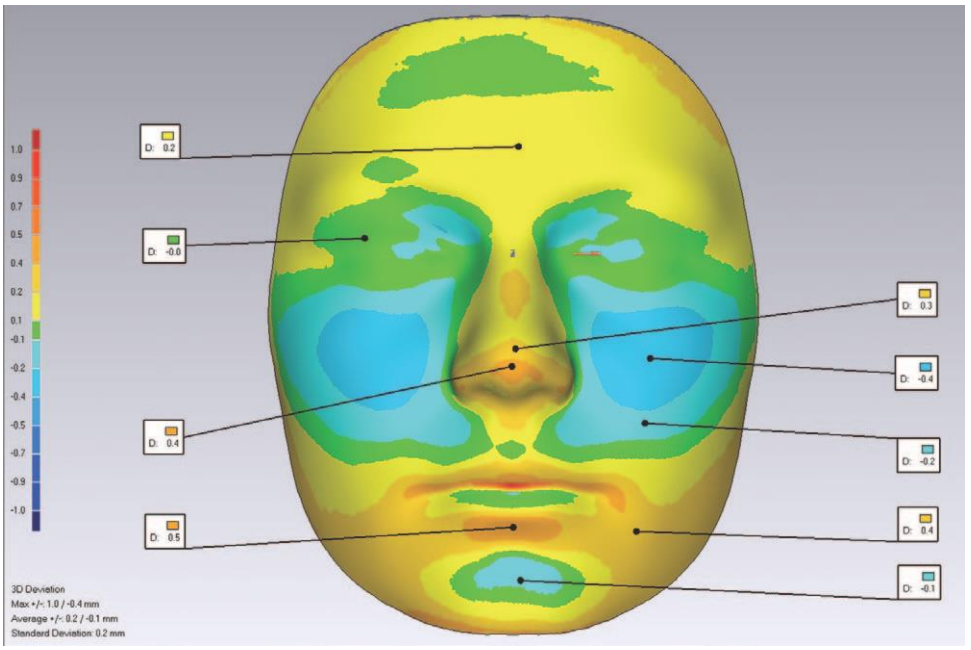


Figure 2 The green areas represent no difference in the atopy and control groups (0 mm). The blue area indicates less prominent cheeks and chin point in the atopic group (0.1–0.4 mm) the deeper blue representing greater facial retrusion in the atopic group. The yellow areas are those prominent features in the atopic face—prominent forehead, nose, lower lip and wider forehead, nose and lower jaw (0.1–0.5 mm).

with reported nasal breathing compared with healthy controls (Solow *et al.*, 1984; McNamara, 1981; Linder- Aronson, 1979; Solow and Kreiborg, 1977).

Previous data and results from the 3D study of the influ- ence of asthma on face shape of 4747 children from Avon Longitudinal Study of Parents and children (Al Ali *et al.*, 2012) showed shorter mid-face height in asthmatic females (0.4 mm) compared with non-asthmatic children. The conflic- tion with results in this study could be explained by the fact that the relationship between atopy and asthma is not straight- forward (Carroll *et al.*, 2006). The available epidemiological evidence suggests that the proportion of asthma cases that are attributed to atopy is less than one-half, indicating that the importance of atopy as a cause of asthma in individuals may have been overemphasized (Pearce *et al.*, 1999).

Findings in the present study are consistent with the proposed possible contribution of environmental stimuli, such as atopic allergic conditions and breathing difficulty on craniofacial growth and morphology. Atopic diseases, therefore, should be taken into consideration when examin- ing orthodontic patients and when planning treatment for the correction of malocclusion.

Although results have revealed an association between mouth breathing in atopic allergy and modification in cran- iofacial growth and morphology, there is a need to know how much nasal obstruction has to occur before an effect on facial growth is observable? Is this a reversible condition and is there a time dependent relationship? These questions required a fundamental premise of being able to define nasal obstruction its position and severity (Vig, 1998).

Conclusion

The results of this study indicate that face shape differences were present in atopic children compared with matched control. The major features included increased mid-face height and total anterior face height. The research method- ology provides a framework for the investigation of environ- mental factors that can influence craniofacial development using 3D facial imaging.

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APPENDIX 4

Project Proposals

Reference:

B1485

Title

The influence of breathing disorders on face shape.

Date(s)

17/01/2013 *(approved)* / 17/01/2013 *(received)*

Outline

Aims: To explore the effect of breathing disorders including asthma, atopy allergic rhinitis and sleep disordered breathing on face shape at age 15 years and to evaluate the effect of adenoidectomy and tonsillectomy on face shape.

Hypothesis: Breathing disorders, adenoidectomy and tonsillectomy have no effect on face shape in late adolescent.

Background: Respiratory activity may have an influence on craniofacial development and interact with genetic and environmental factors. It has been suggested that certain medical conditions such as asthma have an influence on face shape. Altered mechanics of breathing may influence the development of craniofacial structures and tends to result in significant changes in face shape particularly increased face height and retrusive mandible. However, removal of adenoids and tonsils has been reported to have a significant effect on obstructive breathing and if conducted early will normalize dentofacial morphology. ALSPAC provides the opportunity to explore a longitudinal data set with detailed facial morphology measures in late childhood on a large, representative sample.

Appendices

Three-dimensional laser surface facial scans were obtained. Differences in the twenty-one reproducible facial landmarks (x, y, z co-ordinates) for the various groups will be evaluated as well as average facial shells will be created for asthmatic, atopic allergic rhinitis, sleep disordered breathing and healthy controls to explore surface differences.

Study design: observational longitudinal cohort study.

Confounding factors: height, weight, BMI, pubertal status.

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PI | Affiliation

Richmond, Stephen (Prof) | *University of Cardiff (UK)*

Co-applicants

- **, |** *Not used 0 (Not used 0)*
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Keywords

Face Shape

Respiratory

Next action:

Main menu >>>

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APPENDIX 5

Project Proposals

Reference:

B2191

Title

The exploration of environmental and genetic contributions to facial shape.

Date(s)

27/02/2014 *(approved)* / 25/02/2014 *(received)*

Outline

Aim:

To employ novel techniques to explore the environmental and genetic contributions to facial shape at 25 years of age and change in face shape from 15 to 25 years of age.

PI | Affiliation

Richmond, Stephen (Prof) | *University of Cardiff (UK)*

Co-applicants

- **,** | *Not used 0 (Not used 0)*
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Keywords

Face Shape

Mothers

Next action:

Main menu >>>

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APPENDIX 6

Questionnaire Topic Guide

This document summarises the questionnaires that have been completed by different participants in the study, indicating the timepoints and number completed and providing an overview of the topics covered within each questionnaire.

Time points for capture of topics in Questionnaires

About the mother

Timepoint	Sampling Period	Questionnaire title	No. returned
8 -42 wks gest	Sept 90 - Oct 92	Your Environment	13545
12 wks gest	Nov 90 – Aug 93	About Yourself	12448
18 wks gest	Nov 90 – Sept 92	Having a Baby	13190
32 wks gest	Mar 91 – Jan 93	Your pregnancy	12418
8 weeks	May 91 – Apr 93	Me and my baby	11710
8 months	Apr 92 – Oct 93	Looking after the baby	11210
21 months	Sept 92 – Nov 94	Caring for a toddler	10310
33 months	Oct 93 – Nov 95	Your health events and feelings	9638
47 months	Nov 94 – Jan 97	Mother's new questionnaire	9501
5 y 1 mth	Jan 96 – mar 98	Study mother's questionnaire	8975
6 y 1 mth	Feb 97 – Mar 99	Mother's lifestyle	8528
7 y 1 mth	Aug 98 – Mar 00	Mother and home	8326
8 y 1 mth	Sept 99 – May 01	Mother and family	7911
9 y 1 mth	Oct 00 – Apr 02	Mother of a 9 year old	7982
10 y 1 mth	Aug 01 – Apr 03	You and your surroundings	8075
11 1 mth	Jul 02 – May 04	Lifestyle and health of mother	7595
12 y 1 mth	May 03 – May 05	Twelve years on	7051
12 y 6 mth	May 04 – Oct 04	Adult learning	5378
17 y 8 mth	Jul 09 – Sept 09	About Eating	5661
18 y 6 mth	May 10 – Nov 10	You and your life	*Not yet available*
19 y 10 mth	Oct 11 -	You and your study young person aged 19+[a]	*Being collected*

[a] this questionnaire also asked questions about her daughter

About the partner

Timepoint	Sampling Period	Questionnaire title	No. returned
12 wks gest	Nov 90 – Aug 93	You and your environment	8621
18 wks gest	Nov 90 – Sep 92	Partner's questionnaire	9957
8 weeks	May 91 – Apr 93	Being a father	8350
8 months	Apr 92 – Oct 93	The baby and me	7099
21 months	Sept 92 – Oct 93	A toddler in the house	6153
33 months	Oct 93 – Nov 95	Partner's health, events and feelings	5452
47 months	Nov 94 – Jan 97	Partner's new questionnaire	5101
5 y 1 mth	Jan 96 – Mar 98	Study partner's questionnaire	4522
6 y 1 mth	Feb 97 – Mar 99	Partner's lifestyle	4462
7 y 1 mth	Aug 98 – Mar 00	Partner and home	4036
8 y 1 mth	Sept 99 – May 01	Father and the family	4046
9 y 2 mth	Oct 00 – Apr 02	Father of a 9 year old	3664
10 y 2 mth	Aug 01 – Apr 03	Father and surroundings	4161
11 y 2 mth	Jul 02 – May 04	Lifestyle and health of partner	3639
12 y 1 mth	May 03 – May 05	Partner – about me	3297
12 y 6 mth	May 04 – Oct 04	Partner adult learning	2700
19 y 8 mth	Aug 11 –	Home Life	*Being collected*

About the child/young person – completed by the mother

Timepoint	Sampling Period	Questionnaire title	No. returned
4 weeks	Apr 91 – Apr 93	My young baby boy/girl	12344
6 months	Jul 91 – Aug 93	My daughter/son	11478
15 months	Aug 92 – May 94	My infant daughter/son	11067
18 months	Oct 92 – Aug 94	Girl/boy toddler	11120
24 months	Jun 93 – Feb 95	My little girl/boy	10422
30 months	Jan 94 – Aug 95	My study son/daughter	10340
38 months	Sept 94 – Apr 96	My 3 year old boy/girl	10137
42 months	Nov 94 – Oct 96	My son/daughter's health & behaviour	10053
54 months	Jul 95 – Aug 97	My young 4 year old boy/girl	9715
57 months	Jan 96 – Nov 97	Development and health of my son/daughter	9521
5 y 5 mth	Oct 96 – Jul 98	My five year old son/daughter	9003
5 y 9 mth	Feb 97 – Jul 99	My school boy/girl	8691
6 y 5 mth	Nov 97 – Jul 99	My daughter/son growing up	8568
6 y 9 mth	Mar 98 – Nov 99	My son/daughter at school	8505
7 y 9 mth	Jul 98 – Oct 00	My son/daughter's well-being	8259
8 y 7 mth	May 00 – Sept 01	My son/daughter's health	8331
8 y 7 mth	May 00 – Sept 01	My son/daughter at home and at school	8296
9 y 7 mth	Feb 01 – Nov 02	Your son/daughter at 9	8221
10 y 8 mth	Feb 02 – Nov 03	Girl/boy health and happiness	7851
11 y 8 mth	Dec 02 – Nov 04	Being a boy/girl	7478
13 y 1 mth	May 04 – Apr 06	My teenage son/daughter	7159
14 y 2 mth	May 05 – Dec 06	Wellbeing of my teenage son/daughter	7108
16 y	Mar 07 – Feb 09	Year 11 questionnaire for parents and children	5964
16 y 6 mth	Oct 08 - Jul 09	Your son/daughter 16+ years on	5720

About the child/young person – completed by the child/young person

Timepoint	Sampling Period	Questionnaire title	No. returned
7 y 9 mth	Jul 98 – Oct 00	My teeth	7123
8 y 1 mth	Sept 99 – May 01	Me and my school	7682
8 y 7 mth	May 00 – Sept 01	Some more about me	8189
9 y 2 mth	Oct 00 – Apr 02	My world	8574
9 y 7 mth	Feb 01 – Nov 02	My hands, my feet and me	8062
10 y 2 mth	Nov 01 – Apr 03	Rings and things	8318
10 y 8 mth	Feb 02 – Nov 03	Teeth and things	7789
11 y 2 mth	Jul 02 – May 04	School life and me	7908
11 y 8 mth	Dec 02 – Nov 04	Watches and funny feelings	7566
12 y 1 mth	May 03 – May 05	All around me	7500
13 y 1 mth	May 04 – Apr 06	Food and things	7136
13 y 1 mth	May 04 – Apr 06	Reading and singing	7125
13 y 10 mth	Jul 05 – Dec 06	Travelling, leisure and school	6905
13 y 11 mth	Sept 05 – Jan 07	Experiences, thoughts and behaviour	6213
14 y 1 mth	Jan 06 – Mar 07	Life of a teenager	6032
16 y	Mar 07 – Feb 09	Year 11 questionnaire for young people	5435
16 y	Apr 08 – May 08	You and your friends	3032
16 y 6 mth	Oct 07 – Aug 09	Life of a 16+ teenager	5126
18 y 2 mth	Mar 10 – Oct 10	Internet use [a, b]	1584
18y 7 mth	Aug 10 -	Your changing life	*Not yet available*
19 y 8 mth	Sept 11 -	You and your body aged 19+ [c]	*Being collected*

[a] Completed online
[b] Data embargoed
[c] This questionnaire went to daughter's only

Puberty questionnaires – completed by the mother or the child/young person up to 13 y 1mth, completed by the young person from 14 y 7mth

Timepoint	Sampling Period	Questionnaire title	No. returned
8 y 1 mth	Sept 99 – May 01	Growing and Changing	6255
9 y 7 mth	Feb 01 – Nov 02	Growing and Changing 2	7017
10 y 8 mth	Feb 02 – Nov 03	Growing and Changing 3	6629
11 y 8 mth	Dec 02 – Nov 04	Growing and Changing 4	6293
13 y 1 mth	May 04 – Apr 06	Growing and Changing 5	6075
14 y 7 mth	Apr 06 – Sept 07	Growing and Changing 6	5148
15 y 7 mth [a]	Nov 06 – Sept 09	Growing and Changing 7	4861
16 y	Mar 07 – Feb 09	Growing and Changing 8	4755
17 y	Apr 08 – Jan 10	Growing and Changing 9	4366

[a] **completed as part of the 15+ clinic**

The following table indicates the data collected in each puberty Q according to gender

	Boys	Girls
Height	X	X
Weight	X	X
Vigorous physical activity	X	X
Pubic hair development	X	X
Testes, scrotum, penis development	X	
Breast development		X
Voice change	X	
Periods		X
Oral contraceptives		X

Please note that the following tables only detail the overall topics that are covered within the questionnaires. More specific information on the scales and exact questions used can be obtained from the ALSPAC documentation

Topics covered in Qs about the mother

Timepoint	8-42 wks gest	12 wks gest	18 wks gest	32 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 1 mth	10 y 1 mth	11 y 1 mth	12 y 1 mth	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
General physical health																					
Current health and symptoms		X	X	X	X	X	X	X	X	X	X		X	X		X	X			X	
Medical history – parents		X											X								
Medical history – grandparents		X											X								
Short form health survey (SF36)																				X	
Allergies		X											X			X					
Hearing problems		X											X		X						
Vision problems		X											X								
Speech problems		X																			
Bladder problems		X			X	X	X	X	X	X	X			X		X					X
Chest pains												X				X				X	
Dizziness and balance																X					
Infections			X	X	X								X				X				
Sleep					X	X	X			X		X				X					
Eating disorders			X																X		
Psychosis symptoms in family																				X	
Congenital malformations	X																				
Medications/Drugs taken			X	X	X	X	X	X	X	X	X			X	X		X			X	
Complementary/Alternative medicines			X				X				X			X			X				
Accidents and injuries		X										X				X				X	
Hospital admissions		X	X		X	X	X	X	X		X			X		X	X				
Surgery		X											X								
Contact with health services							X	X			X										
Visited dentist					X			X													
Self-reported anthropometry		X			X							X	X	X			X			X	
Physical activity			X	X		X	X	X				X	X			X				X	

Timepoint	8-42 wks gest	12 wks gest	18 wks gest	32 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 1 mth	10 y 1 mth	11 y 1 mth	12 y 1 mth	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
Obstetric Health/history																					
Location of study child birth					X																
Delivery of study child					X																
Effects of study pregnancy			X																		
Contraceptive use		X			X	X	X	X	X	X	X		X	X		X	X			X	X
Menstruation		X				X	X	X	X	X	X		X	X		X	X			X	X
Other Pregnancies			X			X	X	X	X	X	X	X	X	X		X	X			X	
Problems during pregnancies						X	X		X	X				X							
Difficulties with getting pregnant									X	X											
Infertility			X																		
Time to conception			X							X	X			X		X				X	
Hysterectomy/oophorectomy													X			X				X	
Menopause																					X
Unwanted/excess hair																					X
HRT															X		X			X	
Mental Health																					
Depression			X	X	X	X	X	X		X	X					X				X	
Anxiety			X	X	X	X	X	X		X	X	X	X							X	
Feelings			X				X							X							
Life events			X		X	X	X	X	X	X	X			X		X				X	
Childhood life events				X																	
Body image			X																		
Personality			X																		
Job satisfaction						X															
Locus of control		X									X									X	
Self esteem								X		X										X	
Diet/Nutrition																					
Food frequency questionnaires				X					X				X				X				
Beverages only												X									
Dietary supplements			X	X	X	X	X	X	X	X	X			X	X		X				
Dieting				X																	
Special diets				X					X				X				X				

Appendices

Timepoint / Caffeine intake	8-42 wks gest	12 wks gest	18 wks gest	32 wks gest	8 wks X	8 mths	21 mths	33 mths	47 mths X	5 y 1 mth	6 y 1 mth	7 y 1 mth X	8 y 1 mth X	9 y 1 mth	10 y 1 mth	11 y 1 mth X	12 y 1 mth X	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
Attitudes towards food/eating													X								
Food purchases/influences																X					
Social variables																					
Education				X						X		X	X					X			
Grandparental education				X									X								
Occupation/Employment			X	X	X	X	X	X	X	X		X	X		X	X				X	
Social class				X																	
Marital status/presence of partner	X					X	X	X	X		X	X	X	X	X		X			X	
Household income								X	X			X	X			X				X	
Household expenditure									X			X	X			X				X	
Financial difficulties				X		X	X	X		X		X				X				X	
Ethnicity				X									X								
Household composition	X	X				X	X	X	X			X	X		X					X	
Other children									X			X	X		X					X	
Biological father involved with study child							X	X	X			X	X		X					X	
Social support	X	X			X	X	X			X	X			X			X			X	
Social network		X					X			X	X			X			X			X	
Help with household chores					X	X				X	X	X		X			X				
Childhood home		X						X													
Care in childhood		X						X													
Abuse in childhood				X				X													
Religious beliefs		X								X	X			X							
Discrimination											X		X								
Partner																					
Partner's education				X						X			X								
Partner's occupation				X			X	X	X		X		X	X			X			X	
Partner's social class				X																	
Partner's ethnicity													X								
Partner's children									X												
Partner's health						X	X	X	X		X			X			X				
Partner's smoking			X		X		X	X	X		X		X	X		X	X				

Appendices

Timepoint Partner's alcohol intake	8-42 wks gest	12 wks gest	18 wks gest X	32 wks gest	8 wks	8 mths X	21 mths X	33 mths X	47 mths X	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 1 mth X	10 y 1 mth	11 y 1 mth	12 y 1 mth	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
Partner aggression/affection		X				X		X	X		X		X				X			X	
Relationship with partner							X	X	X		X		X	X			X			X	
Partner satisfaction											X			X							
Partner's height																				X	
Partner's laterality																				X	
Partner's eye/hair colour																				X	
Housing variables																					
House moves	X					X	X	X		X					X					X	
Housing tenure	X					X	X	X		X		X			X					X	
Council tax band															X	X				X	
Type of heating	X					X	X	X		X		X			X						
Type of cooker	X					X	X	X		X		X			X						
Number of rooms	X					X	X	X		X		X			X						
Amenities in the home	X					X	X	X		X		X			X						
Problems in the home	X					X	X	X		X		X			X						
Damp/mould in the home	X					X	X	X		X		X			X						
New furniture/decoration						X	X	X		X		X			X						
Noise							X	X		X		X			X						
Temperature of rooms							X	X		X		X			X						
Neighbourhood variables																					
Quality of neighbourhood	X					X	X	X		X	X				X					X	
Social problems	X							X							X					X	
Crime	X						X	X													
Environmental exposures																					
Use of chemicals	X					X		X	X		X			X	X	X					
Electrical items	X																				
Occupational exposures			X										X		X	X					
X-rays	X	X	X	X	X	X															
Scans			X	X	X			X													
Mobile phones												X		X	X	X	X				

Appendices

Timepoint Problems with animals in home	8-42 wks gest X	12 wks gest	18 wks gest	32 wks gest	8 wks	8 mths X	21 mths X	33 mths X	47 mths X	5 y 1 mth	6 y 1 mth	7 y 1 mth X	8 y 1 mth	9 y 1 mth	10 y 1 mth	11 y 1 mth	12 y 1 mth	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
Pets						X	X	X	X			X	X		X						
Noise							X	X		X					X						
Heavy traffic near home						X	X	X		X		X									
Substance use																					
Cigarette smoking	X		X	X	X	X	X	X	X	X	X	X	X			X	X			X	
Passive smoke exposure				X				X	X		X					X					
Rules about smoking in home									X	X	X	X			X						
Alcohol intake	X			X		X	X	X	X	X		X	X				X			X	
Illicit drugs			X		X	X	X	X													
Grandparental smoking													X								
Parenting																					
Previous breastfeeding			X																		
Feelings towards pregnancy			X																		
Preparation for birth				X																	
Feeding intentions				X																	
Attitudes to breastfeeding				X																	
Feelings during labour/delivery					X																
Antenatal classes					X																
Mother's feelings towards study child						X		X			X	X									
Partner's feelings towards study child						X	X	X			X	X		X			X				
Things for baby/child						X		X													
Accident prevention items						X		X													
Parenting skills/behaviour						X															
Parenting score							X	X													
Childcare																					
Plans				X	X																
Who/how often					X	X			X												
Study child attends when ill									X												

Appendices

Timepoint	8-42 wks gest	12 wks gest	18 wks gest	32 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 1 mth	10 y 1 mth	11 y 1 mth	12 y 1 mth	12 y 6 mth	17 y 8mth	18 y 6 mth	19 y 10 mth
About the study child																					
Ear problems in study child								X													
Study child's feelings towards siblings									X			X	X								
Study child SDQ									X			X	X								
Child's health and time off work									X												
Employment status																					X
Friendships																					X
Academic ability and enjoyment																					X
Other																					
Early sexual experiences				X																	
Holidays(incl travel abroad)						X															
Attitude towards health services								X	X												
Hair/eye colour																				X	
Laterality								X												X	
schooling								X													
Travel to work								X		X			X		X	X				X	
Attitude to work										X			X		X						
Transport										X						X				X	
TV viewing													X			X					
Feelings towards pets									X												
Sibling SDQ									X				X								
Feelings towards non-study child									X			X	X								
Gambling behaviour											X									X	
Crime/antisocial behaviour																	X				
Family life/Other people's lives																				X	

Topics covered in Qs about the partner

Timepoint	12 wks gest	18 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 2 mth	10 y 2 mth	11 y 2 mth	12 y 1 mth	12 y 6 mth	19 y 8 mth
General physical health																	
Current health and symptoms	X		X	X	X	X	X	X	X			X		X	X		
Medical history – parents	X										X						
Medical history – grandparents	X																
Allergies	X										X			X			
Hearing problems	X										X						
Vision problems	X										X						
Bladder problems	X													X			
Chest pains										X				X			
Dizziness and balance														X			
Infections	X										X						
Sleep			X	X	X	X		X		X				X			
Congenital malformations	X																
Contraception														X			
Medications/Drugs taken				X	X	X	X	X	X			X	X		X		
Complementary/Alternative medicines					X										X		
Accidents and injuries	X									X				X			
Hospital admissions				X	X	X	X	X	X			X		X	X		
Surgery	X									X							
Contact with health services									X								
Self-reported anthropometry	X									X	X	X			X		
Physical activity		X			X	X				X	X			X	X		
Mental Health																	
Depression			X	X	X	X		X	X		X			X			X
Anxiety			X	X	X	X		X	X		X			X			
Life events			X	X	X	X	X	X	X			X		X			X
Thoughts and feelings												X					
Maternal care/warmth as child	X																
Childhood life events	X																
Body image																	

Appendices

Timepoint Personality	12 wks gest	18 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 2 mth	10 y 2 mth	11 y 2 mth	12 y 1 mth	12 y 6 mth	19 y 8 mth
Job satisfaction																	
Locus of control	X								X								X
Self esteem						X		X									X
Diet/Nutrition																	
Food frequency questionnaires		X					X				X				X		
Beverages only										X							
Dietary supplements				X	X	X	X	X				X	X		X		
Special diets		X					X				X						
Caffeine intake		X					X							X	X		
Eating behaviours											X			X			
Social variables																	
Education								X		X	X					X	
Grandparental education											X						
Occupation/Employment			X	X	X	X		X		X	X		X	X			
Social class																	
Marital status/presence of partner	X					X	X	X	X	X	X	X			X		
Biological father to study child	X																X
Household income										X	X			X			
Household expenditure								X		X	X			X			
Financial difficulties				X	X	X		X		X				X			X
Ethnicity											X						
Household composition							X			X	X						X
Other children	X						X			X	X						
Social support		X	X	X	X			X	X			X			X		X
Social network		X			X			X	X								
Helped with household chores			X	X		X			X	X							
Childhood home	X					X											
Care in childhood	X																
Abuse in childhood				X		X											
Household composition as a child	X																
Siblings						X					X						

Appendices

Timepoint	12 wks gest	18 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 2 mth	10 y 2 mth	11 y 2 mth	12 y 1 mth	12 y 6 mth	19 y 8 mth
Religious beliefs								X	X			X					
Discrimination									X								
Partner																	
Partner aggression/affection	X			X		X			X		X	X			X		X
Feelings towards partner since birth			X	X													
Partner's health					X	X	X		X			X			X		
Relationship with partner					X	X			X		X	X			X		
Partner's alcohol intake					X		X										
Partner's smoking							X					X		X	X		
Partner is biological mother									X	X							X
Partner's education								X								X	
Partner's employment							X					X			X		
Partner's feeling towards child									X			X			X		
Partner's ethnicity											X						
Parenting																	
Reaction and feelings towards pregnancy		X															
Reaction and feelings towards birth			X														
Attitude towards breastfeeding			X														
Helped with child			X														
Attitude towards fatherhood			X	X	X												
Paternal enjoyment				X	X		X			X							
Lives with study child										X							X
Feelings towards having more children									X								
Feelings towards older child										X							
Housing variables																	
House moves	X									X							X
Housing tenure										X							X
Council tax band																	X
Type of heating										X							
Type of cooker										X							

Appendices

Timepoint Number of rooms	12 wks gest	18 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 2 mth	10 y 2 mth	11 y 2 mth	12 y 1 mth	12 y 6 mth	19 y 8 mth
Amenities in the home										X							
Problems in the home						X				X							
Damp/mould in the home										X							
New furniture/decoration										X			X				
Noise						X	X			X			X				
Temperature of rooms	X									X							
Feelings about home	X												X				
Neighbourhood variables																	
Quality of neighbourhood	X					X	X			X			X				X
Social problems	X					X	X			X			X				X
Crime	X									X			X				X
Opinion of neighbourhood	X									X							X
Environmental exposures																	
Use of chemicals	X			X		X	X	X			X	X	X				
Electrical items				X													
Occupational exposures												X					
X-rays	X																
Mobile phones											X		X	X			
Problems with animals in home																	
Pets						X	X				X						
Noise										X							X
Heavy traffic near home										X							X
Substance use																	
Cigarette smoking		X	X	X	X	X		X		X	X			X	X		
Passive smoke exposure						X	X	X				X		X	X		
Alcohol intake		X	X	X	X	X	X	X		X	X				X		
Illicit drugs		X	X	X	X			X	X			X					
Other																	
Travel to work					X	X		X		X			X	X			

Appendices

Timepoint Family life – statements about the home	12 wks gest	18 wks gest	8 wks	8 mths	21 mths	33 mths	47 mths	5 y 1 mth	6 y 1 mth	7 y 1 mth	8 y 1 mth	9 y 2 mth	10 y 2 mth	11 y 2 mth	12 y 1 mth	12 y 6 mth	19 y 8 mth
Feelings towards pet						X	X										
Study child: strengths & Difficulties							X										
Laterality						X											
Activities in spare time								X									
Gambling									X								
TV viewing														X			
Crime															X		

Topics covered in Qs about the child/young person, completed by the mother

Timepoint	4 weeks	6 mth	15 mth	18 mth	24 mth	30 mth	38 mth	42 mth	54 mth	57 mth	5 y 5 mth	5 y 9 mth	6 y 5 mth	6 y 9 mth	7 y 9 mth	8 y 7 mth [a]	8 y 7 mth [b]	9 y 7 mth	10 y 8 mth	11 y 8 mth	13 y 1 mth	14 y 2 mth	Year 11	16 y 6 mth
Physical health																								
Current health and general symptoms	X	X		X		X		X		X		X		X	X	X			X	X	X	X		
Seen doctor	X	X		X		X				X		X		X		X			X			X		
Hospital admissions	X	X		X		X		X		X		X		X		X					X			
Surgical procedures		X		X		X		X		X		X		X		X				X				
Accidents and injuries		X	X		X		X		X		X		X			X				X				
Medications/Drugs taken		X	X		X		X		X		X		X		X	X			X	X	X	X		
Reactions to medicines																					X			
Complementary/Alternative medicines				X					X		X		X		X	X								
Immunisations		X		X		X												X						
Allergies, eczema and asthma	X	X		X		X		X	X	X	X	X		X		X			X	X	X	X		X
Diarrhoea/gastrointestinal problems		X		X		X		X	X	X	X	X		X		X				X				X
Convulsions/seizures		X		X		X		X		X		X		X		X				X	X	X		
Infections				X		X		X		X		X		X	X	X			X		X			
Stools	X	X		X		X		X																
Time off school due to ill-health															X	X			X	X		X		
Hearing problems		X	X		X	X	X		X		X		X			X				X	X			
Vision problems		X	X		X	X	X		X		X		X			X				X	X			
Speech problems							X		X		X		X	X		X			X	X		X		
Growth problems				X	X			X	X		X	X	X	X	X	X								
Other problems requiring specialist		X	X				X		X		X		X			X				X		X		
Toilet training			X		X		X																	
Bed wetting /Bladder problems									X		X		X		X			X						
Sleeping	X	X		X		X		X		X		X		X				X		X	X			
Fatigue																					X			X
Crying	X	X		X		X		X																
Teeth/dental problems		X	X		X		X		X		X		X				X							
Tics/Twitches		X		X				X				X	X					X			X	X		

Appendices

Timepoint Sunburn	4 weeks	6 mth	15 mth	18 mth	24 mth	30 mth	38 mth	42 mth	54 mth	57 mth	5 y 5 mth	5 y 9 mth	6 y 5 mth	6 y 9 mth	7 y 9 mth	8 y 7 mth [a]	8 y 7 mth [b] X	9 y 7 mth	10 y 8 mth	11 y 8 mth	13 y 1 mth	14 y 2 mth	Year 11	16 y 6 mth
Self-reported anthropometry		X					X		X		X	X	X					X			X			X
Mental and cognitive issues																								
Development	X	X	X	X		X		X		X		X		X										
Parental concerns over development				X		X		X	X	X	X	X		X										
Behaviour	X			X				X							X							X		
Temperament		X			X		X			X														
Language/vocabulary			X		X		X			X		X		X				X						
Communication			X	X			X							X				X						
Gender behaviour						X		X		X														
Temper tantrums/rages				X		X		X			X	X	X											X
Parent-child conflict													X											
Strengths and difficulties														X				X		X	X			
DAWBA															X				X			X		
Antisocial activities															X				X					X
Social development			X					X		X				X										
Social cognition															X				X	X		X		X
Mood and Feelings																		X		X	X			X
Body image																			X		X	X		X
Eating disorders																					X	X		X
Attitude towards animals																				X				
Self harm																								X
Life events				X		X		X		X		X		X			X							
Diet/Nutrition																								
Breastfeeding/bottle feeding	X	X	X		X																			
Food frequency questionnaire		X	X		X		X		X					X			X	X			X			
Feeding difficulties	X	X	X	X	X		X		X				X	X			X	X						
Eating behaviours		X	X		X		X		X		X		X	X			X	X	X		X			
School/packed lunch											X			X			X	X						
Dietary supplements	X		X		X		X		X					X				X	X	X		X		
Special diet									X		X						X				X			
Food allergies				X		X		X	X		X			X										

Appendices

Timepoint	4 weeks	6 mth	15 mth	18 mth	24 mth	30 mth	38 mth	42 mth	54 mth	57 mth	5 y 5 mth	5 y 9 mth	6 y 5 mth	6 y 9 mth	7 y 9 mth	8 y 7 mth [a]	8 y 7 mth [b]	9 y 7 mth	10 y 8 mth	11 y 8 mth	13 y 1 mth	14 y 2 mth	Year 11	16 y 6 mth
Environmental exposures																								
Passive smoke		X	X		X		X						X											
Contact with pets			X		X		X		X		X		X											
Sleeping environment		X		X		X			X			X		X				X						
Busy roads					X																			
Sunlight												X					X							
Hygiene					X		X		X		X		X											
Social variables																								
Children in household		X		X																				
Siblings		X		X										X		X	X	X		X				
Religion																		X		X				
Friendships																		X		X				X
Romantic relations																								X
Parenting variables																								
Measures of Parenting		X		X	X		X	X		X	X			X			X	X		X				
Discipline/punishment																		X		X				X
Own space														X			X	X	X	X				
Disagreements																								X
Childcare/Schooling																								
Childcare – Who/where/when			X		X		X		X	X			X				X	X		X				
Attends school									X	X			X											
Type of school													X				X	X	X	X	X			
Transport to/from school									X	X			X				X	X	X	X				
School enjoyment									X	X			X		X		X	X	X	X	X			
Favourite subjects																		X		X				
Behaviour/emotions after school																	X	X						
Special needs at school															X				X					
Educational problems															X			X	X					
Disciplinary problems																		X		X				
Parental aspirations for school/career																		X		X				X

Appendices

Timepoint	4 weeks	6 mth	15 mth	18 mth	24 mth	30 mth	38 mth	42 mth	54 mth	57 mth	5 y 5 mth	5 y 9 mth	6 y 5 mth	6 y 9 mth	7 y 9 mth	8 y 7 mth [a]	8 y 7 mth [b]	9 y 7 mth	10 y 8 mth	11 y 8 mth	13 y 1 mth	14 y 2 mth	Year 11	16 y 6 mth
Employment																								
Current employment status																								X
Job title																								X
Substance Use																								
Alcohol							X		X					X			X	X		X	X			X
Cigarettes																		X		X				X
Drugs																		X		X				X
Activities																								
TV viewing							X	X		X		X	X											
Toys/activities					X	X				X	X		X	X										
Book reading									X		X													
Out of school activities									X								X	X		X				X
Outings						X		X	X			X	X							X				
Indoor /Outdoor activities							X						X				X							
Favourite activities																		X		X				
Help in the home														X		X		X	X	X				
Activities with adults										X	X			X				X		X				X
Activities with siblings														X			X	X		X				
Parental monitoring																								X
Computers/internet																								X
Other																								
Pacifier use/thumb sucking		X			X		X	X			X	X												
Laterality								X																
Pocket money																								X

[a] My son/daughter's health
[b] My son/daughter at home and at school

Topics covered in Qs about the child/young person, completed by the child/young person

Timepoint	7 y 7 mth	8 y 1 mth	8 y 7mth	9 y 2 mth	9 y 7 mth	10 y 2 mth	10 y 8 mth	11 y 2 mth	11 y 8 mth	12 y 1 mth	13 y 1 mth [1]	13 y 1 mth [b]	13 y 10 mth	13 y 11 mth	14 y 1 mth	Year 11	16 y	16 y 6 mth	18 y 2 mth	18 y 7 mth	19 y 8 mth
Physical health																					
Current health																				X	
Short form health survey (SF36)																				X	
Asthma, eczema and allergies																		X		X	
Skin reactions to jewellery/watches						X			X												
Headaches								X													
Limb pain											X										
Bladder/bowel problems																					X
Fatigue											X		X					X			
Fitness													X								
Accidents														X				X		X	
Dental health	X						X														
Visiting the dentist	X						X														
Contraceptive use																					X
Menstruation																					X
Pregnancy																					X
Hirsutism																					X
Mental/cognitive issues																					
Psychosis like symptoms									X			X			X			X			
Locus of control																		X			
Moods and feelings																		X		X	
Self-image					X								X								
Body image							X							X							
Dieting behaviour														X						X	
Eating disorders														X				X		X	
Antisocial behaviour														X							
Life events																		X			
Sensation seeking																		X		X	

Appendices

Timepoint Deliberate self-harm	7 y 7 mth	8 y 1 mth	8 y 7mth	9 y 2 mth	9 y 7 mth	10 y 2 mth	10 y 8 mth	11 y 2 mth	11 y 8 mth	12 y 1 mth	13 y 1 mth [1]	13 y 1 mth [b]	13 y 10 mth	13 y 11 mth	14 y 1 mth	Year 11	16 y	16 y 6 mth	18 y 2 mth	18 y 7 mth	19 y 8 mth
Deliberate self-harm																		X			
Opinions on social difficulties				X																	
Opinions on ethnic differences										X											
Feelings and experiences**														X							
Confidence with new situations																X					
Diet/nutrition																					
Drinks	X						X														
Tea and coffee										X											
Fruit and vegetables										X											
School dinners/packed lunches											X										
Partial FFQ											X										
Environmental exposures																					
Pets			X	X																X	
Mobile phone use						X															
Social variables																					
Bedroom - sharing				X																	
Sleeping environment				X																	
Siblings										X											
Ethnicity										X											
Neighbourhood															X						
Friendships																	X			X	
Parenting																					
Relationship with parents					X										X						
Parental involvement with school																X					
School/education																					
Type of school																X					
School enjoyment		X	X					X					X		X	X					
Difficulties at school		X	X					X													
Bullying at school		X																			

Appendices

Timepoint / Behaviour at school	7 y 7 mth	8 y 1 mth	8 y 7mth	9 y 2 mth	9 y 7 mth	10 y 2 mth	10 y 8 mth	11 y 2 mth	11 y 8 mth	12 y 1 mth	13 y 1 mth [1]	13 y 1 mth [b]	13 y 10 mth	13 y 11 mth	14 y 1 mth	Year 11	16 y	16 y 6 mth	18 y 2 mth	18 y 7 mth	19 y 8 mth
School ability/performance		X	X		X								X		X	X					
Computer use									X							X					
Travel to school													X								
Key stage 3 grades													X								
Aspirations for grades													X			X					
Aspirations for further education													X			X					
Attitudes towards learning															X	X					
Maths and maths teacher													X								
GCSE choices													X								
Attendance																X		X			
Clubs/activities in school																X					
Qualifications																				X	
Current studying status																				X	
University application																				X	
Employment																					
Job aspirations									X				X								
Current occupation																		X		X	
Job Title																		X		X	
Unemployment																				X	
Substance Use																					
Alcohol														X [c]				X		X	
Smoking														X [c]	X			X		X	
Drugs														X [c]	X			X		X	
Activities																					
Computers			X						X										X		
Games consoles			X																		
Internet			X																X		
Mobile phones						X															
Toys				X																	
Reading												X									

Timepoint / Singing	7 y 7 mth	8 y 1 mth	8 y 7mth	9 y 2 mth	9 y 7 mth	10 y 2 mth	10 y 8 mth	11 y 2 mth	11 y 8 mth	12 y 1 mth	13 y 1 mth [1]	13 y 1 mth [b]	13 y 10 mth	13 y 11 mth	14 y 1 mth	Year 11	16 y	16 y 6 mth	18 y 2 mth	18 y 7 mth	19 y 8 mth
Musical instruments												X									
Listening to music												X									
Weekend activities													X			X					
General activities														X				X	X		
Other																					
Laterality					X																
Earrings and other jewellery						X															
Wearing a watch									X												
Bullying by siblings										X											
Road safety													X								
Transport use													X					X		X	

[a] Food and things
[b] Reading and singing
[c] attitudes towards rather than actual use