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TIMING OF HARD PALATE REPAIR AND FACIAL GROWTH IN PATIENTS WITH UNILATERAL CLEFT LIP AND PALATE

by

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Abstract

Lateral cephalometric radiographs from the growth archive of the Sri Lankan Cleft Lip and Palate Project were analyzed to elucidate the relationship between timing of hard palate repair and facial growth in patients with unilateral cleft lip and palate (UCLP). One hundred and twenty-five adult patients with nonsyndromic UCLP operated on at different ages for hard palate repair were recruited and their last cephalometric radiographs were used in the cross sectional analysis; 104 patients with nonsyndromic UCLP operated on at different ages for hard palate repair and their 290 cephalometric radiographs were available in the longitudinal analysis. The design utilized statistical control for gender, age, and other covariates such as the timing and surgeon of lip repair as well as the technique and surgeon of hard palate repair. Results showed that the length of the alveolar maxilla (PMP-A, $p = 0.05$) and the anteroposterior alveolar jaw relation (ANB, $p \leq 0.001$), but not the mandibular measurements (Ar-Gn, Ar-Go-Gn, SNB, S-N-Pog, SN-MP; all $p > 0.05$), were related to the timing of hard palate repair. These results suggest that in patients with UCLP late hard palate repair has a smaller adverse effect than early hard palate repair on the forward growth of the maxilla, and that timing of hard

palate repair does not significantly affect the growth of the mandible.

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1

Introduction

Patients with operated cleft lip and palate often suffer from maxillary retrusion. Much of the anteroposterior growth disturbance of the midfacial skeleton results from the surgical procedure (Graber, 1949; Ortiz-Monasterio *et al.*, 1959; Bishara *et al.*, 1976; Mars and Houston, 1990; Capelozza Filho *et al.*, 1993; Liao and Mars, 2005a). The surgical procedure with the greatest inhibiting effect on midfacial growth is almost certainly the hard palate repair (Graber, 1954; Ross, 1987a; Mars and Houston, 1990; Liao *et al.*, 2002; Liao and Mars, 2005a, b, c). The idea that hard palate repair is detrimental to maxillary growth originates with the clinical observation of Gillies and Fry (1921) and the experimental and clinical works of Herfert (1958). In this report, he is the first to suggest that the nature of palate repair, which includes raising a palatal mucoperiosteal flap, affects the growth centres of the hard palate and leads to aberrations of maxillary growth. Whether the apparent adverse effects of hard palate repair on maxillary growth are due to de-vascularization, disturbance of periosteum, or simply the restrictive effect of the scar, has been debated. In general, the idea of a reduced blood supply to the

maxillary skeleton after hard palate repair has not been accepted. However, one popular theory of abnormal maxillary growth following hard palate repair in patients with cleft palate, proposed by Ross (1970), is that excessive postoperative scar tissue, formed by undermining of soft tissues and creation of denuded palatal bone, adjacent to the pterygo-palatine-tuberosity sutures can inhibit the forward growth of the maxilla.

At the time of hard palate repair, a common problem experienced by the cleft surgeon is insufficient tissue in the cleft region. Either the surgery can be done by undermining with or without denudation of the palatal bone or the surgeon can borrow tissue from the adjacent areas; neither alternative is considered to be ideal from the point of view of maxillary growth. To reduce the problem, some surgeons choose to postpone surgery but this may have consequences for speech development. According to the survey of the Eurocleft Project, the timing of hard palate repair shows extreme variation in different centres, from birth to 13 years (Shaw *et al.*, 2000). Because of concerns regarding airway, anaesthetics, and haemorrhage risks, cleft palate repair has never been widely performed in the neonatal period. Generally, there are four common routines for timing of palate repair:

1. Early complete palate repair (3 to 9 months)

2. Late complete palate repair (12 to 24 months)
3. Two-stage palate repair with early closure of the hard palate (3 to 6 months) and then velar closure (6 to 24 months)
4. Two-stage palate repair with early velar closure (3 to 9 months) and delayed closure of the hard palate (2 to 9 years)

Withholding hard palate repair to study the effect of timing on speech and facial growth may not be possible on ethical and humanitarian grounds, if speech is disturbed after delaying hard palate repair past the age of early speech development. However, in the developing world, it is possible to find patients with cleft lip and palate reaching childhood, adolescence, or even adulthood who have had no surgical repair of the palate due to various factors such as lack of facilities, lack of awareness, cultural perception, or socioeconomic circumstances. The growth archive of the Sri Lankan Cleft Lip and Palate Project therefore provides an important alternative to study retrospectively the effect of timing of hard palate repair on facial growth in patients with cleft lip and palate by evaluating the facial morphology and growth of the Sri Lankan patients with cleft lip and palate operated on at different ages, from birth to adulthood, for hard palate repair. The present study was designed to answer the question.

2

Systematic Review

2.1 Introduction

The effect of the timing of hard palate repair, especially grossly delayed repair, on facial growth has been well recognized since the early 1900s. Gilles and Fry (1921) observed narrowing and backward displacement of the maxillary arch in patients who had surgical repair of the hard palate, and noted that the earlier the surgery, the greater the deformity. They proposed, therefore, to surgically close only the soft palate and obturate the hard palate with a prosthesis. However, there were no further reports on whether this procedure was actually adopted or whether it was successful. This philosophy was introduced to clinical practice both by Slaughter and Pruzansky (1954) and by Schweckendiek (1978), but in their approach the hard palate was closed with surgery several years after the soft palate repair, which took place in infancy. Slaughter and Pruzansky never published any specific follow up report about the facial growth and development of the particular group of patients. Patients with clefts operated on by Schweckendiek had good maxillary growth and dental occlusion (Schweckendiek, 1978), despite a rather crude result (i.e.,

subjective judgment) analysis by today's standards. Hence, it was suggested that the hard palate should be closed past the age of 12 to 14 years so that the growth of the maxilla might continue undisturbed for as long as possible.

Since then, the Zurich group (Hotz *et al.*, 1978; Hotz and Gnoinski, 1979) and the Göteburg group (Friede *et al.*, 1980, 1987) also used the two-stage method successfully, though the timing of hard palate repair differed (7 and 9 years-of-age, respectively, for the Zurich and Göteburg groups). Admittedly, not every team found superior maxillary growth after delayed hard palate repair, but most teams used the concept of delayed hard palate closure, at least from the point of view of maxillary growth. In 1984, Robertson and Jolleys in Manchester abandoned the delayed hard palate closure until 5 years of age in favour of an early one-stage technique because they found no demonstrable difference in maxillary growth (Robertson and Jolleys, 1991). On the other hand, delayed hard palate repair was and still is enthusiastically promoted by the Zurich and Göteburg groups.

Evidence for the benefit of delayed hard palate repair on maxillary growth has been scanty, though Bardach *et al.* (1984) provided some evidence that maxillary growth using the Schweckendiek procedure was superior, and Friede and Enemark (2001) found favourable maxillary growth after delayed hard palate repair until the

age of 9 years in their long-term follow up study. However, Friede *et al.* (1999) still questioned whether it is necessary to delay hard palate repair until 9 years rather than 5 years because similar and satisfactory maxillary morphology was found in the two samples operated on at the two different ages. On the other hand, Blijdorp and Egyedi (1984) found no maxillary growth difference between patients with repair of the palate at 3 and 6 years of age. Noverraz *et al.* (1993) found no difference between repair of the hard palate at 1.5 years, 4.6 years, and 9.4 years; Rohrich *et al.* (1996) found no difference between 10 months and 4 years; and Swennen *et al.* (2002) found no difference between 6 months and 2.5 years. Ross (1987b) in his extensive multi-centre study found that palate repair prior to 12 months of age provided better maxillary growth than palate repair after 20 months including delayed hard palate repair at 4 to 7 years, but he presumed that the surgery was carefully performed.

Not all authorities agree that the timing of palate repair is an individual matter. Aduss and Pruzansky (1968) decried the use of chronological age as a guide to the timing of palate repair. They concluded that cleft width was a major determinant instead. That is, cleft palate should be closed when the cleft width is small so the adverse effect of palate repair on maxillary growth would be less pronounced.

However, they did not provide any evidence to support their surgical policies. Berkowitz (1985) also suggested an individual approach for deciding the age for closure of the palate according to the cleft width. However, this report was built on observation and discussion of individual patients only. Late hard palate repair should, in theory, be less damaging than early hard palate repair; on the assumption that the more maxillary growth that has occurred, the less there remains to be disturbed. The assumption is supported by the good maxillary growth results after palate repair with the Schweckendiek procedure in which hard palate closure was generally delayed past the early teenage years (Schweckendiek, 1978; Bardach *et al.*, 1984; Ross, 1987b). While it is true that an unoperated palate results in excellent jaw relationships (Ortiz-Monasterio *et al.*, 1959; Mestre *et al.*, 1960; Dahl, 1970; Bishara *et al.*, 1976; Mars and Houston, 1990; Capelozza Filho *et al.*, 1993; Liao and Mars, 2005a), delayed hard palate repair past the age of 12 to 14 years seems to produce favourable jaw relationships (Schweckendiek, 1978; Bardach *et al.*, 1984; Ross, 1987b), and hard palate repair by the age of 2 years often results in maxillary retrusion, the facial growth data regarding delay of hard palate closure until age 2 to 9 years are quite equivocal and contradictory. Such conflicting findings suggest that there could be some critical period—a pubertal growth phase—during which

time hard palate repair may have a more pronounced impact on maxillary growth.

2.2 Methods

To evaluate the effect of timing of hard palate repair on facial growth in patients with cleft lip and palate, a systematic review was undertaken with special reference to cranial base, maxilla, mandible, jaw base relation, and incisor relation.

To find the relevant articles appropriate for this review, a search was conducted according to the following search strategy: (1) The electronic database Medline (via PubMed) from 1966 to December 2004 was searched using a combination of the following keywords: 'facial growth', 'cleft lip palate', and 'timing of hard palate repair'; (2) The *Cleft Palate-Craniofacial Journal* (formerly the *Cleft Palate Journal*) from 1964 to November 2004 was hand searched; and (3) The reference lists of the retrieved publications were also hand searched to identify any relevant publications, not already identified using the above two search strategies. The selection criteria for inclusion were reports in English, and exclusion of case reports, case-series (a case-series was defined as including less than 10 patients), and the studies with no control or comparison group in the sample.

2.3 Results

A total of 15 studies met the inclusion criteria for the following review (Robertson and Jolleys, 1974; Hotz *et al.*, 1978; Schweckendiek, 1978; Hotz and Gnoinski, 1979; Bardach *et al.*, 1984; Blijdorp and Egyedi, 1984; Friede *et al.*, 1987; Ross, 1987b; Noverraz *et al.*, 1993; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002). All studies were retrospective and non-randomized. Five studies used cephalometry and casts (Robertson and Jolleys, 1974; Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Friede *et al.*, 1987; Rohrich *et al.*, 1996), seven used cephalometry (Hotz *et al.*, 1978; Ross, 1987b; Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002), and three used casts (Schweckendiek, 1978; Hotz and Gnoinski, 1979; Noverraz *et al.*, 1993). The 15 studies included in the results of the review are summarized in Table 2.1 (see pages 85 through 93). The variables used in the 15 studies and the significant variables from statistics or clinical examination are included in Table 2.2 (see pages 94 through 101). A review of these studies disclosed that problems often exist in the area of methods. The methodological quality of the 15 studies was then evaluated using a checklist (Greenhalgh, 2001) and the results are provided in Table 2.3 (see pages 102 through

107). None of the 15 studies were methodologically ideal. All but four (Ross, 1987b; Noverraz *et al.*, 1993; Friede and Enemark, 2001; Swennen *et al.*, 2002) had multiple methodological deficiencies.

2.3.1 Cranial Base

Of the 15 studies that met the selection criteria, eight (Blijdorp and Egyedi, 1984; Ross, 1987b; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) examined the timing of hard palate repair and the growth of the cranial base (Table 2.2).

Of the eight studies, seven (Blijdorp and Egyedi, 1984; Ross, 1987b; Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) evaluated the effect of timing of hard palate repair on the cranial base angle and only two (Smahel, 1994; Rohrich *et al.*, 1996) on the length of the anterior cranial base (S-N). Despite methodological deficiencies, there is total agreement that variation in the timing of hard palate repair does not affect the growth of the cranial base in terms of the cranial base angle (NSBa) and the length of the anterior cranial base (S-N) appreciably (Table 2.2).

2.3.2 Maxilla

Of the 15 studies that met the selection criteria, 13 (Robertson and Jolleys, 1974;

Hotz *et al.*, 1978; Schweckendiek, 1978; Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) examined the timing of hard palate repair and the growth of the maxilla (Table 2.2).

Of the 13 studies, six (Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Friede *et al.*, 1999; Friede and Enemark, 2001; Swennen *et al.*, 2002) evaluated the effect of timing of hard palate repair on the length of the maxilla (PMP-A) and ten (Robertson and Jolleys, 1974; Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) on the protrusion of the maxilla (SNA). The results from the relevant studies are conflicting. Three (Smahel, 1994; Friede *et al.*, 1999; Swennen *et al.*, 2002) studies concluded that variation in the timing of hard palate repair does not affect the length of the maxilla (PMP-A) significantly, while one (Ross, 1987b) opposed this view, one (Friede *et al.*, 1987) depended on the type of cleft, and the other one (Friede and Enemark, 2001) depended on the age of evaluation (Table 2.2). However, the timing of hard palate repair differed considerably (range 2-108 months, Table 2.1). Seven (Robertson and Jolleys, 1974; Blijdorp and Egyedi, 1984; Friede *et al.*, 1987; Smahel, 1994;

Friede *et al.*, 1999; Nandlal *et al.*, 2000; Swennen *et al.*, 2002) studies concluded that variation in the timing of hard palate repair does not affect the protrusion of the maxilla (SNA) significantly, while another two (Bardach *et al.*, 1984; Ross, 1987b) opposed this view and the other one (Friede and Enemark, 2001) depended on the age of evaluation (Table 2.2). Similarly, the timing of hard palate repair differed considerably (range 2-158 months, Table 2.1).

2.3.3 Mandible

Of the 15 studies that met the selection criteria, 11 (Robertson and Jolleys, 1974; Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) examined the timing of hard palate repair and the growth of the mandible (Table 2.2).

Of the 11 studies, nine (Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) evaluated the effect of timing of hard palate repair on the protrusion of the mandible (SNB) and six (Ross, 1987b; Friede *et al.*, 1987; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) on the inclination of the mandibular plane (SN-MP).

Despite methodological deficiencies, all but one (Ross, 1987b) agreed that variation in the timing of hard palate repair does not affect the protrusion of the mandible (SNB) significantly, and there is total agreement that variation in the timing of hard palate repair does not affect the inclination of the mandibular plane (SN-MP) significantly (Table 2.2).

2.3.4 Jaw Base Relation

Of the 15 studies that met the selection criteria, eight (Bardach *et al.*, 1984; Ross, 1987b; Friede *et al.*, 1987; Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002) examined the timing of hard palate repair on the jaw base relation (ANB). The results from the relevant studies are conflicting. Four (Smahel, 1994; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Swennen *et al.*, 2002) studies concluded that variation in the timing of hard palate repair does not affect the jaw base relation (ANB) significantly, while another three (Bardach *et al.*, 1984; Ross, 1987b; Friede and Enemark, 2001) opposed this view and the other one (Friede *et al.*, 1987) depended on the type of cleft (Table 2.2). However, the timing of hard palate repair differed considerably (range 2-158 months, Table 2.1).

2.3.5 Incisor Relation

Of the 15 studies that met the selection criteria, only five (Robertson and Jolleys, 1974; Blidorp and Egyedi, 1984; Friede *et al.*, 1987; Noverraz *et al.*, 1993; Swennen *et al.*, 2002) examined the timing of hard palate repair on the incisor relation (overjet [Swennen *et al.*, 2002], anterior cross bite [reverse overjet] score [Robertson and Jolleys, 1974; Blidorp and Egyedi, 1984; Friede *et al.*, 1987], Goslon yardstick [Noverraz *et al.*, 1993]). The results from the relevant studies are also conflicting. Four (Robertson and Jolleys, 1974; Blidorp and Egyedi, 1984; Noverraz *et al.*, 1993; Swennen *et al.*, 2002) studies concluded that variation in the timing of hard palate repair does not affect the incisor relation significantly, while the other one (Friede *et al.*, 1987) depended on the type of cleft (Table 2.2). Similarly, the timing of hard palate repair differed considerably (range 2-113 months, Table 2.1).

2.4 Discussion

Articles reviewed do not provide conclusive evidence of a relation between the timing of hard palate repair and the growth of the maxilla in patients with cleft lip and palate. The reasons for conflicting results from the selected studies are the variation in the timing of hard palate repair in their samples (2-158 months, Table 2.1), variables used (Table 2.2), and their methodological deficiencies (Table 2.3).

These methodological deficiencies may be summarized as follows (study numbers as per Table 2.1):

1. Inappropriate sampling
    - Non-random or non-consecutive selection (1-5, 7, 8, 10, 12, 13)
    - Small sample size (1, 2, 4, 8-13)
    - Wide age distribution (6, 11, 13)
    - Mixture of different types of clefts (2, 3, 11, 13)
    - Ignoring sexual dimorphism (1-5, 13)
    - Not matching technique of hard palate repair (7, 11, 12, 14)
2. Inadequate assessment
    - Different methods of image production, if a cephalometric study (1, 2, 5, 6, 8, 11)
    - Different observer(s) for experimental and control groups (1-5, 8, 10, 12, 13, 15)
    - Not reporting method error (1-8, 10-12, 14)
    - Not assessing "blindly" (1-6, 8, 10, 12-15)
3. Inappropriate statistics (3, 4, 8-10, 12, 14)
4. Follow up too short (1, 2, 4, 8, 13, 15)

2.5 Conclusions

On the basis of the selected studies, the following conclusions about the effect of timing of hard palate repair on facial growth in patients with cleft lip and palate can be made:

1. Variation in the timing of hard palate repair does not affect the growth of the cranial base in terms of the cranial base angle and the length of the anterior cranial base appreciably.
2. The effect of timing of hard palate repair on the growth of the maxilla in terms of the length and protrusion of the maxilla as well as on the jaw base relation and incisor relation has not been established.
3. Variation in the timing of hard palate repair does not affect the growth of the mandible in terms of the protrusion of the mandible and the inclination of the mandibular plane appreciably.

However, the conclusions about the effect of timing of hard palate repair on the growth of the cranial base and mandible are far from robust because of small samples and poor quality of most selected studies. There is a need for further research.

3

Aims and Hypotheses

3.1 Aims

The purposes of the present study were to:

1. Investigate whether timing of hard palate repair, before versus after pubertal peak velocity age (PPVA), had a significant effect on facial growth in patients with unilateral cleft lip and palate (UCLP) by performing a cross sectional analysis. The aim of conducting the cross sectional study was to understand the long-term effect of timing of hard palate repair, before versus after PPVA, on facial growth in patients with UCLP.
2. Investigate whether timing of hard palate repair before PPVA had a significant effect on facial growth in patients with UCLP by performing a longitudinal analysis. The aim of conducting the longitudinal study was to understand the effect of timing of hard palate repair before PPVA on facial growth, and to comment on the appropriate age at hard palate repair for patients with UCLP.

3.2 Hypotheses

The hypotheses to be tested were:

1. Timing of hard palate repair has a significant adverse effect on the growth of the maxilla.
2. Late hard palate repair has a smaller adverse effect than early hard palate repair on the growth of the maxilla.
3. Timing of hard palate repair does not significantly affect the growth of the mandible.

4

Materials and Methods

The study was approved by the Institutional Review Board of the University of Ruhuna, Galle, Sri Lanka, and the University of London, London, UK in 1990.

4.1 Patients

Patients were selected from the growth archive of the Sri Lankan Cleft Lip and Palate Project (Mars *et al.*, 1990). These data were collected by Dr. M. Mars and his team during their expeditions to Sri Lanka in 1984, 1985, 1986, 1988, 1990, 1995, 1998, and 2002. Selection was determined according to the following criteria:

1. Sri Lankan patients with nonsyndromic UCLP.
2. No presurgical orthopaedics.
3. One lip repair.
4. Palate repair (one or two-stage, hard and then soft) by the British surgical team.
5. No orthodontic treatment or other craniofacial surgery such as alveolar bone grafting, velopharyngeal surgery, orthognathic surgery, or distraction

osteogenesis prior to cephalometric assessment.

6. At least one cephalometric radiograph after lip and palate repair taken at the age of 17 years or older (cross sectional study), or
7. At least two cephalometric radiographs after lip and palate repair in patients who had hard palate repair before PPVA (longitudinal study)

PPVA was defined as the age of the highest increment in the effective length of the basal jaws (Ar-ANS and Ar-Gn, respectively, for the maxilla and mandible) during the pubertal growth phase. Because of differences in ethnicity as well as nutritional and socioeconomic status, it would be expected that PPVA occurred later in a normal Sri Lankan (14 years for females and 16 years for males) than in a normal British population by two years (Eveleth and Tanner, 1990; Bhatia and Leighton, 1993).

4.1.1 Patient Characteristics in the Cross Sectional Study

To determine the effect of timing of hard palate repair, before versus after PPVA, on facial growth in patients with UCLP, the study of facial growth was cross sectional in design meaning that the included patients all fulfilled criteria 1-6. A total of 125 patients who met the above criteria were recruited and their last cephalometric radiographs were used in the cross sectional study. Table 4.1 provides the

characteristics for all patients (see pages 108 through 111). There was a preponderance of males (65 percent). Large percentages of the patients underwent lip repair by local surgeons without having documentation of the cleft subtype (complete or incomplete) (38 percent) and the definite surgical technique for lip repair (48 percent). Most patients received one-stage palate repair (73 percent), hard palate repair before PPVA (66 percent), palatal mucoperiosteal flap for hard palate repair (73 percent), and the von Langenbeck procedure for soft palate repair (85 percent). Ten different surgeons, six consultants and four specialist registrars, performed all primary palate repairs.

4.1.2 Patient Characteristics in the Longitudinal Study

To determine the effect of timing of hard palate repair before PPVA on facial growth in patients with UCLP, the study of facial growth was longitudinal in design meaning that the included patients all fulfilled criteria 1-5, and 7. A total of 104 patients and their 290 cephalometric radiographs were available in the longitudinal study. Figure 4.1 is a plot of the distribution of the 290 cephalometric radiographs by age (see page 137). Table 4.2 provides the characteristics for all patients (see pages 112 through 116). There was a preponderance of males (62 percent). Large percentages of the patients underwent lip repair by local surgeons without having

documentation of the cleft subtype (complete or incomplete) (24 percent) and the definite surgical technique for lip repair (41 percent). Most patients (82 percent) had two or three cephalometric assessments. Most patients received one-stage palate repair (60 percent), palatal mucoperiosteal flap for hard palate repair (60 percent), and the von Langenbeck procedure for soft palate repair (88 percent). Ten different surgeons, six consultants and four specialist registrars, performed all primary palate repairs.

4.2 Surgical Treatment History

One investigator (Y.-F. L.) examined each patient's surgical record. Details of primary lip and palate repair were recorded, including age at the time of the surgery and the techniques used. The origin of surgeons (local surgeon, British team) who undertook the primary lip repair, and the grade of surgeons (consultant, specialist registrar) who undertook the primary palate repair were also detailed, because facial growth outcome may be related to the skill of surgeons, as developed in the Discussion (see pages 46 and 47).

4.3 Cephalometry

4.3.1 Acquisition of Lateral Cephalometric Radiograph

Lateral cephalometric radiographs were obtained for each patient at one or several time points. Figure 4.2 shows a pair of lateral cephalometric radiographs taken at two different ages from one patient (see page 138). Every lateral cephalometric radiograph was taken on the same cephalostat according to the standardized cephalometric guideline with the natural head position and the teeth in centric occlusion. The distance from the focus to the mid-sagittal plane was 152.5 cm and the distance from the mid-sagittal plane to the film was 16 cm. This arrangement produced an enlargement factor of 10.5%. A specialist trained in orthodontics was present during acquisition. The average effective dose for a lateral cephalometric radiograph was estimated to be 0.1 mSv.

4.3.2 Landmark Definition and Digitization

For tracing of cephalometric radiographs and marking of landmarks, each cephalometric radiograph was placed on the top of a light box and covered with a transparent acetate paper. One investigator traced all the cephalometric radiographs, marked the landmarks, and digitized the radiographic tracings without knowledge of the patient's previous surgical treatment history. A total of 21 points were marked in order to characterize the cranial base, maxilla, mandible, and

denture. Figure 4.3 illustrates the landmarks and reference lines or planes used on a cephalometric radiograph in the present study (see page 139). Every landmark was defined by anatomical structures or their intersections and all landmarks and their anatomical definitions are listed in Table 4.3 (Riolo *et al.*, 1974; Ross, 1987c) (see pages 117 through 120). After fixation of the cephalometric tracing on the digitization table, the digitization was carried out and the landmark data were subsequently transferred to a computer for computation of variables by use of the Gela program, which is an AutoCAD-based software program and has been validated by a previous study (Worrell, 2003).

4.3.3 Computation of Variables

To describe the facial morphology, a total of 19 linear and 12 angular variables were calculated (Ross, 1987c). A linear variable is a distance between two landmarks. An angular variable is defined as an angle formed by three landmarks or an angle between two lines each defined by two landmarks. The variables describe the craniofacial region: cranial base, maxilla, mandible, jaw relation, facial height, and denture. All variables used in the present study are listed in Table 4.4 (see pages 121 through 123).

4.3.4 Error of the Method

The sources of error contributing to the total error of the method were the cephalometric acquisition procedure and the landmark localization, having errors e_{acq} and e_{la}, respectively. The landmark localization error may, in turn, be divided into the errors from the procedure of marking of the landmark points, e_{mark}, the alignment of the acetate paper on the digitization table, e_{al}, and the procedure of digitization of the landmark points, e_{dig}.

The total error may, accordingly, be written as (Hermann, 2000):

$$e_{total} = \sqrt{e_{la}^2 + e_{acq}^2}$$

where

$$e_{la} = \sqrt{e_{dig}^2 + e_{al}^2 + e_{mark}^2}$$

Because every lateral cephalometric radiograph was taken on the same cephalostat, the main source of error due to the acquisition procedure was the positioning of the head in the cephalostat (Baumrind and Frantz, 1971). By using a mathematical model, however, Ahlqvist *et al.* (1986, 1988) demonstrated that minor malposition of the head is of little importance for the total error, because the errors were generally less than 1% in linear measurements and 1 degree in angular measurements for malposition of the head up to 5 degrees. Malposition of the head

of more than 5 degrees is unlikely, because it would be obvious to the examiner and should be corrected immediately. The main contributor to the total error was, therefore, the landmark localization, e_{la} :

$$e_{total} \approx e_{la}.$$

e_{la} was calculated by duplicate tracing, marking of landmarks, and digitization of 30 randomly selected cephalometric radiographs at least one month apart by the same investigator (Y.-F. L.).

4.4 Statistical Analysis

Descriptive analysis was performed for the purpose of summary statistics. Data were expressed as % (n) except where otherwise stated.

4.4.1 Statistical Analysis in the Cross Sectional Study

Multiple linear regression analysis using SPSS v11.0 (SPSS Inc., Chicago, IL) was undertaken to assess whether timing of hard palate repair, before versus after PPVA, had a significant effect on facial growth adjusted for appropriate covariates in the cross sectional study. Apart from the covariate which was of interest (i.e., timing of hard palate repair: before versus after PPVA), the choice of other covariates for the models reflected both theoretical and analytic considerations. For example,

gender and age at last cephalometric assessment were included as covariates in the models because gender and age are known determinants of facial morphology. The remaining potential covariates (i.e., timing of lip repair, surgeon of lip repair: local surgeon versus British team, technique of hard palate repair: palatal mucoperiosteal flap versus vomerine mucoperiosteal flap, and surgeon of hard palate repair: consultant versus specialist registrar) that were significant at 0.15 level in the bivariate analyses were retained in the models. The results were reported as regression coefficients with 95% confidence intervals. Each of the regression coefficient for the timing of hard palate repair was the mean difference (mm or degrees) in the craniofacial measurement between patients who had hard palate repair before and after PPVA (after PPVA − before PPVA). P values were two sided and considered to be significant if equal to or less than 0.05.

4.4.2 Statistical Analysis in the Longitudinal Study

Mixed-model analysis using SPSS v12.0 (SPSS Inc., Chicago, IL) was undertaken to assess whether timing of hard palate repair before PPVA had a significant effect on facial growth adjusted for appropriate covariates in the longitudinal study. Mixed models, also called multilevel, random effects, or random coefficient models, are used for data that are hierarchical (e.g., between patients, and within patients) in

nature (Diggle *et al.*, 1994; Cnaan *et al.*, 1997; Sullivan *et al.*, 1999; Twisk, 2003). The main feature of these data is that the assessments within patients are not independent from one another and that has to be taken into account in the model. Repeated measurements in the longitudinal study require the use of mixed models or other strategies that account for this lack of independence. Mixed models were used in the present longitudinal study because they are the most flexible means of analyzing such data, meaning they can be applied in the situation when the number of repeated measurements differs between patients, and there are many missing assessments. These models were also used to allow for the time-dependent covariate, such as cranial base size, which may differ at each assessment age.

The model contains a fixed effect and a random effect (random intercept and slope). Fixed effects are used to model the means of the dependent variables and the effects of the independent variables on the means of the dependent variables; random effects are used to model heterogeneity in the intercepts and slopes of the individuals, and this heterogeneity can be represented by an appropriate frequency distribution. The general idea of a mixed model for longitudinal data is that there is natural heterogeneity across individuals in their responses over time. This heterogeneity are then included in the model as random variables, i.e., random

effects (Twisk, 2003).

In each mixed model, a main effects-only model that included the covariates which were of interest (i.e., timing of hard palate repair, and age at cephalometric assessment) and potential confounding variables was first determined. The age variable was centred at age 20 years (i.e., age at cephalometric assessment in years minus 20), so the intercept represented the mean of the dependent variable at age 20 years. The choice of other covariates for the final models reflected both theoretical and analytic considerations. For example, gender was included as a covariate in the final models because gender is a known determinant of facial growth. Cranial base size (Ba-N) was included as a covariate in the final models of the maxillary, mandibular, and facial height linear measurements, because absolute facial linear measurements can be affected by the cranial base size variation, as developed in the Discussion (see pages 62 and 63). The remaining potential covariates (i.e., timing of lip repair, surgeon of lip repair: local surgeon versus British team, technique of hard palate repair: palatal mucoperiosteal flap versus vomerine mucoperiosteal flap, and surgeon of hard palate repair: consultant versus specialist registrar) were retained in the final model if their inclusion altered the unadjusted regression coefficient for any covariate in the model by > 10%. Possible 2-way interactions

between the covariates in the models were then examined. In addition to the timing of hard palate repair–by-age interaction which was of interest, interactions that were significant at 0.05 level were retained in the final model.

The results were reported as regression coefficients with 95% confidence intervals. Each of the regression coefficient for the timing of hard palate repair was the effect of timing of hard palate repair on the mean (mm or degrees) of the craniofacial measurement at age 20 years (intercept); each of the regression coefficient for the timing of hard palate repair-by-age interaction was the effect of timing of hard palate repair on the growth rate (mm/yr or degrees/yr) (slope) of the craniofacial measurement. P values were two sided and considered to be significant if equal to or less than 0.05.

5

Results

5.1 Error of the Method

The error of the method, *s(i)*, was calculated by using Dahlberg's formula (1940), which has been most widely used by orthodontic investigators:

$$s(i) = \sqrt{\sum d^2 / 2n}$$

where d is the difference between two duplicate measurements and n is the number of pairs of measurements (n = 30). The mean of *s(i)* was 0.3 mm (SD 0.1mm, range 0.2-0.5 mm) for linear variables, and 0.4 degrees (SD 0.2 degrees, range 0.2-0.7 degrees) for angular variables.

5.2 Facial Morphology and Timing of Hard Palate Repair, Before Versus After PPVA, in the Cross Sectional Study

The results showed that there was significant association between the cranial base angle (NSBa, $p < 0.05$), the depth of the bony pharynx (Ba-PMP, $p = 0.01$), the length of the alveolar maxilla (PMP-A, $p = 0.05$), the effective length of the maxilla (Ar-ANS, $p = 0.05$; Ar-A, $p < 0.05$), the anteroposterior jaw relation (ANS-N-Pog, p

< 0.05; ANB, p < 0.01) and the overjet (p < 0.01), and the timing of hard palate repair. The other craniofacial measurements was unrelated to the timing of hard palate repair (all p > 0.05) (Table 5.1, see pages 124 through 127).

5.3 Facial Growth and Timing of Hard Palate Repair Before PPVA in the Longitudinal Study

The results showed that timing of hard palate repair had a significant effect on the means of the length of the cranial base (S-N, S-Ba, Ba-N; all p < 0.001) at age 20 years (intercepts) and on the growth rates (slopes) (all p < 0.001). The timing of hard palate repair also had a significant effect on the means of the length and protrusion of the alveolar maxilla (PMP-A, p = 0.05 and SNA, p < 0.001; respectively) and the anteroposterior alveolar jaw relation (ANB, p = 0.001) at age 20 years but not on the growth rates, whereas the timing of hard palate repair had a significant effect on the growth rate of the position of the maxillary incisors (SN-UI, p < 0.001) but not on the mean at age 20 years. In addition, either the means of the other craniofacial measurements at age 20 years or the growth rates was not significantly associated with the timing of hard palate repair (all p > 0.05) (Table 5.2, see pages 128 through 135; Figures 5.1 through 5.15, see pages 140 through 154).

6

Discussion

6.1 Study Design and Methods

The effect of timing of hard palate repair on the growth of the maxilla in patients with cleft lip and palate still remains controversial. The main reason is the lack of adequate convincing evidence. There are four major challenges involved around this issue: (1) ethics, (2) confounders, (3) longitudinal data analysis, and (4) long-term follow up. These are described in detail as follows.

First, it may be unethical to withhold surgery to study the effect of timing of hard palate repair on facial growth, if speech is disturbed after delaying hard palate repair past the age of early speech development (Cosman and Falk, 1980; Jackson *et al.*, 1983; Bardach *et al.*, 1984; Witzel *et al.*, 1984; Noordhoff *et al.*, 1987; Rohrich and Byrd, 1990; Rohrich *et al.*, 1996; Lohmander-Agerskov, 1998).

Secondly, the facial growth outcome of operated patients depends on a number of factors. For example, genetic inheritance, gender, age, ethnicity, and the cleft type are all well-known determinants of facial growth in patients with cleft lip and palate. Favourable maxillary growth and dental occlusion after palate repair with

the Schweckendiek procedure have strongly suggested the benefit of delaying hard palate repair until adolescence (Schweckendiek, 1978; Bardach *et al.*, 1984; Ross, 1987b). Facial growth outcome may also be technique-sensitive. The deforming effects of surgically denuded palatal bones are supported in animal studies (Kremenak *et al.*, 1967; 1970a, b; Kremenak, 1984). Minimal exposure of palatal bones, as with a vomerine mucoperiosteal flap, should in theory adversely affect maxillary growth less than a palatal mucoperiosteal flap. The two best centres for facial growth outcome in the Eurocleft multi-centre study performed a vomerine mucoperiosteal flap for closure of the hard palate at the time of lip repair (Shaw *et al.*, 1992). The outcome reflecting the minimal interference is possibly due in part to the limited exposure of the palatal bone during repair. On the other hand, clinical experience has led some surgeons to suspect that closure of the hard palate with a vomerine mucoperiosteal flap may lead to arrest of maxillary growth (Pruzansky and Aduss, 1967; Bergland and Sidhu, 1974; Friede and Johanson, 1977; Friede *et al.*, 1980), possibly because of the scar tissue adjacent to the vomero-premaxillary suture following repair (Friede, 1978; Delaire and Precious, 1985; Friede, 1998; Liao and Mars, 2005c). There is increasing belief that the surgeon's skill, which is influenced by cumulative surgical experience and the

annual volume of procedures undertaken (Williams and Sandy, 2003), may have more influence on facial growth outcome than the timing or technique used for hard palate repair (Ross, 1987a; Shaw *et al.*, 1992).

Thirdly, longitudinal data from operated patients can have undesirable characteristics from a statistical viewpoint. For example, longitudinal data are often obtained at irregular time intervals. Available data are incomplete because patients often miss scheduled visits due to lack of motivation, noncompliance, or other factors. Any one of these characteristics is sufficient to compromise traditional statistical methods, leading to inappropriate statistical analyses in most previous longitudinal studies. That is, to compare the groups at each time point, using, for two (or more than two) groups, a two-sample t-test (analysis of variance if more than two groups) or chi-square test, or a non-parametric equivalent. There are a number of reasons why this is inappropriate. The within-patient changes over time are ignored; the successive tests are not independent; the process may involve many significance tests, increasing the probability of type I error; and it may be difficult to reach an overall conclusion about the difference between groups, and impossible to obtain a single estimate of this difference (Petrie *et al.*, 2003). Nowadays the statistical methods, i.e., mixed models or other strategies, exist and

the computer software is readily available to accommodate longitudinal analysis of observational studies and controlled clinical trials, and it is important that these methods are employed when appropriate.

Fourthly, the facial growth outcome studies of operated patients are not usually continued long enough to provide convincing results. That is, facial growth is usually evaluated at an age before the pubertal growth phase. Because longitudinal facial growth studies have clearly demonstrated that maxillary retrusion in operated patients with UCLP is indeed progressive and worsens especially during the pubertal growth phase (Hayashi *et al.*, 1976; Ross, 1987a; Semb, 1991), the benefit of delayed hard palate repair on maxillary growth can only be demonstrated after facial growth is complete.

However, in the developing world, it is possible to find patients reaching childhood, adolescence, or even adulthood who have had no surgical repair of the palate due to factors such as lack of facilities, lack of awareness, cultural perception, or socioeconomic circumstances. The growth archive of the Sri Lankan Cleft Lip and Palate Project therefore provides an important alternative to study retrospectively the effect of timing of hard palate repair on facial growth by evaluating the facial morphology and growth of the Sri Lankan patients operated on

at different ages for hard palate repair, dependent on the time when the British surgical team went there (1985, 1986, 1990) and when the unoperated patients attended the team clinic (Ward and James, 1990) (nature's experiment). In addition, limited genetic variation would be expected in a Sri Lankan population because Sri Lanka is an island. The study also selected patients with the same ethnic background (Asian Sri Lankan) and cleft type (UCLP), and adjusted for gender, age, and other covariates such as the timing and surgeon of lip repair as well as the technique and surgeon of hard palate repair. Cranial base size (Ba-N) (Ross, 1987c) was included as a covariate in the longitudinal analysis of the maxillary, mandibular, and facial height linear measurements, because absolute facial linear measurements could be affected by cranial base size variation (Ross, 1965; Liao and Mars, 2005a), as discussed below (see pages 62 and 63).

Furthermore, the cross sectional design focused on the effect of timing of hard palate repair, before versus after PPVA, due to the assumption that hard palate repair may have a more pronounced impact on maxillary growth during a pubertal growth phase, as developed in the Systematic Review (see pages 19 and 20). The cephalometric radiographs taken at age 17 years, or older where available were used in the cross sectional analysis because facial growth has been more fully expressed,

on the assumption that facial growth after PPVA is minimal. The longitudinal design focused on the effect of timing of hard palate repair before PPVA due to its current use according to the survey of the Eurocleft Project (Shaw *et al.*, 2000). The choice of a longitudinal approach is based on two factors: first, almost all the data, in contrast to the majority of data for patients who had hard palate repair after PPVA, were collected longitudinally. Secondly, there are several advantages of a longitudinal approach. A longitudinal study has more statistical power than a cross sectional study for a fixed number of patients; a longitudinal study can provide information about individual growth, whereas a cross sectional study cannot; and a longitudinal study can separate age effects (i.e., changes over time within patients) from cohort effects (i.e., differences between patients at baseline) (Diggle *et al.*, 1994).

6.2 Effect of Timing of Hard Palate Repair on Facial Growth

6.2.1 Adult Facial Morphology in Patients Repaired Before Versus After PPVA

Lateral cephalometric radiographs from 125 adult patients with nonsyndromic UCLP operated on at different ages for hard palate repair were used in the cross

sectional analysis. The cross sectional analysis showed that the timing of hard palate repair, before versus after PPVA, significantly affected the depth of the bony pharynx and the length of the alveolar maxilla after adjusting for gender, age, and technique of hard palate repair. All other dentofacial morphological deviations associated with the timing of repair could be explained by these basic deviations.

The cross sectional study demonstrated that the effect of timing of hard palate repair was partly on the forward displacement of the basal maxilla and partly on the anteroposterior development of the maxillary dentoalveolar process. Palate repair is known to inhibit the forward displacement of the basal maxilla and the anteroposterior development of the maxillary dentoalveolar process (Ross, 1987b; Liao and Mars, 2005c). It seems reasonable that the more forward the displacement of the basal maxilla and the greater the anteroposterior development of the maxillary dentoalveolar process, the less there remains to be disturbed. The finding is consistent with previous almost normal maxillary growth results following palate repair using the Schweckendiek procedure in which hard palate repair is generally delayed to past the age of 12 to 14 years (Schweckendiek, 1978; Bardach *et al.*, 1984; Ross, 1987b). As a consequence, the effective length of the maxilla (Ar-ANS, Ar-A), which depended on the forward displacement and anteroposterior

development of the maxilla, was greater in patients with late repair than early repair (by 2.6 mm and 3.3 mm, respectively). Also, the timing of hard palate repair had a slightly larger effect on the forward displacement of the basal maxilla (Ba-PMP) than on the anteroposterior development of the maxillary dentoalveolar process (PMP-A), with 2.4-mm and 1.8-mm increase with late repair, respectively. The possible explanation is that the more mature the craniofacial structural region, as measured by e.g., the length of the alveolar maxilla (PMP-A) (Bhatia and Leighton, 1993), the less responsive it is to the timing of hard palate repair.

Contrary to a previous study (Ross, 1987b), it was found that the timing of hard palate repair had no effect on the downward growth of the basal maxilla, as evidenced by the similar anterior and posterior height of the basal maxilla (N-ANS and R-PMP, respectively) in patients with early and late repair. This may be explained by a previous finding (Liao and Mars, 2005c) that palate repair probably has no effect on the downward displacement of the basal maxilla or on palatal remodelling, perhaps because the scar tissue, formed following closure of the palate, does not across the sutures associated with downward displacement of the basal maxilla and also runs transversely or sagittally instead of vertically. The reduced posterior height of the basal maxilla is a common finding in operated patients (Dahl,

1970; Krogman *et al.*, 1975; Hayashi *et al.*, 1976; Semb, 1991; Smahel *et al.*, 1993; Ozturk and Cura, 1996; Swennen *et al.*, 2002). This deviation may be the result of the clefts rather than of lip or palate repair (Smahel *et al.*, 1993; Ozturk and Cura, 1996; Hermann *et al.*, 1999; Liao and Mars, 2005b, c) because the posterior height of the basal maxilla is also equally reduced in unoperated patients (Bishara *et al.*, 1985; Mars, 1993; Liao and Mars, 2005c), in "only lip operated" patients (Smahel and Mullerova, 1986; Mars, 1993), and in infants prior to primary surgery (Han *et al.*, 1995; Hermann *et al.*, 1999). Taken together, the timing effect of hard palate repair on maxillary growth was restricted to the basal maxilla in the anteroposterior position, and to the maxillary dentoalveolar process in the anteroposterior position and dimension. This, taken with the greater anteroposterior jaw relation (ANS-N-Pog, ANB) and larger overjet in patients with late repair as compared to early repair (by 2.7 degrees, 3.3 degrees, and 2.9 mm, respectively), supports the hypothesis that the timing of hard palate repair adversely affects the growth of the maxilla significantly, and that late repair has a smaller adverse effect than early repair on the growth of the maxilla.

In addition, the finding of similar mandibular size (Ar-Go, Go-Gn, Ar-Gn, Ar-B, Ar-Pog), shape (Ar-Go-Gn), and position (SNB, S-N-Pog, SN-MP) in patients with

early and late repair agreed with those of Bardach *et al.* (1984) and Ross (1987b), suggesting that timing of hard palate repair has no effect on the growth of the mandible. It may also be that palate repair has no effect on the growth of the mandible, perhaps because of its distance from the field of surgery, as supported by previous studies (Ross, 1987b; Silva Filho *et al.*, 1992; Capelozza Filho *et al.*, 1996; Liao and Mars, 2005c). As a consequence, the vertical development of the face, anteriorly (N-Men) and posteriorly (S-Go), which depended on the position and shape of the mandible, was comparable in patients with early and late repair. The increased steepness of mandibular plane and obtuse gonial angle are common findings in "lip as well as palate operated" older children and adults (Dahl, 1970; Hayashi *et al.*, 1976; Smahel and Brejcha, 1983; Ross, 1987c; Smahel *et al.*, 1993; Ozturk and Cura, 1996). These basic deviations of the mandible are also present in "only lip operated" older children and adults (Dahl, 1970; Mars, 1993), and in unoperated older children and adults (Bishara *et al.*, 1976; Isiekwe and Siwemimo, 1984; Mars and Houston, 1990; Silva Filho *et al.*, 1992; Capelozza Filho *et al.*, 1993; Liao and Mars, 2005a) but not in newborn infants (Han *et al.*, 1995; Hermann *et al.*, 1999), indicating that the changes in mandibular position and shape in patients with UCLP are not related to intrinsic or iatrogenic effects (Liao and Mars, 2005b, c), but

to functional (compensatory) effects secondary to decreased patency of the nasopharyngeal airway, as suggested by Ross (1970). Decreased patency of the nasopharyngeal airway in patients with cleft palate can turn purely nasal respiration into an oronasal or even an oral breathing pattern (Warren *et al.*, 1969; Kimes *et al.*, 1988), which, in turn, will elicit some compensatory mechanism. This neuromuscular recruitment may induce alterations in the position of the mandible at rest by clockwise rotation and the shape of the mandible by angle remodelling (Liao and Mars, 2005a), though the mechanism is poorly understood.

The adverse effect of palate repair on the position of maxillary incisors has been well illustrated by Ross and Johnston (1972). This effect is mainly due to the scar tissue covering the denuded palate bone, attached to the underlying bone and periodontal ligament, which leads to palatal deflection of the anterior maxillary dentoalveolar process accompanied by more upright maxillary incisors (Wijdeveld *et al.*, 1991; Leenstra *et al.*, 1995; Kim *et al.*, 2002). The finding that the position of the maxillary incisors (SN-UI) was not related to the timing of hard palate repair may be attributed to the technique used to close the hard palate, either the vomerine mucoperioteal flap or the von Langenbeck procedure, which results in limited denuded palatal bone adjacent to the anterior maxillary dentoalveolar process.

However, it is uncertain whether this was a result of a small effect of the hard palate repair using the vomerine mucoperioteal flap or the von Langenbeck procedure on the position of the maxillary incisors, or the adaptive change of the maxillary incisors in position by proclination despite early repair in response to the less favourable anteroposterior jaw base relation (ANS-N-Pog, ANB).

It was further observed that the timing of hard palate repair was related to the shape but not the size of the cranial base, as evidenced by the larger cranial base angle (NSBa) but similar length of the cranial base (S-N, S-Ba, N-Ba) in patients with late repair as compared to early repair. It seems unlikely that palate repair should affect the shape of the cranial base (Ross, 1987b; Capelozza Filho *et al.*, 1996; Liao and Mars, 2005c), because of its distance from the field of surgery. The difference in shape of the cranial base between patients with early and late repair therefore may be due to chance. This view is supported by cephalometric studies which have consistently shown that the timing of hard palate repair does not affect the growth of the cranial base (Blijdorp and Egyedi, 1984; Ross, 1987b; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002).

6.2.2 Facial Growth After Repair in Patients Repaired Before PPVA

Two hundred and ninety lateral cephalometric radiographs from 104 patients with nonsyndromic UCLP operated on at different ages for hard palate repair before PPVA were used in the longitudinal analysis. The longitudinal analysis showed that the timing of hard palate repair before PPVA significantly affected the length of the alveolar maxilla and the position of the maxillary incisors after adjusting for gender, age, and cranial base size. All other dentofacial morphological deviations associated with the timing of repair could be explained by these basic deviations.

The longitudinal study demonstrated that the effect of timing of hard palate repair was on the anteroposterior development of the maxillary dentoalveolar process, as evidenced by the significant association between the length of the alveolar maxilla (PMP-A) at age 20 years and the timing of hard palate repair in patients who had hard palate repair before PPVA. The observation follows a previous long-term follow up study (Friede and Enemark, 2001), which demonstrated a longer alveolar maxilla in patients with repair at age 9 years than 3 months. This finding was expected partly because palate repair is known to inhibit the anteroposterior development of the maxillary dentoalveolar process (Ross, 1987b; Liao and Mars, 2005c). Also, the cross sectional finding indicates that hard palate repair after PPVA results in a longer alveolar maxilla than repair before PPVA.

The possible modulations of this association by age were next explored. Interestingly, the association was not modulated by age, as evidenced by the non-significant association between the growth rate of the length of the alveolar maxilla and the timing of hard palate repair. This is illustrated in Figure 5.1 (see page 140). The lack of association with age indicates that the differential effect of timing of hard palate repair on the anteroposteior development of the maxillary dentoalveolar process at age 20 years is due to the differential development being undisturbed before closure of the hard palate. That is, the maxillary growth advantage from delaying hard palate repair is still maintained after surgery. Previous studies have also shown that unoperated hard palate leads to superior anteroposterior development of the maxillary dentoalveolar process (Smahel and Mullerova, 1986; Ross, 1987b; Friede *et al.*, 1987; Smahel *et al.*, 1993), and that the difference in the length of the alveolar maxilla between repair at 3 months and 9 years remains relatively constant over time (Friede and Enemark, 2001).

Consistently with previous studies (Ross, 1987b; Swennen *et al.*, 2002), the present longitudinal study also demonstrated that the timing of hard palate repair had no effect on either the forward displacement or the anteroposterior development of the basal maxilla, as evidenced by the non-significant association between the depth

of the bony pharynx (Ba-PMP) or the length of the basal maxilla (PMP-ANS) at age 20 years and their growth rates, and the timing of hard palate repair. These are illustrated in Figures 5.2 (see page 141) and 5.3 (see page 142), respectively. The former finding was not expected because palate repair can inhibit the forward displacement of the basal maxilla (Ross, 1987b; Liao and Mars, 2005c). However, it was observed that hard palate repair after PPVA had a smaller adverse effect than repair before PPVA on the forward displacement of the basal maxilla, suggesting that palate repair has a threshold effect on the forward displacement of the basal maxilla. This means that palate repair does not affect the forward displacement of the basal maxilla until the onset of the pubertal growth phase. In other words, the idea of deferring hard palate repair as a less traumatic procedure to the forward displacement of the basal maxilla may only be true when delaying repair after the pubertal growth phase, or at least after PPVA. This view is supported by a previous study (Ross, 1987b) that unoperated hard palate leads to superior forward displacement of the basal maxilla, and that the depth of the bony pharynx is normal at age 11 years in the early, medium, late, and delayed hard palate repair groups, but equally reduced at ages 15 and 17 years. Longitudinal studies have also shown that unfavourable forward growth of the maxilla worsens especially during the pubertal

growth phase in operated patients (Hayashi *et al.*, 1976; Ross, 1987a; Semb, 1991), and that the depth of the bony pharynx, unlike the length of the alveolar maxilla, does exhibit a marked pubertal growth spurt in a normal population (Bhatia and Leighton, 1993). As a consequence, the timing of hard palate repair had a significant effect on the protrusion of the alveolar maxilla (SNA) (Figure 5.4, see page 143) but not the basal maxilla (S-N-ANS), which depended on the position and length of the maxilla. The hypothesis that the timing of hard palate repair adversely affects the growth of the maxilla significantly, and that late repair has a smaller adverse effect than early repair on the growth of the maxilla is supported by the finding of the longer alveolar maxilla (PMP-A), more protruded alveolar maxilla (SNA), greater anteroposterior alveolar jaw relation (ANB) (Figure 5.5, see page 144), and a tendency toward larger overjet in patients with late repair as compared to early repair.

As would be expected, this longitudinal study also confirmed previous reports that the timing of hard palate repair was unrelated to either the downward growth of the basal maxilla (Figure 5.6, see page 145) (Smahel, 1994; Rohrich *et al.*, 1996) or the growth of the mandible (Figures 5.7 through 5.10, see pages 146 through 149) (Robertson and Jolleys, 1974; Blijdorp and Egyedi, 1984; Bardach *et al.*, 1984; Ross,

1987b; Friede *et al.*, 1987; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002), given the evidence that palate repair has no effect on either the downward growth of the basal maxilla (Liao and Mars, 2005c) or the growth of the mandible (Ross, 1987b; Silva Filho *et al.*, 1992; Capelozza Filho *et al.*, 1996; Liao and Mars, 2005c). This, taken with the cross sectional finding about the mandibular measurements, supports the hypothesis that the timing of hard palate repair does not significantly affect the growth of the mandible.

Another interesting finding in this longitudinal study is that the position of the maxillary incisors was related to the timing of hard palate repair, and this association became weaker with age, as evidenced by the non-significant association between the position of the maxillary incisors (SN-UI) at age 20 years but its growth rate and the timing of hard palate repair. This is illustrated in Figure 5.11 (see page 150). The adverse effect of palate repair on the position of maxillary incisors has been well illustrated by Ross and Johnston (1972), as discussed above (see page 55). The differential position of the maxillary incisors, shortly after repair, between patients with early and late repair confirmed the effect of palate repair and its timing on the position of maxillary incisors. This may be explained by the differential

responsiveness of the anterior maxillary dentoalveolar process to the palate repair, possibly relating to the differential maturity. That is, the less mature the anterior maxillary dentoalveolar process, the more retroclined the maxillary incisors shortly after repair. Patients with early repair tended to have more retroclined maxillary incisors shortly after repair. Yet they exhibited favourable maxillary incisor adjustment by proclination (i.e., dentoalveolar compensatory mechanism) to achieve a better dental occlusion (overjet) in the long term (Figure 5.12, see page 151) in response to the less favourable anteroposterior alveolar jaw relation (ANB) (Solow, 1980). In other words, the positional disadvantage of maxillary incisors from early hard palate repair is lost in the long term. This ability of the maxillary incisor adjustment associated with early repair in response to the unfavourable alveolar jaw base relation may be attributed to the technique used to close the hard palate (i.e., the von Langenbeck or the vomerine mucoperiosteal flap), which produces limited scar tissue adjacent to the anterior maxillary dentoalveolar process, as discussed above (see page 55). Ross (1987d) has also found that the von Langenbeck procedure for palate repair has more favourable maxillary incisor adjustment than the push-back procedure, and this difference becomes bigger over time.

Importantly, it was also found that the growth in size of the cranial base was

related to the timing of hard palate repair, and this association became stronger with age, as evidenced by the significant association between the length of the cranial base (S-N, S-Ba, Ba-N; all $p < 0.001$) at age 20 years and its growth rate (all $p < 0.001$) and the timing of hard palate repair. It was found that late repair resulted in decelerated growth of the cranial base (Figures 5.13 through 5.15, see pages 152 through 154). Yet previous studies have consistently shown that the growth of the cranial base irrespective of its size or shape is unrelated to timing of hard palate repair (Blijdorp and Egyedi, 1984; Ross, 1987b; Smahel, 1994; Rohrich *et al.*, 1996; Friede *et al.*, 1999; Nandlal *et al.*, 2000; Friede and Enemark, 2001; Swennen *et al.*, 2002). It seems unlikely that palate repair should affect the size of the cranial base (Ross, 1987b; Capelozza Filho *et al.*, 1996; Liao and Mars, 2005c), because of its distance from the field of the surgery. This disagreement therefore may be explained by differences in the body growth, which is related to growth of the craniofacial skeleton (Ross, 1965; Liao and Mars, 2005a), and change in body growth may be attributed to the secular trend. The secular trend in height and adolescent development reflects the influence of environmental factors on an individual's genetic potential for linear growth and development. Since the turn of the century, children in average economic conditions have been getting taller and

reaching maturity earlier. In industrialized countries, the trend is stabilizing but still continues in some developing countries (e.g., Sri Lanka), mainly due to improved nutrition, control of infectious disease through immunizations and sanitation, and increased availability of health and medical care, i.e., modernization (Tanner, 1989). The assumption that the secular trend was responsible for the difference in body growth associated with different timing of hard palate repair is based on two factors: first, the wide range of year of birth in patients (1972 to 1990), because of their different ages when attending the team clinic, as discussed above (see page 49); and secondly, the stronger association between the growth of the cranial base and the timing of hard palate repair after than before the onset of puberty (Figures 5.13 through 5.15, see pages 152 through 154), suggesting different ages of onset of puberty. Future research focusing on their general growth and maturation is needed to test the hypothesis.

6.3 Clinical Implications

6.3.1 Delay Hard Palate Repair Until PPVA?

Although the results of the present cross sectional study suggest that hard palate repair after PPVA has a smaller adverse effect than hard palate repair before PPVA

on the growth of the maxilla, delaying hard palate repair until PPVA is not recommended clinically for patients with UCLP because the goal of palate repair is normal speech without disturbance of midfacial growth. Moreover, midfacial growth disturbance should be minimized but not at the expense of the speech impairment. Bardach *et al.* (1984) provided some evidence that maxillary growth using the Schweckendiek procedure was excellent; however, more than 80 percent of these patients had developed impaired speech with velopharyngeal insufficiency and articulation problems.

6.3.2 Delay Hard Palate Repair To Late Primary Dentition, Mixed Dentition, or Early Permanent Dentition?

Although the results of the present longitudinal study suggest that late hard palate repair before PPVA has a smaller adverse effect than early hard palate repair on the growth of the maxilla, delaying hard palate repair past the age of 4 years is not recommended clinically for patients with UCLP because previous studies have consistently demonstrated significant speech impairment associated with delayed closure at 4 to 9 years of age (Cosman and Falk, 1980; Jackson *et al.*, 1983; Witzel *et al.*, 1984; Noordhoff *et al.*, 1987; Rohrich *et al.*, 1996; Lohmander-Agerskov, 1998).

Despite wide variation in the timing of hard palate repair in current use according to the survey of the Eurocleft Project, more than 90 percent of the 201 registered centres complete closure before 3 years (Shaw *et al.*, 2000). More recently an 18-month ceiling, reflecting an attempt to increase the likelihood of normal speech development, has gained wide acceptance, at least in North America (Rohrich *et al.*, 2000; Kirschner *et al.*, 2000). It is agreed that better speech development is associated with early repair, on the theory that a more normal oral structure should enhance a child's speech development in a normal learning process. However, there are few data to answer how early is early enough (Dorf and Curtin, 1982; Kirschner *et al.*, 2000; Hardin-Jones and Jones, 2005). In addition to the unanswered question, future research focusing on the technique of hard palate repair and facial growth should be of clinical importance.

6.4 Limitations of the Study

There are certain limitations in the present study. First, many patients underwent lip repair by local surgeons and accordingly did not have documentation of the cleft subtype (complete or incomplete) or surgical technique for lip repair. However, this can be applied to patients with UCLP, and the technique of lip repair has no

significant impact on craniofacial growth (Ross, 1987e). Secondly, variation in the surgical protocols and surgeon's skill may influence the facial growth outcome. To address this issue, an attempt was made to prevent bias by including possible determinants of facial growth, such as the timing and surgeon of lip repair as well as the technique and surgeon of hard palate repair, as potential covariates in the analysis. In the end, the surgeon of hard palate repair has not been adjusted because there was no significant surgeon effect. The finding is consistent with a previous study (Williams and Sandy, 2003); however, this might be a reflection of difficulty of case mix which could not be confirmed in a retrospective study. Thirdly, the size of the initial cleft, which might be associated with subsequent facial growth outcome, could not be assessed because infant maxillary dental casts were not available. However, there is evidence to suggest that the size of the cleft is not related to subsequent facial growth outcome (Schwartz *et al.*, 1984; Suzuki *et al.*, 1993; Johnson *et al.*, 2000). Finally, it is acknowledged that increasing the power (i.e., the ability to demonstrate an effect or association if one exists) of the study by having more patients might have yielded more robust conclusions.

7

Conclusions

The following conclusions about the effect of timing of hard palate repair on facial growth in patients with UCLP can be made:

1. Timing of hard palate repair has a significant adverse effect on the growth of the maxilla.
2. Hard palate repair after PPVA has a smaller adverse effect than hard palate repair before PPVA on the growth of the maxilla. This timing effect is on the forward displacement of the basal maxilla and on the anteroposterior development of the maxillary dentoalveolar process.
3. Late hard palate repair before PPVA has a smaller adverse effect than early hard palate repair on the growth of the maxilla. This timing effect primarily affects the anteroposterior development of the maxillary dentoalveolar process.
4. Timing of hard palate repair does not significantly affect the growth of the mandible.

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Appendix A

(Tables 2.1 through 5.2)

TABLE 2.1. DETAILS OF EXAMINED STUDIES REGARDING TIMING OF HARD PALATE REPAIR AND FACIAL GROWTH IN PATIENTS WITH CLEFT LIP AND PALATE

					Surgery			Evaluation	
Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Sequence & Age (months)	Technique of HP Repair	No. of Surgeon(s)	Age (years)	Method
1. Robertson and	X-sectional	20	CUCLP (a)	UK	L+A+SP(3)	-	1	3(lat ceph), 4.5(cast)	Lat ceph, cast
Jolleys (1974)		20	CUCLP (a)	UK	L+SP(3)→HP(12-15)	PMF	1*	3(lat ceph), 4.5(cast)	
2. Hotz et al.	X-sectional	33	21CUCLP,12CBCLP (a)	Switzerland	L(6)→SP(18)	-	?	4-6	Lat ceph
(1978)		20	11CUCLP, 9CBCLP (a)	Switzerland	L(3)→HP+SP(30-36)	PMF	?	4-6	
3. Schweckendiek	X-sectional	266	131CUCLP, 45CBCLP, 90CP	Germany	SP(6-8)→L(7-9)→HP(144-168)	?	2	Adult	Cli exam, cast
(1978)		?	Non-cleft normal	Germany	-	-	-	Adult	

TABLE 2.1 (CONTINUED).

Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Surgery: Sequence & Age (months)	Surgery: Technique of HP Repair	Surgery: No. of Surgeon(s)	Evaluation: Age (years)	Evaluation: Method
4. Hotz and Gnoinski	Longitudinal	20	CUCLP (b)	Switzerland	L(6)→SP(18)	-	?	Birth, 0.5, 1.5, 5	Cast
(1979)		26	Non-cleft normal	UK	-	-	-	Birth, 0.5, 1.5, 5	
5. Blijdorp and Egyedi	X-sectional	54	CUCLP	Netherland	L+HP(3)→SP(66-78)	Veau	1	Adult	Lat ceph, cast
(1984)		51	CUCLP	Netherland	L+HP(3)→SP(28-42)	Veau	1*	Adult	
6. Bardach et al.	X-sectional	43	UCLP(26M17F)	Germany	SP(8)→L(8.6)→HP(158.4)	?	1	17.2(range 12-24)	Lat ceph, cast
(1984)		35	Non-cleft normal(20M15F)	USA	-	-	-		

TABLE 2.1 (CONTINUED).

Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Surgery: Sequence & Age (months)	Surgery: Technique of HP Repair	Surgery: No. of Surgeon(s)	Evaluation: Age (years)	Evaluation: Method
7. Ross	Longitudinal	32	CUCLP(32M) - Delayed HP	(c1)	→SP→HP(48-84)→ (d1)	?	?	11.0(32)†	Lat ceph
(1987)		127	CUCLP(127M) - Late	(c2)	→HP,SP(21-33)→ (d2)	?	?	15.2(127)†	
		195	CUCLP(195M) - Medium	(c3)	→HP,SP(12-20)→ (d3)	?	?	11.3, 15.3, 17.3 (192, 195, 123)†	
		44	CUCLP(44M) - Early	(c4)	→HP,SP(≤11)→ (d4)	?	?	11.0(40)†, 15.2(44)†	
		52	CUCLP(52M) - Unoperated HP	(c5)	→SP→	-	?	19.6(52)†	

TABLE 2.1 (CONTINUED).

					Surgery			Evaluation	
Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Sequence & Age (months)	Technique of HP Repair	No. of Surgeon(s)	Age (years)	Method
8. Friede et al.	X-sectional	16	16CUCLP(14M2F)	Sweden	L(2.5)→SP(8.8)→L/N (18.1)	-	?	7	Lat ceph, cast
(1987)		18	18CUCLP(12M6F),	Sweden	L+HP(2.1)→SP(7.6)→L/N (19.1)	VMF	?	7	
		7	7CBCLP(5M2F)	Sweden	L(2.9)→SP(10.4)→L/N (19.8)	-	?	7	Lat ceph, cast
		8	8CBCLP(6M2F)	Sweden	L+HP(1.5)→HP(4.1)→SP(9.5) →L/N (20.5)	VMF	?	7	

TABLE 2.1 (CONTINUED).

Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Surgery: Sequence & Age (months)	Surgery: Technique of HP Repair	Surgery: No. of Surgeon(s)	Evaluation: Age (years)	Evaluation: Method
9. Noverraz et al.	Mixed-longit	18	CUCLP (a)	Netherland	L(6)→SP(13)→HP+A(113)	Modified vL	2	4.3, 8.0, 11.8, 17.1	Cast
(1993)	udinal (b)	26	CUCLP (a)	Netherland	L(6)→SP(13)→HP(55)	Modified vL	2*	4.3, 8.0, 11.8, 17.1	
		18	CUCLP (a)	Netherland	L(6)→SP(13)→HP(18)	Modified vL	2*	4.3, 8.0, 11.8, 17.1	
		26	CUCLP - Unoperated HP (a)	Netherland	L(6)→SP(13)	-	2*	4.3, 8.0	
10. Smahel	X-sectional	12	CUCLP(12M)	Czech	→HP(72)→	Push-back	?	Adult	Lat ceph
(1994)		12	CUCLP(12M)	Czech	→HP(48)→	Push-back	?	Adult	

TABLE 2.1 (CONTINUED).

					Surgery			Evaluation	
Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Sequence & Age (months)	Technique of HP Repair	No. of Surgeon(s)	Age (years)	Method
11. Rohrich et al. (1996)	X-sectional	23	16CUCLP, 7CBCLP (14M9F)	UK	L(3.4)→SP(11.4)→HP(48.6)	VMF	1	18.2(range 14-21)	Lat ceph, cast
		21	15CUCLP, 6CBCLP (12M9F)	UK	L(3.4)→HP+SP(10.8)	Push-back	1	17.0(range 15-19)	
12. Friede et al. (1999)	X-sectional	20	CUCLP(14M6F) (a)	Sweden	L(2.1)→SP(8.1)→L/N(17.2) →HP+A(102.5)	MF	?	7, 10, 13, 16 (20, 20, 20, 13)†	Lat ceph
		17	CUCLP(12M5F) (e)	Latavia	L/N(7.8)→SP(20.2)→HP(61.9) →A(114.8)	PMF (one-flap)	?	7, 10, 13, 16 (2, 5, 7, 3)†	

TABLE 2.1 (CONTINUED).

Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Surgery: Sequence & Age (months)	Surgery: Technique of HP Repair	Surgery: No. of Surgeon(s)	Evaluation: Age (years)	Evaluation: Method
13. Nandlal et al. (2000)	X-sectional	11	6CUCLP, 5CBCLP	India	L→HP+SP(36-78)	Push-back	?	8.3(range 6-14)	Lat ceph
		17	15CUCLP, 2CBCLP	India	L→HP+SP(24-36)	Push-back	?	10.7(range 6-14)	
		22	17CUCLP, 5CBCLP	India	L→HP+SP(8-24)	Push-back	?	10.2(range 6-14)	
14. Friede and Enemark (2001)	Longitudinal	30	UCLP(23M7F) (b)	Sweden	L(2)→SP(8)→L/N(18)→HP+A(104)	?	?	10.5, 13.1, 15.9 (30, 29, 30)†	Lat ceph
		30	UCLP(25M5F) (b)	Denmark	L+HP(3)→SP(22)→A(119)	VMF	?	11.9, 13.9, 15.8 (29, 30, 26)†	

TABLE 2.1 (CONTINUED).

Study Number / Author(s)	Design	No. of Samples	Cleft Type & Subtype	Population Studied	Surgery: Sequence & Age (months)	Surgery: Technique of HP Repair	Surgery: No. of Surgeons	Evaluation: Age (years)	Evaluation: Method
15. Swennen et al.	X-sectional	36	CUCLP(23M13F) (a)	Germany	L(5.8)→HP(29.1)→SP(32.3)	VMF	?	10.0(range 9.0-11.1)	Lat ceph
(2002)		26	CUCLP(17M9F) (a)	Belgium	SP(3)→L+HP(6.2)	VMF	2	10.4(range 8.8-11.2)	

Definition of abbreviations: (C) U (B) CLP = (complete) unilateral (bilateral) cleft lip and palate; CP = cleft palate; L = lip; L/N = lip/nose; A = alveolus; HP = hard palate; SP = soft palate; vL = von Langenbeck; MF = mucoperiosteal flap; PMF = palatal mucoperiosteal flap; VMF = vomerine mucoperiosteal flap; M = male; F = female.

* Same surgeon(s) as the other group(s).

? Did not provide in the study.

† Number of samples is provided in the parenthesis.

(a) Had presurgical orthopaedics.

(b) Some had pharyngoplasty.

(c1) Switzerland, UK; (c2) Australia, Canada, Denmark, Norway, Sweden; (c3) Australia, Canada, New Zealand, Norway, Sweden, USA; (c4) Canada, New Zealand, Sweden, USA; (c5) Germany, others.

(d1) 49% had alveolar repair, (d2) 39% had alveolar repair, (d3) 27% had alveolar repair, (d4) 77% had alveolar repair.

(e) No presurgical orthopaedics.

TABLE 2.2. VARIABLES USED IN EXAMINED STUDIES REGARDING TIMING OF hard PALATE REPAIR AND FACIAL GROWTH IN PATIENTS WITH CLEFT LIP AND PALATE (STUDY NUMBERS AS PER TABLE 2.1)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cephalometry															
Cranial base															
Cranial base angle (degree)					x $_{N\text{-}S\text{-}Ar}$		x $_{NSBa}$			x $_{N\text{-}S\text{-}Co}$		x $_{N\text{-}S\text{-}Ar}$	x $_{NSBa}$	x $_{NSBa}$	x $_{NSBa}$
S-N (mm)										x	x				
Maxilla															
Pharynx (Ba-PMP, mm)							(a)								x
Length (mm)							(b) $_{PMP\text{-}ANS}$	↑/x (d)		x $_{PMP\text{-}A}$		x $_{PMP\text{-}A'}$		↑/x (e)	x $_{PMP\text{-}A}$
							(c) $_{PMP\text{-}A}$	$_{PMP\text{-}A'}$						$_{PMP\text{-}A}$	

TABLE 2.2 (CONTINUED).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Effective length (mm)							(f) $_{\text{Ba-ANS}}$				x $_{\text{Ar-ANS}}$				x $_{\text{Ba-ANS}}$
							(c) $_{\text{Ba-A}}$								Ba-A
Protrusion (degree)	x $_{\text{SNA}}$	↑ $_{\text{N-ANS-Pr}}$			x $_{\text{SNA}}$	x $_{\text{SNA}}$	(f) $_{\text{Ba-N-ANS}}$	x $_{\text{SNA}}$		x $_{\text{SNA}}$		x $_{\text{SNA}}$	x $_{\text{SNA}}$	↑/x (g)	x $_{\text{Ba-N-ANS}}$
							(c) $_{\text{Ba-N-A}}$			S-N-Pr				SNA	Ba-N-A
							(c) $_{\text{SNA}}$								SNA
Anterior height (N-ANS, mm)							(h)			x	x				↓/x (i)
Posterior height (R-PMP, mm)							(j)								↑/x (k)
SN-PP (degree)								x				x		↑/x (l)	↓/x (i)

TABLE 2.2 (CONTINUED).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Mandible															
Total length (mm)							x Co-Gn				x Ar-Pog				x Co-Gn
Ramus length (mm)										↑ Co-Go					
Body length (mm)										x Go-Gn					
Gonial angle (degree)					x Ar-Go-Gn					x MP-RL		x MP-RL			
Protrusion (degree)	x S-N-Pog				x SNB	x SNB	(m) Ba-N-B	x SNB		x SNB		x SNB	x SNB	x SNB	x Ba-N-Pog
							Ba-N-Pog			S-N-Pog		S-N-Pog	S-N-Pog	S-N-Pog	Ba-N-B
							SNB								SNB
SN-MP (degree)							x	x				x	x	x	x

TABLE 2.2 (CONTINUED).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Jaw base relation															
ANS-N-Pog (degree)							(c)								x
ANB (degree)						x	(c)	↑/x (d)		x		x	x	↑	x
NAPog (degree)	x					x		↓/x (h)		↓		x	x	↓	
PP-MP (degree)												x		x	
Denture															
UI position (degree)												x SN-UI	x SN-UI	x SN-UI	x Ba-N-UI
LI position (degree)												x LI-MP	x LI-MP	x LI-MP	x Ba-N-LI
Overjet (mm)															x

TABLE 2.2 (CONTINUED).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cast															
Maxilla															
Arch width (mm)	x $_{CC', EE'}$		x	↑/x (n) $_{TT'}$	x $_{44', 66'}$			x $_{CC', EE'}$			x $_{33', 66'}$				
Arch length (mm)	x							x							
Arch circumference (mm)				↓/x (0)											
Cross bite score															
Anterior	x				x			↓/x (p)							
Lateral (cleft)								↓/x (p)							

TABLE 2.2 (CONTINUED).

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lateral (noncleft)								x							
All								↓/x (p)							
Goslon yardstick									x						
Clinical Examination															
Maxilla															
Length (mm)			x												

Definition of abbreviations: $_{CC'}$ = primary canine-primary canine'; $_{EE'}$ = primary molar-primary molar'; $_{TT'}$ = tuberosity-tuberosity'; $_{33'}$ = canine-canine'; $_{44'}$ = premolar-premolar'; $_{66'}$ = molar-molar'.

↑ Increased magnitude in the late (or delayed) hard palate repair group.

↓ Decreased magnitude in the late (or delayed) hard palate repair group.

x No difference between the groups.

(a) Unoperated HP > Delayed HP, Late, Medium, Early.

(b) Unoperated HP > Delayed HP, Medium, Early > Late.

(c) Unoperated HP > Medium, Early > Delayed HP, Late.

(d) ↑ for CUCLP, x for CBCLP.

(e) ↑ at the age of 16 years, x at the age of 10 and 13 years.

(f) Unoperated HP, Early > Delayed HP, Late, Medium.

(g) ↑ at the age of 10 and 13 years, x at the age of 16 years.

(h) Unoperated HP, Delayed HP, Medium, Early > Late.

(i) ↓ for female and pooled subjects, x for male subjects.

(j) Unoperated HP > Delayed HP, Late, Medium > Early.

(k) ↑ for male subjects, x for female and pooled subjects.

(l) ↑ at the age of 10 and 16 years, x at the age of 13 years.

(m) Early > Unoperated HP, Delayed HP, Late, Medium.

(n) ↑ at birth, x at the age of 5 years.

(o) ↓ at the age of 5 years, x at birth.

(p) ↓ for CUCLP, x for CBCLP.

TABLE 2.3. CHECKLIST OF METHODOLOGICAL QUALITY OF EXAMINED STUDIES (STUDY NUMBERS AS PER TABLE 2.1)

Criterion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
A. Who was the study about?															
1. How were subjects recruited (randomly, consecutively, others)?	?	?	?	?	?	R	?	?	C	?	R	?	?	C	C
2. Who was included in, and who was excluded from, the study?															
(1) Selected sample of same population	Y	Y	Y	N	Y	N	N(a)	Y	Y	Y	Y	N	Y	N	N(a)
(2) Selected sample of nonsyndromic	?	?	?	?	?	?	Y	?	Y	Y	Y	Y	Y	Y	Y
(3) Selected sample of same cleft type	Y	N	N	Y	Y	Y(b)	Y	Y	Y	Y	N	Y	N	Y(b)	Y

TABLE 2.3 (CONTINUED).

Criterion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
B. Was the design of the study sensible?															
1. What other assessment being considered?	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-
2. What outcomes were measured, and how?															
(1) Ascertained same cephalostat and method of image production, if a cephalometric study	?	?	-	-	?	?	N(a)	?	-	Y	?	N(c)	Y	N(c)	N(c)
(2) Ascertained same observer(s) for experimental and control groups	?	?	?	?	?	Y	Y	?	Y	?	Y	?	?	Y	N
(3) Was an error method reported?	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	Y

TABLE 2.3 (CONTINUED).

Criterion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
(4) Were the variables used valid?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
(5) Was assessment of outcome "blind"?	?	?	?	?	?	?	Y	?	Y	?	Y	?	?	?	?
C. Was the study adequately controlled?															
1. Was the control or comparison group appropriate, if a case-control or other non-randomized comparative study?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were the groups comparable in all important aspects except for the variable being studied?															
(1) Age matched	Y	Y	?	Y	?	?	Y(d)	Y	Y	?	N(e)	Y	N(e)	Y	Y

TABLE 2.3 (CONTINUED).

Criterion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
(2) Gender matched	?	?	?	?	?	N(f)	Y	N(f)	-	Y	N(f)	N(f)	?	N(f)	N(f)
(3) Technique of hard palate repair matched	-	-	-	-	Y	-	?	-	Y	Y	N	N	Y	N	Y
(4) Could there be any other confounding?	Y(g)	N	N	N	Y(h)	N	Y(i)	N	Y(h)	Y(h)	Y(j)	Y(j)	N	Y(j)	Y(j)
D. Were analysis and presentation of data appropriate?															
1. Was there a statement adequately describing or referencing all statistical procedures used?	N	N	-	-	N	Y	N	Y	Y	Y	N	Y	N	Y	Y
2. Were the statistical analyses used appropriate?	?	?	-	-	?	Y	?	N	N	N	?	N	?	N	Y
3. Was the presentation of statistical material satisfactory?	N	N	-	-	N	N	N	Y	Y	N	N	N	N	Y	Y

TABLE 2.3 (CONTINUED).

Criterion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
4. Were confidence intervals given for the main results?	N	N	-	-	N	N	N	N	N	N	N	N	N	N	N
5. Was the conclusion drawn from the statistical analysis justified?	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
E. Was the study large enough?	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	N	N
F. Was the study continued for long enough, and was follow up complete enough, to make the results credible?	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N

Definition of abbreviations: Y = yes, N = no, ? = did not provide in the study, C = consecutively, R = randomly.

(a) Adjusted to the cranial base length (Ba-N).

(b) Different subtype of UCLP (complete or incomplete)

(c) Adjusted to the same magnification.

(d) Used the Medium group as the standard, and adjusted its age to the mean age of the other groups.

(e) Wide age range.

(f) Frequency of gender matched ($p > 0.05$).

(g) Had primary alveolar repair in the Delayed Hard Palate repair group.

(h) Some had pharyngeal flaps.

(i) Wide variety of treatment, and different surgeons.

(j) Different surgeons.

TABLE 4.1. SUMMARY OF PATIENT CHARACTERISTICS IN THE CROSS SECTIONAL STUDY

Characteristics	Patients (n = 125) % (n)
Demographic	
Gender	
Male	65 (81)
Female	35 (44)
Subtype of cleft	
Complete	60 (75)
Incomplete	2 (2)
Not recorded	38 (48)
Distribution of cleft	
Right	26 (32)
Left	74 (93)
Mean age (SD) (range) at last cephalometric assessment, yr	23 (6) (17-44)
Lip Repair	

TABLE 4.1 (CONTINUED)

Characteristics	Patients (n = 125) % (n)
Mean age (SD) (range) at repair, yr	6.7 (9.0) (0.02-35.5)
Technique	
Millard	43 (54)
Other (Tennison / Skoog / Straight Line)	9 (11)
Not recorded	48 (60)
Surgeon origin	
Local	46 (58)
British	54 (67)
Palate Repair	
Stage of palate repair	
One-stage	73 (91)
Two-stage (hard* and then soft)	27 (34)
Hard Palate Repair	
Mean age (SD) (range) at repair, yr	12.3 (9.9) (0.3-39.4)

TABLE 4.1 (CONTINUED).

Characteristics	Patients (n = 125) % (n)
Age at repair	
Before PPVA	66 (83)
After PPVA	34 (42)
Technique	
Palatal mucoperiosteal flap	73 (91[†])
Vomerine mucoperiosteal flap	27 (34)
Surgeon grade	
Consultant	73 (91)
Specialist registrar	27 (34)
Soft Palate Repair	
Mean age (SD) (range) at repair, yr	13.1 (9.7) (0.8-39.4)

TABLE 4.1 (CONTINUED).

Characteristics	Patients (n = 125) % (n)
Technique	
Von Langenbeck	85 (106)
Wardill push-back	6 (8)
Not recorded	9 (11)
Surgeon grade	
Consultant	68 (85)
Specialist registrar	32 (40)

Definition of abbreviation: PPVA = pubertal peak velocity age.

* A vomerine mucoperiosteal flap at the time of lip repair.

† 86 von Langenbeck, 5 Wardill push-back.

TABLE 4.2. SUMMARY OF PATIENT CHARACTERISTICS IN THE LONGITUDINAL STUDY

Characteristics	Patients (n = 104) 290 cephalometric radiographs % (n)
Demographic	
Gender	
Male	62 (65)
Female	38 (39)
Subtype of cleft	
Complete	74 (77)
Incomplete	2 (2)
Not recorded	24 (25)
Distribution of cleft	
Right	27 (28)
Left	73 (76)

TABLE 4.2 (CONTINUED).

Characteristics	Patients (n = 104) 290 cephalometric radiographs % (n)
No. of radiographs per patient	
Two	41 (43)
Three	41 (43)
Four	15 (15)
Five	3 (3)
Lip Repair	
Mean age (SD) (range) at repair, yr	2.5 (3.5) (0.2-13.9)
Technique	
Millard	47 (49)
Other (Tennison / Skoog / Straight Line)	12 (12)
Not recorded	41 (43)

TABLE 4.2 (CONTINUED).

Characteristics	Patients (n = 104) 290 cephalometric radiographs % (n)
Surgeon origin	
Local	39 (41)
British	61 (63)
Palate Repair	
Stage of palate repair	
One-stage	60 (62)
Two-stage (hard* and then soft)	40 (42)
Hard Palate Repair	
Mean age (SD) (range) at repair, yr	5.2 (4.4) (0.2-13.9)
Technique	
Palatal mucoperiosteal flap	60 (62†)
Vomerine mucoperiosteal flap	40 (42)

TABLE 4.2 (CONTINUED).

Characteristics	Patients (n = 104) 290 cephalometric radiographs % (n)
Surgeon grade	
Consultant	73 (76)
Specialist registrar	27 (28)
Soft Palate Repair	
Mean age (SD) (range) at repair, yr	6.3 (4.2) (0.8-18.9)
Technique	
Von Langenbeck	88 (91)
Wardill push-back	4 (5)
Not recorded	8 (8)
Surgeon grade	
Consultant	62 (64)
Specialist registrar	38 (40)

* A vomerine mucoperiosteal flap at the time of lip repair.

† 60 von Langenbeck, 2 Wardill push-back.

TABLE 4.3. DEFINITIONS OF LANDMARKS AND REFERENCE LINES OR PLANES USED ON A LATERAL CEPHALOMETRIC RADIOGRAPH (FIGURE 4.3)

Landmark / reference line (plane)	Definition
A (A point)	The most posterior point on the curve of the maxilla between the anterior nasal spine and Supradentale.
ANS (anterior nasal spine)	The tip of the median, sharp bony process of the maxilla at the lower margin of the anterior nasal opening.
Ar (articulare)	The tip of the median, sharp bony process of the maxilla at the lower margin of the anterior nasal opening.
B (B point)	The point most posterior to a line from Infradentale to Pogonion on the anterior surface of the symphyseal outline of the mandible.
Ba (basion)	The most inferior, posterior point on the anterior margin of foramen magnum.

TABLE 4.3 (CONTINUED).

Landmark / reference line (plane)	Definition
Gn (gnathion)	The most anterior-inferior point on the contour of the bony chin symphysis.
Go (gonion)	The midpoint of the angle of the mandible. Found by bisecting the angle formed by the mandibular plane and ramus line.
Gol (gonion intersection)	The intersection of the mandibular plane and ramus line.
LI (lower incisor)	The axis of the lower incisor from LIE (lower incisal edge) to LIA (lower incisal apex).
LIA (lower incisal apex)	The root tip of the mandibular central incisor.
LIE (lower incisal edge)	The incisal tip of the mandibular central incisor.
Men (menton)	The most inferior point on the symphyseal outline.
MP (mandibular plane)	The line from Men (menton) tangent to the posteroinferior border of the mandible.

TABLE 4.3 (CONTINUED).

Landmark / reference line (plane)	Definition
N (nasion)	The junction of the frontonasal suture at the most posterior point on the curve at the bridge of the nose.
OP (occlusal plane)	The line through UMT (upper molar mesial cusp tip) and PT (premolar cusp tip)
PMP (posterior maxillary point)	The construct created by dropping a perpendicular to the palatal plane from PTM (pterygo-maxillary fissure).
Pog (pogonion)	The most anterior point on the contour of the bony chin. Determined by a tangent through N (nasion).
PP (palatal plane)	The line through ANS (anterior nasal spine) and PMP (posterior maxillary point).
PT (premolar cusp tip)	The cusp tip of the maxillary second premolar.

TABLE 4.3 (CONTINUED).

Landmark / reference line (plane)	Definition
PTM (pterygo-maxillary fissure)	The most inferior point on the average of the right and left outlines of the pterygo-maxillary fissure.
R (ethmoid registration point)	The intersection of the sphenoidal plane with the averaged greater sphenoid wing.
RL (ramus line)	The line from Ar (Articulare) tangent to the posteroinferior border of the mandible.
S (sella turcica)	The center of the pituitary fossa of the sphenoid bone.
SN (sella-nasion line)	The line through S (sella turcica) and N (nasion).
UI (upper incisor)	The axis of the upper incisor from UIE (upper incisal edge) to UIA (upper incisal apex).
UIA (upper incisal apex)	The root tip of the maxillary central incisor.
UIE (upper incisal edge)	The incisal tip of the maxillary central incisor.
UMT (upper molar mesial cusp tip)	The mesial cusp tip of the maxillary first molar.

TABLE 4.4. DESCRIPTIONS OF LINEAR AND ANGULAR VARIABLES USED ON A LATERAL CEPHALOMETRIC RADIOGRAPH

Variable	Type	Region
S-N	Distance	Cranial base
S-Ba	Distance	Cranial base
Ba-N	Distance	Cranial base
NSBa	Three-point angle	Cranial base
Ba-PMP	Distance	Pharynx
PMP-ANS	Distance	Maxilla
PMP-A	Distance	Maxilla
Ar-ANS	Distance	Maxilla
Ar-A	Distance	Maxilla
S-N-ANS	Three-point angle	Maxilla
SNA	Three-point angle	Maxilla
N-ANS	Distance	Maxilla
R-PMP	Distance	Maxilla
SN-PP	Four-point angle	Maxilla
Ar-Go	Distance	Mandible

TABLE 4.4 (CONTINUED).

Variable	Type	Region
Go-Gn	Distance	Mandible
Ar-Gn	Distance	Mandible
Ar-B	Distance	Mandible
Ar-Pog	Distance	Mandible
Ar-Go-Gn	Three-point angle	Mandible
SNB	Three-point angle	Mandible
S-N-Pog	Three-point angle	Mandible
SN-MP	Four-point angle	Mandible
ANS-N-Pog	Three-point angle	Jaw base relation
ANB	Three-point angle	Jaw base relation
N-Men	Distance	Facial height
S-Go	Distance	Facial height
SN-UI	Four-point angle	Denture
LI-MP	Four-point angle	Denture
Overjet*	Distance	Denture
Overbite†	Distance	Denture

* The distance between incisal edges of maxillary and mandibular central incisors, parallel to occlusal plane.

† The distance between incisal edges of maxillary and mandibular central incisors, perpendicular to occlusal plane.

TABLE 5.1. ASSOCIATION BETWEEN FACIAL MORPHOLOGY AND TIMING OF HARD PALATE REPAIR, BEFORE VERSUS AFTER PPVA (ADJUSTED FOR GENDER AND AGE AT LAST CEPHALOMETRIC ASSESSMENT)

Dependent	Timing of Hard Palate Repair	
Variable	Regression Coefficient* (95% CI)	p Value†
Cranial Base		
S-N, mm	0.8 (-0.9, 2.5)	0.4
S-Ba, mm	-0.3 (-1.9, 1.3)	0.7
Ba-N, mm	2.1 (-0.3, 4.5)	0.09
NSBa, degrees	3.0 (0.2, 5.8)	**0.03**
Maxilla		
Ba-PMP[1], mm	2.3 (0.5, 4.1)	**0.01**
PMP-ANS, mm	0.9 (-0.9, 2.8)	0.3
PMP-A, mm	1.8 (0.0, 3.7)	**0.05**
Ar-ANS, mm	2.6 (0.0, 5.3)	**0.05**
Ar-A, mm	3.3 (0.6, 6.1)	**0.02**
S-N-ANS[1], degrees	0.5 (-1.7, 2.8)	0.6
SNA[2], degrees	1.0 (-1.2, 3.3)	0.4

TABLE 5.1 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair	
	Regression Coefficient* (95% CI)	p Value†
N-ANS, mm	0.9 (-1.2, 2.9)	0.4
R-PMP, mm	0.2 (-1.9, 2.3)	0.9
SN-PP[3], degrees	0.4 (-1.3, 2.0)	0.7
Mandible		
Ar-Go, mm	1.9 (-0.9, 4.6)	0.2
Go-Gn, mm	-1.5 (-4.1, 1.2)	0.3
Ar-Gn, mm	-0.3 (-3.6, 3.0)	0.8
Ar-B, mm	0.4 (-2.7, 3.4)	0.8
Ar-Pog, mm	-0.4 (-3.6, 2.9)	0.8
Ar-Go-Gn, degrees	-0.6 (-5.1, 4.0)	0.8
SNB, degrees	-1.4 (-3.6, 0.7)	0.2
S-N-Pog, degrees	-1.7 (-4.0, 0.7)	0.2
SN-MP, degrees	0.3 (-4.2, 4.7)	0.9
Jaw Relation		
ANS-N-Pog[1], degrees	2.7 (0.3, 5.1)	**0.03**

TABLE 5.1 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair	
	Regression Coefficient* (95% CI)	p Value†
ANB[1], degrees	3.3 (1.0, 5.5)	**0.005**
Facial Height		
N-Men, mm	0.8 (-3.8, 5.4)	0.7
S-Go, mm	0.5 (-2.9, 3.8)	0.8
Denture		
SN-UI[4], degrees	-2.2 (-7.3, 3.0)	0.4
LI-MP, degrees	4.5 (-0.5, 9.5)	0.08
Overjet[2], mm	2.9 (0.8, 5.0)	**0.007**
Overbite, mm	0.3 (-1.4, 2.0)	0.7

Definition of abbreviations: PPVA = pubertal peak velocity age, CI = confidence interval.

* The regression coefficient indicates the mean difference (mm or degrees) in the dependent variable between hard palate repair before and after PPVA. A positive sign indicates a larger value for repair after than before PPVA.

† Significant differences ($p \leq 0.05$) are in boldface.

[1] Also adjusted for technique of hard palate repair.

[2] Also adjusted for timing of lip repair, and technique of hard palate repair.

[3] Also adjusted for timing of lip repair, and surgeon of lip repair.

[4] Also adjusted for timing of lip repair.

TABLE 5.2. ASSOCIATION BETWEEN FACIAL GROWTH AND TIMING OF HARD PALATE REPAIR BEFORE PPVA (ADJUSTED FOR GENDER AND AGE AT CEPHALOMETRIC ASSESSMENT)

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
Cranial Base				
S-N[1], mm	-0.4 (-0.5, -0.3)	**< 0.001**	-0.03 (-0.04, -0.02)	**< 0.001**
S-Ba[1], mm	-0.4 (-0.5, -0.2)	**< 0.001**	-0.04 (-0.06, -0.03)	**< 0.001**
Ba-N[1], mm	-0.7 (-0.9, -0.5)	**< 0.001**	-0.06 (-0.08, -0.05)	**< 0.001**
NSBa[1], degrees	-0.2 (-0.4, 0.1)	0.2	-0.003 (-0.01, 0.01)	0.5

TABLE 5.2 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
Maxilla				
Ba-PMP[2], mm	0.02 (-0.1, 0.2)	0.8	0.001 (-0.01, 0.01)	0.8
PMP-ANS[3], mm	0.04 (-0.1, 0.2)	0.6	-0.003 (-0.01, 0.01)	0.6
PMP-A[3], mm	0.2 (0.0, 0.4)	**0.05**	0.01 (-0.01, 0.02)	0.4
Ar-ANS[2], mm	0.1 (-0.2, 0.3)	0.6	-0.01 (-0.03, 0.01)	0.2
Ar-A[2], mm	0.1 (-0.1, 0.4)	0.3	-0.01 (-0.02, 0.01)	0.5

TABLE 5.2 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
S-N-ANS, degrees	0.2 (0.0, 0.5)	0.1	-0.01 (-0.02, 0.00)	0.2
SNA, degrees	0.4 (0.2, 0.7)	**< 0.001**	-0.003 (-0.02, 0.01)	0.6
N-ANS^3, mm	-0.1 (-0.2, 0.1)	0.2	-0.02 (-0.03, 0.00)	0.1
R-PMP^2, mm	0.2 (0.0, 0.4)	1.0	-0.01 (-0.02, 0.01)	0.2
SN-PP, degrees	-0.1 (-0.2, 0.1)	0.4	-0.004 (-0.02, 0.01)	0.6
Mandible				

TABLE 5.2 (CONTINUED).

Dependent	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
Variable	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
Ar-Go[4], mm	-0.1 (-0.4, 0.2)	0.4	-0.001 (-0.03, 0.02)	0.6
Go-Gn[4], mm	0.03 (-0.2, 0.3)	0.8	-0.01 (-0.03, 0.01)	0.3
Ar-Gn[4], mm	-0.03 (-0.4, 0.3)	0.9	-0.02 (-0.05, 0.01)	0.2
Ar-B[3], mm	0.1 (-0.2, 0.4)	0.6	0.003 (-0.02, 0.03)	0.8
Ar-Pog[3], mm	0.1 (-0.3, 0.4)	0.8	-0.001 (-0.03, 0.02)	1.0
Ar-Go-Gn, degrees	0.2 (-0.2, 0.6)	0.4	0.01 (-0.02, 0.05)	0.5

TABLE 5.2 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
SNB, degrees	0.1 (-0.1, 0.2)	0.6	-0.01 (-0.02, 0.01)	0.3
S-N-Pog, degrees	0.004 (-0.2, 0.2)	1.0	-0.01 (-0.03, 0.00)	0.1
SN-MP, degrees	0.2 (-0.1, 0.6)	0.2	0.02 (0.00, 0.04)	0.09
Jaw Relation				
ANS-N-Pog, degrees	0.3 (0.0, 0.5)	0.1	0.01 (-0.01, 0.02)	0.5
ANB, degrees	0.4 (0.2, 0.6)	**0.001**	0.003 (-0.01, 0.02)	0.7

TABLE 5.2 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
Facial Height				
N-Men[3], mm	0.2 (-0.2, 0.6)	0.3	0.01 (-0.02, 0.04)	0.3
S-Go[3], mm	-0.2 (-0.5, 0.1)	0.3	-0.02 (-0.05, 0.00)	0.09
Denture				
SN-UI, degrees	-0.3 (-0.7, 0.2)	0.2	-0.07 (-0.11, -0.03)	**< 0.001**
LI-MP, degrees	-0.2 (-0.6, 0.2)	0.3	-0.03 (-0.07, 0.00)	0.1

TABLE 5.2 (CONTINUED).

Dependent Variable	Timing of Hard Palate Repair		Timing of Hard Palate Repair-by-Age	
	Regression Coefficient* (95% CI)	p Value†	Regression Coefficient‡ (95% CI)	p Value†
Overjet, mm	0.2 (0.0, 0.4)	0.07	-0.01 (-0.02, 0.01)	0.3
Overbite[5], mm	-0.02 (-0.2, 0.1)	0.8	-0.01 (-0.02, 0.01)	0.3

Definition of abbreviations: PPVA = pubertal peak velocity age, CI = confidence interval.

* The regression coefficient indicates the change in the mean (mm or degrees) of the dependent variable at age 20 years per year increase in the age at hard palate repair. A positive sign indicates a larger value for late than early repair.

† Significant differences ($p \leq 0.05$) are in boldface.

‡ The regression coefficient indicates the change in the growth rate (mm/yr or degrees/yr) of the dependent variable per year

increase in the age at hard palate repair. A positive sign indicates faster growth for late than early repair.

[1] Also adjusted for gender-by-age interaction.

[2] Also adjusted for technique of hard palate repair, and cranial base size.

[3] Also adjusted for cranial base size.

[4] Also adjusted for cranial base size, and cranial base size-by-age interaction.

[5] Also adjusted for timing of lip repair, and gender-by-age interaction.

Appendix B

(Figures 4.1 through 5.15)

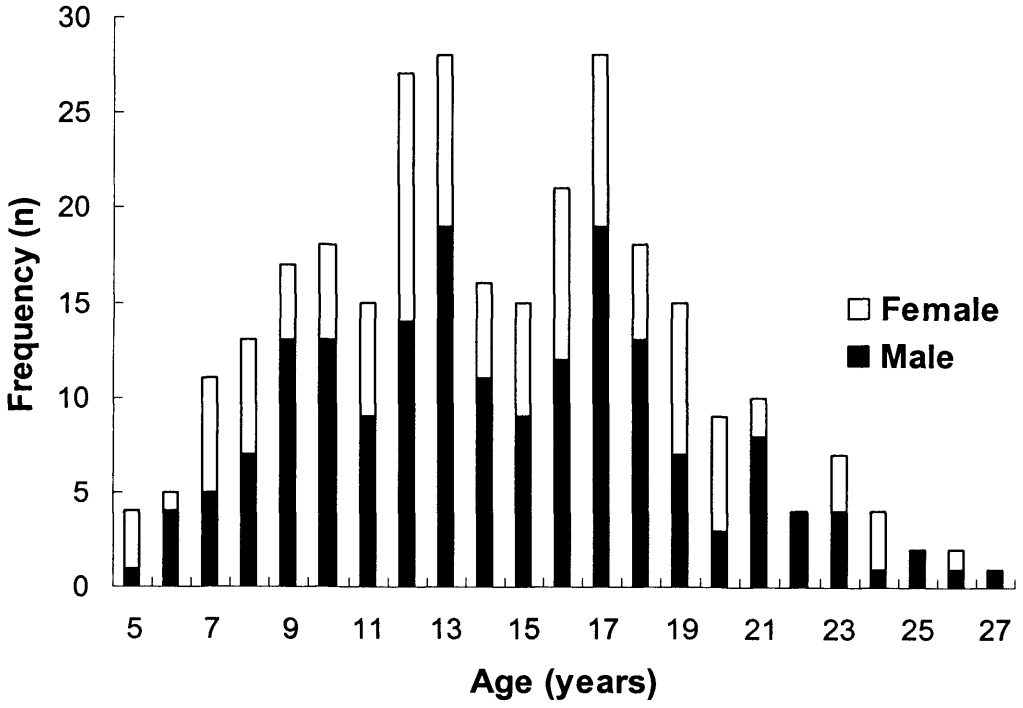

Figure 4.1. Distribution of 290 cephalometric radiographs by age in the longitudinal study. Five patients had cephalometric assessments at age 25 years or older due to their lack of any radiograph taken at age 20 to 24 years.

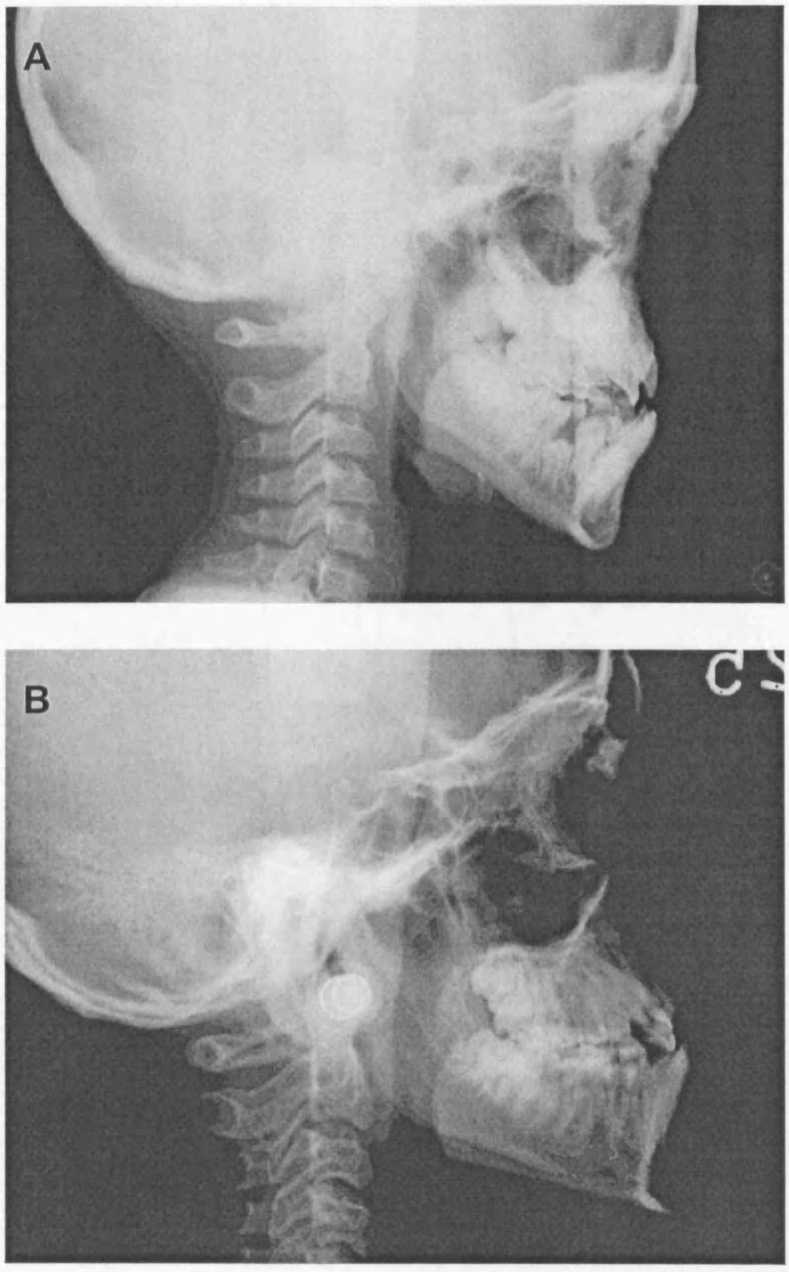

Figure 4.2. A pair of lateral cephalometric radiographs showing growth of the craniofacial region over time of one patient with unilateral cleft lip and palate who had hard palate repair at age 1.3 years. The first radiograph was taken at age 10 years (A, better quality), the second at age 17 years (B).

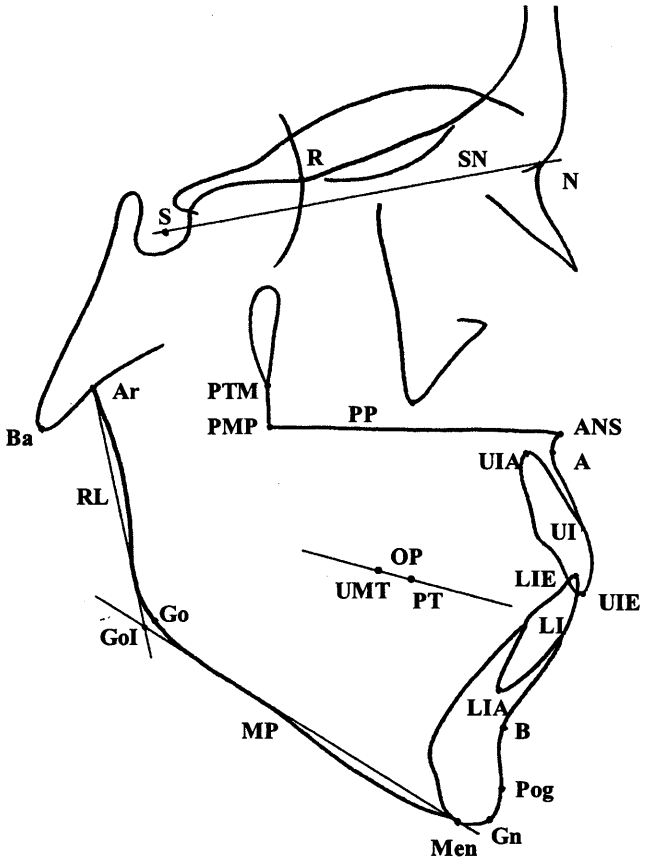

Figure 4.3. Landmarks and reference lines or planes used on a lateral cephalometric radiograph. For definition of the landmarks and reference lines or planes, please refer to Table 4.3.

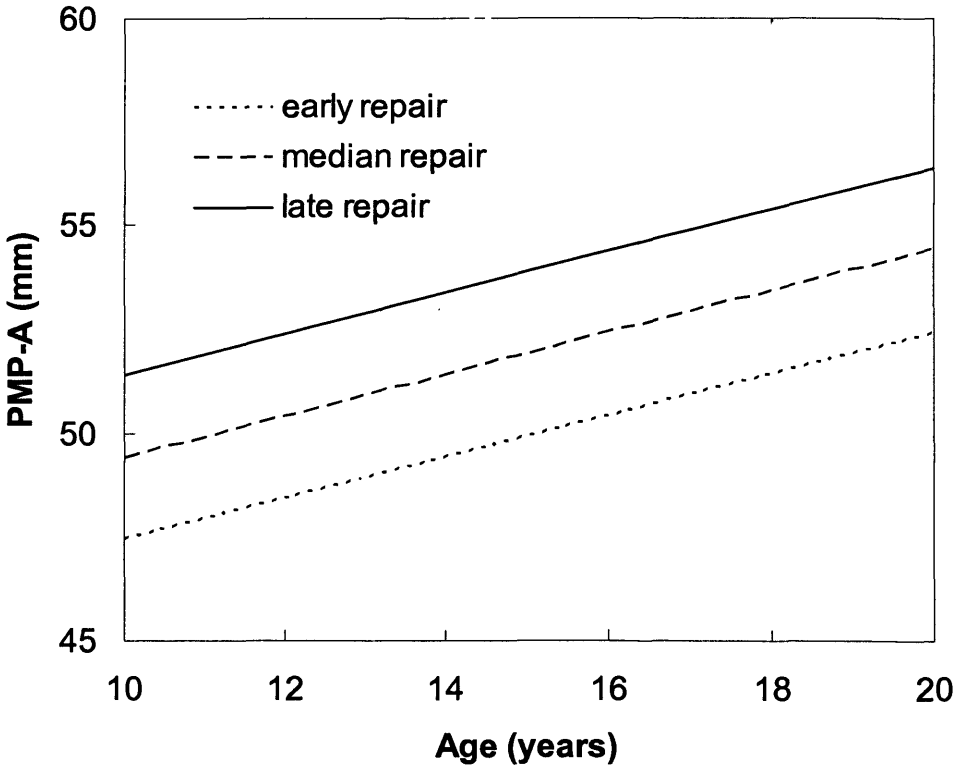

Figure 5.1. Effect of timing of hard palate repair before pubertal peak velocity age on PMP-A in patients with unilateral cleft lip and palate. The three parallel regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on PMP-A at age 20 years, but not on the growth rate. A later repair resulted in a longer adult PMP-A. For definition of PMP-A, please refer to Figure 4.3 and Table 4.4.

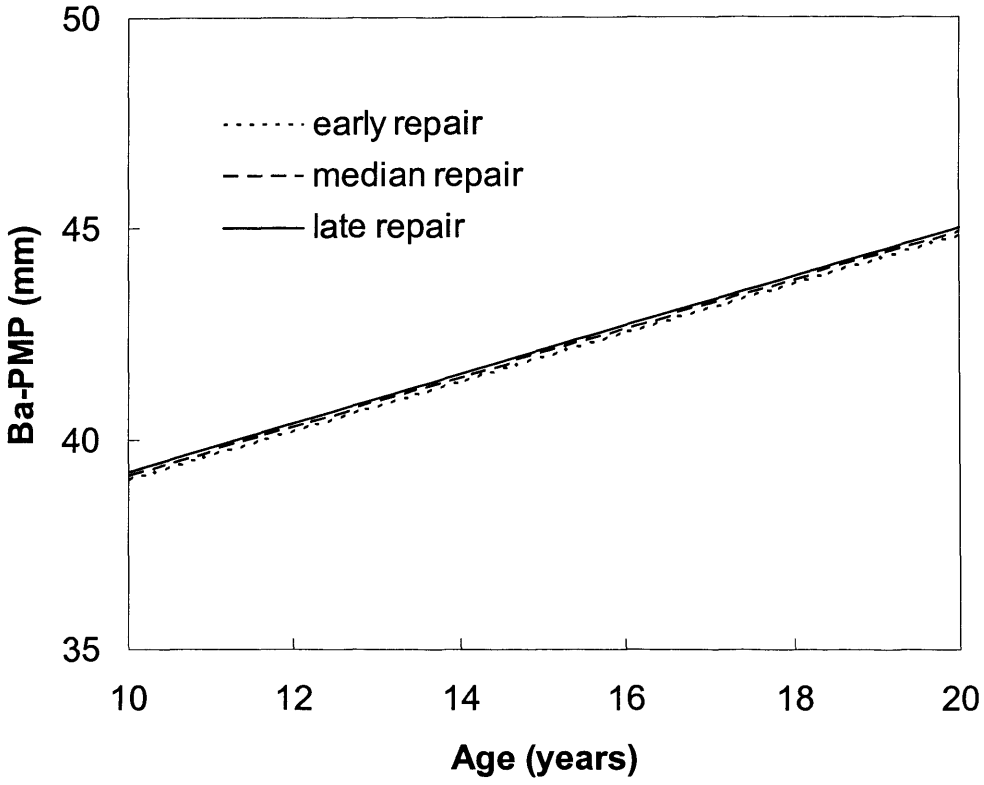

Figure 5.2. Effect of timing of hard palate repair before pubertal peak velocity age on Ba-PMP in patients with unilateral cleft lip and palate. The three overlapping regression lines were generated from the mixed-model analysis when gender = male, technique of hard palate repair = vomerine mucoperiosteal flap, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on Ba-PMP either at age 20 years or the growth rate. For definition of Ba-PMP, please refer to Figure 4.3 and Table 4.4.

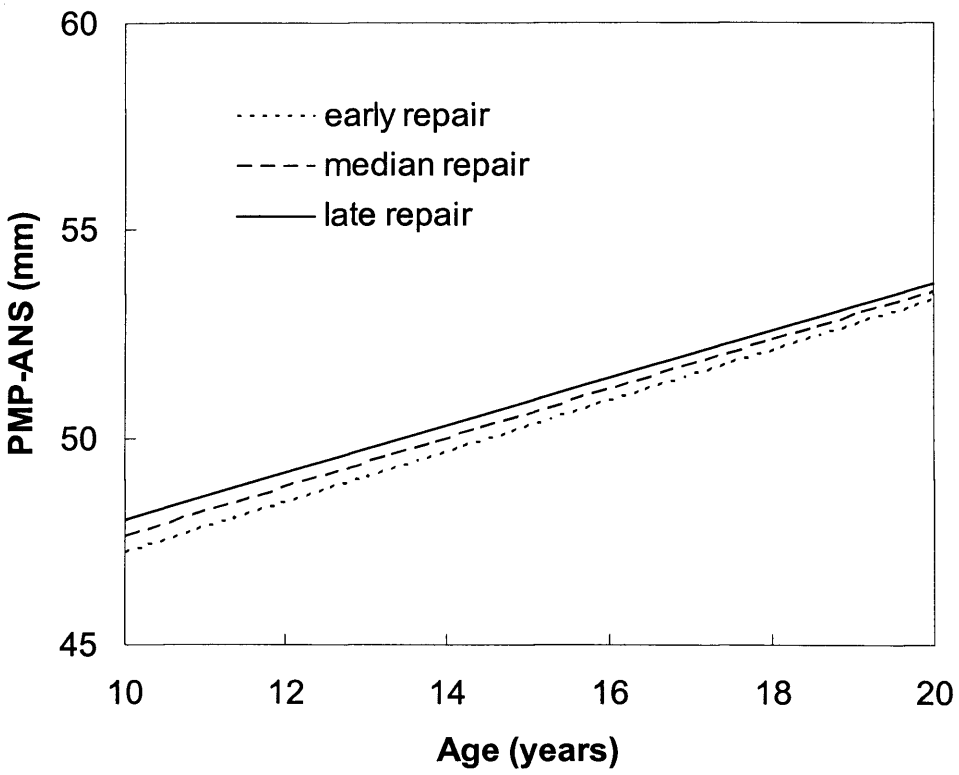

Figure 5.3. Effect of timing of hard palate repair before pubertal peak velocity age on PMP-ANS in patients with unilateral cleft lip and palate. The three convergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on PMP-ANS either at age 20 years or the growth rate. For definition of PMP-ANS, please refer to Figure 4.3 and Table 4.4.

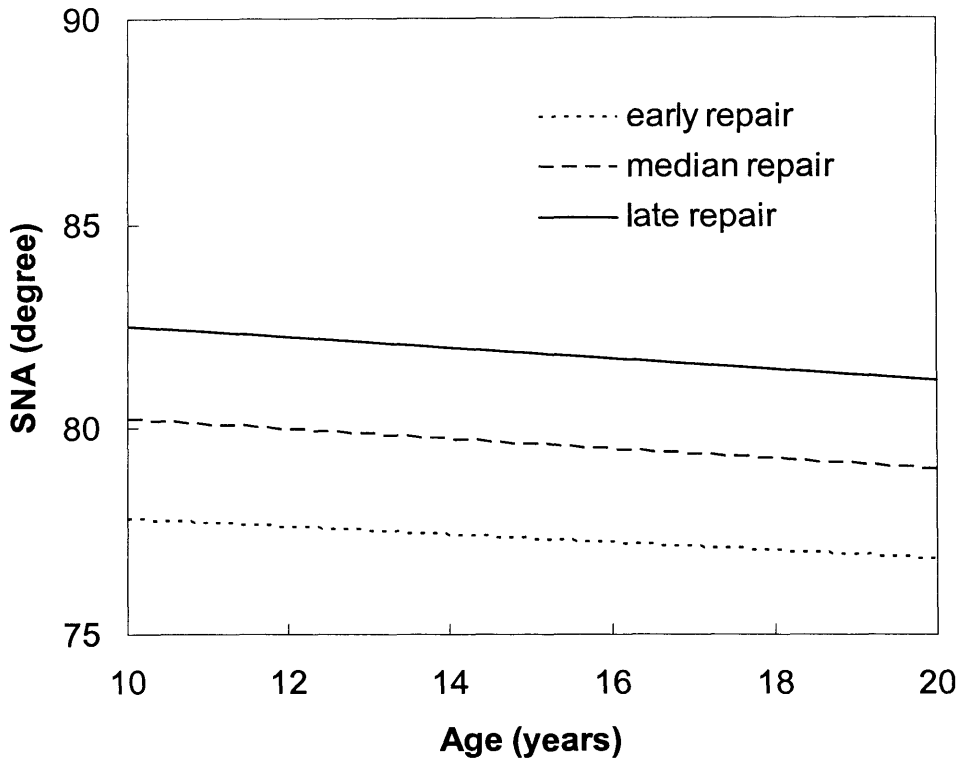

Figure 5.4. Effect of timing of hard palate repair before pubertal peak velocity age on SNA in patients with unilateral cleft lip and palate. The three parallel regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on SNA at age 20 years, but not on the growth rate. A later repair resulted in a larger adult SNA. For definition of SNA, please refer to Figure 4.3 and Table 4.4.

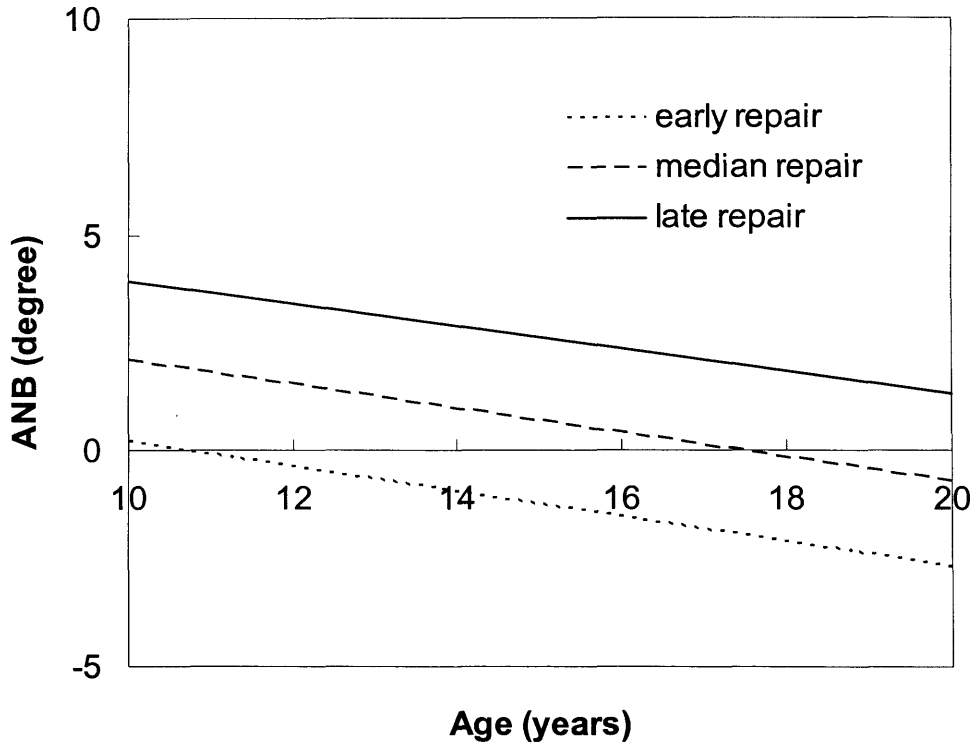

Figure 5.5. Effect of timing of hard palate repair before pubertal peak velocity age on ANB in patients with unilateral cleft lip and palate. The three parallel regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on ANB at age 20 years, but not on the growth rate. A later repair resulted in a larger adult ANB. For definition of ANB, please refer to Figure 4.3 and Table 4.4.

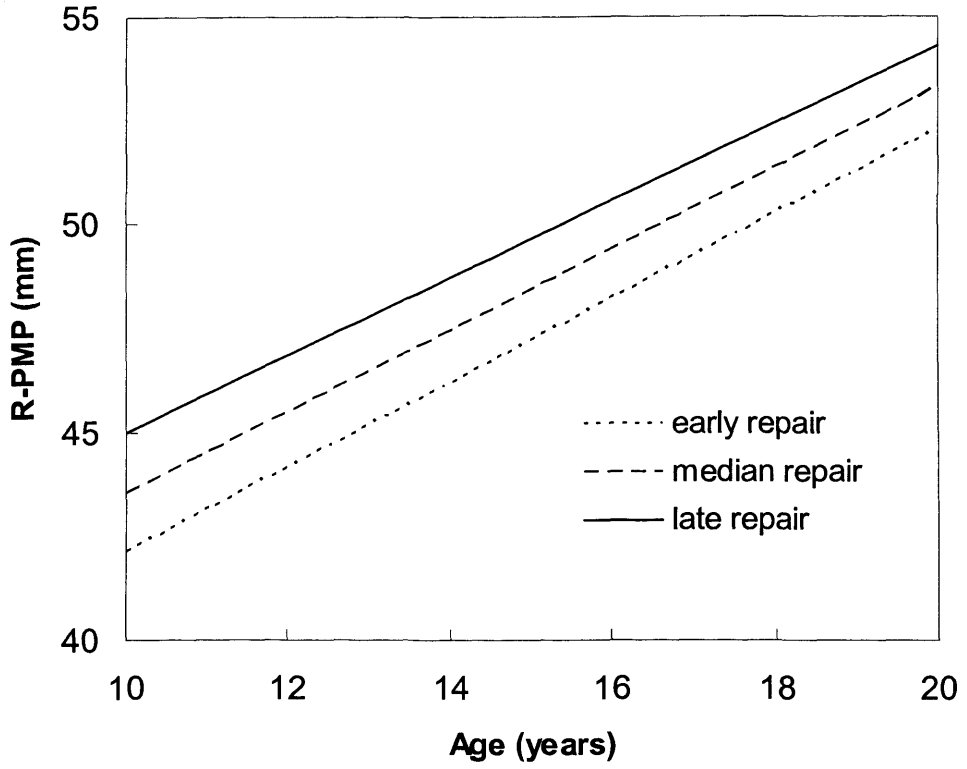

Figure 5.6. Effect of timing of hard palate repair before pubertal peak velocity age on R-PMP in patients with unilateral cleft lip and palate. The three convergent regression lines were generated from the mixed-model analysis when gender = male, technique of hard palate repair = vomerine mucoperiosteal flap, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on R-PMP either at age 20 years or the growth rate. For definition of R-PMP, please refer to Figure 4.3 and Table 4.4.

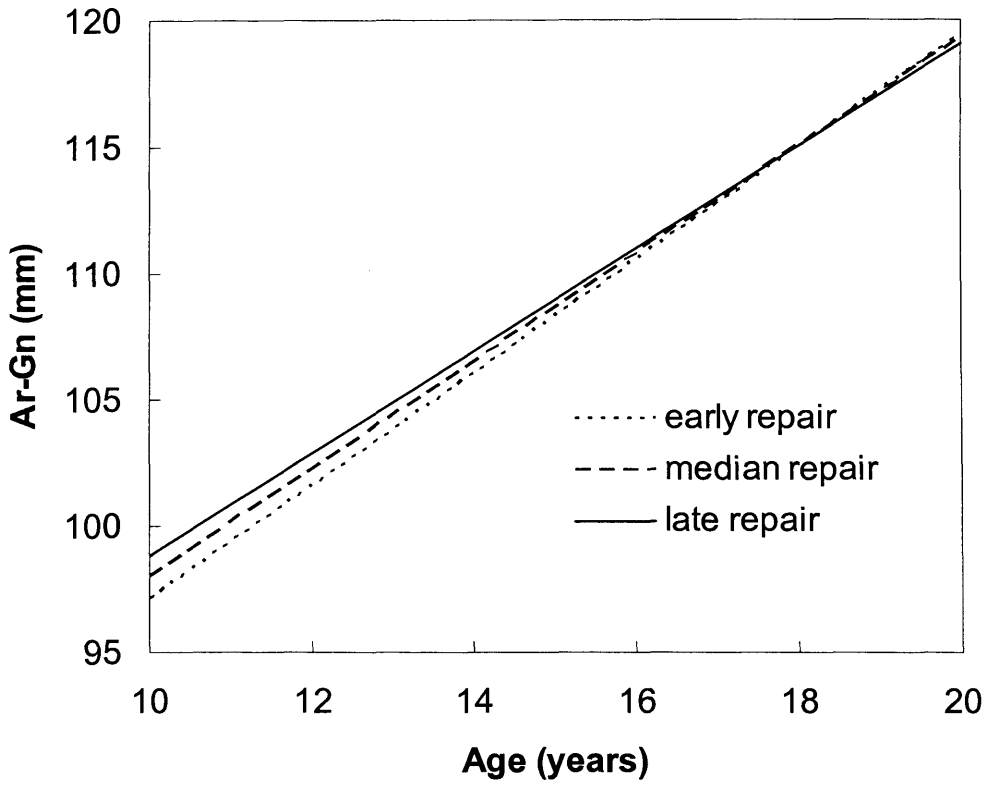

Figure 5.7. Effect of timing of hard palate repair before pubertal peak velocity age on Ar-Gn in patients with unilateral cleft lip and palate. The three convergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on Ar-Gn either at age 20 years or the growth rate. For definition of Ar-Gn, please refer to Figure 4.3 and Table 4.4.

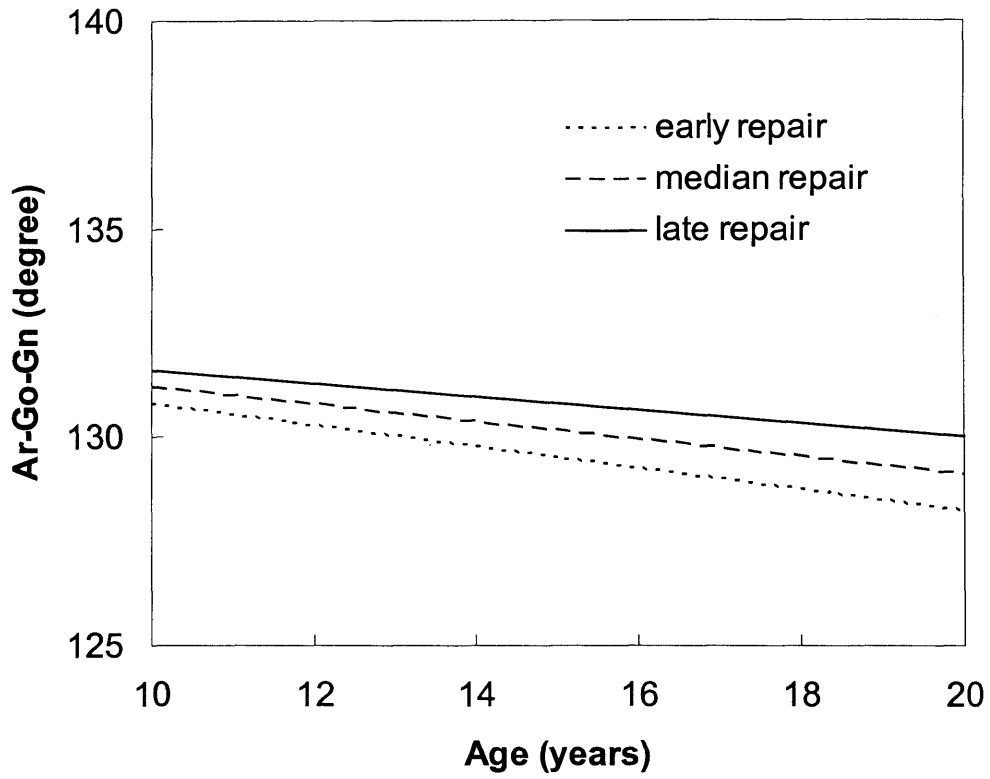

Figure 5.8. Effect of timing of hard palate repair before pubertal peak velocity age on Ar-Go-Gn in patients with unilateral cleft lip and palate. The three divergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on Ar-Go-Gn either at age 20 years or the growth rate. For definition of Ar-Go-Gn, please refer to Figure 4.3 and Table 4.4.

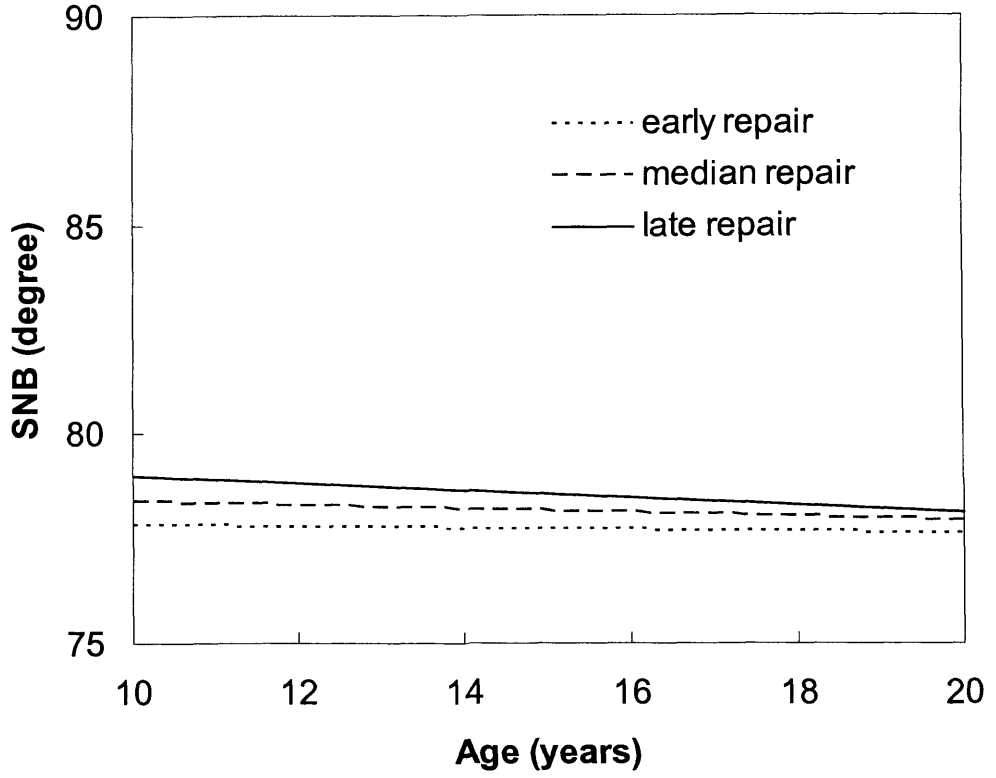

Figure 5.9. Effect of timing of hard palate repair before pubertal peak velocity age on SNB in patients with unilateral cleft lip and palate. The three convergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on SNB either at age 20 years or the growth rate. For definition of SNB, please refer to Figure 4.3 and Table 4.4.

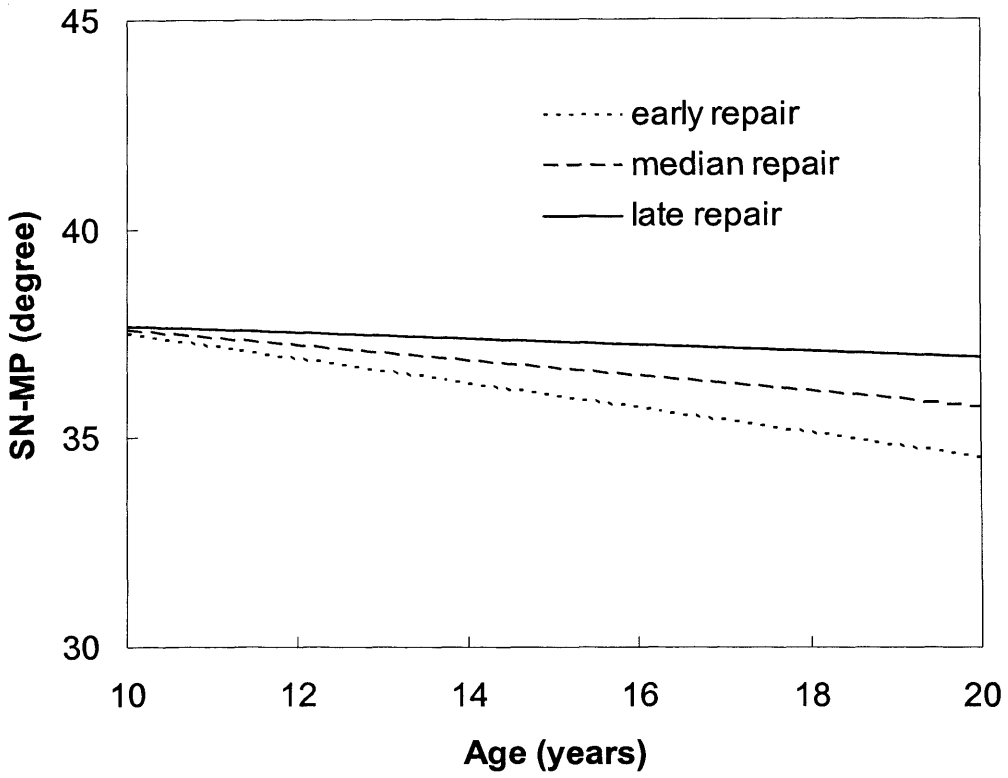

Figure 5.10. Effect of timing of hard palate repair before pubertal peak velocity age on SN-MP in patients with unilateral cleft lip and palate. The three divergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on SN-MP either at age 20 years or the growth rate. For definition of SN-MP, please refer to Figure 4.3 and Table 4.4.

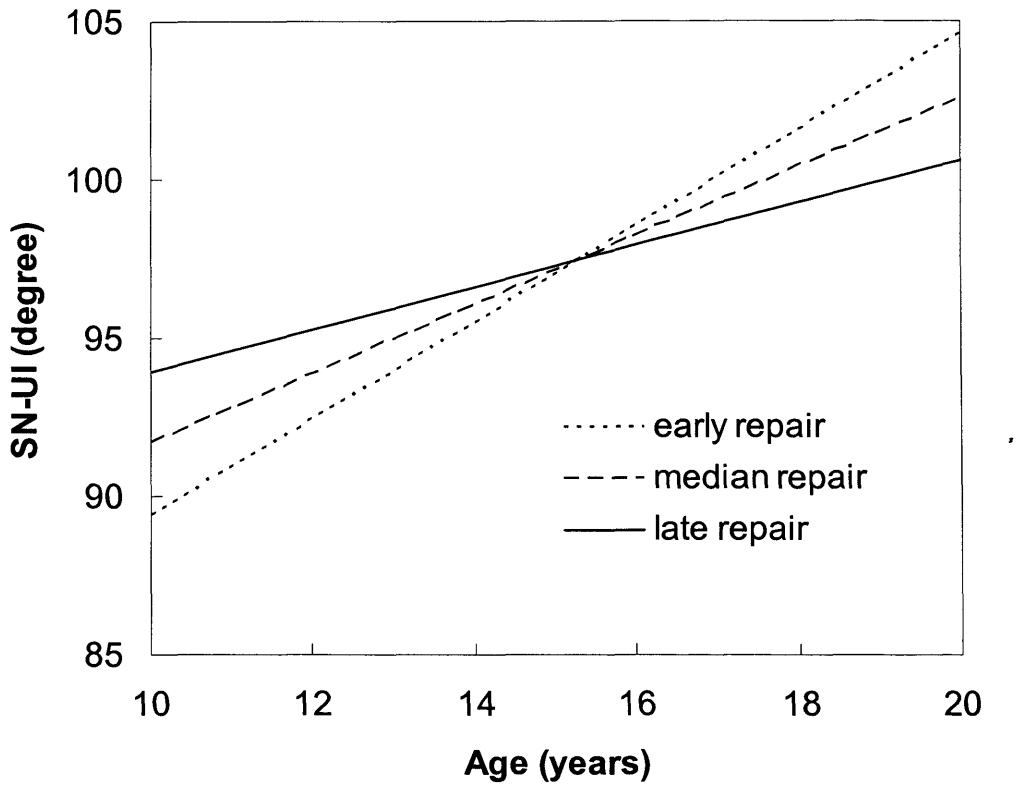

Figure 5.11. Effect of timing of hard palate repair before pubertal peak velocity age on SN-UI in patients with unilateral cleft lip and palate. The three regression lines intersecting at about age 15.5 years were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was no significant effect of timing of repair on SN-UI at age 20 years, but on the growth rate. An earlier repair resulted in faster growth of SN-UI. For definition of SN-UI, please refer to Figure 4.3 and Table 4.4.

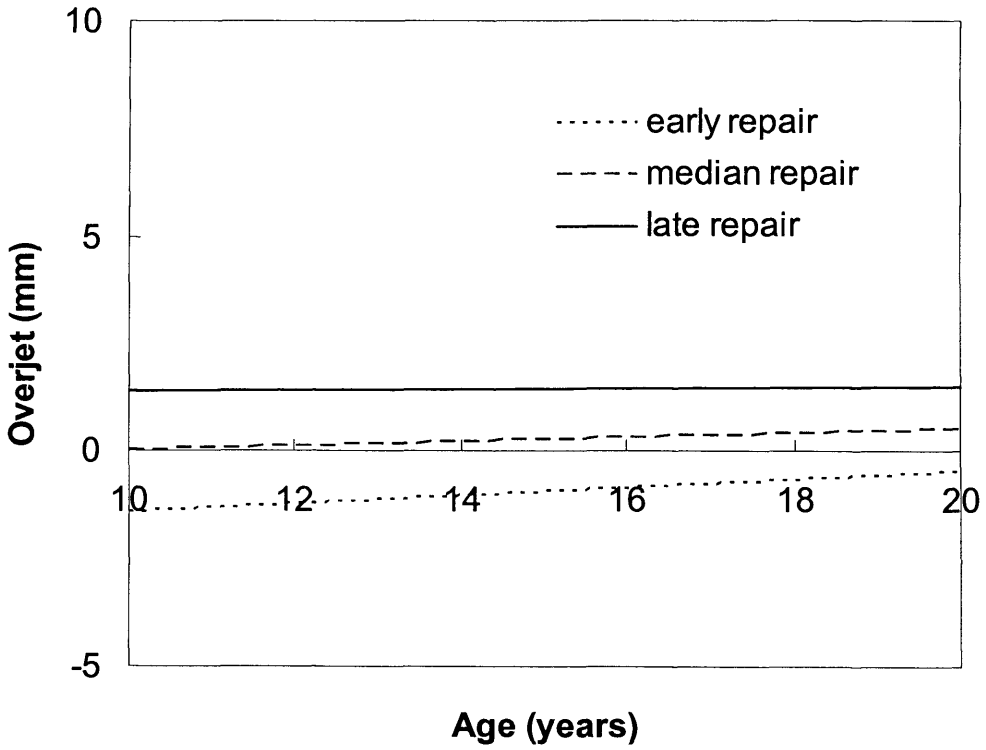

Figure 5.12. Effect of timing of hard palate repair before pubertal peak velocity age on overjet in patients with unilateral cleft lip and palate. The three convergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a marginal significant effect of timing of repair on overjet at age 20 years, but not on the growth rate. A later repair tended to result in a larger adult overjet. For definition of overjet, please refer to Figure 4.3 and Table 4.4.

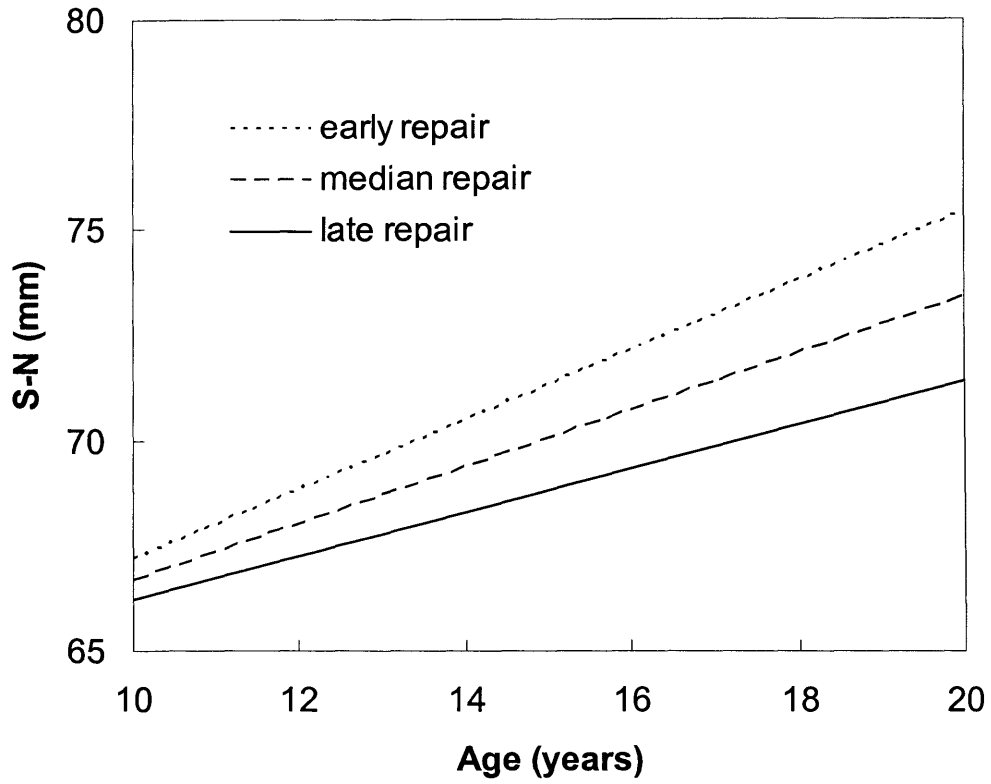

Figure 5.13. Effect of timing of hard palate repair before pubertal peak velocity age on S-N in patients with unilateral cleft lip and palate. The three divergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on S-N at age 20 years and on the growth rate. A later repair resulted in slower growth of S-N and a shorter adult S-N. For definition of S-N, please refer to Figure 4.3 and Table 4.4.

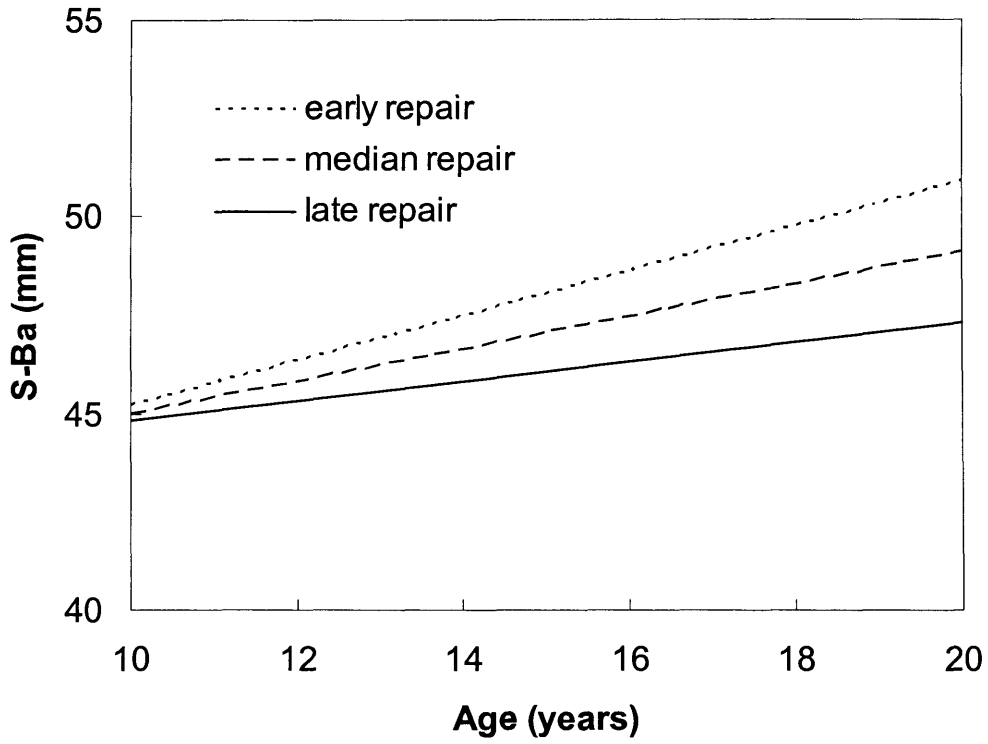

Figure 5.14. Effect of timing of hard palate repair before pubertal peak velocity age on S-Ba in patients with unilateral cleft lip and palate. The three divergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on S-Ba at age 20 years and on the growth rate. A later repair resulted in slower growth of S-Ba and a shorter adult S-Ba. For definition of S-Ba, please refer to Figure 4.3 and Table 4.4.

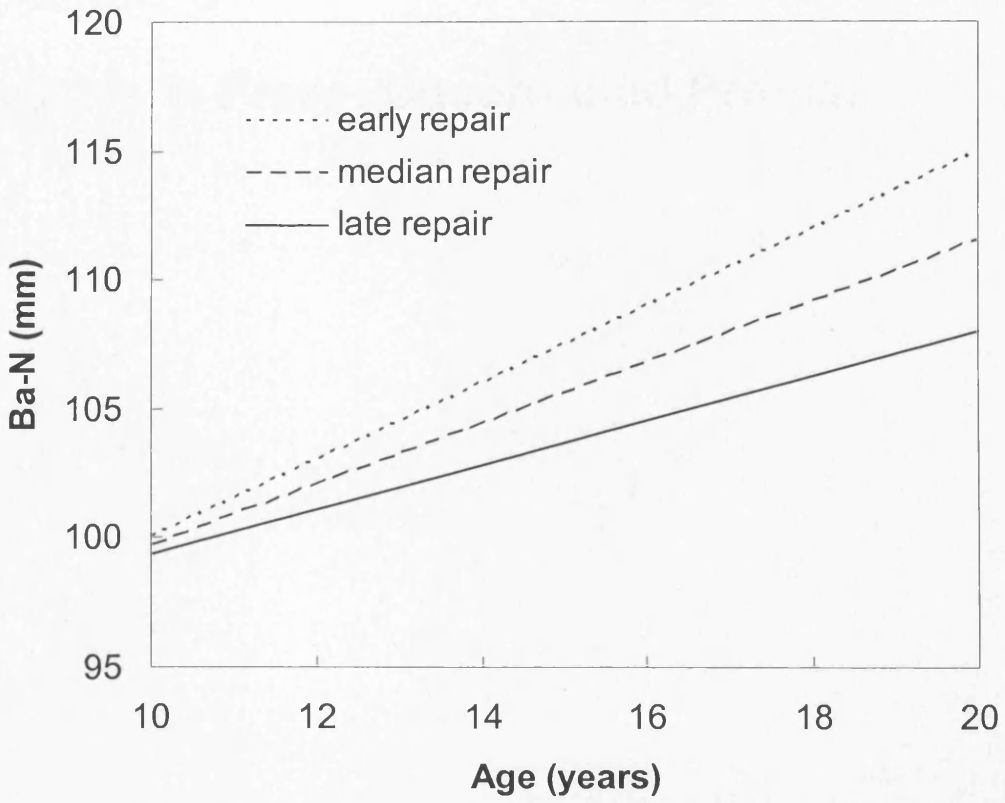

Figure 5.15. Effect of timing of hard palate repair before pubertal peak velocity age on Ba-N in patients with unilateral cleft lip and palate. The three divergent regression lines were generated from the mixed-model analysis when gender = male, and the age at the time of hard palate repair = 0 (early), 5 (median), and 10 (late) years, respectively. There was a significant effect of timing of repair on Ba-N at age 20 years and on the growth rate. A later repair resulted in slower growth of Ba-N and a shorter adult Ba-N. For definition of Ba-N, please refer to Figure 4.3 and Table 4.4.

Appendix C

(Articles in Press: Uncorrected Proofs)

Long-Term Effects of Clefts on Craniofacial Morphology in Patients With Unilateral Cleft Lip and Palate

YU-FANG LIAO, D.D.S.
MICHAEL MARS, F.D.S., PH.D., D.SC.

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Long-Term Effects of Lip Repair on Dentofacial Morphology in Patients With Unilateral Cleft Lip and Palate

YU-FANG LIAO, D.D.S.
MICHAEL MARS, D.SC., PH.D., F.D.S.

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Long-Term Effects of Palate Repair on Craniofacial Morphology in Patients With Unilateral Cleft Lip and Palate

YU-FANG LIAO, D.D.S.
MICHAEL MARS, D.SC., PH.D., F.D.S.