Title
A longitudinal cephalometric study of maxillary and cranial base growth in unilateral cleft lip and palate

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A Longitudinal Cephalometric Study of Maxillary and Cranial Base Growth in Unilateral Cleft Lip and Palate.

Michael Adam Feinberg DDS

Thesis

Submitted in partial satisfaction of the requirements for the degree of:

Master of Science

In

Oral Biology

In the

Graduate Division

Of the

University of California, San Francisco

[redacted]

Acknowledgment

This work has come to be only through the support, cooperation and perseverance of many individuals. I am grateful to every one of them.

I extend my appreciation to my mentor, Dr. Karin Vargervik, who dedicated many hours to the development and undertaking of this project from brainstorming sessions to final editing of the manuscript. Her knowledge and dedication the field of craniofacial development provided me with a strong foundation in the study of facial growth, inspiring my endeavors in the field of craniofacial anomalies. Dr. Ib Nilesen provided me with a wealth of information on normal and abnormal growth, data collection and with direction when obstacles or questions arose. I thank him for his life long committment to clinical and scientific education. I am also grateful to Dr. Stuart Gansky who made significant contributions throghout the development, design and analysis of this project. His statistical expertise, time, patience, and effort have been invaluable.

Dr. James McNamara generously provided access and facilities for collection of control data from the University of Michigan Elementary School Growth Study.

Finally, I would like to thank my family for their love and support. And, my wife, Alison, for her love, patience and encouragement through many long years of educational endeavors.

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Abstract

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To evaluate growth of the maxilla and cranial base in UCLP individuals longitudinally.

Methods:

Retrospective longitudinal (ages 5 to 17) radiographic records of 45 UCLP subjects and 29 control subjects were digitized and measured. Strict inclusion criteria were used in order to obtain a clean sample of non-syndromic UCLP individuals. Cranial base, and maxillary and mandibular sagittal, vertical, and dentoalveolar development were studied through angular measurements. Linear or quadratic regression lines were fitted to data where appropriate to describe growth changes over time.

Results:

Statistically significant differences ($p \leq 0.05$) were evident as follows: UCLP had a more obtuse cranial base angulation with less change over time than controls. UCLP had retruded maxillas with increasing maxillary retrognathia and sagittal jaw discrepancy throughout development. UCLP had a more obtuse palatal plane angulation that did not change over time; controls experienced a clockwise growth rotation. UCLP mandibular plane angle was larger and did not decrease over time as occurred in controls. UCLP maxillary and mandibular incisors began retroclined and increased proclination throughout growth to eventually match controls. Significant gender differences were seen within and between cleft and control groups for several measurements.

Conclusions:

Based on cephalometric analysis, we found the UCLP and control groups to have several statistically significant differences of absolute angular measurements and changes over time. These differences did not suggest specific timing of directional growth changes within either population for skeletal measurements. Special attention should be paid to gender differences both within and between control and UCLP groups.

Key Words: *cleft lip and palate, UCLP, maxilla, cranial base, gender, growth*

Karin Vargervik DDS, Thesis Advisor

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INTRODUCTION

Clefts of the lip and palate are the most common congenital abnormality of the head and neck with a frequency of around 2 per 1000 births (Brattstrom 1991). Combined cleft lip with cleft palate makes up approximately 50% of orofacial clefts, 75-80% are unilateral with the left side affected twice as often as the right. In California, the incidence of cleft lip and palate is approximately 1 in 700. The incidence of children born with cleft lip and palate varies according to ethnic origin, sex and type (syndromic vs. non-syndromic). Present understanding of the etiology is still limited, however, genetic predisposition and environmental factors are, undoubtedly, involved to varying degrees.

Embryology

Cleft lip results from the failure of the median nasal and maxillary processes to fuse. This fusion normally takes place by the 5th week of gestation. Cleft palate results from the failure of the palatine shelves to fuse, where closure normally begins around the 7th week of gestation and is completed by the 9th week. The presence of a cleft lip can hinder the closure of the palate; therefore, a cleft palate in the presence of a cleft lip is considered part of the primary anomaly rather than a separate defect. Clefting of the palate alone is a defect of different etiology.

Etiology

Clefts can be caused by a number of factors early in the first trimester of pregnancy. These factors include infections and toxicity, poor diet, hormonal imbalance, and genetic interferences (i.e. TGF-α, RAR-α, MSX1, and BCL3). Some of the causes may be due to excessive amounts of cortisone, insulin, vitamin A, and aspirin, or deficient amounts of dietary folic acid. Both genetic and environmental factors can contribute to the disturbance in development that results in a cleft lip and/or palate.

Clefts involving the lip, alveolus and palate, and isolated clefts of the palate, can have separate environmental and/or genetic origins. The majority of cleft cases are isolated, meaning that the cleft is not part of a pattern of malformation affecting other organs or systems. However, clefts can also be associated with a syndrome, which can be defined as a collection of two or more major anomalies that occur together with a specific natural history and course of progression. There are over 200 known syndromes that include orofacial clefts (e.g. van der Woude syndrome, Dubowitz syndrome, velocardiofacial syndrome, and Downs syndrome). Syndromic cleft individuals can demonstrate abnormal growth patterns that can stray from expected non-syndromic unilateral cleft lip and palate (UCLP) growth.

Phenotype

One major subgroup of clefts consists of individuals with unilateral clefting of the lip, alveolus and palate (UCLP). In Caucasian populations, this is the most common cleft, occurring twice as often in boys as in girls. Rehabilitation of these patients requires a multidisciplinary approach, involving plastic surgery, otolaryngology, orthodontics, speech therapy, etc. Some aspects of treatment can be viewed as less than optimal due to long-term effects of timing and type of primary surgery. What is optimal for jaw growth is not necessarily socially acceptable to the patient or conducive to the development of good speech (i.e. delaying palate surgery lessens growth impairment and results in better dental arch form, but impairs speech development) (Brattstrom 1991). As a general rule treatment starts shortly after birth and continues throughout the growth period. The universal goal is optimal rehabilitation of the patient physically, psychologically, and socially.

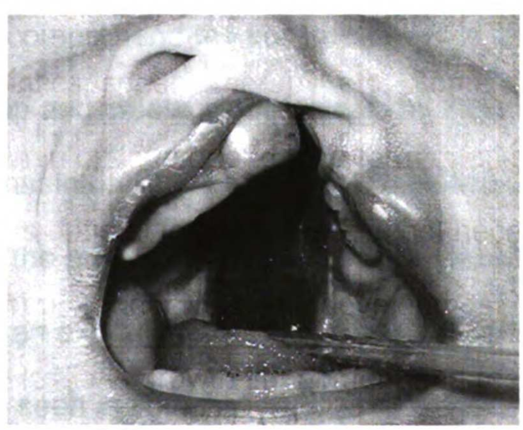

Figure 1: Infant with a complete unilateral cleft lip and palate (UCLP).

Unilateral conditions of cleft lip and palate consistently show an associated skeletal deformity of which maxillary displacement, premaxillary distortion, and malformation of the nose are prominent features (Latham 1969). Much of the growth disturbance of the mid-facial skeleton has been suggested to result from the surgical trauma and scar formation following closure of the alveolus and palate. Latham (1969) noted three features underlying the deformity of UCLP: (1) lateral displacement of the premaxillary region; (2) septal deviation both horizontally and vertically; and (3) upward tilting of the premaxillary alveolar segment. He attributed these findings to altered growth of the nasal septum beginning in the embryonic period. Palmer (1969) found that different surgical methods of palate closure had a significantly different influence on growth, while Ross (1987) reported that all common techniques of palate repair had essentially the same inhibiting effect on facial growth.

In an attempt to better comprehend the vast variability in facial growth characteristics in cleft lip and palate individuals, Dahl (1970) suggested three categories of aberrations: intrinsic, adaptive, and induced. The intrinsic factors are primarily related to the process of cleft formation, but might also influence later development. As an example of adaptive growth, Dahl mentioned the premaxillary protrusion seen in bilateral clefts. The position and growth of the premaxilla influence treatment considerably, not only in infancy but also later in development. The induced aberration is highly related to the surgical management of the cleft. Traditionally, this factor has been given the most attention, since it has been held responsible for the midfacial growth inhibition seen in many cleft patients (Friede 1995).

Normal Growth

Ossification and growth of the cranium occurs in two ways: by growth and ossification of a cartilage model, endochondral ossification, and by a transformation of mesenchymal connective tissue into bone, referred to as intramembranous ossification.

Normal Growth of the Maxilla

The maxilla develops postnatally by intramembranous ossification. Growth occurs by apposition of bone at the sutures that connect the maxilla to other facial bones, the cranium and cranial base, and by surface modeling. The growth pattern of the face directs the maxilla downward and forwards a considerable distance. As the downward and forward movement occurs, the space that would otherwise open up at the sutures is filled in by proliferation of bone at these locations. The sutures remain the same width, and the various processes of the maxilla become larger. Part of the posterior border of the maxilla is a free surface in the tuberosity region. Bone is added at this surface, as the primary and then permanent molars develop and erupt (Enlow and Hans 1996).

According to Enlow (1996), as the maxilla grows downward and forward, its anterior surfaces are remodeled and bone is removed from most of the anterior surface. The anterior part of the alveolar process is a resorptive area, so removal of bone from the surface will cancel some of the forward growth that otherwise would occur by translation of the entire maxilla. However, studies using metallic implants by Bjork have shown that the anterior surface of the zygomatic process of the maxilla is not affected by this remodeling (Bjork and Skieller 1976).

Increase in maxillary height takes place by growth at its processes by apposition at the frontal and zygomatic sutures, and on the alveolar process by eruption of teeth. Apposition also occurs at the floor of the orbits with resorptive remodeling of the nasal floor (Bjork 1966). In fact, the nasal floor is lowered by resorption which generally is greater anteriorly than posteriorly. Bjork also described that the maxilla, on average, is displaced downward and forward during growth. This is associated with varying degrees of vertical rotation. The inclination of the nasal floor to the anterior cranial base, however, is maintained as a result of compensatory differentiated modeling (Bjork and Skieller 1977).

The cartilage of the nasal septum has been hypothesized by Scott (1953) to be a primary force in the downward and forward movement of the maxillary complex due to its relationship to both the cranial base and the maxillary complex. He believed that growth due primarily to the septum will cease once all sutural elements have fused, however, the cartilage can continue to serve as a pacemaker for other aspects of maxillary growth. He described this cartilage as a *growth center* where independent growth occurs rather than a *growth site,* which is merely a location where growth occurs (Scott 1953; 1969).

Opposing Scott's nasal septum theory, Moss developed his functional matrix hypothesis in which every function in the head and neck region is carried out by a functional cranial component composed of a functional matrix (carries out the function) and a skeletal unit (protects and supports the specific functional matrix). Skeletal units can be composed of bone, cartilage or tendinous tissues, while the functional matrix can be composed of soft tissues (muscles, glands, nerves, vessels, fat, etc.) or hard tissues (teeth). The orofacial matrix grows as a result of volumetric expansion of the oronasopharyngeal functioning spaces. Their primary function is to maintain a patent airway and expand the available performance area of the tongue to make elongation and greater mobility possible (Moss and Salentijn 1969). Moss states that there are no growth centers in the skeletal tissues at all. The nasal septal cartilage and mandibular condylar cartilage are loci at which secondary and compensatory periosteal growth changes occur in the size and shape of these skeletal units.

Normal Growth of the Cranial Base

The bones of the cranial base are formed by endochondral ossification. Centers of ossification appear early in embryonic life in the chondrocranium, indicating the eventual location of the basioccipital, sphenoid, and ethmoid bones that form the cranial base. As ossification proceeds, bands of cartilage called synchondroses (spheno-occipital, intersphenoid, and spheno-ethomoidal) remain between the centers of ossification.

The young human synchondrosis consists of a bipolar epiphyseal plate with endochondral ossification, and its structural organization changes with age. The hyaline cartilage is partly replaced by fibrocartilage in the superior part, which becomes narrower through ossification from both sides, and is completely ossified by the age of 12-13 years in girls and some years later in boys. The role of the longest persisting synchondrosis, the spheno-occipital, appears to be in the adjustment changes in cranial base flexure (Thilander 1995).

The cranial base angle n-s-ba, on average, will remain unchanged during development, as described by Melsen (1973). Normal individual variation indicates that slight increases or decreases in angulation can occur. The displacement of the center of sella downward and backward following resorption of part of the floor and of the posterior wall can lead to an increase in the n-s-ba angle. At basion, apposition on the anterior border of foramen magnum, with resorption on the facies externa parties bassilaris ossis occipitalis leads to a decrease in the cranial base angle. However, differential growth in the spheno-occipital synchondrosis, results in an upward and backward displacement of basion leading to a more obtuse cranial base.

Craniofacial Growth of UCLP Individuals

Several longitudinal studies have compared facial growth and development of unilateral cleft lip and palate (UCLP) subjects to that of controls. The findings show great variability in facial growth in patients with UCLP. As most of the studies have focused on a specific age range, gender, and ethnic distribution, it is understandable that results from the different studies vary. It is important to note that few of these studies differentiated between syndromic and non-syndromic cleft individuals.

The maxillary complex in young UCLP subjects (less than 8 years of age) in comparison to control subjects of the same age and sex has been described as being either shorter in antero-posterior length (Krogman, Mazaheri et al. 1975; Smahel, Brousilova et al. 1987) or having normal growth in length (Han, Suzuki et al. 1995; Casal, Rivera et al. 1997; Vargervik 1981). When the age range is extended to age 11 (prior to pubertal growth spurt), some studies demonstrate an increase in the antero-posterior (AP) dimensions (Bishara, Sierk et al. 1979), while others show a decrease in the AP dimensions (Ozturk and Cura 1996). As compared to normals, UCLP subjects after puberty demonstrate either decreased AP dimensions (Hayashi, Sakuda et al. 1976; Johnson 1980; Horswell and Levant 1988; Smahel and Mullerova 1995; Schultes, Gaggl et al. 2000); or no difference (Dahl 1970).

The vertical dimensions of the maxillary complex in UCLP individuals have been shown to be different from normals. In children younger than 8 years, the maxillary height has been described as being either increased (Krogman, Mazaheri et al. 1975), decreased (Smahel, Brousilova et al. 1987), or normal (Han, Suzuki et al. 1995; Casal, Rivera et al. 1997). The vertical dimensions are increased in UCLP individuals up to 11 years of age according to Bishara (Bishara, Sierk et al. 1979). Post-pubertal patients, however, show decreased facial height according to Horswell (1988), Johnson (1980), Hayashi (1976), Schultes (2000), and Smahel (1995).

Cranial base measurements in UCLP subjects have also been variable. Many studies indicate a decreased cranial base length and an acute cranial base angle (Krogman, Mazaheri et al. 1975; Bishara, Sierk et al. 1979; Johnson 1980; Smahel, Brousilova et al. 1987; Krogman, Jain et al. 1982). Horswell (1988) found the length sella-nasion of the anterior cranial base to be similar until 12 years of age after which the growth rate decreased. Hayashi (1976) reported a flattening of the cranial base angle over time with no change in lengths. Smahel (1995) and Dahl (1970) found that UCLP individuals have a significantly more obtuse cranial base angle. Johnson (1980), Han (1995) and Aduss (1971) found no significant angular differences in UCLP individuals.

Untreated UCLP individuals can offer insight into the inherent growth potential unaffected by surgical scarring or soft tissue restrictions. Studies have found the maxillary AP position to be either excessive (Ortiz-Monasterio, Serrano et al. 1966; Pitanguy and Franco 1967; Ortiz-Monasterio, Olmedo et al. 1974; Sakuda, Lowe et al. 1988; Mars and Houston 1990; Yoshida, Nakamura et al. 1992; Capelozza Junior, Taniguchi et al. 1993), normal (Bishara, Krause et al. 1976; Bishara, de Arrendondo et al. 1985; Bishara, Jakobsen et al. 1986), or reduced (Isiekwe and Sowemimo 1984) in comparison to controls. The controls in these studies were matched for ethnicity and age. Bishara (1976) found no significant cranial base difference between untreated UCLP individuals and controls while Capelozza (1993) reported only a difference in one cranial base measurement (Ba-N).

In this study, all subjects included had treatment according to the management protocol at the Center for Craniofacial Anomalies, University of California, San Francisco.

- Immediately after birth: Counseling, feeding instructions, diagnosis by a geneticist, and a pediatric consultation.
- Within first weeks of life: Team evaluation, including hearing evaluation.
- At 10 to 12 weeks: surgical repair of the cleft lip
- Before age 1 year: A second team evaluation followed by surgical repair of cleft palate and placement of pressure equalization tubes.
- Three months after palate repair: Team evaluation, including speech/language assessment.

- Between 2 and 5 years of age: Team evaluations; medical and behavioral intervention as needed (speech therapy, treatment for middle ear disease, fistula repair, soft palate lengthening, etc.).
- At 5 to 6 years of age: Lip and nose revision if necessary.
- At 7 years of age or as maxillary permanent central incisors erupt: Begin orthopedic/orthodontic treatment (Phase I).
- Between 9 and 11 years: Alveolar cleft bone grafting.
- At age 12 or later: Begin full orthodontic treatment (Phase II).
- At the end of orthodontic treatment: Implants are placed to replace missing teeth.
- When growth is nearly completed: Surgical advancement of the maxilla if indicated.
- When orthodontic and prosthetic treatment is completed: Final lip and nose revision.

Purpose and Hypotheses

The primary purpose of this retrospective study was to evaluate growth of the maxilla and cranial base in UCLP individuals versus normal controls longitudinally. This was accomplished by assessing serial lateral cephalometric radiographs of UCLP individuals who had undergone standard surgical cleft lip and palate repair. Longitudinal radiographic records of UCLP subjects and controls were digitized and measured. Strict inclusion criteria were used in order to obtain a homogenous sample of non-syndromic UCLP individuals, allowing meaningful conclusions to be drawn. The following null hypotheses were tested:

1) There is no difference in the selected parameters of (1) cranial base; (2) maxillary and mandibular sagittal, vertical, and dentoalveolar development; or (3) rate of growth between UCLP and control individuals.

2) There is no specific time-point of facial growth and development at which the rate or direction of growth of the cranial base or maxilla changes due to the presence of a cleft.

3) There is no gender difference in the craniofacial morphology or rate of growth within or between UCLP and control groups.

A Longitudinal Cephalometric Study of Maxillary and Cranial Base Growth in Unilateral Cleft Lip and Palate.

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Abstract

Objective:

To evaluate growth of the maxilla and cranial base in UCLP individuals longitudinally.

Methods:

Retrospective longitudinal (ages 5 to 17) radiographic records of 45 UCLP subjects and 29 control subjects were digitized and measured. Strict inclusion criteria were used in order to obtain a clean sample of non-syndromic UCLP individuals. Cranial base, and maxillary and mandibular sagittal, vertical, and dentoalveolar development were studied through angular measurements. Linear or quadratic regression lines were fitted to data where appropriate to describe growth changes over time.

Results:

Statistically significant differences ($p \leq 0.05$) were evident as follows: UCLP had a more obtuse cranial base angulation with less change over time than controls. UCLP had retruded maxillas with increasing maxillary retrognathia and sagittal jaw discrepancy throughout development. UCLP had a more obtuse palatal plane angulation that did not change over time; controls experienced a clockwise growth rotation. UCLP mandibular plane angle was larger and did not decrease over time as occurred in controls. UCLP maxillary and mandibular incisors began retroclined and increased proclination throughout growth to eventually match controls. Significant gender differences were seen within and between cleft and control groups for several measurements.

Conclusions:

Based on cephalometric analysis, we found the UCLP and control groups to have several statistically significant differences of absolute angular measurements and changes over time. These differences did not suggest specific timing of directional growth changes within either population for skeletal measurements. Special attention should be paid to gender differences both within and between control and UCLP groups.

Key Words: *cleft lip and palate, UCLP, maxilla, cranial base, gender, growth*

INTRODUCTION

Unilateral conditions of cleft lip and palate consistently show an associated skeletal deformity of which maxillary displacement, premaxillary distortion, and malformation of the nose are prominent features. Much of the growth disturbance of the mid-facial skeleton has been suggested to result from the surgical trauma and scar formation following surgical repair of the lip and palate. Latham (1969) noted three features underlying the deformity of UCLP: (1) lateral displacement of the premaxillary region; (2) septal deviation both horizontally and vertically; and (3) upward tilting of the premaxillary alveolar segment. Palmer (1969) found that different surgical methods of palate closure had a significantly different influence on growth, while Ross (1987) and Brattstrom (1991) reported that all common techniques of palate repair had essentially the same inhibiting effect on facial growth. Levitt (1999) reported that maxillary growth in cleft subjects is not altered even after secondary alveolar bone grafting.

Several longitudinal studies have compared facial growth and development of unilateral cleft lip and palate (UCLP) subjects to that of controls. The findings show great variability in facial growth in UCLP subjects. As most of the studies have focused on a specific age range, gender, and ethnicity, it is understandable that the results differ among the studies. It is also important to note that few of these studies clearly differentiate between syndromic and non-syndromic cleft individuals.

The maxillary complex in young UCLP individuals (less than 8 years of age), in comparison to control subjects of the same age and sex, has been described as being either shorter in antero-posterior (AP) length (Krogman, Mazaheri et al. 1975; Smahel, Brousilova et al. 1987) or having normal growth in length (Han, Suzuki et al. 1995; Casal, Rivera et al. 1997). When the age range is extended to age 11 (prior to the pubertal growth spurt), some studies demonstrate an increase in the AP dimensions (Bishara, Sierk et al. 1979), while others show a decrease in the AP dimensions (Ozturk and Cura 1996). When UCLP subjects are examined beyond puberty, almost all studies demonstrate either decreased AP dimensions (Hayashi, Sakuda et al. 1976; Johnson 1980; Horswell and Levant 1988; Smahel and Mullerova 1995; Schultes, Gaggl et al. 2000) with one, composed of an all male UCLP sample, showing no difference from normal (Dahl 1970).

The vertical dimensions of the maxillary complex in UCLP subjects differ from normals, but previous reports show varying results as far as type of differences. In subjects younger than 8 years, the maxillary height has been described as being either increased (Krogman, Mazaheri et al. 1975), decreased (Smahel, Brousilova et al. 1987) or normal (Han, Suzuki et al. 1995; Casal, Rivera et al. 1997). In UCLP subjects up to 11 years of age, the vertical dimensions are increased according to Bishara (1979). Post-pubertal individuals, however, show decreased facial heights according to Horswell (1988), Johnson (1980), Hayashi (1976), Schultes (2000) and, Smahel (1995).

Cranial base measurements have also been variable. Many studies indicate a decreased cranial base length and an acute cranial base angle (Krogman, Mazaheri et al. 1975; Bishara, Sierk et al. 1979; Johnson 1980; Smahel, Brousilova et al. 1987; Krogman, Jain et al. 1982). Horswell (1988) found the length sella-nasion of the anterior cranial base to be similar until 12 years of age after which the growth rate decreased. Hayashi (1976) reported a flattening of the cranial base angle over time with no change in lengths. Smahel (1995) and Dahl (1970) found that UCLP individuals have a significantly more obtuse cranial base angle. Johnson (1980), Han (1995) and Aduss (1971) found no significant angular differences in UCLP individuals.

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2) There is no specific time-point of facial growth and development at which the rate or direction of growth of the cranial base or maxilla changes due to the presence of a cleft.

3) There is no gender difference in the craniofacial morphology or rate of growth within or between UCLP and control groups.

Materials and Methods

The subjects included in this study were collected from two centers. All UCLP data were obtained from the UCSF Center for Craniofacial Anomalies. The center's computer database was searched using the keywords "unilateral cleft lip and palate" and "UCLP." All unilateral cleft lip and palate individuals were included as the beginning sampling frame. The patient records of the 279 UCLP individuals were reviewed to obtain records of individuals who met our inclusion/exclusion criteria. Longitudinal data, collected from 1968 to 2002, were used at multiple time points between the ages of 5 and 17. Number of time points varied depending on the frequency of visits to the center with up to 10 time points per individual (Figure 1). Individuals with congenital absence of more than two teeth (evaluated on panoramic radiograph) were excluded from the study. All surgeries must have occurred in the United States following surgical protocols used by the UCSF Craniofacial team. Patients who were syndromic (confirmed with genetics report) or who underwent primary bone grafting or any major undermining surgical procedure were also excluded. Forty-five patients fulfilled these criteria (27 males and 18 females). The major reasons for exclusion were operations done outside the US, syndromic diagnoses, surgical procedures outside the standard UCSF protocol, or records outside of the age range of the study.

Table I: Descriptive statistics: Numbers and percentages of subjects, lateral cephalometric radiographs and gender differences in each group. (N=74 total)

	Subjects		Cephalograms	
	n	**%**	**n**	**%**
Controls				
Total	29	100	281	100
Male	16	55.2	159	56.6
Female	13	44.8	122	43.4
UCLP				
Total	45	100	198	100
Male	27	60	99	50
Female	18	40	99	50
Controls				
Caucasian	*29*	*100*	*281*	*100*
UCLP				
Caucasian	*31*	*68.9*	*131*	*66.2*
Hispanic	*14*	*31.1*	*67*	*33.8*

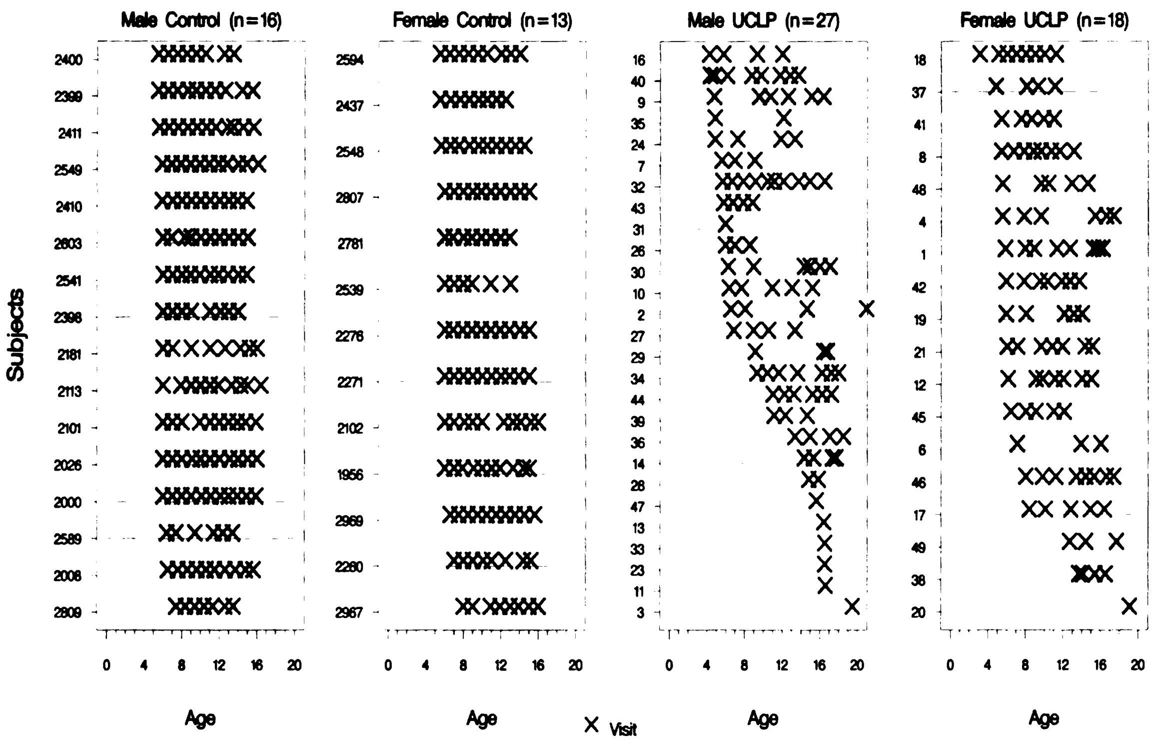

Figure 1: Timing of visits of each individual separated by cleft and gender status.

The control group consisted of 29 (16 male and 13 female) subjects with annual lateral cephalometric radiographs between ages 6 and 16 from the University of Michigan Elementary School Growth Study collected from 1953 to 1971 (Riolo 1974). All controls must have had at least 8 time points (Figure 1) and not have been treated orthodontically as maxillary growth may be influenced through the application of orthodontic forces to the maxilla. The variation from different orthodontic treatment modalities is extremely difficult to account for. No exclusions were based on Angle's Classification, however, the majority of the subjects exhibited a Class I sagittal relationship.

The UCLP group's lateral cephalometric headfilms were all taken on the same cephalostat (magnification of 9.8) by the same technician at the University of California, San Francisco Center for Craniofacial Anomalies. The control group's lateral cephalometric headfilms were all taken on the same cephalostat (magnification of 12.92) by the same technician at the University of Michigan. The serial headfilms for each subject were traced in succession by one investigator (MAF) on standard acetate tracing paper using a fine lead pencil (0.5 mm HB). All double contours were bisected to reduce landmark location error (Broadbent and Golden 1975).

The cephalometric landmarks were digitized using a Numonics™ (Numonics Corporation, Montgomeryville, PA) digitizer and the Cartesian (x and y) coordinates were entered into a cephalometric digitizing program, TIOPS 2000™ (J.B. Joergensen, Germany). A total of fifty-seven hard and soft tissue landmarks were digitized from each tracing into the TIOPS™ program (Figure 2). Differences in magnification were adjusted and equalized by the digitization program. Angular measurements were analyzed exclusively in order to minimize variability in radiographic technique and magnification.

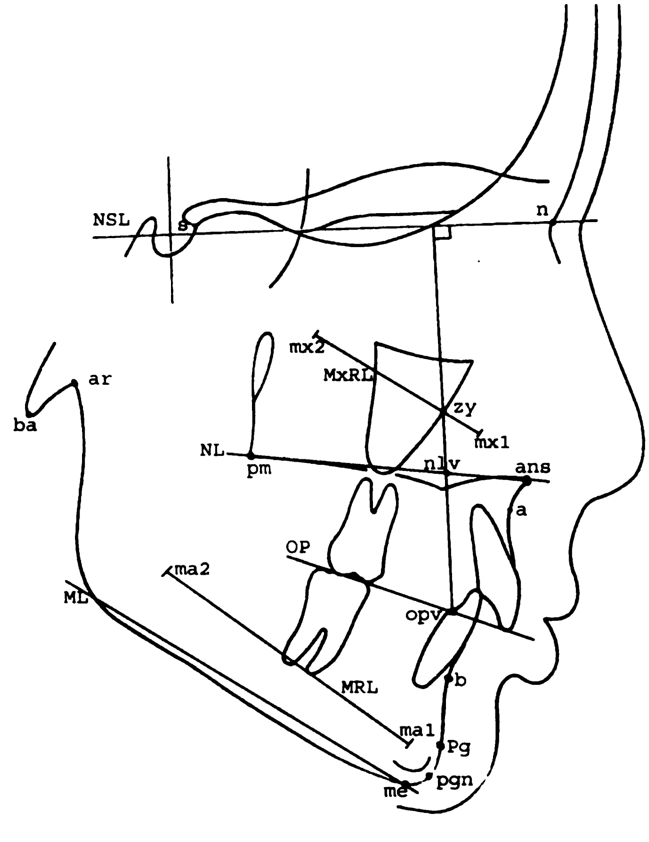

Figure 2: Points and Planes used for Cephalometric Measurements

Statistical Analysis

Lin's concordance and Pearson's product correlations were used to assess reliability of duplicate measurements. While Pearson's correlation only estimates the degree of linear association (i.e. as one increases the other tends to increase), Lin's concordance correlation (Lin 1989) estimates the degree the duplicates are coincident (i.e. exactly the same compared to a 45 degree reference line of equality). The Bland-Altman method (Bland and Altman 1986) of comparing the mean of the duplicates to the differences between the duplicates graphically and with 95% confidence intervals for the difference was also used to assess reliability. Fifteen randomly selected head films were traced twice and digitized twice by the same investigator (MAF) separated by a time interval of 1 week. Lin's concordance, Pearson's product correlation and Bland-Altman statistical analyses were performed with equations in Microsoft Excel (Microsoft, Redmond, WA).

A graph of the subject age at each visit was modified from an SAS macro (Hsu, Zhou et al. 2002). Mixed effects regression models with separate intercepts and age slopes for each of the four gender x cleft status (control or UCLP) groups were used to compare differences in longitudinal growth changes as children aged, which was especially important since UCLP subjects had less regularly timed visits than the controls. Random person effects with exchangeable (compound symmetric) correlation structure accounted for the fact that each person had multiple measures over time. Quadratic slopes were added where indicated. Intercepts and age slopes were compared across the four gender x cleft status groups with F-tests. Analyses were performed using SAS proc mixed (SAS Institute, Inc, Cary, NC). Growth trajectories for each of the four gender x cleft status groups were separately estimated and plotted together using proc traj (Jones, Nagin et al. 2001), a customized SAS/TOOLKIT procedure, to fit semiparametric censored normal mixture models.

Results

Evaluation of digitizing error produced Lin's concordance and Pearson's product correlations of above 0.9 indicating excellent reliability. In analysis of tracing error, 14 of 17 measurements had Lin's concordance and Pearson's product correlations of greater than 0.8, corresponding to very good to excellent reliability. Angles n-s-ar, n-s-ba, and pr-n-a had lower values (between 0.6 and 0.8) corresponding to fair to good reliability. The Bland-Altman method indicated excellent reliability having all measurements within the 95% confidence intervals and hovering around zero with no evident error trends.

Results will be discussed and presented separately for males and females in control and UCLP groups. Combined group data are presented in Tables III and IV. Males and females have been analyzed separately due to gender differences seen in the parameters of this study and in previous publications (Brattstrom 1991; Krogman, Jain et al. 1982; Bishara, Sierk et al. 1979; Jain and Krogman 1983; Long, Jain et al. 1982).

Graphs presented are created by y-intercepts and slopes of fitted regression lines based on calculations of average changes in individual angulations over time in each individual group studied. Positive inclinations of regression lines (positive slope values) indicate an increase in measurement of a specific angle (more obtuse) among subsequent time points. Negative inclinations of regression lines (negative slope values) indicate a decrease in measurement of a specific angle (more acute) among subsequent time points.

Cranial base changes (n-s-ar: Figure 3, n-s-ba: Figure 4)

At age 6, UCLP individuals exhibited a more obtuse cranial base angle than their control counterparts and UCLP females had a significantly more obtuse cranial base angle than both control females and UCLP males (Table V). The slope of n-s-ar is significantly less inclined (flatter) in the combined UCLP group vs. controls. UCLP females had a significantly different slope for n-s-ar with a larger increase in angulation than UCLP males (Table III).

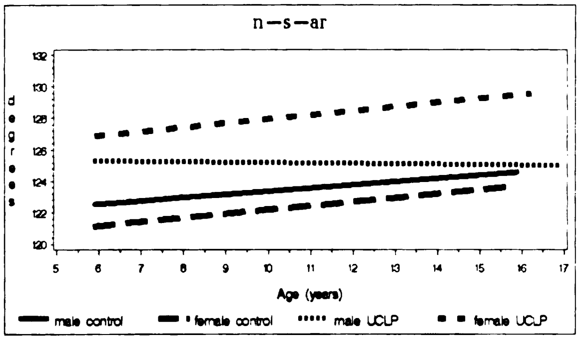

Figure 3: Slope graph of cranial base measurement n-s-ar.

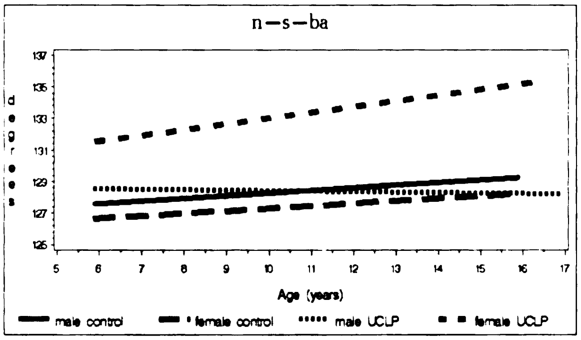

Figure 4: Slope graph of cranial base measurement n-s-ba.

Maxillary changes

***Sagittal* (s-n-a: Figure 5)**

At 6 years of age the angle s-n-a was significantly more acute in the combined cleft sample than in controls and control females had a significantly greater s-n-a angle than UCLP females (Table V). Over time, the maxilla in the cleft individuals became slightly more retruded while a slightly forward growth occurred in controls. UCLP males, females and combined groups had significantly more negative slopes when compared to relatively flat slopes of their control counterparts. In addition UCLP males had a significantly more negative slope than the UCLP females (Table III).

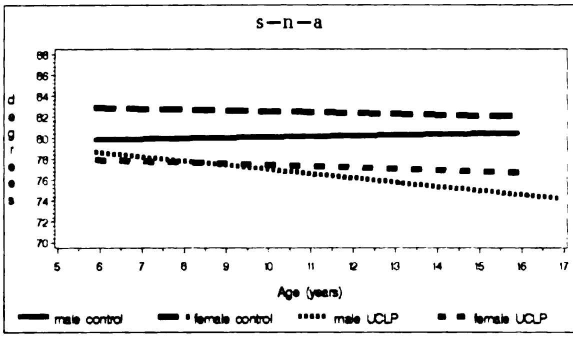

Figure 5: Slope graph of maxillary sagittal measurement s-n-a.

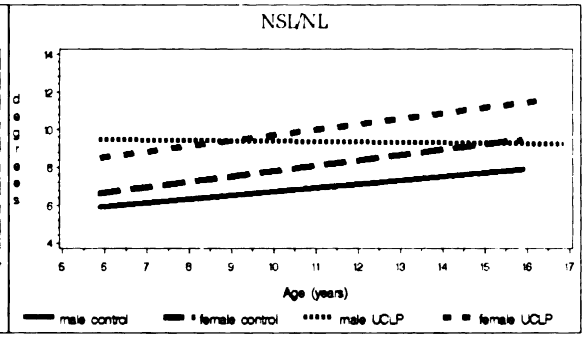

Figure 6: Slope graph of maxillary vertical measurement NSL/NL.

***Vertical* (NSL/NL: Figure 6)**

The palatal plane was significantly steeper in the UCLP male, female and combined groups when compared to their control counterparts at 6 years of age (Table V). The combined control subjects followed a slope of growth that increased the palatal plane angle over time while the combined cleft group had a flat slope (Figure 6 and Table II). Slope differences between UCLP and control groups combined and separately for each gender were suggestive of significance (Table III).

Jaw relationship changes

***Sagittal* (a-n-b: Figure 7, a-n-pg: Figure 8)**

The angles a-n-b and a-n-pg demonstrated that the sagittal jaw relationship was similar in the UCLP and control groups at age 6 (Figures 7 and 8, Table V). All UCLP groups followed a different growth pattern with a significantly steeper negative slope than controls, resulting in a negative sagittal jaw relationship over time. Within the UCLP group, males had a significantly more negative slope than females; while within the control group, females had a significantly more negative slope than males (Tables II and III).

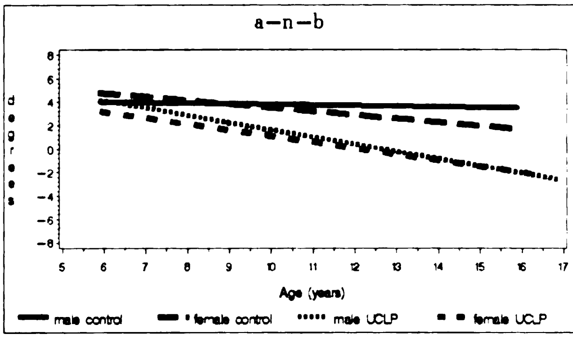

Figure 7: Slope graph of sagittal jaw relationship measurement a-n-b.

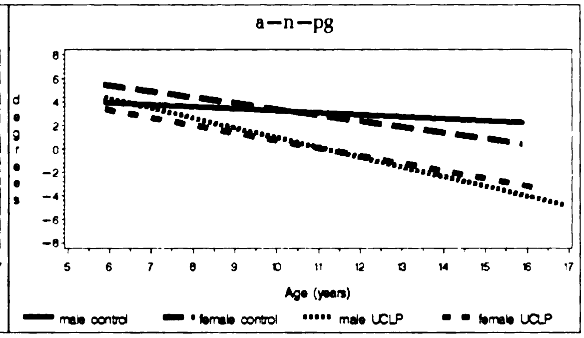

Figure 8: Slope graph of sagittal jaw relationship measurement a-n-pg.

***Vertical* (NSL/ML: Figure 9, NL/ML: Figure 10)**

The UCLP female and combined groups had a higher mandibular plane angle compared to controls at age 6. At this age, control males also had a significantly greater mandibular plane angle than control females (Tables IV and V). As these individuals grew, the angle reduced slightly over time in all groups with more reduction in controls than in UCLP individuals (Table II). UCLP female and combined groups had significantly less reduction in mandibular plane angle than their control counterparts. Control males also had significantly less reduction in mandibular plane angle than control females (Tables II and III).

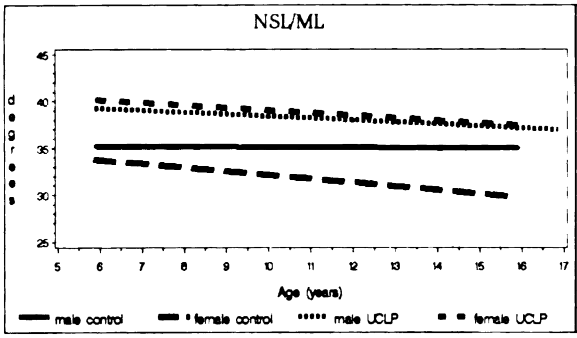

Figure 9: Slope graph of mandibular vertical measurement NSL/ML.

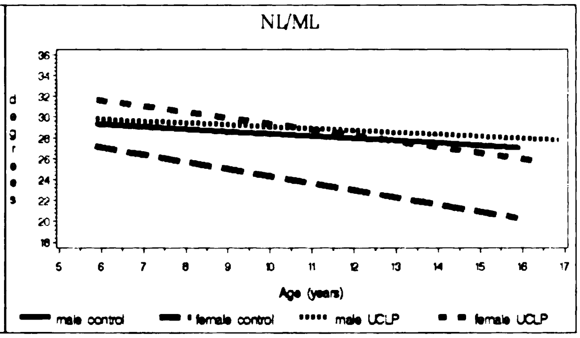

Figure 10:Slope graph of mandibular vertical measurement NL/ML.

Mandibular changes (ML/RL: Figure 11, MBL/ML, s-n-b, s-n-pg: Figure 12)

The gonial angle was not significantly different between cleft and control groups at age 6 (Table V). However, the gonial angle decreased significantly less over time in the UCLP female and combined groups compared with their control counterparts (Tables II and III). MBL/ML was significantly larger in the female controls compared to the female UCLP individuals at age 6 with all groups following similar positive growth slopes (Tables III and V). Sagittal position, by the measures of s-n-pg and s-n-b, showed a trend to be more retrognathic in the UCLP sample compared with the control sample with growth proceeding along a similar slope between the two groups. Control females had a significantly steeper positive slope of s-n-pg than control males (Tables III and V).

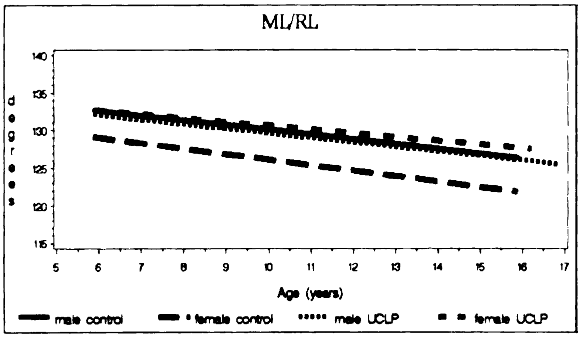

Figure 11: Slope graph of mandibular gonial angle measurement ML/RL.

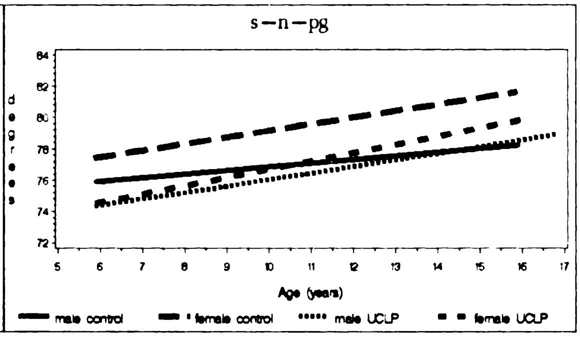

Figure 12: Slope graph of mandibular sagittal measurement s-n-pg.

Dentoalveolar changes (pr-n-a: Figure 13, ML/L1, NL/U1: Figure 14, CL/ML)

The angle pr-n-a (Figure 13) revealed that the maxillary dentoalveolar segment was significantly retruded in the UCLP male, female and combined groups compared with their corresponding controls at age 6 (Tables IV and V). UCLP male and combined groups had a steeper positive slope compared to controls (Tables II and III), leading to a less retruded position over time in UCLP individuals. The angle NL/U1 (Figure 14) uncovered a similar finding in which the maxillary central incisors in all cleft groups began retroclined at age 6 and had a steeper (but non-linear) slope of proclination over time when compared to controls. Female controls had significantly greater upper incisor proclination than males at 6 years of age (Tables III and V).

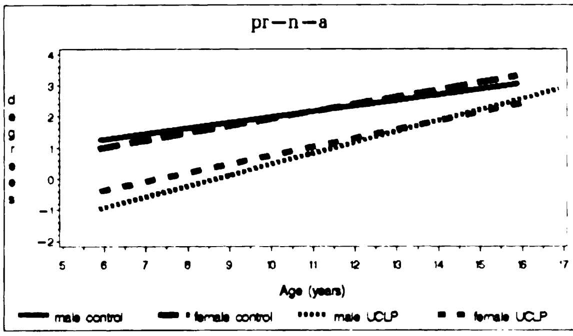

Figure 13: Slope graph of maxillary dentoalveolar measurement pr-n-a.

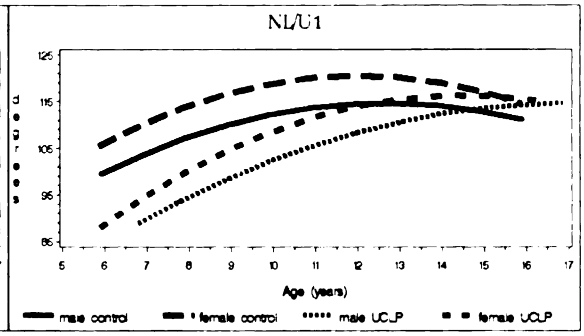

Figure 14: Slope graph of maxillary incisor inclination measurement NL/U1.

The mandibular incisors measured by ML/L1 were retroclined in all UCLP groups compared to controls at age 6 (Tables IV and V). The slope ML/L1 in the female control group was significantly steeper in a positive direction than that of the UCLP females (Tables II and III). This finding was also supported by the findings in the chin angle measurement, CL/ML, which began at age 6 with a significantly more acute angle in all UCLP groups compared to controls (Tables IV and V). At this age CL/ML was also significantly greater in control females than in control males. The angle became more acute over time in UCLP male, female and combined groups compared to their control counterparts (Tables II and III).

Table II: Estimated slope of change during growth with 95% confidence intervals for each variable measured and each of the four groups.

Variable	Slope	95% CI Lower	95% CI Upper
n-s-ar			
female control	0.18	0.06	0.29
male control	0.20	0.11	0.29
female UCLP	0.03	-0.08	0.15
male UCLP	0.11	0.00	0.22
n-s-ba			
female control	0.12	0.01	0.22
male control	0.12	0.04	0.21
female UCLP	0.05	-0.06	0.16
male UCLP	0.07	-0.03	0.17
n-s/s-arp			
female control	-0.12	-0.13	-0.10
male control	-0.09	-0.10	-0.07
female UCLP	-0.03	-0.05	-0.01
male UCLP	-0.04	-0.06	-0.02
ML/RL			
female control	-0.75	-0.91	-0.58
male control	-0.76	-0.90	-0.63
female UCLP	-0.45	-0.62	-0.28
male UCLP	-0.56	-0.72	-0.40
MBL/ML			
female control	0.27	0.19	0.35
male control	0.21	0.14	0.27
female UCLP	0.17	0.09	0.25
male UCLP	0.26	0.18	0.34
s-n-a			
female control	0.00	-0.10	0.10
male control	0.08	-0.01	0.16
female UCLP	-0.19	-0.29	-0.09
male UCLP	-0.46	-0.56	-0.36
s-n-pg			
female control	0.42	0.33	0.51
male control	0.27	0.20	0.35
female UCLP	0.41	0.31	0.50
male UCLP	0.31	0.22	0.40
s-n-b			
female control	0.23	0.15	0.32
male control	0.14	0.06	0.21
female UCLP	0.25	0.16	0.35
male UCLP	0.13	0.04	0.22
a-n-pg			
female control	-0.42	-0.52	-0.32
male control	-0.20	-0.28	-0.12
female UCLP	-0.59	-0.69	-0.49
male UCLP	-0.77	-0.86	-0.67
a-n-b			
female control	-0.24	-0.33	-0.14
male control	-0.06	-0.14	0.01
female UCLP	-0.44	-0.53	-0.34
male UCLP	-0.59	-0.68	-0.50
NSL/NL			
female control	0.27	0.12	0.41
male control	0.14	0.02	0.27
female UCLP	0.08	-0.04	0.21
male UCLP	0.00	-0.12	0.12
NSL/ML			
female control	-0.45	-0.57	-0.32
male control	-0.15	-0.25	-0.05
female UCLP	-0.17	-0.30	-0.04
male UCLP	-0.11	-0.23	0.01
NL/ML			
female control	-0.69	-0.89	-0.48
male control	-0.30	-0.48	-0.11
female UCLP	-0.25	-0.44	-0.07
male UCLP	-0.18	-0.35	-0.01
pr-n-a			
female control	0.24	0.17	0.32
male control	0.17	0.10	0.23
female UCLP	0.24	0.16	0.31
male UCLP	0.34	0.16	0.40
U1/NL			
female control	1.00	0.51	1.49
male control	0.96	0.54	1.38
female UCLP	2.66	2.21	3.10
male UCLP	2.38	1.99	2.78
L1/ML			
female control	0.71	0.40	1.03
male control	0.51	0.23	0.78
female UCLP	0.18	-0.10	0.47
male UCLP	0.84	0.58	1.09
CL/ML			
female control	-0.44	-0.63	-0.25
male control	-0.30	-0.47	-0.14
female UCLP	-0.73	-0.89	-0.57
male UCLP	-0.62	-0.77	-0.47

Table III: Statistical data of cross group comparison of slope data.

SLOPE DATA	UCLP vs Control		female: UCLP vs. control		male: UCLP vs. control		control: male vs. female		UCLP: male vs. female	
	F-Value	P-value	F-Value	P-value	F-Value	P-value	F-Value	P-value	F-Value	P-value
n-s-ar	4.41	0.0364*	2.96	0.0859	1.50	0.2215	0.09	0.7657	0.82	0.0199*
n-s-ba	1.36	0.2440	0.75	0.3865	0.61	0.4353	0.01	0.9400	0.06	0.3662
n-s/s-arp	50.96	<.0001*	38.06	<.0001*	14.45	0.0002*	5.13	0.0240*	0.58	0.4450
ML/RL	9.51	0.0022*	6.14	0.0136*	3.43	0.0647	0.02	0.8953	0.93	0.3360
MBL/ML	0.45	0.5026	3.19	0.0747	1.00	0.3169	1.47	0.2254	2.57	0.1098
s-n-a	55.91	<.0001*	6.59	0.0106*	69.85	<.0001*	1.47	0.2263	14.61	0.0002*
s-n-pg	0.10	0.7536	0.02	0.8835	0.40	0.5250	5.88	0.0158*	2.19	0.1394
s-n-b	0.02	0.8850	0.08	0.7716	0.01	0.9138	2.67	0.1030	3.51	0.0616
a-n-pg	62.15	<.0001*	5.88	0.0158*	83.8	<.0001*	12.33	0.0005*	6.48	0.0113*
a-n-b	62.16	<.0001*	8.26	0.0043*	74.9	<.0001*	7.93	0.0051*	5.13	0.0240*
NSL/NL	6.26	0.0128*	3.54	0.0606	2.72	0.1001	1.63	0.2019	0.89	0.3459
NSL/ML	6.77	0.0096*	9.17	0.0026*	0.27	0.6066	13.08	0.0003*	0.48	0.4907
NL/ML	8.25	0.0043*	9.34	0.0024*	0.81	0.3676	7.59	0.0062*	0.32	0.5705
pr-n-a	4.80	0.0291*	0.02	0.8957	12.43	0.0005*	2.18	0.1406	3.63	0.0575
U1/NL	47.46	<.0001*	24.3	<.0001*	23.31	<.0001*	0.01	0.9133	0.83	0.3628
L1/ML	0.48	0.4892	6.00	0.0148*	2.92	0.0882	0.95	0.3308	11.14	0.0009*
CL/ML	12.78	0.0004*	5.30	0.0219*	7.76	0.0056*	1.16	0.2826	0.92	0.3386

* $p \leq 0.05$

Table IV: Estimated y-intercept at 6 years of age with 95% confidence intervals for each variable measured and each of the four groups.

Variable	Y-Intercept	95% CI Lower	95% CI Upper
n-s-ar			
female control	121.50	118.80	124.10
male control	122.50	120.10	124.90
female UCLP	128.30	125.90	130.60
male UCLP	124.00	122.00	125.90
n-s-ba			
female control	126.90	124.10	129.80
male control	127.70	125.10	130.30
female UCLP	133.20	130.70	135.70
male UCLP	127.50	125.40	129.60
n-s/s-arp			
female control	4.84	4.51	5.18
male control	4.59	4.29	4.89
female UCLP	3.74	3.44	4.04
male UCLP	4.05	3.79	4.32
ML/RL			
female control	129.30	126.10	132.50
male control	133.10	130.20	135.90
female UCLP	133.00	130.20	135.80
male UCLP	132.20	129.70	134.60
MBL/ML			
female control	16.97	15.47	18.48
male control	15.32	13.96	16.67
female UCLP	14.90	13.56	16.24
male UCLP	14.95	13.79	16.11
s-n-a			
female control	82.56	80.41	84.72
male control	79.97	78.03	81.91
female UCLP	78.47	76.58	80.36
male UCLP	79.46	77.84	81.08
s-n-pg			
female control	77.29	75.19	79.39
male control	75.83	73.95	77.72
female UCLP	75.10	73.27	76.94
male UCLP	74.98	73.41	76.54
s-n-b			
female control	77.90	75.83	79.98
male control	75.86	74.00	77.73
female UCLP	75.34	73.52	77.16
male UCLP	75.08	73.53	76.63
a-n-pg			
female control	5.27	3.64	6.90
male control	4.12	2.66	5.58
female UCLP	3.33	1.87	4.79
male UCLP	4.46	3.18	5.73

Variable	Y-Intercept	95% CI Lower	95% CI Upper
a-n-b			
female control	4.66	3.18	6.14
male control	4.11	2.78	5.44
female UCLP	3.09	1.75	4.42
male UCLP	4.36	3.18	5.55
NSL/NL			
female control	6.82	5.95	7.69
male control	5.98	5.28	6.67
female UCLP	9.88	8.34	11.42
male UCLP	8.79	7.56	10.02
NSL/ML			
female control	34.26	30.99	37.53
male control	35.72	32.78	38.66
female UCLP	39.82	36.97	42.66
male UCLP	38.24	35.84	40.65
NL/ML			
female control	25.14	23.82	26.45
male control	29.73	28.70	30.75
female UCLP	29.88	26.74	33.03
male UCLP	31.14	28.92	33.36
pr-n-a			
female control	0.97	0.35	1.58
male control	1.32	0.78	1.87
female UCLP	-0.30	-0.91	0.31
male UCLP	-0.95	-1.53	-0.37
U1/NL			
female control	109.00	106.10	111.90
male control	103.80	101.40	106.20
female UCLP	92.99	88.91	97.08
male UCLP	89.28	85.71	92.85
L1/ML			
female control	90.92	89.00	92.83
male control	88.98	87.43	90.53
female UCLP	82.66	79.63	85.68
male UCLP	79.30	76.75	81.85
CL/ML			
female control	76.98	75.82	78.13
male control	72.96	72.04	73.88
female UCLP	71.93	69.69	74.17
male UCLP	70.54	68.80	72.27

Table V: Statistical data of cross group comparison of y-intercept data.

Y - INTERCEPT	UCLP vs Control		female: UCLP vs. control		male: UCLP vs. control		control: male vs. female		UCLP: male vs. female	
Age 6	**F-Value**	**P-value**	**F-Value**	**P-value**	**F-Value**	**P-value**	**F-Value**	**P-value**	**F-Value**	**P-value**
n-s-ar	12.34	0.0008*	14.78	0.0003*	0.90	0.3463	0.32	0.5712	7.91	0.0064*
n-s-ba	5.86	0.0181*	10.88	0.0015*	0.01	0.9291	0.16	0.6942	12.02	0.0009*
n-s/s-arp	29.51	<.0001*	23.86	<.0001*	7.19	0.0092*	1.24	0.2685	2.45	0.1221
ML/RL	0.99	0.3234	3.03	0.0862	0.22	0.6421	3.03	0.0859	0.21	0.6496
MBL/ML	3.27	0.0750	4.20	0.0441*	0.17	0.6828	2.66	0.1075	0.00	0.9567
s-n-a	5.78	0.0189*	8.13	0.0057*	0.16	0.6899	3.20	0.0780	0.63	0.4294
s-n-pg	2.67	0.1069	2.44	0.1227	0.49	0.4884	1.06	0.3072	0.01	0.9163
s-n-b	3.31	0.0732	3.44	0.0678	0.42	0.5210	2.13	0.1492	0.05	0.8285
a-n-pg	1.19	0.2788	3.12	0.0818	0.12	0.7323	1.10	0.2983	1.33	0.2535
a-n-b	0.97	0.3285	2.47	0.1208	0.08	0.7781	0.30	0.5863	2.04	0.1576
NSL/NL	26.80	<.0001*	11.94	0.0009*	15.73	0.0002*	2.29	0.1345	1.21	0.2741
NSL/ML	7.81	0.0067*	6.53	0.0128*	1.75	0.1900	0.44	0.5107	0.71	0.4023
NL/ML	8.59	0.0046*	7.72	0.0070*	1.34	0.2516	30.08	<.0001*	0.43	0.5163
pr-n-a	35.84	<.0001*	8.47	0.0048*	32.20	<.0001*	0.75	0.3899	2.37	0.1281
U1/NL	85.51	<.0001*	40.79	<.0001*	45.66	<.0001*	7.68	0.0072*	1.86	0.1766
L1/ML	58.99	<.0001*	21.20	<.0001*	41.87	<.0001*	2.46	0.1211	2.87	0.0948
CL/ML	21.73	<.0001*	15.94	0.0002*	6.06	0.0163*	29.42	<.0001*	0.96	0.3309

*** $p \leq 0.05$**

Discussion

Craniofacial morphology and rate of growth – Hypothesis 1

Cranial base changes (n-s-ar: Figure 3, n-s-ba: Figure 4)

The general trend of growth change in the cranial base angle of both control and UCLP individuals in this study was relatively no change in angulation of the cranial base over time. This finding is similar to that reported by Brodie (1955). He observed much individual variation in the n-s-ba angle at the start of the observation period (age 3), followed by little change in each individual over time until growth was complete. Melsen (1974) described that the cranial base angle n-s-ba, on average, remains unchanged during development. Normal individual variation, as well as measurement error, provides the possibility for slight increases or decreases in angulation to occur. Melsen attributed changes in cranial base angulation to the following: (1) displacement of sella downward and backwards following resorption on part of the floor and posterior wall can lead to an increase in the n-s-ba angle; (2) at basion, apposition on the anterior border of foramen magnum, with resorption on the facies externa parties bassilaris ossis occipitalis resulting in a decrease in the cranial base angle; and (3) differential growth in the spheno-occipital synchondrosis, leading to an upward and backward displacement of basion would lead to a more obtuse cranial base. These minor modifications will lead to little change in the cranial base angle over time. Thilander (1995) also recognized that the spheno-occipital synchondrosis appears to allow for adjustment changes in cranial base flexure.

In our study, the cranial base angulation of cleft individuals, especially the UCLP female group, was significantly more obtuse than in the control individuals. Our findings support those observed in cross sectional and longitudinal studies of individuals at various stages of growth from 4 to 20 years of age, in which Smahel (1995), Hayashi (1976), and Dahl (1970) noted a more obtuse cranial base angle in their UCLP subjects when compared to controls.

Differing from our findings, Krogman (1975; 1982), in longitudinal studies of UCLP individuals ages 6 months to 10 years and Bishara (1979), in UCLP subjects aged 5 and 6, noted an acute n-s-ba angle compared to their control groups. Bishara (1979), in a study of UCLP subjects aged 7 to 10 years, and Johnson (1980), in a study of UCLP subjects aged 13.5 to 15.5 years, reported a trend towards a more acute cranial base angle in UCLP individuals. Han (1995) and Aduss (1971) found no significant difference or trend in cranial base angulation of UCLP individuals when compared to controls.

The reliability of the measurements of n-s-ar and n-s-ba angles in our study are low relative to other measurements (0.6 to 0.8) but are still within an acceptable range. This measurement error is expected due to difficulty in landmark identification (Baumrind and Frantz 1971). Since the differences between groups for these measurements is more than 4 times the standard deviation of the tracing error, the conclusions drawn can be considered accurate.

Maxillary changes

***Sagittal* (s-n-a: Figure 5)**

Growth of the maxilla has been thoroughly described through implant studies performed by Bjork (1966). He showed that the maxilla, on average, is displaced downward and forward during growth. We observed control females as having a significantly more forward position of the maxilla relative to the anterior cranial base than control males at age 6, both significantly greater than cleft individuals who followed a more negative slope of change demonstrating increasing maxillary retrognathia. This finding is supported by Dahl (1970), Krogman (1975), Bishara (1986), Smahel (1995), Hayashi (1976) and Suzuki (1996) who noted a more posterior position of the maxilla in relation to the anterior cranial base in their UCLP groups compared to controls in various age groups. Smahel (1995), Hayashi (1976) and Han (1995) found the tendency for the maxilla to become more retrognathic over time in the UCLP group than in controls. Vargervik (1981) found that, given a retrusive maxilla, orthodontic treatment of UCLP individuals can decrease the sagittal deficiency and contribute to a more forward maxillary growth.

In contradiction with our results, Bishara (1979), in a longitudinal study of UCLP individuals aged 5 to 10 years, Daskalologiannakis (1997) in a longitudinal study of UCLP individuals aged 9 to 15 years, and Aduss (1971) noted no statistically significant difference in maxillary sagittal position when compared to a control population.

***Vertical* (NSL/NL: Figure 6)**

Our results indicate that the palatal plane angle in both male and female cleft individuals is more obtuse than in non-cleft individuals. The control subjects followed a slope of growth that led to an increase in the palatal plane angle over time, while the cleft group had a relatively flat slope. The control subjects followed Bjork's predicted maxillary growth trajectory (Bjork 1966), growing both downward and forward, while the cleft group appeared to grow straight downward. Our findings are also similar to those from Dahl (1970), Han (1995), Suzuki (1996), and Horswell (1988), who reported a significantly more obtuse palatal plane angle in UCLP individuals when compared to controls at various stages of growth from 6 months to 20 years of age. In contradiction to our study, Smahel (1995) noted a decrease in the palatal plane angle over time in UCLP subjects. This observation was only a trend in our male UCLP sample.

Jaw relationship changes

***Sagittal* (a-n-b: Figure 7, a-n-pg: Figure 8)**

The sagittal jaw relationships of UCLP and control individuals in the current study were similar at age 6 and then diverged over time to where a negative sagittal relationship developed in the UCLP sample. Our findings are supported in studies by Hayashi (1976) who studied UCLP individuals aged 4 to 18 years, and by Suzuki (1996) in a study of UCLP individuals at age 20. They found the a-n-b angle to be significantly smaller, or more negative, for UCLP subjects than for controls at all ages.

***Vertical* (NSL/ML: Figure 9, NL/ML: Figure 10)**

The UCLP group in our study maintained a steeper mandibular plane angle than the control group as growth progressed. As these individuals grew, the angle reduced slightly over time in all groups with more reduction in controls than in UCLP individuals (Table II). UCLP female and combined gender groups had significantly less reduction in mandibular plane angle than the control counterparts. In support of our findings, studies by Dahl (1970), Smahel (1987), Johnson (1980), Casal (1997), and Hayashi (1976) found statistically significantly greater mandibular plane angles in UCLP subjects when compared to controls at various stages of growth from 4 to 20 years of age.

Dentoalveolar changes (pr-n-a: Figure 13, L1/ML, U1/NL: Figure 14, CL/ML)

Our findings of significantly retroclined upper and lower incisors and decreased procumbency of the dentoalveolar complex in both jaws are similar to the findings of Dahl (1970), Smahel (1987), Casal (1997), Hayashi (1976) and Smahel (1995) who reported significantly retroclined upper and lower incisors in UCLP groups in comparison to control groups at various stages of growth from 4 to 20 years of age. Suzuki (1996) observed retroclined lower incisors in UCLP individuals with a more obtuse interincisal angle at age 20 when compared to controls.

We observed a steep positive slope of change in which the measurements of the incisors and dentoalveolar complex in UCLP individuals became comparable to the measurements of control individuals towards the end of growth. This is most likely due to orthodontic intervention in the UCLP population. Vargervik (1981) reported that orthodontic treatment in UCLP individuals can counteract the inhibitory forces of scaring and a tight lip on tooth eruption and dentoalveolar development and can establish proper incisal relationships.

Timing of Growth Changes – Hypothesis 2

Based on our assessment and on the proper fitting of either linear or quadratic regression lines to our data, only two angular measurements demonstrated significant curvilinear growth patterns. A curvilinear regression line versus a straight regression line would indicate that (1) growth is non-linear, or (2) at a certain point in development, growth trajectories change from one slope to another (i.e piecewise linear). The only measurements to demonstrate curvilinear changes were dentoalveolar (NL/U1 and ML/L1). Perhaps larger samples would show non-linear growth patterns in other measures, but linear growth seemed sufficient in the controls where there were more regularly times visits and less variation. None of the skeletal measurements demonstrated a specific time-point of facial growth and development at which the rate or direction of jaw growth changed due to the presence of the cleft

Gender Differences – Hypothesis 3

The most striking findings from our study are the gender differences between male and female UCLP individuals and even between male and female control individuals that were evident in many measurements and growth characteristics. Some studies have noted gender differences in UCLP populations similar to our findings. Brattstrom (1991) found a statistically significant difference in the cranial base angle n-s-ba, in which female UCLP individuals had a more obtuse angle than UCLP males. Krogman (1982) found a similar trend in his female UCLP group. Bishara (1979) noted a gender difference within a UCLP group in which there were different growth profiles in male and female cleft subjects. Other studies such as Long (1982) and Jain (1983) noted no angular measurements distinguishing UCLP males from females in subjects from 6 months to 10 years of age.

Statistically significant gender differences found in our study:

Control: Male vs. Female

Slope: s-n-pg, a-n-pg, a-n-b, NSL/ML, NL/ML

Y-intercept (Age 6): NL/ML, CL/ML

UCLP: Male vs. Female

Slope: n-s-ar, s-n-a, a-n-pg, a-n-b, L1/ML

Y-intercept (Age 6): n-s-ar, n-s-ba

Male: Unique UCLP vs Control (no female significance)

Slope: pr-n-a

Y-intercept (Age 6): none

Female: Unique UCLP vs Control (no male significance)

Slope: ML/RL, NSL/ML, NL/ML, L1/ML

Y-intercept (Age 6): n-s-ar, n-s-ba, MBL/ML, s-n-a, NSL/ML, NL/ML

Many instances in which the absolute measurements and slopes were gender specific for statistically significant differences both between and within the UCLP and control population were evident and have not been previously reported. Note that y-intercept differences between males and females at age 6 are, in some cases, due to earlier maturation of female individuals in which males follow behind by approximately 2 years. Of most interest are gender differences in slopes, which determine direction and rate of growth. These differences are indicative of gender based growth patterns; those statistically significant indicate a need for further study in this area.

Limitations

Some possible limitations of this study should be noted: (1) a somewhat modest sample size, although larger than most studies cited; (2) any potential incompatibilities of groups due to geographical or large difference between years of collection of control versus cleft information; (3) operator error in tracing / digitization; (4) limitations in taking full account of growth direction / rotational changes without use of implants; (5) differences in regularity of visits of the UCLP group versus the control group; and (6) large variability within all groups studied which limits the ability to draw generalizable conclusions.

The large variability seen both within each group studied and within the separate gender groups might explain some amount of contradictory findings reported in the past. Even though our sample was relatively limited, it was larger than many others reported. Given that control individuals had more regularly limited visits compared to UCLP individuals, statistical models were utilized to adjust for those differences while accounting for within person correlation. Moreover, we were able to determine more than one type of growth trend through statistical programs within groups of sex, gender, and cleft status individuals adjusting for age and timing of visits (unreported data). Variability of this sort was evident in every skeletal region analyzed. This finding is important because it strongly suggests that absolute measurements and growth trends used for populations are averages which may not apply well in individual prediction due to natural variation.

Conclusions

Hypothesis 1: There is no difference in selected parameters of craniofacial morphology or rate of growth between UCLP and control individuals.

- The null hypothesis is rejected in that we found many significant, consistent patterns of differences between the UCLP and control population in cranial base, maxillary, mandibular and jaw relationship measurements. The UCLP population had differences in absolute measurements and direction of growth in all of these areas. UCLP had a more obtuse cranial base angulation with less change over time than controls. UCLP had retruded maxillas with increasing maxillary retrognathia and sagittal jaw discrepancy throughout development. UCLP had a more obtuse palatal plane angulation that did not change over time; controls experienced a clockwise growth rotation. UCLP mandibular plane angle was larger and did not decrease over time as occurred in controls. UCLP maxillary and mandibular incisors began retroclined and increased proclination throughout growth to eventually match controls.

Hypothesis 2: There is no specific time-point of facial growth and development at which the rate or direction of growth of the cranial base or maxilla changes due to the presence of a cleft.

- The null hypothesis cannot be rejected as we failed to fit any non-linear regression lines to any of our skeletal measurements which would indicate that most growth, even in UCLP individuals occurs in a linear fashion. Only dentoalveolar changes were obviously non-linear. However, a larger study might find significant nonlinear skeletal growth.

Hypothesis 3: There is no gender difference in the craniofacial morphology or rate of growth within or between UCLP and control groups.

- The null hypothesis is rejected due to the multiple examples in which there were statistically significant absolute measurement and slope differences between male and female UCLP individuals and even between male and female control individuals. These gender differences have not been previously reported.

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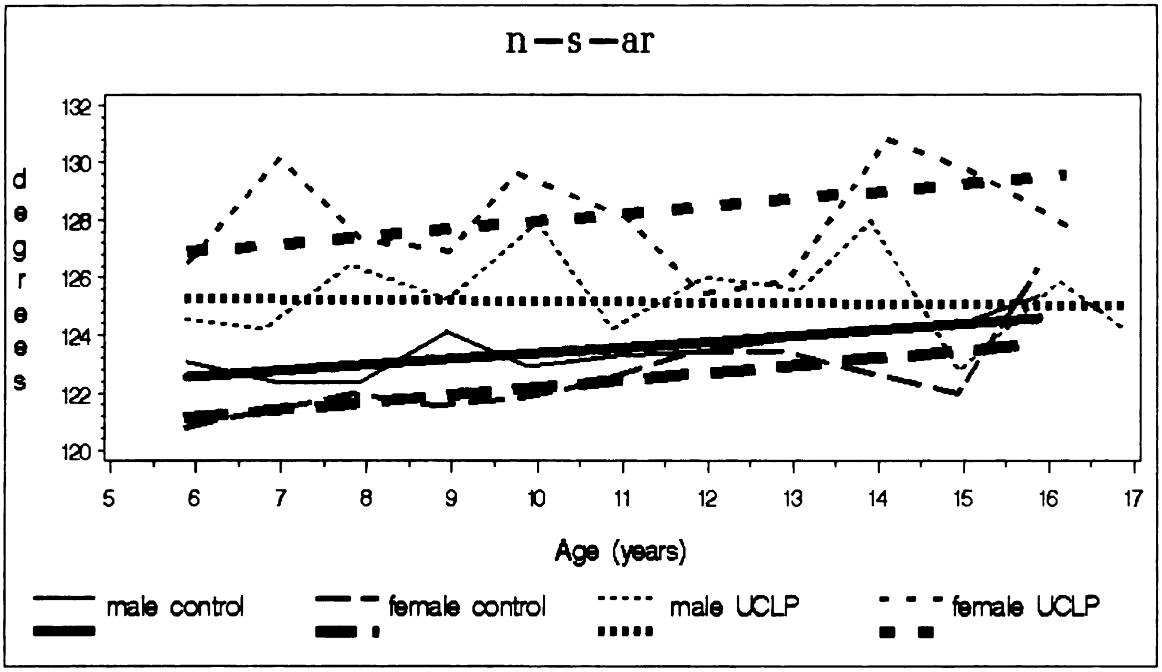
Error Calculations	n-s-ar	n-s-ba	n-s / s-arp	ML/RL	MBL/ML	s-n-a	s-n-pg	s-n-sm
DIGITIZING								
Bland Altman								
Mean	0.09	-0.09	0.01	-0.02	0.06	0.07	0.01	0.03
S.D.	0.35	0.37	0.06	0.80	0.86	0.22	0.18	0.16
Mean + 2 S.D.	0.79	0.65	0.13	1.57	1.78	0.52	0.37	0.35
Mean - 2 S.D.	-0.62	-0.83	-0.11	-1.61	-1.66	-0.37	-0.35	-0.30
Correlations								
Pearson's Product	0.98	0.96	0.99	0.99	0.97	0.98	0.99	1.00
Lin's Concordance	0.97	0.96	0.98	0.99	0.97	0.98	0.99	1.00
TRACING								
Bland Altman								
Mean	-0.69	-0.05	0.08	-0.44	-0.26	-0.19	-0.12	-0.07
S.D.	1.63	1.40	0.17	2.83	0.85	0.48	0.62	0.52
Mean + 2 S.D.	2.56	2.76	0.42	5.22	1.45	0.76	1.12	0.97
Mean – 2 S.D.	-3.94	-2.86	-0.26	-6.10	-1.97	-1.14	-1.36	-1.11
Correlations								
Pearson's Product	0.65	0.75	0.92	0.92	0.98	0.90	0.84	0.94
Lin's Concordance	0.60	0.70	0.89	0.89	0.96	0.85	0.83	0.94

Error Calculations	a-n-pg	a-n-sm	NSL/NL	NSL/ML	NL/ML	pr-n-a	U1/NL	L1/ML	CL/ML
DIGITIZING									
Bland Altman									
Mean	0.03	0.05	-0.01	-0.01	0.01	-0.06	-0.09	0.01	-0.13
S.D.	0.18	0.12	0.28	0.73	0.82	0.19	0.84	1.05	0.86
Mean + 2 S.D.	0.38	0.30	0.56	1.45	1.64	0.32	1.60	2.11	1.60
Mean - 2 S.D.	-0.32	-0.20	-0.57	-1.47	-1.63	-0.44	-1.77	-2.09	-1.85
Correlations									
Pearson's Product	0.98	1.00	0.99	0.99	0.99	0.99	0.98	0.98	0.99
Lin's Concordance	0.98	1.00	0.99	0.99	0.99	0.98	0.98	0.98	0.99
TRACING									
Bland Altman									
Mean	-0.09	-0.15	-0.63	0.21	0.84	0.25	-1.32	-0.22	-0.91
S.D.	0.44	0.48	1.02	0.71	0.87	0.74	1.73	2.65	2.11
Mean + 2 S.D.	0.79	0.81	1.41	1.64	2.58	1.72	2.14	5.08	3.31
Mean – 2 S.D.	-0.97	-1.11	-2.67	-1.22	-0.90	-1.22	-4.78	-5.52	-5.13
Correlations									
Pearson's Product	0.87	0.94	0.95	0.99	0.99	0.75	0.93	0.84	0.95
Lin's Concordance	0.87	0.94	0.92	0.99	0.99	0.72	0.89	0.82	0.93

Figure 1

Error calculation chart: Bland Altman, Pearson's Product Correlation, Lin's Concordance.



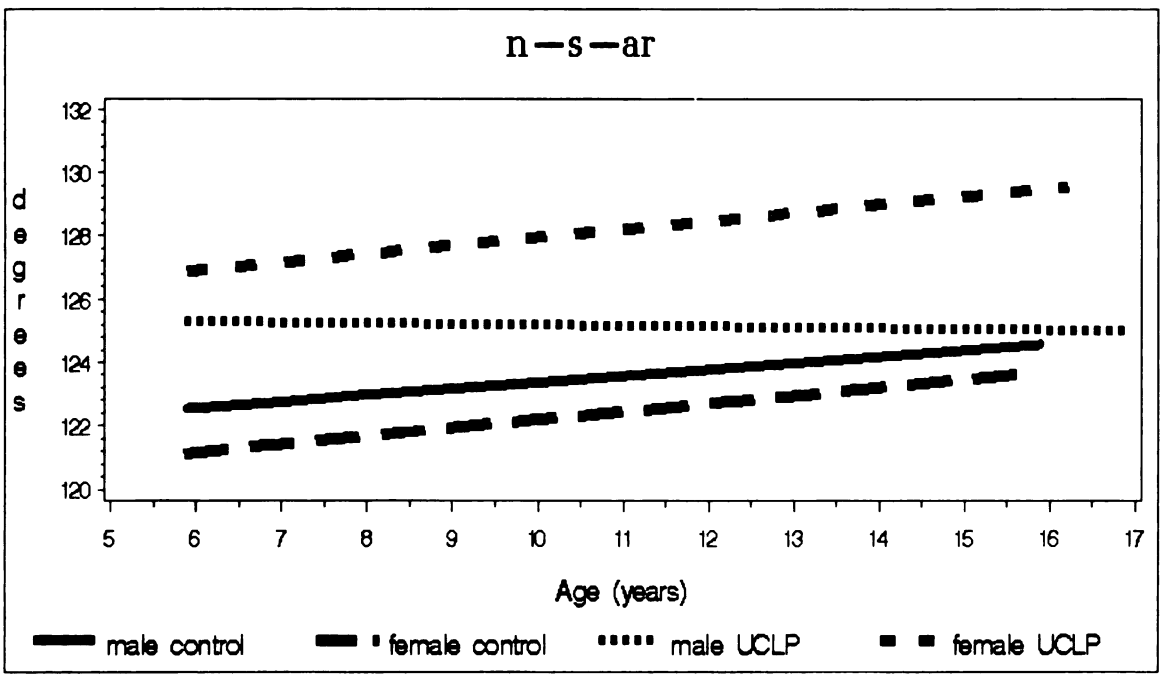
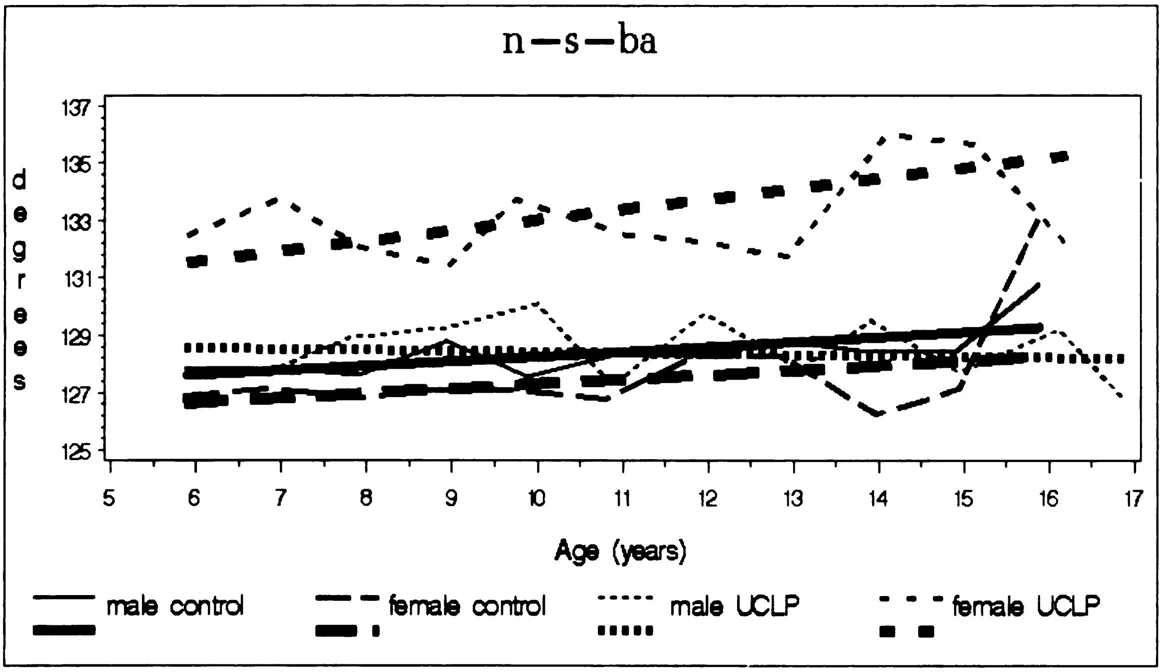


Figure 2

Top:	**Slope graph of cranial base measurement n-s-ar with mean data.**
Bottom:	**Slope graph of cranial base measurement n-s-ar without mean data.**



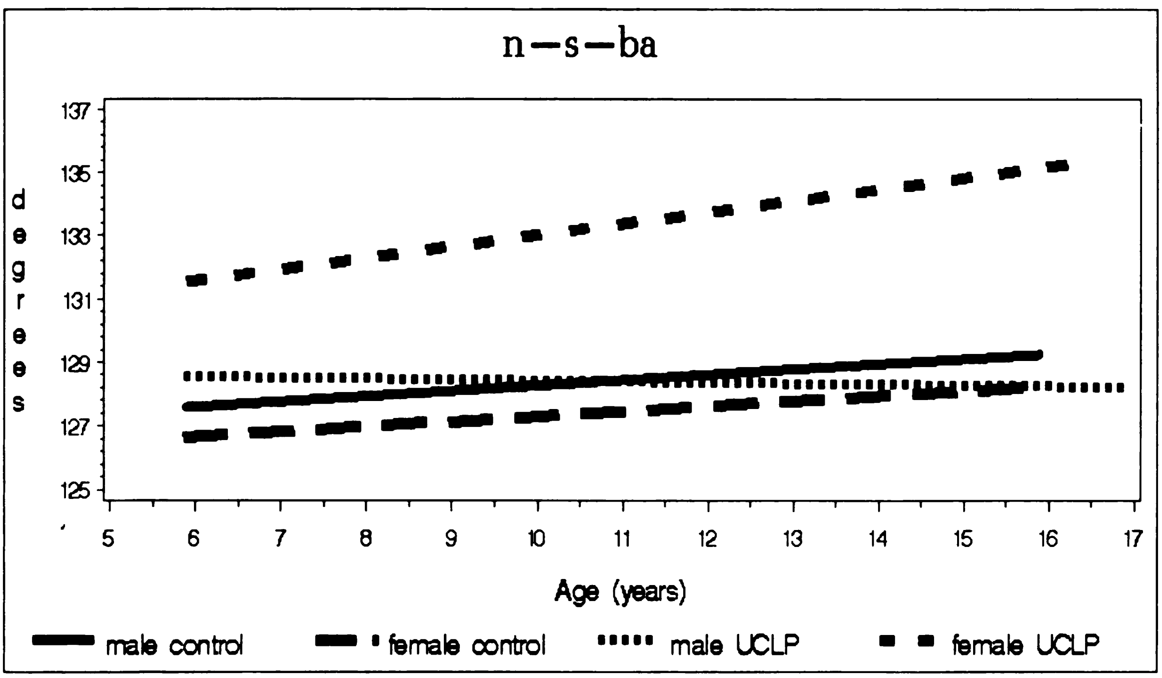
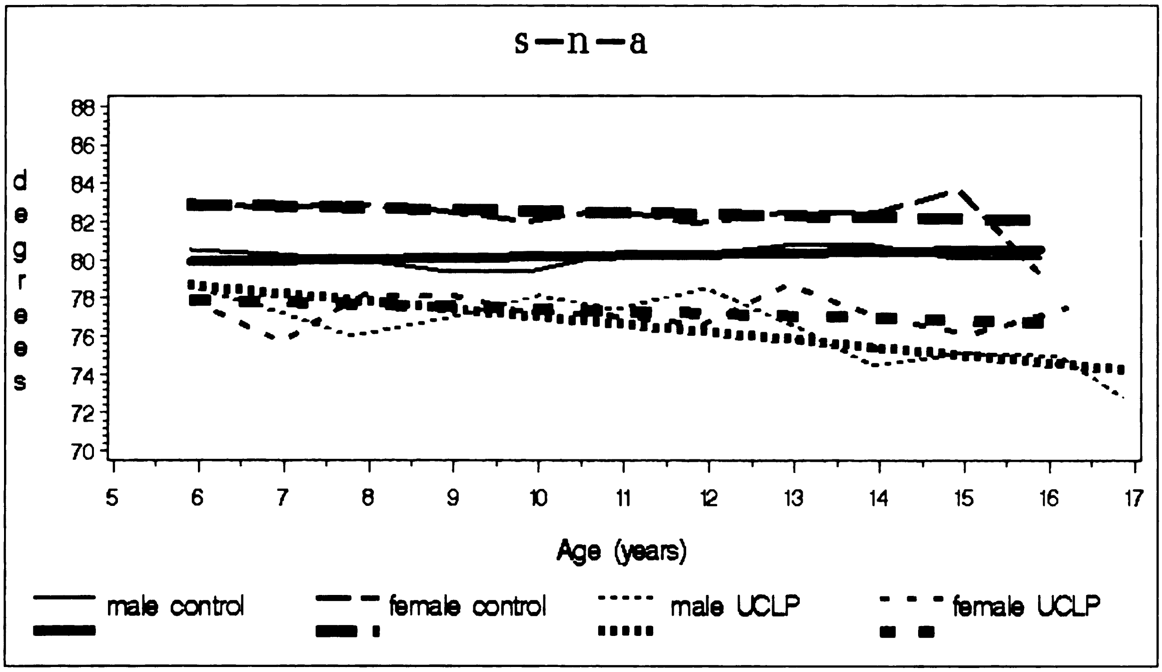


Figure 3

Top: Slope graph of cranial base measurement n-s-ba with mean data.
Bottom: Slope graph of cranial base measurement n-s-ba without mean data.



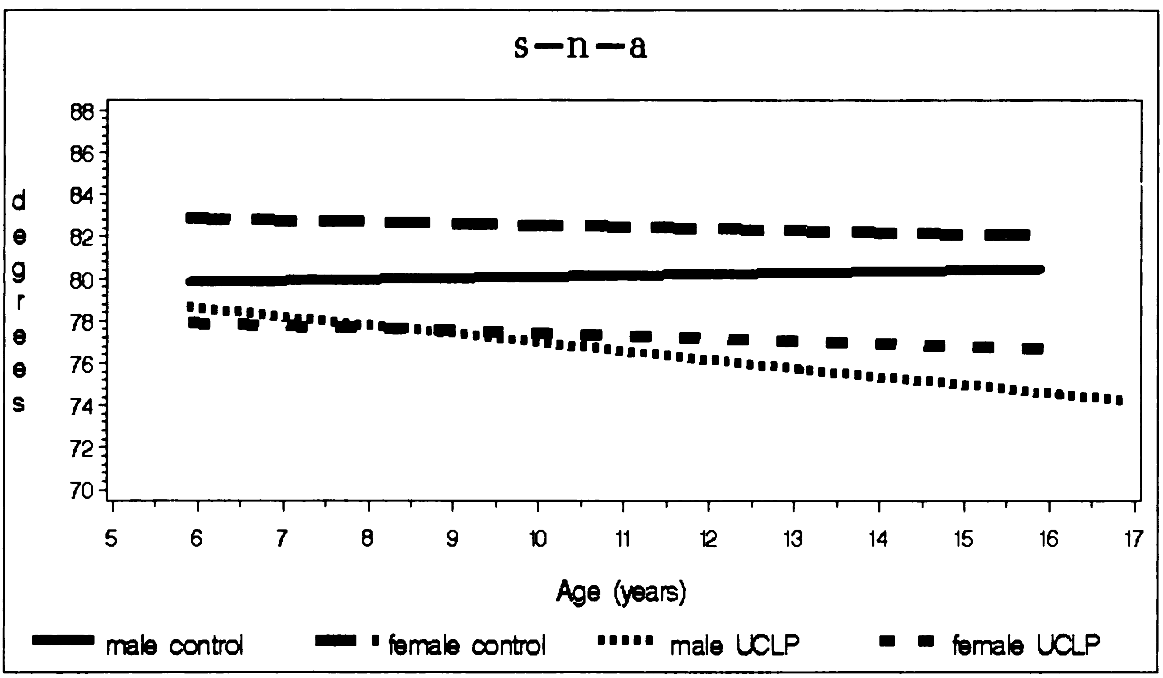
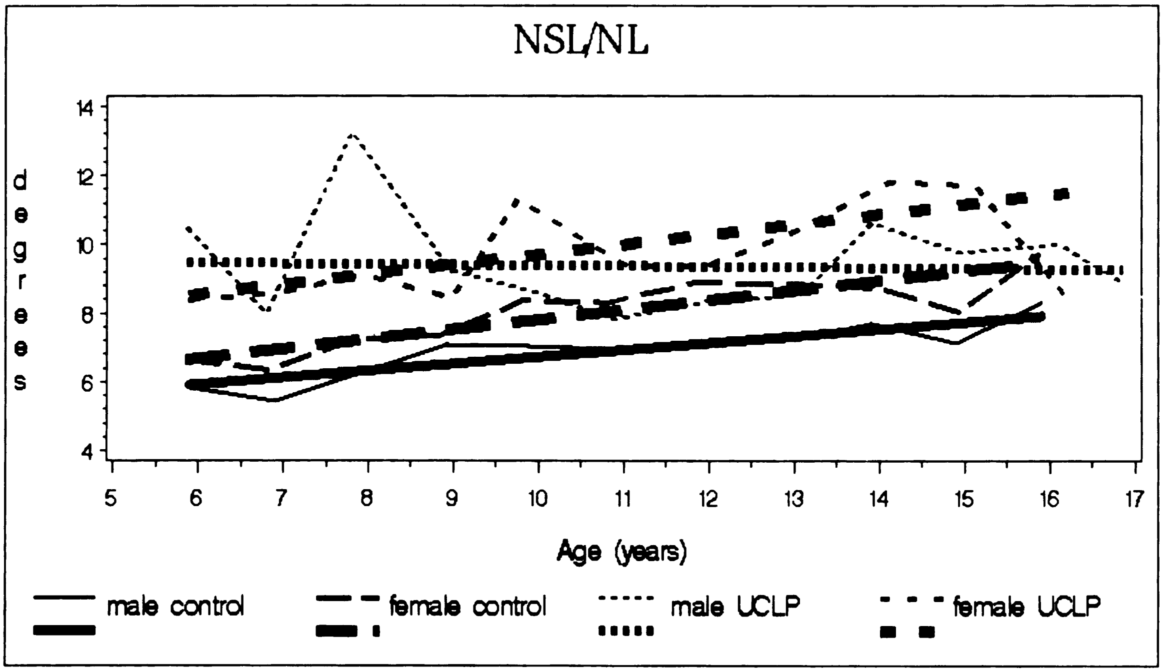


Figure 4

Top: Slope graph of maxillary sagittal measurement s-n-a with mean data.
Bottom: Slope graph of maxillary sagittal measurement s-n-a without mean data.



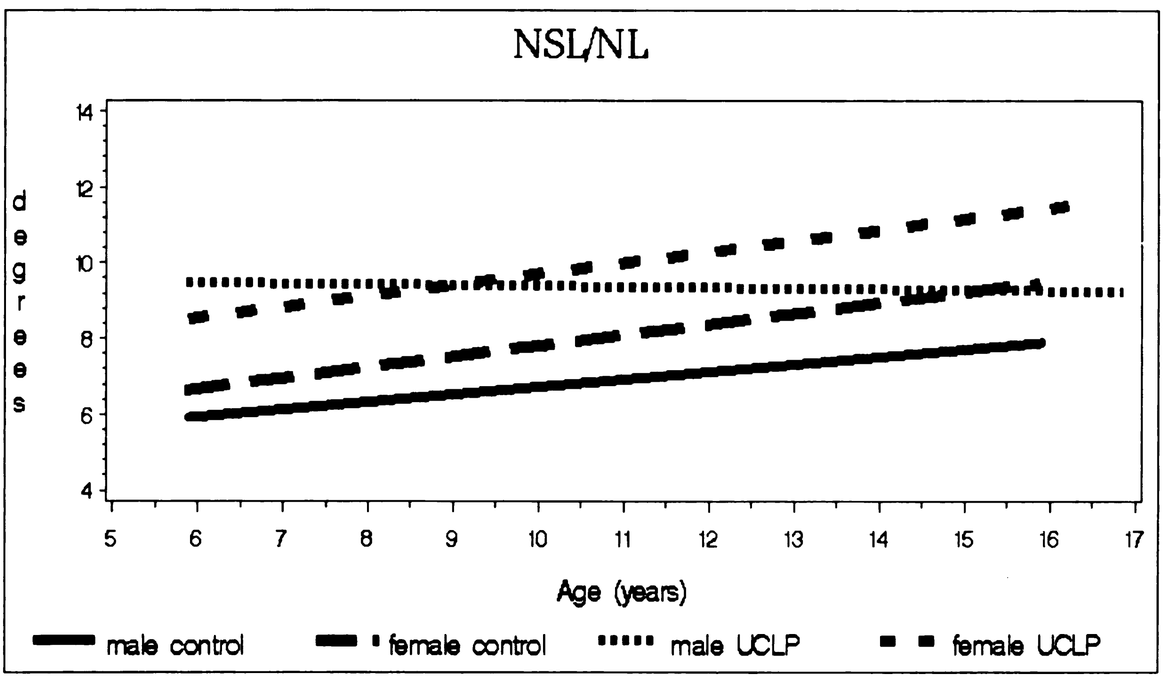
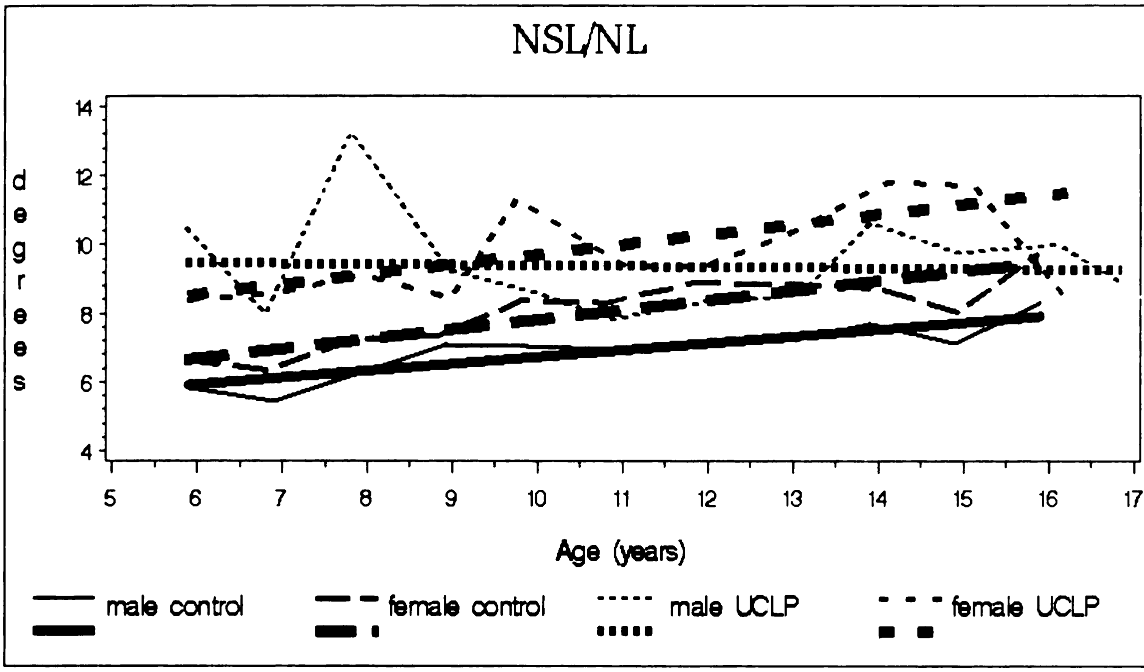


Figure 5

Top:	**Slope graph of maxillary vertical measurement NSL/NL with mean data.**
Bottom:	**Slope graph of maxillary vertical measurement NSL/NL without mean data.**



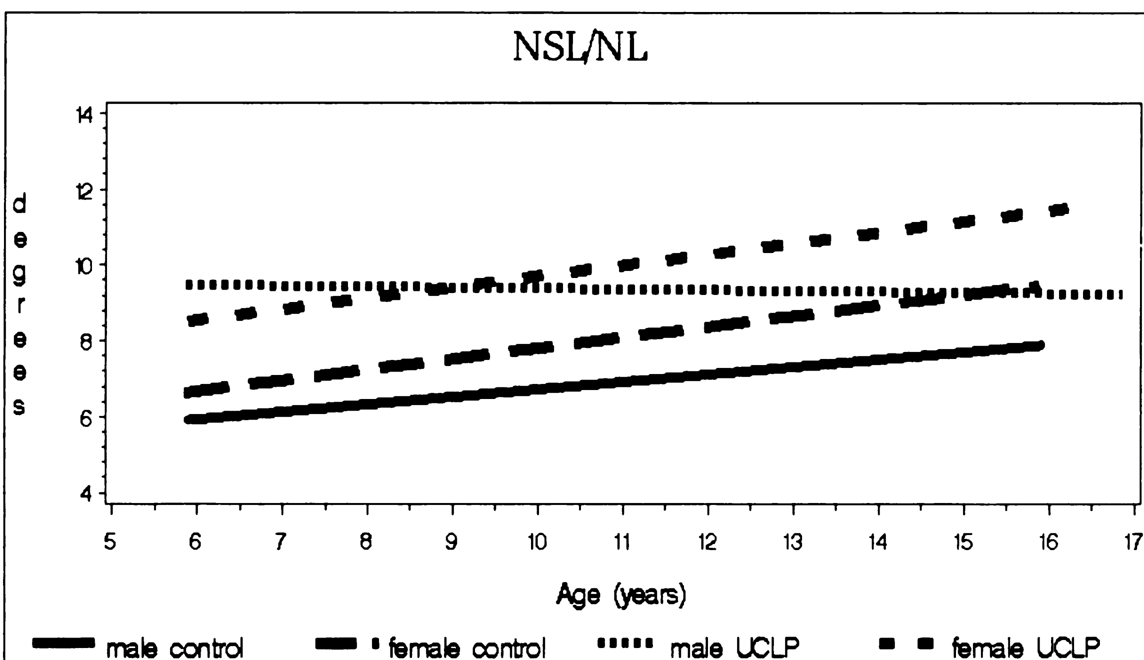
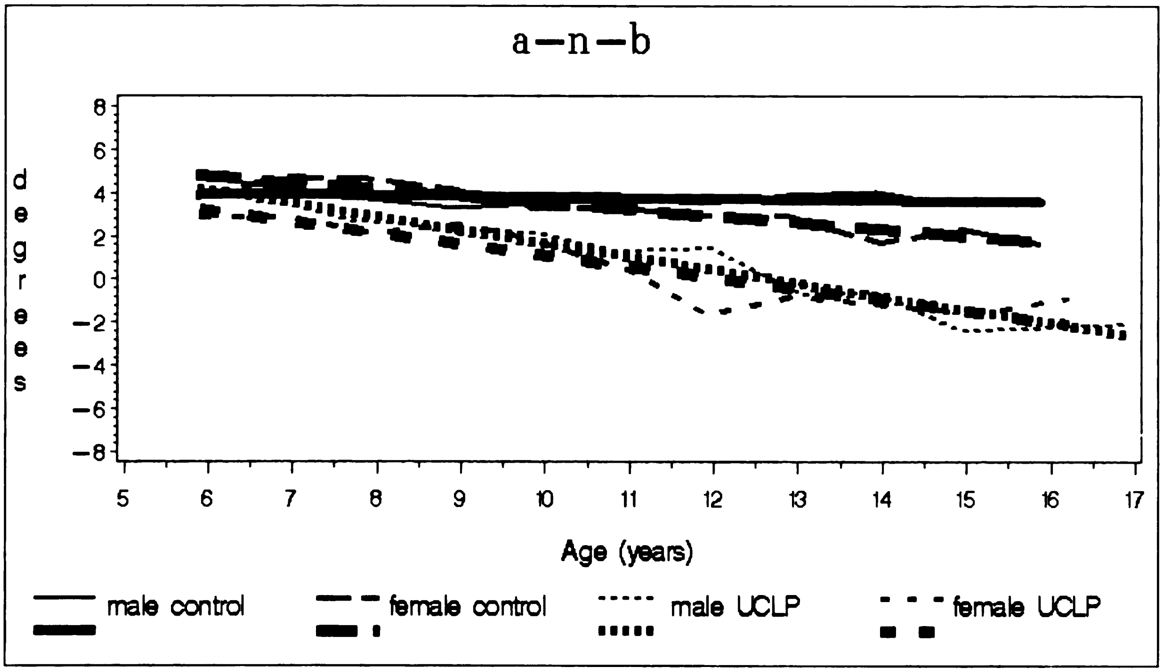


Figure 5

Top: Slope graph of maxillary vertical measurement NSL/NL with mean data.
Bottom: Slope graph of maxillary vertical measurement NSL/NL without mean data.



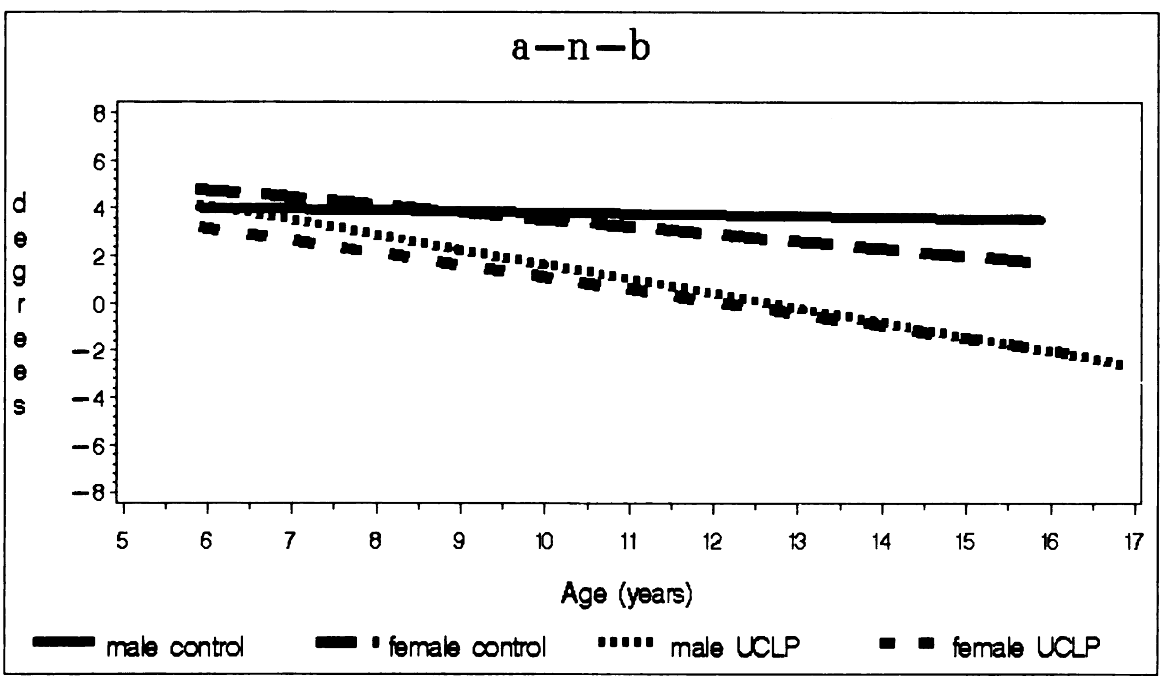
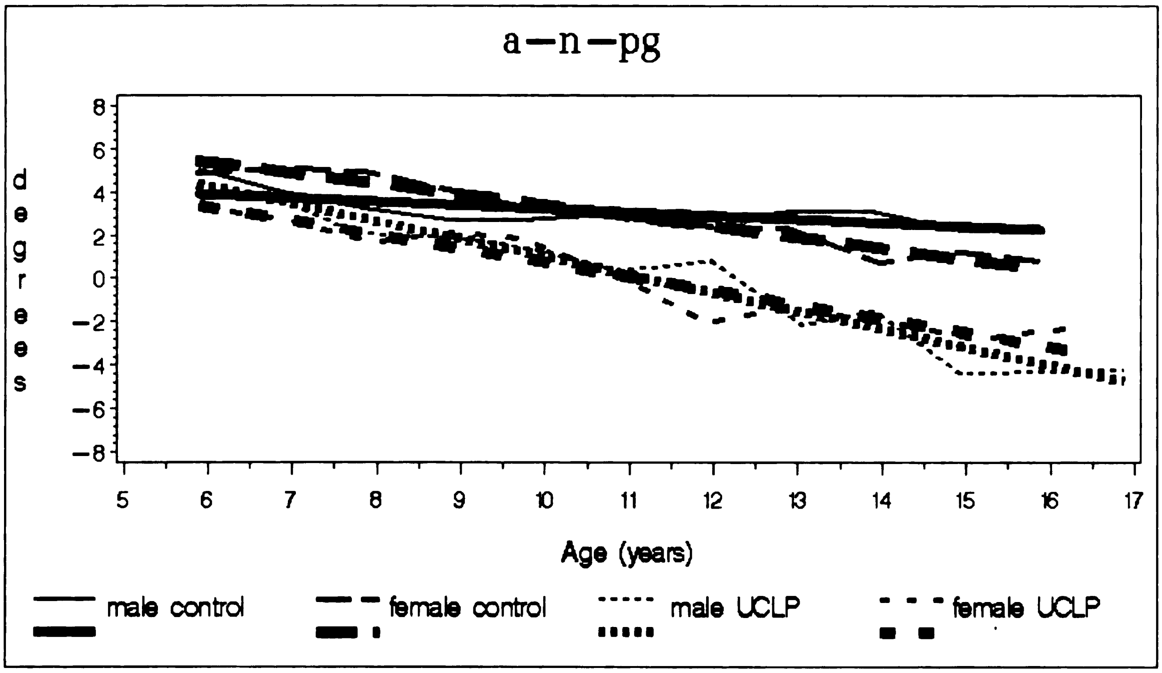


Figure 6

Top:	**Slope graph of intermaxillary measurement a-n-b with mean data.**
Bottom:	**Slope graph of intermaxillary measurement a-n-b without mean data.**



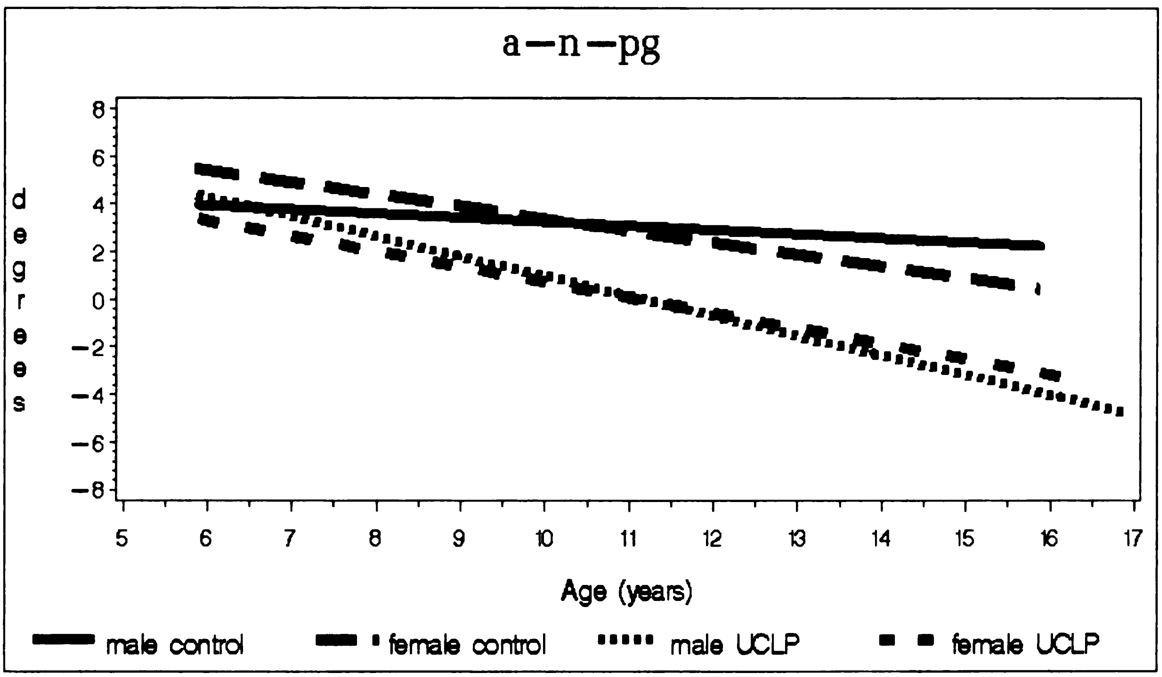
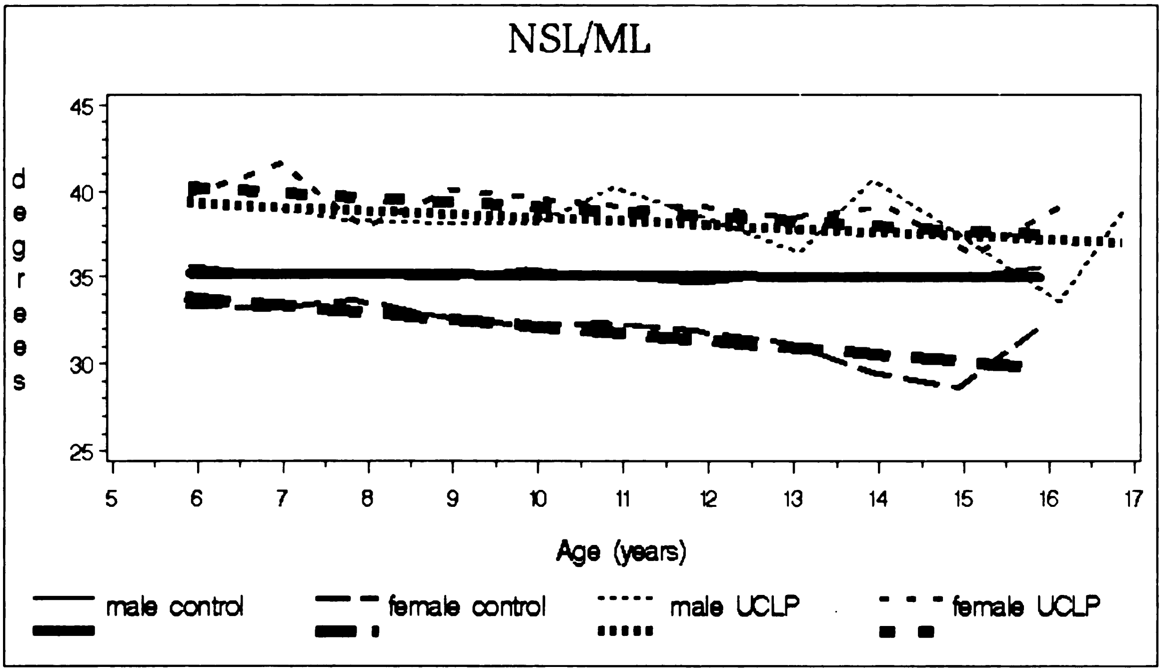


Figure 7

Top: Slope graph of intermaxillary measurement a-n-pg with mean data.
Bottom: Slope graph of intermaxillary measurement a-n-pg without mean data.



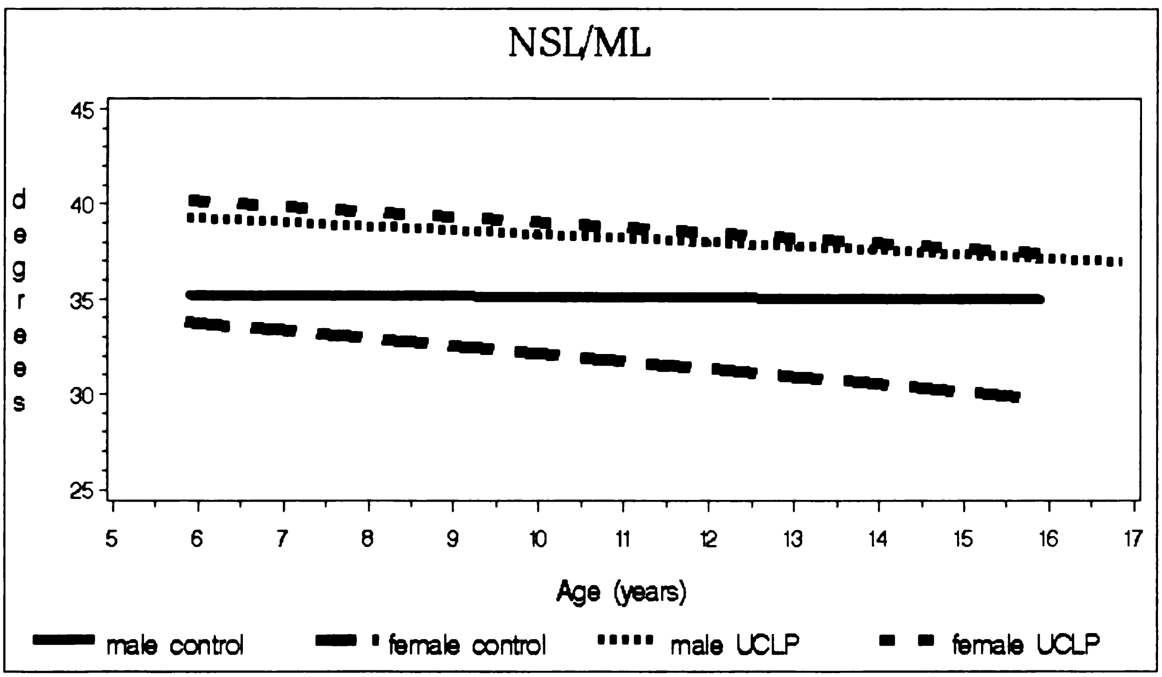
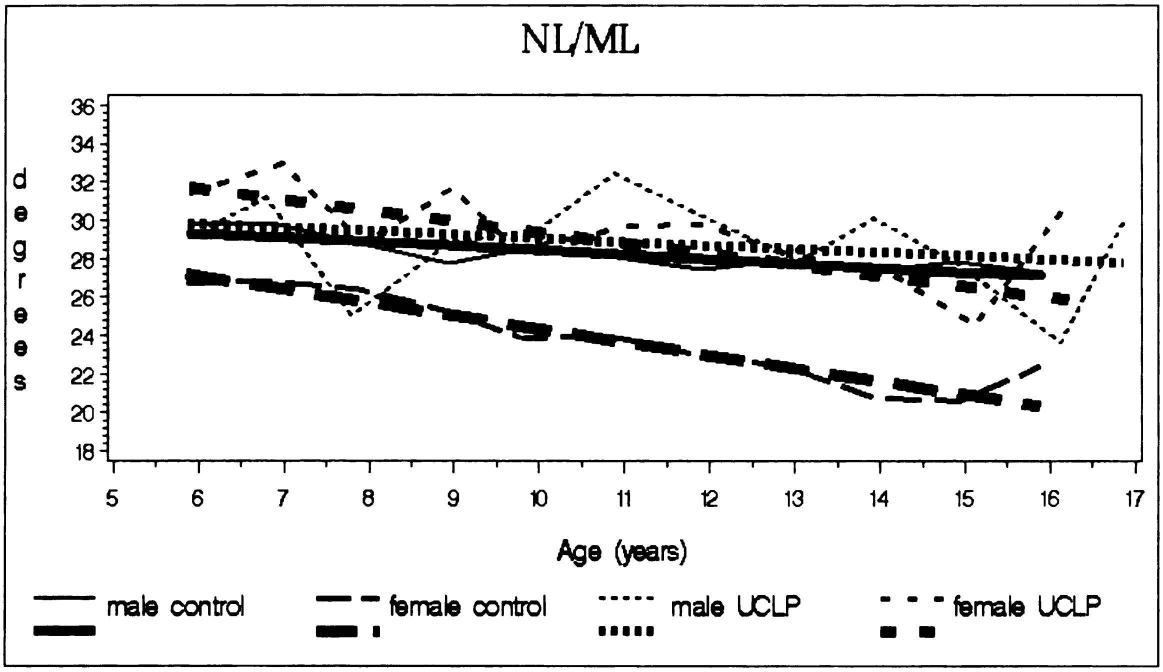


Figure 8

Top:	**Slope graph of mand. vertical measurement NSL/ML with mean data.**
Bottom:	**Slope graph of mand. vertical measurement NSL/ML without mean data.**



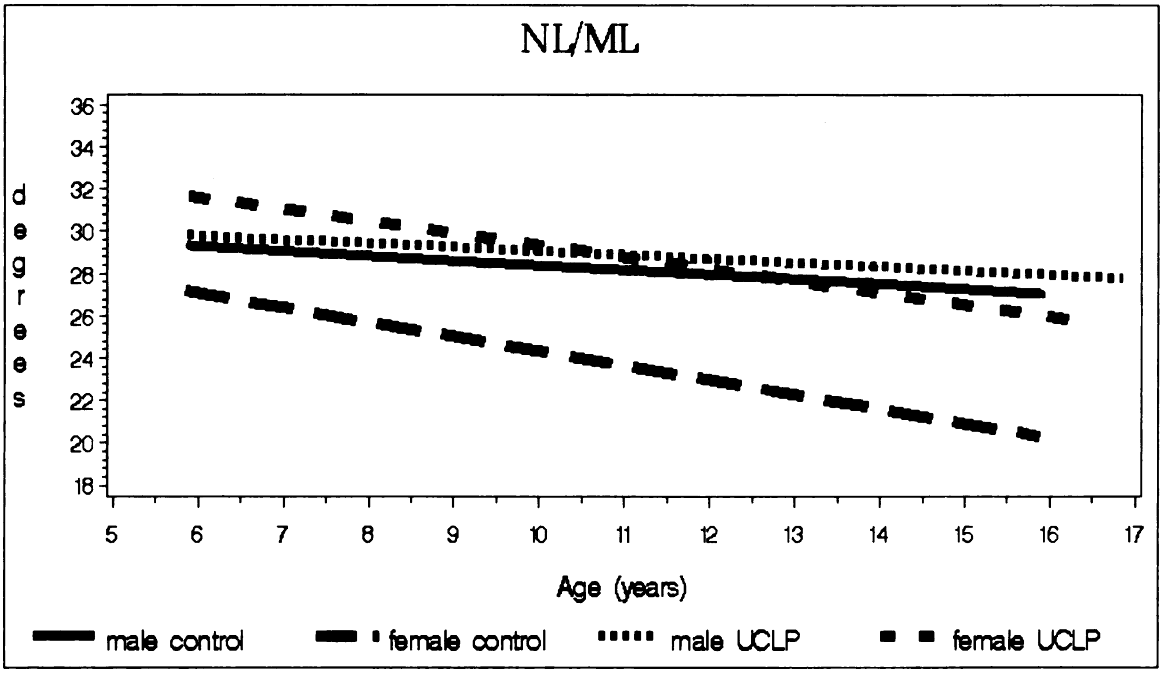
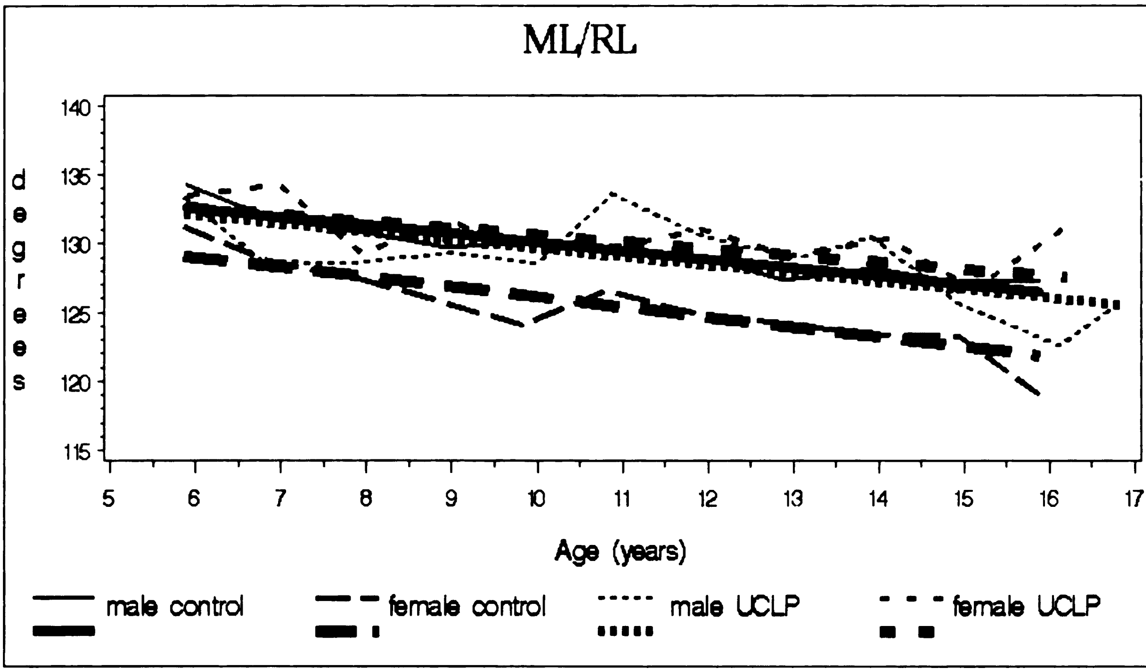


Figure 9

Top:	**Slope graph of mand. vertical measurement NL/ML with mean data.**
Bottom:	**Slope graph of mand. vertical measurement NL/ML without mean data.**



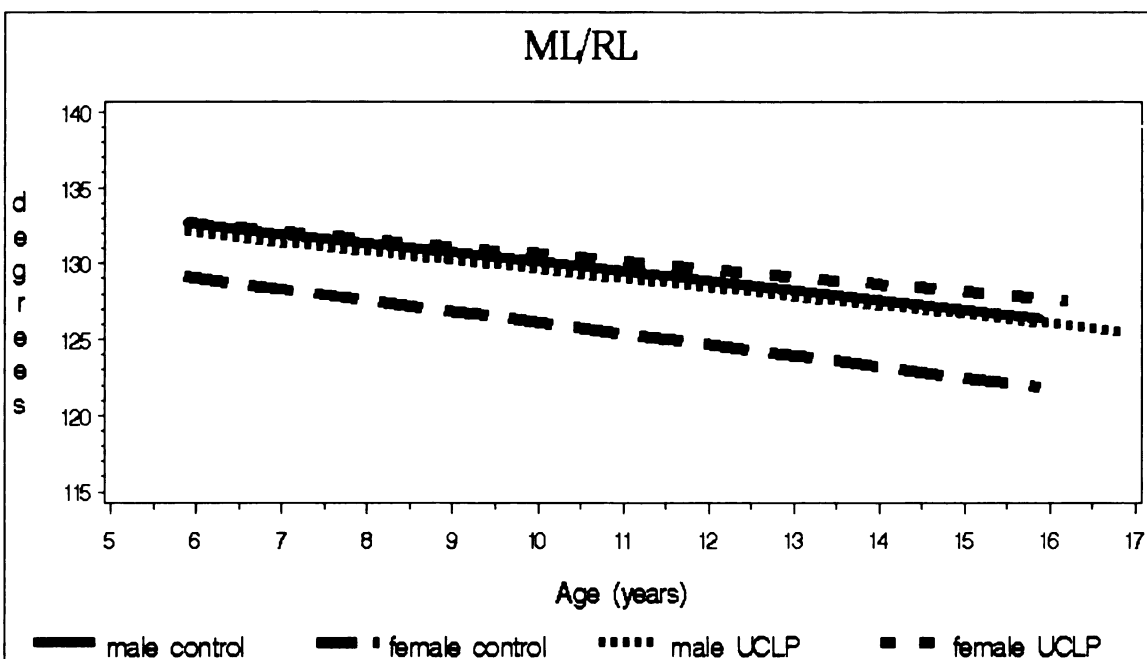
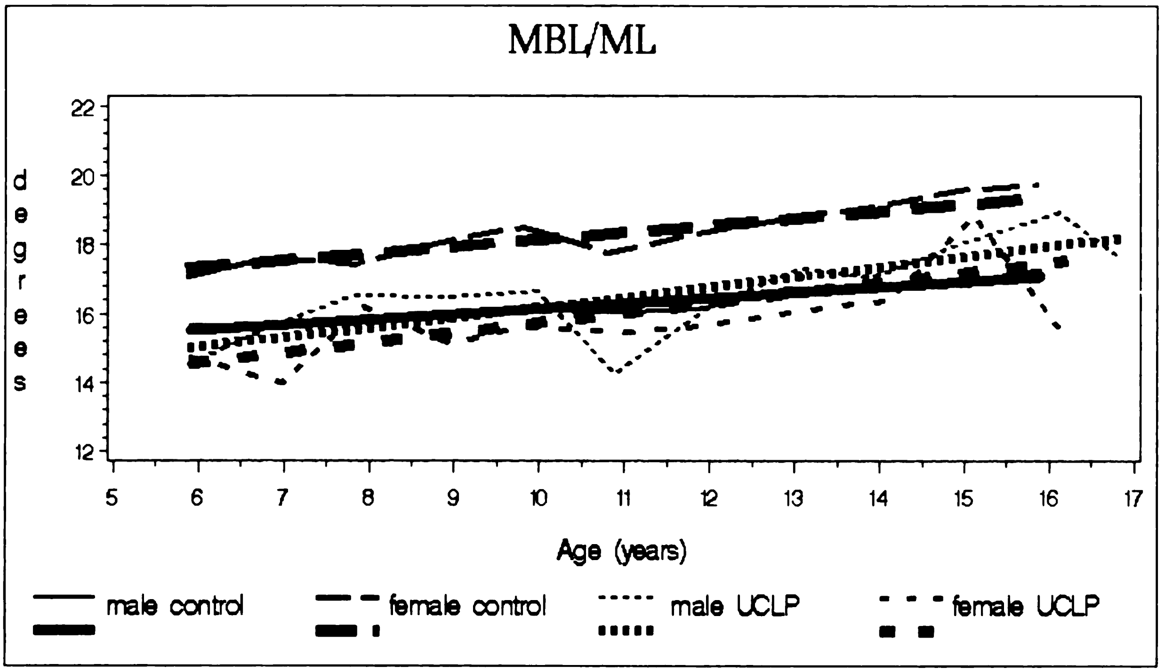


Figure 10

Top: Slope graph of mand. shape measurement ML/RL with mean data.
Bottom: Slope graph of mand. shape measurement ML/RL without mean data.



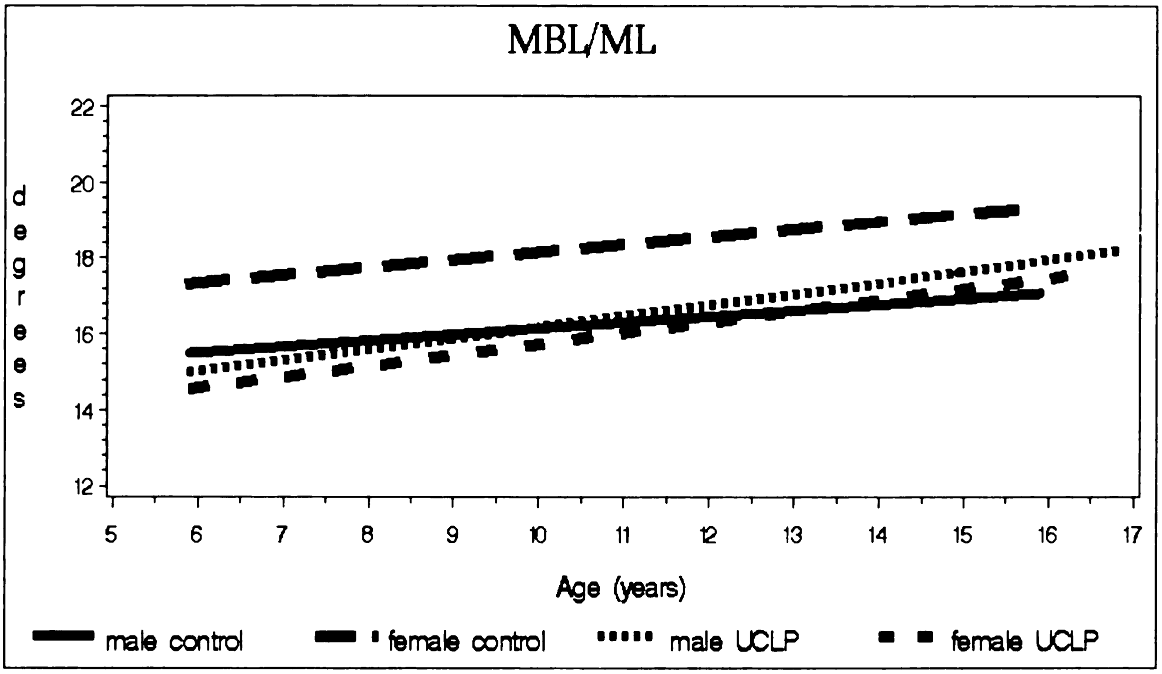
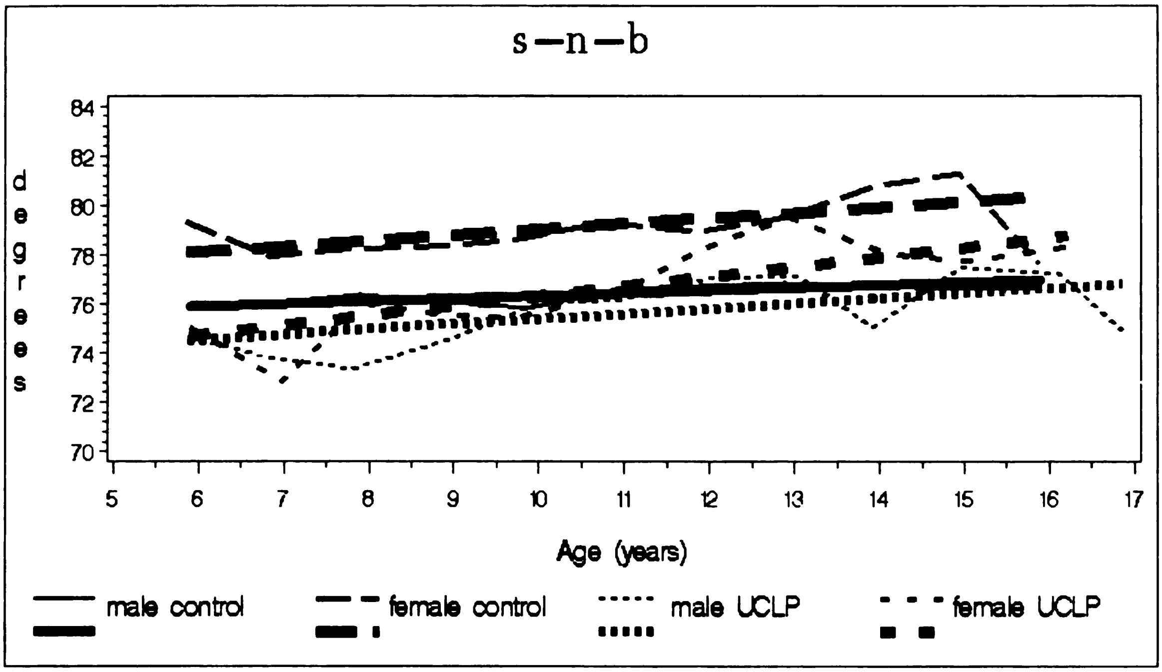


Figure 11

Top: Slope graph of mand. position measurement MBL/ML with mean data.
Bottom: Slope graph of mand. position measurement MBL/ML without mean data.



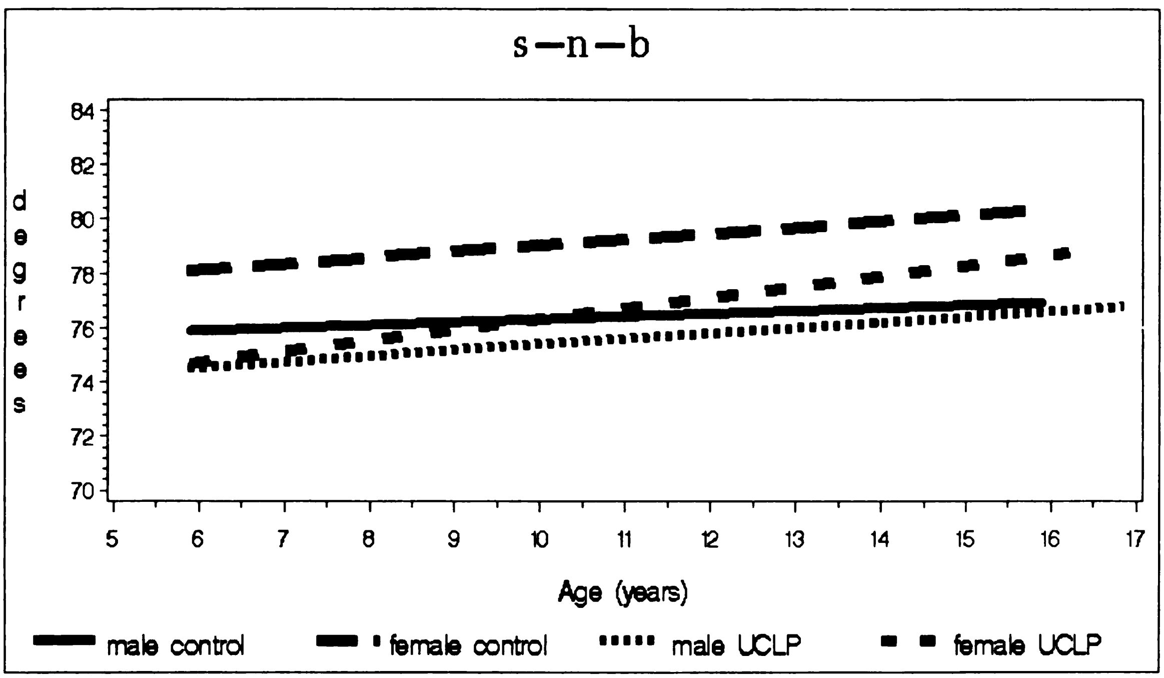
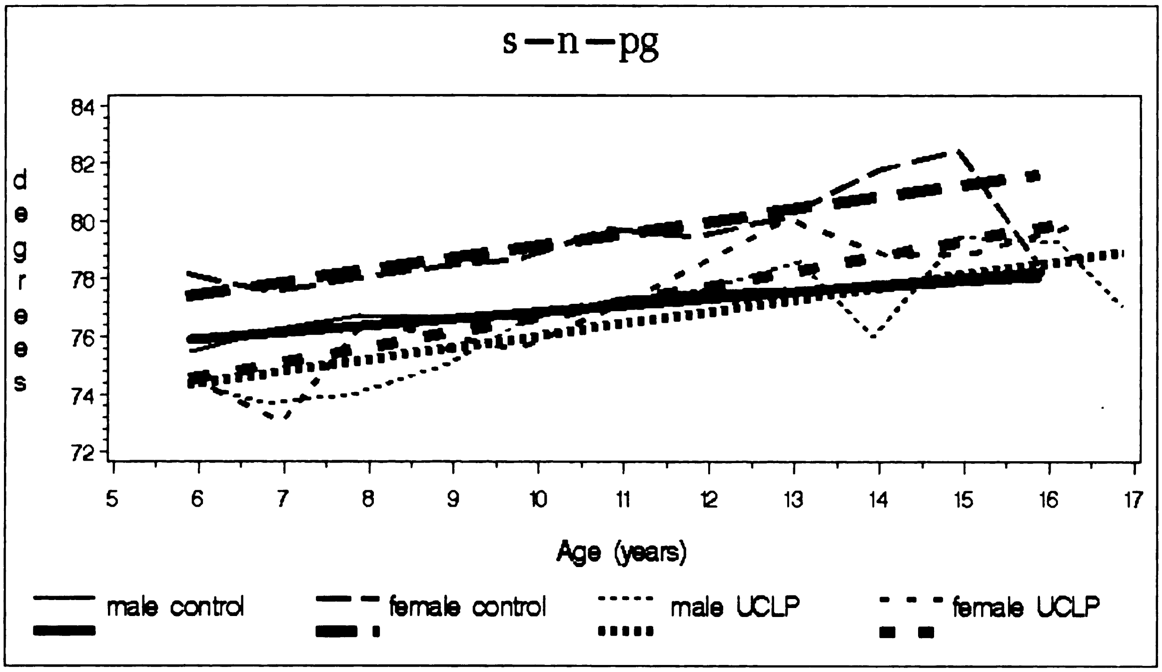


Figure 12

Top: **Slope graph of mand. sagittal measurement s-n-b with mean data.**
Bottom: **Slope graph of mand. sagittal measurement s-n-b without mean data.**



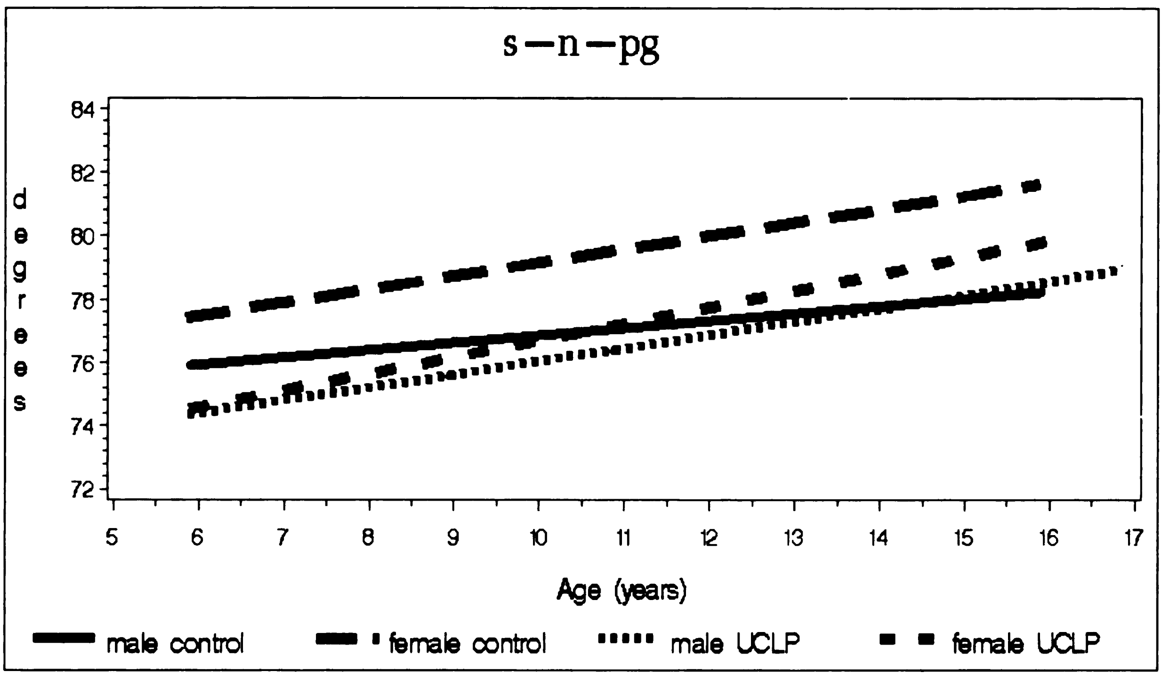
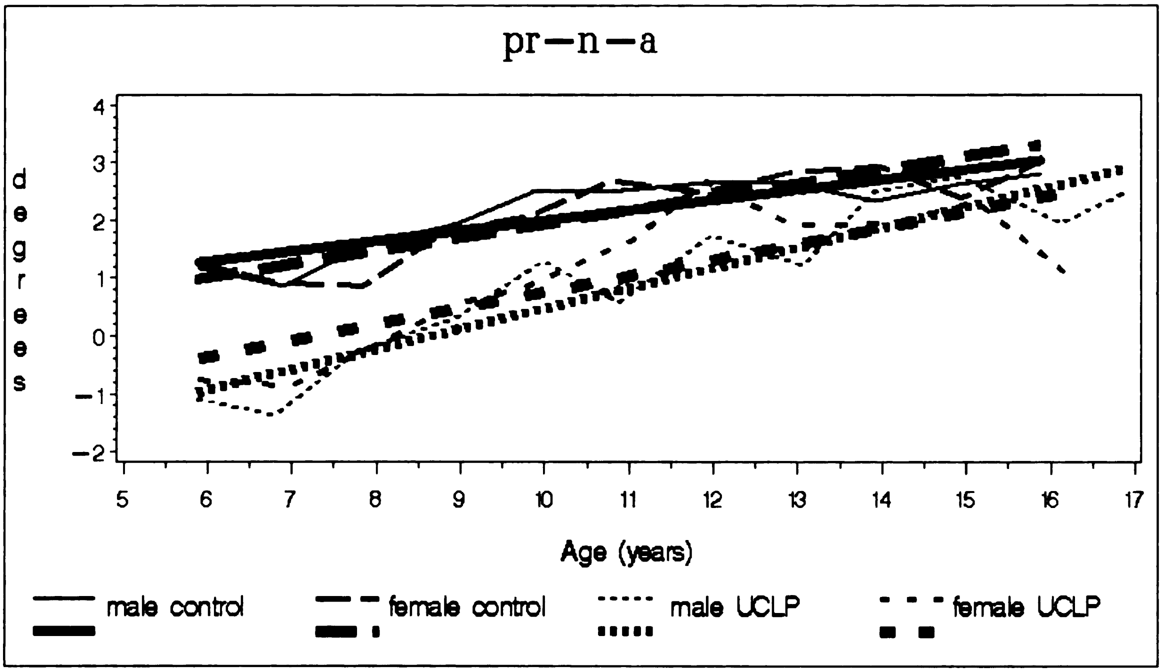


Figure 13

Top: **Slope graph of mand. sagittal measurement s-n-pg with mean data.**
Bottom: **Slope graph of mand. sagittal measurement s-n-pg without mean data.**



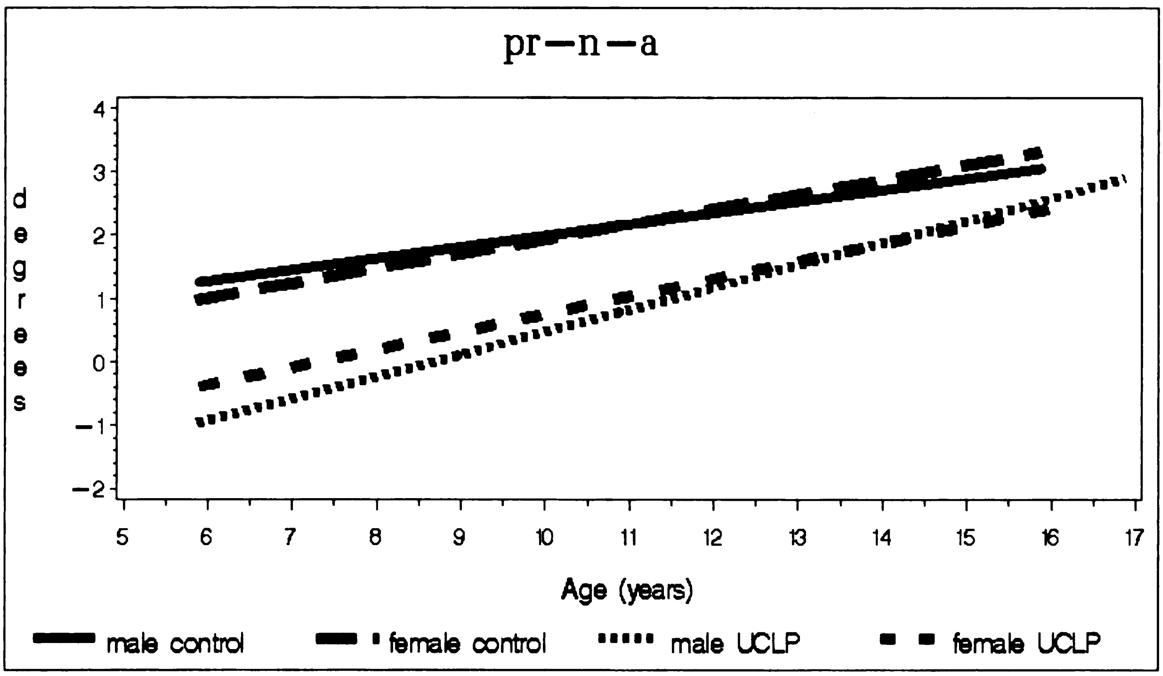
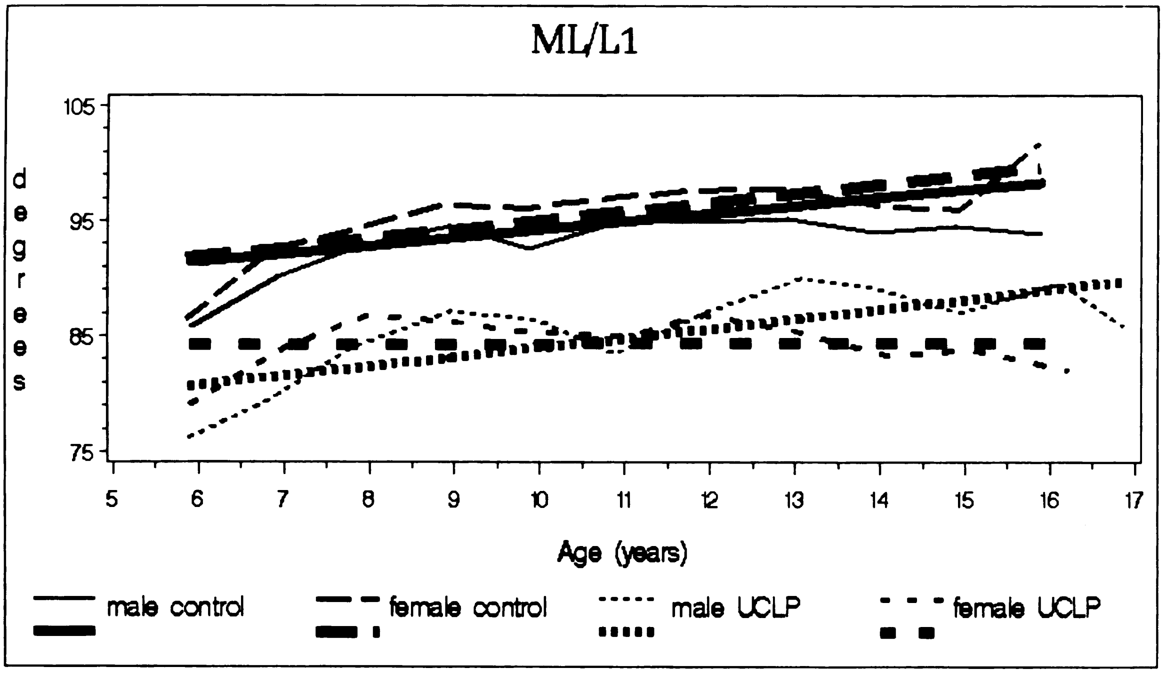


Figure 14

Top: Slope graph of maxillary dentoalveolar angle pr-n-a with mean data.
Bottom: Slope graph of maxillary dentoalveolar angle pr-n-a without mean data.



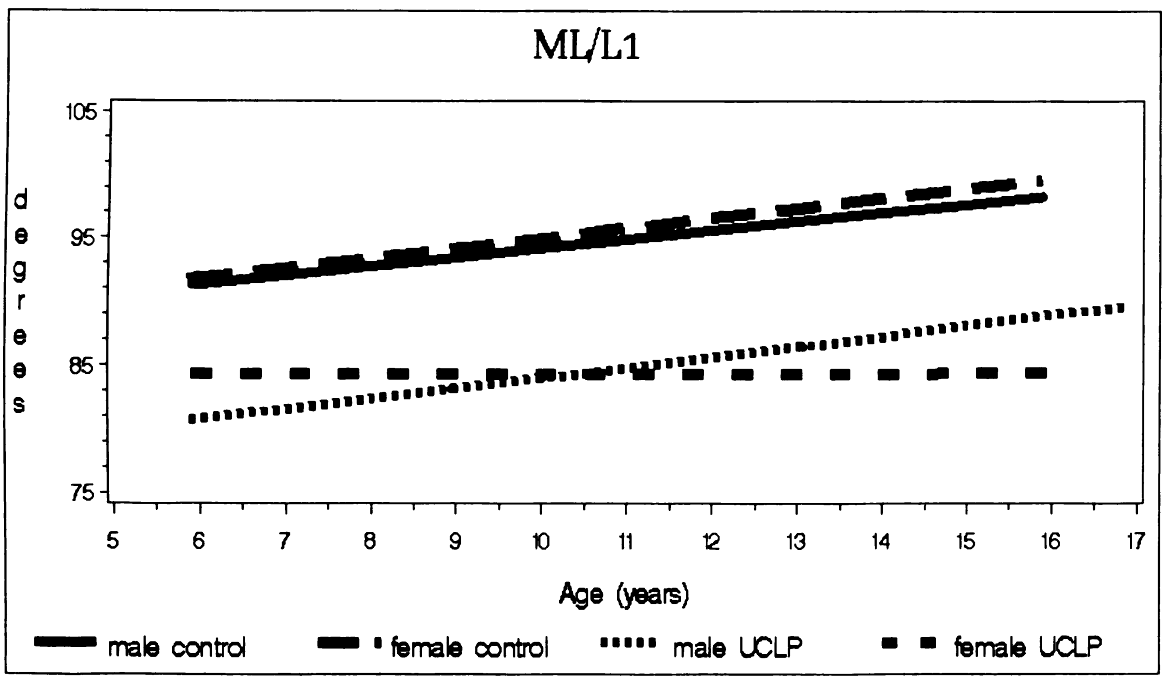
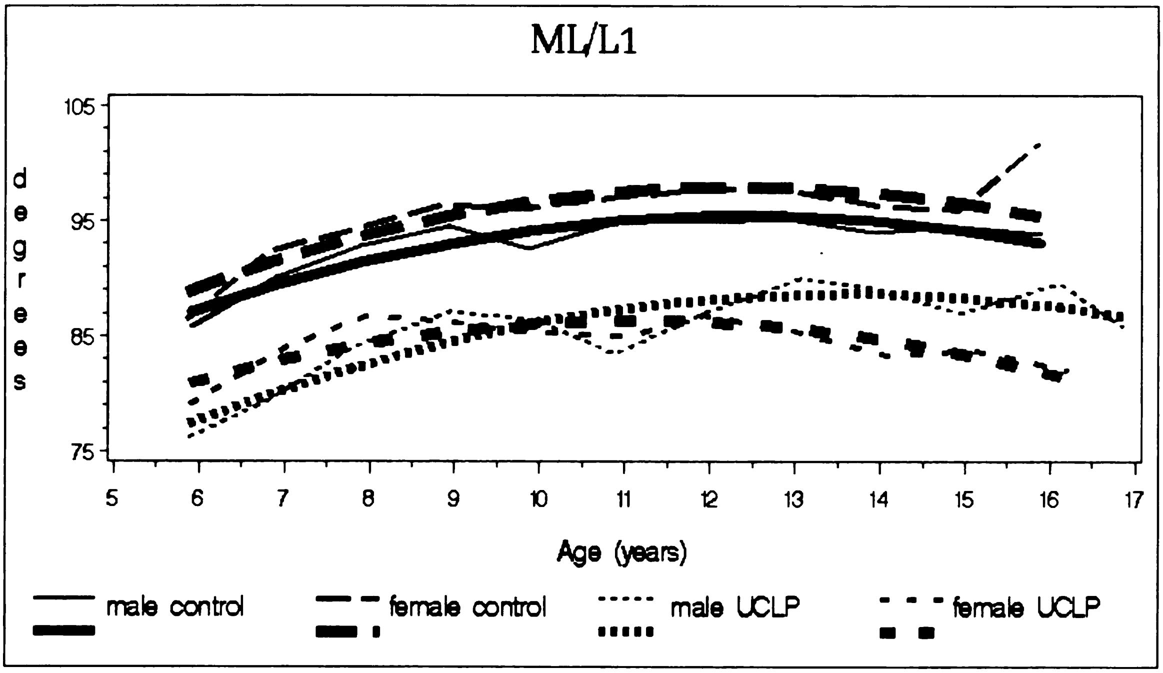


Figure 15

Top: **Slope graph of mand. incisor inclination ML/L1 with mean data.**
Bottom: **Slope graph of mand. incisor inclination ML/L1 without mean data.**



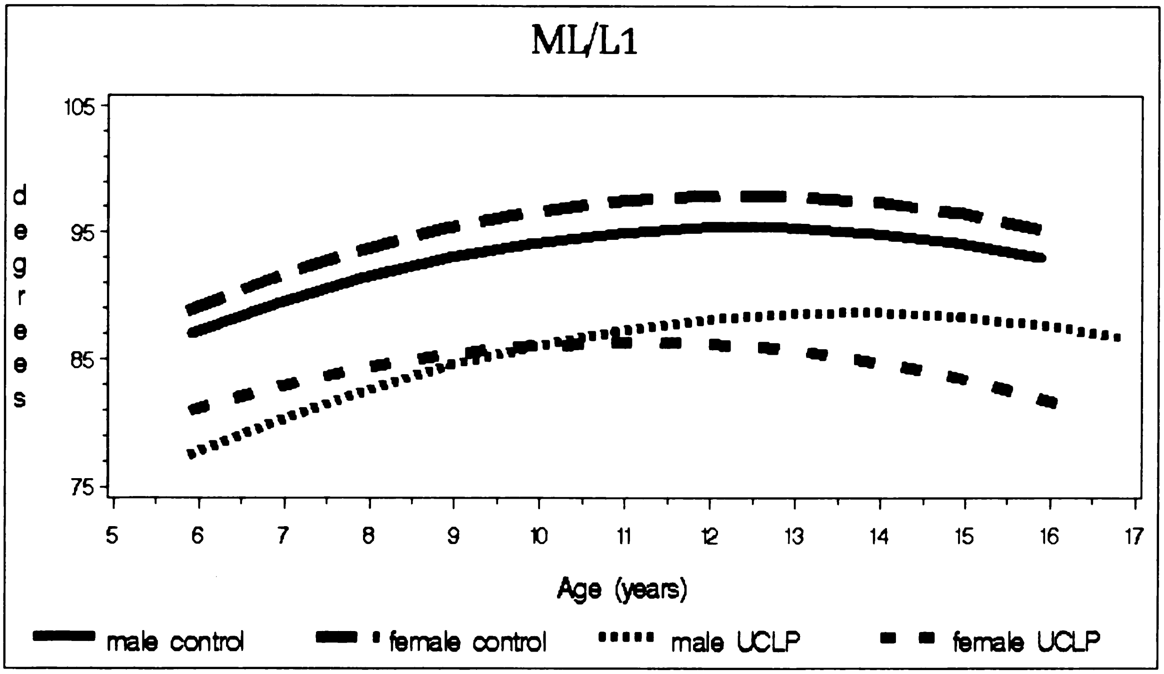
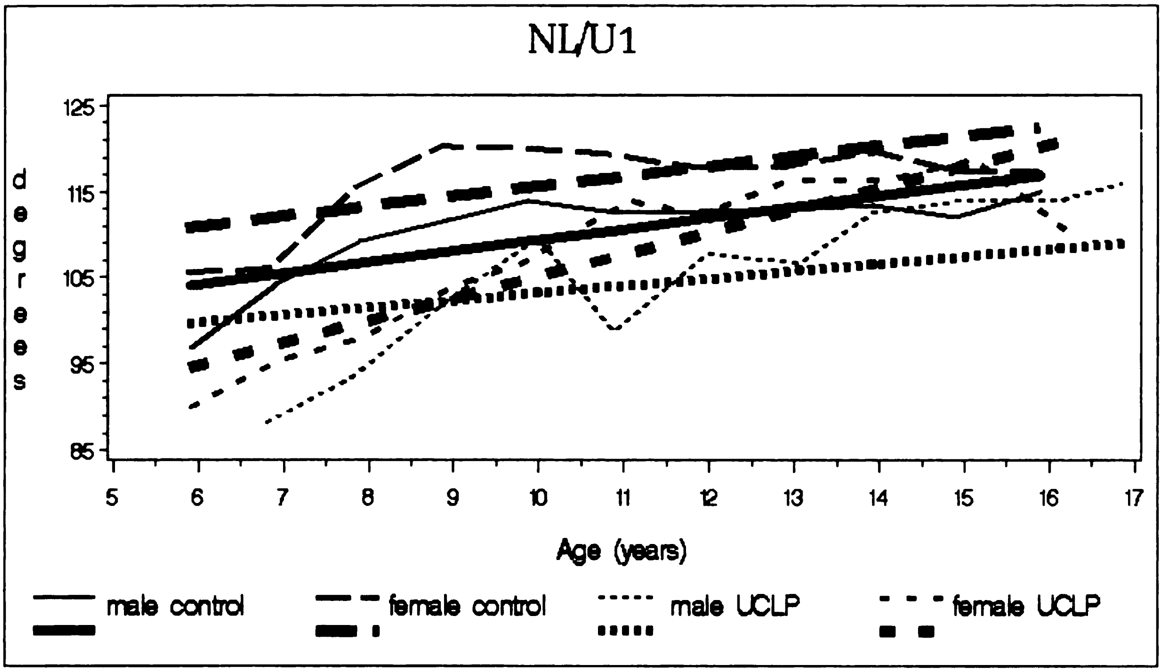


Figure 16

Top: **Curvilinear graph of mand. incisor inclination ML/L1 with mean data.**
Bottom: **Curvilinear graph of mand. incisor inclination ML/L1 without mean data.**



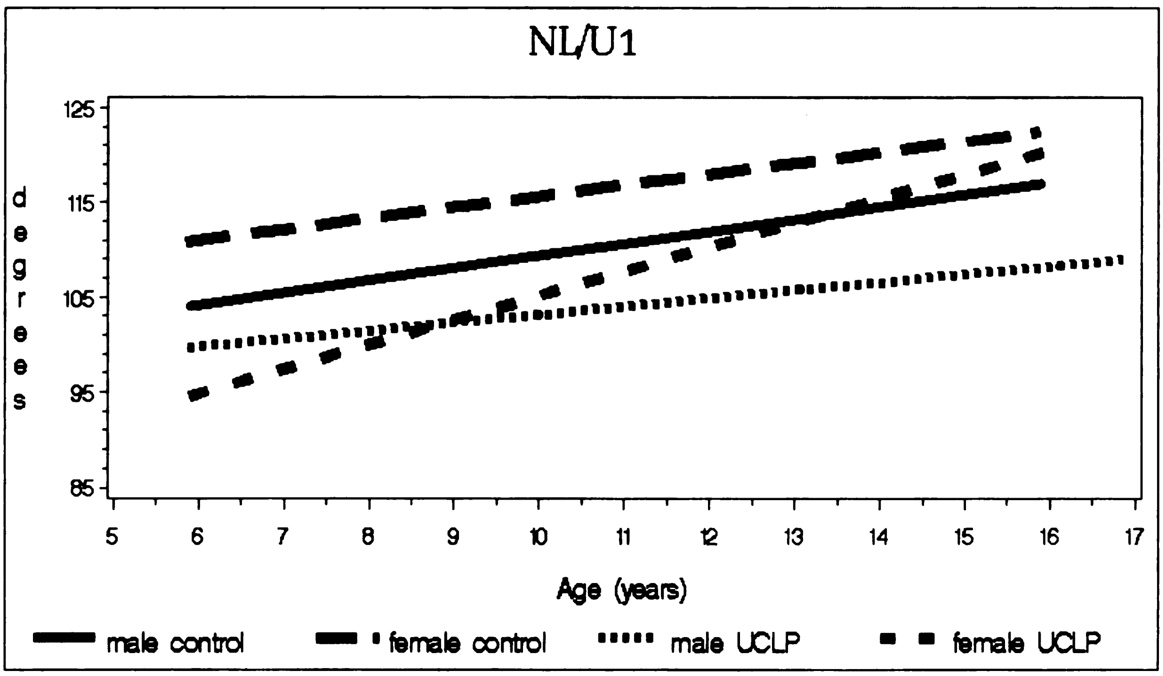
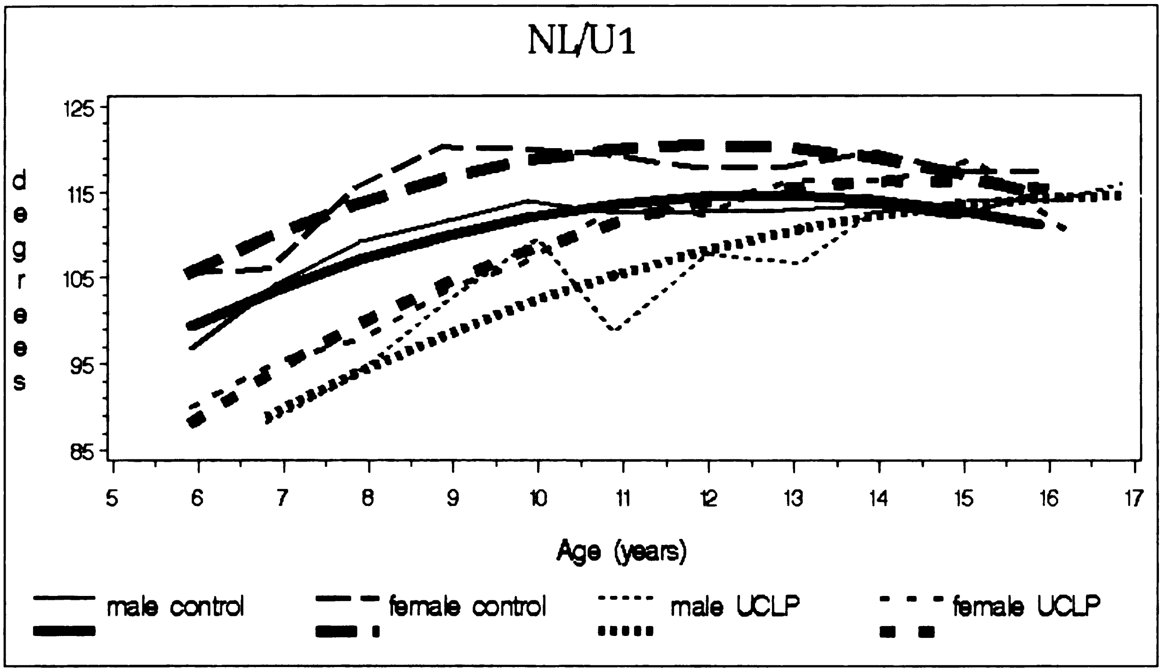


Figure 17

Top:	**Slope graph of maxillary incisor inclination NL/U1 with mean data.**
Bottom:	**Slope graph of maxillary incisor inclination NL/U1 without mean data.**



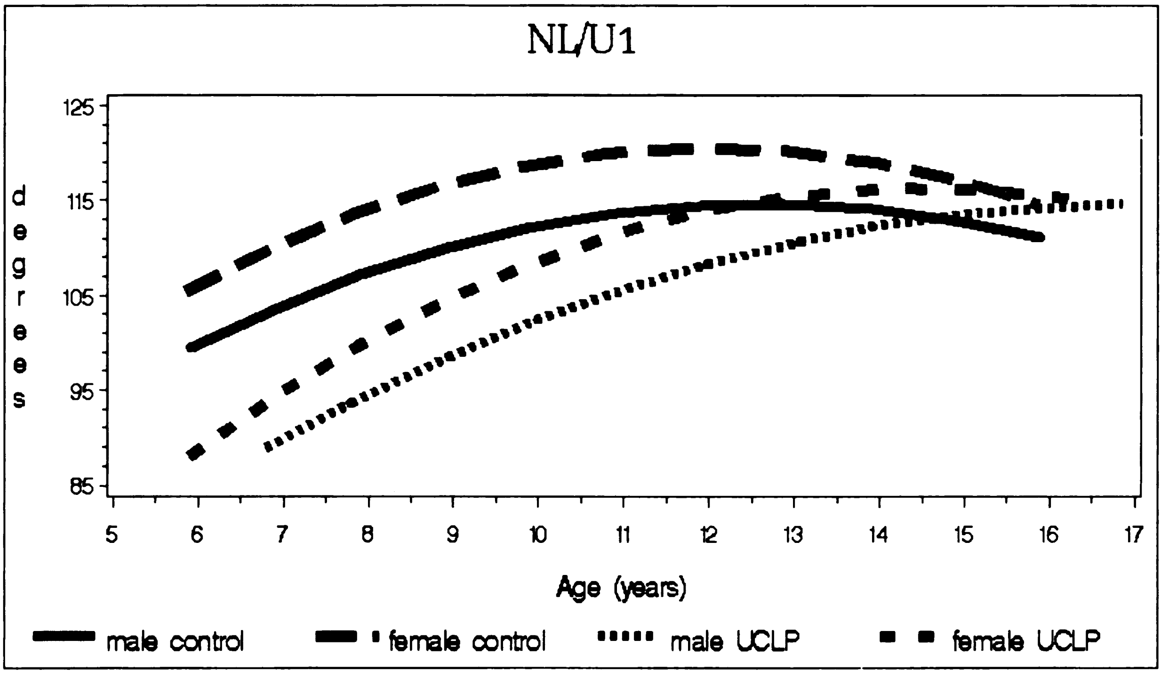
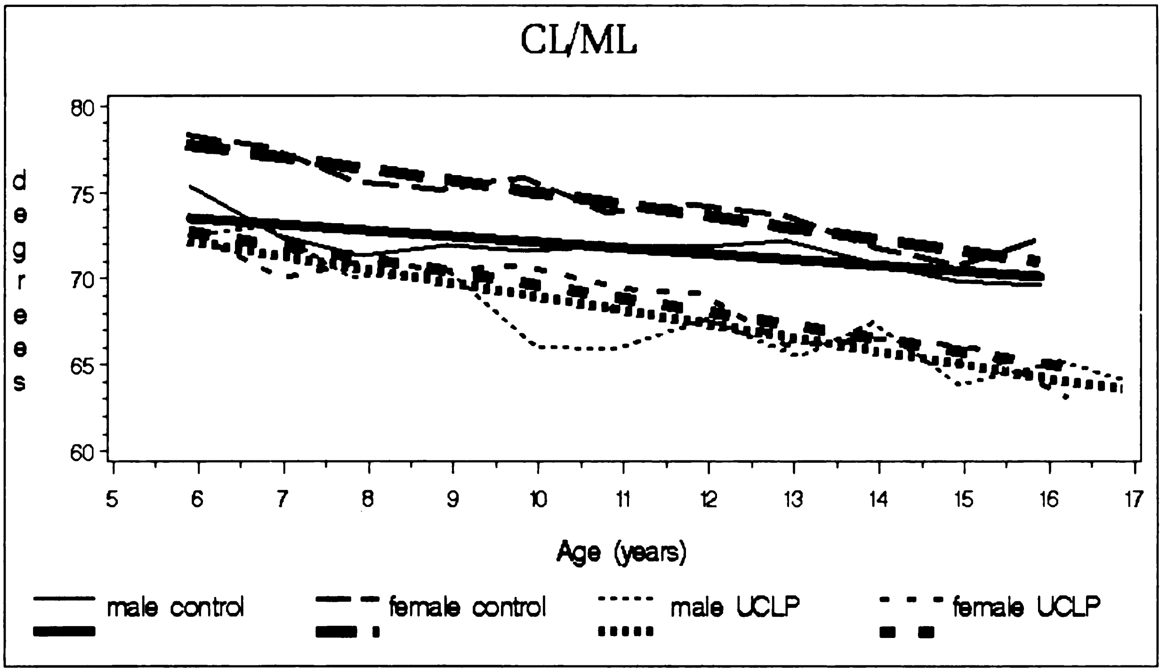


Figure 18

Top: Curvilinear graph of maxillary incisor inclination NL/U1 with mean data.
Bottom: Curvilinear graph of maxillary incisor inclination NL/U1 without mean data.



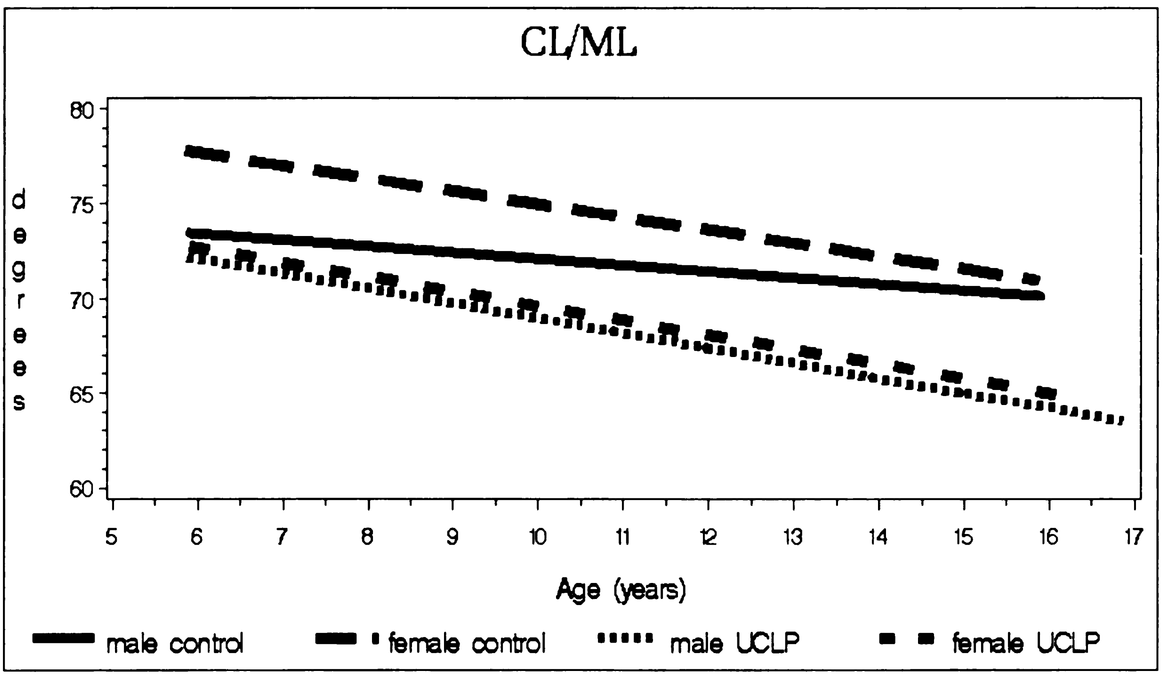


Figure 19

Top: **Slope graph of chin angle CL/ML with mean data.**
Bottom: **Slope graph of chin angle CL/ML without mean data.**

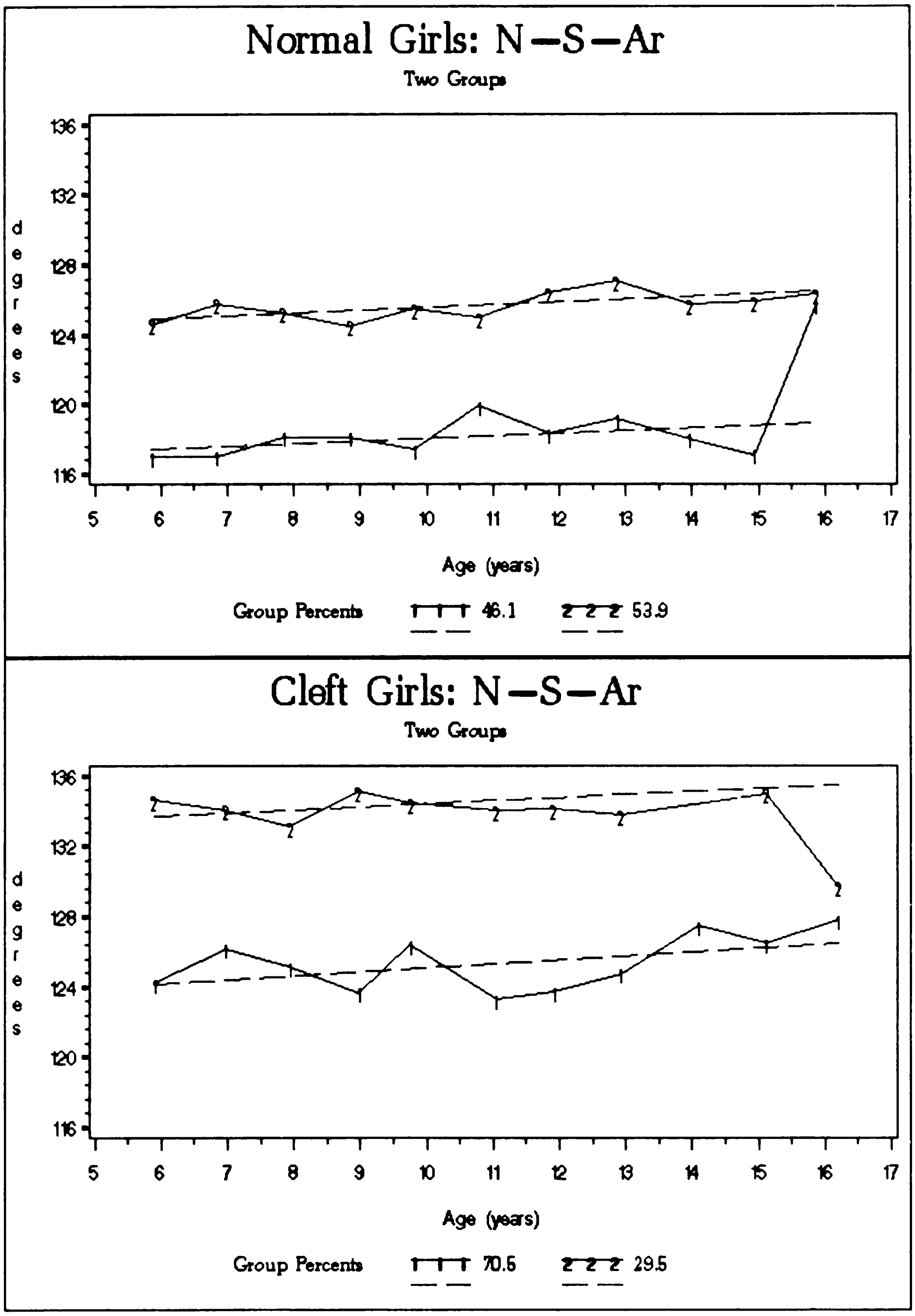


Figure 20

Top: Graph depicting variability of n-s-ar angle within female control group.
Bottom: Graph depicting variability of n-s-ar angle within female UCLP group.

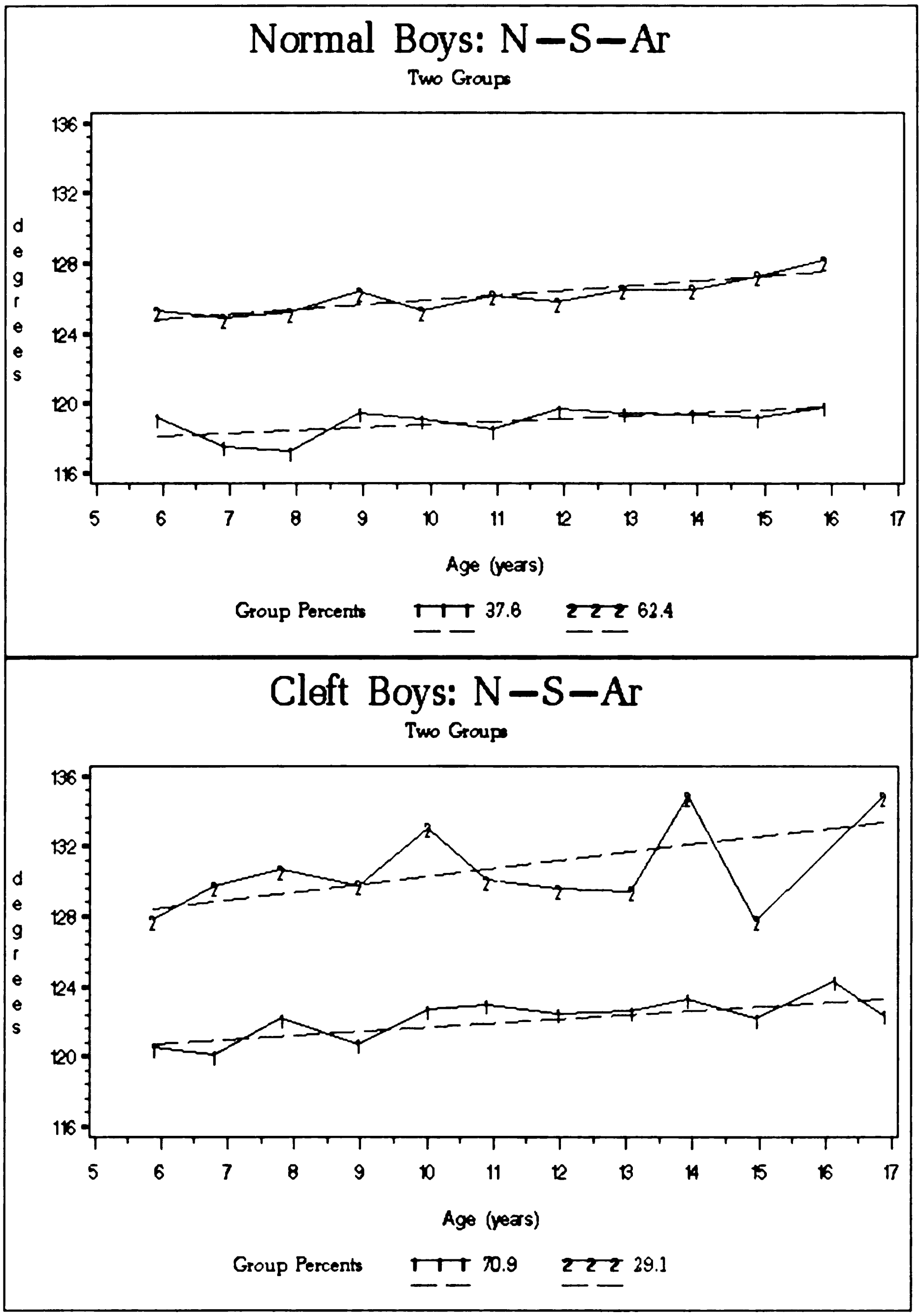


Figure 21

Top: Graph depicting variability of n-s-ar angle within male control group.
Bottom: Graph depicting variability of n-s-ar angle within male UCLP group.

For reference

Not to be taken from the room.