Somatic growth of non-syndromic cleft lip and/or palate subjects compared with the general population in a developing country

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CONTENTS

ABSTRACT

A number of studies of somatic growth in non-syndromic cleft lip and palate (CL/P) subjects in developed countries have found small differences from the general population. In contrast there is a dearth of such growth studies in developing countries which enable comparison with the local population. The aim of this thesis is to record the growth in CL/P subjects having primary surgery in Sri Lanka and analyse differences in growth from the non-cleft population. Much of the developing world is affected by undernutrition and the question arises whether growth is further compromised in CL/P subjects. In the context of the Sri Lanka Cleft Lip and Palate Project, one of whose aims has been to provide primary lip and palate surgery for affected individuals of all ages, a subsidiary question ensues: does the age at surgery affect growth outcomes?

To evaluate these postulates in 364 CL/P subjects aged 3 months to 64 years, measurements of height, weight, head circumference, arm circumference, skin fold thickness and Tanner pubertal stage were performed. In addition hand x-rays were selectively obtained. Data was collected on one to five occasions in five visits to Sri Lanka over 19 years. A comparison was made with a non-cleft population in a cross-sectional study of 3,265 individuals aged from three months to 24 years, done in collaboration with the Paediatric Department of the University of Ruhuna, Sri Lanka. Growth, the tempo of growth and pubertal change, and skeletal maturation were delayed and final stature reduced in both CL/P and non-cleft subjects compared to subjects in the developed world. Applying the British 1990 Growth Reference CL/P subjects were more adversely affected than the non-cleft population in stunting (height <-2SD) underweight (weight <-2 SD) and thinness in frequency and severity throughout most of the growth period. Catch-up growth in subjects with CL/P occurred in puberty, to that of the noncleft population. Primary palate surgery performed in childhood had lower prevalence of undernutrition indices than if adolescent or adult at the time of surgery. The growth of cleft lip, in whom early nutrition is not compromised, was similar to those with cleft palates, in whom pre-surgical nutrition could have been impaired. This suggests other factors in addition to nutrition may be influential, such as parental emotional responsiveness and societal inclusion. These findings may inform future local educational and management strategies to improve growth outcomes.

ABBREVIATIONS

As used in the text and tables

BA	bone age
BCLP	bilateral cleft lip and palate
BMI	body mass index
CDGP	constitutional delay in growth and puberty
CL/P	cleft lip and/or cleft palate
CL(P)	cleft lip with or without a cleft palate
CP	cleft palate
FOG	fathers occupation group
GH	growth hormone
HC	head circumference
IOTF	International Obesity Task Force
LMS	lamba-mu-sigma statistical programme
MUAC	mid upper arm circumference
N	number
NCHS	National Centre for Health Statistics
NHANES	National Health and Nutrition Examination Survey
SD	standard deviation
SDS	standard deviation score (Z score)
SE	standard error
SEAR	South East Asian Region
sft	skinfold thickness
SL	Sri Lanka
UCLP	unilateral cleft lip and palate
UNICEF	United Nations Childrens Fund
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

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1.1 General introduction

Cleft lip and/or palate (CL/P) is the commonest craniofacial malformation with a world wide incidence of 1 in 500 to 1 in 1500, varying with race and gender. The incidence in Sri Lanka is between 1 in 700 and 1 in 1000 births (Amaratunga and Chandrasekera 1989, Mudiyanse 1999). It is estimated 120,000 children world-wide are born annually with this anomaly, and of these 85% live in the developing world. What I mean by a developing country is referred to by the World Bank (2009) as a low-income country who's gross national income GNI is less than $995 per capita, and lower-middle income country GNI of $996 – $3,945 per capita. Between 21% and 32% affected individuals have associated physical defects or delayed cognitive or motor development, (Tolerova and Cervenka 1998, Milerad et al. 1997). The majority are without such problems and are termed nonsyndromic. Their growth may be significantly affected by nutritional and social factors operating to their disadvantage compared with other children. The consequences in terms of somatic growth of a congenital abnormality of the CL/P type in a developing country have not been extensively explored before. The information derived could be useful in parental and community education, and delivery of care to affected individuals and their families, thereby reducing the consequences of undernutrition.

1.2 The Sri Lanka Cleft Lip and Palate Project

The Sri Lanka Cleft Lip and Palate Project for the study of the natural history of CL/P and the impact of surgery was initiated in 1984 by Dr Michael Mars, an orthodontist at Great Ormond Street Hospital for Children. It resulted in 741 operations on 647 individuals conducted in 1985, 1986 and 1990 (Mars 1996). A close working relationship developed with the Faculty of Medicine of the University of Ruhana, with co-authorship of the original paper describing the project (Mars 1990). The author became involved in 1990 in which year two visits took place. The first involved selection and assessment of subjects prior to surgery, the second delivered care to patients in the perioperative period. Follow up visits took place in 1995, 1998, 2000, 2002, and February 2009 for review and collection of data.

1.3 Background to the study

Fabricus of Aquapendent (1619) recorded inanition due to prolonged undernutrition and death in infants with CL/P, which he attributed to feeding difficulties. Relatively recent observers have provided little additional evidence as to the major cause of impaired growth in CL/P (Drillien et al. 1966, Avedian and Ruberg 1980, Jones 1988). Drillien found respiratory infection to be associated with undernutrition more often than expected by chance. Lee et al. (1997) maintain that with appropriate nutritional management growth impairment is minimised and returns to normal by the age of two years. After more prolonged follow up, to late adolescence, others have demonstrated that growth may be affected for far longer periods. Ultimately, adult height may be affected (Bowers 1987, 1988, Cunningham and Jerome 1997). The nature of growth impairment in CL/P in developed countries is therefore controversial.

In a developing country the burden of undernutrition in the population at large may add to growth impairment in individuals with CL/P. The provision of restorative surgery to the lips and palate, and the age of the individual at the time of surgery are factors that may alter subsequent growth outcomes. Thus, surgery for individuals from infancy to adulthood, to whom it was previously unavailable, would be an opportunity to observe the effects of CL/P on growth in a unique way.

1.4 PHOTOGRAPHS OF THE PROJECT

Michael Mars and five year old boy with cleft palate

Sri Lanka Growth Project at the SOS Child Welfare Clinic

Subject 333 with delayed puberty, 13, 16 and 25 years old

Sri Lanka Cleft Lip and Palate Project 1990, team and Sri Lankan counterparts

CHAPTER 2: LITERATURE REVIEW

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The scope of this literature review will encompass studies of growth in subjects with cleft lip and/or palate (CL/P), including skeletal maturity, in the developed and developing world. The pervasive prevalence of undernutrition in the geographical region of South East Asia will be briefly reviewed, to give context to the results of the study.

Growth is a dynamic process that is characterised by periods of varying speed or velocity altering the individual's size and proportions in a manner unique to that individual's genetic inheritance, physical characteristics and environmental influences. The interplay of these factors have caused controversy about growth in CL/P ever since the report in 1960 of 596 children aged five to 15 years seen from 1955-9 in the Hospital for Sick Children, Toronto. The authors reported differences in height and weight by sex and cleft type from controls and stated:

'the study leaves us with an impression that the physical development of the cleft children is impaired'.

This sentence initiated the debate as to the nature of growth impairment following surgical repair that has continued in the developed and developing worlds.

2.1 GROWTH STUDIES IN SUBJECTS WITH CL/P IN DEVELOPED COUNTRIES

Several studies have explored the relationship of nonsyndromic CL/P with growth in children in the developed countries of Europe and North America. A number of studies, though not all, have shown that oral clefts are associated with some degree of impaired growth in height and weight, commencing before birth.

2.1.1 Prenatal growth

Spyropoulos and Burdi (2001) compared body size and organ weight of 47 fetuses with three cleft types. 27 had cleft palate, seven cleft lip, 13 cleft lip and palate, with 120 'controls' matched for fetal age from 13 to 36 weeks gestation. Crown-rump length and body weight were within one standard deviation of the control group. 100% of all lung weights were consistently smaller, as were 80% of suprarenal glands. Aberrant organ growth, whether larger or smaller, was greatest in cleft lip

and palate (28%), and smallest in cleft palate (16%). These variations only became evident from 24 weeks gestation and were present at birth.

2.1.2 Size at birth

Studies prior to the 1970's failed to distinguish between premature infants and growth retarded infants, so rendering comparison difficult. Only three Northern European studies, extracted from national congenital malformations registers, were comprehensive and large enough for statistically useful conclusions to be drawn (Becker et al. 1998, Jensen et al. 1988, Lilius and Nordstrom 1992).

Becker excluded syndromic infants, which many others failed to do, making interpretations and comparisons difficult (Lutz 1959, Drillien et al. 1966, Rintala and Gylling 1967, Lilius and Nordstrom 1992, Jensen et al. 1988). Only Ranalli and Mazaheri (1975) found CL/P infants larger at birth, and not significantly so. Duncan et al. (1983) stated birth weights were comparable with controls. In much larger studies where cleft type could be analysed, reduced birth weight was found in infants born after 37 weeks. Becker reported it in cleft palate and cleft lip and palate, Jensen in cleft palate males, and Lilius in bilateral cleft lip and palate of either sex. Thus while there is consensus that birth weight is reduced between 93 and 220 grams, the type and severity of facial cleft and sex associated with a significant reduction varies. Length was reduced in Becker's study in isolated cleft palate and cleft lip and palate, and in Jensen's study of cleft palate females. These studies were of Caucasian newborns. There is no comparable data from other populations or racial groups.

2.1.3 Growth and nutrition in the first nine years

Nutrition is potentially compromised by the impaired sucking and swallowing ability of infants with a cleft of the palate, with or without cleft lip (Maserai et al. 2005). In the studies reviewed, primary cleft surgery was electively performed at three months for cleft lip and between eight months and 24 months for palate closure.

Drillien et al. (1966), in Edinburgh, assessed 169 children aged one to nine years. 123 were nonsyndromic, and were compared with 124 unaffected sibling controls. A trend was seen in those without a family history of clefting, with growth one SD (16th

centile) below the mean in height (38%) and weight (32%) of a local growth reference.

Weight gain in infants was studied by Avedian and Ruberg (1980). In a cohort of 37 infants 25 showed an early fall from the 30th to the 20th centile of the National Centre for Health Statistics (NCHS) growth reference. By six months of age 17 had demonstrated catch-up. They cited Paradise (1974) with similar experience in 38 infants. Following poor weight gain in the first two months they demonstrated catch up which began by three months of age.

Jones (1988) compared weight gain in 202 unselected CL/P infants in the first four months. Two regimens were examined: home, and prolonged hospital in-patient feeding. Significantly, the hospitalised group gained less well at 134 grams per week compared with 151 to 163 grams per week at home, and hospitalised cleft palate least well at 118 grams per week.

Pandya and Boorman (2001) retrospectively found growth faltering as a downward shift of two SD in 13% of 64 nonsyndromic infants with clefts of the palate followed up to 18 months. This did not change when nursing support was introduced for 57 infants studied prospectively, although there were significant improvements in weight gain among syndromic infants.

Seth and McWilliams (1988) followed 77 nonsyndromic infants with cleft palate in Pittsburgh, born between 1975-79, 29 with cleft palate alone and 48 with unilateral cleft lip and palate. They were weighed frequently during the first two years of life. Both sexes lagged behind the NCHS reference by more than one kilogram at 15, 21 and 24 months for males, and 15 months for females. Analysis included change from their birth percentile, which was lower in 78% of the 40 males (p = 0.02) and 71% of 21 females (p = 0.72) weighed between 20 to 24 months. Perhaps surprisingly, nutritional and feeding problems as a cause were considered minimal because of close support by the paediatric staff.

Ranalli and Mazaheri (1975) in Denver, reported on the longitudinal growth records of 279 nonsyndromic CL/P children from birth to six years. Up to three years of age males tended to lag in weight more than females compared with their control population averages, but neither achieved statistical significance. No relationship of

weight gain pattern to cleft type was found and by five years all had caught up with controls and in some individuals slightly exceeded the norm.

Jensen (1988) reported a longitudinal study of all CL/P births in Denmark from birth to 22 months. Of 678 births, 24 died, 602 of the survivors were successfully traced. 40 (5.9%) of the total were malformed, including 14 with Pierre Robin Sequence. At two months the males with cleft lip were significantly lighter than controls comparing values by T tests, but not as much as those with cleft palate with or without cleft lip, and males with cleft palate were shorter. Both sexes at 22 months were significantly shorter and lighter in the cleft palate groups.

Lee et al. (1997) conducted a longitudinal study in the North of England of 69 children of 83 eligible

(81%) aged from birth to four years and included data on 14 (21%) who were syndromic. Weight at birth, preoperatively and at follow up at a mean age of 25 months were available. The isolated cleft palate median weight SDS preoperatively was -0.3 SD of the British 1990 growth reference (Freeman et al. 1995), significantly lower than other cleft types. At two years there was no significant difference in weight between cleft types. The authors attributed this to improved nutrition post operatively which lead to catch up growth. They concluded that cleft palate significantly influenced the likelihood and severity of failure to thrive before palatal surgery, as had Jones (1988) and Jensen et al. (1988).

Nystrom et al. (1992) examined 60 non-syndromic cleft palate children between three and six years old. Mean SDS for height of those with cleft palate was compared with 50 local controls. At three years, in males the difference was – 0.4 SD and females – 0.6 SD; at six years it had reduced to – 0.1 SD for both sexes. Mean SDS for weight in cleft palate females was - 0.6 SD and - 0.5 SD at three and six years compared with controls.

In summary, early growth impairment was common, and usually resolved by two to three years old. Cleft palate was most severely affected and growth velocity in females remained below the mean up to six years old.

2.1.4 Growth in mid-childhood through puberty to adult

Duncan et al. (1983) in Westchester County, State of New York, followed 65 children's height longitudinally for 11 years. 29% had abnormalities thought not to cause growth retardation, and 16% had birth weights below two and a half kilograms. The children with cleft palate (48%) were all below the 50th centile of the National Institutes of Health (NIH) growth reference after eight years old, and 26% were consistently below the fifth centile. Growth in children with CL/P after four years old was bimodal, short and tall, with 65% below 50th centile, and 21% above the 90th centile. The growth pattern of those with cleft palate was thought to simulate that of growth hormone deficiency (GHD), linking it embryologically to failure of midline development, including the pituitary gland.

Jensen et al. (1983) performed the only study of longitudinal growth linked to skeletal maturation and length of radius, others are cross sectional studies of growth and hand-wrist bone age. Jensen compared 48 males with cleft lip and palate aged six to 20 yrs with 85 Danish male controls; the males with cleft lip and palate were shorter throughout. The mid-childhood and pubertal growth spurt were six months later, and less marked than controls, but prolonged, allowing catch up to non cleft norms by 19 years of age. Bone age delay was consonant with height. This pattern of growth is suggestive of constitutional growth delay in puberty but was not commented upon as such.

Bowers et al. (1987, 1988) hypothesised about steroid hormonal influences on cleft formation and growth in utero to puberty. Cross-sectional data from 209 nonsyndromic children with CL/P aged two to 18 years old were compared with the NCHS reference. Subjects with cleft lip only and bilateral cleft lip and palate were close to the mean, and were not analysed. A subgroup of 144 children with cleft palate and unilateral cleft lip and palate mean SDS for unilateral cleft lip and palate (UCLP) and isolated cleft palate (CP) were:

		Height (SD)	BMI (SD)
UCLP	male	-0.49	-0.34
	female	-0.31	
CP	male	-0.85	-0.64
	female	-0.51	

A quarter of the children with cleft palate were <-2 SD in height. Males were more affected by change than females. Mean SDS in male height increased from 2 years to 18 years in UCLP by 0.39 SD, and CP 0.33 SD, but decreased in females, UCLP by - 0.67 SD, CP -0.97 SD. Males with unilateral cleft lip and palate demonstrated catch up. Females grew better up to eight years old followed by progressive decline in height SDS. The breakdown by sex, into three age and two cleft-type cohorts, created 12 cells, four of which contained fewer than ten subjects, only one more than 16. Cells were then reassembled into various pooled groups that appeared to support the authors' hypothesis. They postulated that changes in specific adrenocortical hormones and their metabolites were orchestrating these differences between the sexes and age groups in the following way. They postulated a "cybernetic approach" comprising command (accurate genetic instruction) and functional output (growth modified by nutrition and hormones) of clefting and growth. Factors slowing growth cause clefting during embryogenesis, and also postnatally. The same gene products and metabolic processes are present and may operate before and after birth. Dehydroepiandrosterone (DHEA)/testosterone/sex steroid receptors, act in embryogenesis, and during growth, by genetic alteration in the steroid pathway. Supportive findings include male predominance in CL(P), and L handedness may be increased in cleft people (Lees 2004) as testosterone may influence cerebral dominance as it begins to be secreted between 5 - 8 weeks of embryogenesis. It would follow that postnatal growth would differ from average at adrenarche and puberty. In BCLP they observed normal growth, and propose sex linked genes controlling mid line fusion, supported by 3rd & 4th branchial arch malunion syndrome. In CP midline clefting there was no sex difference in their series, and so they postulated growth deficit was related to maldevelopment of midline structures and anterior pituitary horomone dysfunction.

A search of the literature failed to identify subsequent endocrine research to support this melange of theories.

Laitenen et al. (1994) analysed 58 nonsyndromic longitudinal growth records, from among 104 that also included subjects with Pierre Robin sequence, aged one month to 12 years old. A comparison with the Finnish growth reference used subjects' SDS height and weight as a percentage deviation from the mean. Cleft palate females

were significantly shorter at 0.3 and 0.8 years, though values were not reported. Mild growth failure occurring in the first year was attributed to infections and feeding difficulties, with complete catch up by one year.

Cunningham & Jerome (1997), in contrast to Bowers' papers, reported a longitudinal study from Seattle of 324 subjects, of whom 262 were white American, nonsyndromic individuals aged from two to 18 years, between 1972 and 1994. Their height centile for each year was compared with the NCHS growth reference. The groups grew similarly with no significant intergroup variability between cleft types. As a whole they grew close to the 40th centile from two to 10 years old, 60% of male and 70% of female yearly interval points differing significantly from the population mean. Plotting the growth velocity allowed for race-independent comparisons with the NCHS reference, and from two and a half to 12 years, 64% of the males were above the 50th percentile, but only 36% of females. It was concluded that individuals with CL/P had a consistent growth pattern below the mean for the general (white) population. When all races were included the growth velocity suggested catch up in males, with a likelihood that females would remain short as adults. The similarity between the observed growth pattern in males and that of constitutional delay in growth and puberty as a common cause of delay in growth was noted.

In general, the studies beyond two years of age showed that males grew better in height than females in the face of earlier growth impairment, and demonstrated catch up. Females with cleft palate were especially vulnerable to growth impairment, more so than other forms of CL/P. As a group, females with CL/P tended to be shorter adults than their noncleft peers. Absence of information on socioeconomic background, nurture and on stages in puberty when anthropomorphic data obtained, rendered it difficult to assess the influence these important cofactors might have been exerting on growth processes.

2.1.5 Adult stature

Dahl (1970) studied 210 adult males who were a heterogeneous group of syndromic and nonsyndromic individuals. The 30% with cleft lip were 5.7 cm shorter, the 48% with unilateral or bilateral cleft lip and palate were 4.4 cm shorter at 174.3 cm, and the 22% with isolated cleft palate were "significantly shorter" than controls. This is a

landmark study, a wide ranging review of problems associated with CL/P, but flawed by a lack of detail of growth. As an early contribution, it increased awareness of the potential for impaired growth to persist into adult life.

2.1.6 Catch-up growth

The phenomenon of catch up, an acceleration of growth after removal of the cause of growth failure, has been observed in subjects with CL/P following surgery to enable normal feeding.

Studies have described the occurrence of catch up growth in singletons by the age of three months (Paradise 1974), six months (Avedian and Ruberg 1980), a year (Laitenen et al. 1994), two years (Lee et al. 1997), or three years (Ranalli and Mazaheri 1975). Twin studies by Ross and Johnson (1972) similarly reported catch-up in the affected monozygous twin; Bowers et al. (1988) observed it in males with unilateral cleft lip and palate in adolescence. Cunningham and Jerome (1997) referred to a constitutional growth delay type of pattern occurring in adolescent males. Jensen et al. (1983) described a persistent delay in growth and skeletal maturation from six years, with prolongation of growth to nineteen years.

Azcona and Stanhope (1997) sounded a note of caution in response to the assertion of Lee et al. that growth was normal by two years of age. While agreeing that early catch up is important, they pointed out that midline defects are associated with developing endocrine deficiencies, especially growth hormone deficiency. They recommended growth should be monitored throughout childhood in children with clefts.

2.1.7 Studies with no difference in growth between subjects with clefts and controls

Studies finding no significant difference from the normal population for subjects with CL/P comprised singleton studies in Dutch, Russian, Flemish, and German populations. Twins studies were the subject of three American reports.

Felix-Schollaart's (1992) longitudinal study of 45 Dutch infants compared them with 50 controls from birth to two and a half years old. A comparison with the NCHS reference of 112 Russian children aged four to ten years with nonsyndromic cleft lip and palate, included analysis of parental height (Nackashi et al. 1998). Heliovaara et

al. (1994) studied cross sectional data on 116 mainly non-syndromic cleft palate 16 to 20 year olds born between 1968 and 1971 and compared them with Finnish norms. Hertrich (1990) from Nurenberg reported on 38 females and 78 males with skeletal maturity as a hand and wrist bone age (BA) assessed by Greulich and Pyle (1958) (G&P) between 7.3 to 17.4 years old. Two heights were also obtained, one in childhood and the other after 17 years old. Although all cleft types were included they were not differentiated nor was it clear whether they were nonsyndromic. The female mean age of 10.7 years correlated with a mean BA of 10.0 years, males of mean age 11.3 years correlated with a mean BA of 10.8 years. Both sexes were shown to have a significant 'delay' in BA, on or just above the observational error of 0.5 years for G&P. The height obtained after 17 years of age compared with local standards was –1 cm for females and + 3 cm for males. Their growth was compared with the 50th centile of the UK Tanner reference, itself 30 years old at the time. They were taller by 3 cm for females and 6 cm for males, confirming satisfactory growth, but against a reference probably no longer relevant to the population. Both local and international references showed females were not as well grown as males.

Same sex twins discordant for CL/P in studies comprised six pairs in Ross and Coupe (1965), 14 pairs in Hunter (1975) and 45 pairs in Hunter and Dijkman (1977). The aim was to demonstrate the effect of CL/P on growth in the same genome when monozygous (MZ), and same environmental background when dizygous (DZ) twins were compared. All studies were cross sectional. When sufficiently large numbers were available for comparison no consistent pattern of differential growth was found up to ten years of age, or between the adult pairs.

2.1.8 Factors postulated to contribute to impaired growth in the developed world

Factors alleged to contribute to impaired growth in CL/P include severe feeding problems in infancy (Spriestersbach et al. 1973), feeding difficulties and infections (Ross and Johnson 1972), feeding and intestinal disorders (Drillien et al. 1966, Lee at al. 1997), infection of the upper airway (Drillien et al., 1966, Seth and McWilliams 1988), and restorative cleft operations (Drillien et al 1996, Ranalli & Mazaheri 1975, Seth and McWilliams 1988). Paradise (1994) studied the frequency of middle ear disease in CL/P infants, comparing the benefits of breast milk against cows milk, or

soy milk formulae, but omitted to also record weight during follow up, thereby missing an opportunity to shed some light on the frequently posited mechanism of recurrent infection.

Drillien et al., (1966) found chronic or recurrent middle ear problems in 47% children with clefts compared with controls 5%, and recurrent lower respiratory symptoms 14% versus 7% in controls in the first four years of life.

Felix-Schollaart et al. (1992) found some significant correlations for feeding and early respiratory infection in a multivariate one-way analysis of variance. The presence of feeding difficulties and intestinal disorders at 12 to 18 months, compared with no symptoms, were correlated with weighing a mean 0.93 kilogram less at two and a half years. Airway infection under three months was associated with a mean weight 0.59 kilogram less and 1.7 cm shorter at two and a half years. Put in perspective it accounted for 5% of the variance in length compared with 14% for feeding difficulties and intestinal disorders. No link was found with the timing or performance of cleft surgery. The authors were careful to point out that these findings:

'did not account for differences among the CL/P groups and controls, as suggested by the literature'.

Heliovaara et al (1994) found no significant effect on linear growth, only dental arch dimensions, specifically the more jaw operations the less arch growth.

Hormonal factors or interactions may be triggered *in utero* or be endogenous to the underlying causes of CL/P (Bowers et al. 1987, Laron 1969, Rudman et al. 1979). GH deficiency occurs in the general population with a prevalence of 1:3000. Rudman surveyed CL/P individuals 30 years ago when hormone assays were in their early stages of development and found the incidence in individuals with CL/P to be 40 times commoner, at 1.3%. This is still a very small proportion of the total number of children with CL/P, and of those among them who cause clinical concern because of growth failure in early childhood. Infancy is a time when GH deficiency is unlikely to have a measurable effect, in accordance with the Infant-Child-Puberty model of Karlberg (1989). This identifies three phases, linking them with a mathematical model of components working additively. The first, continuation of the fetal nutritional phase postnataly, is succeeded by the childhood phase controlled by

growth hormone. The third component in puberty is dependent on sex hormones working synergistically with growth hormone. In the model, GH deficiency becomes manifest after infancy, by which time the overwhelming majority of those with CL/P with growth faltering have shown catch up. The likelihood of severe persistent growth impairment due to GH deficiency in the absence of appropriate treatment removes these individuals from the more general concern about the relatively small reduction in final adult height detected in published series. This was confirmed on screening several hundred children with CL/P, who were not of pathologically short stature. No abnormally low levels of growth hormone (GH) were found (Gacs 1981, Koster 1984). Although it is superficially an attractive hypothesis, with the physical proximity during a critical stage of embryogenesis of the two organs, one the palate and the other the adenohypophysis, a partial deficiency of GH in isolated cleft palate or CL/P lacks evidence to support it. The increasing sophistication of assays for growth hormone related factors may make this an area of research worthy of revisiting in later childhood and adolescence.

Molecular biology studies link *persistent* growth disturbances to intrauterine environmental factors such as tobacco and alcohol (Khoury et al. 1988) and/or gene(s) regulating lip and palate development (Murray 2002, Romitti et al. 1998). Thus, although several malign influences are postulated to account for impaired growth, the weight of evidence strongly supports only early nutritional inadequacy, and much less so respiratory infections. This is then followed by a period of catch up. This process may be incomplete in early childhood and take until puberty for it to be compensated for.

2.1.9 Contrary findings between studies

In studies in developed countries where a difference has been found between CL/P and controls they lack agreement as to the magnitude of impairment, the timing of its appearance, whether it is transient (Ranalli and Mazaheri 1975, Jensen et al. 1983, 1988, Laitinen et al. 1994, Nystrom et al. 1992, Lee et al. 1997) or permanent (Dahl 1970, Duncan et al. 1983, Roitman and Laron 1978, Rudman et al. 1978,), or likely to be so for only one, or some, of the cleft types (Bowers et al. 1988, Cunningham and Jerome 1997).

Reasons for discrepant findings between these studies:

1. Most studies of growth have insufficient numbers, so subgroups are usually too small to address questions with confidence as to their statistical validity.
2. The age ranges are skewed to contain a large number of young subjects.
3. A mixture of subjects who are syndromic and nonsyndromic.
4. A mixture of different cleft types, causing confusion as to conclusions drawn.
5. Inter-observer measurement error may obscure small differences.
6. Age groups overlapping, and factors operating at particular ages may be obscured by pooling them.
7. General failure to correlate skeletal age and pubertal status to growth.
8. The lack of appropriate follow-up (Habel et al. 1995) and failure to identify children subsequently as syndromic.

Despite 50 years of interest in growth impairment on the part of investigators, uncertainty as to the prevalence, fundamental causes, and outcomes remain.

2.2 GROWTH OF SUBJECTS WITH CL/P IN DEVELOPING COUNTRIES

2.2.1 Studies of nonsyndromic CL/P in developing countries

Studies of the effect on growth of individuals with nonsyndromic CL/P living in a developing country have only relatively recently entered the literature.

Studies demonstrating differences from the non-cleft population include that of Montagnoli et al. (2005). They reported a large cross sectional study of 881 Brazilian children aged one to 24 months, with 81% from lower and lower middle class socioeconomic groupings. The 10th centile of the NCHS reference was the cut off for growth impairment. In isolated cleft lip 29% had weight impairment, 19% height impairment. In cleft lip and palate the proportions were 36% and 33%, and isolated cleft palate 34% and 39% respectively. Breast feeding levels were 45% in cleft lip, 10 to 12% in other groups, and feeding difficulties were implicated in the growth differences observed. The study lacked comparable values for noncleft infants, so the prevalence below the 10th centile in weight and height for isolated cleft lip may have approximated the norm for that socioeconomic grouping. In addition, had information been available on whether and when surgery had been performed, the

reader could have gained a better understanding of the nature and timing of growth impairment.

A cross sectional study of 640 children by Lazarus et al. (1999) in Cape Town, South Africa, excluded severe craniofacial syndromes and analysed weight immediately prior to surgery. 22% were less than –2 SD, and 8% less than -3 SD on the National Centre for Health Statistics (NCHS) reference chart, the World Health Organisation (WHO) cut offs for underweight and severe underweight. The prevalence of underweight under one year old was 27%, one to two years 45%, two to five 49% and over five years 24%. There was no sex difference, and provision of feeding plates did not alter the nutritional state during the period in the 1980's when they were prescribed. Children with cleft lip were significantly less likely to be underweight, 21%, than children with cleft of the palate, 32%, with or without a cleft lip, but significantly more than socioeconomically similar noncleft controls at 14%. Children over one year at surgery were one and a half times more likely to be underweight than those operated under one year of age.

In a short report Grippaudo and Kennedy (1999) assessed height and weight of 39 Filipino clinically nonsyndromic children with clefts, aged seven months to 13 years. Only 32 measurements were entered on the Filipino population centile charts, which stopped at 14 years. All but five children were unoperated. 67% were on or below the 10th centile for height and 56% for weight. No significant difference was found in height distribution between the sexes, or cleft types, which included 13 with cleft lip. Measurements were made with a tape measure and spring balance, casting some doubt on the accuracy of the plotted data, but certain trends were evident. The height recorded in 12 of 13 children under four years old lay between the third centile and 10th centile, an age at which inaccurate height measurement could readily occur and potentially lead to a false conclusion. 14 of 19 over that age lay above the 10th centile for height, and the 16 children under the 10th centile for weight were distributed more evenly by age. No child was <-2 SD in height or weight on the local chart. The authors were of the opinion that upper respiratory infections against a background of chronic upper airway disease contributed to nutritional difficulties in causing growth impairment. All had experienced episodes of mild to moderate upper airway

infection, although none were hospitalised for this. How this differed from the experience of the noncleft population, or any group of children, was not evident.

2.2.2 Studies of CL/P in developing countries showing no difference from the non-cleft population

In Thailand, Gopinath and Muda (2005) studied 60 children under six years with nonsyndromic CL/P, and 161 controls. The prevalence of infections and lower height centiles were significantly more common in the CL/P group in the first six months only, but 71% came from the lowest socioeconomic group, compared with 11% of the controls, presumably due to selection bias. Increased rates of fever and diarrhoea in the children with CL/P were attributed to the giving of formula milk, due to the inability of the mothers to maintain a supply of breast milk.

Jurutratanasirikul et al. (2008) retrospectively reviewed a group of 153 Thai children, 23% cleft lip only, at a mean age of 2.4 years, median 0.5 years, range 0 to 17 years. Applying locally derived SDS from the Thai National Growth Reference for children under 20 years of age, they found the 133 children who were nonsyndromic had height, weight, and head circumferences not significantly different from the general population: weight was –0.14 SD +/- 1.45, height –0.11 SD +/- 1.42, head circumference 0.22 SD +/- 1.25.

Alkofide and Barakati (2002) from Riyadh, Saudi Arabia, reported on 63 nonsyndromic cleft patients aged six to 25 years, seen in a central urban orthodontic clinic, and compared with published data on local controls. Cleft surgery was performed at three months for lips and 18 months for palates. In the accompanying tables only 51 of the 63 had heights and weights compared, 12 were aged 10 to 14 years and 21 were more than 14 years old. The authors concluded there were no significant differences between the noncleft controls and types of cleft in height, weight, or head circumference.

Studies concerning growth in CL/P individuals in developing countries are limited in number and comparability. The lack of an international reference in some studies prevented further comparisons between them. None were systematic studies with sufficient numbers or duration of follow up to inform on growth to maturity after surgery.

2.3 SKELETAL MATURITY IN CL/P

2.3.2 Skeletal maturity in CL/P in developed countries

Worldwide variation in rates of skeletal maturation have been extensively studied in diverse populations (Eveleth and Tanner 1990). All the studies reviewed used radiographs of the hand and wrist and are cross sectional unless stated otherwise. Snodgrass (1954) studied 32 children, and found the skeletal age based on the Todd standards for the hand lagged behind chronological age more than six months in 3 children (10%).

Bone age (BA) is the age at which a child is on the 50th centile for skeletal maturity. Menius et al (1966) in the first systematic study combined BA with height, weight and dental age in 48 children aged five to 19 years, with a preponderance of unilateral cleft lip and palate. Greulich & Pyle (1959) plates were adapted for scoring subjects and local controls. The BA was 'delayed' in approximately 40% of males. The ratio of males to females was 2:1. The delay of up to -2 SD was equivalent to 22 months. The height and weight were below 'standard limits' for age in half the males and females with delayed BA. The BA 'delay' was independent of age, with, surprisingly, no catch up from 16 to 19 years of age. They must have been significantly delayed in pubertal development, but no clinical information was given. Przezdziak (1969) in a Polish study of the bone ages of 147 children one to 10 years old using Todd's BA standards found delay in half of the children; up to one quarter by two or more years, and one quarter by one year, for both sexes, and independent of cleft type. No control group or information about associated anomalies was reported. 'Delayed' BA was attributed to respiratory and ear infections. Fleischer-Peters and Reichardt (1981), from Nuremberg, Germany, compared children with clefts of the palate aged seven to 15 years. The 109 boys' mean age was 11.1 yrs and 79 girls' mean age 10.6 years. Using the Greulich & Pyle atlas (1971) the BA was 'delayed' for both sexes by approximately six months between the ages of seven to 15 years. There was no catch-up in BA within the period of the study, the concomitant of which was likely to be a prolonged puberty, though no relevant data was provided to evaluate this further.

Jensen et al. (1983) compared the longitudinal growth of 48 males with unilateral and bilateral cleft lip aged six to 20 years, averaging eight annual wrist x-rays, with 85 Danish male controls. The Tanner and Whitehouse TW2 (1975) method of assessing skeletal maturity employs a system of allocating individual bones of the hand and wrist a maturity score. Using the radius, ulna, and small bones (RUS) the BA's were 'delayed' by 3.8 to 11.5 months and median height was 1.0 to 3.3 cm below the 50th centile between eight and 10 years old. Growth in height continued until at least 19 years old. This was consistent with a constitutional delay pattern, but was not commented upon.

Prahl-Andersen (1979) used TW1 (an earlier edition of TW2) to assess the BA of 48 males and 25 females aged four to 14 years. In addition their dental age and 15 anthropological measurements including height, weight, and subcutaneous fat, were compared with 486 Dutch controls. The type of cleft and presence of a syndrome were not reported. Compared with the controls, there was no significant difference in height, weight and arm circumferences, but subcutaneous fat thickness of triceps and subscapular areas were significantly less. The individual BA plots of boys with clefts were illustrated, evenly distributed around the line of mean BA of controls; the BA of female clefts was said to be advanced compared with controls but no data was included to evaluate this unusual finding.

Geier and Dahlmann (1988) of East Berlin's Humboldt University compared 96 children, 65% males, with unilateral and bilateral cleft palates, aged seven to 14 years, with 155 similarly aged controls, using the TW2 method. They were divided by age into four groups, and analysed combining all the cleft types as the numbers in each group were otherwise too small. The males with clefts were mean − 0.80 years (range −0.54 to −0.97), compared with the controls 0.12 years. In contrast, females with clefts recorded in table four of the article showed an increase in their bone age from -0.6 years at seven years to +0.54 years at 14 years. This study may have contained syndromic children, and no correlation was made with linear growth, pubertal staging, or social class, though 'general psychosocial development' and susceptibility of the male sex to abnormalities were invoked.

Jochmann and Dubel (1983), from East Germany, examined 27 females and 56 males aged nine to 16 years old and compared them with 114 controls; cleft type and

presence of associated abnormalities were not stated. The BA's were compared using von Bjork local standards. The younger children had advanced BA's, males by 3.5 years at eight years old, females one year advanced at nine years. In children aged 11 to 16 the BA progressively became delayed, by -0.65 years at the chronological age of 16 years old in males, and by -1.5 years in 16 year old females. There are no parallels with other cleft lip and palate studies showing accelerated growth in height or BA in such an early period of somatic development followed by progressive delay. It left unresolved at what age the children reached maturity, and the authors offered no hypotheses to account for these curious results. The local x-ray reference used may have been relevant to this finding.

Hertrich's (1990) findings have been reviewed in the growth section.

Anastassov et al. (1993) investigated the relationship between BA and predisposition to facial skeletal Class III dentition in which the mandible protrudes beyond the maxilla. In this series the maxilla was underdeveloped, with mid-face retrusion in 55 children (30 males) aged 10 months to 13 years with unilateral cleft lip and palate in Northern France. 49 were nonsyndromic and the remaining six had conditions unlikely to affect growth. A Class III jaw relationship developed in 18, and 37 were satisfactory. From the Greulich & Pyle (1971) SDS the BA was 'delayed' by –2 SDS in 31% and –3 SDS in 4%. The proportion in Class III children was 50% compared with 24% in those with normal jaw relationships, a significant difference. In the 11 children who had more than two palate operations, 8 were BA 'delayed' by –2 SD, compared with 8 of the 44 who had fewer operations. The authors concluded that multiple palate operations and malocclusion of the jaws were linked to delayed bone age. They opined that bone age 'delay' was a risk factor in malocclusion, and early identification was required, though no hypothesis was formulated to lend support for this conclusion.

2.3.2 Synthesis of CL/P skeletal maturity studies in developed countries

Males appeared likely to have 'delayed' BA, from the age of seven years, manifest continuously as a 0.5 year delay to 19 years (Jensen et al. 1983), or a 0.8 year delay between 7 and 14 years (Geier and Dahlmann 1988). Two studies found both sexes equally affected by a six months delay, from 7 to 15 years in Fleischer-Peters and

Reichardt's (1981) study, and a one to two year delay affecting half the children of both sexes under 10 years in Przezdziak's (1969) study. Menius et al. (1966) found that males were twice as likely as females to have significant persistent skeletal immaturity up to nineteen years old. One paper postulated that delayed BA predisposed to Class III malocclusion. Two investigators found females with advanced bone ages (Geier and Dahlmann (1988), Prahl-Andersen (1979); advanced BA in younger children was succeeded by delayed BA in 16 year olds in the study of Jochmann and Dubel (1983). When cleft types were reported they were mainly unilateral or bilateral cleft lip and palate. No indication of the presence of other malformations or syndromes was usually given. No links with pubertal status or menarche in the case of girls were reported, which would have been helpful in understanding the variation in findings.

2.3.3 Skeletal maturity in Indian children

Early radiological studies from the Indian subcontinent focused on the appearance and rate of fusion of epiphyses, from birth to 16 years (Hassan and Narayan 1963, Jit and Singh 1971, Gaind et al 1980), and stratified by age into preschool age (Bajaj et al. 1967, Prakash and Chopra 1974), to 10 years (Banik et al. 1970, 1971), and school age (Sharat et al. 1970). The timing of appearance of the epiphyses in relation to social class, nutrition and presence of anaemia have also been the subject of study (Ghosh et al. 1966, Banik et al. 1972, Maniar et al. 1974, Gaind et al. 1980).

A study of 1085 children aged one to 11 years olds in Bombay (Mumbai) used Greulich and Pyle (Maniar et al. 1974). They compared 266 children with marasmus, some with oedema, with 680 from lower and 139 from higher socioeconomic groups. The marasmic group's bone ages fell away progressively from the other groups between one and five years old, and appeared to undergo maturation arrest for two years, by which time the study had ended. The lower income group was one to two years delayed compared with the upper income group, who closely followed the American norms. The emergence of ossification centres in young malnourished children was often delayed up to two years; their appearance was a source of error as they were smaller, with marked rarefaction and thinning of the bone cortex.

In these studies information available between appearance and fusion of epiphyses was ignored (Prakash and Cameron 1981).

Studies in which investigators have compared Indian children for skeletal maturity using TW2 is limited to two. Prakash's first study (Prakash and Bala 1979) comprised 137 deprived preschool children. In the first year of life the Indian children had a proportion of ossification centres that were advanced compared with the TW2 reference. By five years they were about one year behind. Environmental poverty, lack of maternal education about nutrition, sanitation and food were factors the authors commented on.

Prakash next studied 298 well-off Indian schoolchildren aged six to 14 years (Prakash and Cameron (1981). The girls' heights were close to the British 50th centile, weight close to the 25th centile. The boys started on the 50th centile and moved to the 25th after nine years old. The TW2 RUS maturity scores for boys were all above the 50th centile, being close to the 75th at six years and eight to 12 years. The girl's means were all between 50th and 75th centiles except at six years of age when it was on the 25th centile. The authors concluded the lower heights of the Indian boys in adolescence were not due to delayed maturity.

The conclusion to be drawn is that under conditions of adequate nutrition and well being, skeletal maturity in Indian children closely followed the TW2 SDS for age and sex. No studies involving Sri Lankan children were found.

2.4 UNDERNUTRITION IN DEVELOPING COUNTRIES

2.4.1 Undernutrition and its potential impact on the present study

Waterlow (1986) coined the term stunting to describe impaired growth in height of below -2 SD. He differentiated it from the stunted individual, a term used by Tanner to describe those with an underlying skeletal cause for impaired growth. Despite this, the term has disparaging connotations. Unless quoting from the literature, –2 SD in height will be used in place of 'stunting'.

Environmental factors are powerful determinants of the stature of individuals and populations. The contribution of the environment has been known for centuries, and succinctly summarised by the founder of French public health:

Human height becomes greater and growth takes place more rapidly, all things being equal, in proportion as the country becomes richer, comfort more general, houses, clothes and nourishment better and labour, fatigue and privation during infancy and youth less: in other words, the circumstances which accompany poverty delay the age at which complete stature is reached and stunt adult height' (Villerme LR 1829, quoted in Eveleth and Tanner, 1990, p.191).

Undernutrition and malnutrition exert their effects maximally during periods of rapid growth. The most vulnerable children are therefore those under two year and those in puberty. The consequences are somatic growth retardation, impaired intellectual development, and delayed sexual maturation (Hamilton et al. 1984). Affected individuals are predisposed to anaemia from iron deficiency, low bone density and later osteoporosis. Black et al. (2003) estimate that

'stunting, severe underweight and intrauterine growth restriction are responsible for 2.2 million deaths and 21% of disability-adjusted life-years (DALYS) for children younger than 5 years'.

Being –2 SD in height is a consequence that also increases obstetric risk (Gopalan 1989) and the likelihood of giving birth to low birth weight infants (Kramer 1987). Low birth weight individuals and children –2 SD in height are at high risk of obesity and coronary heart disease as adults consequent upon the insulin resistance syndrome, including adults in developing countries (Mi et al. 2000, Eriksson 2005). The consequences of thinness in adults are often reported as chronic energy deficiency (CED), a term originally used to measure inadequate household food supply. Adults with CED, defined as a BMI <18.5 have more sickness, reduced work capacity, lower income, lower social activity and higher proportion of low birth weight infants (James 1994). Factors include rural or urban sectors, occupation, education, social status, caste, and religion (Bharati et al. 2007).

2.4.2 Mechanisms of causation of impaired growth

Costello (1989), investigating the nutritional impact on growth of seasonal malnutrition in Nepalese children aged from birth to six years old, found it was limited to under two year olds. Satyanara et al. (1986) found 65% to 70% of the difference in adult height to be linked to –2 SD in height under 18 months old when followed up over 20 years (Waterlow 1986). Thus despite removal of the restraint on growth the subjects failed to regain the full height potential they had lost during the

period of undernutrition. The mechanisms involved have been investigated by Liu et al (1999). They examined 4,487 children at 18 years. Height at six months, puberty and final height were found to be closely linked using a computerised visual representation of the Infant-Child-Puberty model of growth that was developed by the senior author, Karlberg (1989). Liu et al. found delay in the onset of the childhood phase equated with -2 SD in height, and resulted in a reduced adult height by five cms in a healthy Swedish population. They also confirmed a second factor, absence of a compensatory delay in the onset of puberty, accounting for the sustained reduction in height attained. The reduced nutritional component was statistically significant for adult height impairment without the pubertal component.

2.4.3 Classification and nomenclature of undernutrition

The World Health Organisation identifies low height for age, low weight for age and low weight for height as -2 SD of the NCHS/WHO international reference population (Lavoi-Pierre et a.1 1983, de Onis et al. 2004). -2 SD in height, underweight and wasting or thinness are the terms commonly linked to these cut offs. BMI, weight/height^2, is established as a practical means of assessing overweight and underweight in the developing and developed worlds. Intervention strategies have been introduced based on known increased morbidity above defined thresholds in adults such as a BMI of 25 (overweight) and 30 (obesity), and below 17 (thinness) at the other end of the spectrum. Evidence of a correlation between mortality in children and the severity of malnutrition is strong (Black et al. 2003, Pelletier and Frongillo, 2003). However, clear data on morbidity related to wasting/thinness in children is lacking. Cameron (2007) attributes this to a paucity of appropriate data with meaningful cut-offs. Identifying the latter has led to a challenge to the present WHO definition of thinness in adolescents as the fifth centile of the American National Health and Nutrition Examination Survey (NHANES) (Must et al. 1991). Cole et al (2007) proposed an extension of their established child and adolescent International Obesity Task Force (IOTF) classification for obesity to include underweight, to coincide with the –2 standard deviation score for adults at 18 years. This approximates to 80% of the median BMI, which is equivalent to the existing WHO definition of wasting in children (low weight for height). Cole therefore

proposed the term wasting be equated to thinness in children, and to mean low BMI for age. The cut off –2 SDS is at a BMI of 17 kg/m^2 at 18 years old, the WHO grade two for thinness in adults. BMI 18.5 and 16.0 provide cut offs of –1 SD and –3 SD at 18 years. The three SDS cut offs are extrapolated between the ages of two and 18 years as grades of thinness. Severe thinness <-3 SD approximates to grade three, moderate –2 to –2.99 SD to grade two, mild –1 to –1.99 as mild thinness grade one. Based on 200,000 subjects from six countries around the world it affords international comparisons of thinness in children and adolescents. Disparity from the WHO under 5 growth standard exists, where the IOTF extrapolated BMI 17 cut off between ages two and five years lies between the –1 to –2 SD lines. Although the WHO Child Growth Standards (2006) for children under five years provides for under two year olds, it is a drawback that the IOTF grades do not extend to include this age for it is during this period that monitoring for malnutrition and intervening has the potential for the greatest impact on morbidity and mortality. Cameron (2007), pointed out that using the same cut offs for both sexes without adjusting for the tempo of pubertal development in statistical analysis while constructing the graphs, was unusual. Nevertheless he considered the charts especially useful in countries in which both over- and under-nutrition are occurring simultaneously as a result of rapid economic change.

Inter-population comparisons of growth at adolescence are incomplete without assessing pubertal status, which is recommended by the WHO Expert Committee on Anthropometry (1986). The population median maturational age is subtracted from the international reference chart median age, and the difference is added or subtracted from the corresponding reference for age specific comparison. Cultural difficulties in obtaining details beyond enquiry about menstruation inhibit otherwise detailed comparisons (Shahabuddin et al. 2000). However, even when pubertal stages are available, results are commonly reported and compared in an uncorrected format (Garnier et al. 2005, Simondon et al 1998). A reason may be that as catch up frequently occurs during a delayed and possibly prolonged puberty, it is the eventual growth outcome that is certain. The WHO recommendation appears more honoured in the breach than fulfilment.

2.4.4 The South-East Asia region, Sri Lanka, and prevalence of undernutrition

The South East Asia Region has great diversity in physical and population size, from India to the Maldives, in geographical size 7th to 210th, population 2nd to 176th. The infant mortality rate of Bhutan is the tenth highest in the world at 102 per 1000 live births; India, Myanmar, Nepal, Bangladesh, Maldives range from 57 to 74, Indonesia 37, Sri Lanka 19; Thailand with 17 per 1000 births is 116th (Central Intelligence Agency World factbook).

Tanner's aphorism *'growth is a mirror of conditions in society'* encapsulates arguably the most resilient of proxies for children's health and how societies provide nurture (Tanner 1999). In this regard Sri Lanka is a paradox within what has been described as the Asian enigma (Ramalingaswami et al 1996): despite experiencing a debilitating civil war it does not suffer from major food shortages, has a health service accessible to all, and high levels of literacy. Yet it is largely indistinguishable from its neighbours in international comparisons of indices of undernutrition (de Onis et al. 2003, WHO 2006). The Sri Lanka per capita income at $US 4,200 *per annum* places it 150th in the world, the proportion of the population below the poverty line is 22% at 97th, and literacy 90% at 118th in the world. Life expectancy is 75 years, 83rd in the world. It has a largely rural population, 41% live on 2$ a day, 16% to 22% of births are low birth weight, and the immunisation rate at one year is 99%. Overall, it ranks 102nd on the Human Development Index, a United Nations tool for comparison using a composite of measures (Ministry of Health 1998, United Nations Human Development Programme report 2007/8). Nutritional diseases are common with high prevalence in Sri Lankan children of anaemia, 45% and clinical Vitamin A deficiency, 0.6% (WHO 2006).

On a scale of severity of prevalence of undernutrition, less than 20% is low, 20-29% moderate, 30-39% high, and >40% very high (Golden 1994). In children under five years in the South-East Asia region (SEAR), the geographical area of the present study, the prevalence of -2 SD in height is 35% and underweight 37%. This is above the average of 27% and 23% respectively for growth faltering in developing countries (de Onis et al. 2003).

Children

WHO (1997) cites the under five year old prevalence of -2 SD in height in Sri Lanka as 25% compared with 30% in the Maldives, 38% Indonesia, 45% India, 47% Bangladesh, and 63% in Nepal. Underweight, –2 SD in weight, in Sri Lanka at 40% compares with 36% in Indonesia, 38% Bhutan and Maldives to 47% in India, Bangladesh and Nepal.

A number of recent reports from SEAR include national and district surveys. They are categorised in three bands, according to prevalence of –2 SD for height. Prevalence of underweight as –2 SD weight, and thinness as –2 SD BMI are included where reported.

- Low prevalence

Karnataka, India: –2 SD height 9%, underweight 31% (Joseph et al. 2002).

Purulia district, India: –2 SD height 18%, underweight 34% (Chowdhury et al. 2008).

- Moderate prevalence

Pakistan 1: –2 SD height 27%, underweight 20%, thin 15% (Onyango et al. 2007).

Pakistan 2: –2 SD height 17%, underweight 30%, a national survey of urban children aged five to 14 years (Jafar et al. 2008).

Malaysia: –2 SD height 29%, underweight 26% (Marjan et al. 1998).

- High prevalence

Maldives: –2 SD height 37%, underweight 40%, thin 20% (Onyango et al. 2007).

Nepal: –2 SD height 43%, underweight 45 to 50%, (Ghosh et al. 2009).

Pakistan: –2 SD height 35%, underweight 30% in children in a squatter settlement (Mian et al. 2002).

West Bengal, India: –2 SD height 40% (Som et al. 2007).

It is evident that across the SEAR the background prevalence of undernutrition is relatively stable, at 30 to 40%, while height –2 SD is the more variable, from country to country. This is usually ascribed to the chronicity of undernutrition, the longer and more severe the more likely –2 SD height ensues, and the less likely catch up occurs.

Adolescents

Under conditions of adequate nutrition 25% of an individual's adult height is attained in adolescence. This is therefore an important period for comparison of growth outcomes.

Among the most deprived, in rural Bangladesh, Shahabuddin et al (2000) found 65% had a BMI below the fifth centile, falling from 95% at 10 years to 12% at 17 years. This was a function of the change in prevalence in -2 SD in height from 34% at age 10 to 65% at 17 years old as weight was maintained or increased in puberty. The authors appealed for a narrowing of the BMI cut–off, to lower it for areas with chronic undernutrition with height less impaired than weight to give greater relevance to its use. The need for the IOTF grades for thinness was becoming apparent (WHO 2006).

Adolescents with height less than -2 SD studied in Latin America, the Asian subcontinent, Africa and the Philippines did not improve their mean height centile across the entire eight years of adolescence (Kurz 1996). It may be an argument for extending the age of termination of such studies, as puberty was likely to be delayed or prolonged. This was noted to be particularly relevant in males (WHO 2006) in whom growth continues throughout puberty, in contrast to females, who grow earlier in puberty.

Although prevalence of –2 SD in height 16% and underweight 10% was low for Bangladesh in the Ahmed et al. (1986) study of urban schoolgirls, its significance lay in parents being middle class and well educated. The assumption would normally be that this advantage would have prevented significant undernutrition. Instead it raises questions about the origins of growth retardation in developing countries. Not only are there large differences within countries related to poverty, but when even relatively impoverished families migrate from poorer developing countries to more affluent developed ones, the growth of their children improves (Kelly et al. 1997). It questions the basis of prolonged food supplementation programmes. They have been largely unsuccessful in altering height outcomes, despite a good dietary intake that includes micronutrients (Rosado 1999). Attempts to correlate impaired growth in height to recurrent infectious diarrhoeal disease have also been largely unsuccessful, as such episodes are usually followed by periods of catch-up growth. Of particular

relevance to the present study, respiratory diseases have little or no long-term impact on growth (Bhan et al. 2001). Evidence is accruing that chronic enteric pathogens, such as Giardia lamblia, are the likely cause of impaired growth in height, by altering gut enterocyte function (Lunn 2000, Goto et al. 2002).

2.5 SUMMARY

This review has examined growth in children with CL/P in the developed and developing world. The completeness of growth faltering and catch up in early childhood, versus changes in height velocity during childhood with variable catch up in adolescence are the subject of controversy. Two rather different growth patterns are described, and debated, in the developed world. The first argues that undernutrition may play a part in early growth impairment, but after surgical repair of the palate near complete catch up occurs. The second maintains that growth potential may be programmed differently in CL/P, starting in utero, and despite surgery facilitating improved feeding, long term growth patterns may result in three height outcomes: normal, normal after catch-up, or some loss of adult height. In the developing world the growth of the general population may be affected by undernutrition. In some developing countries the growth of infants and young children with CL/P is more impaired than the noncleft population. Very limited information is available on growth in later childhood and adolescence, and virtually none on adults. The literature on skeletal maturity in CL/P in the developed world shows a trend to relative immaturity for age, but findings are far from consistent.

2.6 AIMS OF THE STUDY

This thesis is an observational study that set out to collect data over a prolonged period in a group of individuals with CL/P who were likely to suffer greater challenges to growth than the noncleft population. It was therefore determined:

- To record the growth of subjects with nonsyndromic CL/P. Their selection minimised the potential confounding effect of syndromes that may affect growth.
- To carry out a growth survey of the local population to develop a growth reference for local use where previously there was none. Contemporaneously to assess pubertal status and menarche for the same purpose.

These data to be used to evaluate the following hypotheses:

Hypothesis 1. Do changes in somatic growth relate to the timing of surgical closure of the cleft lip and/or palate?

Hypothesis 2. Does growth to adulthood of subjects with CL/P differ from that of the noncleft Sri Lankan population?

Hypothesis 3. Individuals with cleft lip do not share the mechanical difficulties of those involving a cleft of the palate comprising CL(P) and CP. Do they show similar growth to those with no cleft?

Hypothesis 4. Does skeletal maturity obtained from hand and wrist x-rays of subjects with CL/P and noncleft individuals differ?

Hypothesis 5. Do observations and conclusions drawn have translational potential in management for both groups as individuals and as populations?

CLINICAL AND ANALYTICAL METHODS

3.1 SUBJECTS AND CLINICAL METHODS

3.1.1 Introduction

This study set out to ascertain somatic growth in subjects with previously unoperated CL/P presenting to the Sri Lanka cleft lip and palate project (SLCLPP), and to compare their growth with a local non cleft population. It has three components. Firstly, a growth study of nonsyndromic subjects with CL/P, measurements taken at the time of operation, and at follow-up. This constituted a mixed longitudinal and cross-sectional collection of data.

Secondly, a growth survey of a representative Sri Lankan non-cleft population which is cross-sectional, and hereafter called the SL Reference, to compare their growth with the CL/P subjects.

Third, hand and wrist radiographs for skeletal maturity of CL/P, and a control population of selected non-cleft subjects from the SL Reference growth survey. The radiographs of the CL/P subjects constituted a mixed cross-sectional and longitudinal study, the non-cleft subjects a cross-sectional study.

All subjects were evaluated for growth by the same anthropometric methods and are considered jointly for this purpose.

Ethical approval was obtained from both the University of Ruhuna Ethics Committee and the Great Ormond Street Research Ethics Committee, copies in Appendix A1 to 4. For the radiological study, printed patient/parent information was provided. Signed consent was obtained for the examination from a parent in the case of schoolchildren, or the individual themselves over that age. This method was deemed sufficient for participants to be made aware of the benefits to society and risks to the individual involved, as the literacy rate of Sri Lankan adults is 92%, and secondary school enrolment is 87% (UNICEF 2009).

3.1.2 Selection of subjects for study

Cleft lip and palate subjects

The subjects of this study were drawn from those who were selected for operation in the SLCLP Project. The project team made three surgical visits to Sri Lanka, each of which was preceded by newspaper advertisements placed by the Professor of

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Paediatrics, Professor Sanath Lamabadusuriya, four weeks before arrival of the team. In addition, referrals to the project were received from local colleagues of the Professor. After the team had begun work, affected individuals were also identified in public places such as bus stops and market places, and approached directly in the street by senior members of the SLCLPP. A stratified process of triage, giving priority to the young and previously unoperated, safe for surgery in the limited facilities, with developmental potential for speech, was devised to deal with the hundreds of potential patients who attended on each occasion (Mars et al. 1990). People came predominantly from the surrounding Southern Province. A small number travelled from as far afield as war torn Jaffna in the northernmost point of the Island, and Hill Country tea estates which are known to have the poorest of populations (UNICEF 2001).

Only those receiving primary cleft surgery performed by SLCLPP surgeons, and attending for follow up were included in this study. In a small number of subjects (5 males and 7 females) previous primary repair of lip or palate had been attempted. These had completely broken down and the individuals were assessed and treated as for primary repair.

All CL/P patients were then assessed by history and examination for evidence of additional abnormality. This was found in 10 percent, and those subjects were excluded. Chromosomal analysis was not available in Sri Lanka and so subjects were identified as nonsyndromic by clinical examination only. Dr Melissa Lees, who subsequently became Consultant Clinical Geneticist to the North Thames Cleft Unit, made a significant late contribution to this evaluation during her participation in the 1998 visit. Subjects who had syndromic features were treated surgically but were not recalled for follow up visits.

Growth survey location

The survey centre was Galle, the largest city in the Southern Province. In 2001 the population was 90,000 with 26% below the World Bank poverty level compared with Colombo the capital, with a 650,000 population, at six percent. The Southern Province is among the poorest on the island (Vishwanath and Yoshida 2007).

Growth survey subjects

Recruitment was arranged by the staff of the Paediatric Department of the University of Ruhuna to provide a representative cross section of the Sinhalese population. Settings were: infant and preschool welfare and immunisation clinics; three types of school, namely local rural, national urban which are government financed, and single sex private schools; young adults, in a technical college in Galle, garment factories in Galle Fort, and in enterprise zones in which the rural population provided the majority of the young work force, urban sewing schools, and workers in hospitals. Selection was contingent on parental permission. Exclusions comprised skeletal malformations limiting height, scoliosis, and hemiplegia, and cyanotic congenital heart disease.

3.1.3 Clinical documentation

Basic clinical information collected from all subjects comprised age, sex, and rural or urban residence. Socioeconomic categorisation was by father's occupation group (FOG) into three classes corresponding to the divisions of the Sri Lanka Government Statistician's classification. The breakdown of number of subjects per occupation, for each study, is shown in table B3.1.1 in Appendix B. All tables and figures contained in appendices are prefixed by the relevant letter.

Subjects and their families were questioned about chronic medical conditions, consanguinity, birth rank and number of siblings. Pubertal females were asked if they had menstruated and, if an age of commencement was recalled it was recorded. Subjects with clefts were classified by cleft type as follows:

- Cleft lip only, all varieties, including those with alveolar clefts (CL)
- Bilateral cleft lip and palate (BCLP)
- Cleft palate only (CP)
- Unilateral cleft lip and palate (UCLP)

Additional information included age at lip and/or palate operation, history of recurrent upper respiratory tract infections and chronic middle ear disease (CME), unilateral or bilateral deafness, and a family history of CL/P.

3.1.4 Measurements and equipment

Anthropometric measurements were obtained for height using a Seca infantometer reading to 1mm, the Holtain 'portable' stadiometer in 1990, and Leicester portable height measure reading to 1mm thereafter. Weight was recorded from portable electronic baby weighing scales accurate to 0.015 kg, and electronic floor scales accurate to 0.1 kg. The subjects were weighed in light clothing, without shoes and socks, and height was measured, with head positioned in the Frankfurt horizontal plane. Weight was recorded in 10 g units for infants, 100 g units for children and adults, and height in millimetre units for all ages. Body mass index (BMI) was calculated as the ratio of weight (kg)/height^2 (m). Age was recorded in years to two decimal places.

A plastic tape was used for head circumference, and mid upper arm circumference with the arm hanging loosely by the side; measurements were recorded in cms.

The skinfold thickness (sft) of triceps and subscapular areas were recorded using Holtain callipers to the nearest 0.2 mm. The average of two measurements was used. Pubertal development was assessed according to the five stages described by Tanner (1962). Axillary hair was classified using a four stage scale: A0 = none, A1 = slight growth, A2=moderate growth, A3=adult.

The Prader orchidometer was used to compare testicular size in mls. The larger of an individual's testes was recorded.

Radiological study for skeletal maturity, and cephalometry of the jaws, was limited to 20 subjects of each sex within a two year age period, performed once only, to provide cross-sectional data. Subjects were aged from six years to twenty years old. Thus x-rays were obtained at 6 to 7 years in 40 subjects, 8 to 9 years 40 subjects, and so on to 19 to 20 years 40 subjects, in addition to the anthropometry measurements obtained in all subjects. A standard x-ray of the left hand and wrist was obtained, positioning the middle finger in line with the forearm, the thumb in the position of rest. The cephalometric study and some of the SL Reference growth data have already been presented in a PhD (Worrell 2003).

3.1.5 Anthropometry training and data collection for the growth survey

Collection of the data was by teams of six junior doctors from the University of Ruhuna Paediatric Department, led by Dr N Lyinarrachchi, Senior Lecturer. She liaised with the nurseries, school principals, institutions and factories. AH supervised the junior doctor anthropometry induction. Practising on five infants measured supine and five older children, they worked in pairs, one measuring, the other recording. Interobserver reliability to within 0.5 cm for height, head and arm circumference, and 1 mm for the average of two readings of skinfold thickness were the working standards. Teams were checked in the field.

Reliability of inter-observer measurements

The precision of measurements between observers was tested by the kappa statistic. For weight the kappa statistic was 1.0, as it was a digital readout. For height and head circumference substantial agreement was achieved, 90 to 92%, kappa 0.70 to 0.74, and for skinfold thickness moderate agreement, 72 to 75%, kappa 0.46 to 0.57. Puberty rating was performed once only on each child, with one male doctor in each pair using the Prader orchidometer. Examination of adolescent schoolchildren and young adults was by a doctor of the same sex for cultural reasons.

3.2 GROWTH SURVEY OF A SRI LANKAN NON-CLEFT POPULATION

The aim was to meet the requirements for a satisfactory reference within limited resources and time constraints of Sri Lanka cleft lip and palate project team visits.

Sample size

The smallest sample size recommended by Cole (2002) for a growth reference distance curve is 50 per year per sex from 0 to 20 years. After an initial survey in 1996, of subjects up to 18 years old, demonstrated that height had not levelled out, it was decided to extend the age of data collection to 24 years. Ages at collection were not at equal intervals; this is permissible as the LMS statistical programme treats age as a continuous variable, and the analysis is a form of regression.

Sampling

Sampling took place in community clinics, school offices or screened off areas in the institutions and work places. Sites were within one hour's drive of Galle, a distance of up to 30 kilometres.

3.2.1 Construction of the growth chart

The LMS Chartmaker constructs centile curves from reference data. The LMS programme Chartmaker Light version 1.67 was used (Cole and Green 1992, Cole et al. 1998, Freeman et al. 1995). It summarises the reference data in terms of three curves, the median (M), coefficient of variation (S) and skewness (L), the latter expressed as a Box-Cox power as they change with the independent variable age. These curves are fitted as cubic splines (a polynomial curve constructed piecewise) using penalised likelihood (a trade off between roughness and goodness of fit) by non-linear regression and the extent of smoothing required can be expressed in terms of smoothing parameters or equivalent degrees of freedom (edf). Raising and lowering the edf changes the deviance. The LMS Chart Maker Light programme allows choice of the variables, for height and weight, and fit can be improved by rescaling the age. Height and weight are monotonic; the BMI and skin folds growth curve is non monotonic requiring a log transform of the age to be performed, commencing at a power of 0, to improve the fit. The curves are handled individually, starting with M, then L and finally S. The curves are adjusted for the edf required. Initial settings are L curve (skewness) one edf corresponding to a normal distribution at all ages. The M curve (Median) is set at three edf for a curvilinear trend over time and the S curve (coefficient of variation) set at two edf for a linear trend. The programme sorts the values by age into Standard Deviation Scores (SDS). The distribution chosen was the 7 centiles at 0.67 SD intervals, 2, 1.33, 0.67, 0, -0.33, -1.33, -2 SD equating to 98th, 91st, 75th, 50th, 25th, 9th and 2nd centiles as most appropriate for the data.

The data was cleaned, by examining the distributions of height, weight, BMI, head and arm circumference and skin fold thickness for normality, before and after transformation. Outliers not due to a systematic error in measurement or notation of results suitable for correction, and which were biologically implausible, were deleted

on a one to one basis. After conversion to British SDS a cut off of -4 SD is recommended for smaller scale reference chart inclusion. However a cut off of -5 SD was chosen. This was appropriate as the stature of several individuals was clinically evident to be extremely small yet they were in a relatively good state of health. The processes of model fitting, graphical display, model checking and model saving were initiated, applying the steps illustrated in figure 3.2.1.1.

Figure 3.2.1.1 Reference male height, showing SDS (Z score) data plot and centiles
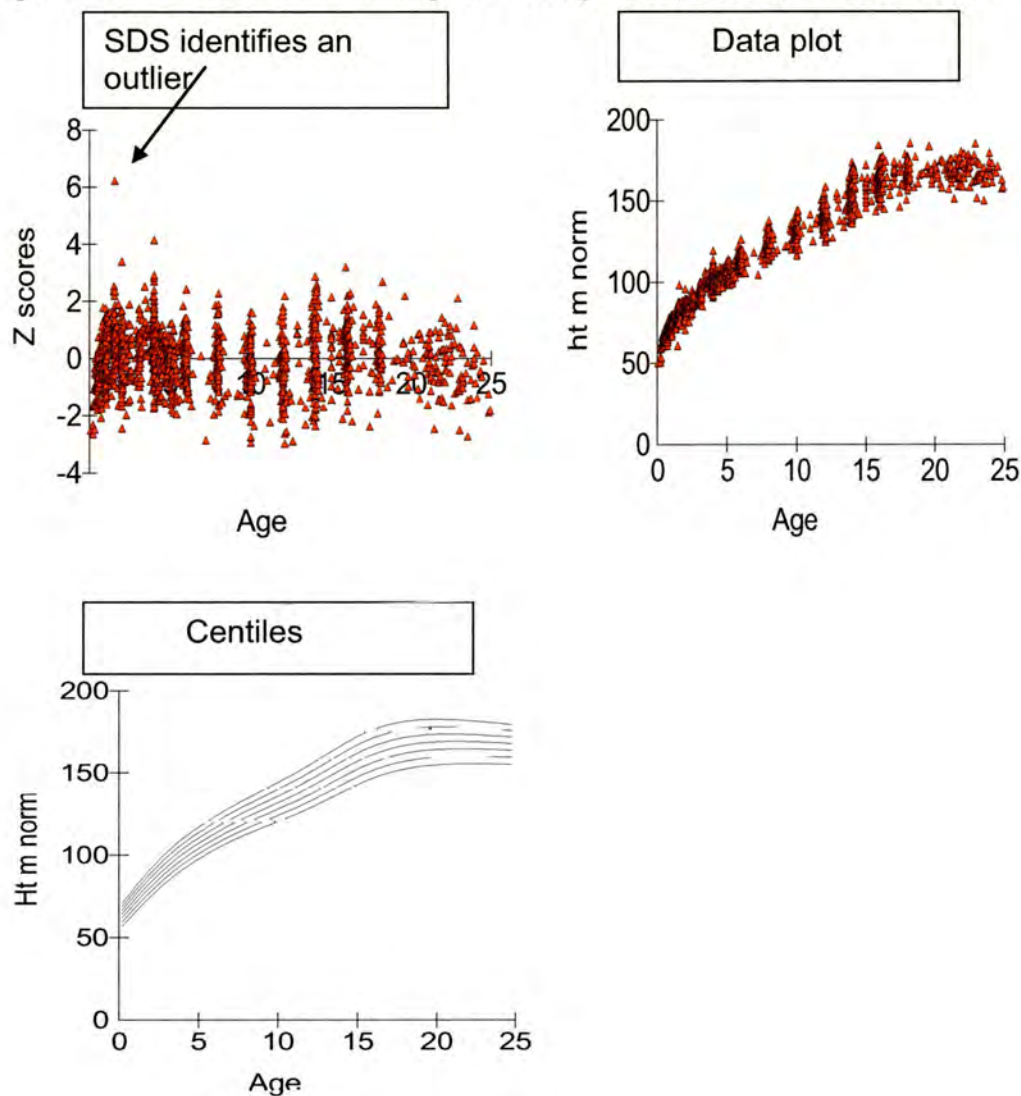
Model fitting began with the selection of L,M,S values for the predictor variable age.
Typical edf values:

Height: L1, M6, S2.

Weight: L3, M7, S3.

BMI: Power 0, L2, M5, S3.

Head circumference: Power 0.2, L0, M7, S4.

Arm circumference: L1, M6, S4.

Triceps skinfold thickness: Power 0, L2 M5, S3.

Subscapular skinfold thickness: Power 0, L3, M6, S3.

The LMS models obtained were saved in text form tabulated by age at monthly intervals from one month to 300 months (24 completed years) tab delimited and exported into Excel. The LMS Growth British spreadsheet was then pasted with the LMS Chartmaker data in a text file.

When analysing data to convert to Sri Lanka reference SDS in subjects older than the upper age of the programme, they were treated as if the upper age limit was frozen at that value. This was 24 years for height, weight and BMI. The curves generated were satisfactory up to 23 years for head circumference, 22 years for arm circumference and skinfold thicknesses.

3.2.2 Selection of international growth reference

The British growth reference was chosen for its comprehensive coverage by age. The charts and Growth Comparator span the ages 33 weeks gestation to 23 years for height, weight and BMI, and head circumference from 23 weeks gestation to 17 years in females and 18 years in males (Freeman et al. 1995). By comparison, the 2000 CDC charts, successor to the 1977 NCHS growth reference, cover the age range 0 to 20 years for height and weight, BMI from 2 years to 20 years old and head circumference up to three years old (www.cdc.gov/GrowthCharts/). The WHO growth reference takes in under five year olds at present, and hence it was unsuitable.

3.2.3 Statistical analysis and presentation of results

Using the presently derived SL Reference, and the British growth reference, standard deviation scores (SDS) were obtained via the LMS Growth Comparator to provide SD scores for height, weight, BMI and head circumference. Minitab Release 14 was used for statistical analyses. Significance level was <0.05.

Presentation of results

Significance levels in tables were given and identified as follows: * = p <0.05, ** = <p 0.001, *** = <p 0.0001, for ease of perusal.

Where age is stratified the following terms are used interchangeably in the text: under two years old = infants; two to nine years old = children/childhood; ten to 18.9 years = adolescents; 19 years and above = adults/adulthood. The age of adolescence is as defined by WHO (1986). Tables in the appendix are prefixed by the subsection letter A, B (on a CD in the back cover pocket) or C.

CHAPTER 4

RESULTS: GROWTH SURVEY, CL/P GROWTH STUDY AND SKELETAL MATURITY SURVEY

4.1 RESULTS OF GROWTH SURVEY

4.1.1 Subject profile comparison with national demography for suitability as a growth reference.

The study was conducted in three periods, in 1996, 1999, and 2004. In 2001 the planned data collection was abandoned due to a strike by university staff after recruiting 72 subjects. Data was obtained from 3,321 individuals aged from 3 months up to 25 years.

Figure 4.1.1 The Sri Lanka Reference population age profile.
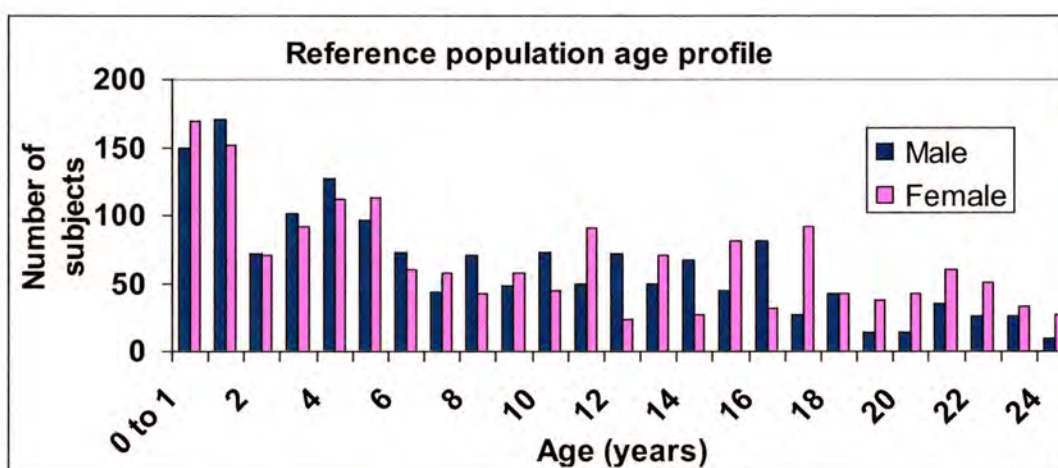
Relatively large groups were recruited under 5 years to improve the reliability at the lower age edge of the data. For each sex 150 per year were included for the first two years, and 71 to 127 from two years to five years old. Between the under fives and over 19 years they averaged 57 males (27-81) and 54 (24-81) females per year of age. Recruitment was less than originally planned, principally in two age groups; in the first four months of life a total of 17 infants from both sexes, and in males from 19 to 24 years a total of 124, comprising 14-35 subjects per year, the lowest cohort being nine at 24 years. The smallest groups for females were 24 at 12 years, 27 at 14 years and 32 at 16 years. Two percent, 57, of the data sets were eventually discarded for inadmissible or inadequate data, leaving 1,583 males, 49% of the total, and 1,682 girls for inclusion in the chart making process.

4.1.2 Comparison of potential confounders with national statistical data

The proportions of major demographic confounders for the national statistics and the growth study population were compared. Three major factors to consider were place of domicile as rural populations are generally poorer, socioeconomic grouping, and low birth weight. Ethnicity was not assessed as all subjects were Sinhalese.

Table 4.1.2.1 Comparison of national demographic variables with growth study subjects.

Fathers occupation[1]	Growth Study Classification[2]	Income level	National %	SL Reference %
Major groups 1-3	FOG 1	higher	11[1]	12
Major groups 4-6	FOG 2	middle	33[1]	31
Major groups 7-9	FOG 3	lower	56[1]	57
Rural			71[1]	62
Urban			29[1]	38
Low birth wt <2.5 kgs			16[3]	14

[1] Standard Occupational Classification for Sri Lanka 1971 (Ministry of Statistics and Census).
[2] Fathers occupational group (FOG) with minor modifications of [1] table B3.1.1
[3] Ministry of Health, Sri Lanka, Annual Health Bulletin 1998.

The population study proportions, in table 4.1.2.1, were within the 95% confidence intervals for the national prevalence. As such they confirmed that the subject profile of the data was a fair representation of the population, and suitable for the purpose of the study.

The medical background of the Sri Lanka Reference population was scrutinised for potential confounders, errors and omissions.

Exclusions:	Male	Female	Total
Congenital heart disease, cyanotic or restrictive	1	4	5
Deformed limbs/kyphoscoliosis	2	3	5
Missing data in the set eg date of birth, variables>2	13	6	19
Inadmissible data	19	9	27
Total			57 (2%)

Medical conditions accepted for inclusion	Male	Female	Total
Asthma	92	124	216 (7%)
Goitre (under treatment)	4	7	11 (0.3%)

Miscellaneous conditions: Migraine/headaches (26), epilepsy (21), eczema (14), gastritis (15), urine infections (8), rheumatic fever (5), arthritis (4), nephritic syndrome (3), menstrual irregularity (4), atrial septal defect (2), perianal abcess (1), Hirschsprung's disease (1).

Episodes of malaria, dengue, streptococcal infection, dysentery, snakebites and pneumonia are common, and often recurrent. Information on acute episodes such as these was not recorded.

Very low birth weight, under 1.5 kgs, comprised 17 individuals who were included as they were without significant medical problems.

Consanguinity for a first or second degree relationship between parents had a prevalence of 12%. Family size was recorded by total size of sibship: one 21%, two 33%, three 24%, four 12%, five 5%, six or more siblings 5%.

4.1.3 Sri Lanka Reference population growth data

Tables B4.1.3.1 and 2 show the SL Reference individual growth data with British SDS for each subject. Tables 4.1.3.3 and 4 show the data as means and SD by year of age. The latter tables are also shown with minimum and maximum values in tables B4.1.3.3 and 4.

The trend was for mean values to fall progressively with age, well below the British 50th centile, for height, weight, BMI and head circumference up to 16 years in females, and almost 18 years in males. A detailed comparison with the Cleft group and British reference will be presented in section 4.2.3.

Table 4.1.3.3 Male SL Reference height, weight, BMI and head circumference (HC) mean, SD and British (B) SDS, Arm circumference (MUAC), Triceps (T) and Subscapular (S) mean and SD.

N	%	Age (years)	Ht (cms)	Ht SD	Ht B SDS	Wt (kgs)	Wt SD	Wt B SDS	BMI (kg/m²)	BMI SD	BMI B SDS	HC (cms)	HC SD	HC B SDS	MUAC (cms)	AC SD	T (mms)	T SD	S (mms)	S SD
149	9	0.65	69.1	5.35	-0.31	7.42	1.34	-1.46	15.46	1.60	-1.85	43.10	2.64	-2.06	14.36	1.36	6.33	1.18	8.09	1.69
171	11	1.45	79.2	5.13	-0.67	9.47	1.37	-1.72	15.12	1.59	-1.84	45.83	1.72	-2.58	14.81	1.32	6.05	1.22	8.01	1.99
72	3	2.32	86.7	4.28	0.88	10.82	1.48	-1.93	14.76	1.44	-1.57	46.70	1.39	-2.95	14.74	1.38	5.66	1.35	8.11	2.28
101	6	3.46	95.6	5.71	-0.58	13.92	2.21	-1.13	14.32	1.39	-1.62	48.14	1.87	-2.52	15.06	1.31	5.74	1.60	8.04	2.10
127	8	4.34	102.8	4.94	-0.51	15.54	2.33	-1.04	14.67	1.49	-1.06	49.18	1.58	-2.16	15.29	1.52	6.11	2.10	7.88	2.22
97	6	5.45	108.9	5.48	-0.77	16.50	2.73	-1.63	13.83	1.38	-1.73	48.89	1.78	-2.58	15.50	1.62	6.18	2.33	7.64	2.21
73	5	6.33	113.0	3.52	-1.00	17.69	2.40	-1.75	13.81	1.27	-1.64	49.73	1.81	-2.32	15.76	1.45	6.49	1.90	7.28	2.34
44	3	7.75	122.0	5.45	-0.81	20.46	3.07	-1.69	13.69	1.39	-1.74	50.02	1.77	-2.40	16.21	1.60	5.88	1.32	6.64	1.82
71	5	8.27	124.3	4.90	-0.93	21.14	3.19	-1.85	13.63	1.21	-1.87	50.67	1.41	-2.08	16.44	1.42	6.01	1.46	7.26	1.86
48	3	9.76	129.6	5.38	-1.24	23.80	3.40	-1.96	14.11	1.29	-1.68	50.87	1.86	-2.22	16.55	1.62	7.73	3.22	7.93	3.20
73	5	10.26	132.5	6.21	-1.14	25.10	3.17	-1.85	14.28	1.24	-1.66	51.59	1.76	-1.86	17.40	1.52	7.07	2.31	8.00	2.03
49	3	11.78	140.2	5.95	-0.99	30.06	6.83	-1.62	15.20	2.83	-1.65	51.47	1.26	-2.20	18.26	2.13	8.18	4.23	8.62	4.00
72	5	12.21	141.0	7.48	-1.17	29.87	6.00	-1.90	14.91	2.02	-1.91	51.47	1.75	-2.29	18.22	2.23	7.38	3.93	8.12	4.04
50	3	13.72	150.0	8.57	-1.25	35.80	7.24	-1.77	15.77	1.97	-1.78	52.44	1.97	-2.02	20.14	2.34	6.33	1.58	6.99	1.42
67	4	14.21	153.7	9.27	-1.23	38.21	7.99	-1.75	16.03	2.04	-1.79	53.13	1.78	-1.69	20.36	2.30	7.38	2.81	8.70	3.74
45	3	15.63	160.2	7.48	-1.49	43.87	8.25	-1.94	16.99	2.32	-1.67	52.81	2.06	-2.12	21.89	3.03	7.46	1.99	7.06	2.45
81	5	16.20	163.5	6.84	-1.40	46.18	6.91	-2.00	17.21	1.79	-1.63	53.74	1.56	-1.73	21.90	2.14	7.17	2.38	7.18	2.65
27	2	17.67	165.7	7.20	-1.58	48.68	6.36	-2.49	17.68	1.61	-1.72	53.66	2.45	-2.05	23.60	2.82	8.29	2.78	6.18	1.24
42	3	18.53	167.6	6.03	-1.37	51.19	7.45	-2.37	18.19	2.31	-1.72	53.95	1.69	-1.93	23.34	2.12	8.97	3.29	6.56	2.17
14	1	19.46	169.9	5.18	-1.17	54.51	6.13	-2.01	18.93	2.36	-1.48	53.61	1.67	-2.13	23.47	2.65	9.62	3.52	6.85	2.44
14	1	20.46	169.0	5.19	-1.22	57.86	9.05	-1.72	20.26	2.96	-1.04	51.01	1.09	-3.65	21.86	1.83	9.55	3.31	6.41	3.14
35	2	21.42	167.1	6.27	-1.27	59.29	3.68	-2.08	20.88	0.99	-0.48	53.71	1.44	-2.07	24.00	2.58	10.76	3.59	8.06	3.36
26	2	22.35	170.0	8.26	-1.21	55.20	5.64	-2.29	19.00	0.49	-1.86	54.49	1.36	-1.62	24.65	2.46	12.39	5.04	8.06	3.64
26	2	23.37	169.1	5.24	-1.22	57.95	4.05	-1.77	20.52	0.62	-1.02	54.43	1.30	-1.65	24.78	2.42	10.49	3.72	7.22	3.02
9	0.5	24.43	171.3	4.98	-0.98	66.22	5.98	-0.66	22.69	1.04	-0.19	55.19	1.50	-1.21	26.19	2.73	11.81	4.24	9.48	4.81

Table 4.1.3.4 Female SL Reference height, weight, BMI and head circumference (HC) mean, SD and British (B) SDS, Arm circumference (MUAC), Triceps (T) and Subscapular (S) mean and SD.

N	%	Age (years)	Ht (cms)	Ht SD	Ht B SDS	Wt (kgs)	Wt SD	Wt B SDS	BMI (kg/m²)	BMI SD	BMI B SDS	HC (cms)	HC SD	HC B SDS	MUAC (cms)	AC SD	T (mms)	T SD	S (mms)	S SD
169	10	0.66	66.9	5.11	-0.65	7.37	1.26	-1.00	16.38	1.67	-0.81	42.36	2.15	-1.78	14.28	1.50	7.19	1.95	8.00	2.18
152	9	1.51	77.7	5.47	-0.96	9.15	1.56	-1.71	15.13	1.77	-1.54	45.15	1.59	-2.34	14.55	1.80	6.59	2.14	7.26	2.08
71	4	2.40	86.8	6.29	-0.74	11.27	1.90	-1.32	14.94	1.90	-1.16	46.35	1.07	-2.69	14.70	1.45	6.77	2.12	7.48	2.03
92	6	3.49	94.3	7.49	-0.69	13.76	2.84	-1.06	14.14	1.48	-1.21	47.70	1.42	-2.51	14.86	1.56	6.89	2.55	8.02	2.59
112	7	4.49	102.4	5.78	-0.61	15.28	2.61	-1.13	13.93	1.59	-1.07	48.52	1.06	-2.64	15.26	1.61	7.44	2.78	7.65	2.89
113	7	5.46	107.5	6.16	-0.86	16.60	1.24	-1.32	14.42	2.59	-1.09	48.73	1.03	-2.66	15.17	1.47	8.40	2.67	7.18	2.62
60	4	6.20	113.0	5.31	-0.84	17.02	2.17	-1.65	13.92	2.24	-1.42	49.40	1.24	-2.39	16.32	1.96	7.94	2.84	9.07	2.93
58	4	7.72	122.2	6.25	-0.65	21.08	3.74	-1.35	14.14	2.46	-1.49	49.71	1.51	-2.62	16.91	2.56	8.29	5.96	9.08	2.68
41	2	8.20	124.2	5.95	-0.72	22.07	5.11	-1.41	14.32	3.31	-1.51	50.29	1.50	-2.27	17.69	3.09	12.70	8.60	9.75	3.67
58	4	9.68	132.4	5.50	-0.68	26.58	4.71	-1.11	15.22	3.00	-1.17	50.87	1.32	-2.21	18.46	2.31	9.66	4.16	10.95	3.29
45		10.05	132.5	7.29	-0.98	25.48	3.58	-1.56	14.58	2.22	-1.55	50.94	1.25	-2.24	19.14	2.62	10.57	3.29	1.97	3.17
91	5	11.75	141.6	7.07	-0.95	31.24	5.91	-1.40	15.62	2.95	-1.53	51.41	1.51	-2.22	20.16	2.94	11.58	4.50	11.97	4.42
24	4	12.01	142.3	7.30	-1.05	30.38	4.40	-1.70	15.06	2.64	-1.97	51.93	1.46	-1.87	20.24	2.49	10.79	3.08	11.17	3.57
71	4	13.67	152.0	5.81	-0.95	40.48	6.49	-1.22	17.61	3.33	-1.00	52.29	1.76	-1.88	20.89	2.48	11.61	3.97	13.31	4.42
27	2	14.06	150.8	7.49	-1.38	39.14	6.56	-1.73	17.32	3.38	-1.30	52.66	1.47	-1.67	21.94	2.46	13.86	4.56	14.08	5.09
81	5	15.53	154.4	5.37	-1.37	44.88	8.89	-1.58	18.86	3.80	-0.90	52.55	1.45	-1.96	21.36	3.08	12.41	5.52	12.84	4.81
32	2	16.20	154.9	4.63	-1.41	43.04	6.53	-2.03	17.94	2.70	-1.34	52.16	1.16	-2.33	21.23	2.28	11.08	3.54	10.85	3.22
92	6	17.58	155.2	4.77	-1.32	45.01	6.52	-1.95	18.72	2.78	-1.12	52.87	1.57	-1.91	21.90	2.76	13.41	4.90	12.24	4.02
42	3	18.32	155.3	5.29	-1.34	44.04	6.81	-2.20	18.24	2.46	-1.25	52.60	1.57	-2.11	21.78	2.11	13.84	5.71	12.12	3.94
38	2	19.47	156.1	6.51	-1.28	45.07	6.76	-2.06	19.08	3.27	-1.44	52.26	1.36	-2.35	21.35	4.00	12.68	4.60	13.48	5.61
42	3	20.64	155.7	4.78	-1.32	45.13	5.19	-2.03	18.56	2.29	-1.43	52.68	1.00	-2.04	20.60	2.96	11.33	4.06	11.71	3.72
60	4	21.52	156.2	4.81	-1.25	46.26	6.22	-1.86	19.10	2.69	-1.32	53.16	1.11	-1.69	21.30	2.63	12.10	4.36	12.11	4.28
51	3	22.34	155.4	6.15	-1.40	46.56	6.10	-1.81	19.35	2.80	-1.33	53.44	1.32	-1.49	21.77	2.67	11.69	4.30	12.00	4.56
33	2	23.37	154.4	5.18	-1.56	45.61	4.63	-1.87	19.19	2.29	-1.14	53.38	2.19	-1.54	21.40	2.30	12.08	4.47	11.90	4.01
27	2	24.49	156.3	6.17	-1.23	45.20	6.21	-1.62	19.49	3.14	-1.72	52.59	1.90	-2.11	20.94	2.72	13.29	5.18	12.49	4.50

4.1.4 Sri Lanka Reference population LMS centiles. Height, weight, BMI and head circumference compared with British growth centiles

LMS and SDS tables, and Sri Lanka Reference (SL Reference) growth charts of seven growth variables comprising height, weight, BMI, head circumference, arm circumference, triceps and subscapular skin fold thickness are in Figures B4.1.4.1 and B4.1.4.2. Selected examples are presented to illustrate trends identified in the SL Reference population when compared with the British growth reference.

Figure 4.1.4.3 Scatterplot of male SL Reference values on British growth reference.
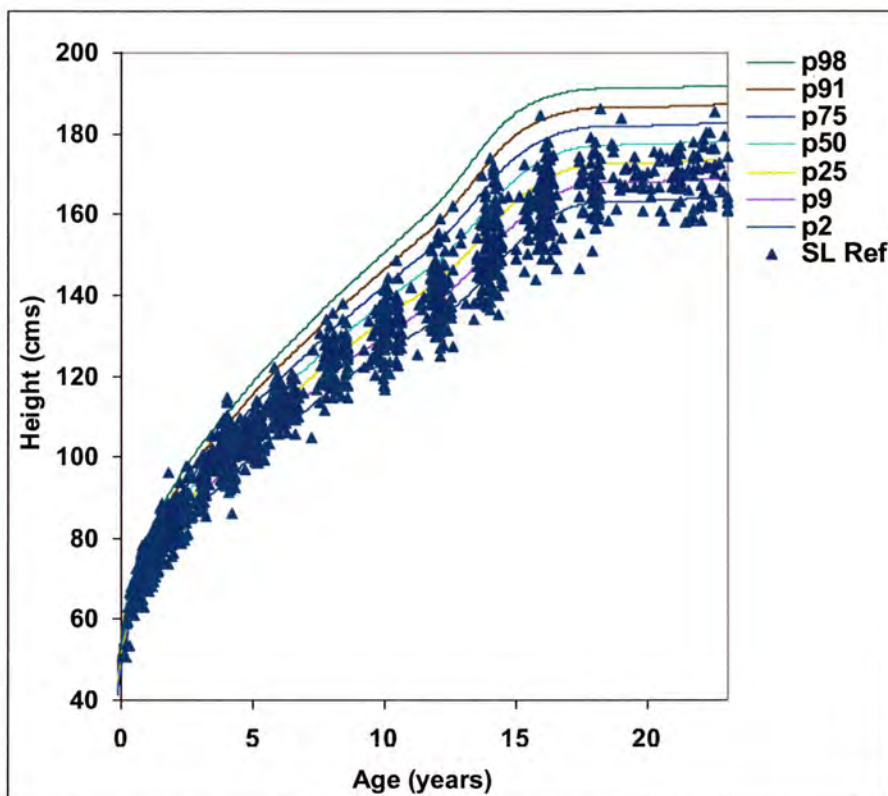
In figure 4.1.4.3 the pattern of data plots shows subjects' ages between 10 to 18 years were predominantly in even years. This was from subjects in the first major data collection. The subsequent collections filled in predominantly at the edges of the data, in early childhood and among young adults. The LMS programme incorporated this data seamlessly as it treats age as a continuous variable. The distribution of individual data plots shows diminishing height for age, and delay in the tempo of growth, manifest as a shift to the right relative to the British centiles.

Figure 4.1.4.4 Height of SL Reference males overlaid on British growth reference.
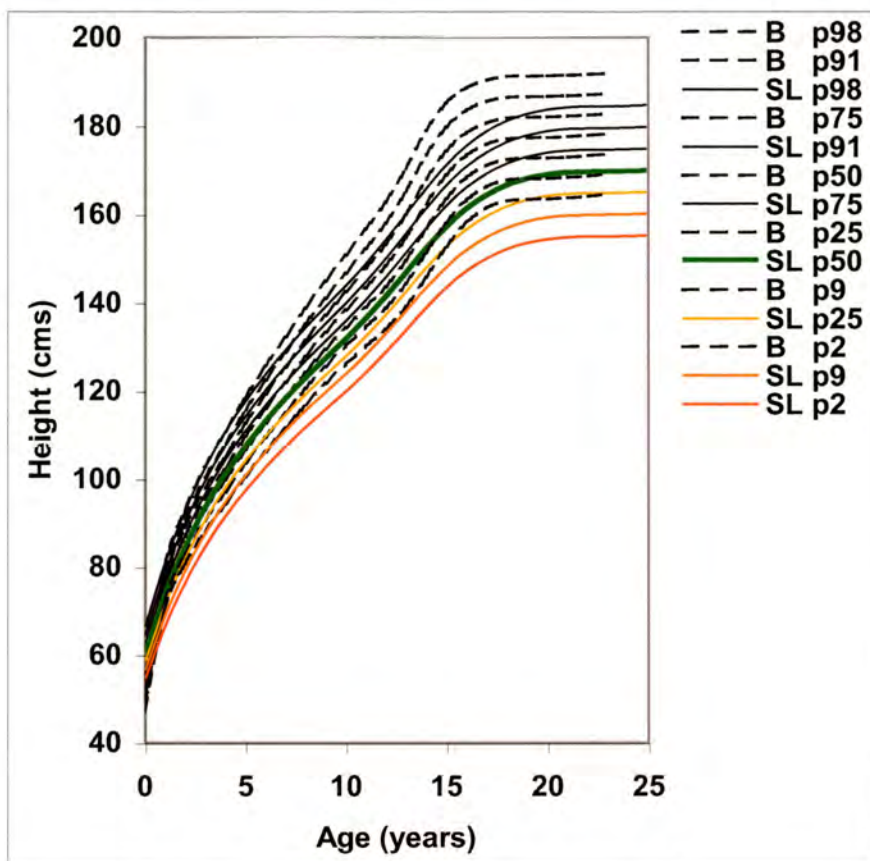
In figure 4.1.4.4 the key for percentages on the right of the graph is listed in order, SL Reference compared with British. Displacement downwards of the SL Reference height compared with the British centiles began in infancy, with the SL Reference 50th centile initially close to the British 25th centile. In puberty growth acceleration was delayed and muted. Here, unlike the British reference, the SL Reference growth curve lacked upward momentum; the 50th centile for height of the male SL Reference population fell, close to the 9th centile of the British reference. The 75th centile for SL Reference approximated to the British 25th centile, contrasting 25% of the SL Reference population above this cut off with 25% of the British below.

Figure 4.1.4.5 Height of SL Reference females overlaid on British growth reference.
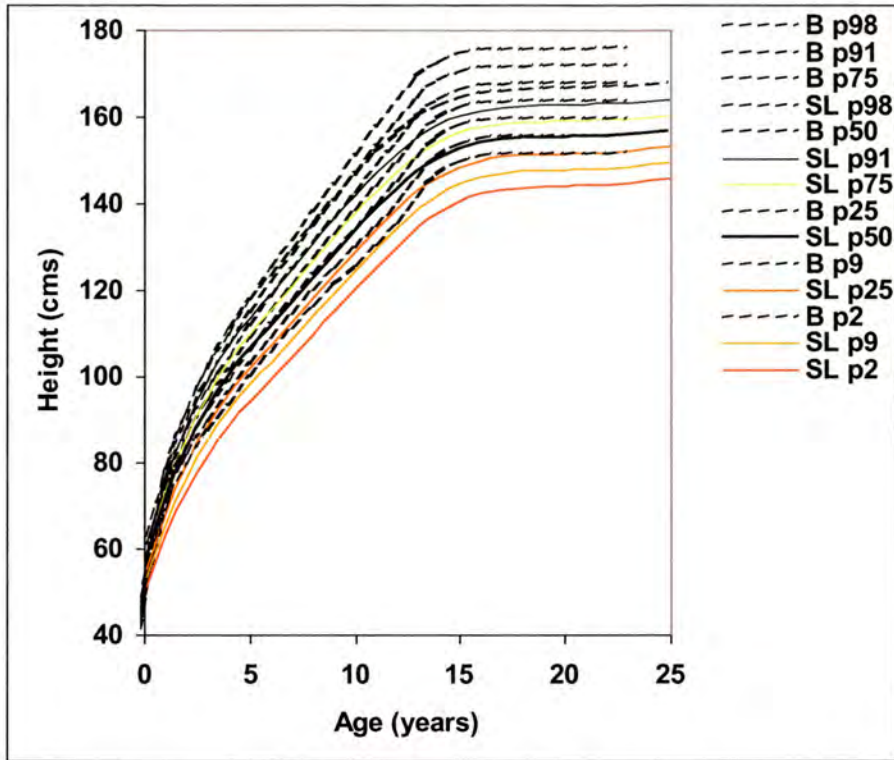
In figure 4.1.4.5 the female SL Reference 50th centile was closest to the 9th British centile during most of the growth period. Flattening of the growth curve appeared almost complete by 18 years in females, and 21 years in males. However, even by 24 years, growth in height had not completely levelled off in either sex. A final age for height completion was not determined, having increased by nine mm in males, and 13 mm in females, as shown in LMS median (M) for height, figures B4.1.4.1 and 2.

Figure 4.1.4.6 Weight of SL Reference males overlaid on British growth reference.
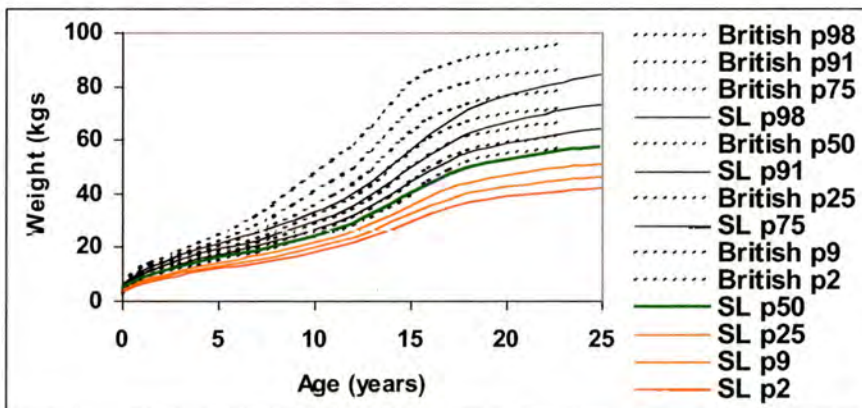
Figure 4.1.4.7 Female weight SL Reference and British growth reference.
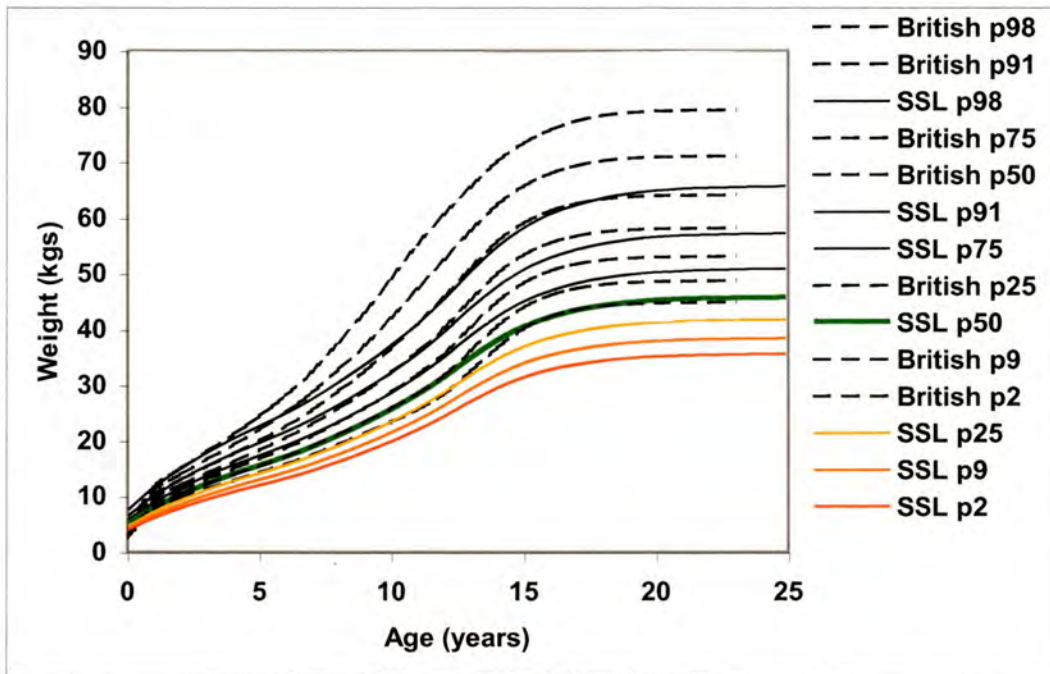
The 50th centile for weight fell away rapidly in the first year in figure 4.1.4.6 and 7. The trend thereafter was for males to follow the British 2nd centile, females the 9th centile, until puberty when it progressively declined to the 2nd centile or below for adults of both sexes. The difference between SL Reference centiles for height and weight thus approximated to one centile channel for a time.

Figure 4.1.4.8 Female BMI SL Reference and British growth reference.
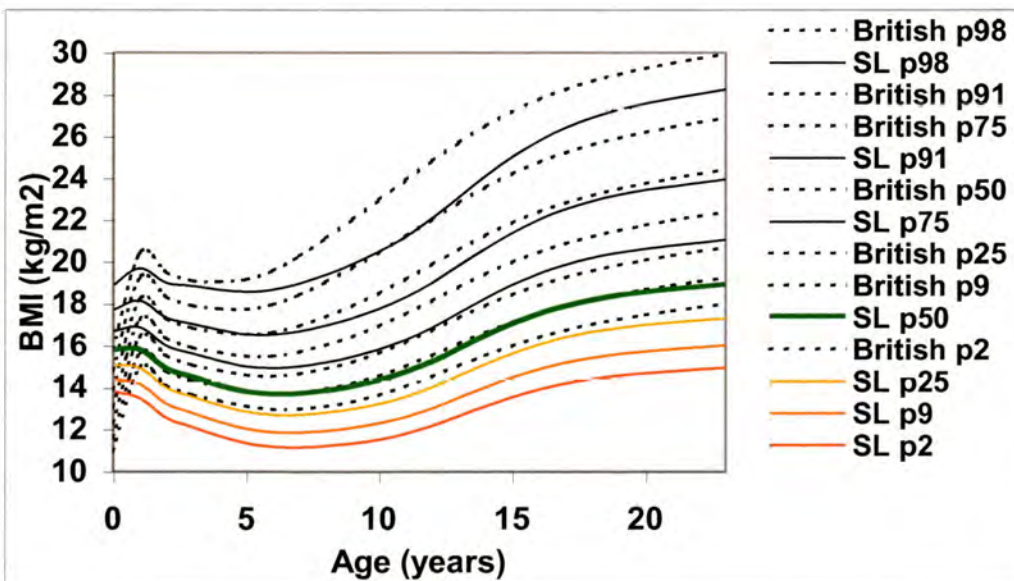
In figure 4.1.4.8, the SL Reference 50th centile BMI followed the 9th British centile. This applied for both sexes. In infancy the early BMI peak was reduced, partly through too few subjects in the first few months, and the wide range of values as growth faltering affected a substantial proportion, evidenced by the wide SD of their SDS in tables B4.1.3.3 and B4.1.3.4. After the nadir in BMI at about five years old, adiposity rebound occurred, within the boundary of the previous centile line.

Figure 4.1.4.9 Male head circumference SL Reference (SL) and British (B) centiles.
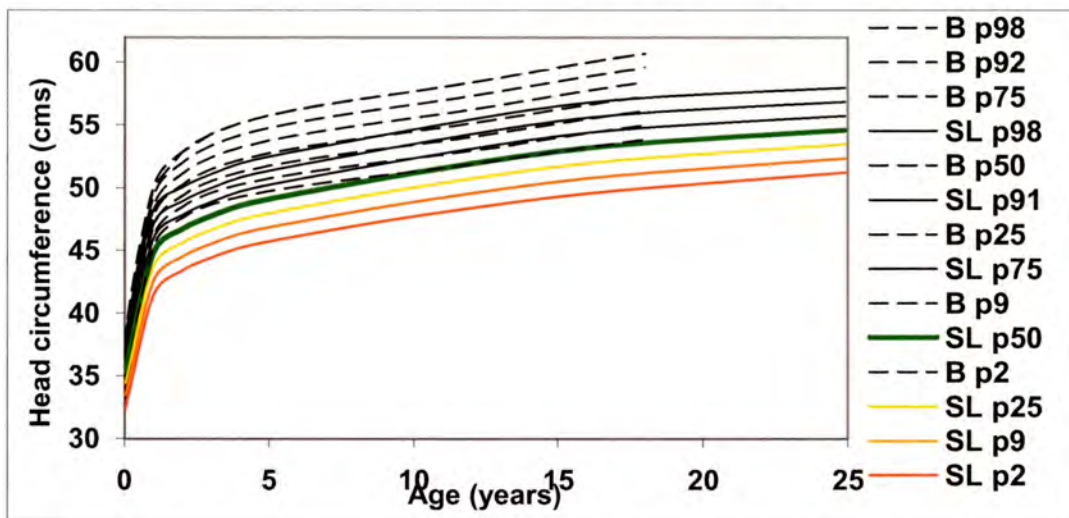
Figure 4.1.4.10 Female head circumference SL Reference (SL) & British (B) centiles.
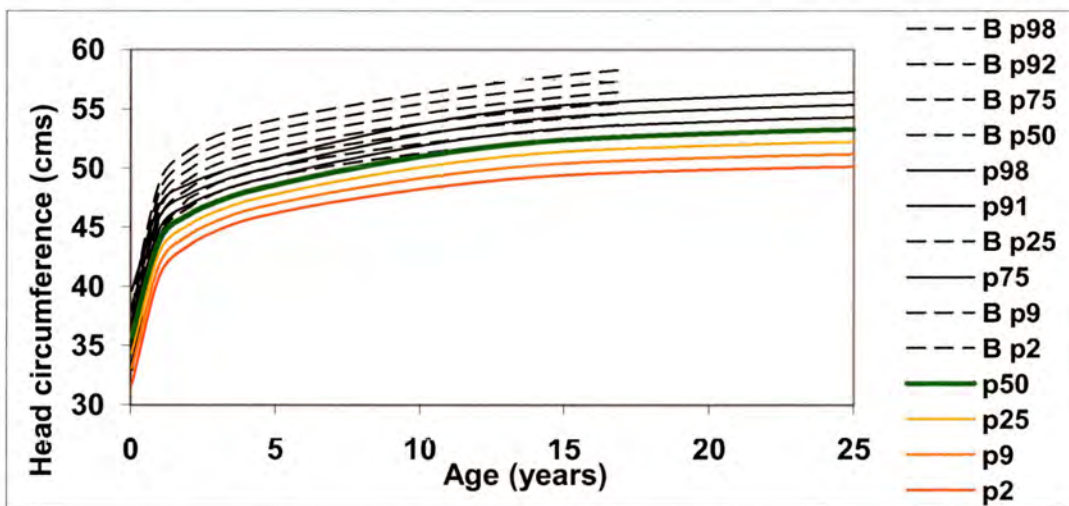
In figures 4.1.4.9 and 10 the 50th centile for the SL Reference population head circumference of both sexes lay below the British 2nd centile, from between the ages of one and two years up to adulthood. This was a full centile line difference from the

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position of height, and female weight before puberty variables on British centiles, 0.67 SD lower for most of the growth period.

4.1.5 LMS centile charts for mid-upper arm circumference, triceps and subscapular skinfold thicknesses

The Sri Lanka Reference data will be compared with selected studies from the literature.

Figure 4.1.5.1 Mid-upper arm circumference male and female SL Reference.
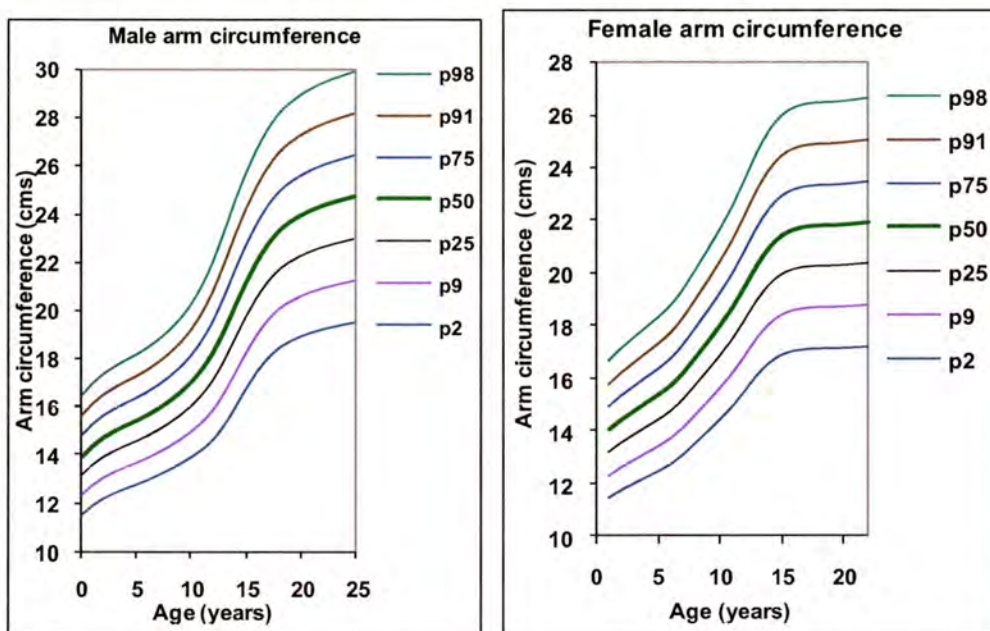
In figure 4.1.5.1 both sexes' mean mid-upper arm circumference (MUAC) was 14 cm in infancy. In males it rose to 24 cms by 20 years old, two cms greater than females. The edf of the female chart was 0.6.2 with no constant applied to the data to cause the sharp levelling off after 15 years of age. In a US reference (Najjar and Rowland 1987) from birth to 18 years the range was 15.8 to 29.8 cms in males, 15.0 to 27.5 cm in females. Studies over the same age range in similar populations to this study are limited. Thai children were 14.5 cm to 24 cm males, 14.2 to 22.7 cms in females, and Turkish children aged six to 17 years male means ranged from 17 to 23.6 cms, girls 15.5 to 20.9 cms (Khanjanashthi et al., in Eveleth and Tanner, 1990, Ozturk et al. 2009), mean values similar to the present study.

Figure 4.1.5.2 Male triceps and subscapular skinfold thickness SL Reference.
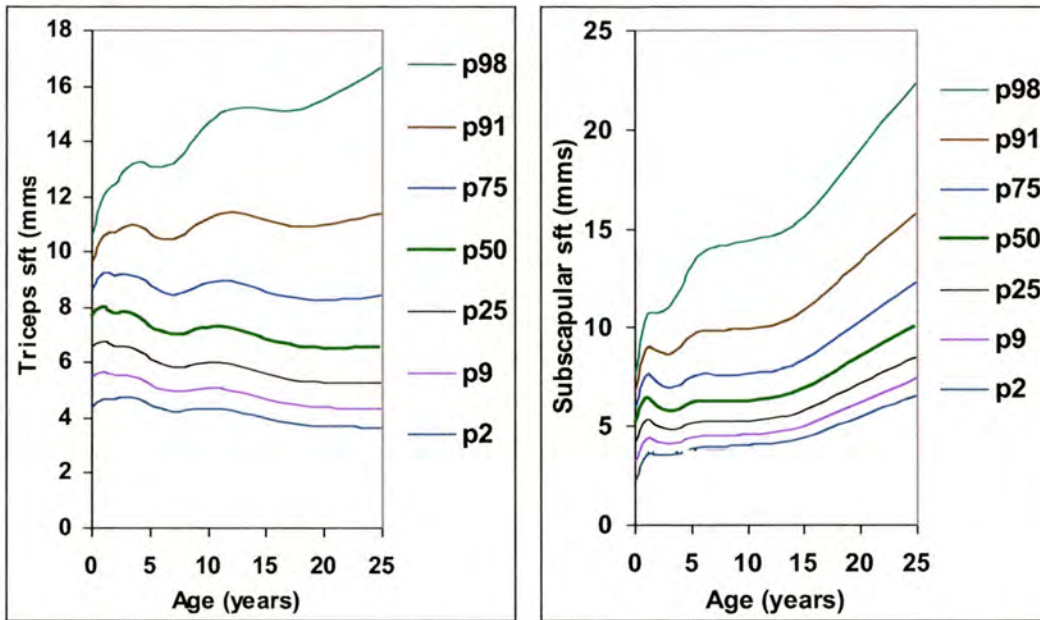
Figure 4.1.5.3 Female triceps and subscapular skinfold thickness SL Reference
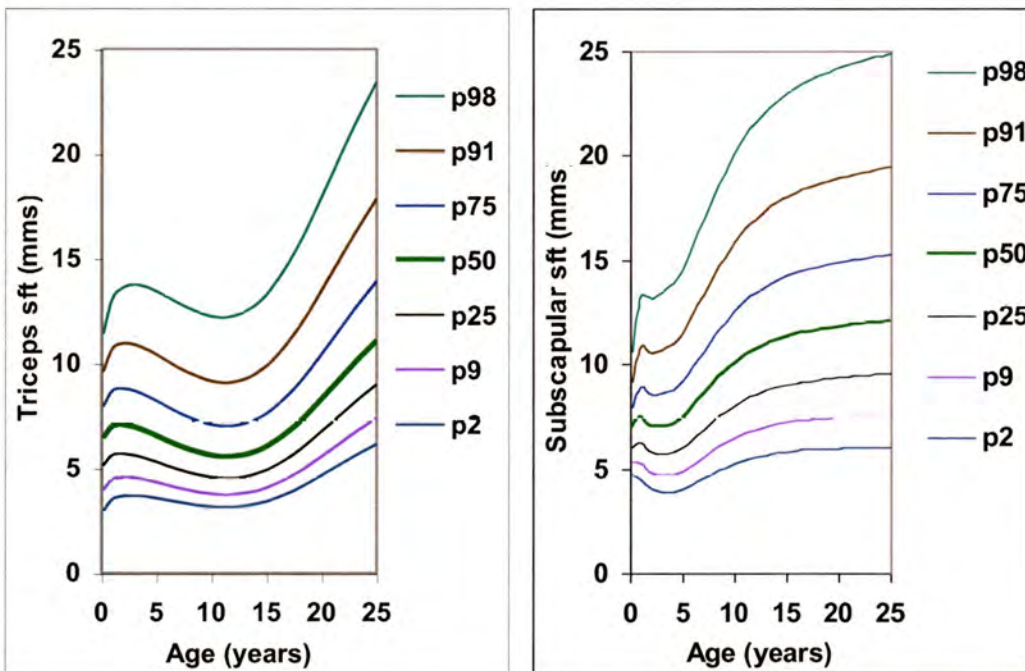
In figure 4.1.5.2 the 50th centile for triceps skinfold thickness (sft) in males was eight mm at one year, falling to six mms at 18 years. The National Centre for Health Statistics NHANES II survey (Owen 1982) of American children mean for the same age span was ten mm falling to eight mms. In figure 4.1.5.2 the mean SL Reference males subscapular sft was 5 mm which rose to ten mm over the same time period. In

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females, figure 4.1.5.3, the triceps skin fold rose from six to ten mms, compared with ten to 18 mms for NHANES II. Subscapular sft in SL Reference females 50th centile was similar to the NHANES II. From seven mm at one year it rose to 12 mm at 18 years. It appeared that SL Reference subjects preserved their trunk body fat but had reduced fat on their limbs compared with American children. Thai children aged birth to 17 years median values for triceps for males were ten to 12.7 mm, females 10.1 to 19.8 mm, close to the 98th centile for the SL Reference population, and closer to the mean values for American children.

The WHO (2009) under five year old Child Growth Standards Multicentre Growth Reference Study has added head circumference, arm circumference, triceps and subscapular skin folds. The 50th centile arm circumference is 13.5 cms in infancy for males, 13 cm for females, 14.5 cms and 14.2 cms at one year, increasing to 16.5 cms and 16.9 cms at five years for males and females respectively. The mean values from three months to five years for subscapular sft are 7.7 mm at three months to 5.5 mm at five years, triceps 9.8 mm to 7.6 mm boys, and to 8.8 mms for girls. All values are similar to the mean SL Reference.

These differences between the SL Reference and international references will be used to contextualise the growth patterns of a subgroup of individuals within the local population, comprising those with CL/P.

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4.2 GROWTH OF SUBJECTS WITH CL/P

4.2.1. Demographic results

The study of subjects with CL/P comprised 364 (58% male) individuals from whom 755 data sets were obtained.

Table 4.2.1 CL/P number of subjects and proportion.

	CL		BCLP		UCLP		CP	
	N	%	N	%	N	%	N	%
Male	32	15	33	16	121	58	24	11
Female	18	12	19	13	66	42	51	33
Total	50	14	52	14	187	51	75	21

The proportions were cleft lip (CL) 14%, cleft of lip and palate 65%, of which 14% were bilateral cleft lip and palate (BCLP) and 51% were unilateral cleft lip and palate (UCLP), and cleft palate (CP) 21%.

In this mixed cross-sectional and longitudinal study 154, 59% male, were seen once and 211, 58% male, on two to five occasions over a 20 year period.

Table 4.2.2 Data collection: number of data sets per subject, pooled male and female.

	1 data	2 data	3 data	4 data	5 data	Total N
Subjects	154	93	57	57	3	364
% of total	42	26	16	16	1	

The proportion of data sets of each cleft type was similar to the distribution of subjects within each type. The male to female ratio was 1:2 for CP, 1.3:1 CL(P). The 755 data sets were complete for height, weight, and BMI, with missing values for head circumference six, arm circumference 23, triceps and subscapular skinfold thickness 15. Tables B4.2.1 and 2 show the individual data sets of the male and female CL/P groups.

Figure 4.2.1.1 Age at data collection for male and female subjects with CL/P.
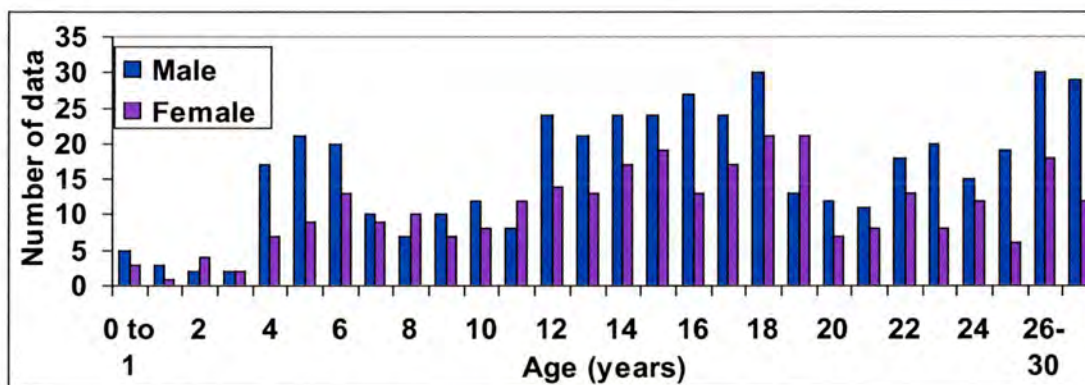
Age at data collection is shown in figure 4.2.1.1. Age ranged from two months to 64 years. The largest proportion was subjects between 11 to 20 years old, comprising those who had received surgery at that age plus subjects being followed up after surgery in the first ten years of life.

Age at primary cleft surgery

Figure 4.2.1.2 shows age at primary surgery for lip and figure 4.2.1.3 for palate, both potential variables that could influence somatic growth.

Figure 4.2.1.2 Age at lip surgery
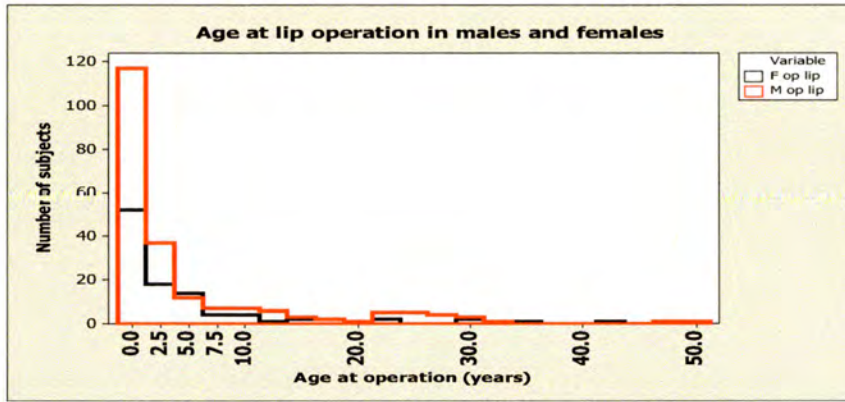
Figure 4.2.1.3 Age at palate surgery
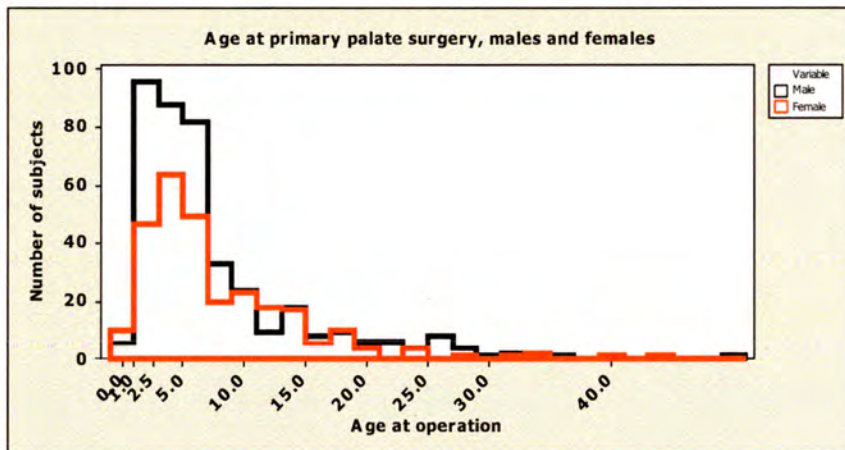
Surgery of the unoperated lip, whether as CL or in association with another type of cleft, was performed in 291 subjects, shown in figure 4.2.1.2. Age ranged from ten weeks to 49 years, median 1.1 years. 21% were over the age of five years. Of the 316 palate surgeries performed and shown in figure 4.2.1.3, the age of subjects ranged from seven months to 50 years old. The median age at operation was 5.8 years and 36% were over ten years old.

4.2.2 Plan of analysis of Reference population and CL/P groups

The analyses of the SL Reference population and CL/P groups are presented as follows:

4.2. Growth patterns of SL Reference and CL/P groups illustrated by data plots and mean height, weight, BMI and head circumference by age and sex plotted on British centiles.

4.3 Growth patterns of CL/P groups illustrated by data plots and mean anthropomorphics plus mid-upper arm circumference and skinfold thickness, by age and sex, on SL Reference centiles.

4.4 Growth comparison of subjects with CL/P including socioeconomic groups, and place of residence with British and SL Reference SDS.

4.5 Nutritional status of SL Reference and Cleft groups, illustrating the prevalence of -2SD and -3SD for height, weight and BMI.

4.5.3 A comparison of growth in subjects with CL versus palate, and evaluate whether CL is different from the SL Reference population.

4.6 Puberty. In considering pubertal change both SL Reference and British growth reference are used to compare growth through the stages of puberty.

4.7 Follow up of up to a mean of 20 years after primary surgery in the CL/P groups, applying SL Reference and British growth references.

4.8 Analysis of medical, family and social variables as potential confounders.

4.9 Skeletal maturity expressed as bone age, changes in relation to chronological age and puberty.

4.2.3 Growth patterns of SL Reference and CL/P on British centiles

The mean and standard deviation of the mean values of height, weight, BMI and head circumference of the SL Reference population and CL/P groups are contained in tables 4.2.3.1 to 4. The mean and SD growth patterns for these four variables are then plotted on British centiles. The numbers of CL/P group subject data below two years of age were small, limiting comparisons to be made for that time period. The growth of cleft types, CL, CL(P), CP were amalgamated as a single group.

Table 4.2.3.1 Male CL/P height, weight, BMI and head circumference (HC) mean, SD, SL Reference (SL) and British (B) SDS.

N	%	AGE years	Ht (cms)	Ht SD	Ht SL	Ht B SDS	Wt (kgs)	Wt SD	Wt SL	Wt B SDS	BMI (kg/m^2)	BMI SD	BMI SL	BMI B SDS	HC (cms)	HC SD	HC SL	HC B SDS
5	1	0.5	63.0	4.30	-1.23	-2.20	6.03	1.34	-0.74	-2.85	15.04	1.50	-0.06	-2.24	40.40	1.50	-1.04	-3.66
3	0.7	1.4	73.9	2.00	-1.16	-2.25	8.80	0.40	-0.40	-2.19	16.17	1.60	0.76	-1.10	45.20	2.20	-0.17	-2.94
2	0.5	2.6	85.2	2.82	-1.13	-2.01	12.40	0.14	0.38	-2.22	14.31	1.10	-0.10	-1.51	47.40	1.80	0.02	-2.50
2	0.5	3.7	93.2	4.40	-1.22	-1.69	11.60	1.38	-1.43	-3.05	13.76	1.27	-0.42	-2.11	47.70	2.17	-0.51	-2.98
17	4	4.5	98.0	6.30	-1.23	-1.81	13.10	1.71	-1.15	-2.73	13.63	1.05	-0.43	-2.06	47.80	1.99	-0.75	-3.16
21	5	5.5	104.2	4.20	-1.05	-1.78	14.80	1.48	-0.85	-2.56	13.62	0.83	-0.18	-1.87	48.70	1.48	-0.46	-2.80
20	5	6.3	106.4	5.60	-1.39	-2.38	14.99	1.87	-1.24	-3.40	13.2	1.34	-0.39	-2.31	48.40	1.73	-0.83	-3.17
10	2	7.3	113.1	4.40	-1.03	-2.01	16.98	1.52	-0.88	-2.92	13.28	1.08	-0.23	-2.14	48.50	0.90	-0.99	-3.29
7	2	8.3	117.8	9.90	-1.00	-1.03	20.10	3.99	-0.24	-2.52	12.71	0.73	-0.80	-2.77	49.70	2.10	-0.48	-2.74
10	2	9.3	123.8	6.50	-0.73	-1.86	20.91	2.50	-0.56	-2.70	13.64	1.27	-0.13	-2.01	49.70	2.00	-0.67	-2.89
12	2	10.5	127.0	2.85	-1.10	-2.18	22.45	2.14	-0.80	-2.88	13.91	1.21	-0.15	-2.05	49.80	1.50	-0.83	-3.04
8	2	11.4	133.7	8.70	-0.71	-1.70	24.84	4.50	-0.64	-2.82	13.77	1.08	-0.44	-2.45	50.90	2.20	-0.36	-2.46
24	5	12.4	140.3	10.20	-0.48	-1.54	27.53	5.60	-0.58	-2.65	13.92	1.21	-0.58	-2.62	50.30	1.83	-0.92	-3.06
21	5	13.3	141.2	6.40	-1.08	-2.00	29.16	4.00	-0.85	-2.73	14.57	1.23	-0.39	-2.48	50.70	1.70	-0.93	-2.98
24	5	14.4	148.1	9.50	-0.88	-2.04	33.30	6.57	-0.77	-2.69	15.04	1.52	-0.46	-2.56	51.60	1.87	-0.70	-2.66
24	5	15.3	156.6	6.10	-0.24	-1.76	39.15	6.30	-0.30	-2.60	16.36	1.86	0.05	-2.71	52.20	1.87	-0.57	-2.61
27	6	16.3	162.2	7.97	0.01	-1.54	43.20	7.30	-0.21	-2.82	16.23	1.92	-0.36	-2.39	52.10	1.90	-0.80	-2.71
24	5	17.4	161.4	7.90	-0.52	-2.13	45.00	5.78	-0.38	-3.02	17.25	1.57	-0.08	-1.95	52.40	1.80	-0.77	-2.71
30	7	18.4	163.2	6.20	-0.54	-2.10	45.31	5.50	-0.63	-3.45	17.1	1.74	-0.41	-2.32	53.00	2.10	-0.50	-2.50
13	3	19.4	163.6	6.84	-0.66	-2.01	47.30	5.27	-0.56	-3.34	17.74	1.98	-0.25	-2.24	53.00	2.50	-0.53	-2.50
12	3	20.4	161.3	6.60	-1.07	-2.27	47.20	3.37	-0.74	-3.59	18.02	1.61	-0.28	-2.17	52.30	1.20	-0.93	-2.91
11	2	21.2	163.2	4.10	-0.86	-2.08	47.74	4.65	-0.77	-3.60	17.92	1.74	-0.46	-2.49	52.80	1.53	-0.66	-2.60
18	4	22.3	163.3	4.72	-0.87	-2.16	48.04	5.52	-0.85	-3.76	17.97	1.63	-0.59	-2.48	53.40	1.56	-0.32	-2.25
20	5	23.1	164.5	6.81	-0.71	-2.02	52.71	7.37	-0.34	-2.85	19.55	3.00	0.12	-1.62	53.78	1.93	-0.11	-2.04
17	4	24.4	164.1	8.14	-0.77	-2.07	52.23	9.19	-0.52	-2.95	19.33	2.73	-0.14	-1.67	53.85	2.43	-0.07	-1.99
10	2	25.2	162.2	7.25	-1.03	-2.35	47.33	8.23	-1.15	-3.79	17.93	2.61	-0.90	-2.46	52.53	1.47	-0.81	-2.76
59	13	32.2	162.3	6.94	-1.02	-2.34	49.96	6.61	-0.80	-3.42	18.96	2.36	-0.33	-1.80	52.65	1.99	-0.74	-2.69

Table 4.2.3.2 Male CL/P mid upper arm circumference (MUAC), triceps (T) and subscapular (S) skinfold thickness, mean and SL Reference SDS (SL), and testes volume.

N	%	AGE (years)	MUAC (cms)	MUAC SL	T (mms)	T SL	S (mms)	S SL	TESTES (mls)
5	1	0.5	11.7	-1.95	6.7	-0.81	8.3	0.15	1
3	0.7	1.4	13.0	-1.09	4.9	-1.81	7.9	0.09	1
2	0.5	2.6	14.1	-0.37	7.0	-0.43	9.5	0.73	1
3	0.5	3.7	13.9	-0.95	4.6	-2.09	9.7	0.82	1
18	4	4.5	14.2	-0.80	4.7	-1.88	7.2	-0.21	2
21	5	5.5	14.8	-0.53	5.2	-1.28	7.6	0.25	1
20	5	6.4	14.4	-0.97	4.2	-2.09	6.3	0.43	1
10	2	7.3	15.0	-0.72	4.6	-1.64	6.7	-0.36	2
8	2	8.3	15.6	-0.50	4.5	-1.77	6.2	-0.50	2
10	2	9.3	15.8	-0.57	4.9	-1.46	6.3	-0.70	2
13	2	10.5	16.7	-0.30	5.5	-1.02	6.2	-0.62	2
8	2	11.4	17.3	-0.33	6.4	-0.43	7.4	-0.16	3
26	5	12.4	17.6	-0.54	5.7	-0.80	6.6	-0.60	4
20	5	13.3	18.4	-0.54	6.1	-0.50	7.0	-0.36	4
26	5	14.4	19.3	-0.56	5.7	-0.66	7.0	-0.51	7
26	5	15.3	21.0	-0.21	6.2	-0.30	6.5	-0.31	12
28	6	16.3	21.1	-0.50	6.2	-0.24	6.6	-0.28	15
24	5	17.4	22.5	-0.18	6.7	0.05	7.3	0.00	18
29	7	18.4	23.3	0.02	6.6	0.03	6.5	-0.22	18
11	3	19.4	23.3	-0.20	7.6	0.44	8.4	0.76	17
11	3	20.4	23.7	-0.14	6.2	-0.14	8.3	0.53	20
11	2	21.4	23.7	-0.16	7.7	0.47	6.6	-0.18	19
12	4	22.4	24.2	-0.06	6.6	0.04	7.7	0.50	22
4	5	23.6	24.1	-0.10	7.9	0.52	10.5	1.47	20
5	4	24.4	25.0	0.23	7.4	0.34	10.5	1.37	20
5	2	25.4	23.9	-0.18	5.6	0.03	7.2	0.41	20
59	13	32.2	24.7	0.12	8.2	0.60	7.9	0.35	20

Table 4.2.3.1 Male CL/P height, weight, BMI and head circumference (HC) mean, SD, SL Reference (SL) and British (B) SDS.

N	%	AGE years	Ht (cms)	Ht SD	Ht SL	Ht B SDS	Wt (kgs)	Wt SD	Wt SL	Wt B SDS	BMI (kg/m²)	BMI SD	BMI SL	BMI B SDS	HC (cms)	HC SD	HC SL	HC B SDS
3	1	0.4	60.93	3.47	-0.44	-1.97	5.10	0.69	-1.42	-3.23	13.74	0.75	-0.89	-2.79	39.20	0.75	-1.77	-3.54
1	0.3	1.2	73.90		0.07	-1.63	9.10		0.54	-1.53	16.66		1.01		44.10		-0.12	-3.52
3	1	2.3	81.47	8.90	-0.90	-2.46	10.10	1.14	-0.40	-2.47	15.22	1.97	0.60	-0.75	47.10	2.10	0.44	-2.65
2	0.6	3.6	90.20	0.22	-1.37	-2.44	11.05	0.79	-1.17	-3.35	13.58	1.02	-0.20	-1.93	45.60	1.77	-1.25	-4.4
7	2	4.9	97.87	3.51	-1.44	-2.46	12.56	1.03	-1.35	-3.53	13.11	1.49	-0.31	-2.21	46.56	0.67	-1.17	-4.09
9	3	5.5	100.80	7.21	-1.46	-2.57	13.90	2.18	-1.09	-3.16	13.68	1.31	0.04	-1.52	46.94	1.29	-1.14	-3.96
13	4	6.4	110.60	7.59	-0.55	-1.55	16.29	2.76	-0.63	-2.45	13.32	1.11	-0.23	-1.83	48.22	1.51	-0.68	-3.31
9	3	7.4	114.40	6.62	-0.87	-1.87	16.84	2.71	-1.08	-3.04	12.87	1.11	-0.57	-2.27	48.07	1.40	-1.03	-3.59
10	3	8.5	118.60	6.95	-1.21	-2.14	18.70	2.79	-1.15	-2.98	13.29	0.56	-0.45	-2.01	48.85	1.35	-0.86	-3.28
7	2	9.8	121.54	7.71	-1.88	-2.59	19.25	2.64	-1.92	-3.78	13.03	0.57	-0.89	-2.50	48.69	1.45	-1.22	-3.59
8	3	10.5	128.70	5.57	-1.27	-1.91	20.56	2.36	-1.97	-3.67	12.41	1.05	-1.51	-3.29	48.57	2.06	-1.42	-3.77
13	4	11.5	132.10	6.51	-1.51	-1.98	22.26	4.54	-2.13	-3.56	12.76	1.84	-0.41	-2.04	49.59	1.73	-1.02	-3.31
14	5	12.3	140.50	6.31	-0.69	-1.30	28.29	2.84	-0.90	-2.12	14.33	0.97	-0.71	-2.30	50.00	1.18	-0.86	-3.15
13	4	13.4	143.40	6.54	-0.87	-1.78	31.64	5.95	-0.74	-2.15	15.39	2.01	-0.46	-2.15	50.51	1.66	-0.77	-3.1
17	6	14.5	151.10	8.58	-0.08	-1.78	41.70	7.51	0.58	-1.28	18.26	2.52	0.61	-0.79	51.42	1.48	-0.37	-2.78
19	6	15.4	153.10	6.28	-0.01	-2.26	37.89	5.64	-0.32	-2.56	16.16	2.04	-0.48	-2.20	51.16	1.72	-0.57	-3.11
13	4	16.4	153.70	5.56	-0.10	-2.82	41.68	4.88	0.05	-2.80	17.64	2.02	0.06	-1.47	52.03	1.57	-0.13	-2.78
17	6	17.4	152.00	5.67	-0.49	-3.46	42.96	5.49	0.07	-3.31	18.59	2.17	0.32	-1.15	51.35	1.33	-0.52	-3.28
21	7	18.4	153.10	7.81	-0.35	-3.46	42.16	5.95	-0.17	-4.05	17.99	2.12	-0.02	-1.58	52.09	1.80	-0.12	-2.85
21	7	19.4	150.80	7.09	-0.75	-3.80	40.78	5.46	-0.47	-4.79	17.93	2.15	-0.08	-1.79	50.98	1.48	-0.75	-3.5
7	2	20.6	151.63	3.55	-0.63	-3.72	44.69	6.06	0.13	-4.11	19.44	2.72	0.45	-1.14	51.50	0.57	-0.50	-3.19
8	3	21.4	149.94	6.18	-0.94	-4.01	42.01	6.10	-0.29	-4.96	18.69	1.84	0.16	-1.58	52.04	1.40	-0.24	-2.88
13	4	22.4	153.38	5.89	-0.42	-3.58	41.92	6.00	-0.29	-5.16	17.82	3.18	-0.12	-2.26	51.54	1.53	-0.55	-3.17
8	3	23.3	151.70	3.88	-0.75	-3.88	42.29	9.63	-0.20	-5.16	18.38	4.34	0.09	-2.17	51.75	1.80	-0.47	-3.05
12	4	24.2	151.37	5.76	-0.87	-3.93	41.69	5.74	-0.27	-5.33	18.20	1.93	0.00	-1.95	51.62	1.94	-0.58	-3.12
6	2	25.3	150.10	6.41	-1.08	-4.12	43.77	5.31	0.06	-4.75	19.43	2.89	-0.31	-2.56	52.35	1.97	-0.18	-2.69
30	10	32.1	150.80	6.34	-0.97	-4.02	43.88	7.46	0.08	-4.72	19.30	3.02	0.42	-1.50	51.72	1.22	-0.52	-3.06

Table 4.2.3.4 Female CL/P mid upper arm circumference (MUAC), triceps (T) and subscapular (S) skinfold thickness, mean and SL Reference SDS (SL).

N	%	AGE years	MUAC (cms)	MUAC SL	T (mms)	T SL	S (mms)	S SL
3	1	0.4	11.70	-1.95	6.70	-0.05	8.30	0.62
1	0.3	1.2	13.00	-1.09	4.90	-1.09	7.90	0.35
3	1	2.3	14.10	-0.37	7.00	-0.02	9.50	0.91
2	0.6	3.6	13.90	-0.95	4.60	-1.25	9.70	1.03
7	2	4.9	14.22	-0.80	4.70	-1.06	7.20	0.28
9	3	5.5	14.80	-0.53	5.20	-0.66	7.60	0.51
13	4	6.4	14.40	-0.97	4.20	-1.27	6.30	0.05
9	3	7.4	15.00	-0.72	4.60	-0.85	6.70	0.33
10	3	8.5	15.60	-0.50	4.50	-0.82	6.20	0.20
7	2	9.8	15.80	-0.57	4.90	-0.44	6.30	0.33
8	3	10.5	16.70	-0.30	5.50	-0.05	6.20	0.31
13	4	11.5	17.30	-0.33	6.40	0.41	7.40	0.81
14	5	12.3	17.60	-0.54	5.70	0.06	6.60	0.48
13	4	13.4	18.40	-0.54	6.10	0.19	7.00	0.59
17	6	14.5	19.30	-0.56	5.70	-0.13	7.00	0.48
19	6	15.4	21.00	-0.21	6.20	0.00	6.50	0.15
13	4	16.4	21.10	-0.50	6.20	-0.17	6.60	0.02
17	6	17.4	22.50	-0.18	6.70	-0.13	7.30	0.14
21	7	18.4	23.30	0.02	6.60	-0.39	6.50	-0.44
21	7	19.4	23.30	-0.20	7.60	-0.17	8.40	0.14
7	2	20.6	23.70	-0.14	6.20	-1.11	8.28	-0.15
8	3	21.4	23.70	-0.16	7.69	-0.56	6.64	-1.05
13	4	22.4	24.21	-0.06	6.60	-1.28	7.70	-0.75
8	3	23.3	24.10	-0.10	7.90	-0.83	10.47	0.07
12	4	24.2	24.95	0.23	7.40	-1.21	10.50	-0.07
6	2	25.3	23.93	-0.18	5.60	-2.24	7.22	-1.30
30	10	32.1	24.71	0.12	8.20	-0.86	7.90	-0.99

Height

Figure 4.2.3.1 Male height mean, +/- 1 SD SL Reference (SLR) and CL/P on British centiles. Vertical lines dropped from the centiles are explained in text.
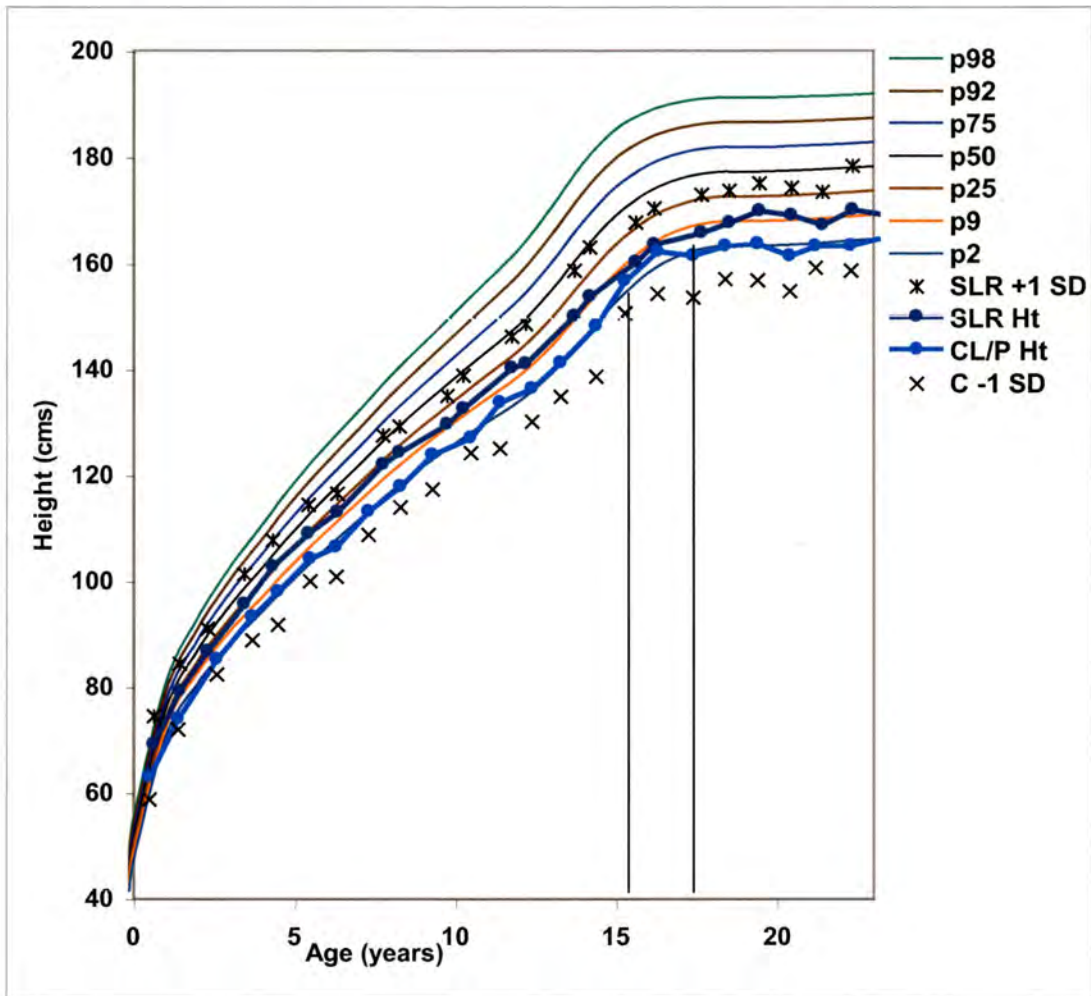
The mean height for age of male SL Reference in figure 4.2.3.1 lay on or above the British 25th centile during childhood, falling as adolescence commenced to the 9th centile (identified as orange). Except for a slight lag between 15 and 19 years, mean height remained on the 9th into adulthood.

By comparison, the CL/P group males were distributed around the 2nd centile, until 15 years old. Then, for two years the heights of CL/P and SL Reference were in closer proximity, bracketed by the vertical lines on the graph. Both occupied the space between the 2nd and 9th centiles. The two groups then diverged, the CL/P group returning to the 2nd centile in adulthood. As adults the mean heights of SL Reference and CL/P were separated by an inter-centile line interval, which is 0.67 SD.

Figure 4.2.3.2 Female height mean, +/- 1 SD SL Reference (SLR) and CL/P on British centiles. Vertical lines dropped from the centiles are explained in text.
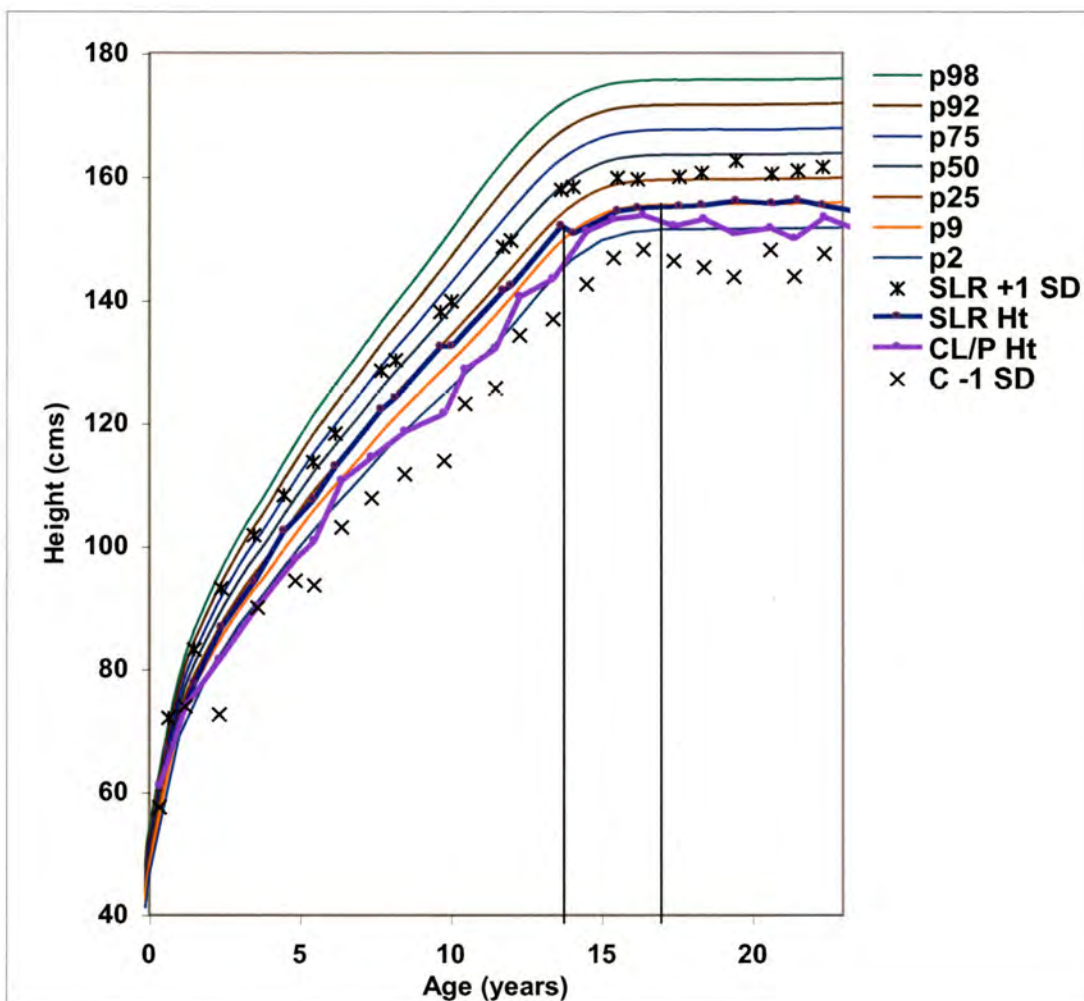
The female SL Reference mean height in figure 4.2.3.2 followed the British 25th centile from three years to ten years old. It then fell towards the 9th centile at 14 years, where it remained up to adulthood. Females with CL/P settled on the 2nd centile from early childhood until mid adolescence. A rise to the 9th centile resulted in close proximity of CL/P to SL Reference between 14 and 16 years of age, identified by the vertical lines from the growth curve to the x-axis. Thereafter they diverged, SL Reference to the 9th centile, females with CL/P to the 2nd centile.

Weight

Figure 4.2.3.3 Male weight mean, +/- 1 SD of SL Reference (SLR) and CL/P on British centiles.
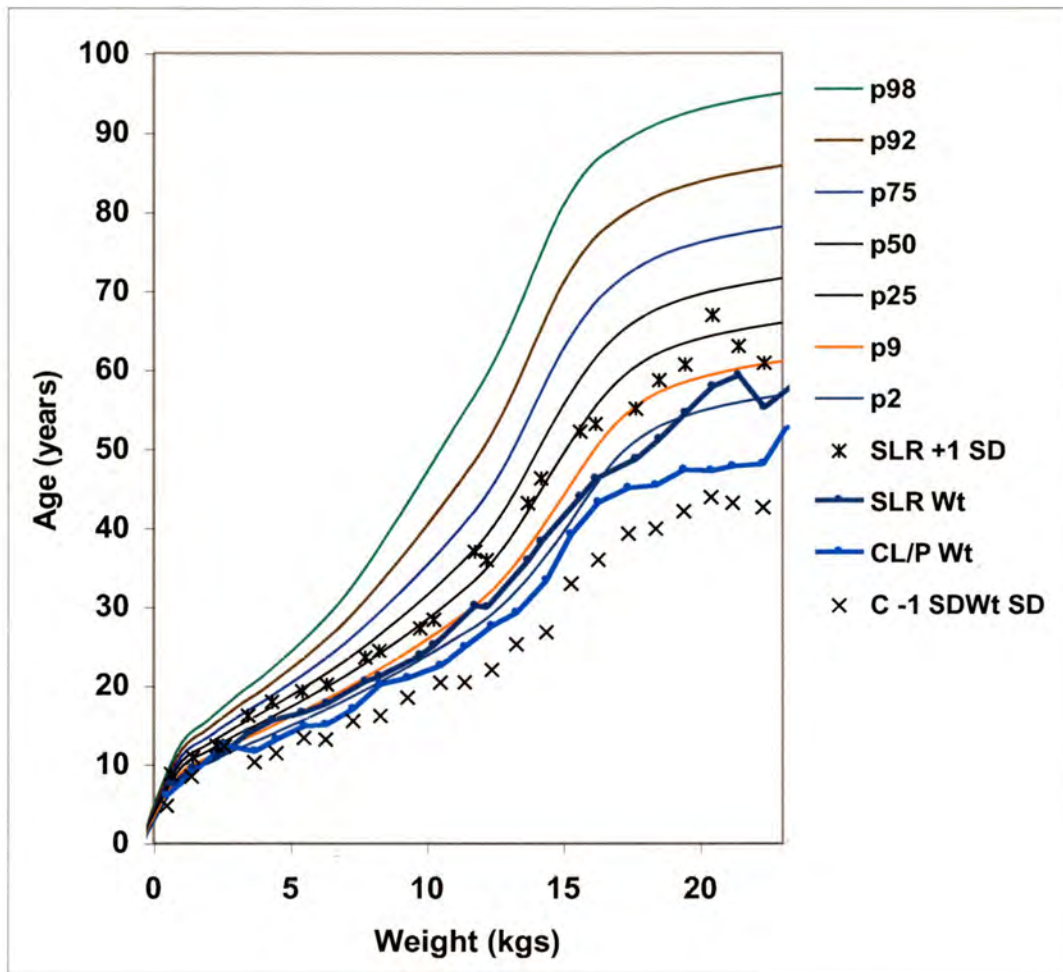
On British centiles the mean weight for age of SL Reference males and females in figures 4.2.3.3 and 4 followed a major centile line lower than their respective mean heights. Males fell from the 9th centile and continued along the 2nd centile until 15 years old. For two years it fell below the 2nd centile until at 19 years the mean weight rose towards the 9th centile.

The mean weight of CL/P group males fell below the 2ud British centile in the first year of life, where it remained below the SL Reference group. It diverged further below the 2nd centile from 18 years of age as weight gain levelled off.

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Figure 4.2.3.4 Female weight mean, +/- 1 SD of SL Reference (SLR) and CL/P on British centiles.
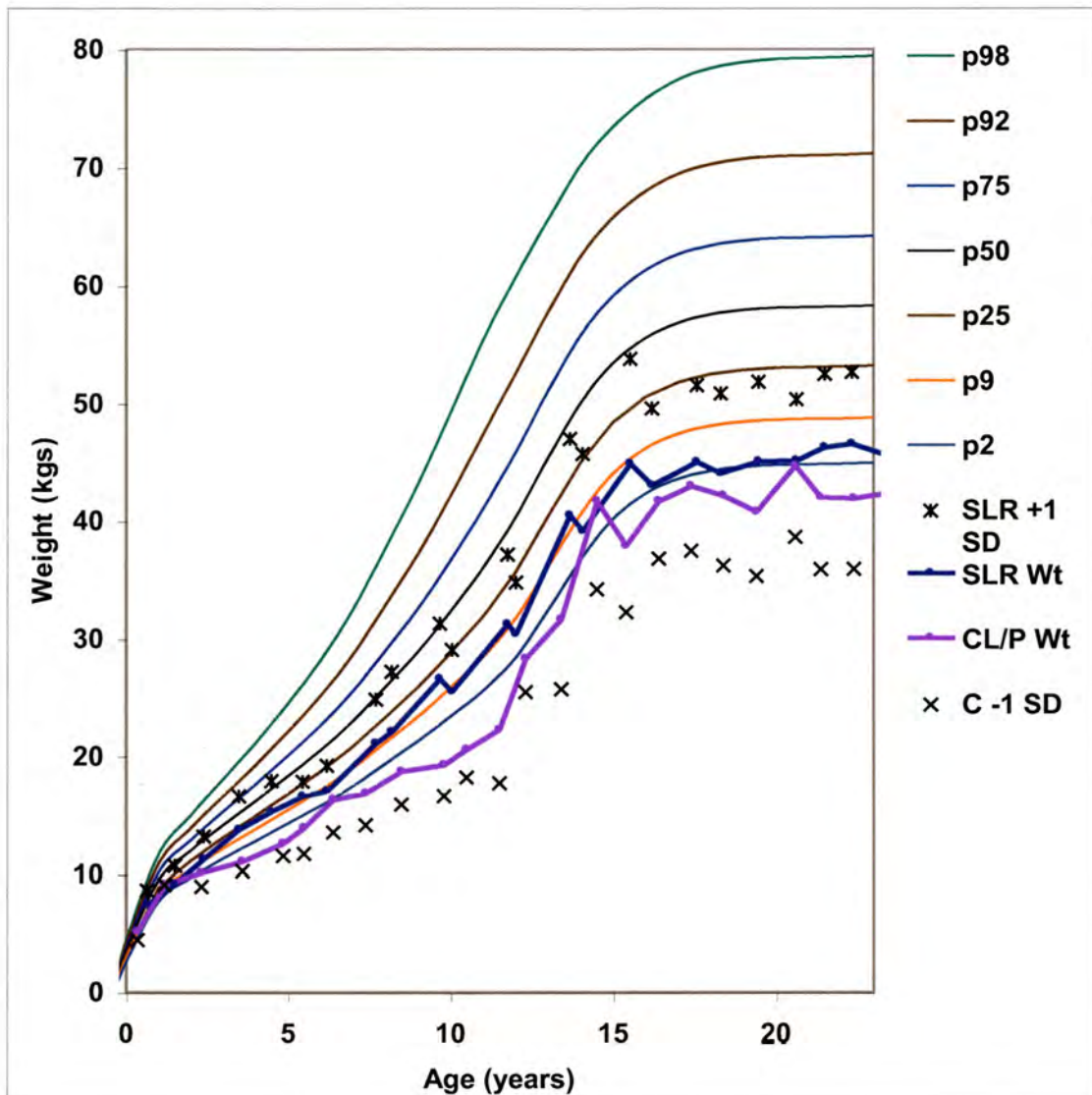
In figure 4.2.3.4 the mean weight of female SL Reference and CL/P groups diverged from three years old. Excluding a single data point at seven years, the gap between them progressively widened until 12 years of age. A rapid but incomplete narrowing followed, reflecting an increase in the mean weight of females with CL/P while SL Reference females continued along the 9th centile. An overlap at 15 and 21 years between SL Reference and CL/P were inconsistent with the surrounding data. SL Reference mean weight drifted lower, to the 2nd centile, with the CL/P group maintaining its position below.

Body Mass Index (BMI)

Figure 4.2.3.5 Male BMI mean, +/- 1 SD of SL Reference (SLR) and CL/P on British centiles.
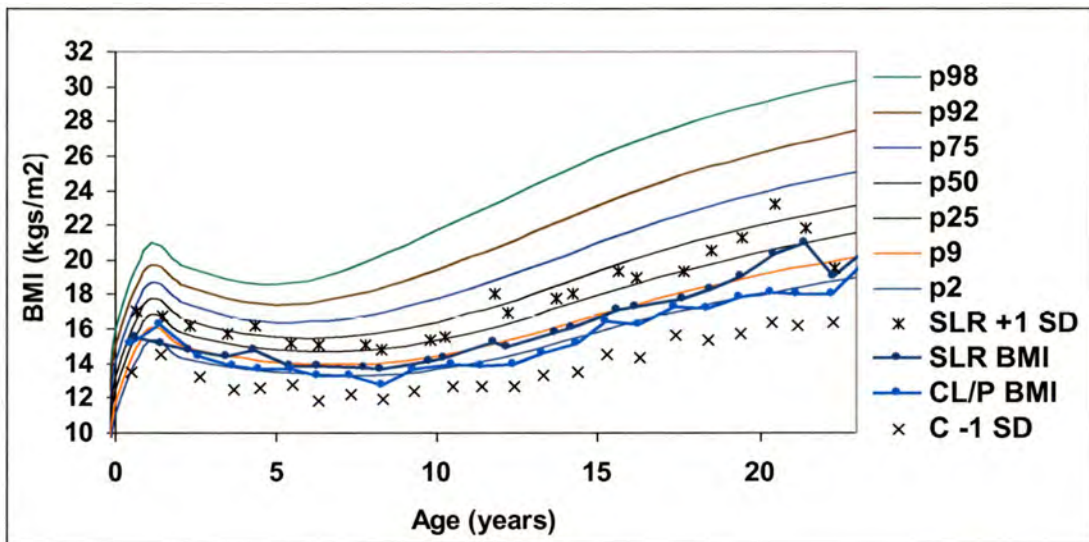
Figure 4.2.3.6 Female BMI mean, +/- 1 SD of SL Reference (SLR) and CL/P on British centiles.
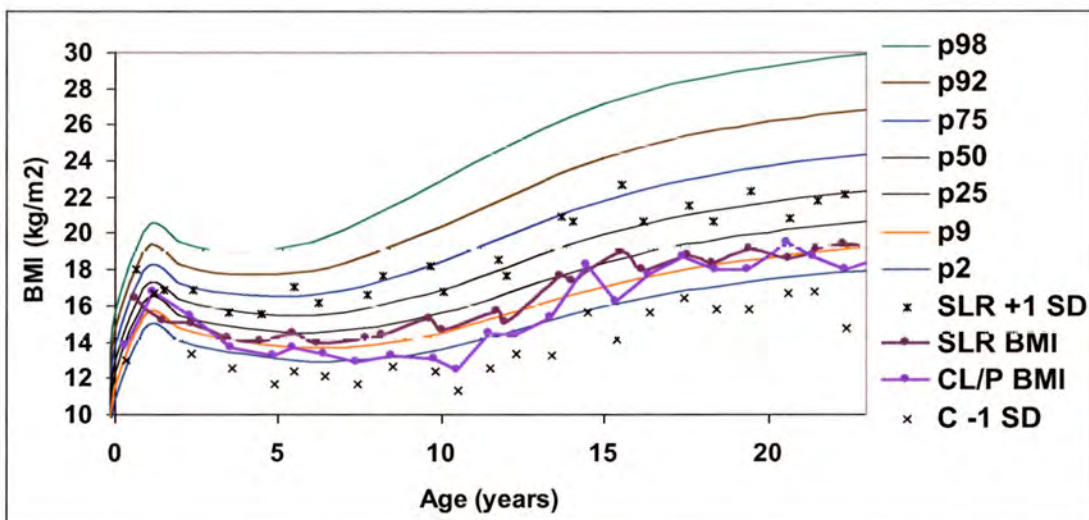
In figures 4.2.3.5 and 6 the SL Reference mean BMI was close to the British 9th centile, with CL/P groups on the centile line below, in both sexes from two years old to 15 years. This relationship continued in the males, but for females from 16 years upwards the SL Reference population and CL/P group shared the 9th British centile.

Head circumference

Figure 4.2.3.7 Male head circumference (HC) mean+/- 1 SD of SL Reference (SLR) and CL/P on British centiles.
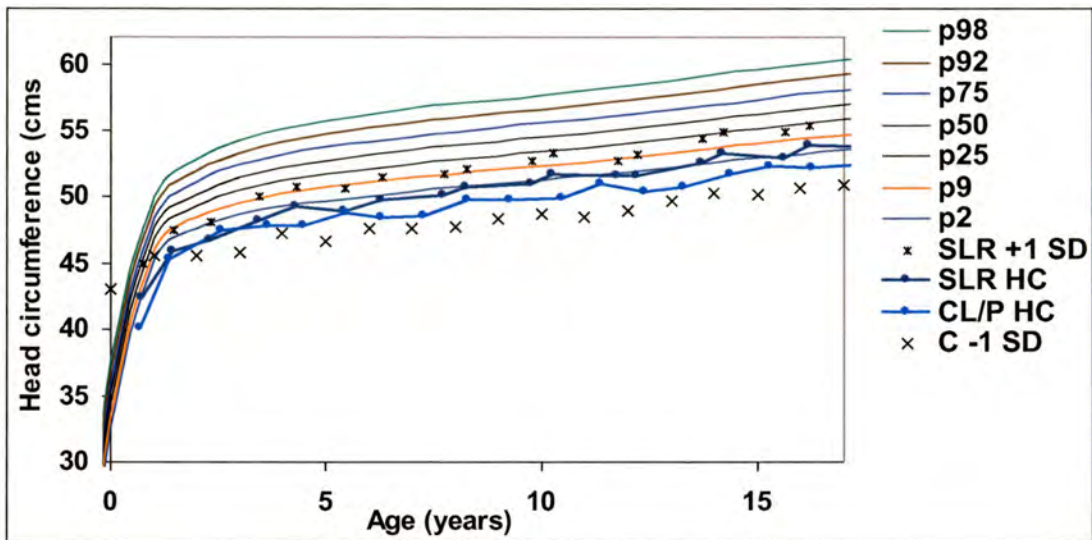
Figure 4.2.3.8 Female head circumference (HC) mean +/- 1 SD SL Reference (SLR) and CL/P on British centiles.
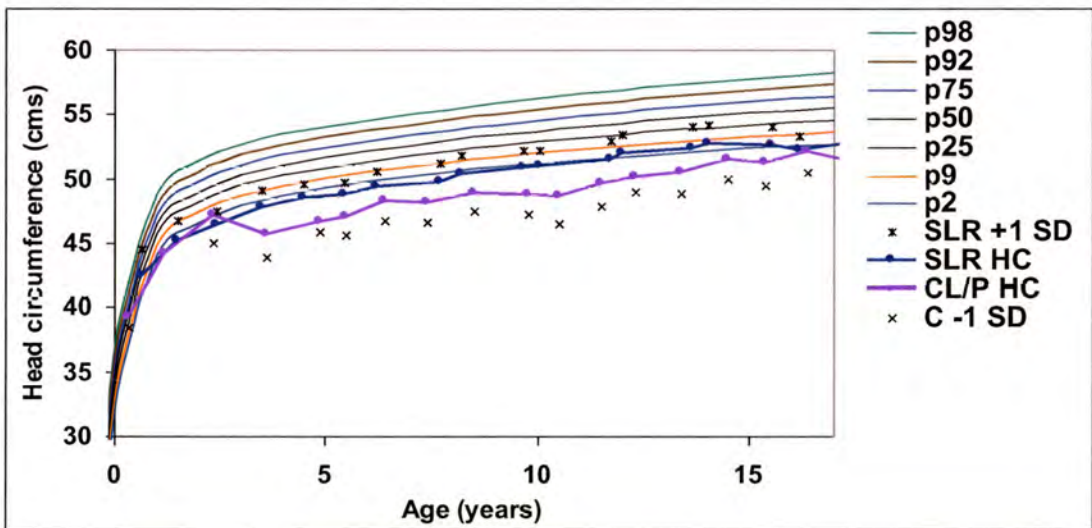
Figures 4.2.3.7 and 8 show for both sexes' the SL Reference subjects' head circumference lay somewhat below the 2nd British centile from one year old, and continued to do so throughout childhood. After ten years old it rose to lie close to the 2nd centile. Females with CL/P aged under three years lay close to the SL Reference mean values. With that exception, the CL/P means for both sexes continued well below the 2nd British centile from infancy to adulthood.

4.3 GROWTH PATTERN OF SUBJECTS WITH CL/P ON SL REFERENCE CENTILES

4.3.1 Selected data plots and all mean values on SL Reference centiles

The complete set of data plots, and mean CL/P anthropometry are illustrated in Figures B4.3.1 and 2.

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Height

Figure 4.3.1.3 Male CL/P height data plots on SL Reference centiles.
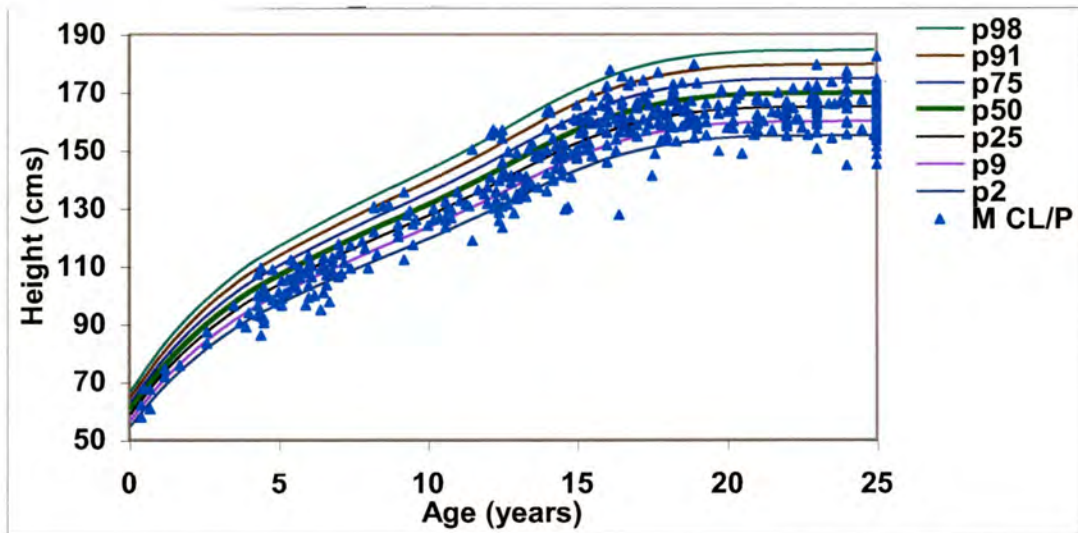
Figure 4.3.1.4 Female CL/P height data plots on SL Reference centiles.
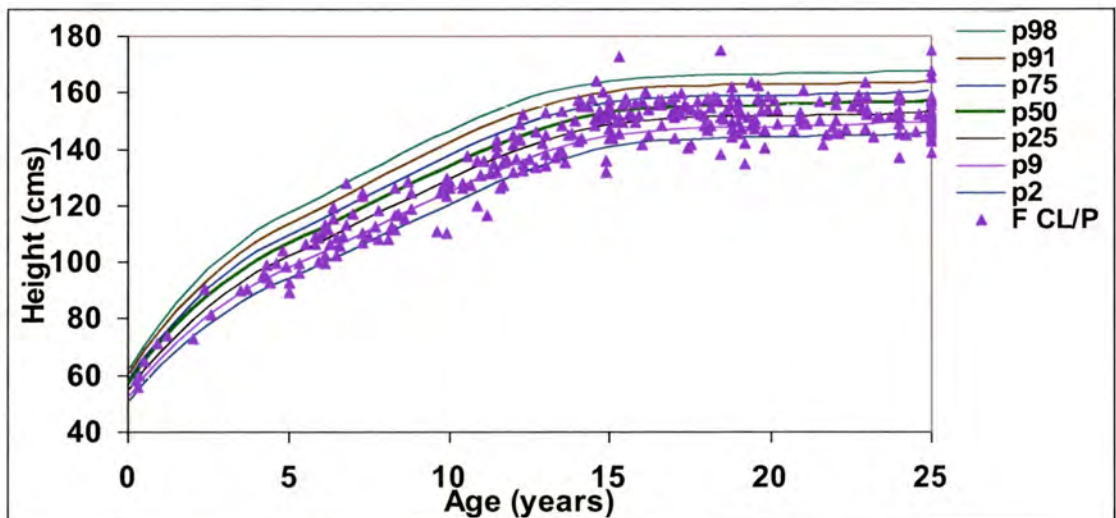
Figures 4.3.1.3 and 4 show height data plots of CL/P groups on SL Reference centiles. 12% of males and 13% of females were below the 2nd centile for this population, 79% and 70% respectively below the 50th centile. The distribution across the age groups of children, adolescents and adults varied little.

Figure 4.3.1.5 Male CL/P mean height and −1 SD on SL Reference centiles.
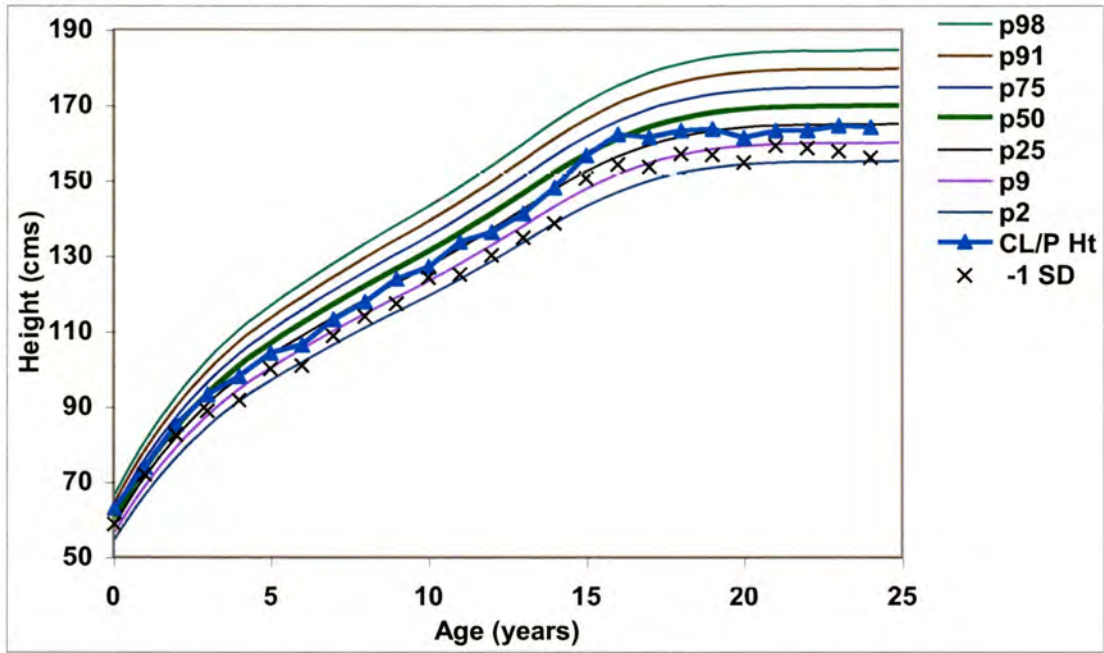
Figure 4.3.1.6 Female CL/P mean height and −1 SD on SL Reference centiles.
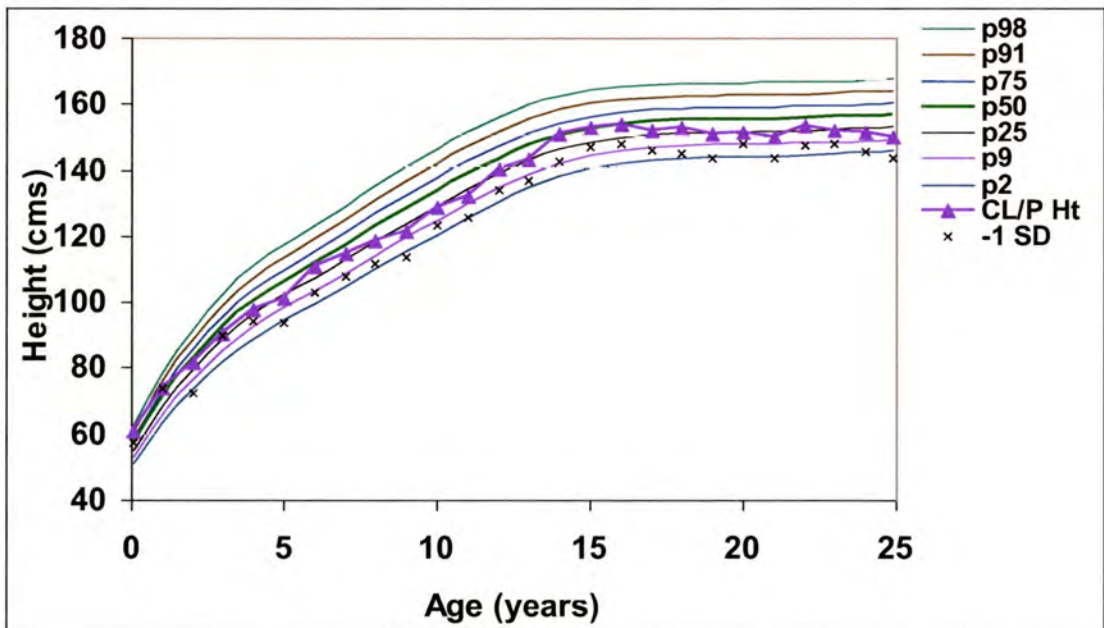
In CL/P groups on SL Reference charts figures 4.3.1.5 and 6, before the age of five the mean height of males and females fell to between the 25th and 9th centile, until 13 years in females and 15 years in males. The means of both sexes then showed catch up, to lie on the 50th centile for two to three years, before appearing to fall back as adults to the 9th to 25th centile. This inconsistency with the normal process of growth suggested the presence of two populations, one better grown than the other. It was hypothesised that those who were already adult by the age of surgery were less likely to have potential for growth compared with those who received surgery before becoming adult. The groups were identified as Old Cohort, the subjects who received surgery as adults from 19 years upwards, and Young Cohort who received surgery before 19 years, and had become adults at follow up. The Mann-Whitney test was used for a comparison of medians. The test makes no assumption of normality of distribution, and is suitable for small sample size.

Table 4.3.1.1 Comparison of medians of height by age at palate surgery.

Cohort	N	Median	Difference in cms (95% Confidence interval)	W value	p
M Old	33	157.70	-4.20	1764	0.003
M Young	110	163.90	(-6.90 to –1.50)		
F Old	14	147.05	-4.75	409	0.004
F Young	84	151.65	(-8.20 to –1.70)		

Males and females in the Old Cohort were significantly shorter than the Young Cohort. The table 4.3.1.1 shows this was by a median difference of approximately four cms. This finding was consistent with the hypothesis that there were two adult cohorts accounting for the observed reduction in mean height between adolescent and adult populations.

Weight

Figure 4.3.1.7 Male CL/P weight data plots on SL Reference centiles.
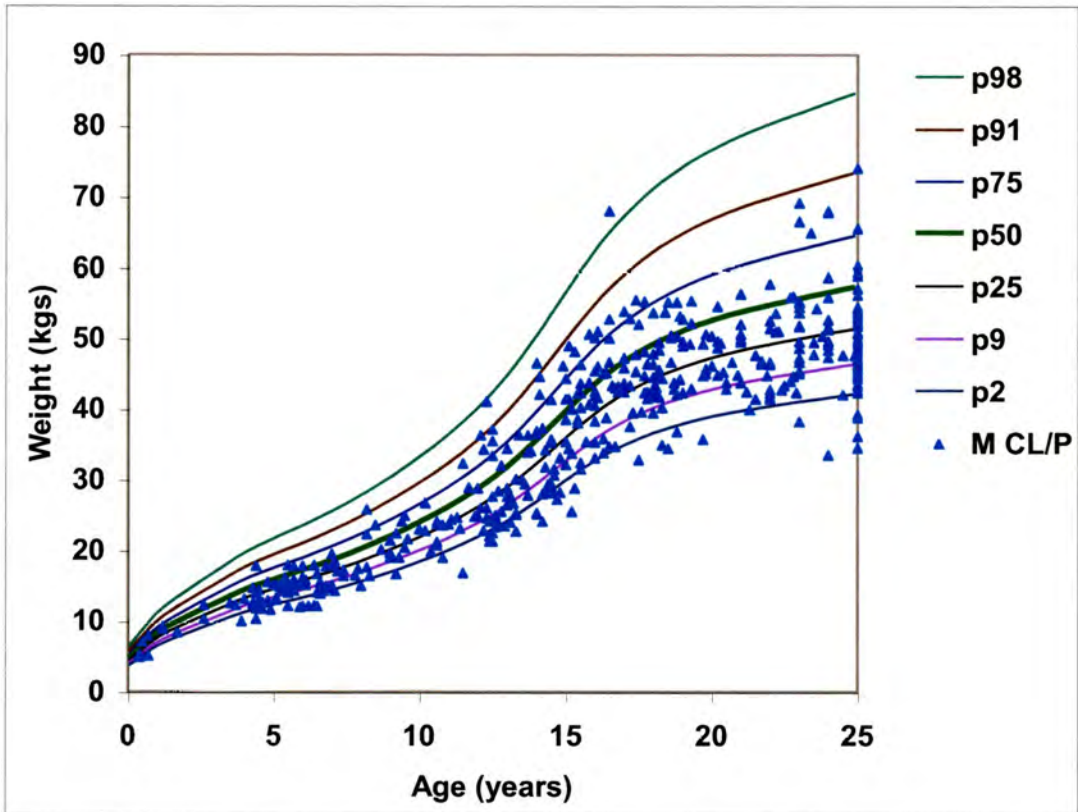
Figure 4.3.1.8 Female CL/P weight data plots on SL Reference centiles.
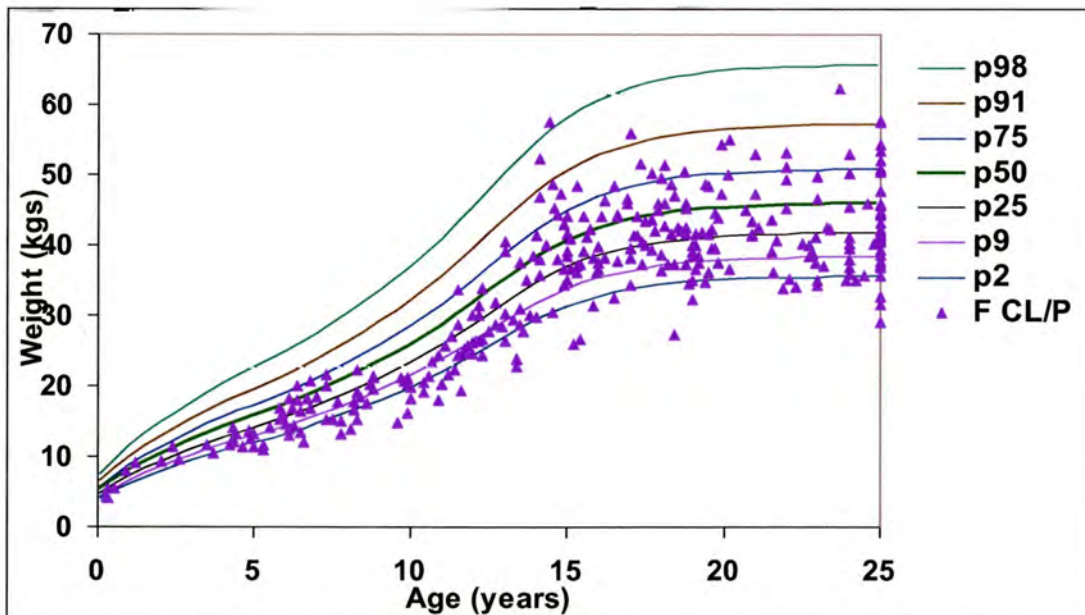
In figures 4.3.1.7 and 8 the proportion below the 2nd centile for SL Reference weight was seven percent for CL/P males, five percent of females. 82% of males up to 15 years, and 74% of females up to 12 years lay below the 50th centile.

Figure 4.3.1.9 Male CL/P mean weight and −1 SD on SL Reference centiles.
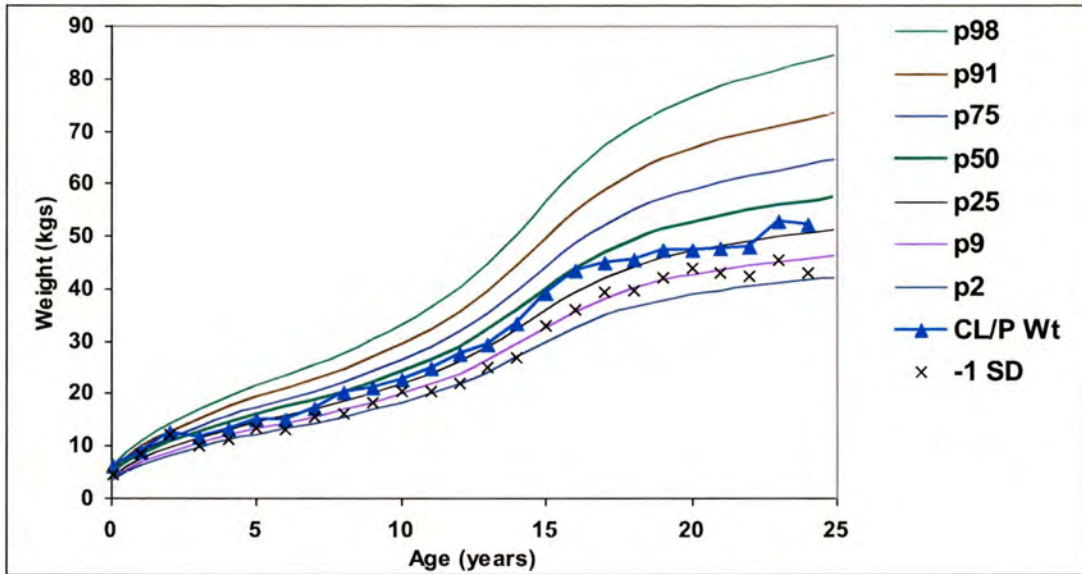
Figure 4.3.1.10 Female CL/P mean weight and −1 SD on SL Reference centiles.
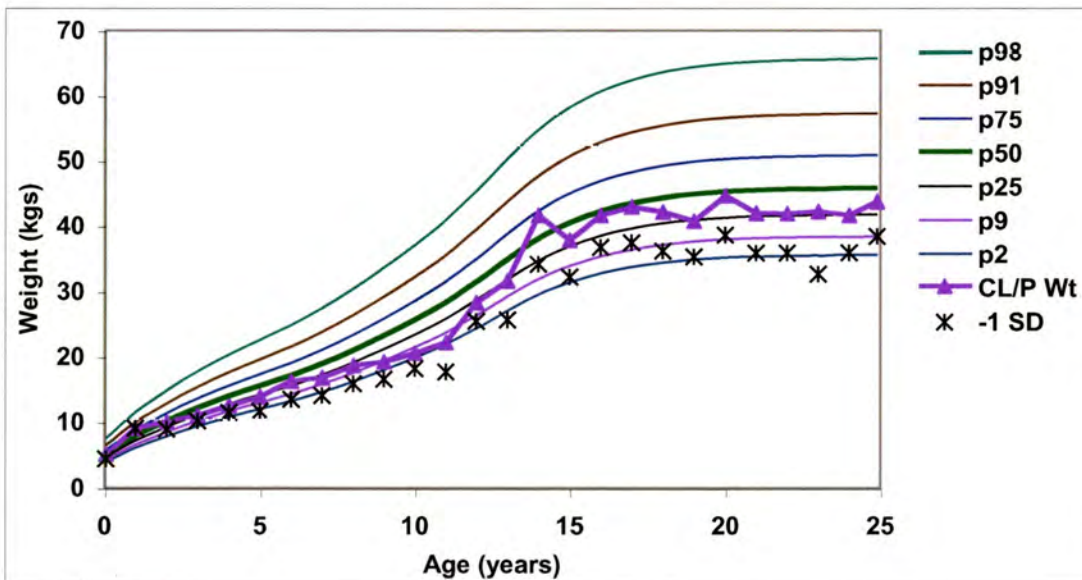
In figures 4.3.1.9 and 10, CL/P group males showed a greater tendency to follow the 25th centile, whereas the females with CL/P showed flattening of the mean weight growth trajectory in later childhood until 12 to 13 years. The mean for both sexes steadily rose thereafter to the mean for the SL Reference population, in late adolescence, before settling on the 25th centile as adults.

BMI

Figure 4.3.1.11 Male CL/P mean BMI and −1 SD on SL Reference centiles.
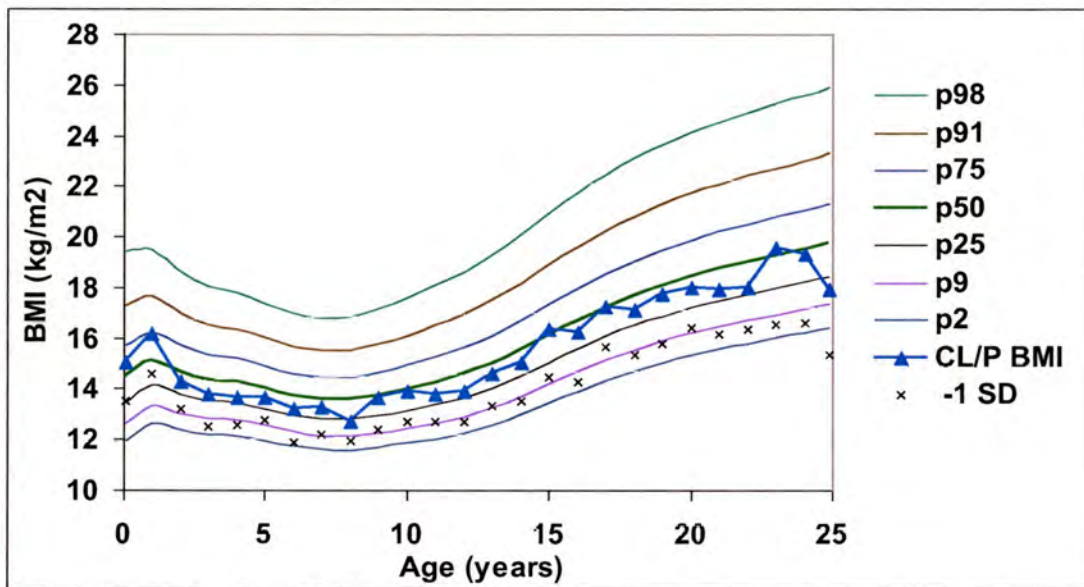
Figure 4.3.1.12 Female CL/P mean BMI and −1 SD on SL Reference centiles.
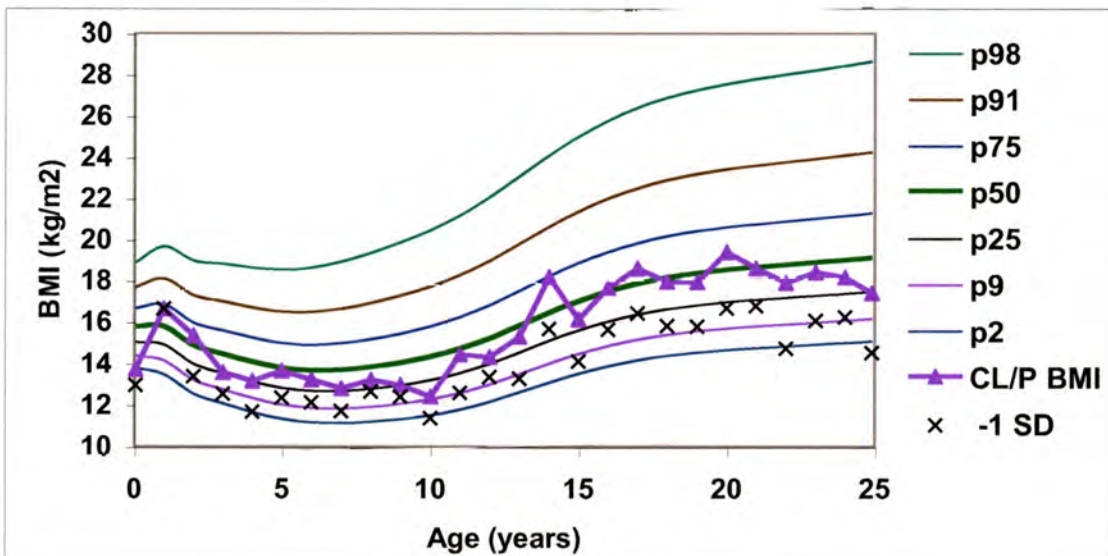
The mean BMI for both sexes in figures 4.3.1.11 and 12 was between the 25th and 50th centile. Thus, despite the fluctuations in height and weight with age the proportions remained constant.

Head circumference

Figure 4.3.1.13 Male CL/P mean head circumference (CL/P HC) and –1 SD on SL Reference centiles.
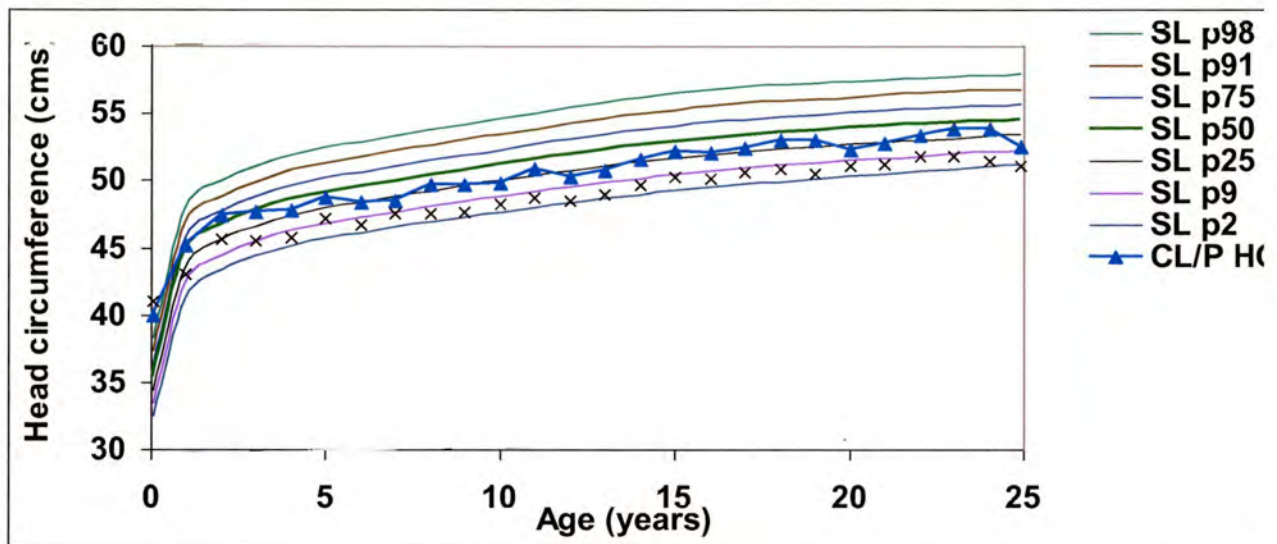
Figure 4.3.1.14 Female CL/P mean head circumference (Cleft HC) and –1 SD on SL Reference centiles.
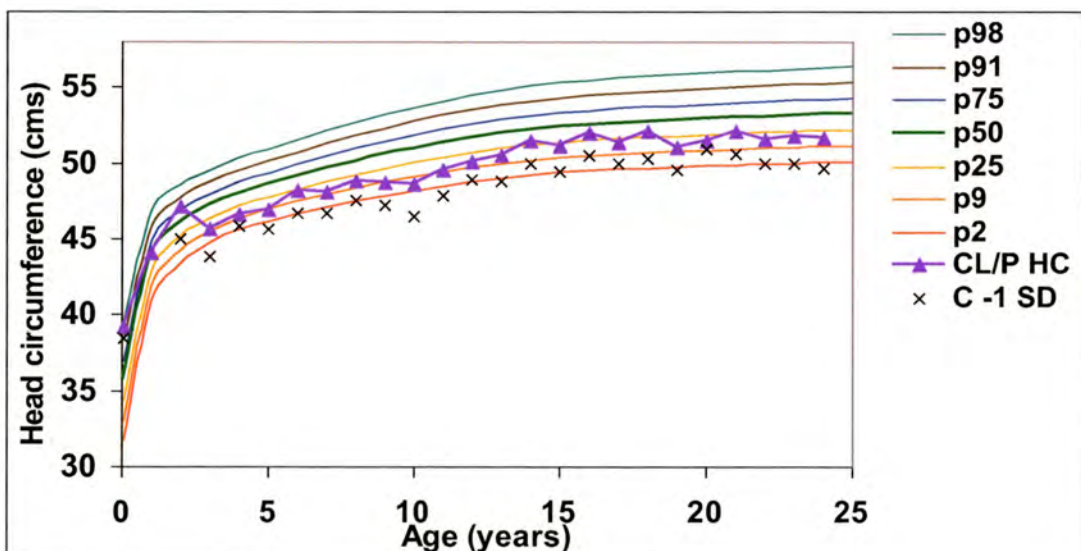
In table 4.3.1.13 and 14, the ten CL/P male subjects, and seven females, two years old and under, mean head circumferences were on the 50th centile. Over two years old the male mean head circumference lay on the 25th centile. The female CL/P group dipped close to the 9th centile from two years to the end of childhood, and by mid adolescence had risen to the 25th centile.

Mid-upper arm circumference

Figure 4.3.1.15 Male CL/P mean mid upper arm circumference (CL/P AC) and −1 SD on SL Reference centiles.
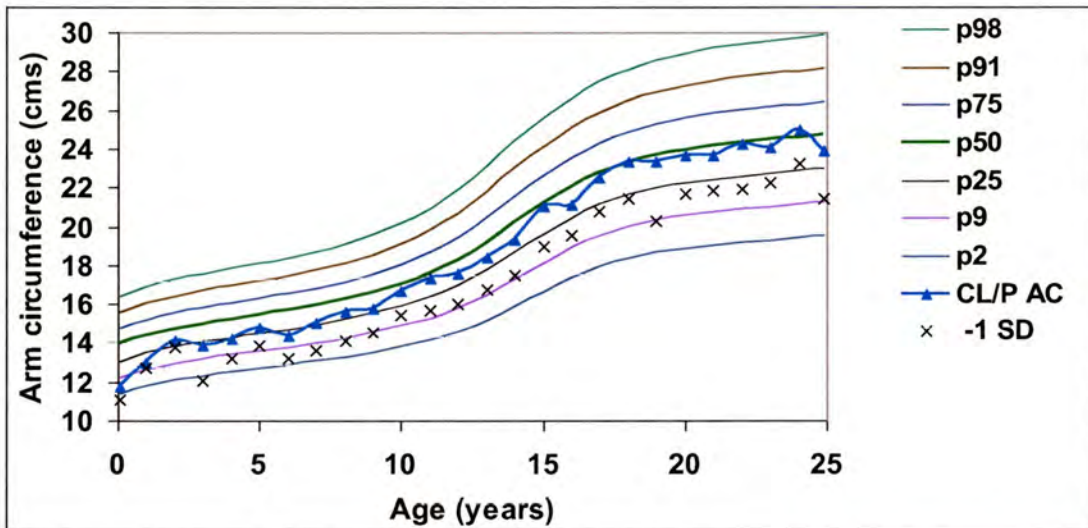
Figure 4.3.1.16 Female CL/P mean mid upper arm circumference (CL/P AC) and 1 SD on SL Reference centiles.
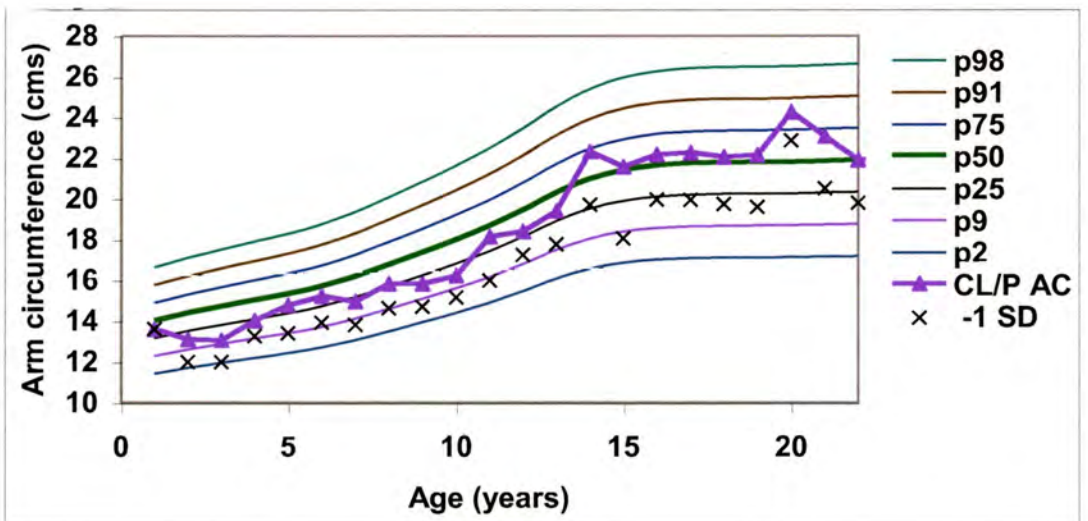
In figures 4.3.1.15 and 16 mean mid upper arm circumference was on the 25th centile from early childhood to 15 years in CL/P males, 13 years in females, then rose to the mean for the SL Reference population.

Triceps and subscapular skinfold thickness

Figure 4.3.1.17 Male CL/P mean triceps (T) sft on SL Reference centiles.
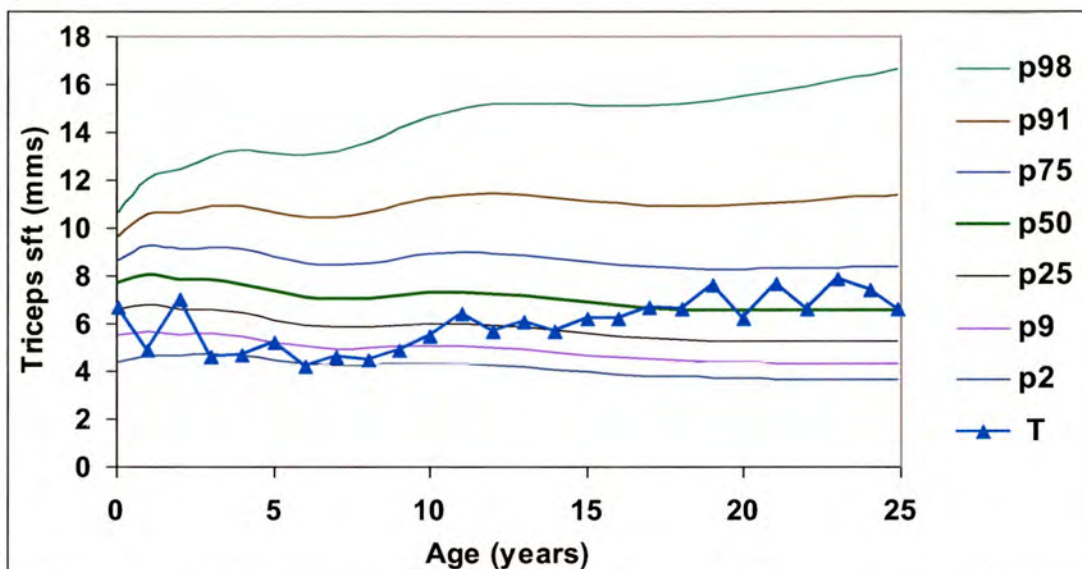
Figure 4.3.1.18 Male CL/P mean subscapular (S) sft on SL Reference centiles.
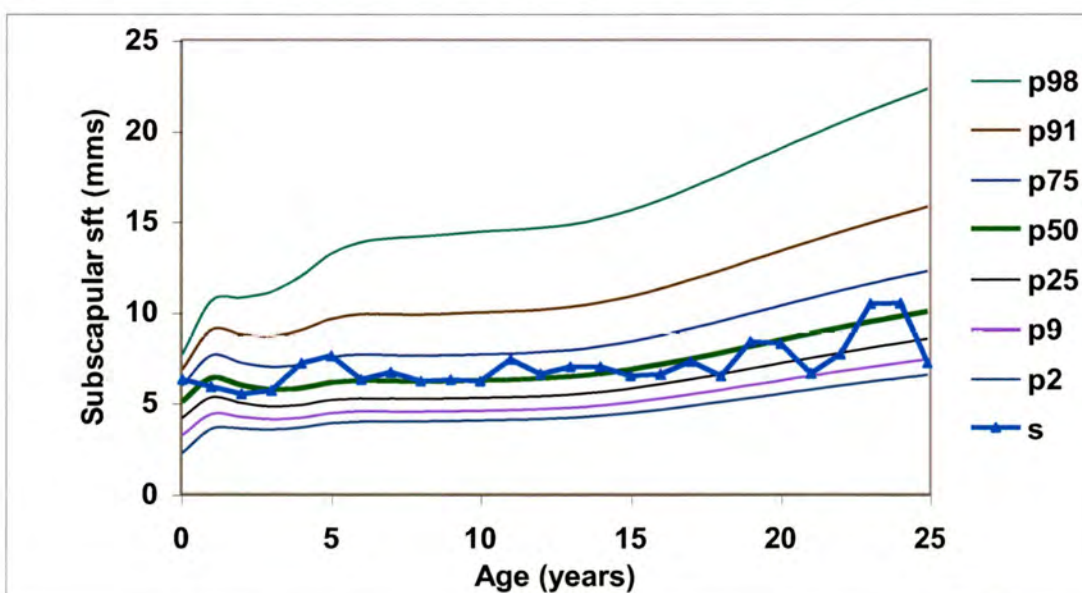
Figure 4.3.1.19 Female CL/P mean triceps (T) sft on SL Reference centiles.
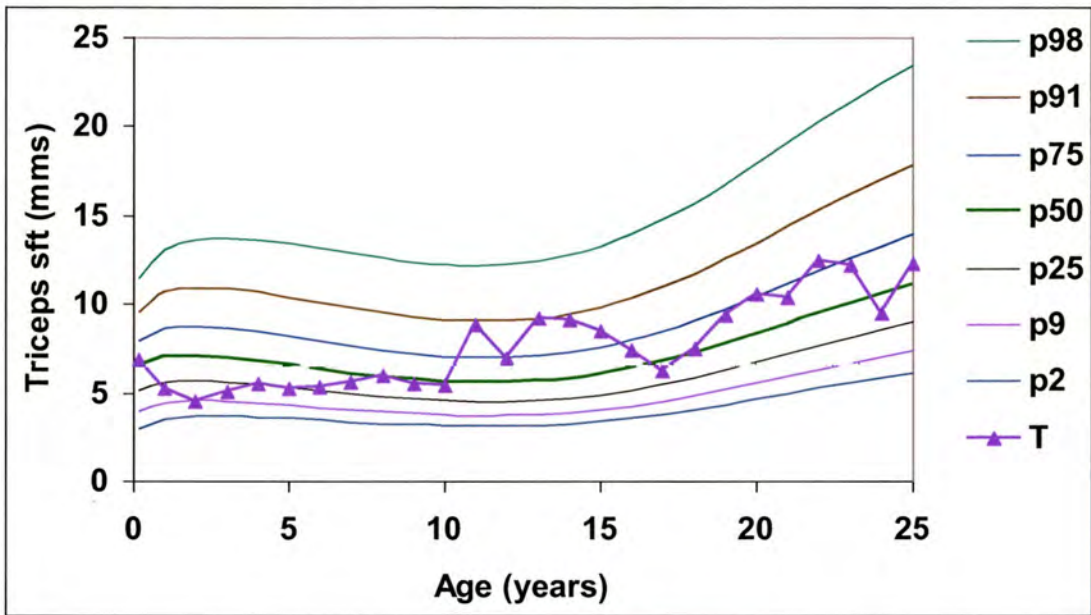
Figure 4.3.1.20 Female CL/P mean subscapular (S) sft on SL Reference centiles.
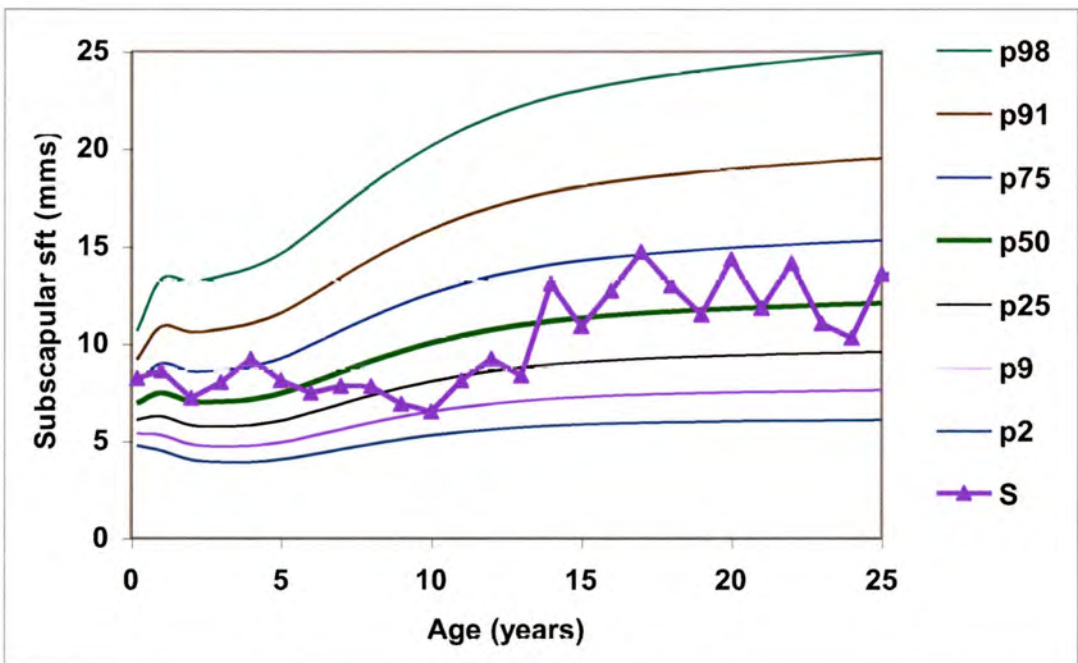
In figures 4.3.1.17 to 20 the male triceps skinfold thicknesses in the CL/P group was low, between the 2nd and 9th centiles in childhood, increasing to the mean for the SL Reference population by late adolescence. The female triceps were also comparatively thin, but only in childhood up to nine years old.

4.4 COMPARISON OF SL REFERENCE AND CL/P GROUPS APPLYING BRITISH SDS AND SL REFERENCE SDS

Tables 4.2.3.1 and 3 on pages 64 and 66 were tabulated by year of age. The SL Reference population means, as British SDS of four parameters, height, weight, BMI and head circumference relationships are now considered graphically.

Figure 4.4.1 Male SL Reference height, weight, BMI, head circumference (head) as British SDS.
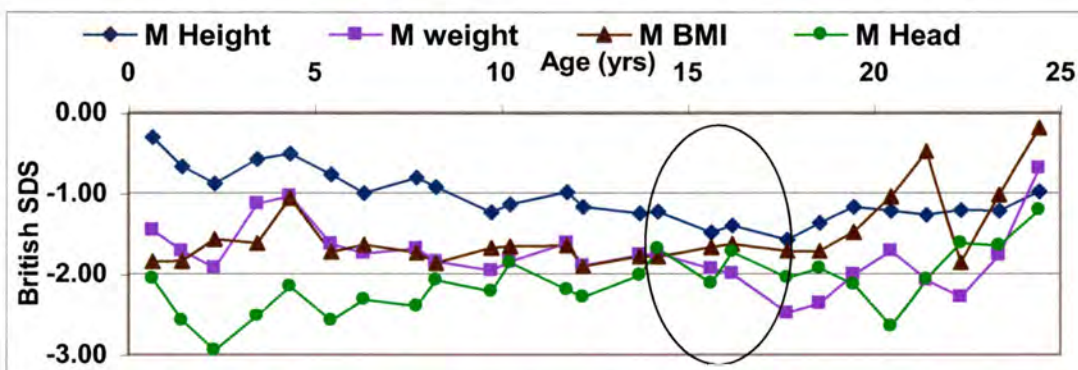
Figure 4.4.2 Female SL Reference height, weight, BMI, head circumference (head) as British SDS.
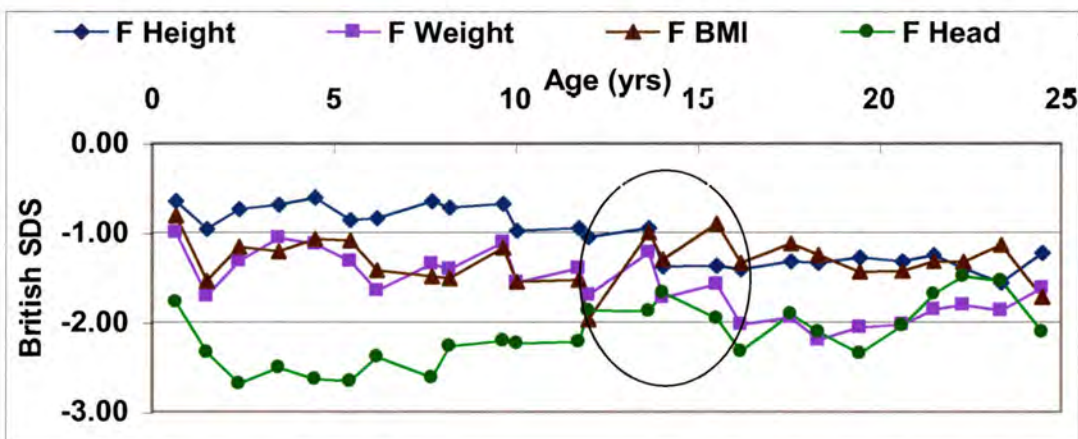
From two years old to the end of adolescence, SL Reference males' growth parameters in Figure 4.4.1 showed convergence from opposite ends of the British SDS axis. Mean height averaged –0.5 SD under 2 years, to –1.60 SD by late adolescence; mean head circumference –2 to –3 SD in childhood, to just above –2 SD. Mean weight and BMI oscillated between –1 SD and –2 SD. During the period

of closest convergence (circled), between 15 and 17 years, British SDS was −1.5 to −2 SD for height, weight, BMI and head circumference. From 19 years onwards the four variables showed a trend to converge around −1 SD.

SL Reference females in figure 4.4.2 showed similar trends with closest convergence between −1 and −2 SD circled, corresponding to 12 to 16 years. Unlike males there was no evidence of a general shift upwards of continued improvement in growth parameters as they grew older.

4.4.1 Comparison of CL/P as SL Reference & British SDS by age cohort

The mean and SD of the seven anthropomorphic variables are illustrated in figures 4.4.1.3 to 10 below, stratified into four age cohorts. The supporting tables are C4.4.1.1, 2 and 3. The two references, SL Reference and British, share the same y-axis. Although laid on the same figure, they are not directly comparable, but they do illustrate trends and differences between them.

Figure 4.4.1.3 Mean height of CL/P as SL Reference & British SDS by age cohort.
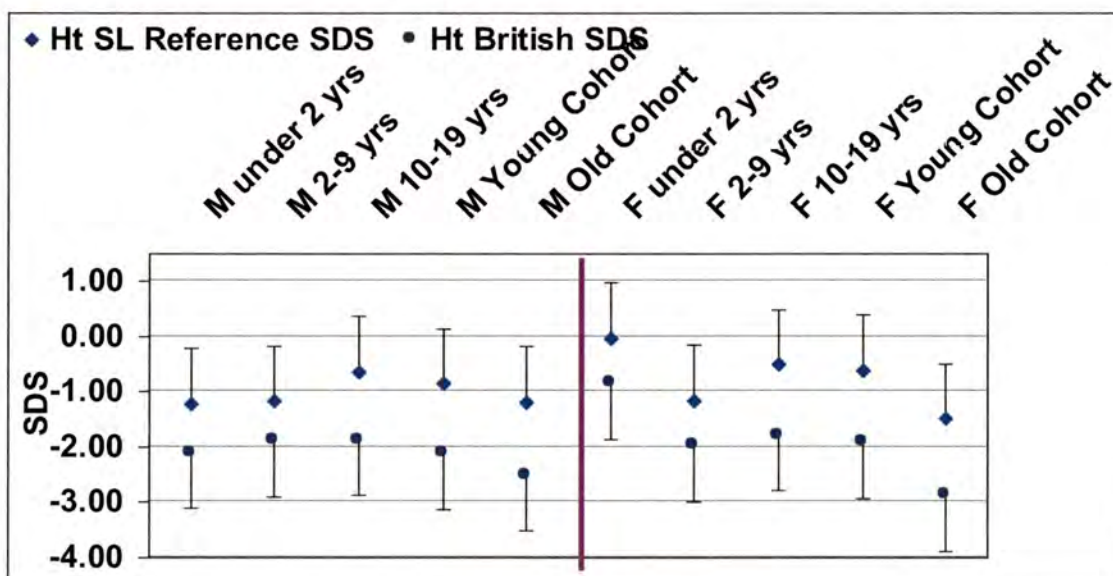
The mean height SDS represented in figure 4.4.1.3 of male and female CL/P show similar trends by age cohort between their mean British SDS and the SL Reference population. As anticipated by the progressive reduction by age in height of the SL

Reference adults compared with the British, the mean SD and bars of the two references move progressively apart in adolescence and adulthood.

The mean height, as British SDS, of adolescents with CL/P was greater than adults, as previously analysed for linear height in table 4.3.1.1, page 76. Young Cohort adult mean height was -2.12 SD in males and -1.95 SD in females, Old Cohort -2.52 SD in males, -2.83 SD in females.

Applying the SL Reference, SDS in height in CL/P males and females in figure 4.4.1.3 rose from infancy, when it was approximately -1.2 SD for both sexes, to approximately -0.5 SD in adolescence. The Old Cohort mean height was -1.18 SD for males, -1.44 SD for females.

The difference between the Young and Old cohorts in height SDS was evident using either growth reference.

Figure 4.4.1.4 Mean weight of Cleft groups as SL Reference & British SDS by age cohort. SD bars set at 1.2.
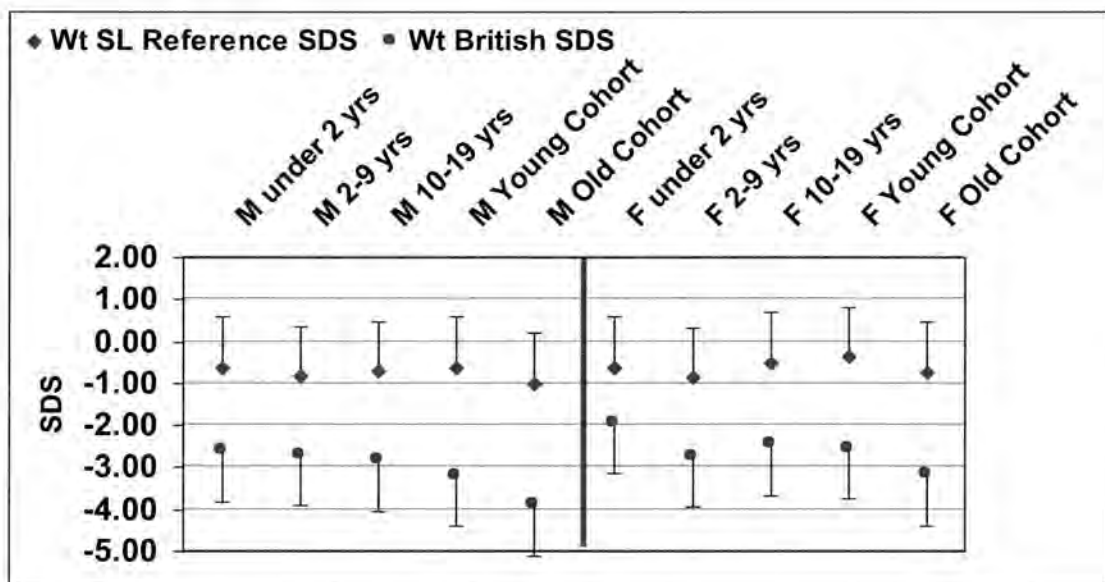
In figure 4.4.1.4 the male CL/P cohorts showed progressive reduction in British SDS for mean weight. From under two year olds to Young Cohort it continued to fall, and further still in Old Cohort to almost –4 SD in weight. Females with CL/P were in a relatively steady state between childhood and Young Cohort, but also fell in Old Cohort to <-3 SD in weight.

Applying the SL Reference provided contrasting growth patterns to the British SDS. The mean weight SDS did not fall below –1 SD for either sex in any age cohort with a maximum difference between cohorts of 0.48 SD. This compared with a fall in British SDS, by 0.97 SD to 1.30 SD, to a mean of –3.91 SD for males, and -2.92 SD in females.

Figure 4.4.1.5 Mean BMI of CL/P as SL Reference and British SDS by age cohort. SD bars on data points set at 1.2.
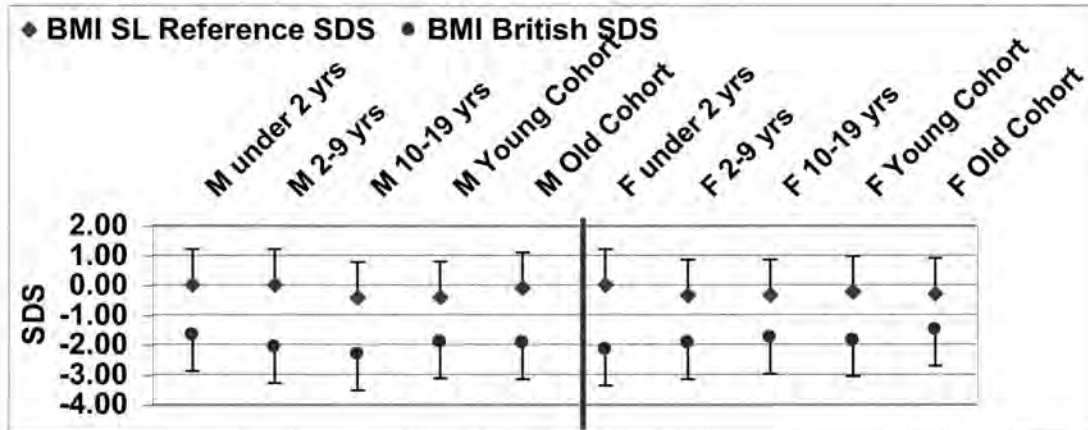
The SD of mean BMI in figure 4.4.1.5 was wider than for other growth variables. The mean differences between CL/P and SL Reference were small, and fluctuated close to –2 SD of the British SDS.

Figure 4.4.1.6 Mean head circumference (HC) of CL/P as SL Reference and British SDS by age cohort. SD bars set at 1.1.
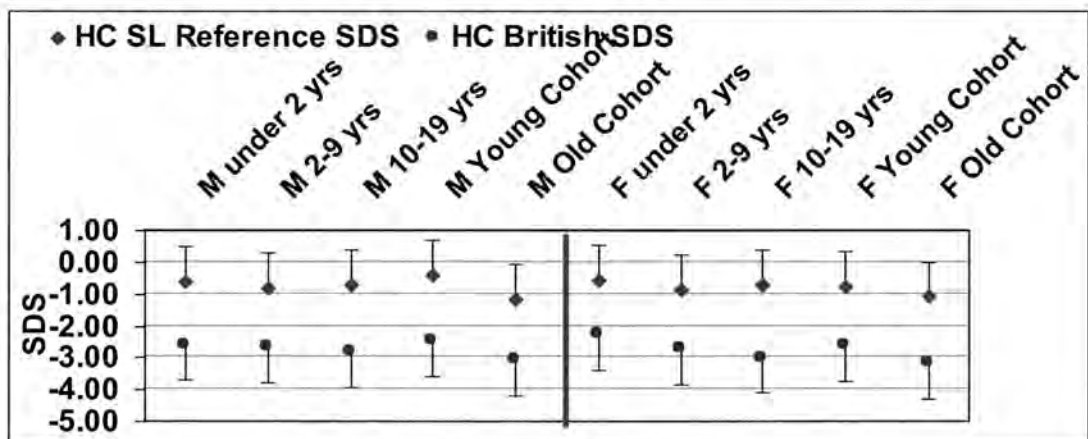
Mean head circumference in figure 4.4.1.6 as British SDS was intermediate between height and weight, within the –2 SD to –3 SD range except for Old Cohort which was below the –3 SD. The mean head circumference showed a persistent difference between SL Reference and CL/P of –0.39 to –1.15 SD.

4.4.2 Mean growth of CL/P in age cohorts compared with SL Reference

Figure 4.4.2.1 Mean mid upper arm circumference (MUAC) of CL/P as SL Reference SDS by age cohort.
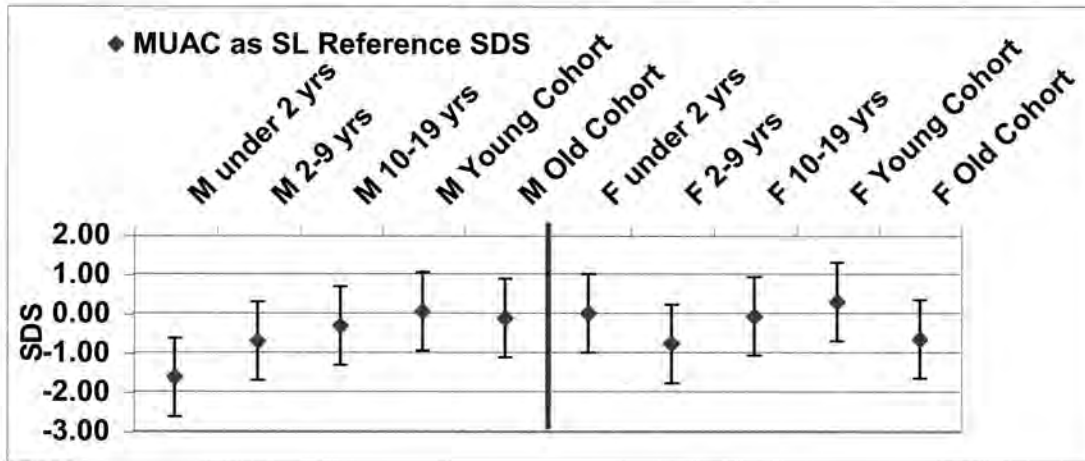
The mid-upper arm circumference trend in figure 4.4.2.1 showed that with increasing age it rose from -0.7 SD in children with CL/P to 0 SD in the Young Cohort adults, in both sexes. The exception was females in the Old Cohort.

Figure 4.4.2.2 Mean triceps sft of CL/P as SL Reference SDS by age cohort.
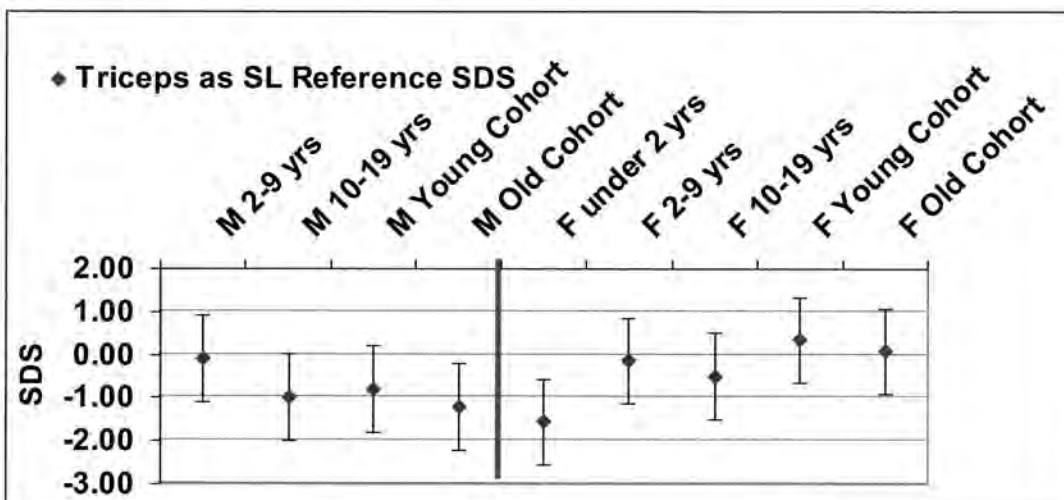
The male CL/P group triceps sft in figure 4.4.2.2 was approximately one SD below the SL Reference in the ten to 19 years cohort, and both adult cohorts. This was not replicated in females.

Figure 4.4.2.3 Mean subscapular skinfold thickness of CL/P as SL Reference SDS by age cohort.
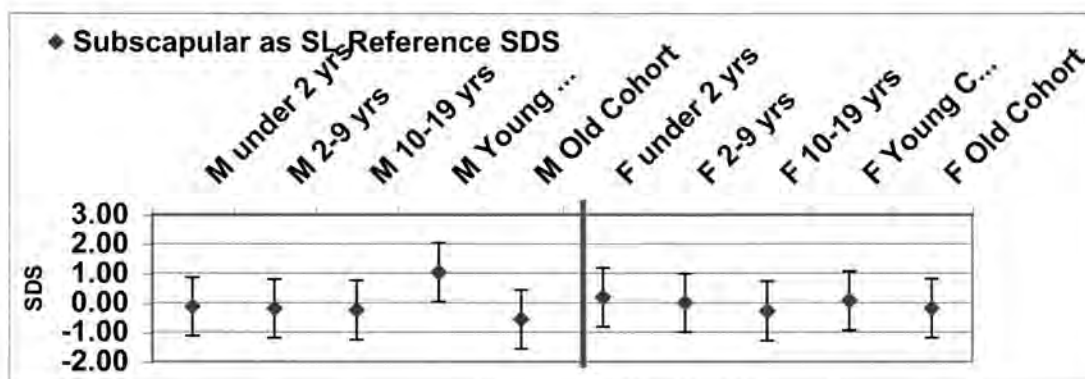
In figure 4.4.2.3 the mean subscapular sft of CL/P groups was similar to SL Reference, except in the Young Cohort. Mean SDS for arm circumference, triceps and subscapular skinfold thickness were lower in Old Cohort than Young Cohort subjects by 0.15 SD to 0.95 SD.

4.4.3 CL/P Old Cohort versus Young Cohort

The growth of the Old Cohort compared with the Young Cohort is shown as SL Reference SDS.

Table 4.4.3.1 Growth of Old Cohort compared with Young Cohort as SL Reference SDS

Young Cohort	N	Height SD	Weight SD	BMI SD	HC SD
Male	121	-0.78	-0.62	-0.42	-0.39
Female	92	-0.65	-0.39	-0.24	-0.78
Old Cohort					
Male	39	-1.18	-1.00	-0.11	-1.15
Female	12	-1.44	-0.54	-0.30	-1.09

The Old Cohort was smaller in height and weight, and had smaller head circumference. The female Old Cohort MUAC had previously been found to be

smaller too. Surgery prior to adulthood appeared to benefit growth, and added to adult height by a mean of 0.40 SD male to 0.8 SD female, weight 0.38 SD male, 0.15 SD female and head circumference 0.76 SD male, 0.31 SD female.

4.4.4 Socioeconomic group and growth in SL Reference and CL/P

Table 4.4.4.1 Fathers Occupation Groups (FOG) 1, 2 and 3 of SL Reference groups, compared by British SDS for male (M) and female (F).

FOG	No	%	Height SDS		Weight SDS		BMI SDS		HC SDS	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
M FOG 1	208	13	-0.71	1.07	-1.50	1.13	-1.47	1.26	-2.18	1.19
M FOG 2	542	34	-0.74	1.15	-1.58	1.24	-1.58	1.31	-2.20	1.18
M FOG 3	833	52	-1.06	1.14	-1.90	1.22	-1.79	1.32	-2.34	1.16
Total	1583									
F FOG 1	177	11	-0.71	1.29	-1.13	1.19	-0.96	1.39	-2.03	1.17
F FOG 2	457	27	-0.69	1.26	-1.42	1.20	-1.42	1.44	-2.21	1.12
F FOG 3	1048	62	-1.09	1.25	-1.59	1.31	-1.23	1.51	-2.20	1.19
Total	1682									

The mean height of subjects in table 4.4.4.1 of both sexes shows the highest two socioeconomic groups, making up 48% of the study population, SDS for height, weight, and BMI for both sexes were a mean of 0.3 SD greater than the lowest group, FOG 3. Head circumference had the lowest mean SDS below –2 SD, varying little between groups.

Table 4.4.4.2[1] Fathers occupation groups (FOG) 1, 2 and 3 of CL/P groups, compared by British & SL Reference SDS, for male (M) & female (F) height, weight, BMI, mid upper arm circumference (MUAC), triceps sft (T), subscapular sft (S). [1] supporting table C4.4.4.2: mean, SD and range for the 7 variables.

FOG	N	%	British SDS				SL Reference SDS						
			Height	Weight	BMI	HC	Height	Weight	BMI	HC	MUAC	T	S
M FOG 1	18	4	-1.08	-1.88	-1.67	-1.96	-0.01	-0.12	0.00	0.60	0.42	0.36	0.64
M FOG 2	90	21	-1.73	-2.99	-2.41	-2.53	-0.93	-0.59	-0.77	-0.60	-0.47	-0.06	-0.24
M FOG 3	343	76	-2.11	-3.06	-2.10	-2.77	-1.25	-0.77	-0.32	-0.73	-0.29	-0.95	0.07
Total	451												
F FOG 1	9	3	-2.33	-3.03	-1.92	-2.78	-1.30	-1.29	-0.32	-0.63	-1.09	-0.82	-0.92
F FOG 2	56	18	-2.05	-2.87	-2.12	-2.88	-0.84	-0.63	-0.55	-0.48	-0.06	-0.28	-0.03
F FOG 3	239	79	-1.84	-2.45	-1.75	-3.11	-0.62	-0.42	-0.22	-0.84	-0.17	-0.23	-0.20
Total	304												

The male CL/P group in table 4.4.4.2 shows subjects in FOG 1 were close to the SL Reference population for British and SL Reference SDS. In females with CL/P in FOG 1, group size of nine, and three of the data sets representing one subject, was not a normal distribution of the data.

Among males with CL/P, a difference of one British SD was present between FOG 1 and FOG 3 for height, weight, and 0.8 SD for head circumference. FOG 2 values were intermediate, but much closer to FOG 3 than FOG 1. Applying the SL Reference SDS, similar difference in SDS between the male Fathers Occupation Groups was seen for all seven variables. In contrast, the females with CL/P showed no difference between Fathers Occupation Groups. There was no trend in the expected direction of lower SDS in the poorest FOG category for any of the seven variables.

4.4.5 Place of residence and growth

SL Reference

Table 4.4.5.1 Male (M) and female (F) SL Reference rural or urban (R/U) dweller, British SDS growth variables.

Male			Height SDS		Weight SDS		BMI SDS		HC SDS	
R/U	N	%	mean	SD	mean	SD	Mean	SD	Mean	SDS
M Rural	990	63	-1.10	1.14	-1.96	1.15	-1.85	1.24	-2.29	1.19
M Urban	593	37	-0.58	1.05	-1.24	1.23	-1.30	1.36	-2.07	1.12
Total	1,583									
R/U	N	%	mean	SD	mean	SD	Mean	SD	Mean	SDS
F Rural	1004	60	-1.03	1.25	-1.56	1.26	-1.27	1.47	-2.20	1.18
F Urban	678	40	-0.82	1.29	-1.40	1.29	-1.22	1.50	-2.17	1.15
Total	1,682									

The rural proportion of SL Reference of 62% (95% CI 0.59 to 0.63), was similar to the national statistic of 71%. Urban males were the least compromised in growth in table 4.4.5.1, and urban females followed. Urban males were a mean of 0.52 SD taller and 0.72 SD heavier than their rural male counterparts who were also 0.55 SD thinner. There was little difference between the mean SDS of the four growth parameters in urban and rural females, but neither was as light or thin as rural males.

All groups had similarly disproportionately small mean head circumference SDS compared with their length SDS.

CL/P groups

The rural CL/P proportion, 76% (95% CI 0.72 to 0.78), was similar to the general population, and significantly closer than SL Reference, 62% (95% CI 0.11 to 0.17).

Table 4.4.5.2[1] Rural & Urban CL/P groups compared by British, SL Reference SDS, for M & F height, weight, BMI, MUAC, triceps sft (T), subscapular sft (S).

	N	%	British SDS				SL Reference SDS						
			Ht	Wt	BMI	HC	Ht	Wt	BMI	HC	MUAC	T	S
M Rural	327	73	-2.07	-3.06	-2.10	-2.74	-0.9	-0.77	-0.43	-0.70	-0.36	-0.45	-0.31
M Urban	124	27	-1.82	-2.83	-2.10	-2.58	-0.67	-0.63	-0.39	-0.52	-0.34	-0.54	-0.19
Total	451												
F Rural	243	80	-1.95	-2.53	-1.73	-3.03	-0.74	-0.54	-0.22	-0.74	-0.90	-0.17	-0.21
F Urban	61	20	-1.61	-2.62	-2.19	-3.21	-0.42	-0.53	-0.53	-0.86	-0.47	-0.28	-0.23
Total	304												

[1] supporting table C4.4.5.3: mean, SD and range for the 7 variables.

Rural and urban clefts in table 4.4.5.2 show the same trend as the SL Reference population; urban residents with CL/P were a little taller and heavier than their same sex rural counterparts, British and SL Reference SDS range 0.00 SD to 0.34 SD. Rural males with CL/P were again the smallest and lightest group by British and SL Reference SDS. Rural and urban CL/P subjects were thinner, they had smaller mean MUAC, and less subcutaneous fat than the mean values for the SL Reference population, and the urban CL/P residents were similar, for skinfold thickness, but the female MUAC showed a mean difference of 0.43 SD.

4.5 NUTRITIONAL STATUS IN SL REFERENCE AND CL/P GROUPS

4.5.1 Prevalence of moderate and severe nutritional impairment

Undernutrition among the SL Reference population and CLP groups are presented in grades of moderate (-2 to –2.99 SDS) and severe (<-3SD) by year of age, in figures 4.5.1.1,3,4, and 5. Prevalence data is in supportive tables C4.5.1.1, 2, 3, and 4.

Height

Figure 4.5.1.1 Height <-2 SD & <-3 SD British SDS in Reference & Cleft groups.
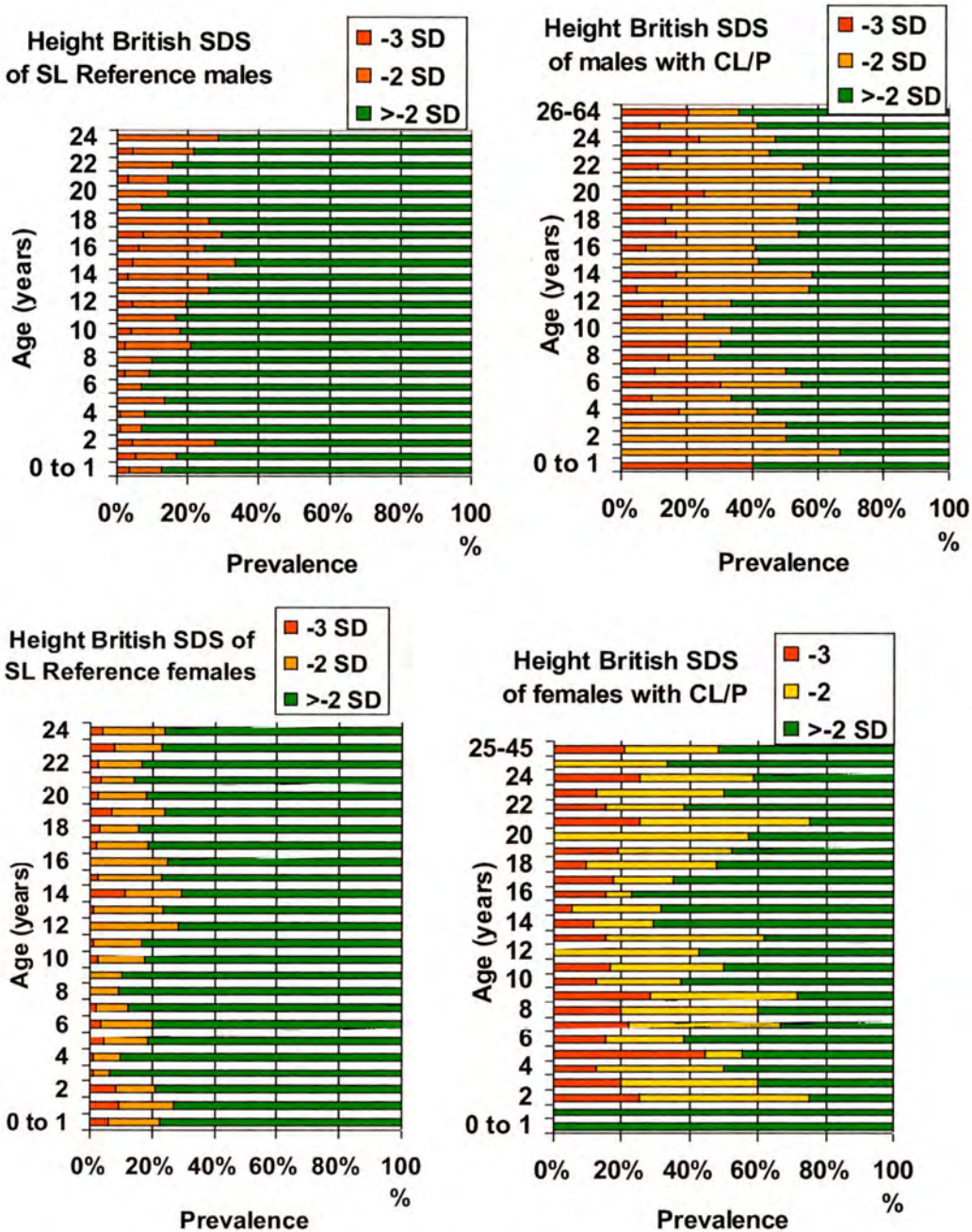
In figure 4.5.1.1 the SL Reference population prevalence of height <-2 SD overall was 19% for males and females. In under two year olds it was 21% in males and 24% in females, and up to nine years old stunting prevalence was seven to 20 percent. It peaked at 28% in males and 30% in females between 13 and 19 years. In

both sexes the prevalence in adults was 16 to 17%. Severe stunting <-3 SD had a mean prevalence of three to four percent from infancy to 25 years old.

In CL/P groups the prevalence of <-2 SD was 49% overall, more than twice that of the SL Reference population. Peaks in prevalence of up to 60% occurred in both sexes; in females between six and eight years, and 11 to 12 years; in males 13 to 14 years. From 18 years upwards the prevalence increased in males to average 34% moderate, 21% severe, and in females 25% moderate, 17% severe. Old Cohort adults were significantly more frequently affected as a proportion than Young Cohort adults, and more severely affected. Prevalence of pooled male and female <-2 SD in the Old Cohort was 75% (35/47) versus 54% (105/194) of the Young Cohort. Prevalence of severely affected <-3 SD was 60% of all <-2 SD in the Old Cohort, compared with 27% of the Young Cohort. Difference between the cohorts for height <-2 SD was $\chi 2$ (Pearson) = 6.42, significant to p <0.01, and <-3 SD was $\chi 2$ 19.36, significant to p <0.0001.

Fluctuation in prevalence of <-2SD in height with age described a cubic curve.

Figure 4.5.1.2 Cubic graph of age versus height <–2 SD British SDS of male SL Reference.
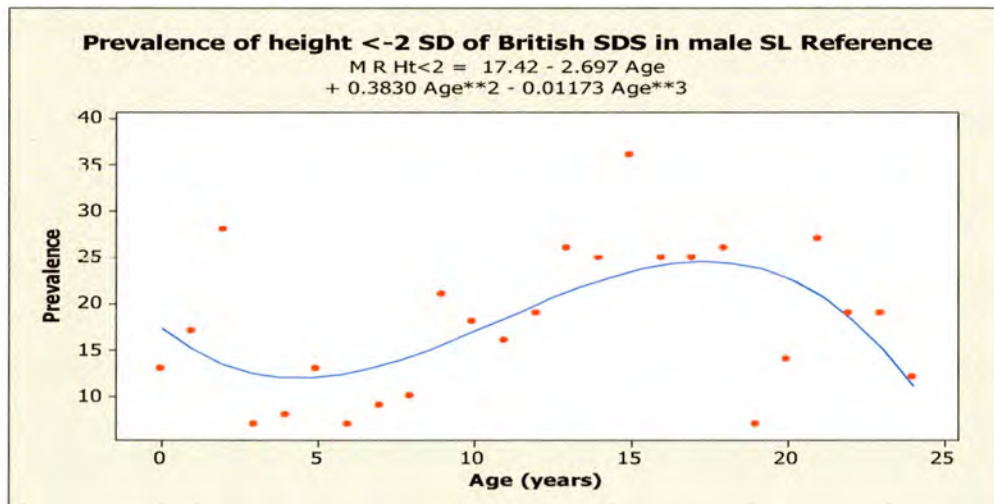
In figure 4.5.1.2, from the left the curve tracked the reduction in prevalence of –2 SD in height, during a general deceleration of growth in childhood. The second part of the curve was the inverse of the adolescent growth spurt. A third part, a reduction in prevalence, emerged as height continued gradually to increase at an age when well-to-do populations have ceased to grow.

Weight

Figure 4.5.1.3 Weight <-2 SD, -3 SD British SDS in SL Reference and Cleft groups.
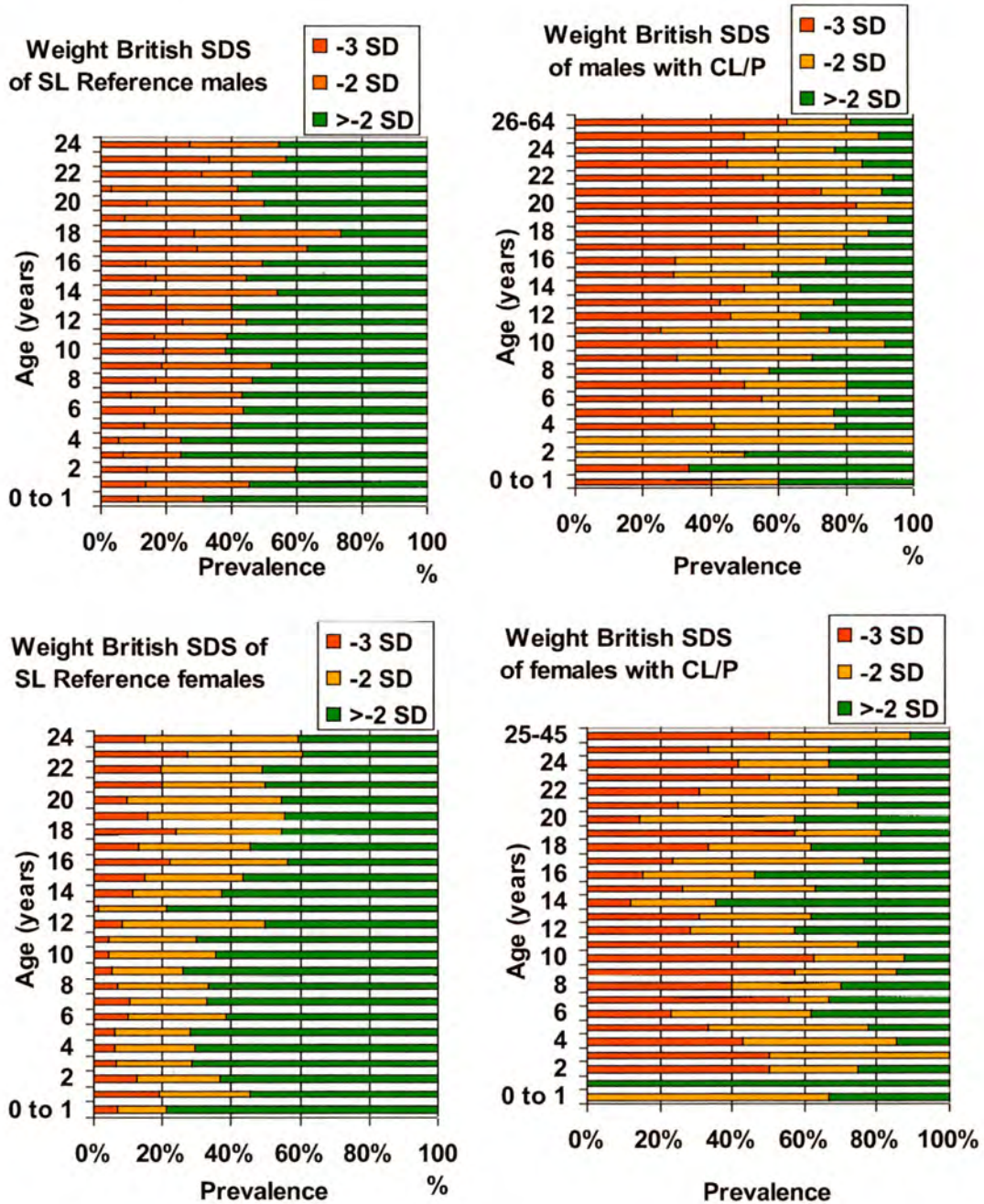
Figure 4.5.1.3 shows that underweight of <–2 SD was more prevalent in CL/P groups than in the SL Reference population: proportionately more males were affected, and they were more likely to be severely underweight. Overall prevalence of underweight in the CL/P groups and SL Reference respectively were, in males 76% and 42%, females 67% and 37%. CL/P groups were proportionately more likely to be severely

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underweight at <−3 SD, mean CL/P 48% to 50%, SL Reference 11% to 15%. A peak in underweight prevalence occurred at six to nine years affecting all groups; in SL Reference 38% to 52% and CL/P groups 70% to 90%, females always the lower of these pairs. A second peak occurred at 16 to 18 years, up to 74% in SL Reference, and 100% in CL/P; prevalence in adult life year to year was only slightly lower.

Body Mass Index
Figure 4.5.1.4 Male BMI as British SDS in SL Reference and Cleft groups.
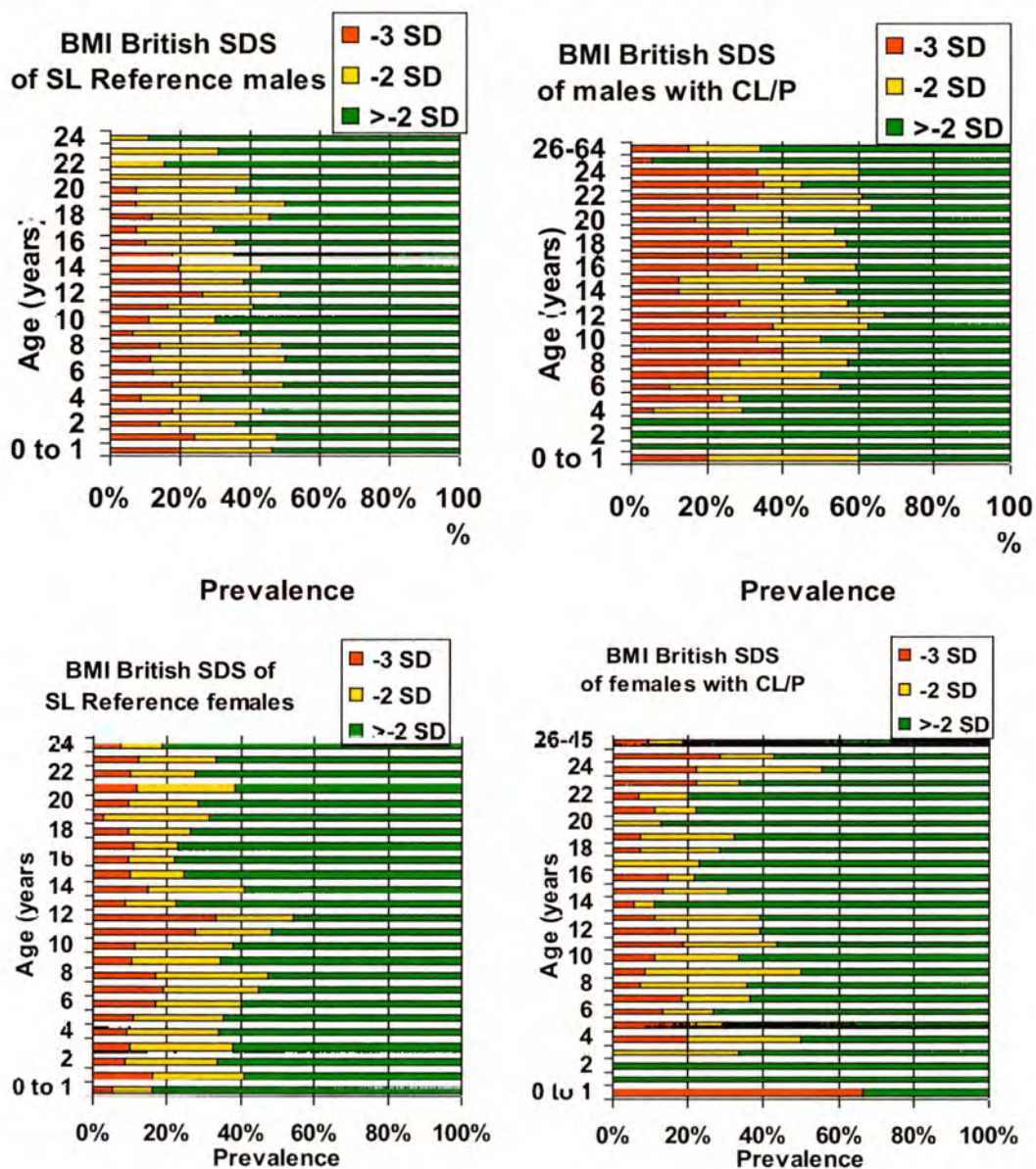
In figure 4.5.1.4 the overall prevalence of thinness, applying the cut off of <-2 SD of the British BMI growth reference, was 23 to 47%. There was considerable overlap between the sexes of the prevalence of severe thinness in both SL Reference and

CL/P groups. Prevalence ranged from three to 63% of the BMI from year to year. Mean prevalence was highest in CL/P males, <-2 SD 49%, -3 SD 25%. Concern for food safety for women prompted comparison of prevalence of thinness <−2 SD in SL Reference adults. Prevalence was 31% males, 33% females, but severity of −3 SD was 2% in men and 12% in women. The difference was statistically significant, $\chi 2$ 8.74, p 0.003. The prevalence in adults of both sexes with CL/P was 43% and 40%, which was representative of the small, non-significant differences in indices of undernutrition in this group. At the other end of the spectrum, the prevalence of obesity in SL Reference females was four percent, overweight two percent, males two percent and one percent. No subjects with CL/P were obese, and one percent of males were overweight.

Cumulative distribution of height, weight, and BMI SDS

Figure 4.5.1.5 Cumulative frequencies of SL Reference and CL/P height, weight, and BMI as British SDS.
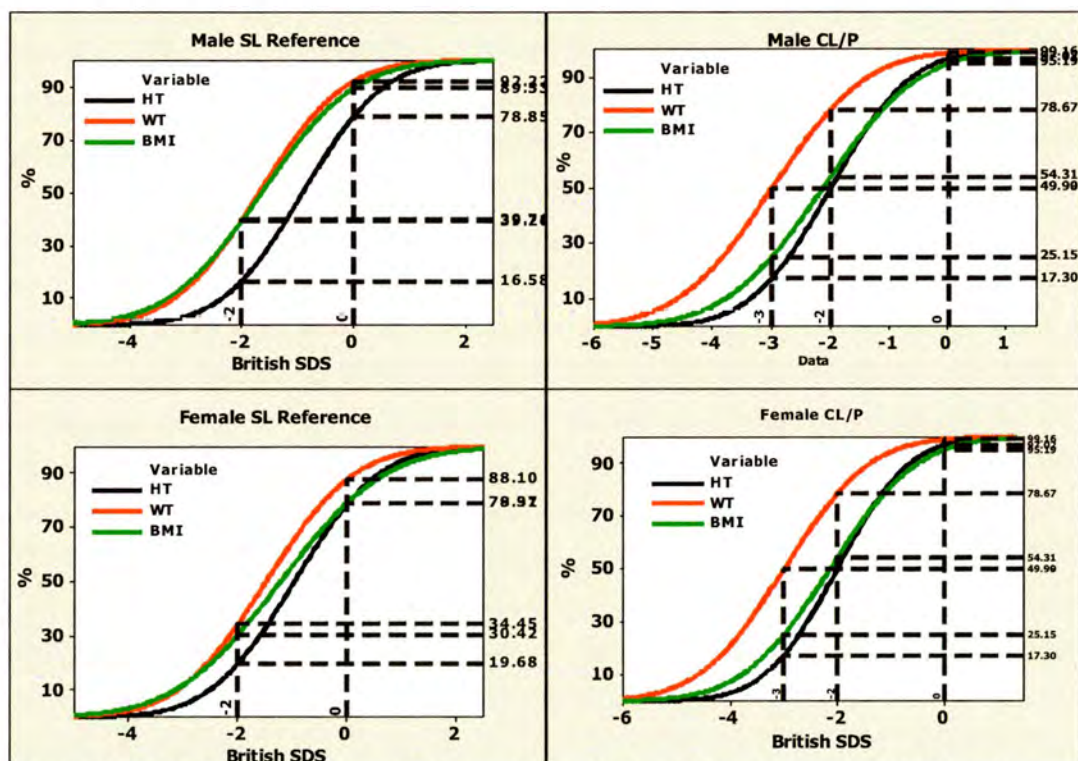
Figure 4.5.1.5 shows the cumulative relationship of three growth variables for comparison. Mean weight was shifted to the left by 0.5 to 1.0 SD compared with height; the wider the difference between weight and height, the more BMI lay close

to height. As height is relatively better preserved in the Sri Lanka population than weight this is reflected in their relationship as defined by BMI as weight/height m^2. The result is a flatter BMI distribution curve and a narrower band of values across both SL Reference and CL/P than seen in height and weight separately.

The SD lines illustrate the proportion <0 SD, which is over 79% of values for SL Reference and 91% for CL/P. Changes in prevalence data relate to cut offs such as <-2 SD and -3 SD due to the shift to the left of height and weight.

A comparison of IOTF thinness grades with British SDS

Figure 4.5.1.6 IOTF thinness grades v British SD for SL Reference and CL/P groups
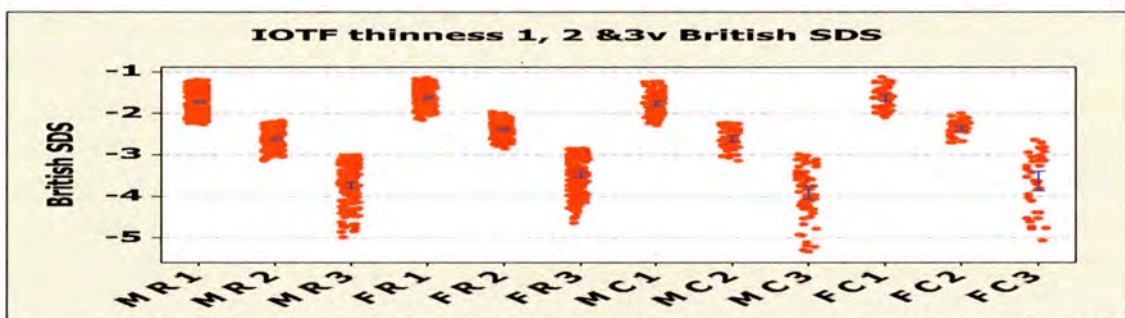
MR = male Reference, FC = female Reference, MC = male Cleft, FC = female Cleft

The age range covered by the children's IOTF grades is two to 18 years. A comparison between the British SDS -1 SD to -3 SD and IOTF grades 1, 2 and 3 in figure 4.5.1.6, supporting table C4.5.1.5, shows an overlap of values. These occurred where the curve of the IOTF grades differed from the British SDS. The trend was for British SDS close to the cut off to be categorised within the less severe IOTF thinness grade above it. Thus, the proportion of -2 SD British SDS in IOTF thinness grade one was 15%, and -3 SD in grade two was 11%. The effect was to reduce the proportion identified by IOTF grades as at risk in grades one and two, and over represent the numbers in grade three by five percent.

Subcutaneous fat skin fold thickness and arm circumference

Mean SL Reference SDS for triceps and subscapular skinfold thickness (sft) and mid upper arm circumference (MUAC) in subjects <-2 SD in height were compared. The cut off of height <-2 SD was chosen for its association with long term undernutrition, compared with underweight which could be altered by shorter term fluctuations.

Table 4.5.1.6 Comparison SDS SL Reference and CL/P in subjects <-2 SD in height.

	Triceps SDS	Subscapular SDS	MUAC SDS
M SL Reference	−0.71	0.12	-0.28
F SL Reference	0.10	0.59	-0.38
M CL/P	-1.05	0.12	-0.44
F CL/P	-0.21	-0.17	-0.30

In table 4.5.1.6 the CL/P mean for subscapular fat was close to the SL Reference 50th centile. The triceps sft SDS in males was reduced, more in the CL/P group than SL Reference, and females with CL/P were intermediate. The MUAC SDS was reduced in all four groups. The male CL/P group appeared most affected.

4.5.2 Nutritional status and Fathers Occupation Group

Figure 4.5.2.1 Prevalence of <-2 SD British SDS in height & weight by age cohort and Fathers Occupation Group (FOG) of SL Reference (R) and CL/P (C) groups.
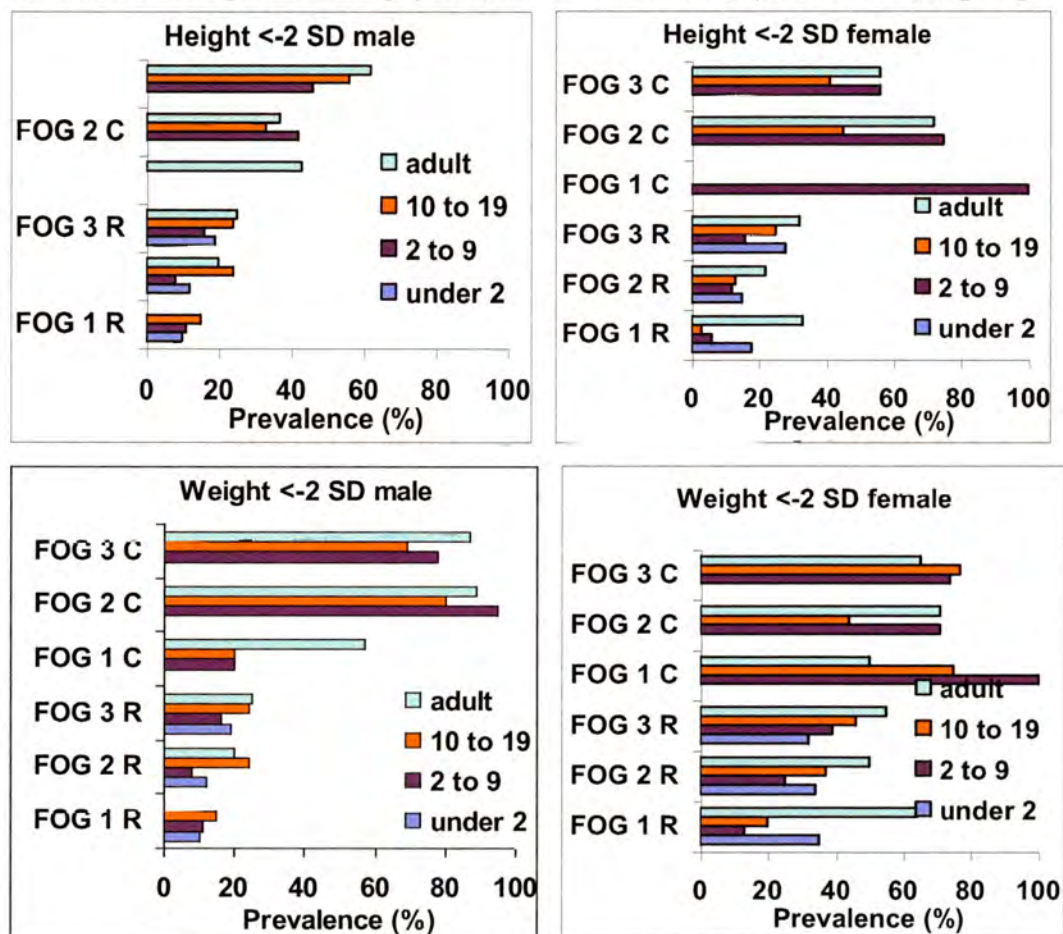
In figure 4.5.2.1 the prevalence of <-2 SD in height within SL Reference FOG 2 and FOG 3 more than doubled in the same FOG of the CL/P group. This held within each

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age cohort, for males and females, with one exception. In underweight females the smallest difference was found in FOG 2 adolescents, with 37% prevalence in SL Reference and 44% in the CL/P group.

Prevalence of height and weight <-2SD in males and height in females in the childhood cohort, in FOG 2 and FOG 3, were between eight percent and 16% in SL Reference, and 42% to 95% in Clefts.

By adolescence the prevalence in underweight in these two FOGs had increased, in SL Reference male adolescents and adults to 24%, while in males with CL/P it was greater than 69%.

Among the SL Reference population, adult females from all three Fathers Occupational Groups had the highest prevalence of -2 SD of the age cohorts. For height the range was 22 to 33%, and weight 50% to 64%. FOG 1 Cleft groups were small and limited the comparisons that could be made.

Table 4.5.2.1 Height <-2 SD British SDS $\chi2$ (in 2 x 3 tables) difference in prevalence between Fathers Occupation Group 1, 2 & 3 within each SL Reference and CL/P group.

Population containing FOG 1,2 & 3	$\chi2$	p
M SL Reference	29.56	<0.0001 ***
M CL/P group	24.38	<0.0001 ***
F SL Reference	27.50	<0.0001 ***
F CL/P group	3.25	ns

Table 4.5.2.2 Weight <-2 SD British SDS $\chi2$ (2 x 3 tables) difference in prevalence between Fathers Occupation Group 1, 2 & 3 within each SL Reference and CL/P group.

Population containing FOG 1,2 & 3	$\chi2$	p
M SL Reference	12.95	<0.001 **
M CL/P group	19.41	<0.0001 ***
F SL Reference	234.98	<0.0001 ***
F CL/P group	1.20	ns

Tables 4.5.2.1 and 2 show FOG was significantly related to prevalence of <-2 SD British SDS in height and weight for both sexes in the SL Reference population, and male CL/P group, $\chi2$ p <0.001 to 0.0001, but not the female Cleft group.

Body mass index

Figure 4.5.2.3 Prevalence of thinness by age cohort and Fathers Occupation Group (FOG) for SL Reference (R) and CL/P (C) groups, male (M) and female (F).
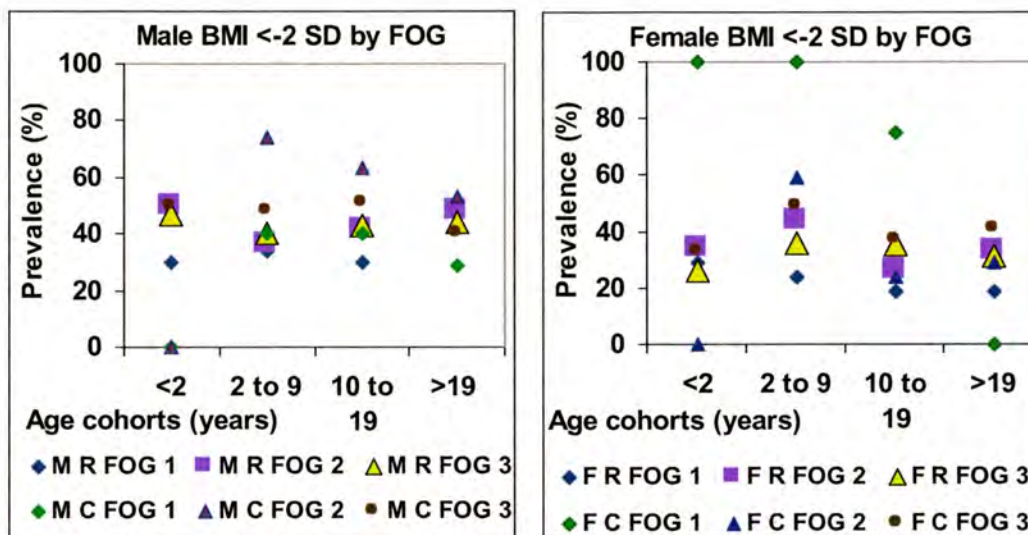
Figure 4.5.2.3 shows similarity in prevalence of thinness between FOG 2 and FOG 3 in SL Reference and CL/P groups by age cohort, and sex, ranging between approximately 33% to 45%. Exceptions were: CL/P group male and female FOG 2 in childhood 74% and 59%; CL/P group FOG 2 males in adolescence 63%. CL/P group FOG 1 was small with anomalous results. A comparison of different BMI cut offs by FOG and age cohorts is shown in table C4.5.1.5. The difference in proportion between –2 SD and the <5th centile cut off for BMI was similar in each age cohort, and contained approximately 10% of the population.

4.5.3 Comparison of growth of CL versus clefts that include the palate

CL comprised 50 subjects (32 males) and 71 (45 males) data sets. Average age at primary CL surgery was 7.2 years, SD 9.0 (range 0.2 to 31 years), and subjects'age at data collection was 16.8 years SD 10.5 years (range 0.3 to 45 years). 18 subject's sets of data (9 males) were obtained at the time of surgery in 1990. It was hypothesised that those with CL would be less likely to be nutritionally compromised than those with a cleft palate. CL was compared by SDS and prevalence of undernutrition with the CL/P subjects who had palate surgery.

The lowest socioeconomic group, FOG 3, comprised 57% of SL Reference, and 75% of CL/P groups. This 18% difference was a potential for error when comparing small differences between groups. As detection of small differences could be instructive, an adjustment was derived by stratifying the non-cleft SL Reference population SDS, according to Fathers Occupation Group and age cohort. The adjustment range extended 1.11 SD, from 0.63 SD to –0.48 SD, as set out in table C4.5.3.1.

Figure 4.5.3.1 CL mean height and weight as SL Reference SDS, adjusted for Fathers Occupation Group and age cohort.
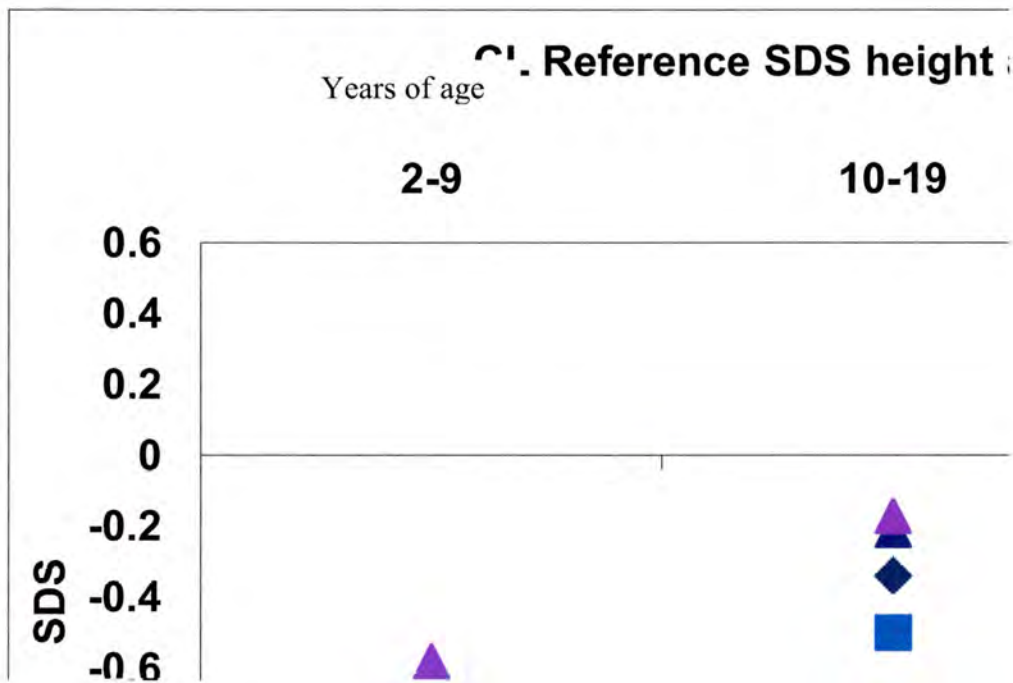
Figure 4.5.3.1, with means and ranges in table C4.5.3.2, shows SL Reference SDS for CL subjects by age group.

The overall pattern for both sexes showed catch up in height. This was from approximately –1 SD of the SL Reference in childhood to –0.50 SD males, –0.17 SD females in adolescence. It was very similar in increase in SD and growth pattern to the CL/P groups presented previously in graph form in figure 4.3.1.5 and 6.

To provide further confirmation of the difference between CL and SL Reference groups the prevalence of undernutrition was assessed. A suitable comparison group was SL Reference Fathers Occupation Group 3. The latter was selected for comparison as 25 of 26 of female CL and 27 of 45 of male CL subjects were in Fathers Occupation Group 3.

Table 4.5.3.2 CL v SL Reference Fathers Occupation Group 3 prevalence of <-2 SD British SDS in height, weight, and BMI.

Group	N	Height %	Weight %	BMI %
M CL	45	44	67	38
M SL Reference	833	20	47	42
F CL	26	38	65	65
F SL Reference	1048	25	42	33

Table 4.5.3.3 CL v SL Reference prevalence of <-2 SD British SDS in height weight and BMI compared by $\chi2$.

	<-2 SD	$\chi2$	p
Male CL v M SL Reference	Height	13.94	0.001 **
Female CL v F SL Reference	Height	1.84	ns
Male CL v M SL Reference	Weight	5.97	0.01 *
Female CL v F SL Reference	Weight	4.86	0.01 *
Male CL v M SL Reference	BMI	0.19	ns
Female CL v F SL Reference	BMI	12.18	0.001 **

Table 4.5.3.2 shows the prevalence of undernutrition in CL compared with the selected SL Reference group, and statistical differences in table 4.5.3.3. CL was significantly different from SL Reference for prevalence of <-2 SD in weight in both males and females, height in males and BMI in females, $\chi2$ values p 0.01 to 0.001. This finding lends weight to the difference in SDS found in children with CL indicating that these subjects experienced more undernutrition than the SL Reference population.

A comparison of group means for CL(P), BCLP, UCLP and CP found no significant difference or trend worthy of comment and are not considered further.

4.6 PUBERTY IN SL REFERENCE POPULATION AND CL/P GROUPS

Pubertal changes categorised by Tanner stages were analysed in 847 SL Reference subjects, 43% of them male, and 286 CL/P data sets of which 55% were male.

4.6.1 Pubertal stages

Table 4.6.1.1 Male pubertal stages, age at appearance: CL/P, SL Reference, and British ranges. Low = first appearance, Med = median, High = oldest age detected.

Genitals	CL/P					Reference					British		
	N	Low	Mean	Med	High	N	Low	Mean	Med	High	99th	50th	1st
G2	10	11.1	13.6	13.8	16.0	84	10.6	13.4	13.2	16.4	9.1	12.0	14.9
G3	23	11.5	14.3	14.2	17.5	62	11.8	14.2	14.6	17.8	10.5	13.0	15.5
G4	26	12.1	15.3	15.4	20.7	117	13.6	15.6	16.0	18.0	11.4	14.0	16.6
Pubic hair													
P2	13	12.5	13.6	13.4	15.4	64	11.2	13.6	13.6	16.7	9.5	12.5	15.5
P3	16	12.8	15.0	14.5	17.6	47	12.6	14.5	14.2	16.1	10.9	13.6	16.3
P4	24	12.1	15.7	15.2	20.7	100	12.8	15.8	16.1	18.8	12.0	14.5	16.6
Testes													
4 ml +	59	11.1	12.4	12.1	15.3,	71	10.6	11.9	12.1	14.4	8.4	11.1	14.0
12 ml +	50	12	15	16	19	102	12	15	14	18	11.1	14.0	16.9

Table 4.6.1.2 Female pubertal stages, age at appearance in CL/P, SL Reference, and British ranges.

Breast	CL/P					Reference					British		
	N	Low	Mean	Med	High	N	Low	Mean	Med	High	99th	50th	1st
B2	14	10.3	12.7	12.3	14.0	75	9.5	12.4	12.3	15.3	7.3	11.0	14.8
B3	21	11.5	13.5	13.5	16.0	77	10.1	13.3	13.5	16.0	8.9	12.0	15.1
B4	14	11.4	15.1	15.1	19.7	89	11.9	14.4	14.3	17.3	9.6	13.2	16.6
Pubic Hair													
P2	17	10.7	13.0	12.7	15.8	72	9.5	11.8	12.7	15.3	8.6	11.8	15.2
P3	12	11.5	13.8	13.5	17.0	67	11.9	13.4	13.5	16.0	9.4	12.7	16.0
P4	16	13.0	15.1	15.0	19.4	111	11.9	14.8	16.0	19.9	10.4	13.6	16.8
			Mean	SD				Mean	SD				
Menses	126	9.0	13.73	1.1	18	347	9.0	13.41	1.1	18.0	10.3	13.0	15.7

Figure 4.6.1.1 SL Reference pubertal stages proportion of each stage by year of age.
Male
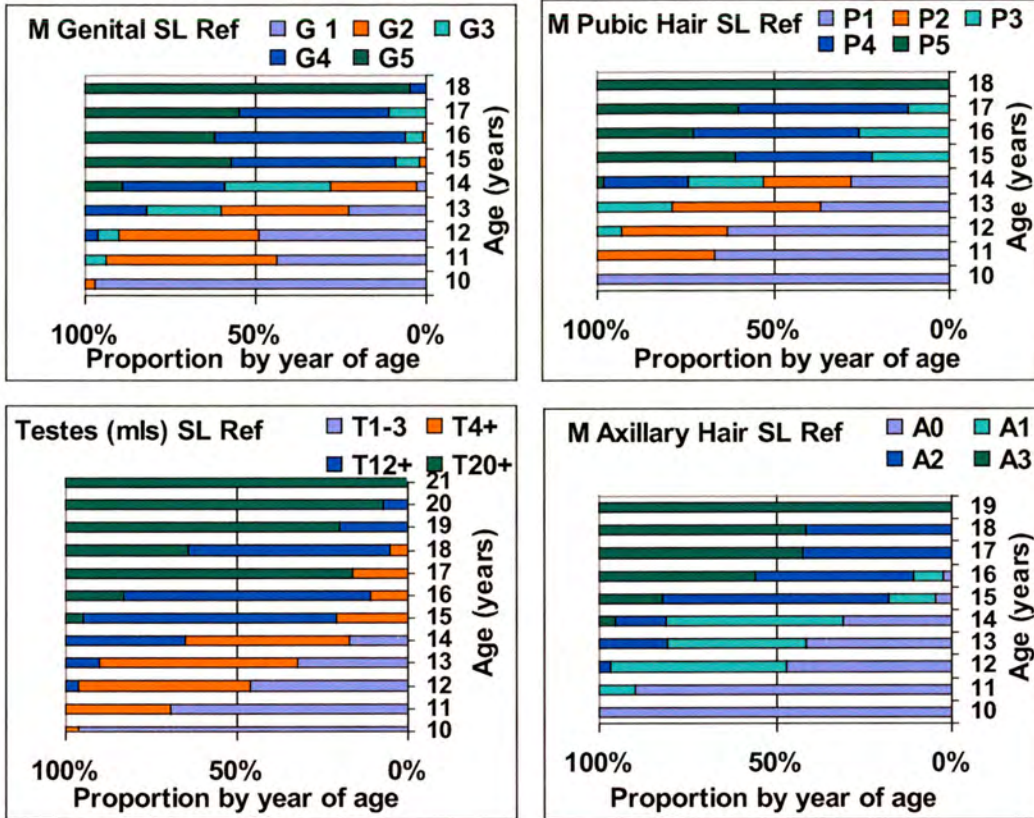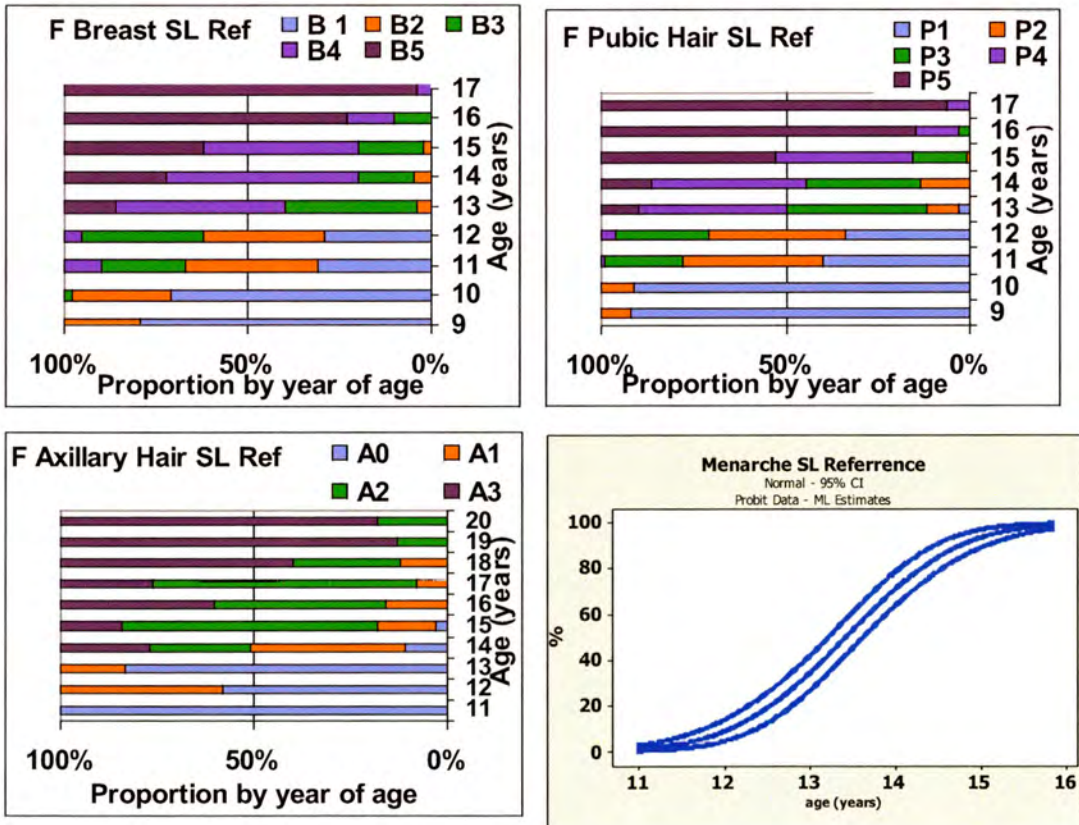
Female

Figure 4.6.1.3 CL/P pubertal stages proportion of each stage by year of age.
Male
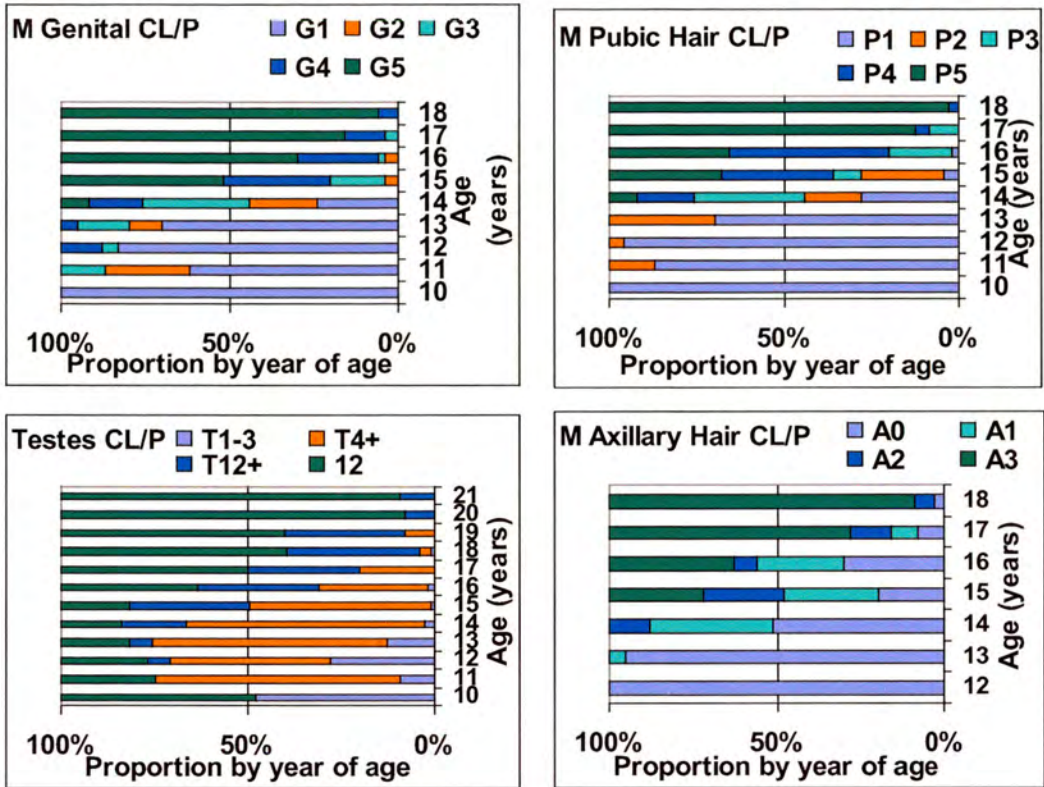
Female
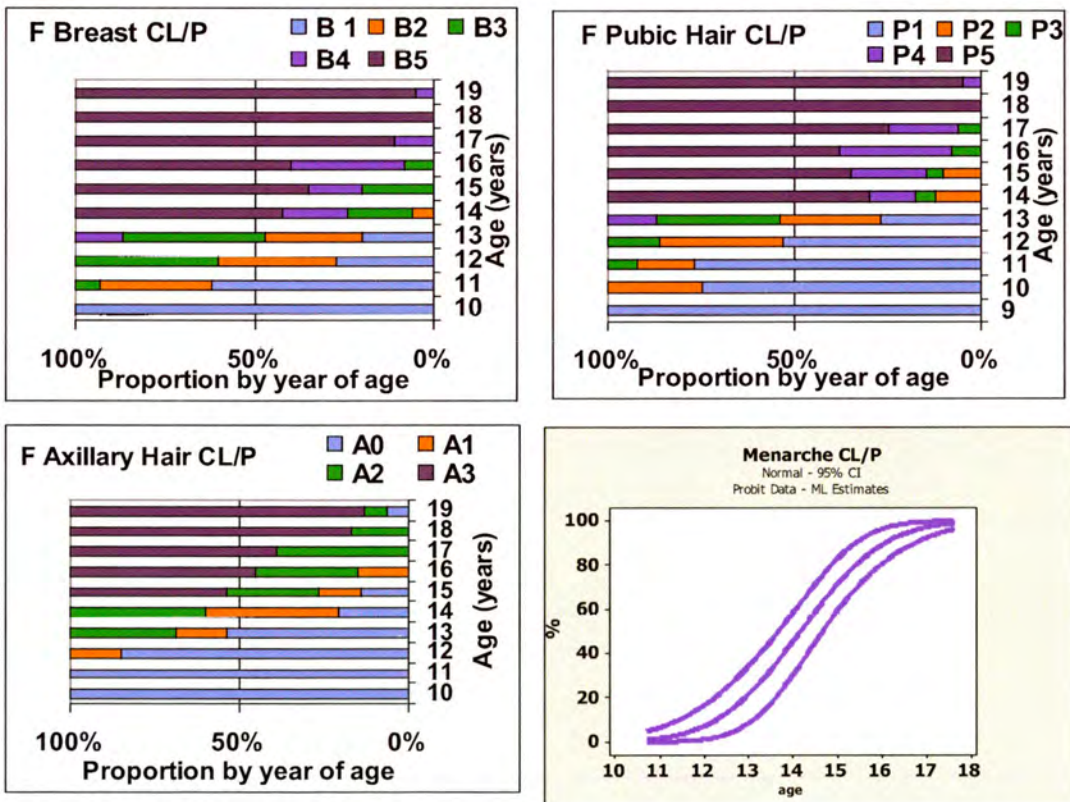
Male genital development first appeared, in the form of four millilitre (ml) testes, at 10.6 years in the SL Reference population, and at 11 years in the CL/P group. The mean age was 11.9 years in the SL Reference group, and 12.4 years in males with CL/P. 12 ml testes were present in both groups by a mean age of 15 years. Breast development appeared at 9.5 years in SL Reference females, and at 10.3 years in females with CL/P. Pubic hair stages usually appeared with each genital and breast stage, after an interval of one to ten months.

Axillary hair appeared at 12 years in girls, 13 years in boys; adult stage three was present shortly after menarche, and from 15 years old in boys.

The mean duration of puberty G2-5 for males was 3.9 years for SL Reference subjects and 3.3 years for males with CL/P. For females, the B2-5 period was 4.5 years for both Reference and CL/P groups.

4.6.2 Menarche

The status–quo method was used to calculate the mean age of menarche (MAM) by probit analysis. Data comprised each subject's age and the binary answer to whether she had commenced menstruating. The cumulative mean age and SD for female SL Reference and females with CL/P are shown in figures 4.6.1.1 and 2, bottom right.

MAM for SL Reference and CL/P: SL Reference   13.41 years, SD 1.29

                                                             CL/P   14.15 years, SD 1.48

Socioeconomic status and place of residence were also compared between the groups, for Fathers Occupation Group 3 and rural dwellers, as they were the associated variables most likely to influence the timing of menarche.

The MAM were:

FOG 3 SL Reference 13.49 years SD 1.36	FOG 3 CL/P 14.28 years SD 1.51
Rural SL Reference 13.62 years SD 1.41	Rural CL/P 14.24 years SD 1.56

MAM in Fathers Occupation Group 3 CL/P was delayed 0.79 years compared with Reference. The difference in Rural MAM between SL Reference and CL/P was 0.62 of a year. The CL/P group had a particularly wide SD, which when divided by the MAM equalled a coefficient of variation (CV) of 10.4%. The SL Reference CV was 9.6%, normal range 9.2 to 10.0%. The other CV's ranged from 10.1% to 11.0%.

4.6.3 WHO recommended evaluation of growth by pubertal stage

Growth was stratified by pubertal stage as recommended by WHO (1988). The median age of appearance of a genital or breast stage was subtracted from the mean age of appearance on the British centile chart. The difference was then subtracted from the mean chronological age of the SL Reference population. This allowed age-specific SL Reference and Cleft group data to be compared with same-age reference data. From tables 4.6.1.1 and 2, this difference for each pubertal stage in males was 1.2 to 2.0 years, and females 1.2 to 1.5 years. The Figure 4.6.3.1, with supporting tables C4.6.3.1 and 2, show changes in height, weight and BMI as mean British SDS in successive pubertal stages. For simplicity, in the figures and tables of growth, male genital (G) and female breast (B) stages share a position on the axis, so G2 and B2 are designated G2/B2. The value for each sex is plotted.

Figure 4.6.3.1 Height and weight changes as British SDS at puberty stages G2 to G5, B2 to B5, adjusted according to WHO recommendation.
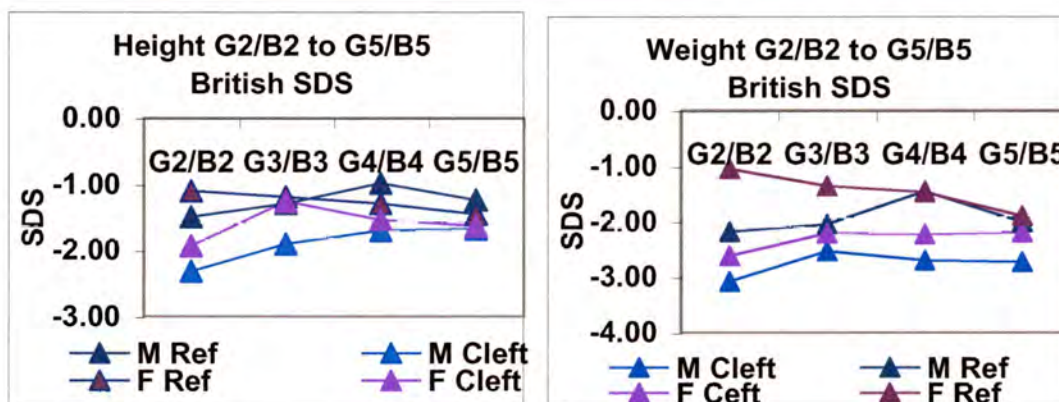
Figure 4.6.3.2 BMI changes as British SDS at puberty stages G2 to G5, B2 to B5.
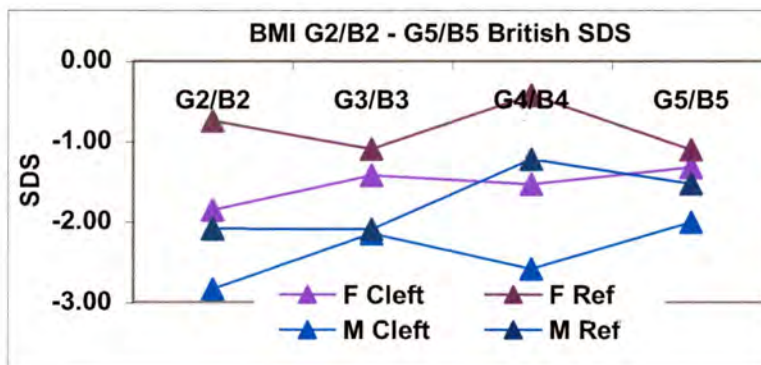
In figure 4.6.3.1, from G2/B2 to G4/B4 males gained in height approximately 0.5 SD in both SL Reference and CL/P groups. Females in the SL Reference showed a small loss, -0.18 SD, compared with a gain of 0.4 SD in subjects with CL/P.

Bringing the WHO adjusted age forward did result in an apparent improvement or maintenance of SDS during the period of more active growth in puberty. By the end of puberty, stage G5/B5, the gains were less impressive or lost in SL Reference, 0.25 SD males, and –0.35 SD in females. However, for CL/P the gain was maintained, 0.64 SD in males, 0.30 SD in females, indicating real catch up had taken place. Changes in weight and BMI, from their pre-pubertal SDS were not consistent in trend in figures 4.6.3.1. and 2.

Comparison of pubertal stages applying the SL Reference

A comparison, adjusting for age cohort, and Fathers Occupation Group, was made for growth in each pubertal stage, between CL/P groups and the SL Reference population. The SD incremental adjustments made were based on table C4.5.3.1. Values plotted below are shown in tables C4.6.3.1 and 2.

Figure 4.6.3.3 CL/P group SL Reference SDS at puberty stages G2 to G5, B2 to G5.
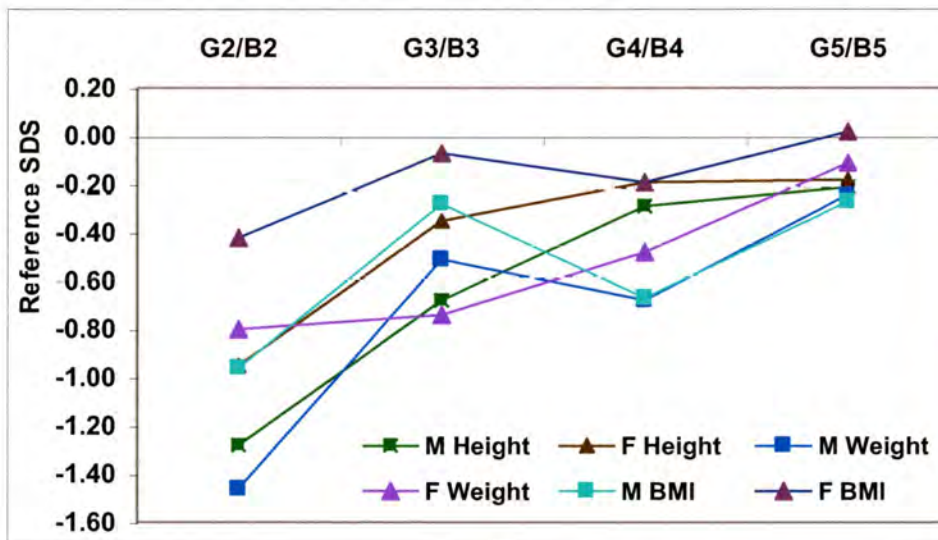
Figure 4.6.3.3 shows catch up by both sexes of the SL Reference adjusted SDS of the CL/P group from G2 to G5 and B2 to B5. In males the gain was just over 1 SD in height and weight, and 0.7 SD for BMI; in females with CL/P the gain was 0.7 SD in

height, weight and BMI. A more comprehensive improvement in SDS was identified than by applying the British SDS.

4.6.4 Prevalence of undernutrition in different stages of puberty

Changes in prevalence of the indices of stunting, underweight and thinness are shown in table C4.6.4.1, and are illustrated in the following figures:

Figure 4.6.4.1 Prevalence of <-2 SD height British SDS in G2 to G5 and B2 to B5.
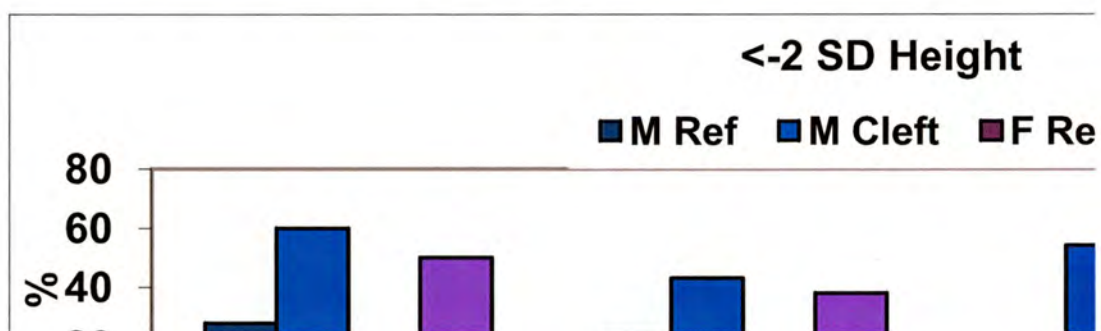
Figure 4.6.4.2 Prevalence of <-2 SD weight British SDS in G2 to G5 and B2 to B5.
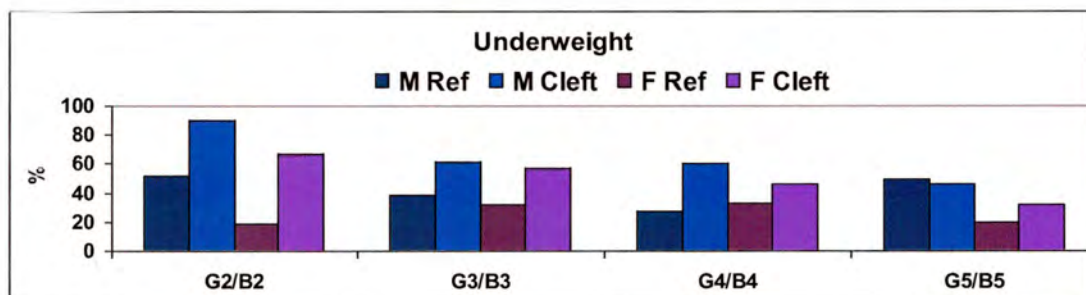
Figure 4.6.4.3 Prevalence of <-2 SD BMI British SDS in G2 to G5 and B2 to B5.
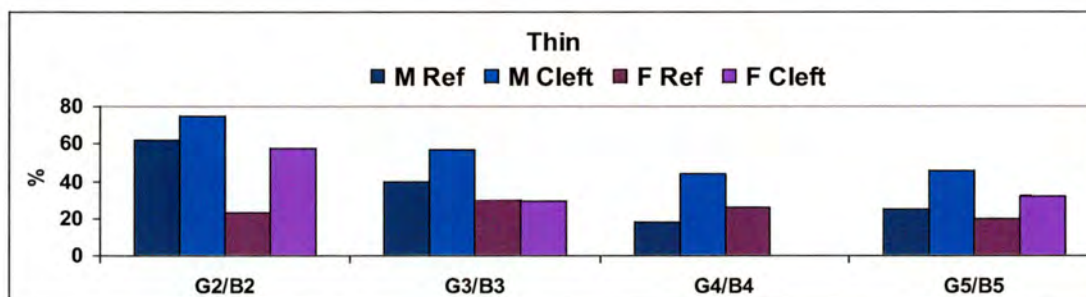
In figures 4.6.4.1, 2 and 3 male and females with clefts were more likely to be <-2SD in height, underweight and thin. Prevalence of <-2 SD in height and weight in figures 4.6.4.1 and 2 showed a trend towards reduction from beginning to end of puberty in all four groups, excluding male SL Reference. Thinness, using the British -2 SD cut off, shown in figure 4.6.4.3, also tended to be less prevalent with each advancing stage of puberty.

For statistical analysis, pooling of data from both sexes of -2 SD prevalence for SL Reference compared with CL/P groups was appropriate, as the sex prevalence of undernutrition was similar within these two categories for each pubertal stage.

Table 4.6.4.2 χ2 differences between the prevalence of <-2 SD in each pubertal stage of SL Reference and CL/P groups.

	<-2 SD Height				Underweight				Thin			
SL Ref	G2/B2	G3/B3	G4/B4	G5/B5	G2/B2	G3/B3	G4/B4	G5/B5	G2/B2	G3/B3	G4/B4	G5/B5
v CL/P	7.45	5.82	12.28	41.93	15.13	6.24	9.12	28.38	5.83	0.32	2.04	28.5
p	0.01	0.02	0.0005	0.0001	0.0001	0.01	0.003	0.0001	0.02	ns	ns	0.0001
	*	*	***	***	***	*	**	***	*			***

ns = not significant

Significant differences between SL Reference and CL/P in prevalence of -2 SD cut offs of undernutrition were identified by χ2, and shown in table 4.6.4.2. They varied between 0.01 to 0.0001 in significance for height and weight, and persisted in CL/P and SL Reference throughout puberty. Only thinness in mid puberty stages G3/B3 and G4/B4 showed no significant difference. Numbers were too small to analyse prevalence of undernutrition in CL/P groups by pubertal stage.

The IOTF grades were analysed for comparison of severity of thinness by pubertal stage, illustrated below, data in tables C4.6.3.1 and 2.

Figure 4.6.4.4 IOTF thinness grades (-1, -2, -3) shown as a proportion (%) of the total of all IOTF thinness grades for that pubertal stage.
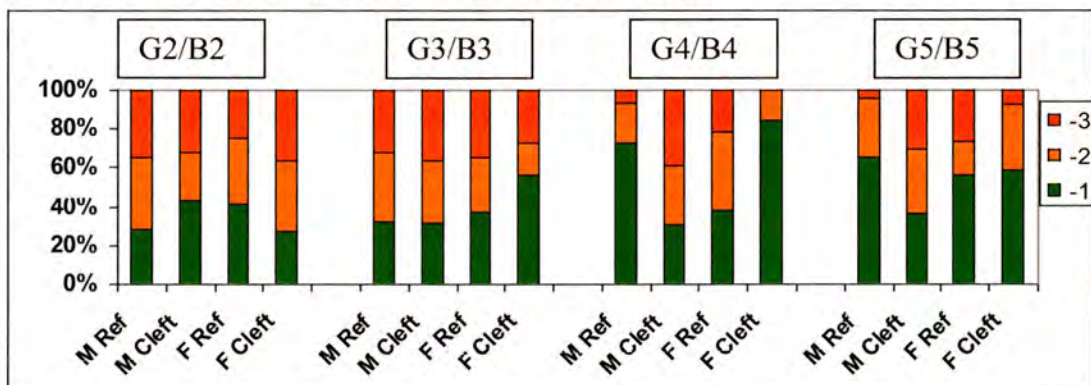
In figure 4.6.4.4 the SL Reference male and CL/P female IOTF grades showed a marked reduction in prevalence of thinness grade three, from 33% in G2 and G3 to three or four percent in G4 and G5. IOTF grade three in Male CL/P at 20-32%, and female SL Reference at 9-16%, changed little in their proportion at each stage in puberty. There was no uniform trend between sexes, SL Reference or CL/P category.

4.7 FOLLOW UP AT A MEAN OF 5, 10, 15 AND 20 YEARS AFTER PALATE SURGERY

Of the 314 males and females with cleft palate (UCLP, BCLP, CP) 291 were seen at follow up at least once. The non-returns were 23 subjects from the 127 who received palate surgery in 1990, a rate of 18%.

4.7.1 Differences between cohorts stratified by age at palate surgery

The effect of age at surgery on growth was analysed by stratifying, into under two years old at palate surgery (Infant cohort), and two years and above (Delayed Surgery cohort). The Infant cohort comprised 42 subjects with 91 data sets; males and females were pooled for analysis. The Delayed Surgery cohort comprised 249 subjects with 507 data sets.

Table 4.7.1.1 Number of observations per cleft palate subject followed up

Age at palate operation	Number of data sets per subject (%)					Subjects followed up		
	1	2	3	4	5	M	F	Total
Subjects <2 years	17 (36)	7 (16)	8 (18)	9 (20)	1 (2)	31	11	42
Subjects >2 years	113 (45)	65 (26)	46 (18)	22 (9)	3 (1)	143	106	249

Two or more data sets were obtained in 64% of the 42 Infant cohort and 44% of the 249 Delayed Surgery cohort, as shown in table 4.7.1.1.

Palate-to-follow-up intervals were aggregated into five-year periods using the British SDS, chosen for comparison as it was independent of Fathers Occupation Group.

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Height

Figure 4.7.1.1 Mean height with 95% confidence interval (CI) bars, as British SDS at 5, 10, 15 and 20 years after palate surgery.
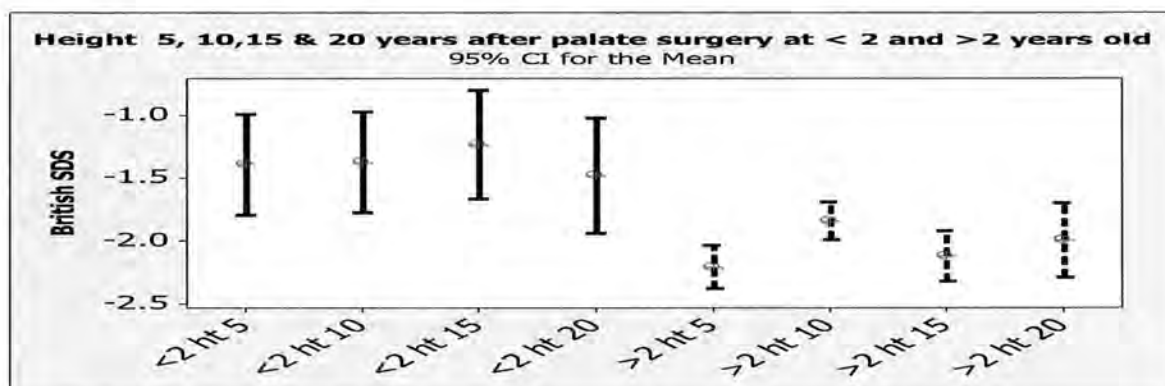
In figure 4.7.1.1 the mean SDS for the Infant cohort in each time interval was discrete from the Delayed Surgery cohort at follow up, except at 20 years which showed overlap in the 95% Confidence Interval bar.

Table 4.7.1.2 Mean height and SD as British SDS on 5 to 20 year follow up after palate surgery.

	<2 years at palate surgery			>2 years at palate surgery			Means and their difference	
Years FU	No data	Mean ht SDS	Ht SD	No data	Mean ht SDS	Ht SD	Difference between sample means	95% CI
5	31	-1.39	1.09	140	-2.21	1.17	0.82	0.37 to 1.27
10	28	-1.34	1.03	188	-1.85	1.03	0.51	0.10 to 0.92
15	15	-1.24	0.78	94	-2.13	0.98	0.89	0.36 to 1.42
20	17	-1.48	0.89	64	-2.00	1.19	0.52	-0.10 to 1.10

The Infant cohort in table 4.7.1.2 was –1.24 to –1.48 SD and less growth impaired than the Delayed Surgery cohort by 0.52 to 0.89 British SDS. The 95% Confidence Interval was significant for difference at 5, 10 and 15 years between the two cohorts.

Weight

Figure 4.7.1.2 Mean weight with 95% confidence interval (CI) bars as British SDS at 5, 10, 15 and 20 years after palate surgery.
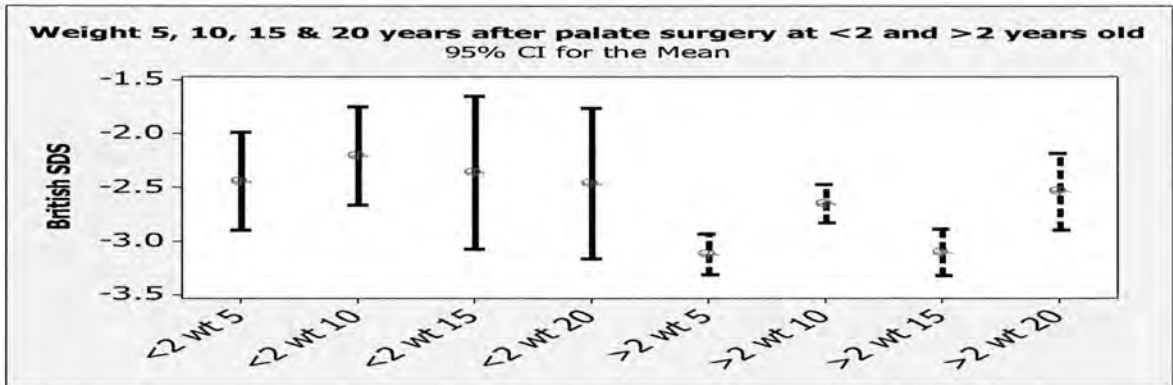
In figure 4.7.1.2, and supporting table C4.7.1.3, the Infant cohort's mean weight SDS was between -2.21 SD and -2.47 SD, higher than in the Delayed Surgery cohort by 0.07 to 0.91 SD, with no trend over time. There was a wide overlap of the 95% CI between the two cohorts.

Body Mass Index

Figure 4.7.1.3 Mean BMI with 95% confidence interval (CI) bars as British SDS at 5, 10, 15 and 20 years after palate surgery.
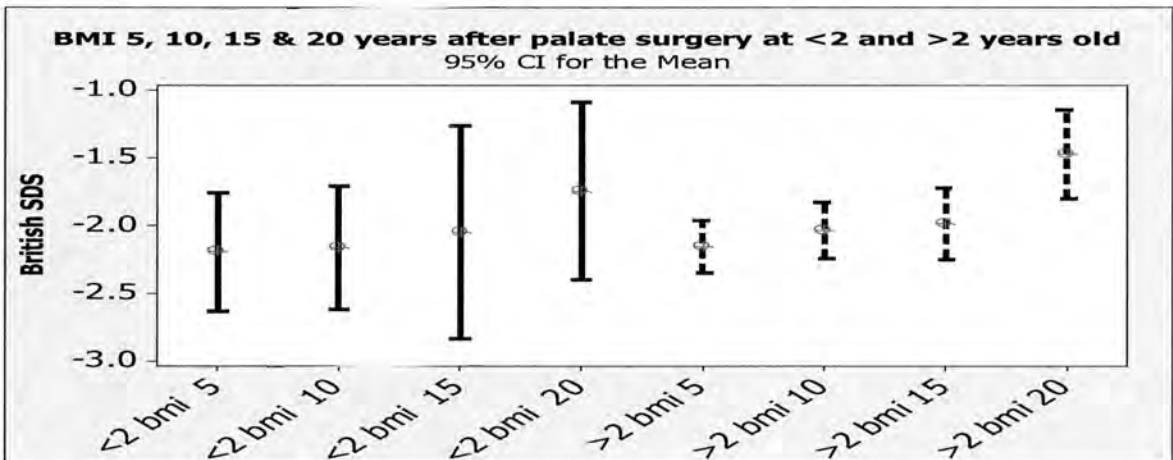
In figure 4.7.1.3, supporting table C4.7.1.4, the BMI mean SDS ranged between

-1.47 SD to -2.19 SD, showing a similar time related trend in SDS in both Infant Cohort and Delayed Surgery Cohort over the 20 year follow up. Mean and SD follow up BMI is in table C4.7.1.3, and illustrated below.

4.7.2   Undernutrition in the follow up group after palate surgery

The prevalence of undernutrition of <-2 SD in height, weight, and BMI at follow up was compared for the Infant Cohort and Delayed Surgery Cohort as a whole, as group size of the former was too small to divide into five yearly age periods.

Table 4.7.2.1 A $\chi2$ comparison of Infant Cohort versus Delayed Surgery cohort prevalence of undernutrition at follow up after palate surgery,

	< 2 yrs 91 records (76% males)			>2 yrs old 507 records (58% males)			$\chi2$	p
Parameter	N	Males %	<-2 SD %	N	Males %	<-2 SD %		
Height <-2 SD	29	75	32	252	61	51	10.07	0.002 **
Weight <-2 SD	57	74	63	371	63	73	-	
BMI <-2 SD	45	80	50	227	62	44	-	

Table 4.7.2.1 shows the prevalence of <-2SD in height was significantly less in the cohort who were younger at operation, $\chi2$ 10.07, p 0.002. The prevalence of <-2 SD for weight and BMI were similar between the two cohorts.

4.8 ADDITIONAL HEALTH, FAMILY AND SOCIAL FACTORS

4.8.1 Examination of potential confounders

Having examined age at palate operation, rural or urban residence and socioeconomic group by Fathers Occupation Group, additional potential confounders of growth were considered, and are shown in table 4.8.1.1.

Table 4.8.1.1 Subjects with CL/P medical, family and socioeconomic factors.

Variable	Male N	% of 212	Female N	% of 154
URTI + Chronic Ear Discharge	63	30	30	19
Hearing impaired	59	28	36	23
Chronic medical condition	26	12	28	18
Consanguinity 1st degree	41	20	26	17
Consanguinity 2+ degrees	13	6	13	8
Family history	15	7	28	17

Respiratory infections and chronic ear discharge

The prevalence in CL/P of recurrent upper respiratory tract infections (URTI) and chronic ear discharge (CED) was 26%. Hearing impairment was reported in 26% of individuals with CL/P, with overlap in 14% of the two groups of symptoms. Prevalence of these conditions was not elicited from the SL Reference population.

Chronic medical conditions

Chronic medical conditions comprised mainly asthma, migraine, bowel disorders, and chronic anaemia. A few individuals had rheumatic fever, juvenile chronic arthritis, or diabetes mellitus. This was a miscellany of potential confounders. Prevalence of chronic medical conditions in the SL Reference population of seven percent, compared with CL/P of 14%, was statistically significantly different, χ^2 22.77, p 0.0001. Although conditions are not usually linked to CL/P their increased prevalence may be associated with exacerbation of asthma through recurrent infection related to the CL/P, and/or psychological factors inducing migraine or stress related headaches.

Consanguinity

Consanguinity in Sri Lanka is common. A reduced genetic pool may increase the incidence of CL/P and influence growth. Among CL/P families first-degree relationships were 18%, second degree were seven percent, for a combined total of 25%. This compared with the SL Reference population prevalence of 12% consanguinity. This difference was statistically significant, $\chi2$ 47.92, p 0.0001

Family history

Family history of CL/P may affect attitudes to care. Prevalence in the CL/P group was 12%.

Table 4.8.1.2 Family size in SL Reference population and CL/P groups

N of siblings[1]	Reference 2582 age 2-24 yrs	%	CL/P 266 aged 2-24 years	%
Siblings 1	510	20	35	13
Siblings 2	849	33	31	12
Siblings 3	631	24	67	25
Siblings 4	345	13	62	23
Siblings 5+	247	10	88	33

[1] Siblings includes the subject; siblings born during follow up are included. The proportion (%) is based on a total 218 males, 163 females.

Number of siblings in SL Reference and CL/P families with children aged between two to 24 years in table 4.8.1.2 were compared. Small families with two children or less were present in 53% of SL Reference compared with 25% CL/P; medium sized families with three or four children comprised 38% of SL Reference, and 48% of CL/P; large families with five children or more were nine percent of the SL Reference versus 33% of the CL/P families. Differences between SL Reference and Cleft groups were statistically significant for small, $\chi2$ 74.67, p <0.0001, and large families, $\chi2$ 128.49, p <0.0001.

4.8.2 Regression analysis of potential confounders of height in CL/P

Age, and age at palate operation are continuous variables that, when regressed against height, fit a polynomial distribution. The other variables, in tables 4.8.2.1 and

2 below, are likely to have linear relationships. Each variable was therefore analysed individually, against height as the dependent variable, by fitted line regression, shown in tables C4.8.2.3 and 4. The sum of variances totalled >100% in the table, arrived at by different equations, quadratic and linear.

Table 4.8.2.1 Male CL/P variance (%) of each independent variable, 451 data sets, up to 442 were used.

Variable	L or Q	R^2 %	R^2 (adj) %	F	p
Age	Q	88.9	88.9	1768.30	<0.0001
Age at palate op	Q	12.1	11.7	27.27	<0.0001
Rural domicile	L	0	0	0.09	0.7
Fathers occupation group	L	0.1	0	0.25	0.6
URTI + chronic ear discharge	L	1.1	0.9	5.07	0.03
Deaf	L	1.3	1.0	5.76	0.02
Chronic medical conditions	L	2.2	2.0	10.28	<0.001
Consanguinity	L	0.6	0.4	2.78	0.1
Family history	L	6.2	5.9	28.92	<0.0001
N siblings	L	5.1	4.9	24.19	<0.0001

L=Linear, Q=quadratic, R^2=variance, F=F-ratio

Table 4.8.2.2 Female CL/P variance (%) of each independent variable, 303 data sets (1 incomplete).

Variable	L or Q	R^2 %	R^2 (adj) %	F	p
Age	Q	82.4	82.3	703.59	<0.0001
Age at palate op	Q	7.2	6.5	10.59	<0.0001
Rural or urban	L	0.2	0	0.55	0.5
Fathers occupation group	L	0.6	0.3	1.84	0.2
URTI + chronic ear discharge	L	0	0	0.4	0.9
Deaf	L	0.3	0	0.81	0.4
Chronic medical conditions	L	0.9	0.5	2.65	0.1
Consanguinity	L	2.3	1.9	6.98	<0.009
Family history	L	0.3	0	1.04	0.3
N siblings	L	0.5	0.1	0.81	0.3

L=Linear, Q=quadratic, R^2=variance, F=F-ratio

Age was the dominant variable in tables 4.8.2.1 and 2, for males and females with CL/P R^2 adjusted accounting for 82% to 89% of the variance. This was followed by age at palate operation with 7% to 12% of the variation. Other variables were very

small in proportion and importance. Males had four variables showing significant linear regression with height: URTI + CED, chronic medical conditions, family history, and number of siblings; a fifth, deafness, was not truly independent of URTI + CED. In females with CL/P only one variable, consanguinity, was significant. This lack of congruence between the sexes and very small proportions of the variance suggested a Type 1 error. Alternatively, finding a number of statistically significant variables that may affect growth, congregating in males, could be attributable to the greater vulnerability of males. Rural and Fathers Occupation Group 3 were large categories and the distribution of linear height was not distinguishable from urban dwellers, and other Fathers Occupation Groups.

Regression analysis using height SDS as the dependent variable

Applying British SDS to CL/P height SDS the most significant factors were analysed in three stages. First, best subset regression to identify major factors from among the variables collected. Secondly there followed their multiple regression. Finally, single linear plots of each of these variables for their individual contribution to the variance in height. Analyses are in tables C4.8.2.5 and 6.

Male best subset regression found five factors most significant: age at palate operation, Fathers Occupation Group, URTI + CED, family history and number of siblings.

Regression gave the equation:

Male CL/P British SDS for height = - 1.03 - 0.0249 Age at palate surgery - 0.294 Fathers Occupation Group - 0.131 URTI + CED + 0.527 Family history - 0.139 N of siblings.

The British SDS in height was a negative value, and had a negative relationship of 0.03 SD per year after palate surgery, 0.29 SD Fathers Occupation Group, 0.13 SD for URTI + CED, and 0.14 SD for each sibling, and a positive relationship with a family history of CL/P of 0.53 SD.

The variance, R^2 17% and R^2 adjusted 16%, was a low value accounted for after the transformation of height to a SDS. Regression was statistically significant, F = 13.75, $p < 0.0001$. Four of the factors were significant at $p < 0.005$; one factor at p 0.03, was URTI + CE

Figure 4.8.2.1 Regression plot of British SDS versus age at palate surgery, Fathers Occupation Group, and number of siblings.
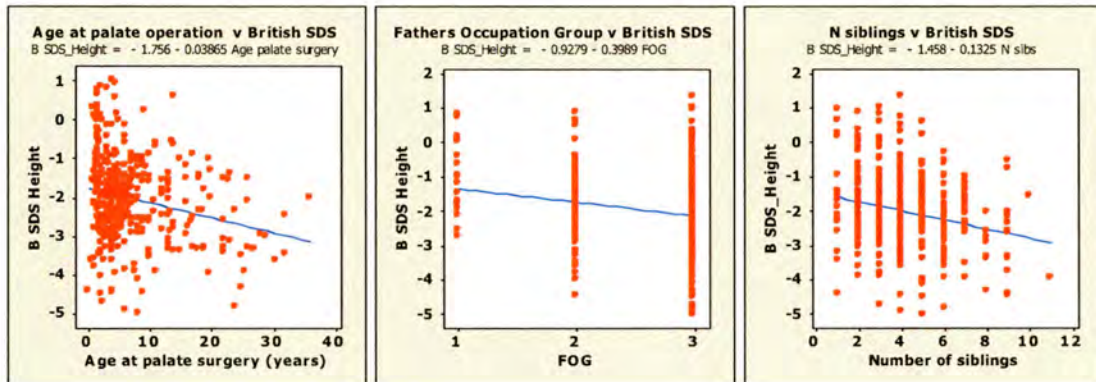
Three factors, shown in figure 4.8.2.1, that contributed most to the variance, as R^2 adjusted, were age at palate surgery 5%, FOG 4%, and number of siblings 6%. URTI + CED and Family history contributed 1% each to the variance, an insignificant proportion.

Female best subset regression found four factors most significant: age, age at palate operation, rural or urban, and number of siblings. On regression the equation was:

Female CL/P British SDS for height = - 1.47 + 0.0241 age - 0.0565 Age at palate surgery + 0.437 urban - 0.130 N of siblings.

The British SDS in height, a negative value, had a positive relationship with age of 0.02 SD per year, and urban 0.44 SD. The relationship was negative, after palate operation at 0.06 SD per year, and 0.13 SD for siblings. The proportion of the variance was R^2 15% and R^2 adjusted 14%. Regression was statistically significant, F = 13.75, p <0.000. Each of the four factors had a statistical significance of p <0.005. The two factors that contributed most to the variance as R^2 adjusted were age at operation 6%, and number of siblings 6%.

The confounders in order of significance, after age, were age at palate surgery, family size, Fathers Occupation Group as a socioeconomic indicator, and family history. Respiratory illness whether as URTI + CED, or asthma, was statistically significant but made only a small contribution.

4.9 A SURVEY OF SKELETAL MATURITY OF THE SL REFERENCE POPULATION AND SUBJECTS WITH CL/P

The purpose of the survey was to observe for differences in skeletal maturity, in both cleft and non cleft subjects, from the British TW3 RUS reference.

Skeletal maturity assessed by hand and wrist X-rays using the TW3 RUS method is presented as Bone Age (BA). BA is the age at which an individual child's skeletal age is on the 50th centile. One standard deviation for RUS bone age approximates to one BA 'year', between five years and 14 years chronological age (CA) in females, and up to 16 years CA in males. CA-BA is 'advanced' if BA is greater than CA, or 'delayed' if less than CA. A BA <- 2 SD or two years 'delay' between these age limits is accepted as outwith normal (Tanner et al. 1975, 2001).

This chapter subsection is hybrid, combining subjects, and reliability studies, with the results. Raw data of RUS TW3 scores and SDS for all subjects are in table B4.9.1.

4.9.1 Subject demographics and reliability study

Figure 4.9.1.1 Age of subjects by sex, SL Reference or CL/P and number of data
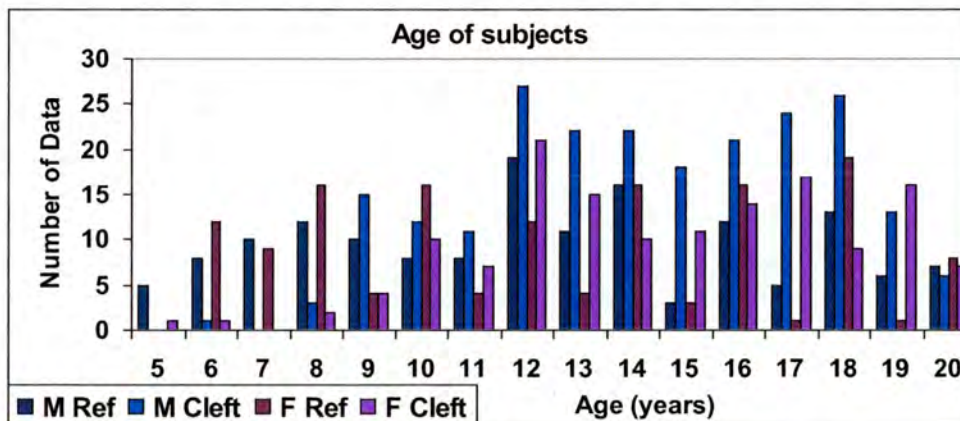
The subjects were aged from 5 years to 20 years. Distribution of 661 readable x-rays among the groups comprised SL Reference males 23%, females 22%, CL/P males 33%, females 22%.

Table 4.9.1.1 Group totals of readable x-rays available for examination

	Male Reference	Female Reference	Male Cleft	Female Cleft	Total	
					No	%
Age range (years)	5-20	6-20	6-20	5-20		
BA RUS <1000	120	91	157	71	439	67
BA Mature	35	49	64	74	222	33
Total	155	140	221	145	661	100

In table 4.9.1.1 SL Reference subjects had one x-ray each. Of the 98 female CL/P female subjects 62% had a single x-ray, 23% two, and 13% had three x-rays, a total of 145. Of the 131 male CL/P subjects 49% had one, 32% two and 19% had three x-rays, totalling 221 x-ray films for scoring. Mature x-rays were found in 222, 33% of all films and are not considered further. Unreadable films comprised 12, 2% of the total.

The distribution by cleft type comprised 8% CL, 16% CP, 11% BCLP, 65% UCLP, similar to the distribution of the somatic growth studies.

Reliability study

To assess intra-observer reliability, duplicate RUS TW3 assessments were performed eight weeks apart on 112 SL Reference population x-rays by AH. For inter-observer reliability Professor P Hindmarsh (PH) was the independent rater, using a standard set of 20 x-rays covering the age range three years to maturity.

The mean, SD and SE of difference in bone age within and between raters are:

	Difference within rater (AH)			Difference between raters (AH and PH)		
Bone Age (yr)	Mean	SD	SE	Mean	SD	SE
RUS	0.28	0.34	0.03	0.05	0.39	0.09

The mean differences were not significant within and between raters. The SD indicates that the same x-ray rated by AH would not differ by more than 0.68 'years' in 95% of ratings, and between raters AH and PH by more than 0.78 'years'. The same stage rating was given by a single observer in over 93% of records, and 89% of records between observers AH and PH. Within and between rater correlations were both 0.99 These reliability ratings are comparable with Beunen and Cameron 1980, Prakash and Cameron 1981, and above the 67 to 83% agreement between raters found by Tanner et al 1994.

4.9.2 SL Reference and CL/P BA by group, age, and sex

The mean BA differences over the age range five years to 20 years between SL Reference and CL/P groups were not significant, 0.22 year for males and 0.32 year females. This was within the intra-observer error of 0.68 years. Mean TW3 RUS scores converted to BA were broadly similar between cleft types. This including CL subjects whose mean 'delay' of 1.21 BA years was lower than in subjects who had a cleft of the palate, at a mean delay of 0.90 BA years. This was concordant with the similarity in height SDS of CL and subjects with palatal clefts.

Table: 4.9.2.1 Male SL Reference & CL/P mean BA, SD, CA-BA 'delay', and range by age.

MALE SL REFERENCE							MALE CL/P GROUP						
Age yrs	N	BA Yrs	SD	CA-BA 'delay'	BA Range Min	Max	Age yrs	N	BA Yrs	SD	CA-BA 'delay'	BA Range Min	Max
5.5	5	4.82	0.15	0.68	4.77	5.61							
6.6	8	5.52	0.95	1.05	3.96	6.33	6.2	1	3.84	0	2.36	3.90	8.33
7.3	11	6.68	1.34	0.61	4.40	7.33							
8.6	12	7.47	0.98	1.10	5.72	8.75	8.4	3	7.80	0.65	0.6	6.89	8.34
9.5	11	7.86	1.25	1.65	7.26	10.20	9.1	14	8.00	1.59	1.10	4.8	10.26
10.8	8	8.89	1.14	1.90	7.44	10.71	10.4	13	8.83	0.88	1.57	7.82	10.78
11.2	8	10.19	1.03	1.01	8.73	11.15	11.5	11	10.27	0.90	1.23	8.54	12.59
12.7	19	11.00	0.65	1.69	8.99	11.72	12.4	27	11.05	1.82	1.35	8.05	12.57
13.4	11	11.93	1.36	1.47	9.22	13.69	13.4	21	11.84	1.38	1.56	9.66	15.58
14.6	16	13.77	1.30	0.82	11.72	16.00	14.5	23	13.42	1.53	1.08	10.32	16.11
15.8	3	15.12	0.83	0.65	14.36	16.00	15.6	18	14.84	1.66	0.76	10.69	16.50
16.2	12	14.90	0.93	0.60	13.43	16.00	16.5	21	16.05	0.60	0.45	15.07	16.50
17.6	5	16.50	0.00	0.00	-	-	17.5	24	16.10	0.88	0.40	-	-
18.4	13	16.19	0.76	0.30	15.49	16.00	18.5	26	16.38	0.24	0.12	-	-
19.0	6	16.50	0.00	0	-	-	19.3	13	16.48	0.04	0.02	-	-
20.3	7	16.50	0.00	0	-	-	20.6	6	16.50	0	0.01	-	-

Table: 4.9.2.2 Female SL Reference and CL/P mean BA, SD, CA-BA 'delay', and range by age.

FEMALE SL REFERENCE							FEMALE CL/P GROUP						
Age yrs	N	BA Yrs	SD	CA-BA 'delay'	BA Range min	max	Age yrs	N	BA Yrs	SD	CA-BA 'delay'	BA Range Min	Max
6.8	12	5.77	0.58	1.03	5.32	6.89	5.9	1	4.89	0.00	1.00	-	-
7.2	9	5.39	0.65	1.79	4.01	6.53	6.1	2	5.73	0.00	1.64	5.94	6.26
8.7	16	7.07	1.28	1.67	5.41	9.26	8.2	2	6.33	0.00	1.62	5.22	7.05
9.1	4	6.94	1.18	2.17	5.89	8.64	9.5	4	8.5	1.07	1.12	8.22	9.97
10.9	16	9.20	0.76	1.69	8.62	11.38	10.5	10	8.24	1.38	2.24	6.37	11.36
11.1	4	8.57	1.47	2.55	6.78	9.90	11.3	7	9.7	1.22	1.66	7.35	12.34
12.8	12	11.10	0.94	1.72	9.16	12.72	12.4	21	11.3	1.41	1.10	8.03	14.09
13.1	3	11.90	0.32	1.14	11.68	12.28	13.5	15	13	0.98	0.46	12.19	15.01
14.6	16	14.11	0.98	0.46	13.17	15.00	14.5	9	14.7	0.94	-0.24	13.68	15.45
15.3	3	14.20	1.33	0.77	12.70	15.00	15.4	11	14.2	1.60	0.86	11.59	16.50
16.3	16	14.80	0.53	0.18	14.48	15.00	16.5	14	14.8	0.56	0.20	13.37	16.50
17.0	1	15.00	0	0	-	-	17.6	17	15	0.00	0.00	-	-
18.0	19	15.00	0	0	-	-	18.6	9	15	0.00	0.00	-	-
19.0	1	15.00	0	0	-	-	19.8	16	14.9	0.24	0.08	-	-
20.0	8	15.00	0	0	-	-	20.5	7	15	0.00	0.00	-	-

From tables 4.9.2.1 and 2, BA 'delay' prior to the commencement of puberty was greatest at nine to ten years old, 1.5 to 1.9 BA 'years' for males, 2.2 'years' for females. SL Reference subjects at 11 years old were similarly 'delayed' by 2.6 'years'. For both sexes mean BA was 'delayed' from childhood until well into adolescence, except in females at 14.5 years, when it appeared slightly advanced. The BA standard deviation was unusually wide at ages that were likely to include children entering and progressing through puberty at different rates.

Comparison of SL Reference and Cleft group BA and chronological age

Figure 4.9.2.1 Mean annual BA for SL Reference (Ref) and CL/P (Cleft) groups plotted against chronological age (CA).
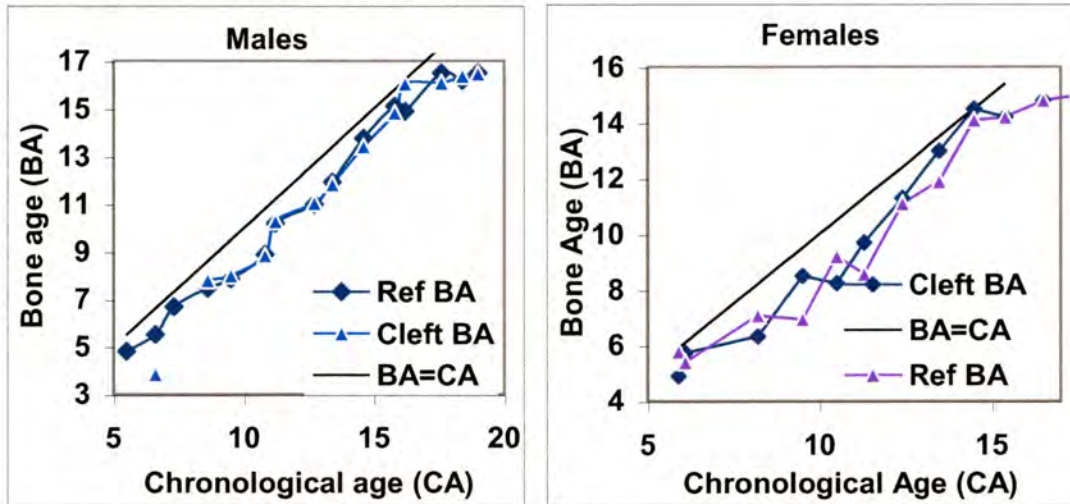
In tables 4.9.2.1 and 2, the mean values for BA, depicted in figure 4.9.2.1, lagged behind chronological age throughout childhood from 5 years onwards. Bone age 'delay' was greatest between nine and 12 years old. Bone age then advanced relative to chronological age through puberty. Females began catching up about a year earlier than males to be less than one BA year behind by 13 to 14 years.

Figure 4.9.2.2 Prevalence of two years 'delay' in BA for SL Reference (Ref) and CL/P (Cleft) groups.
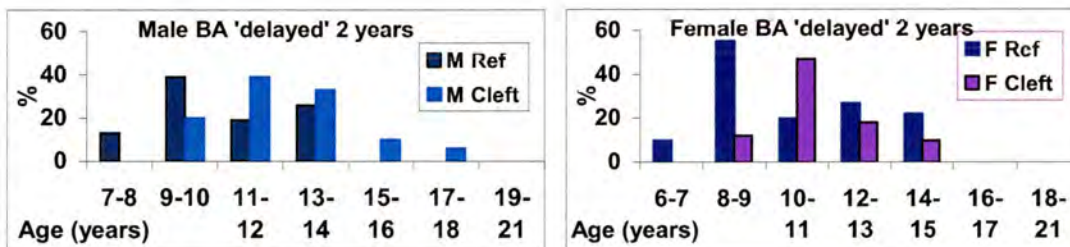
Owing to group size, data for the prevalence of 'delay' of two years or more, outwith the normal range of BA, was pooled in two-year periods. Figure 4.9.2.2 demonstrates a time related sequence of peaks of prevalence of between 39% and 55%, over a three year age period. The first peak at eight to nine years was female SL Reference, the second between nine to 11 years were the female CL/P group and male SL Reference. The final peak, in the male CL/P group, was between 11 and 12 years of

age. Overall, the prevalence of delay of two years or more in BA was similar for all groups at 10 to 19%.

4.9.3 Skeletal age

Bone age (BA) divided by the chronological age (CA), derives skeletal age (SA). Thus SA = BA/CA. A ratio of >1.0 is advanced, <1.0 is delayed. It is an indicator of relative velocity of an individual or group compared with the TW3 RUS 50th centile for age.

Figure 4.9.3.1 Skeletal age as BA/CA data plots
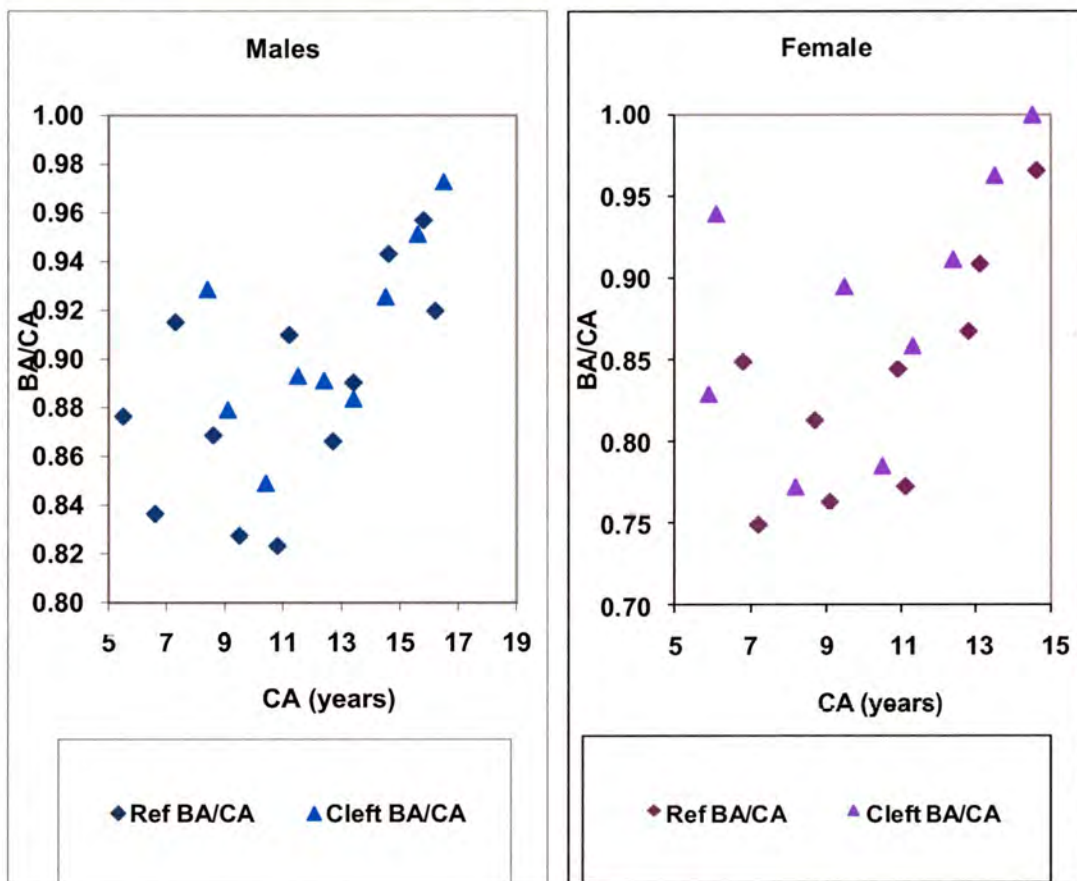
The fall in figure 4.9.3.1 of SA to a nadir at seven to nine years in females, and nine to 11 years in males, was succeeded by rapid catch up during the pubertal growth spurt, which came progressively closer to 1.0 as fusion took place. The distribution of SL Reference and CL/P data points of the relationship between BA delay and chronological age appeared polynomial. This prompted analysis to determine their significance.

Figure 4.9.3.2 The polynomial relationship between CA-BA and CA.
(Although a negative value on the Y-axis is illustrated, it is to identify 'delay' as
additional growth potential).
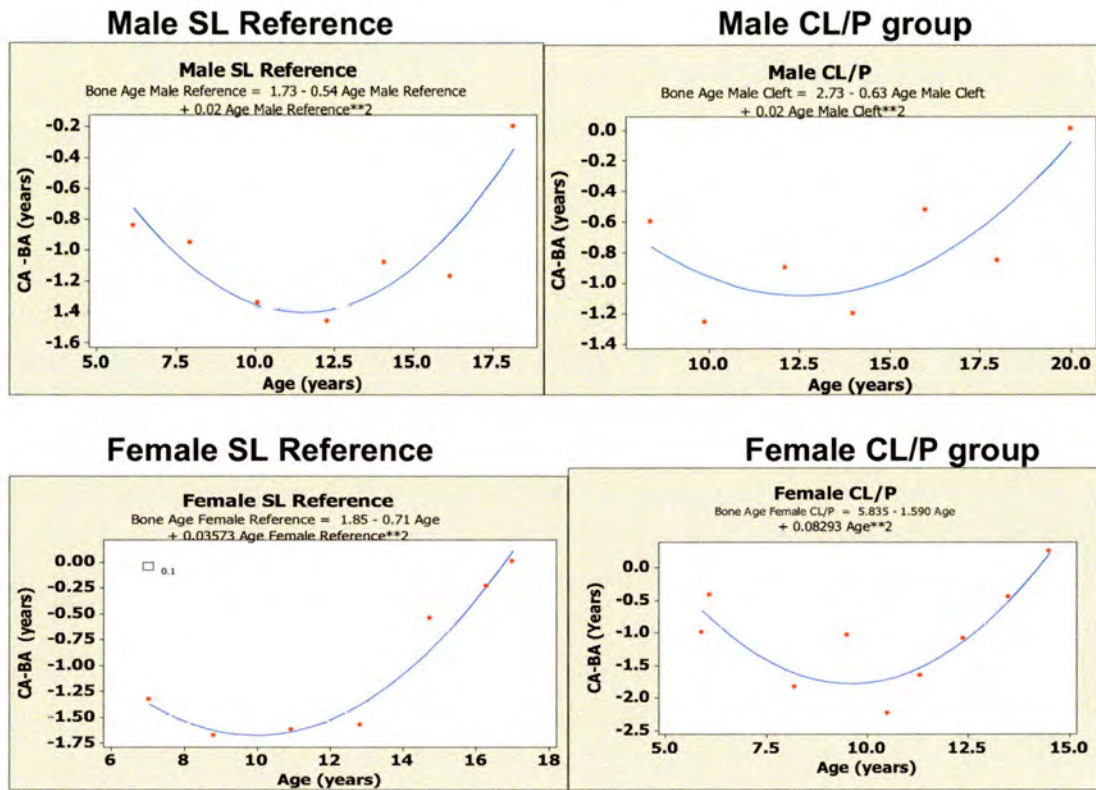
The relationships, illustrated in figure 4.9.3.2, were quadratic and significant for SL
Reference males, F = 17.76, p 0.01 and females, F = 39.65, p 0.01. Similarly
significant for CL/P group females, F 9.77, p 0.01, it was not for CL/P group males,
F 4.90 p 0.08, shown in tables C4.9.3.1 and 2. They all showed a rather uniform time
related association of delay in skeletal maturity that paralleled the delay in onset of
pubertal growth in height, explored in section 4.7.

Age at fusion of epiphyses

British TW3 RUS 50th centile ages for completion of growth are 14.5 years in
females, and 16.5 years in males, while 3rd centiles (-2 SD) are 16.5 years for females
and 18.5 years respectively. In only 7% of the total, 31 subjects, did skeletal
maturity occur after the British 50th centile, and all by 20 years of age. They
comprised 12% of SL Reference males (4 subjects) and 1% females (1 subject). In

CL/P group males there were 27% (19 subjects), and females 12% (7 subjects). Only six subjects were below the third centile, all with CL/P, five males and one female. The progression to maturation was therefore more rapid for the majority in SL Reference than British subjects around the age when complete epiphyseal closure was normally occurring, despite the 'delay' in BA at earlier ages.

4.9.4 Menarche, BA and Skeletal Age

Female SL Reference skeletal maturity was completed by 16.6 years. Mean age of menarche (MAM) + 2 SD (98%) was 15.5 years of age, and the same proportion, 98%, of SL Reference hand wrist x-rays, were skeletally mature. In females with CL/P 15% were still skeletally immature at the same age. There was a very high correlation between BA and chronological age as expressed in skeletal age (SA) at MAM. SA was 0.97 MAM of 13.4 years for SL Reference and SA of 1.0 at 14.2 years for CL/P.

4.9.5 Socioeconomic factors and x-ray data collection

It had proved difficult to recruit control subjects from the rural areas. SL Reference subjects and their families who consented to x-ray were predominantly from rural and urban areas relatively close to the x-ray facility in central Galle. The majority, 91%, were from FOG 3, and this may have accounted for at least some of the difference between SL Reference, and CL/P groups of whom 74% were from the same socioeconomic group.

4.9.6 SUMMARY OF OBSERVATIONS LISTED BY SUBSECTION

4.1 SL Reference centile charts compared with international growth references

The growth sample of 3,321 subjects aged two months to 25 years was representative of the Sri Lankan population. They were generally smaller, leaner, later in growth. Specifically:

- From infancy to adulthood the SL Reference 50th centile for height fell from the British 25th to the 9th centile, weight from the 9th to the 2nd centile, and lacked a pubertal upward curve in height comparable with the British chart.

- Despite levelling off in height of females at 18 years and males at 21 years, growth continued into the third decade. Between the ages 20 to 24 years, males grew a mean of 9 mm, females 13 mm. This was more than young British adults of the same age.

- BMI of the SL Reference 50th centile was on the British 9th centile.

- The cranium was small. Head circumference 50th centile approximated to the 2nd British centile.

- Fat distribution on the trunk was close to the American NHANES II reference, but arms had less fat and thinner mid upper arm circumference measurements.

4.2 Growth patterns of mean SL Reference and CL/P anthropometry plotted on British centiles

- The CL/P data comprised 364 subjects, 58% male, who generated 755 data sets over a 20 year follow up. Median age at lip surgery was 1.1 years, palate surgery 5.8 years old, range seven months to 50 years. Age at surgery was dependent on age at presentation and the interval between surgical team visits.

- Growth of CL/P subjects was less than SL Reference in childhood, in late adolescence they merged for a period of 2 years, only to diverge as adults.

- Height of SL Reference and CL/P subjects were separated by two centile lines (1.34 SD) during childhood, the British 2nd and 25th centile. In adolescence it fell to a single centile line difference, until they shared the 9th centile for a two year period, before diverging once more. Mean BMI tracked a similar course.

- Weight and head circumference followed a similar trend, but were displaced downwards by a further centile line, to the 2nd centile for SL Reference and below for CL/P.

- A disproportionate smallness in SL Reference head circumference was consistently present, shown as British height 9th centile to head circumference 2nd centiles.

4.3 CL/P growth mean values plotted on SL Reference centiles

- CL/P means for height and weight were between the 9th to 25th centile up to the adolescent growth spurt, when they caught up to the 50th centile. Approximately 12% of height, and 6% of weight values were below the 2nd centile.

- CL/P mean adult height was lower than adolescence. Analysis disclosed two populations, differing by a mean of 4 cms. The Old Cohort, who had palate surgery as adults, was the shorter group. The Young Cohort, receiving palate surgery before adulthood, was the taller of the two groups.

- CL/P BMI was close to the 50th centile.

- Head circumference remained below the 25th centile.

- Arm circumference in CL/P followed the 25th centile throughout childhood, increasing to the 50th centile in adolescence.

- Males with CL/P mean triceps sft was on the 2nd SL Reference centile in childhood, rising to the 50th centile by the end of adolescence. In contrast the CL/P mean subscapular sft of both sexes was preserved, continuously close to the mean.

4.4 Growth comparison of subjects with CL/P including socioeconomic groups, and place of residence, with British and SL Reference SDS

- Applying SDS to the CL/P data permitted direct comparison, between variables, and where British SDS showed convergence. From early childhood means ranged from –0.5 SD for height to –2.7 SD head circumference with weight and BMI occupying the –1 to -2 SD intervals between them. All four variables came to lie between –1 and –2 SD in adolescence. The trend persisted into adulthood.

- Differences in CL/P mean height SDS for Young and Old Cohort adult applying British and SL Reference SDs were comparable; respectively in males 0.30 SD and 0.40 SD, females 0.88 SD and 0.79 SD.

- The SL Reference mean weight SDS for CL/P did not fall below –1 SD, in either sex, in any age cohort; maximum difference between cohorts was 0.48 SD. This contrasted with a progressive fall in British weight SDS with age for both SL Reference and CL/P. The British SDS became more negative for CL/P by between 0.97 SD to 1.30 SD, to a mean of –3.91 SD for males, and -2.92 SD females.

- Mean CL/P head circumferences applying SL Reference in Young Cohort adults were larger, by 0.76 SD in males and 0.31 SD in females, than the Old Cohort. This difference could be clinically significant for intellectual development and consistent with the long term effects of undernutrition on growth.

- The rebasing of height, weight and head circumference of controls, as the SL Reference SD score (SDS), using the LMS Growth Comparator, provided a tool for comparing severity clinically relevant to Sri Lanka. Comparing anthropometric variables applying the SL Reference, the male CL/P group weight and triceps sft were –1 SD, in a steady state across the age cohorts. The similarity of means for CL/P and SL Reference subscapular sft supported relative sparing of fat on the trunk. In both sexes, BMI and subscapular sft were reduced by approximately 0.3 SD, seemingly similarly affected by undernutrition.

- Fathers Occupation Groups (FOG) mean values were compared within the SL Reference population. Applying the British SDS, the better off in FOG 1 and FOG 2 mean heights were –0.7 SD, and socioeconomically poorest FOG 3 was –1.1.SD. Males and female values were remarkably similar.

- Females in SL Reference FOG 1 had the highest British SDS for weight, with male FOG 3 the lightest, and thinnest, by SDS value.

- SL Reference head circumference mean was <-2 SD of the British SDS in both sexes, in all three FOG. The disproportionate smallness in head circumference between SL Reference and British charts was noted when comparing centiles.

- CL/P FOG 1 males were taller and heavier than FOG 3 by 1 SD of the British growth reference; FOG 2 males were intermediate. In females with CL/P, variation between FOG 2 and 3 was <0.4 SD, in either direction.

- Prevalence of −2 SD in height and underweight was significantly different between the three FOG, except for females with CL/P who, independent of socioeconomic grouping, appeared similarly undernourished.

- Rural and Urban: Urban subjects were the tallest and heaviest, males more than females. Among those with CL/P, rural males were the smallest and lightest.

4.5 Nutritional status of SL Reference population and CL/P groups applying British SDS

The terms nutritional status and undernutrition are as applied to anthropological growth studies; no systematic nutritional assessment of food intake, or indices such as haemoglobin, were done.

- Prevalence of moderate and severe undernutrition in SL Reference had two peaks. The total <−2 SD in height first peak was 21% to 24% in infancy, the second was 28% to 30% in adolescence, with prevalence of severe, −3 SD, up to 4%. In CL/P prevalence doubled, and was up to 60% in the early stages of puberty, with the proportion −3 SD being approximately one third of the total.

- Underweight <−2 SD averaged 42% of males and 37% of females, with severe 15% and 11% respectively of SL Reference. This peaked between six to nine years and 16 to 18 years of age at 83%. The mean prevalence in CL/P groups was 76% males and 67% females, with a peak of 100%. Mean prevalence of −3 SD was 48% to 50%, and in Old Cohort adults at 60% was twice that in the Young Cohort.

- Thinness <−2 SD in SL Reference and females with CL/P varied between 18% and 54%, linked to the fluctuations in height and weight. Mean prevalence was 33% to 40%, severe 12% to 15%, females having the lower values. In SL Reference adults this was reversed for the severely thin, significantly more prevalent in females than males (p 0.003). Males with CL/P were more frequently affected, with a mean prevalence of <−2 SD of 49%, and severe thinness −3 SD of 25% for all ages.

- Comparing BMI British SDS with IOTF grades 1 to 3 of thinness, the latter categorised fewer in the next most severe grade of SDS, thereby reducing the number identified as at risk.

- In subjects <−2 SD in height, triceps subcutaneous fat and mid upper arm circumference were reduced in both sexes with CL/P and SL Reference males, and MUAC of females, when compared with the SL Reference SDS.

- The difference in prevalence of height and weight <-2 SD between Fathers occupational group (FOG) was significant, from FOG 1 to 3, applying $\chi 2$. Females with CL/P were the exception; prevalence was similar in all three FOGs. Being in a higher socioeconomic group was advantageous with regard to stature and weight for males, but not for females.

- The prevalence of thinness in FOGs averaged 33% to 45%, and was similar, group to group.

4.5.3 Growth in CL compared with cleft palate

- Mean height in subjects with CL was one SD below the SL Reference in childhood. Catch-up in adolescence was similar to those with cleft palate.

- The difference in prevalence of undernutrition between SL Reference and CL was significant. The presence of CL affected height for males, weight for both sexes and thinness in females (p 0.01 to 0.001).

4.6 Puberty

- Onset was delayed by a mean of approximately one and a half years in both sexes, but was of similar duration, compared with British means.

- Probit analysis of mean age of menarche in SL Reference females showed rapid progression to menarche at 13.4 years, compared with 14.2 years in CL/P subjects who also had a wider SE score. Menarche was more delayed in rural and lower socioeconomic groups for both SL Reference and CL/P.

- WHO adjusted pubertal stages of the SL Reference population G2/B2 to G4/B4, of mean British SDS for height, showed a gain for males of 0.49 SD of which 0.25 SD was retained by stage G5, and lost in females, falling to –0.35 SD by stage B5.

- In contrast with SL Reference young adults, height gained as shown by British SDS in subjects with CL/P was maintained, 0.64 SD males, 0.30 SD females.

- Adjusted SL Reference SDS by age and FOG of CL/P subjects identified a more comprehensive catch up with their Sri Lanka peers. Height and weight increased by 1 SD in males. An increase of 0.7 SD for male BMI and female height, weight and BMI also occurred.

- Prevalence in British SDS of –2 SD height and underweight was significantly different between SL Reference and CL/P for each stage of puberty, applying $\chi 2$ (p 0.01 to 0.0001). Prevalence tended to reduce towards the end of puberty.

4.7 Follow-up 20 years after palate surgery

Results from both sexes were pooled, and mean values reported.

- The Infant cohort was under two years at palate surgery. Their British SDS for height was approximately -1.4 SD at each five-year interval. The Delayed Surgery cohort was aged two years and above at palate surgery. Their height SDS ranged from -1.8 to -2.21 SD over the same period. The 95% confidence interval differences between the two cohorts were significant at five, ten and 15 years.
- Prevalence of height below -2 SD was significantly less in the Infant cohort, applying $\chi 2$ (p 0.002). There was no significant difference in prevalence in underweight or thinness.

4.8 Confounders

The confounders in order of statistical significance, were family size, and family history. From regression analysis most of the variance for both sexes was accounted for by age 82-89%, and age at palate surgery 7-12%. In addition to those already identified, Fathers Occupation Group as a socioeconomic indicator, urban residence, and respiratory illness, whether as upper respiratory tract infection plus chronic ear discharge or asthma, were statistically significant but each contributed only between less than one and up to six percent to the variance.

4.9 Skeletal maturity

Skeletal maturity was assessed from 439 hand wrist x-rays, of 211 (57% male) SL Reference and 228 (69% male) CL/P subjects. Results were reported in Bone Age (BA) 'years'.

- Mean BA of CL subjects was similar to those with cleft of the palate.
- Mean BA for age was similar between SL Reference and CL/P subjects within each sex, as was the proportion more than two years 'delayed'.

- BA 'delay' prior to the commencement of puberty, greatest at nine to ten years chronological age, was 1.5 to 1.9 BA 'years' for males, 2.2 'years' for females.
- BA advanced rapidly in all subjects, compared with the British TW3, as they progressed through puberty. Female mean BA and chronological age coincided at menarche. In 93% of all subjects epiphyseal closure occurred by the 50th centile age of RUS TW3. All epiphyses were closed by 20 years of age.

CHAPTER 5: DISCUSSION

CHAPTER 5

DISCUSSION

5.1 Introduction

This chapter brings together three observational studies for discussion. First is the SL Reference growth project, second the growth of subjects with CL/P, and third a survey of skeletal maturity of the two groups. The purpose of the discussion is to compare them with other regional and local studies, assess their significance and translational potential for change in management of individuals with and without CL/P in a developing country.

5.2 GROWTH AND SKELETAL MATURITY STUDIES

5.2.1 SL Reference growth study

How representative the SL Reference growth study was internationally, and of the Sri Lankan population locally, was examined. Comparison of age cohorts, with Indian subcontinent and local surveys for prevalence, was by bands of undernutrition (Golden 1994). South East Asia Region studies are reviewed in Chapter 2.

In children, aged up to ten years old, the SL Reference prevalence of -2 SD in height at 14% was in the low prevalence band of less than 20%, with others from India and Pakistan (Chowdhury et al. 2008, Joseph et al. 2002, Jafar et al. 2008). SL Reference underweight of -2 SD mean value was 36%, in the high prevalence band of 30% to 40%. Representative studies in the same band were from Pakistan (Onyango et al. 2007, Jafar et al. 2008), Maldives (Onyango et al. 2007), Bhutan, and Indonesia (WHO 1997). Thinness was 36% in the SL Reference study. Few other studies reported BMI -2SD; the Maldives, 20%, and Pakistan, 15% (Onyango et al. 2007). Below -2SD, only one study, of Nepalese children, reported the proportion of severely malnourished -3 SD for height and weight, at 11% for both sexes (Ghosh 2009), compared with 3% for height and 12% weight in the SL Reference children. The SL Reference prevalence for severe thinness -3 SD was 13%, with no comparator found.

These recent studies confirm the continuing nutrition challenge to the South East Asia Region, and that the SL Reference shares the Asian characteristic of lower prevalence for height <-2 SD than weight, with varying prevalence of thinness. Two growth studies have taken place recently in Sri Lanka, both using the NCHS 2000 growth reference. The first was the UNICEF study (State of the World's children 1996-2005) authored by Piyasena and Mahamithawa (2003). They studied 7,000 children and women from 7 representative climatic regions, 90% living in rural areas. In both studies, the age pattern of onset of undernutrition in height and weight in infancy, with limited catch-up at three to four years old in the SL Reference population, was similar to previous studies (Martorell and Habicht 1986, Eveleth and Tanner 1990). Up to 11 years old a prevalence of −2 SD in height of 15% to 20%, and underweight 30 to 33%, was also closely comparable. They differed in the prevalence of thinness in childhood, UNICEF at a mean of 17%, and doubled at ten years, reaching 51% at 11 years. The present study means were 31% for males and 18% for females over the same time period. The UNICEF and SL Reference results might have been significantly closer had the same growth reference been used (Eckhardt and Adair 2002).

The second, a study of 1,224 eight to 12 yr olds was sited in Colombo, the country's major urban area (Wickramasinghe et al. 2004). Timed at the transition from childhood to adolescence, it found a much lower prevalence of −2 SD for height, five percent, and underweight, seven percent, but a moderate level of thinness of 24% using the 5th centile cut-off for BMI. This mismatch of relative preservation of height with increased prevalence of thinness was remarkably similar to that reported by de Onis et al. (2001) in middle-class healthy adolescent boys in Calcutta. Unlike the present study, no correlation in those studies was made with stages of puberty, which the authors acknowledged might have informed the observed growth disjunction.

Colombo's low prevalence of deprivation and undernutrition compared with the rest of the Island is remarked on in the literature in different ways. Wilson and Sutherland (1953) reported that the age of menarche was considerably earlier than those living in rural areas, and ascribed it to better nutrition and greater population heterogenicity than in rural areas. A survey by Brink et al (1978) found a difference of two and a half times more underweight in rural children aged up to six years, than children

from selected private schools in Colombo. The nutritional advantage of children of the affluent families of Colombo, also noted by Wickramasinghe et al. in their study, prompted them to report:

'A problem of undernutrition of an impressive magnitude exists in the rural Sri Lanka preschool population'.

As anticipated by that report, the present study found that prevalence of undernutrition in subjects from rural and lower socioeconomic groups was greater than urban and higher groups, at all ages. However, the difference in prevalence between these confounders was less marked in the present study, reflecting the smaller socioeconomic differentiation between urban and rural areas outside Colombo. The small difference in proportion of rural subjects between the SL Reference study (62%) and the national figure (71%) was not significant and unlikely to have altered the present findings. Light industry such as garment factories were sited in employment zones in rural areas as well as in the town of Galle. Agricultural smallholdings, fishing, tourism, construction industries, even government services and offices were in relatively close proximity to each other. The study area is densely populated and Sri Lanka is itself the size of Ireland, yet contains a population of 19 million.

In SL Reference population adolescents, that WHO defines as aged between 10 years and 19 years old, growth fell away to the 9th centile. No catch-up was observed. These findings coincide with previous studies of adolescents in Latin America, the Indian subcontinent, Africa, and the Philippines, reported by Kurz (1996). None showed evidence of catch-up for either sex. Indeed, Nepalese girls and Ecuadorians at 18 years old ended below their starting positions at 10 years of age on the NCHS centile chart. So too did females in the present study, falling from the 25th to the 9th on the British centile, to where SL Reference males had already fallen by ten years old.

Nutrition studies of adolescents in the Indian subcontinent have shown the shortfall in energy and essential micronutrients of the daily recommended allowance occurred in over 80%, even when the prevalence of undernutrition was in the low band (Ahmed et al 1998, WHO 2006).

A comparison of published undernutrition prevalence studies including the SL Reference and CL/P groups is summarised in table 5.2.1. In five of the studies, prevalence of <-2 SD in mean height showed a similar trend for males and females. It rose from ten years old in an incremental fashion, until 15 years of age in females, and to the end of adolescence in males (Shahabuddin et al 2000, Vijayaraghavan et al. 2000).

Table 5.2.1 Comparison of adolescent undernutrition mean prevalence data (%).

	% <-2 SD height range			% Thinness <-2 SD; *<5th c in italics* with mean, and direction of range (-to-)		
Location	Mean	M	F	Mean	M	F
SL Cleft	45	49	40	51	55	46
SL Reference	22	18 to 29	21	34	37 (67 to 29)	38 (54 to 29)
Sri Lanka[1]	-	-	-	33	47 (57 to 32)	22 (46 to14)
Bangladesh [2] (L) Bangladesh [3]	48	33 to 77	34 to 63 49	*67*	*75 (93 to 8)*	*59 (96 to 16)* *10*
India (L) [4]	32	20	45	*55*	*69*	*37*
Nepal (L) [4]	47	47	47	*36*	*49*	*25*
Calcutta [5]	-	4 to 19	-	-	*30 (32 to 28)*	-
India [6] (L)	-	35 to 60	33 to 47	-	-	-
India urban [7]				*30*	*38*	*19*

SL Cleft & SL Reference = this thesis. [1] Piyasena and Mahamithawa UNICEF report (2003). [2] Shahabuddin et al. 2000, (L) = Lower income groups. [3] Rah et al. 2009. [4] Quoted in Kurz 1996. [5] de Onis (2001) middle class children aged 7-16 years.
[6] Vijayaraghavan et al. 2000. [7] Das and Bisai 2009.

Prevalence of thinness for both sexes showed large progressive falls during adolescence in three of four studies reporting prevalence by year of age. Between ten and 12 years old thinness peaked, and the proportion then fell to between a half to one tenth of the peak, by the end of adolescence. Table 5.2.1 shows first the peak and then the end of adolescence values in brackets in four studies. Three studies' prevalence of -2SD for height were approximately two thirds that for thinness, in the SL Reference, and lower income groups in Bangladesh and India. The fourth study,

of Calcutta boys relatively well grown in height with low prevalence of -2SD in height, showed a rather stable prevalence of thinness three times greater applying the -2 SD cut off, and five-fold greater applying the <5th centile cut-off (de Onis et al 2001). The authors argued against applying data from well-nourished populations in which there was a skew towards higher values for age, and favoured the production of local charts.

A comparison of Indian girls aged 10 to 17 years, urban well to do versus rural, contrasted their difference in annual BMI. The urban females were well nourished, with mean BMI closely comparable to US reference values. The rural females were IOTF thinness grade 1 until 17 years old when they also achieved grade 0, applying the Growth Comparator for BMI to IOTF on the results reported in WHO (2006).

In adults the SL Reference prevalence of <-2 SD height remained steady, and underweight increased. Prevalence of SL Reference female thinness increased, to a pre-menarcheal level of 31%, and in the UNICEF study, 36%.

As puberty progresses height is potentially more compromised as lack of nutritional intake limits growth, while the increase in BMI related to secondary sexual changes in muscle development in males and fat distribution in females appear to take precedence. This is seen as an evolutionary mechanism to ensure reproductive survival for genes from one generation to 'play again' in the next (see Wells et al. 2007). Once adulthood is achieved it is likely that adverse factors, related to pregnancy, and the status of women (Chen et al. 1981), become important.

5.2.2 CL/P growth compared with other clinical noncleft nutrition studies

Prevalence of undernutrition in studies undertaken for risk assessment and medical intervention surveys was used to compare Sri Lankan children with CL/P aged two to nine years old with other children in South East Asia. The CL/P –2 SD for undernutrition in height, weight and BMI prevalence were all in the very high band. In Indonesia, a prevalence of –2 SD height of 55%, and underweight 10% was recorded in slum children with helminthiasis (Hadju et al. 1995). The boys had lower nutritional status on comparing SDS with the girls. Antihelminthic treatment made only a small incremental change in SDS weight on follow-up several months later,

similar to Bangladeshi children aged two to five years who failed to show improvement in growth despite regular deworming treatment (Northrop-Clewes et al. 2001). In Bihar, India, the prevalence of –2 SD for height was 54% in a very deprived tribal area at high risk of anaemia (Rao and Vijay 2006). Bangladeshi children hospitalised for diarrhoeal illness had a 16% prevalence of –3 SD for height (Chisti et al. 2007) with very high prevalence of –2 SD height and weight. In a tertiary hospital treating surgically 475 children with congenital heart disease in Kerala South India, the prevalence of –2 SD in height was 26%, underweight 59%, and thinness 56%, in the first 2 years of life. After surgery, follow up 2 years later found there was no change in prevalence of –2 SD in height, but weight SDS rose from a mean of –2.19 SD to –1.42 SD, BMI from –2.09 SD to –1.15 SD (Vidyanathan et al. 2009).

The prevalence of undernutrition was generally very high in these medical conditions, greater than those reported from apparently well children in the same geographical area. The consensus of findings in these focused studies was that persistent malnutrition after corrective intervention may be predicted by factors that include the nutritional status at presentation, birth weight, and parental stature.

The effect of CL/P on the growth of adolescents was similar to that of the most nutritionally impaired of populations in table 5.2.1. The prevalence of severity rose disproportionately in –3 SD in height and weight, due to a shift to the left of the Gaussian distribution reflecting the undernutrition of the entire CL/P group of subjects.

The prevalence of undernutrition in Brazilian infants with CL/P <–1.3 SD in height and weight, applying the NCHS SDS, was found in approximately a third, with cleft lip least affected in height at 19% (Montagnoli et al. 2005). Immediately prior to operation, in South African infants between two and five years old, prevalence of being underweight <-2 SD of the NCHS SDS was 49% (Lazarus et al. 1999), compared with 14% of noncleft South African children, and 76% in this study of CL/P. Grippaudo and Kennedy's report of Filipino children with CL/P compared with the general population on a local Philippines chart showed that under five years old 92% were moderately small and light, between the 3rd and 10th centiles. Those five years to 13 years old had height mildly below average, with 74% above the 10th

centile, but for weight 84% were below the 10th centile. None were <-2 SD for the Philippines population, compared with 17% of the Sri Lankan children with CL/P applying the SL Reference SDS for the same age period.

BMI in growth studies

The appropriate BMI cut-off for defining thinness is agreed in childhood as −2 SD, and is gaining acceptance for use in adolescence. In the present studies, had the 5th centile cut-off been used, this would have added eight to ten percent to the total, applying the British growth reference. In contrast, IOTF thinness cut-offs of grades 2 and 3, between two and 18 years, reduced the number of subjects categorised as a specific grade of thinness by 11 to 15% compared with the closest SDS of −2 SD and −3 SD. A similar result could be anticipated deploying the IOTF grades versus the present CDC 2000 growth reference, subject to a caveat concerning the difference between British and US growth references. While this would be expected to lead to more effective use of resources in developing countries, a note of caution is appropriate concerning the clinical robustness of such cut-offs. The subjects in the present growth study appeared well enough for day-to-day activities. However, malnourishment contributes to 50 to 60% of all child deaths (Black et al. 2003), and the validity of variables and cut-offs chosen for clinical use across the paediatric age group continue to require study (Cameron 2007). At the other end of the nutrition spectrum, the prevalence of overweight in Sri Lanka school children aged eight to twelve in Colombo the capital was linked to greater family income and physical inactivity, with overweight of 13% and obesity 6% (Wickramasinghe et al. 2004). The trend towards a national increase in obesity in the presence of undernutrition characterises developing countries in nutritional transition. This had not yet emerged outside of the capital Colombo at the time of the other Sri Lanka growth studies. Young Sri Lankan women in the UNICEF report, largely from a rural population, were more likely to be underweight, 36%, than overweight, which was seven percent, or obese, one percent (Piyasena and Mahamithawa 2003). The present study's finding in the SL Reference population was half the UNICEF figure for overweight, and larger than the 0.3% in a WHO (2007) study of over 2,000 Sri Lankan adolescents. Comparative studies between continents show that

undernutrition in women is a satisfactory proxy for men's except in South East Asia. The prevalence of thinness is generally greater in Asian women, lending support to concerns for sex related deprivation (Nube and van den Boom 2004). The present study confirmed this sex related trend was present in the SL Reference population in severely thin adults. In addition, females with CL/P had similar prevalence for undernutrition in height and weight, and SDS, in each of the three socioeconomic groups, independent of age. Higher social class was not protective compared with males with CL/P and SL Reference females.

The sum of the nutritional impairments and deficiencies contribute to chronic energy deficiency. Defined by a BMI <18.5 kg/m^2, prevalence was 50% of all adult groups, except for the SL Reference males of 16%. The debilitating effects on capacity for work, social status, and implications for the next generation of continuing high rates of low birth weight infants constitute a cycle of deprivation to be broken (Bharati et al. 2007).

Head circumference

Head circumference in the SL Reference population was disproportionately low compared with height, and that of the subjects with CL/P was lower still. This may be reflected in reduced cognitive ability. The long-term legacy in developing countries of impaired nutrition, anaemia, tropical diseases, environmental toxins, and lack of early sensory stimulation, has been estimated to increase rates for severe intellectual disability up to seven-fold (Bergen 2008). Lesser degrees of cognitive impairment are ascribed to undernutrition at critical phases of development (Olness 2003) with attendant implications for educational attainment and function in adult life. As no psychometric tests were performed the consequences of reduced head circumference in this population are conjectural at present.

5.2.3 Tempo of puberty, undernutrition and menarche

The fluctuations in prevalence of undernutrition were shown by graphs in section 4.5 to be cubic functions of the mismatch in time of pubertal events between the study populations and the international growth reference. This was confirmed by using the correction advised by WHO when comparing pubertal growth in widely differing

tempos of growth between populations. Normal growth velocity compared with the British SDS was shown. The limiting factor to final adult stature was the onset and rapidity of the pubertal process once initiated. Despite the delayed onset of puberty, SL Reference and CL/P groups did not benefit from a commensurate average period of puberty to allow growth. The tempo was rapid, and the intensity of puberty reduced, compared with British adolescents (Marshall and Tanner 1974). This was consistent with the view that Asian Indians may be programmed for an earlier menarche (Bagga and Kulkarni 2000, Parent et al. 2003, Qamra et al. 1991, Wickramasinghe et al. 2009). By extension this is likely to include males in the lack of an extended period of time for growth. See skeletal maturity section.

Menarche

Age of menarche is an index of the socioeconomic and nutritional status of a country or group. In Sri Lanka, Balasuriya and Fernando (1983), and Prakash and Pathmanathan (1984), investigated the age of menarche in different ways. Balasuriya and Fenando used recall by 3,960 girls. In those from a relatively better off socioeconomic background it was 13.8 years in Kandy, 14.0 years in Jaffna, and in the poorer and isolated setting of Nuwarra Eliya it was 14.7 years. Prakash and Pathmanathan using status-quo and probit analysis in Jaffna found it to be 13.78 years with a SD of 1.0 years. Despite the differences in method, agreement was close. In the 1950's Wilson and Sutherland (1953), using probit analysis, reported on 1,130 girls. They found those in Colombo began menstruating at 12.8 +/- 1.24 years, with rural girls at 14.39 +/- 1.73 years. The disparity between urban and rural menarche was marked, not least for the young age of the Colombo girls, and the authors commented on their better nutrition. A recent survey of pubertal change in 1,850 girls recorded a mean menarche of 11.3 years in Colombo and a location on a relatively prosperous part of the coastal strip 30 Km away (Wickramasinghe et al. 2009). The authors attributed this extraordinary finding to improvements in nutrition, reduction in infections and improved socioeconomic status. In the Indian subcontinent females of upper socioeconomic status with good nutrition have been reported to have a mean menarche of 12.0 year (Qamra et al 1991), and high caste Brahmins 12.6 years (Bagga and Kulkarni 2000). Parent et al. (2003), reviewing

variations worldwide, found Mediterranean, Asian and Indian females' menarche was a year, or more, younger than Northern Europeans. A possible conclusion to draw is that Sri Lankan females, genetically similar to Asian Indians, may be programmed for earlier menarche than other racial groups. Whether the Colombo observations will be replicated is yet to be seen. In most developed countries reduction in the age of menarche is slowing as optimal conditions for growth are achieved. Only small advances have been reported from them in the past 20 to 30 years (Whincup et al. 2001), but this will not necessarily be the case in developing countries in the future.

A way of comparing populations' mean age at menarche taking into account environmental factors, such as nutrition and literacy is the coefficient of variation (CV) (Parent et al. 2003). The CV is derived by dividing the SD by the mean age of menarche. A low CV obtained in well off conditions is usually between 9.2 to 10.0%, and a larger CV is found in underprivileged conditions (Parent et al. 2003). Applying this calculation to Wilson's 1953 data, Colombo girls' CV in 1953 was 9.7%, rural girls CV 12%, confirming the impression at the time about their socioeconomic and environmental status. In the present studies, female SL Reference CV was 9.6%, suggesting the population contained a relatively large pool of well-nourished females. The CV derived for females with CL/P was 10.5%, and increased further in rural and lower socioeconomic groups, reflecting their suboptimal nutritional and environmental backgrounds. These observations might be expected to be reflected in their skeletal maturity, discussed in the next section.

5.2.4 Skeletal maturity

In studies of undernutrition some investigators have found bone age less retarded than height, but the majority of authors report the converse (Golden 1994). This study included children from six years old to maturity. The prevalence and severity of delayed skeletal maturity of the Reference subjects were similar to the CL/P groups. Contrary to the studies of Jensen et al. (1983) and Geier and Dahlmann (1988) that only boys had 'delayed' BA, the prevalence of –2 SD BA in Sri Lanka Reference and CL/P groups showed no sex difference, indeed both sexes and groups were similarly affected. The concept of BA 'delay' was discussed in section 4.9.

In developed countries 'delay' in BA in CL/P is associated with impaired stature (Snodgrass 1954, Menius et al. 1966, Przezdziak 1969, Fleischer-Peters and Reichardt 1981, Jensen et al. 1983, Geier and Dahlmann 1988, Hertrich 1990). Similarly in this study the mean BA 'years delayed' in Reference and CL/P groups were associated with lower SDS in height. The gap between chronological age and BA narrowed from a delay of two years at nine years old to zero in 93% of subjects by 15 years in females, and 16.5 years in males. This contrasts with those studies that found a consistent 'delay' in BA up to 15 years (Fleischer-Peters and Reichardt 1981), or a failure of maturation in male BA between 16 and 19 years (Menius et al. 1966). None in the Sri Lanka groups became progressively more delayed in skeletal maturity as they came closer to 16 years old, and thus differ from the children Jochmann and Dubel (1983) reported from Germany. This study also failed to confirm an 'advanced' BA in females with CL/P as reported by Prahl-Andersen (1979). On present evidence of growth delay with commensurate BA 'delay' it is problematic to account for such a finding and Prahl-Anderson omitted to present an explanation or propound an hypothesis to account for the finding.

Following on from that observation, the absence of a discernable difference between SL Reference and CL/P, especially in the prepubertal phase, was worthy of comment. Possible explanations include the observer error of 0.68 'years' masking a difference, and a greater preponderance of SL Reference subjects recruited from the lowest socioeconomic group.

The rapidity of bone age advancement in puberty proved surprising, and more so for epiphyseal closure by 93% of SL subjects within the 50th centile for age of the British reference. It was commensurate with the short time period of pubertal advancement from stage two to stage four. The consequence of the two parallel events was that despite delayed growth and onset of puberty the period of growth was short. This also lends support to previous observations about menarche and the earlier completion of skeletal maturity in Asian populations (Tanner et al. 2001, Zhang et al. 2008).

5.3 INTERPRETATION OF RESULTS

5.3.1 How do factors invoked in the controversy surrounding growth in subjects with CL/P in developed country studies apply in a nutritionally deprived setting?

Infections

Infections are common. Drillien et al. (1966) implicated them in growth impairment in children with CL/P in South East Scotland. Evidence, as distinct from hypotheses, linking chronic or recurrent respiratory infections in children with CL/P growth, is limited to a single study by Felix-Schollaart (1989). Her analysis found it to be statistically significant but of small effect, up to two and a half years of age. A review by Bhan et al. (2001) of growth in developing countries found respiratory infections had only a minor effect.

Among 190 subjects with CL/P, in the Sri Lanka Cleft Lip and Palate Project, the incidence of perforated tympanic membranes was 13 to 17 % compared with 3% of controls (Albert et al. 1990). Questioning of subjects and their families identified the fact that chronic or recurrent respiratory infections were being diagnosed as asthma, which may indeed have been exacerbated. When compared with the SL Reference population, the association with chronic medical conditions, including asthma, was statistically significant. However, on linear regression analysis the contribution to the variance of growth in height was negligible, about one percent. Other confounders found to be more statistically significant were number of siblings, consanguinity, and family history. Family size has a direct bearing on nutrition and food distribution, and consanguinity is likely to exert a stronger genetic influence on growth than in the non-consanguinous. From multiple regression analysis, a positive family history was identified as making a positive contribution to height in males, but not in females. How this might be advantageous to the individual with CL/P is open to speculation that includes psychological as well as physical factors.

Micronutrients

Anaemia in the developing world is common, affecting a half of infants, and a quarter of children and adolescents in Sri Lanka (UNICEF 2009). Micronutrient deficiencies such as the trace mineral zinc contribute to susceptibility and ability to

recover from infection. Supplementation with zinc may improve the growth in height of malnourished infants; the outcomes and mechanism are the subject of some controversy (Umeta et al. 2000, Doherty et al. 2002).

Signs of vitamin A deficiency are present in one percent of Sri Lankan children (UNICEF 2004). A link between significantly lower levels than controls in constitutional delay of growth and puberty, although within normal limits, led investigators to hypothesise that vitamin A deficiency may play a role in constitutional delay in growth and puberty in developing countries (Buyukgebiz A, Bober E, Buyukgebiz B 1997).

Size at birth

The relatively small reduction in birth weight of newborns with CL/P in developed countries (Becker et al. 1998, Jensen et al. 1988, Lilius and Nordstrom 1992) is overshadowed in developing countries by the high prevalence rates of low birth weight. Common contributing factors include reduced size of the fetus due to maternal small stature (Golden 1994), also called maternal constraint, ill health and poor nutrition (UN HDP 2007/8). Low birth weight may play a part in shaping the tempo and magnitude of growth in individuals with CL/P, as will be discussed.

5.3.2 Catch-up or constitutional growth delay?

Growth faltering, a failure to meet one's expected potential, is a concomitant of significant feeding difficulties in CL/P. Regaining growth momentum is by the mechanism of catch-up, an as yet unexplained phenomenon. Several studies in developed countries have reported it in CL/P in infancy (Avedian and Ruberg 1980, Paradise 1974, Laitenen et al. 1994) and early childhood (Lee et al. 1997, Ranalli and Mazaheri 1975). Implicit in the definition of catch-up is to achieve in part or whole a target height and/or weight. In the context of a developing country this could be to achieve the local mean, 0 SD.

The finding that palate surgery under two years old improved height attained at follow-up confirmed the work of previous researchers of the benefit of early nutritional improvement (Martorell et al. 1994, Li et al. 2003). From two until nine years the prevalence of undernutrition as British SDS at –2 SD, and severe –3 SD

undernutrition for height and weight in the groups with CL/P was twice that of the SL Reference population. During childhood, subjects with CL/P had not improved their position on the growth centiles, confirming that full catch-up growth was improbable.

Short stature in adolescence is due in the main to infection and insufficient nutrition in the first three years of life (Kurz 1996). Adolescents with CL/P were at a substantial disadvantage as they entered puberty, at 0.6 SD below the SL Reference population in height and 0.8 SD in weight, applying the British SDS. The prognosis for final height depended on the outcome of the pubertal growth spurt.

Correcting for pubertal delay, as WHO recommend, found height of SL Reference males actually increased by 0.5 SD. Females remained in status quo for their British SDS during the pubertal growth spurt. There was therefore an epiphenomenon of catch-up growth in males. A number of factors acted to degrade this gain when plotted against chronological age. Catch-up came from a low base, was delayed and the intensity muted. It was growth at a normal rather than supranormal velocity (Eveleth and Tanner 1990, page 192), in which the latter accounts for sustained catch-up. As a result males remained on their prepubertal centile, while females fell back a further 0.3 SD. In contrast, male and female subjects with CL/P demonstrated supranormal growth compared with the SL Reference population over the pubertal period.

The relevance of local comparisons came from applying the SL Reference SDS to the CL/P group, adjusted for age and socioeconomic group (FOG). The aim was to eliminate the averaging effect of applying an SL Reference SDS based on age alone. No correction was made for rural residence as it comprised over 60% of the population. In this analysis the closer the SDS was to 0 the more likely 'local' catch-up was complete. This was confirmed, as height, weight and BMI of males and females with CL/P came to lie between 0 SD and -0.2 SD of the SL Reference. Adair (1999) presented evidence that catch up is probable up to 12 years, the upper age of the Filipino children studied, and conditions need to be favourable. This does not contradict the observations of Martorell et al. (1994). Those researchers addressed the extent of reversal in later childhood and adolescence of the effects of earlier growth impairment. Although the potential for catch-up growth increases as

maturation is delayed and the growth period is prolonged, maturational delays in developing countries are usually less than two years. In a study such as the present one, this was insufficient as a proportion to make up for the loss in earlier growth. In the present study, catch-up among those with CL/P was relative, and the population's growth as a whole remained suboptimal. The mechanism for this difference from the non-cleft population is unexplained. As Martorell states:

Improvements in living conditions, as through food supplementation or through adoption, trigger catch-up growth, but do so more effectively in the very young.

The question pertinent to this study is what is the trigger for catch-up growth in adolescence in CL/P?

Anthropometry was performed over a period of 20 years, after primary CL/P surgery at various ages. The data was therefore not the record of a short-term phenomenon attributable to a relatively recent management intervention. Additional factors such as regression towards the mean may have been operating, and consideration should also be given to constitutional delay in growth and puberty (CDGP). This latter phenomenon is characterised by delay in BA accompanying a slowing of the tempo of growth in height from early childhood to adolescence. Shortly before puberty growth may virtually cease, increasing the disparity between subjects with CDGP and normal. Puberty is often delayed but the final height achieved is close to that predicted from the BA. Investigators of growth in adolescents with CL/P in the United States have applied the term CDGP to the pattern of growth observed in males (Bowers et al. 1988, Cunningham and Jerome 1997). The cybernetics mediated by hormonal and nutritional interaction hypothesis put forward by Bowers has not received further supportive evidence, and Cunningham and Jerome attributed the growth to CDGP in the absence of an alternative explanation. A counter to CDGP as a mechanism is that it is now acknowledged to have a substantial genetic component in a proportion of cases, interacting with modifiers in the subject's environment (Sedlmeyer et al. 2002). A further drawback is the lack of a specific test for CDGP so the diagnosis continues to be one of exclusion. A history of early growth failure associated with nutritional deprivation would normally preclude children with CL/P being considered within the category of CDGP. However this criterion was omitted by the American investigators when applying the label of

CDGP. A further confounder, in a population in which growth failure is commonplace and due to a myriad of clearly identifiable cofactors, such as a developing country, is whether it is likely that a phenomenon such as CDGP could be identified as such.

Recent developments in biological paradigms provide a framework for discussion, and the generation of hypotheses potentially amenable to testing. Epigenetic influences may induce different phenotypes by variation in the early life environment and result in life long variations in the regulation of gene transcription. This paradigm is termed the 'developmental origins of health and disease' (DOHaD) (Godfrey and Barker 2001). These are modulated through changes in DNA methylation and covalent modification of histones (Burge et al. 2007). Thus genes may interact with environmental cues in pre-programmed adaptive responses. One such example is the induction of precocious puberty in girls adopted from developing countries (Virdis et al. 1998). It is hypothesised that this is a linked evolutionary adaptive mechanism when environmental conditions are sufficiently positive for growth (Gluckman and Hanson 2006). In the construct under consideration, such plasticity may be associated with CL/P, the cue being the tendency to a reduced birth weight (Becker et al. 1998) in affected fetuses, a recognised association with altered fetal phenotypes (Godfrey and Barker 2001). The postnatal environmental circumstances act as a time related trigger to catch-up at the appropriate biological opportunity to gain lost growth, to a level determined by that of the non-cleft population.

Observation that growth in height continues into the third decade relates to an increase in the LMS Chartmaker mean values for height from 20 to 24 years. In SL Reference males a mean increase of 10 mms, and in females of 13 mms were found. Closer scrutiny of the British growth reference LMS programme shows a similar 10mms increase for British males between 20 and 23 years, and 2 mms increase in British females for the same time period. These confirm small increments of growth continued into the third decade for both sexes, a phenomenon that Cole (2002) and Golden (1994) anticipated. As this phenomenon is also observed in developed country populations, its limited magnitude designates it most appropriately as

extension of the still maturing growth process. If it were larger, and linked in time to pubertal events it would be more appropriate to call it catch-up.

Potential implications of thinness and overweight in these study populations

It could be argued that a significant catch up in height and weight for subjects with CLP, relative to the noncleft population, has been demonstrated and consequently little action is required. The consequence of acceptance of this line of reasoning needs to be considered. It is evident that throughout most of their childhood and adolescence, subjects with CL/P are likely to be more underweight and thinner than their non-cleft peers. This includes those with CL who have been found to be more like the CL/P group than the non-cleft population. Childhood mortality and mild to moderate malnutrition are linked (Pelletier and Frongillo, 2003). In this study it was not possible to determine whether failure to respond to requests to attend for follow-up was due to debility or death. Anthropometric tools such as weighing and the IOTF thinness grades have potential utility in identifying and reducing the risk by triggering interventions that deserve consideration, with caveats about wholesale implementation. Where urbanisation continues apace in the developing world its children are in a state of nutritional transition. High prevalence of undernutrition is found side by side with increasing evidence of diseases of affluence, exacerbated by bad food choices and sedentary habits (Cole et al. 2000, 2007). In this SL Reference population the prevalence of overweight and obesity combined was less than four percent, and less than one percent of Cleft group subjects were overweight. Nevertheless a trend towards an increasing prevalence of obesity has been identified in Sri Lanka in a nutritional survey of Colombo schoolchildren (Wickramasinghe et al. 2004). As a single variable, a low BMI for age does not differentiate between a nutritional emergency and stable undernutrition. In this study the presence of a growth spurt in adolescents of both sexes with CL/P, and onset of menarche at a mean 13.4 years in the SL Reference population suggests that the prevalence of thinness was not due to widespread acute malnutrition. In fact, as adolescence progressed the prevalence of thinness fell in both SL Reference and CL/P groups, in common with other studies of Asian subjects. Attempts to increase final stature by increased nutrition may be inappropriate in some circumstances, depending on

existing weight and fat stores. A subgroup of children with stunting is at risk of the metabolic syndrome consequent on the DOHaD (Branca and Ferrari 2002, Uauy and Kain 2002). These children have been identified as being low weight for age, with weight below –2 SD, but normal weight for height, that is a BMI above -2 SD. In the SL Reference population 8% could be categorised in this manner, and 22% of the CL/P groups. Examination for fat distribution in subjects with –2 SD in height, corresponding to chronic undernutrition, found subscapular skinfold thickness was preserved. This represents trunk fat. The mean triceps subscapular skinfold thickness, representing limb fat, was reduced in thin subjects with CL/P while subscapular subcutaneous fat thickness was maintained, conforming to the phenotype of the 'thin-fat' baby (Yajnik et al. 2002). This is a model of visceral adiposity and insulin resistance found in low birth weight Indian infants at potentially increased risk of subsequent obesity and related disease (Yajnik et al. 2002). Such data suggests that food intake should be monitored through the tactic of BMI measurement. This is in order to prevent excessive calorie intake that could lead to obesity, at the same time ensuring appropriate balance in food quality and micronutrients. Knowledge of the proportion of risk groups, such as thin-fat phenotypes in babies and older age groups, can guide strategic planning and education. The structuring of programmes for a developing country, in 'nutritional transition' from traditional foods to high-energy convenience and 'junk' food, have been reviewed by Corvalan et al (2008). They expound:

'..under- and overnutrition are intertwined problems, often rooted in poverty, that must be tackled in an integrated way with a single agenda and a life course perspective'.

5.3.3 Growth in cleft lip

Examination of the growth of individuals with isolated cleft lip has drawn attention to the similarity between them and individuals with cleft palates. This trend may be discerned in South African children with cleft lip only, with a prevalence of underweight of 21% compared with noncleft children of 14% (Lazarus 1999), and no difference in the Philippines (Gripaudo and Kennedy 1999). This would be an unexpected finding if nutrition were the only major determinant in growth. The

importance of the quality of parenting, among other factors, are highlighted by Branca and Ferrari (2002):

'In a study carried out in rural Chad, caregiver decisions on child feeding, actions taken when a child is ill, domestic workload and even caregiver's level of satisfaction with life have shown to have an influence on children's height for age'.

A web of factors may intertwine to work against individuals with a disability (Yousafzai et al. 2003). They include cultural familial attitudes (Weatherley-White et al. 2005), stigma (Bradbury and Habel 2008), gender discrimination within the family (Sendrowitz 1995, Chen et al., 1981), food allocation and concerns over food security (FAO 2009). In Buddhism, to which 70% of Sri Lankans profess, connotations of bad 'Karma' are attributed to sins in a previous life. This may alter carers' perceptions and reduce the giving of food and affection, both of which are required for optimising growth potential. The withholding of food, love and (expensive) health care from such individuals may all have operated to account for the differences in growth observed. The sum effect has been likened to a synergism, of inadequate nutrition, infection and inappropriate mother-child interactions (Prost 2009).

Eshel et al. (2006) contend that an appropriate warm responsive relationship with an adult carer is as important to the survival and optimal development of children as food, sanitation and access to health facilities. They cite evidence from studies in developing countries of interventions based on home visits promoting maternal responsiveness that have resulted in significant improvement in growth, to resemble that of non-stunted children, as well as improved cognitive ability. Food supplementation in early childhood improves educational attainment among children who completed primary school, an example of a treatment-by-schooling interaction (Li et al. 2003). WHO (2006) lists a series of interventions aimed at improving nutrition and understanding of the needs of children, and changing harmful practices and attitudes.

5.4 COMMENTARY

5.4.1 Local growth charts as tools for analysis and change

The aim of development of the SL Reference growth reference was to meet needs on two counts. Historically, local clinicians have used the 5th centile of the NCHS growth reference as the 50th centile for the population, in common with others in developing countries (de Stefano et al. 2004). This causes problems in grading severity of undernutrition and monitoring progress. A second reason is for comparison of groups submerged within the larger pool of values that is the normal population, which itself has suboptimal growth. These differences may not be readily identifiable on an international reference chart, in which subjects at additional risk, and much of the general population, are below the lowest centile.

There is an inherent incompatibility in the aims of growth charts. Firstly, use as a clinical chart (one to one) may fail to fulfil its other role as a public health chart, to be applied to different groups of children. Secondly, the value of a comparison of local growth with an international reference/standard; how helpful is it to look at the individual's actual growth, versus the *potential* for growth of an *elite* group. This can be summarised as asking: do we want to know how children actually grow versus how they should grow?

Examples of the debate in the literature are encapsulated in the following statements:

'In the developing world chronic and intergenerational undernutrition means that average growth is suboptimal, making the construction of local reference charts difficult if not unethical' (Wright 2005).

A survey of Indian boys well grown in height who were categorised inappropriately, in the clinical opinion of the authors, caused them to question the validity of the accepted international reference:

The NCHS reference data seem inadequate for this sample. Consideration should be given to developing appropriate reference data based on healthy adolescent populations from different ethnic groups. Issues of maturation-related variation in assessing growth during adolescence should be given particular attention. (de Onis et al. 2001)

A study of the growth of apparently well but undernourished Ethiopian children concludes:

Notwithstanding the proven usefulness of the NCHS, NHANES I and II reference standards it may be worthwhile that regional or National standards be developed, as already pointed out by others (de Stefano 2004).

Wright and de Onis are two respected workers in the field of child anthropometry urging different approaches. Are these approaches mutually exclusive, with only one type of chart such as the international reference or is it appropriate to be inclusive of others, which have been locally derived or adapted? A fresh example of the controversy highlighting the difficulties that may ensue is the recently published WHO chart for under fives. This is to be regarded as the internationally accepted reference, indeed as a standard against which all the world's children should be compared (WHO 2006). It is intended to foster international comparability, the development of policies and evaluation of interventions and outcomes with universally understood criteria. However, clinicians have already noted differences from local populations that give cause for concern. Thus, although the charts are welcomed they may not be '*simply transferable*' as Wright et al. (2008) have acknowledged. Acceptance of the WHO standard will substantially alter the reporting of prevalence of underweight, overweight and weight faltering. This data has now been investigated country by country by Ergo et al. (2009). Scrutinising 41 countries' data the authors are of the opinion that the resultant changes in prevalence are sufficiently large to require changes in some programmes of delivery and education. Chinese investigators (Hui et al. 2008) have pointed out that the full genetic potential of their population may not have been reached, precluding them from direct comparison as insufficient generations have passed and Cole (2003) has deliberated that it may take up to six generations before optimal growth is achieved. In a commentary, van Buuren and van Wouwe (2008) point to the widening gap in population growth SDS means between deprived and affluent populations. The new standards, if not subjected to adaptive changes for their populations, could soon be seen as irrelevant to their respective needs. They conclude:

'*It is as yet unclear whether the new standards are applicable to a given child or a specific population'.*

In the present study, development of a local reference chart contributed significantly to the observations and validity of conclusions, and in practice both international and local reference have provided a rounded picture of growth in a nutritionally

vulnerable group. A useful part was also played by the LMS Comparator, by enabling the rapid switching between growth references. Progressively more compact and affordable computers are making the steps followed for this and other studies increasingly accessible (Maleta et al. 2003, Worrell 2003, Zhang et al. 2009). Placing individual CL/P values on SL Reference centiles demonstrated that a pattern of values on the lower centiles had a uniform distribution across them throughout childhood. Those below the British second centile could be accurately categorized for severity on the SL Reference, and their progress plotted appropriately. The adult deficit in height of the SL Reference population was identified on the British reference as having become established before the onset of puberty in males, though females did not appear to be so affected until puberty had commenced. The growth of a cohort with CL/P, comprising mixed cross-sectional and longitudinal growth data, on SL Reference centiles, demonstrated how close to the 50th centile of the Sri Lanka non-cleft population they had come in their catch-up. Where results were unexpected, as in finding a marked reduction in head circumference of both SL Reference and CL/P subjects, developing local reference centiles placed them in clinical context, enabling appropriate evaluation. The addition of reference values for skinfold thickness and arm circumference provided a base line and the facility for close monitoring of underweight, and the emergence of overweight, that may result from changes in feeding habits and therapeutic interventions.

In 5.2.2 a comparison of prevalence relevant to each population was presented of Filipino children with CL/P and the SL children with CL/P. The relevance for planning intervention strategies in each country must be weighed against the application of an international reference without regard to local growth.

Where the subjects with CL/P were similar to the local control and local reference SDS in Thailand (Gopinath and Muda 2005, Jurutratanasirikul et al. 2008) and Saudi Arabia (Alkofide and Barakati 2002), they provided a useful guide to comparative lack of severity, and may have lessons that could be applied in Sri Lanka where large disparities in prevalence between CL/P and SL Reference populations were present.

5.4.2 Translation of studies into therapeutic and societal interventions

Strategies for acute undernutrition were reviewed by a working group (Bhutta et al. 2008). Where there was sufficient food, a gain of 0.25 SD occurred after education about complimentary feeding. Where there was insufficient food, giving food supplements increased height SDS by 0.41 up to 36 months. The authors calculated that stunting could be reduced by 36%, mortality by 25% and disability-adjusted life-years associated with these effects by 25% in the short term. However, the improvement from long-term nutritional supplements to reverse height of −2 SD is very small (Rosado 1999). Long- term benefits in educational achievements have also yielded rather small gains (Li et al. 2003).

Interventions applicable to the population at large, and individuals with CL/P in particular, have been adapted from advice contained in WHO Adolescent nutrition (2006), and WHO/FAO Guidelines on food fortification with micronutrients (2006).

- Improve nutrition, iron and folic acid status by supervised weekly supplementation programmes or by encouraging their purchase, as this has been shown to lead to better compliance.

- Control intestinal parasites.

- Improve home based and literacy skills in subjects and carers, especially women.

- Promote awareness of health, hygiene, nutrition, and family welfare.

- Delay marriage (Sri Lankans do generally delay marriage to mid to late 20's).

- In the absence of effective breast feeding, breast milk expressed into the baby's mouth (personal observation), and written advice and support for clean preparation of ethical milk substitutes with local initiatives as in Kandy, Sri Lanka (Wijikoon 2008).

- Food-based strategies for healthy eating, micronutrients, more fruits (vitamin C) and vegetables (carotene, vitamin A, folic acid), meat (iron) and dairy (calcium, fat, protein). The diet should be less cereal based, though access to other foods may be limited by poverty. Fortification of food with micronutrients as a national policy in Sri Lanka already includes iodised salt in areas where goitre is endemic, such as the highlands. Sri Lankan school girls receive education about the importance of periconceptional folic acid to prevent congenital abnormalities (Lamabadusuryia, personal communication 2009).

- Introduction of Sri Lankan initiated interventions. An example is home based complementary food recipes, using a hand blender to give energy dense foods to prevent infant growth faltering, replacing traditional complementary feeds based on rice water (de Silva et al. 2007).

- Intrahouse food security for girls and women of childbearing age (UNICEF 2001).

- Behavioural change in attitudes about gender at birth and difference in appearance which may lead to infanticide. In Buddhist traditions, reinterpretation of Karma, emphasising the enhancement of one's own Karma in accepting and aiding less fortunate individuals. Involvement of schools, health centres, and mass media in promoting these goals.

Tangible changes in the lives of the Sri Lankan CLP individuals who have received surgery have been the subject of investigation (Bradbury and Habel 2008), and form the basis of ongoing enquiry. Surgery provided measurable change in school attendance, which rose from less than 50% to 93%; some individuals went on to tertiary education, and include a doctor, veterinarian, and secretary to a Member of Parliament. The rate of employment and marriage were comparable to their age related non-cleft peers (Habel et al. 2002). To this can be added that their stature differs little too.

5.4.3 Potential sources of error

- Confounders of growth studies include genetic inheritance, gender, age, ethnicity, and in this study, cleft type and timing of surgery. Comfort was afforded in the limited genetic variation in the population studied, Sri Lanka being an island community with the same ethnic background, namely southern Asian. The rate of consanguineous marriages in the general population of 12%, and subjects with CL/P 20%, reflect cultural norms (Reid 1976). The prevalence of congenital abnormalities in such matings is increased, but information on growth, which might be affected, was not available for comparison.

- Date of birth inaccuracy is a common problem for researchers in studies in the developing world, for which there is no easy solution (Eveleth and Tanner 1990). The under five year olds' dates were, in the main, accurately known in the SL

Reference growth study. 'Road to health' charts, followed by the revised Unicef/WHO chart in 1994, containing the date, were in use routinely in Sri Lanka (Senayake et al. 1997). Confirmation at other ages were less reliable. Parents were questioned, schoolchildren's birthdays were gleaned from the school register, and older students and workers were asked to show their identity card or a driving licence if they had one.

- Recruitment of SL Reference male subjects aged 19 to 24 years was less than planned. Had it been found that the age at leveling off in adult height was much beyond 20 years the numbers recruited would have been unsatisfactory. Males achieved this plateau by 20 years of age. The total of 124 males recruited in the 19 to 24 year period coupled with the statistical handling of growth data in linear regression accumulated enough data to provide useful growth curves with suitable characteristics.

- In Sri Lanka the distribution of CL/P has an incidence of 0.83/1000 births, and isolated CP 0.19/1000 births, with distribution by sex, type and site of cleft similar to Caucasians (Amaratunga & Chandrasekera, 1989). Accepted Northern Europe prevalence figures are CL 25%, UCLP 40%, BCLP 10% and CP 25% (Fogh-Anderson 1942). The present study, by distribution of CL/P type, showed a significant underrepresentation of CL, 50/364, 14% (95% CI 0.10 to 0.17). The return of CL patients for follow-up had low priority for the purpose of the orthodontic and speech aspects of the Sri Lanka Cleft Lip and Palate Project study, so CL patients tended to return by default on hearing of a visit by the team from neighbours or through the media. The response rate to invitations for CL subjects to attend for review in 2004 was 45%, lower than in other cleft types such as BCLP in which it was over 80%. More subjects with CL could have given greater power to the analysis for association with the observed impairment of growth. The proportion with CP may have been underrepresented by a failure to come forward for surgery because facial deformity was absent and families were not informed or failed to appreciate the benefits of cleft surgery for eating and speech.

- The number of subjects with CL/P in the highest socioeconomic group was small, and underrepresented at 4% compared with 12% in the SL Reference population.

At the commencement of the project CL/P surgery had a low priority in Sri Lanka, and it is likely that the better off paid for surgery privately (Mars 1990).

- Birth weight of subjects with CL/P was not reliably recalled, and parents rarely retained the early growth record beyond five years. Birth weight was therefore not included in the analysis. As low birth weight is more frequent in CL/P subjects this was an important variable. The reduction reported in developed country surveys of birth weight is approximately 100 to 200 grams (Becker et al. 1998, Jensen et al. 1988, Lilius and Nordstrom 1992). This would not be significant in well-grown infants. Assuming a proportionate effect, this would equate to a 6% reduction in birth weight in CL/P, and contribute to a small extent to the prevalence of low birth weight in Sri Lanka.

- Low birth weight may be related to smoking in pregnancy; smoking is also related to an increased incidence of CL(P). Recall of maternal smoking in pregnancy was not examined. The prevalence of smoking in women in pregnancy in Sri Lanka was low at the time of the study (Mudiyanse 1999).

- The number of subjects with CL/P aged under two years at the time of surgery was small. This potentially limited conclusions to be drawn about early somatic growth impairment. The reason for the small numbers was that the pool of young patients with unrepaired CL/P in Galle and the surrounding districts within the Southern Province had been depleted by surgery performed in the first two visits in 1985 and 1986. The somatic growth study only began in 1990.

- The wide variation in age at the time of surgery provided a unique cross section of the effect of delay on growth. Larger numbers of subjects seen and measured in infancy could have provided more information on the response to surgery. However, stratification by age group at surgery and followed up over 20 years gave sufficient information to address the question about timing of surgery.

- Longitudinal study data has problems in irregular time intervals of follow-up, and incomplete collection of data due to inconsistent attendance. Cross sectional studies have the disadvantage of loss of individual growth patterns, the effects of change over time within patients, and difference between baseline for individual subjects due to whole cohort effects. Within the mixed longitudinal and cross sectional data obtained, the differences between the non-cleft population and cleft

subjects were sufficiently large to allow for conclusions to be drawn on their nature and extent.

5.5 CONCLUSIONS CONCERNING THE GROWTH OF SUBJECTS WITH CL/P, WITH REFERENCE TO HYPOTHESES GENERATED

All results, discussion of results and conclusions refer to subjects from Sri Lanka.

Hypothesis 1. *Changes in somatic growth relate to the timing of surgical closure of the cleft lip and/or palate.*

Palate surgery in the first two years of life was associated with better outcome for growth, as determined in follow up over 20 years. The most likely explanation is that feeding was improved. This provided an early opportunity to reverse the growth faltering that may already have taken place as a result of inadequate nutrition (Costello 1989). The Infant-Child-Puberty model shows there is an opportunity for nutritional improvement prior to the second, growth hormone phase which in turn leads to an improved platform for pubertal growth (Liu et al. 1999). An additional benefit, potentially amenable to analysis, was reduction in facial disfigurement and nasal regurgitation positively affecting family and carer attachments.

Primary surgery in adulthood was associated with shorter stature in height than adults who received primary surgery in childhood and adolescence. A secular trend in the succeeding two decades after surgery performed in 1985 to 1990 may have been a factor. Favourable environmental factors comprised slow development of sanitation and public health, as well as hospital health services. Unfavourable factors during this period were principally caused by the country's stagnating economy due to a costly civil war. The socioeconomic grouping of most of our subjects would not have shielded them or their families from these detrimental effects. The 2004 Boxing Day tsunami came late in the follow-up period. The disruption and deprivation caused could have had a major effect on physical growth in those operated in 1990 still undergoing puberty. Although we cannot be sure, among the many thousands who died in Galle and its environs some of the SLCLPP subjects almost certainly lost their lives. It continues to have an immense emotional impact on some survivors, as was sadly evident at the most recent follow-up in February 2009.

Hypothesis 2. *Growth to adulthood of subjects with CL/P differs from that of the noncleft Sri Lankan population.*

Despite significant growth retardation and increased prevalence of stunting and underweight in children with clefts, both sexes showed catch-up in height in adolescence which brought their mean height close to the Sri Lanka population mean.

Hypothesis 3. *Individuals with cleft lip do not share the mechanical difficulties of those involving a cleft of the palate comprising CL(P) and CP. Nevertheless they show similar growth.*

Subjects with CL were affected in their growth to a similar degree to those with clefts involving the palate. Nutrition is not usually compromised by the presence of an open lip, and breast feeding is likely to have been established in these Sri Lankan CL subjects. In addition they would not necessarily be more prone to infection than non-cleft individuals. Growth of CL males was generally as affected as CL females, especially in rural areas, though adult CL females were significantly thinner. Sex bias in food provision may have occurred (Chen et al. 1981), but the larger issue may be psychological interaction between the individuals' disability, carers and the outside world, as has been discussed.

Hypothesis 4. *Skeletal maturity obtained from hand and wrist x-rays of subjects with CL/P and noncleft individuals differed.*

Both groups showed delay, SL Reference earlier in late childhood and early adolescence than CL/P and similar between the sexes. Both groups attained skeletal maturity within the upper 2 SD of TW3 mean maturity score by age, although those with CL/P were more likely to be delayed beyond the mean age. These findings were consonant with the shorted period in Sri Lankan subjects between the onset and completion of puberty in UK subjects.

Hypothesis 5. *Observations and conclusions drawn have translational potential in management for SL Reference and CL/P as individuals and as populations.*

Growth characteristics between and within these groups were highlighted and contrasted by the use of international reference growth charts and a locally derived reference, the SL Reference growth chart. The long-term intergeneration time frame within which growth potential may be transformed into optimal stature is a reminder of the span in which such biological events take place. It lends support to the proposition that in the meantime there is a place for the development of local charts to inform those who wish clinically to evaluate, plan strategies and deliver appropriate interventions. The SL Reference growth chart has been presented to the Galle Medical Society, Southern Sri Lanka. Castlemead publishers have agreed to host it on their website to enable free downloads for professionals to use.

5.6 FURTHER DEVELOPMENTS

Basic improvements in the delivery of nutritional support and health services remain humble but vitally important goals.

The active provision of services that support affected infants and their families from birth can preserve lives that would go on to be productive, and contribute to the community. Lessons learnt in nutritional support extended to the general population may turn the tide of chronic energy deficiency. An hypothesis, addressing the unexpected and unexplained form of catch-up growth found in adolescence in CL/P subjects, may be worth exploring in both the developed as well as developing worlds.

5.7 POSTSCRIPT TO THE SRI LANKA CLEFT LIP AND PALATE PROJECT

An enduring legacy as a mode of delivery of care, transfer of skills and research, has been left for the benefit of future individuals with CL/P born in Sri Lanka and other countries in the developing world. The project has become a model of sustained, and sustainable development by building the capacity of the local health services in a partnership fostered over 25 years. Largely due to the tireless efforts of Michael Mars, it has been realised with the assistance of many individuals, Sri Lankan and others, from as far apart as China and Sweden.

Speech therapy provision for the Island at the commencement of the project was from one part-time therapist in the private sector. A major offshoot of the SLCLPP has been the establishment of a School of Speech Therapy, initiated by Dr Mars and Dr Debbie Sell working in collaboration with the Sri Lanka Ministry of Health and the University of Kelaniya. It is now entirely funded by the Government of Sri Lanka, and speech therapist posts have been created for the School's graduates within hospitals and local services, serving the entire country.

Services for CL/P and the development of multidisciplinary teams (MDT) continue to receive government support. Where it started, in Galle, Karapitiya Hospital now has a well-established MDT.

A welcome development was the launching in 2000 of the parent support group, the Cleft Lip and Palate Association of Sri Lanka. The founder Dr Parakrama Wijikoon spent a year as a visiting surgeon at Great Ormond Street Hospital (GOSH) North Thames Cleft Unit. His aim was to improve surgical outcomes in Kandy, a second surgical centre that has been nurtured by the project. Another surgical colleague, Dr Romesh Gunasekera, was also attached to the North Thames Cleft Unit and now works at the Lady Ridgeway Children's Hospital in Colombo. Lectures and practical assistance, including surgical support from Mr Brian Sommerlad of GOSH, continue. On recent visits it has been anecdotally observed that the number of older children with unoperated CL/P coming forward remains low, though there are undoubtedly some in the previously Tamil controlled areas likely to require surgery. Dr Mars continues to receive orthodontists seconded for training. A number of joint projects have developed between the Paediatric Department of the University of Ruhuna and SLCLPP paediatrician, who has also trained some paediatricians now practising in Sri Lanka. It is evident that the collaborative effort has been on several levels and fronts. It has born fruit beyond expectation for all concerned, and it is hoped, will continue to be gratifying for the children and families of Sri Lanka.

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APPENDIX A, B & C

Appendix B on CD, identified in the text by letter prefix B, in order of appearance

APPENDICES (continued)

FACULTY OF MEDICINE,
UNIVERSITY OF RUHUNA
P.O. Box 70, Galle, Sri Lanka.

1 7 JAN 20

Professor Susirith Mendis, MBBS, PhD
DEAN & Professor of Physiology

OFFICE OF THE DEAN

6th January 2000

TO WHOM IT MAY CONCERN

Ethical Approval for Research Project
Title : **"Study of the growth of children in the Southern Province of Sri Lanka"**

The Ethics Committee of the Faculty of Medicine, University of Ruhuna which met on 03.07.1997 gave ethical clearance to the above research project with the following conditions.

1. Children should be radiographed once only.
2. Radiography should be done by a trained qualified radiographer with a properly caliberated machine.
3. All routine precautions necessary during radiography should be adopted.

Prof. Susirith Mendis
Dean & Chairman
Ethics Committee

Dean
Faculty of Medicine
University of Ruhuna
GALLE.

Tel: Off: (09) 34801, 34803, 32288, 34730, 32321; Res: 09-22146; Fax: 09-22314, Int: (+94 9); E-Mail: dean@sri.lanka.net

Ethics permission Great Ormond Street Hospital

Great Ormond Street Hospital for Children NHS Trust
and the Institute of Child Health
(University College London Medical School)

The
child
first
and
always

16 September 1999

Dr A Habel
Consultant Paediatrician
Surgery
GOS

30 Guilford Street
London WC1N 1EH

Telephone: 0171 242 978
Direct Fax: 0171 813 823

Dear Dr Habel,

99SG31   Study of growth of children in the Southern Province of Sri Lanka.

Letter of Support for Clinical Research undertaken in Other Countries

The above research has been reviewed by the Chairman of the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee. The Chairman has agreed to issue a letter of support in line with the Committee's procedures for the appraisal of clinical research projects based in other countries. The scope of this letter of support is described more fully below:

1.   Ethical 'support' is given to studies carried out overseas involving GOS/ICH staff or premises, which the GOS/ICH REC believe comply with broadly stated ethical standards. The GOS/ICH REC do not feel that it is within their remit, nor do they have the training or skills, to assess the full ethical impact of studies carried out overseas. However, the Chairman has considered whether the scientific methods are sound and suitable for the aims of the research, whether drugs or vaccines or devices to be studied meet adequate standards of safety (as applicable), whether there is sound justification for conducting the research in the host country, and consider that the proposed research does not in principle violate the ethical standards applied to UK projects. A letter of 'support' from this Committee is evidence that the research proposal has been considered in that ethical framework and found to be acceptable, but must be regarded as lacking the full authority implied by 'full approvals' given to UK projects in similar circumstances.

2.   The full ethical impact of the study must be considered and approved by an appropriate body in the host country. This body is relied upon to have special

Research and Development Office

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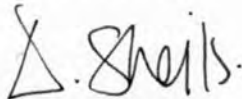
responsibility to determine whether the aims of the research are responsible to the needs and priorities of the host country, for assuring that procedures for selection of subjects, the plans for obtaining informed consent and for ensuring privacy and confidentiality and the level of inducement offered are ethically acceptable.

3. Ethical support is given for a period of 12 months from the commencement of the project. If you wish to start the research more than twelve months from the date of this letter or extend the duration of your 'support' you should seek Chairman's approval.

4. You must seek Chairman's support for proposed amendments to the research for which this approval has been given. Ethical support is specific to this project and must not be treated as applicable to research of a similar nature, eg. using the same procedure(s) or medicinal product(s). Each research project is reviewed separately and if there are significant changes to the research protocol, for example in response to a grant giving body's requirements, you should seek confirmation of continued ethical support.

5. It is your responsibility to notify the Chairman immediately of any information which would raise questions about the safety and continued conduct of the research.

Yours sincerely

Orlagh Sheils
Secretary to the Research Ethics Committee

cc: Dr M Mars, Consultant Orthodonist, Maxillofacial/Dental Surgery, GOS

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කුඩා දරුවන්ගේ වර්ධනය පිළිබඳ අධ්‍යයනය

මේ අධ්‍යයනයේ අරමුණ වන්නේ ළදරු අවධියේ සිට යොවුන් විය දක්වා ළමුන්ගේ වර්ධනය පිළිබඳ වඟු සැදීම සඳහා තොරතුරු එක් රැස් කිරීම වන අතර ඔබගෙන් කෙරෙන ඉල්ලීම වන්නේ ඔබේ අවසරය ලබා දීමෙන් උපකාර කරන මෙන් ය. ඔබ පාසැලෙන් පිට ව ගොස් ඇත්නම්, උපකාර කරන මෙන් අප ඉල්ලා සිටින අතර ම මේ සම්බන්ධයෙන් ඔබේ පවුලේ අය සමඟ කටාබස් කිරීමට ඔබට අවශ්‍ය විය හැකිය.

දරුවන්ගේ වර්ධනය කෙතරම් හොඳින් සිදුවන්නේ ද යන්න දැක ගැනීමට වෛද්‍යවරුන්ට, දන්ත වෛද්‍යවරුන්ට, හෙද හෙදියන්ට සහ වෙනත් සෞඛ්‍ය සේවකයින්ට මෙම අධ්‍යයනය මඟින් උපකාර කරනු ඇත. දරුවකුට වෛද්‍ය උපකාර අවශ්‍ය ද යන්න මෙන්ම වෛද්‍යමය හෝ දන්ත ප්‍රතිකාර සැලසුම් කිරීමට හෝ ඒවා සිදු කිරීමට මෙම තොරතුරු උපකාරී වනු ඇත.

වර්ධනය මනිනු ලැබේ.

අධ්‍යයනය සිදු කරනු ලබන්නේ උස, බර සහ අතේ වටප්‍රමාණය මැනීම මඟින් ය. ශරීරයේ අඩංගු මේද ප්‍රමාණය නිර්ණය කිරීමට උඩුබාහුවේ සහ පිටෙහි සම පරීක්ෂා කර බලනු ඇත. ඇඟිලි දෙකක් වැනි මැනීමේ උපකරණයක් මඟින් එය සිදු කෙරෙනු ඇත. පිරිමි දරුවන්ගේ වර්ධනය පුරුෂ වෛද්‍යවරයෙකු මඟින් පරීක්ෂා කෙරෙන අතර ගැහැණු දරුවන්ගේ එය සිදු කරනු ලබන්නේ ස්ත්‍රී වෛද්‍යවරියන් විසින් ය. මෙම මැනීම් සිදු කරනු ලබන්නේ ප්‍රාදේශීය විකිත්සාගාරයක දී ය.

එක්ස්-කිරණ

දරුවන් කිහිපදෙනෙකුගෙන් මැණික් කටුවේ සහ හක්කේ එක්ස්-කිරණ ඡායාරූපයක් ලබා ගනු ඇත. මෙය යම් යම් රෝග වලදී ප්‍රතිකාර ලබාදීමේදී උපකාරී වන අතර අස්ථී වර්ධනය වන ආකාරය ද එමඟින් පෙන්නුම් කරයි.

මේ එක්ස්-කිරණ ඡායාරූප දෙක පපුවේ ආසාදනයන් සඳහා පරීක්ෂා කිරීම සඳහා ගනු ලබන එක්ස්-කිරණ ඡායාරූප දෙකක් හෝ තුනක ශක්තියට සමාන වේ. වැඩි එක්ස්-කිරණ ඡායාරූප ප්‍රමාණයක් ගැනීම සෞඛ්‍යයට හිතකර නොවේ, නමුත් මෙම අධ්‍යයනයට අවශ්‍ය නිසා භාවිතා කෙරෙන එක්ස්-කිරණ ප්‍රමාණය රුහුණු විශ්ව විද්‍යාලයේ වෛද්‍යවරුන් කණ්ඩායමක් විසින් පරීක්ෂා කොට ගණනය කර ඇති අතර එම භාවිතා කරන එක්ස්-කිරණ ප්‍රමාණය ආරක්ෂිත බව ප්‍රකාශ කර ඇත. මෙම එක්ස්-කිරණ ඡායාරූප ගනු ලබන්නේ ගාල්ල, කොළඹ පාර, සෙන්ට්‍රල් මෙඩිකල් ක්ලිනික් හි දී ය. පරීක්ෂාවන් සිදු කරනු ලබන වෛද්‍යවරුන් විසින් ප්‍රවාහන පහසුකම් සලසා දෙනු ඇත. ප්‍රවාහනය අතරතුරදී සහ විකිත්සාගාරය තුළදී දරුවන්ගේ රැකවරණය පිළිබඳව ඔවුන් වගකීම භාර ගනු ලැබේ.

ලබා ගන්නා තොරතුරු වලට සිදු වන දේ

මෙම තොරතුරු පරිගණකයක ගබඩා කෙරෙනු ඇත, නමුත් නම රහිතව.
මෙම අධ්‍යයනය සඳහා ඔබට අවසර ලබා දීම ප්‍රතික්ෂේප කළ හැකි අතර ඕනෑම අවස්ථාවකදී ඔබට/ඔබේ දරුවාට මෙයින් ඉවත් වීමට හැකිය.
යම් වෛද්‍ය ප්‍රශ්නයක් සොයා ගනු ලැබුවහොත් එය පරීක්ෂාවට ලක් කිරීම සඳහා වෛද්‍යවරුන් විසින් සැලසුම් කරනු ඇත.

මෙම පර්යේෂණාත්මක අධ්‍යයනය සිදු කරනු ලබන ආකාරය පිළිබඳ යම් පැමිණිලි ඇත්නම්, කරාපිටිය, වෛද්‍ය පීඨය, බාලවිකිත්සා දෙපාර්තමේන්තුවේ මුල් තැන උසුලන වෛද්‍ය අමරසේන මහතා සමඟ ඒවා ගැන සාකච්ඡා කළ හැකිය.
ඔබ සමඟ සම්බන්ධව කටයුතු කරන පර්යේෂණ වෛද්‍යවරයා වන්නේ කරාපිටිය, විශ්ව විද්‍යාල බාලවිකිත්සක දෙපාර්තමේන්තුවේ වෛද්‍ය ලියනාරච්චි මහතා ය.
දෙපාර්තමේන්තු දුරකථන අංකය වන්නේ 09-240451

ඔබ එක්ස්-කිරණ ඡායාරූපයක් සඳහා අවසර ලබා දෙන්නේ නම් පහත ලබා දී ඇති ස්ථානයේ අත්සන් කරන්න:

දරුවාගේ නම: ....
පාසැල: ....
පන්තිය: ....

Patient/parent information for radiological study
A STUDY OF THE GROWTH OF YOUNG PEOPLE (ENGLISH ORIGINAL)

The aim of the study is to collect information to make charts of growth of children from infancy to young adults, and you are being asked to help if you are a parent, by giving permission.

If you have left school you are being asked to help, and you may want to talk about it with your family first.

This study will help doctors, dentists, nurses and other health workers to see how well children are growing. The information could help decide if a child needs medical help or to plan and follow medical or dental treatments.

Growth will be measured
The study will be by measuring the height, weight and arm circumference. The skin on the upper arm and back is checked to see how much fat is on the body. It is done using a measurer like a pair of fingers. The maturity of the boys will be checked by a male doctor and the girls by a lady doctor. These measurements will be done in the local clinic.

X-ray
A few people will be asked for an x-ray of the wrist and jaw. This can help in treatment of some diseases, and see how the bones are maturing.

The two x-rays are about the same strength as two or three x-rays of the chest, an examination which is often done to look for infections. Too much x-ray can be unhealthy, but the amount of x-ray in this study has been checked by an independent group of doctors who have said the amount of x-ray to be used is safe. These will be done in the Central Medical Clinic, Colombo Road, Galle. Transport will be arranged by the doctors. They will be responsible for everybody going to the clinic.

What will happen to the information.
The information will be stored on a computer, but not the name.

You do not have to give permission for this study, and you/your child can withdraw at any time.

If a medical problem is found the doctors will arrange for it to be investigated.

If you have any complaints about the way this research study is being done, or has been done, you can discuss them with Professor Amarasena, Head of the Paediatric Department, Faculty of Medicine, Karapitiya.

The research doctor who is in contact with you is Dr Lyinarrachchi of the University Paediatric Department, Karapitiya. The Department phone number is 09-240451

If you are agreeable to an x-ray please sign in the space:

NAME OF CHILD...............................
SCHOOL...
CLASS...

APPENDIX C

Table C4.4.1.1 SL Reference mean, SD, range: height, weight, BMI & head circumference as British SDS, by age cohort

Table C4.4.1.1 SL Reference mean, SD, range: height, weight, BMI & head circumference as British SDS, by age cohort

MALE SL REFERENCE

Height British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
Under 2	320	20	-0.50	1.37	-4.44	2.70
2 to 9.99	633	40	-0.76	1.08	-4.21	2.97
10 to 19	506	32	-1.28	0.98	-4.20	1.50
>19.0	124	8	-1.29	0.92	-3.93	1.07

Weight British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
Under 2	320	20	-1.60	1.10	-4.81	1.86
2 to 9.99	633	40	-1.53	1.25	-4.84	2.19
10 to 19	506	32	-1.93	1.19	-5.00	1.99
>19.0	124	8	-1.88	0.98	-5.00	0.85

BMI British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
Under 2	320	20	-1.84	1.41	-5.00	2.81
2 to 9.99	633	40	-1.53	1.24	-4.98	2.82
10 to 19	506	32	-1.74	1.29	-4.87	2.67
>19.0	124	8	-1.01	0.87	-2.95	1.58

Head circumference British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
Under 2	320	20	-2.34	1.38	-5.00	1.81
2 to 9.99	633	40	-2.41	1.11	-5.00	1.78
10 to 19	506	32	-1.95	1.09	-5.00	1.87
>19.0	124	8	-2.01	1.03	-5.00	0.67

FEMALE SL REFERENCE

Height British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
under 2	321	19	-0.80	1.42	-4.26	2.21
2 to 9.99	605	36	-0.58	1.31	-4.70	2.95
10 to 19	505	30	-1.18	0.95	-3.94	1.64
>19.0	251	15	-1.25	0.93	-4.03	1.86

Weight British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
under 2	321	19	-1.34	1.43	-4.81	2.58
2 to 9.99	605	36	-1.26	1.30	-4.76	3.00
10 to 19	505	30	-1.66	1.15	-4.76	2.05
>19.0	251	15	-1.91	1.03	-4.73	0.71

BMI British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
under 2	321	19	-1.15	1.24	-4.36	2.94
2 to 9.99	605	36	-1.34	1.33	-4.41	2.28
10 to 19	505	30	-1.25	1.48	-4.66	2.67
>19.0	251	15	-1.26	1.26	-5.00	1.41

Head circumference British SDS

Age (yrs)	N	%	Mean	SD	Min	Max
under 2	321	19	-2.05	1.36	-4.57	2.56
2 to 9.99	605	36	-2.54	1.01	-4.61	1.23
10 to 19	505	30	-2.03	1.13	-4.60	1.67
>19.0	251	15	-1.84	1.08	-4.70	1.07

APPENDIX C

Table 4.4.1.2 CL/P mean, SD, and range for SL Reference SDS and British SDS by age cohort

Table C4.4.1.2 CL/P mean, SD, and range for SL Reference SDS and British SDS by age cohort

MALE CL/P GROUP SDS

Age (yrs)	N	%	Height SL Reference SDS Mean	SD	Min	Max	Height British SDS Mean	SD	Min	Max
under 2	8	2	-1.22	0.97	-2.64	0.20	-2.11	1.27	-4.44	0.00
2-9.99	89	20	-1.17	1.09	-3.83	1.20	-1.90	1.15	-4.73	0.94
10 to 19	194	46	-0.63	1.15	-3.76	2.27	-1.88	1.06	-5.00	1.35
>19[1]	121	23	-0.78	0.90	-3.41	1.70	-2.12	0.96	-4.92	0.58
>19 at op	39	9	-1.18	0.92	-3.36	0.29	-2.52	0.99	-4.86	-0.94

Age (yrs)	N	%	Weight SL Reference SDS Mean	SD	Min	Max	Weight British SDS Mean	SD	Min	Max
Under 2	8	2	-0.61	1.02	-2.10	0.47	-2.61	1.42	-5.28	-1.24
2-9.99	89	20	-0.82	0.78	-2.24	2.55	-2.70	0.83	-2.16	1.62
10 to 19	194	46	-0.72	0.96	-3.45	3.10	-2.83	1.17	-6.20	0.52
>19[1]	121	23	-0.62	0.82	-3.59	1.53	-3.20	1.29	-6.12	0.26
>19 at op	39	9	-1.00	0.71	-2.36	0.91	-3.91	1.21	-5.56	-0.98

Age (yrs)	N	%	BMI SL Reference SDS Mean	SD	Min	Max	BMI British SDS Mean	SD	Min	Max
Under 2	8	2	0.24	0.86	-0.97	1.53	-1.69	1.39	-3.77	0.42
2-9.99	89	20	-0.27	0.83	-2.16	1.62	-2.09	1.20	-4.95	0.53
10 to 19	194	46	-0.43	1.00	-3.68	1.95	-2.33	1.28	-5.94	0.07
>19[1]	121	23	-0.42	1.01	-2.36	1.12	-1.93	1.35	-5.36	1.12
>19 at op	39	9	-0.11	1.02	-3.20	1.63	-1.95	1.26	-5.71	0.24

Age (yrs)	N	%	Head circumf SL Reference SDS Mean	SD	Min	Max	Head circumf British SDS Mean	SD	Min	Max
Under 2	8	2	-0.76	0.88	-2.48	0.33	-3.39	1.30	-5.19	-2.36
2-9.99	89	20	-0.68	0.93	-2.90	1.75	-2.90	1.10	-5.40	1.18
10 to 19	194	46	-0.69	1.03	-3.07	2.06	-2.69	1.10	-5.41	0.21
>19[1]	120	23	-0.39	1.05	-2.25	2.57	-2.47	1.14	-6.16	0.78
>19 at op	36	9	-1.15	1.06	-5.05	1.28	-3.09	1.11	-7.16	-0.56

FEMALE CL/P GROUP SDS

Age (yrs)	N	%	Height SL Reference SDS Mean	SD	Min	Max	Height British SDS Mean	SD	Min	Max
under 2	4	1	-0.02	0.32	-0.34	0.38	-0.85	0.28	-1.10	-0.48
2-9.99	62	20	-1.16	1.15	-3.89	2.09	-1.98	1.25	-4.42	1.48
10 to 19	134	51	-0.50	1.19	-3.87	3.38	-1.79	1.06	-4.84	1.89
>19[1]	92	24	-0.65	1.07	-3.41	3.42	-1.95	1.01	-3.41	2.42
>19 at op	12	4	-1.44	0.94	-3.28	-0.38	-2.83	1.02	-5.00	-1.74

Age (yrs)	N	%	Weight SL Reference SDS Mean	SD	Min	Max	Weight British SDS Mean	SD	Min	Max
Under 2	4	1	-0.61	0.65	-1.36	0.07	-1.95	0.91	-2.88	-0.95
2-9.99	62	20	-0.87	0.82	-2.38	0.95	-2.75	1.25	-5.55	-0.45
10 to 19	134	51	-0.50	0.86	-2.28	2.62	-2.47	1.08	-4.20	1.81
>19[1]	92	24	-0.39	0.95	-2.77	2.30	-2.60	1.31	-6.14	0.45
>19 at op	12	4	-0.54	0.91	-2.03	1.73	-2.92	1.34	-5.53	-0.06

Age (yrs)	N	%	BMI SL Reference SDS Mean	SD	Min	Max	BMI British SDS Mean	SD	Min	Max
Under 2	4	1	-0.22	0.93	-1.02	0.83	-2.17	1.74	-3.97	-0.30
2-9.99	62	20	-0.35	0.87	-2.65	1.54	-1.95	1.08	-2.57	1.82
10 to 19	134	51	-0.34	1.08	-4.30	1.91	-1.78	1.33	-5.12	1.13
>19[1]	92	24	-0.24	1.20	-3.32	2.39	-1.87	1.33	-5.59	1.43
>19 at op	12	4	-0.30	0.82	-0.96	2.14	-1.52	1.07	-3.29	1.06

Age (yrs)	N	%	Head circumf SL Ref SDS Mean	SD	Min	Max	Head circumf British SDS Mean	SD	Min	Max
Under 2	4	1	-0.56	0.69	-1.53	0.09	-2.28	1.14	-3.20	-0.61
2-9.99	62	20	-0.87	0.86	-2.57	1.83	-3.72	1.17	-5.14	-0.12
10 to 19	134	51	-0.70	1.02	-3.82	2.33	-3.01	1.22	-5.10	0.42
>19[1]	92	24	-0.78	1.14	-4.22	1.90	-2.63	1.02	-4.62	0.20
>19 at op	12	4	-1.09	1.28	-4.93	1.42	-3.21	1.27	-5.56	-0.77

>19[1] = age at follow up, primary cleft surgery prior to 19 years of age

APPENDIX C

Table 4.4.1.3 CL/P groups mean, SD, range of SL Reference SDS and British SDS by age cohort

Table C4.4.1.3 CL/P groups mean, SD, range of SL Reference SDS by age cohort

MALE CLEFT GROUP SL REFERENCE SDS

Arm circumference Reference SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	8	2	-1.63	0.59	-2.46	-0.89
2-9.9	89	20	-0.71	0.80	-2.72	1.20
10-19	207	46	-0.32	0.90	-2.92	2.56
ADULT	147	32	0.03	0.98	-2.16	3.55
	451					

Triceps sft Reference SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	8	2	-0.09	0.96	-1.12	1.21
2-9	89	20	-0.98	1.06	-3.28	2.20
10-19	207	46	-0.79	1.23	-5.52	1.60
ADULT	147	32	-1.30	1.25	-5.71	3.30
	451					

Subscapular sft SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	8	2	0.13	0.38	-0.41	0.56
2-9	89	20	-0.20	0.93	-3.13	1.63
10-19	207	46	-0.25	0.99	-3.17	2.38
ADULT	147	32	0.62	1.28	-2.41	3.82
	451					

FEMALE CLEFT GROUP SL REFERENCE SDS

Arm circumference Reference SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	4	1	-1.69	1.06	-2.93	-0.4
2-9.9	60	20	-0.77	0.75	-2.46	0.91
10-19	155	51	-0.07	1.11	-2.21	3.10
ADULT	85	28	0.18	1.27	-2.39	2.51
	304					

Triceps sft Reference SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	4	1	-0.14	0.73	-0.94	0.74
2-9	60	20	-0.50	1.10	-2.21	2.94
10-19	155	51	-0.34	1.16	-2.25	2.50
ADULT	85	28	0.06	1.33	-2.8	2.72
	304					

Subscapular sft SDS

Age	Total	%	Mean	SD	Min	Max
Under 2	4	1	0.19	1.04	-1.24	1.26
2-9	60	20	-.27	0.77	-1.99	1.29
10-19	155	51	-0.28	1.07	-2.3	2.22
ADULT	85	28	0.05	1.25	-2.51	2.58
	304					

APPENDIX C
Table C4.4.2.4 FOG of CL/P by British & SL Reference

Table C4.4.4.2[1] Fathers occupation groups (FOG) 1, 2 and 3 of CL/P groups, compared by British & SL Reference SDS, for male (M) & female (F) height, weight, BMI, mid upper arm circumference (MUAC), triceps sft (T), subscapular sft (S).

BRITISH SDS (mean, SD)

FOG	N	%	Ht	SD	Wt	SD	BMI	SD	Head	SD
M 1	18	4	-1.08	1.04	-1.86	1.29	-1.67	1.20	-1.96	1.04
M 2	90	20	-1.73	1.00	-2.99	1.08	-2.41	1.19	-2.53	1.18
M 3	343	76	-2.11	1.06	-3.06	1.27	-2.10	1.29	-2.77	1.06
	451									
F 1	9	3	-2.33	1.30	-3.03	1.09	-1.92	1.05	-2.78	1.59
F 2	56	18	-2.05	0.97	-2.87	1.17	-2.12	1.47	-2.88	1.17
F 3	238	79	-1.84	1.11	-2.45	1.17	-1.75	1.05	-3.11	1.21
	304									

BRITISH SDS (Min, Max)

FOG	N	%	Ht Min	Max	Wt Min	Max	BMI Min	Max	Head Min	Max
M 1	18	4	-2.61	0.80	-4.34	0.62	-3.98	0.70	-4.33	-0.03
M 2	90	20	-3.99	1.35	-5.18	-0.35	-5.31	0.28	-7.16	0.14
M 3	343	76	-5.02	1.02	-6.56	0.26	-7.94	1.12	-6.19	3.55
	451									
F 1	9	3	-4.42	-0.80	-4.73	-0.95	-3.29	-0.30	-6.14	-0.61
F 2	56	18	-4.39	0.29	-5.14	-0.43	-5.80	0.62	-4.98	0.42
F 3	238	79	-4.84	1.89	-5.55	0.69	-5.38	1.43	-6.49	0.21

SL REFERENCE SDS (mean, SD)

FOG	N	%	Ht	SD	Wt	SD	BMI	SD	Head	SD	MUAC	SD	Tric	SD	Subs	SD
M 1	18	4	-0.01	1.03	0.12	1.16	0.00	0.90	0.60	1.04	0.42	1.07	-0.36	1.89	0.64	1.20
M 2	90	20	-0.93	1.05	-0.59	0.93	-0.77	0.80	-0.60	1.08	-0.47	0.88	-0.06	1.56	-0.24	1.17
M 3	343	76	-1.25	1.09	-0.77	0.86	-0.32	0.98	-0.73	0.99	-0.29	0.94	-0.95	1.39	0.07	1.21
F 1	9	3	-1.30	1.10	-1.29	0.68	-0.32	0.77	-0.63	1.10	-1.09	1.23	-0.82	0.88	-0.92	0.60
F 2	56	18	-0.84	1.10	-0.63	1.07	-0.55	1.09	-0.48	0.88	-0.06	1.05	-0.28	1.09	-0.03	1.11
F 3	238	79	-0.62	1.17	-0.42	0.95	-0.22	1.17	-0.84	1.09	-0.17	1.11	-0.23	1.22	-0.20	1.07

SL REFERENCE SDS (Min, Max)

FOG	N	%	Ht Min	Max	Wt Min	Max	BMI Min	Max	Head Min	Max	MUAC Min	Max	Tric Min	Max	Subs Min	Max
M 1	18	4	-1.86	2.02	-1.99	3.10	-2.00	1.95	-2.17	1.67	-1.57	2.30	-5.26	2.93	-2.10	3.82
M 2	90	20	-3.07	2.24	-2.24	1.28	-3.00	1.08	-5.05	1.95	-2.50	2.56	-4.52	1.60	-3.17	3.30
M 3	343	76	-3.83	2.27	-3.59	1.53	-4.7	2	-3.1	2.6	-2.92	3.6	-5.3	3.3	-3.1	3.6
F 1	9	3	-3.28	0.07	-2.72	-0.22	-1.31	0.83	-2.46	0.86	-2.93	0.89	-1.83	0.87	-1.69	0.05
F 2	56	18	-3.89	1.40	-2.77	3.20	-3.20	1.45	-2.41	2.33	-2.27	3.51	-2.21	2.31	-2.28	2.31
F 3	238	79	-3.87	3.42	-2.30	4.22	-4.20	2.39	-4.93	1.89	-2.46	3.25	-3.25	3.94	-2.51	3.22

APPENDIX C
Table C4.4.5.3 Rural & Urban CL/P groups British & SL Reference SDS

Table C4.4.5.3 Rural & Urban CL/P groups British & SL Reference SDS

BRITISH SDS

R/U	N	%	Height	SD	Weight	SD	BMI	SD	Head	SD
M Rural	327	73	-2.07	1.01	-3.06	1.24	-2.10	1.28	-2.74	1.15
M Urban	124	27	-1.82	1.17	-2.83	1.28	-2.10	1.23	-2.58	1.07
	451									
F Rural	243	80	-1.95	1.15	-2.53	1.21	-1.73	1.34	-3.03	1.23
F Urban	61	20	-1.61	0.87	-2.62	1.22	-2.19	1.32	-3.21	1.26
	304									

R/U	N	%	Height Min	Max	Weight Min	Max	BMI Min	Max	Head Min	Max
M Rural	18	4	-5.02	1.35	-6.56	0.62	-5.98	1.12	-7.16	1.18
M Urban	90	20	-4.86	0.94	-6.10	0.52	-5.31	0.28	-7.16	0.14
	451									
F Rural	243	80	-5.09	1.89	-5.69	0.69	-5.80	1.43	-6.14	-0.50
F Urban	61	20	-3.42	0.64	-6.14	-0.50	-6.12	0.36	-7.07	-0.61

SL REFERENCE SDS

R/U	Height	SD	Weight	SD	BMI	SD	Head	SD	MUAC	SD	Tric	SD	Subs	SD
M Rural	-0.90	1.04	-0.77	0.87	-0.40	0.98	-0.70	1.04	-0.36	0.98	-0.01	1.18	-0.95	1.47
M Urban	-0.67	1.16	-0.63	0.91	-0.40	0.96	-0.52	1.08	-0.34	0.87	-0.19	1.31	-0.94	1.37
F Rural	-0.74	1.21	-0.54	0.90	-0.22	1.06	-0.74	1.08	-0.90	1.18	-0.17	1.05	-0.21	1.21
F Urban	-0.42	0.99	-0.53	0.85	-0.53	1.02	-0.86	0.92	-0.47	0.99	-0.28	1.09	-0.43	1.11

R/U	Height Min	Max	Weight Min	Max	BMI Min	Max	Head Min	Max	MUAC Min	Max	Tric Min	Max	Subscapular Min	Max
M Rural	-3.83	2.27	-3.59	2.55	-4.68	1.63	-5.05	2.57	-2.92	3.55	-3.17	3.43	-5.21	3.33
M Urban	-3.76	2.06	-2.35	3.10	-3.00	1.95	-2.50	2.23	-2.15	2.30	-2.15	2.30	-5.71	3.29
F Rural	-3.89	3.42	-2.77	2.62	-3.91	2.39	-4.93	2.33	-2.46	2.21	-2.51	2.58	-3.25	2.90
F Urban	-3.03	2.23	-2.23	1.26	-4.20	1.19	-3.81	0.76	-2.93	2.28	-2.39	3.22	-2.39	3.22

Table C4.5.1.1 Male SL Reference –2 SD and –3 SD British SDS prevalence (%).

Age	N	Height		Weight		BMI	
		-2 SD	-3 SD	-2 SD	-3 SD	-2 SD	-3 SD
0 to 1	149	9	3	20	11	26	20
1 to 2	171	12	5	32	13	24	24
2	72	24	4	46	14	22	14
3	101	6	1	18	7	26	18
4	127	7	1	19	6	17	9
5	97	13	0	27	13	32	18
6	73	7	0	27	16	26	12
7	44	7	2	34	9	39	11
8	71	10	0	30	17	35	14
9	48	19	2	33	19	31	6
10	73	14	4	19	19	19	11
11	49	16	0	22	16	24	16
12	72	15	4	19	25	22	26
13	50	26	0	20	20	18	20
14	67	22	3	34	16	24	19
15	45	29	4	24	18	18	18
16	81	19	6	36	14	26	10
17	27	22	7	33	30	22	7
18	42	26	0	45	29	33	12
19	14	7	0	57	7	43	7
20	14	14	0	36	14	29	7
21	35	11	3	34	40	40	0
22	26	15	0	15	31	15	0
23	26	23	8	27	38	31	0
24	9	22	0	33	33	11	0

Male Age (yrs)	Total Ref pop		<-2 SD Height		Underweight		Thin	
	No	%	-2SD	%	-2SD	%	-2SD	%
<2	320	20	48	15	118	37	147	46
2 to 4.9	300	19	38	13	96	42	101	34
5 to 9.9	333	21	39	12	147	44	144	43
10-18.9	506	31	119	24	229	45	196	39
19-24	124	8	24	19	48	39	39	31
Total	1583	100	268	17	638	40	627	40

Table C4.5.1.2 Female SL Reference –2 SD and –3 SD British SDS prevalence (%).

Age	N	Height		Weight		BMI	
		-2 SD	-3 SD	-2 SD	-3 SD	-2 SD	-3 SD
0 to 1	169	17	6	14	7	11	6
1 to 2	152	18	9	26	19	30	19
2	71	13	8	24	13	28	9
3	92	5	1	22	7	31	11
4	112	9	1	23	6	27	10
5	113	14	4	22	6	28	12
6	60	17	3	28	10	28	20
7	58	10	2	22	10	32	23
8	42	10	0	26	7	37	20
9	58	10	0	21	5	27	12
10	45	16	2	31	4	30	13
11	91	15	1	25	4	29	38
12	24	17	0	43	8	31	50
13	71	20	1	20	1	15	9
14	27	19	11	26	11	30	17
15	81	27	2	28	15	16	11
16	32	25	0	34	22	14	10
17	92	16	2	33	13	13	12
18	42	19	2	31	24	18	11
19	38	21	3	39	16	30	3
20	42	14	5	45	10	21	11
21	60	13	3	30	20	30	13
22	51	16	2	29	20	20	11
23	33	27	6	33	27	24	14
24	27	19	11	44	15	12	8

Female			<-2 SD Height		Underweight		Thin	
Age (yrs)	No	%	-2SD	%	-2SD	%	-2 SD	%
<2	321	19	79	25	104	32	89	28
2 to 4.9	275	16	37	13	85	31	86	31
5 to 9.9	330	20	50	15	103	31	131	40
10-18.9	505	30	88	17	202	40	156	31
19-24	251	15	49	20	101	40	78	33
Total	1682	100	303	18	595	35	536	32

APPENDIX C

Table C4.5.1.3 Male Cleft group –2 SD and –3 SD British reference prevalence (%).

Age	N total	Height -2 SD	Height -3 SD	Weight -2 SD	Weight -3 SD	BMI -2 SD	BMI -3 SD
0 to 1	5	0	40	20	40	20	40
1 to 2	3	67	0	0	33	0	0
2	2	50	0	50	0	0	0
3	2	50	0	50	0	50	0
4	17	24	18	35	41	29	24
5	21	24	10	48	29	43	5
6	20	25	30	35	55	10	45
7	10	40	10	30	50	20	30
8	7	14	14	14	43	57	29
9	10	10	20	40	30	30	20
10	12	67	0	50	42	33	17
11	8	13	13	50	25	38	25
12	24	21	13	21	46	29	38
13	21	52	5	33	43	29	29
14	24	42	17	17	50	13	42
15	24	42	0	29	29	13	33
16	27	33	7	44	30	33	26
17	24	38	17	29	50	29	13
18	30	40	13	27	60	27	30
19	13	38	15	38	54	23	31
20	12	33	25	17	83	25	17
21	11	64	0	18	73	36	27
22	18	44	11	39	56	28	33
23	20	30	15	40	45	10	25
24	17	24	24	18	59	27	13
25	10	50	50	40	50	0	26
26-64	59	20	60	19	63	19	15

Male CL/P population stunting, underweight, thinness by British 1990 Reference

Age (yrs)

Male Age (yrs)	Total Ref pop No	%	Stunted -2SD	%	Underwt -2SD	%	Thin -2 SD	%
<2	8	2	4	50	4	50	3	38
2 to 4.9	21	5	9	43	16	76	10	48
5 to 9.9	68	15	28	41	53	78	36	53
2 to 9	89			41		66		52
10-19	194	43	94	48	144	74	106	55
>19	160	36	88	55	101	63	68	43
Total	451	100	223	49	318	71	223	49

Table C4.5.1.4 Female CL/P group prevalence (%) of –2 SD and –3 SD of British growth reference

Age	N	Height		Weight		BMI	
		-2 SD	-3 SD	-2 SD	-3 SD	-2 SD	-3 SD
0 to 1	3	0	0	67	0	0	0
1 to 2	1	0	0	0	0	0	0
2	4	0	75	25	50	0	0
3	2	100	0	50	50	50	0
4	7	43	0	43	43	43	29
5	9	11	44	44	33	11	22
6	13	23	15	38	23	15	15
7	9	44	22	11	56	22	22
8	10	40	20	30	40	40	10
9	7	43	29	29	57	71	14
10	8	25	13	25	75	13	13
11	12	33	17	33	42	33	50
12	14	43	0	29	29	29	21
13	13	46	15	31	31	38	23
14	17	18	12	24	12	6	12
15	19	26	5	37	26	21	5
16	13	8	15	31	15	8	23
17	17	18	18	53	24	29	12
18	22	38	10	29	33	29	0
19	21	33	19	24	57	33	10
20	7	57	0	43	14	14	0
21	8	50	25	50	25	13	13
22	13	23	15	38	31	15	46
23	8	38	13	25	63	25	38
24	12	33	25	25	42	50	8
25	6	33	0	50	17	0	33
25-45	29	52	21	41	31	14	14

Female CL/P population stunting, underweight, thinness by British 1990 Reference

Female Age (yrs)	No	%	Stunted -2SD	%	Underwt -2SD	%	Thin -2 SD	%
<2	4	19	0	0	2	50	2	50
2 to 4.9	13	16	8	62	11	85	6	46
5 to 9.9	49	20	27	55	34	69	22	45
2 to 9	62			57		73		45
10 to 19	134	30	53	37	83	62	52	39
>19	104	15	60	58	76	73	42	40
Total	304	100	148	49	206	68	124	41

Table C4.5.1.5 SL Reference and CL/P BMI British SDS cut offs for thinness, and IOTF grades, by age cohort and Fathers Occupational Group (FOG).

1. Reference male BMI British SDS cut offs, IOTF grades, age cohorts, and FOG.

Age (years) M FOG 1	Total	BMI <5th C, −2, −3, SDS						<-2 SDS		IOTF THINNESS GRADES					
		<5th	%	-2	%	-3	%	<-2	%	2	%	3	%	2+3	%
<2	40	19	48	7	18	5	13	12	30						
2 to 9	101	44	44	24	25	6	9	30	34	17	19	6	8	23	27
10 to 19	53	23	43	12	21	8	9	20	30	12	19	5	6	17	25
Adult	14	6	43	3	21	1	7	4	29						
Total	208	92	44	46	22	20	10	66	32						
M FOG 2															
<2	111	65	59	33	30	23	21	56	50						
2 to 9	248	119	48	56	25	28	12	84	36	40	17	28	12	68	29
10 to 19	158	84	53	47	27	28	15	75	41	30	18	20	12	50	30
Adult	25	18	72	6	24	6	24	12	48						
Total	542	286	53	142	26	81	15	223	41						
M FOG 3 & 4															
<2	169	96	57	39	23	40	24	79	47						
2 to 9	356	192	54	86	26	46	14	132	40	63	20	41	12	104	32
10 to 19	249	147	59	64	24	49	18	106	43	53	18	44	16	97	35
Adult	57	31	54	19	28	9	16	25	44						
Total	833	466	56	208	25	144	17	352	42						

2. Reference females BMI British SDS cut offs, IOTF grades, age cohorts, and FOG.

Age (years) F FOG 1	Total	BMI <5th C, -2, -3, SDS						<-2 SDS		IOTF THINNESS GRADES					
		<5th	%	-2	%	-3	%	<-2	%	2	%	3	%	2+3	%
<2	17	5	29	3	18	2	12	5	29						
2 to 9	70	21	30	11	19	4	6	17	24	10	16	5	7	16	23
10 to 19	74	21	28	9	9	7	9	14	19	8	8	8	11	14	19
Adult	16	6	38	2	13	1	6	3	19						
Total	177	53	30	25	14	14	8	39	22						
F FOG 2															
<2	65	28	43	15	23	7	11	22	34						
2 to 9	226	116	51	67	30	33	15	100	44	42	19	54	24	96	42
10 to 19	114	40	35	17	15	13	11	30	26	13	11	17	15	30	26
Adult	52	23	44	14	27	3	6	17	33						
Total	457	207	45	113	25	56	12	169	37						
F FOG 3 & 4															
<2	239	95	40	38	16	24	10	62	26						
2 to 9	354	170	48	82	25	37	11	128	36	63	18	56	17	117	35
10 to 19	271	119	44	66	19	46	16	95	35	42	15	59	20	101	35
Adult	183	69	38	31	21	18	10	57	31						
Total	1048	453	43	216	21	126	12	342	33						

PAGE 2. Table C4.5.1.5 CONTINUED

3. CL/P group male BMI British SDS cut offs, IOTF grades, age cohorts, and FOG.

Age (years) M FOG 1	BMI <5th C,			−2 , -3, SDS				<-2 SDS		IOTF THINNESS GRADES					
	Total	<5th	%	-2	%	-3	%	<-2	%	2	%	3	%	2+3	%
<2	1	1	100	0	0	0	0	0	0						
2 to 9	5	2	40	2	40	0	0	2	40	1	20	0	0	1	20
10 to 19	5	3	60	1	20	1	20	2	40	0	0	1	20	1	20
Adult	7	3	43	2	29	0	0	2	29						
Total	18	9	50	5	28	1	6	6	33						
M FOG 2															
<2	1	1	100	0	0	0	0	0	0						
2 to 9	19	15	79	7	37	7	37	14	74	4	21	7	37	11	58
10 to 19	54	41	76	16	30	18	33	34	63	12	22	17	31	29	54
Adult	19	14	74	2	11	8	42	10	53						
Total	93	71	76	25	27	33	35	58	62						
M FOG 3 & 4															
<2	6	3	50	1	17	2	33	3	50						
2 to 10	77	49	64	21	27	16	21	37	48	17	22	14	18	31	40
11 to 20.9	148	97	66	34	23	42	28	76	51	32	22	37	25	69	47
Adult	109	57	52	22	20	22	20	44	40						
Total	340	206	61	78	23	82	24	160	47						

4. CL/P group female BMI British SDS cut offs, IOTF grades, age cohorts, and FOG.

Age (years) F FOG 1	BMI <5th C,			−2 , -3, SDS				<-2 SDS		IOTF THINNESS GRADES					
	Total	<5th	%	-2	%	-3	%	<-2	%	2	%	3	%	2+3	%
<2	1	1	100	0	0	1	100	1	100						
2 to 9	2	2	100	0	0	2	100	2	100	0	0	2	100	2	100
10 to 19	4	3	75	1	25	2	50	3	75	0	0	3	75	3	75
Adult	2	2	100	0	0	0	0	0	0						
Total	9	8	89	1	11	5	56	6	67						
F FOG 2															
<2	0	0	0	0	0	0	0	0	0						
2 to 9	17	11	65	5	29	5	29	10	59	4	24	6	35	10	59
10 to 19	25	8	32	5	20	1	4	6	24	5	20	1	4	6	24
Adult	14	4	29	3	21	1	7	4	29						
Total	56	23	41	13	23	7	13	20	36						
F FOG 3 & 4															
<2	3	1	33	0	0	1	33	1	33						
2 to 9	49	32	65	14	29	10	20	24	49	8	16	13	27	21	43
10 to 19	97	46	47	24	25	12	12	36	37	19	20	16	16	35	36
Adult	90	47	52	19	21	18	20	37	41						
Total	239	126	53	57	24	41	17	98	41						

Table CL/P group male and female BMI as British SDS, cut offs and IOTF grades

Age (years) MALE CLEFT ALL	BMI <5th C,		–2 , -3, SDS				<-2 SDS		IOTF THINNESS GRADES					
	Total	<5th	%	-2	%	-3	%	<-2	%	2	%	3	%	2+3	%
<2	8	63	1		13	2	25	3	38						
2 to 9	101	66	65	30	30	23	23	53	52	22	22	21	21	43	43
10 to 19	207	141	68	51	25	61	29	112	54	44	21	55	26	99	48
Adult	135	74	55	26	19	30	22	56	41						
Total	451	286	63	108	24	116	26	224	50						

Age (years) FEMALE CLEFT ALL	BMI <5th C,		–2 , -3, SDS				<-2 SDS		IOTF THINNESS GRADES					
	Total	<5th	%	-2 SD	%	-3 SD	%	<-2 SD	%	2	%	3	%	2+3	%
<2	4	2	50	0	0	2	50	2	50						
2 to 9	68	45	66	19	28	17	25	36	53	12	18	21	31	33	48
10 to 19	126	57	45	30	24	15	12	45	36	24	19	20	16	44	35
Adult	106	53	50	22	21	19	18	41	39						
Total	304	157	52	71	23	53	17	124	41						

Table C4.5.3.1 Male SL Reference SDS adjustment for FOG 1, 2, 3

Table C4.5.3.1 Female SL Reference SDS adjustment for FOG 1, 2, 3

FOR MALE CL/P 2-9 years

Variable	N	N*	Mean
HT FOG 1	94	0	-0.027
HT FOG 2	226	0	0.174
HT FOG 3	313	0	-0.158
WT FOG 1	94	0	0.056
WT FOG 2	226	0	0.141
WT FOG 3	313	0	-0.174
BMI FOG 1	94	0	0.119
BMI FOG 2	226	0	0.049
BMI FOG 3	313	0	-0.082
HC FOG 1	94	0	-0.124
HC FOG 2	226	0	-0.033
HC FOG 3	312	1	-0.087

FOR FEMALE CL/P 2-9 years

Variable	N	N*	Mean
HT FOG 1	63	0	0.313
HT FOG 2	215	0	0.242
HT FOG 3	327	0	-0.097
WT FOG 1	63	0	0.447
WT FOG 2	215	0	0.032
WT FOG 3	327	0	-0.138
BMI FOG 1	63	0	0.321
BMI FOG 2	215	0	-0.156
BMI FOG 3	327	0	-0.043
HC FOG 1	62	1	0.184
HC FOG 2	215	0	-0.017
HC FOG 3	325	2	-0.073

FOR MALE CL/P 10-19 years

Variable	N	N*	Mean
HT FOG 1	59	0	0.153
HT FOG 2	175	0	0.068
HT FOG 3	286	0	-0.021
WT FOG 1	59	0	0.217
WT FOG 2	175	0	0.107
WT FOG 3	286	0	-0.024
BMI FOG 1	59	0	0.166
BMI FOG 2	175	0	0.116
BMI FOG 3	286	0	-0.017
HC FOG 1	59	0	0.119
HC FOG 2	175	0	0.029
HC FOG 3	286	0	-0.015

FOR FEMALE CL/P 10-19 years

Variable	N	N*	Mean
HT FOG 1	87	0	0.382
HT FOG 2	127	0	0.098
HT FOG 3	329	0	-0.109
WT FOG 1	87	0	0.362
WT FOG 2	127	0	0.051
WT FOG 3	329	0	-0.130
BMI FOG 1	87	0	0.242
BMI FOG 2	127	0	0.059
BMI FOG 3	329	0	-0.013
HC FOG 1	86	1	0.138
HC FOG 2	127	0	-0.046
HC FOG 3	326	3	-0.036

FOR MALE CL/P 20+ years

Variable	N	N*	Mean
HT FOG 1	15	0	-0.198
HT FOG 2	30	0	-0.185
HT FOG 3	65	0	-0.083
WT FOG 1	15	0	0.387
WT FOG 2	30	0	0.310
WT FOG 3	65	0	0.319
BMI FOG 1	15	0	0.731
BMI FOG 2	30	0	0.625
BMI FOG 3	65	0	0.559
HC FOG 1	8	7	-0.360
HC FOG 2	14	16	-0.805
HC FOG 3	31	34	-0.455

FOR FEMALE CL/P 20+ years

Variable	N	N*	Mean
HT FOG 1	11	0	-0.475
HT FOG 2	50	0	-0.005
HT FOG 3	150	0	-0.249
WT FOG 1	11	0	-0.293
WT FOG 2	50	0	-0.382
WT FOG 3	150	0	-0.339
BMI FOG 1	11	0	-0.111
BMI FOG 2	50	0	-0.406
BMI FOG 3	150	0	-0.289
HC FOG 1	11	0	0.073
HC FOG 2	50	0	0.330
HC FOG 3	148	2	-0.094

APPENDIX C

Table C4.5.3.2 Age and difference between mean LIP and SL Reference SDS corrected for age group and Fathers Occupational Group.

Male CL		Height SDS mean (& range)	Weight SDS mean (& range)	BMI SDS mean (& range)
Age	N	CL – SL Ref	CL – SL Ref	CL – SL Ref
<2	2	-1.05, -2.34	0.52, -1.58	1.53, -0.10
2-9	9	-1.17 (1.05 to −2.72)	-0.72 (0.48 to -2.55)	-0.39 (1.62 to −1.53)
10-19	17	-0.34 (2.15 to −2.08)	-0.50 (1.01 to −1.84)	-0.33 (0.82 to −1.66)
Adult	17	-0.50 (0.71 to −1.87)	-0.43 (1.10 to −1.78)	0.13 (1.46 to −3.20)

Female CL		Height SDS mean (& range)	Weight SDS mean (& range)	BMI SDS mean (& range)
Age	N	CL – SL Ref	CL – SL Ref	CL – SL Ref
<2	4	-0.26, 0.31	0.10, -1.33	0.30, -1.02
2-10	6	-0.95 (0.79 to −2.08)	-0.58 (0.27 to -1.41)	0.06 (1.54 to −2.47)
11-18.9	11	-0.21 (2.15 to −2.35)	-0.17 (1.68 to −1.26)	-0.20 (1.36 to −1.89)
Adult	7	-0.12 (0.61 to −1.39)	0.41 (2.06 to −0.80)	0.22 (2.14 to −1.05)

Table C4.6.3.1 Male SL Reference (i) & CL/P (ii) pubertal stage G2 to G5 and growth as British SDS, SL Reference (adjusted) and IOTF grades of thinness.

(i)   Male SL Reference genital (G) stage British SDS and IOTF grades

Stage (N)	British SDS					IOTF GRADES %		
G2 (84)	Mean	SD	Min	Max	<-2 SD %	-1	-2	-3
Height	-1.49	1.00	0.73	-3.8	28			
Weight	-2.18	1.26	-0.35	-4.99	49			
BMI	-2.09	1.38	0.52	-4.48	57	20	27	25
G3 (62)								
Height	-1.29	1.00	1.39	-2.75	24			
Weight	-2.05	1.28	1.73	-4.8	44			
BMI	-2.10	1.40	2.45	-4.87	52	24	26	24
G4 (117)								
Height	-0.98	1.03	1.40	-4.20	16			
Weight	-1.45	1.14	0.81	-4.82	28			
BMI	-1.23	1.16	1.91	-4.48	19	35	10	3
G5 (105)								
Height	-1.24	0.86	1.50	-2.97	19			
Weight	-2.01	1.05	0.66	-4.78	57			
BMI	-1.53	1.06	1.07	-4.42	32	44	20	3

(ii)   Male CL/P genital stages as British SDS and SL Reference SDS adjusted for Fathers Occupation Group, and IOTF grades of thinness

Stage (N)	British SDS					SL Reference SDS		IOTF GRADES %		
G2 (15)	Mean	SD	Min	Max	<-2 SD %	Mean	SD	-1	-2	-3
Height	-2.32	0.78	-1.16	-3.64	60	-1.28	0.75			
Weight	-3.08	1.27	0.30	-5.07	90	-1.46	0.65			
BMI	-2.84	1.38	-0.60	-5.31	90	-0.96	0.90	43	25	32
G3 (18)										
Height	-1.90	1.44	0.09	-5.02	43	-0.68	1.21			
Weight	-2.50	1.25	-0.30	-5.31	54	-0.51	1.21			
BMI	-2.15	1.28	-0.69	-5.26	56	-0.28	1.28	26	26	30
G4 (26)										
Height	-1.70	1.25	0.85	-3.95	54	-0.29	1.21			
Weight	-2.70	1.51	-0.35	-5.88	62	-0.68	1.06			
BMI	-2.59	1.57	0.71	-7.94	46	-0.67	1.18	15	15	19
G5 (94)										
Height	-1.68	0.92	1.35	-3.97	38	-0.21	0.94			
Weight	-2.73	1.15	0.52	-5.98	68	-0.24	0.83			
BMI	-2.07	1.24	0.70	-5.20	45	-0.27	1.01	24	22	20

Table C4.6.3.2 Female SL Reference (i) & CL/P (ii) pubertal stage B2 to B5 and growth as British SDS, SL Reference (adjusted) and IOTF grades of thinness.

(iii) Female breast pubertal stage and British SDS and IOTF grade

Stage (N)	British SDS					IOTF GRADES %		
B2 (75)	Mean	SD	Min	Max	<-2 SD %	-1	-2	-3
Height	-1.10	1.00	1.28	-2.99	21			
Weight	-1.05	1.06	1.58	-3.92	22			
BMI	-0.75	1.55	2.47	-4.29	19	15	12	9
B3 (76)								
Height	-1.19	0.88	1.26	-3.04	20			
Weight	-1.36	1.11	1.25	-3.98	32			
BMI	-1.10	1.65	2.33	-4.21	28	17	13	16
B4 (89)								
Height	-1.28	1.02	1.00	-3.94	20			
Weight	-1.47	1.15	1.85	-4.02	33			
BMI	-0.43	1.45	2.67	-4.02	26	16	17	9
B5 (239)								
Height	-1.45	0.89	1.65	-3.70	26			
Weight	-1.90	1.12	2.05	-4.63	49			
BMI	-1.11	1.32	2.15	-2.50	23	30	9	14

(ii) Female CL/P breast stages as British SDS and SL Reference SDS adjusted for Fathers Occupation Group, and IOTF grades of thinness

Stage (N)	British SDS					SL Reference SDS		IOTF GRADES %		
B2 (12)	Mean	SD	Min	Max	<-2 SD %	Mean	SD	-1	-2	-3
Height	-1.93	0.86	-0.31	-2.91	50	-0.95	0.96			
Weight	-2.62	1.05	-0.68	-4.76	57	-0.80	0.80			
BMI	-2.30	1.29	-0.14	-5.07	58	-0.75	1.09	25	33	33
B3 (23)										
Height	-1.26	1.09	0.46	-3.61	38	-0.35	1.19			
Weight	-2.21	0.98	-0.68	-4.42	57	-0.74	0.79			
BMI	-1.86	1.11	-0.40	-4.78	29	-0.42	0.92	35	10	17
B4 (26)										
Height	-1.54	0.95	-0.37	-3.03	29	-0.19	0.83			
Weight	-2.23	0.68	-0.85	-3.13	57	-0.48	0.81			
BMI	-1.43	0.84	-0.47	-2.38	14	-0.07	0.41	27	5	0
B5 (83)										
Height	-1.63	1.17	1.89	-4.84	33	-0.18	1.22			
Weight	-2.19	1.12	0.90	-5.73	56	-0.11	0.84			
BMI	-1.33	1.14	1.13	-6.00	29	0.02	0.98	30	17	4

Table C4.6.4.1 Changes in prevalence of the indices of stunting, underweight and thinness during pubertal stages, raw data for $\chi 2$ calculation and %.

	-2 SD HEIGHT			UNDERWEIGHT			THIN		
	G2/B2	G3/B3	G4/B4	G2/B2	G3/B3	G4/B4	G2/B2	G3/B3	G4/B4
M SL Reference	20/62	10/47	15/94	32/62	18/47	25/94	38/62	19/47	17/94
F SL Reference	16/75	14/76	19/89	14/75	24/76	29/89	17/75	23/76	23/89
M CL/P	6/10	9/21	13/25	9/10	13/21	15/25	9/12	12/21	11/25
F CL/P	6/12	8/21	4/11	8/12	12/21	5/11	7/12	6/21	0/11
	-2 SD HEIGHT %			UNDERWEIGHT %			THIN %		
M SL Reference	32	21	16	52	38	27	62	40	18
F SL Reference	21	18	21	19	32	33	23	30	26
M CL/P	60	43	52	90	62	60	75	57	44
F CL/P	50	38	36	67	57	46	58	29	0

Raw Data for $\chi 2$

	-2 SD Ht	Underwt	Thin
	G5/B5	G5/B5	G5/B5
M SL Reference	46/241	121/241	61/241
F SL Reference	19/94	41/94	19/94
M CL/P	37/91	65/91	42/91
F CL/P	28/73	43/73	23/73
	-2 SD %	-2 SD %	-2 SD %
M SL Reference	19	50	25
F SL Reference	20	44	20
M CL/P	41	71	46
F CL/P	38	59	32

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Table C4.7.1.3 British mean SDS by age at palate surgery followed up at 5, 10, 15 and 20 years.

Mean weight as British SDS on 5 to 20 year follow up after palate surgery

	<2 years at palate surgery			>2 years at palate surgery		
Years FU	No data	Weight SDS	Weight SD	No data	Weight SDS	Weight SD
5	31	-2.22	1.25	140	-3.13	1.14
10	28	-2.21	1.18	188	-2.65	1.29
15	15	-2.36	1.28	94	-3.11	1.07
20	17	-2.47	1.26	64	-2.54	1.23

Mean BMI as British SDS on 5 to 20 year follow up after palate surgery

	<2 years at palate surgery			>2 years at palate surgery		
Years FU	No data	Mean BMI SDS	BMI SD	No data	Mean BMI SDS	BMI SD
5	31	-2.19	1.19	140	-2.15	1.17
10	28	-2.16	1.18	188	-2.03	1.26
15	15	-2.04	1.42	94	-1.98	1.27
20	17	-1.74	1.28	64	-1.47	1.32

Prevalence (%) of undernutrition at the time of primary surgery, 1990, 124 subjects.

Age	Male N	-2 SD Height	-2 SD weight	-2 SD BMI	Female N	-2 SD Height	-2 SD weight	-2 SD BMI
<2	8	50	50	50	4	0	50	0
2-5	25	48	68	56	17	65	88	47
6-9	12	42	75	67	11	64	91	64
10-19	11	72	82	72	17	47	47	53
>19	14	71	93	71	7	57	43	14

Table C4.8.3 Male CL/P Fitted line regression analysis of independent variables relationship with height.

Polynomial Regression Analysis: ht versus Age

```
The regression equation is
ht = 67.35 + 7.524 Age - 0.1380 Age**2

R-Sq = 88.9%    R-Sq(adj) = 88.9%

Analysis of Variance

Source       DF       SS       MS        F       P
Regression    2    253150   126575   1768.30   0.000
Error       440     31495       72
Total       442    284645

Sequential Analysis of Variance

Source      DF       SS       F       P
Linear       1    183501   800.08   0.000
Quadratic    1     69650   973.03   0.000
```

Polynomial Regression Analysis: ht versus op palate

```
The regression equation is
ht = 129.2 + 3.383 op palate - 0.08768 op palate**2

R-Sq = 12.1%    R-Sq(adj) = 11.7%

Analysis of Variance

Source       DF       SS       MS        F      P
Regression    2     30054   15026.9   27.26   0.000
Error       396    218261     551.2
Total       398    248315

Sequential Analysis of Variance

Source      DF       SS       F       P
Linear       1    24162.4   42.79   0.000
Quadratic    1     5891.4   10.69   0.001
```

Regression Analysis: ht versus urban

```
The regression equation is
ht = 145.5 - 0.778 rural

R-Sq = 0.0%    R-Sq(adj) = 0.0%

Analysis of Variance

Source       DF       SS       MS       F      P
Regression    1       54    54.399   0.09   0.771
Error       449    287120   639.464
Total       450    287174
```

PAGE 2. Table C4.8.3 Male CL/P Fitted line regression analysis of independent variables relationship with height.

Regression Analysis: ht versus FOG

```
The regression equation is
ht = 142.3 + 1.081 foccup

R-Sq = 0.1%   R-Sq(adj) = 0.0%

Analysis of Variance

Source        DF      SS       MS       F       P
Regression     1     160   159.851   0.25   0.618
Error        438  281255   642.134
Total        439  281414
```

Regression Analysis: ht versus urti + COM

```
The regression equation is
ht = 147.4 - 3.347 urti + COM

R-Sq = 1.1%   R-Sq(adj) = 0.9%

Analysis of Variance
Source        DF      SS       MS       F       P
Regression     1    3209   3208.98   5.07   0.025
Error        449  283965   632.44
Total        450  287174
```

Regression Analysis: ht versus Deaf

```
The regression equation is
ht = 146.8 - 7.046 Deaf

R-Sq = 1.3%   R-Sq(adj) = 1.0%

Analysis of Variance
Source        DF      SS       MS       F       P
Regression     1    3636   3635.88   5.76   0.017
Error        449  283538   631.49
Total        450  287174
```

Regression Analysis: ht versus consang 1=n

```
The regression equation is
ht = 149.8 - 3.549 consang 1=n

R-Sq = 0.6%   R-Sq(adj) = 0.4%

Analysis of Variance

Source        DF      SS       MS       F       P
Regression     1    1768   1768.05   2.78   0.096
Error        449  285406   635.65
Total        450  287174
```

APPENDIX C

PAGE 3. Table C4.8.3 Male CL/P Fitted line regression analysis of independent variables relationship with height.

Regression Analysis: ht versus family history

```
The regression equation is
ht = 157.6 - 12.21 family history

R-Sq = 5.7%    R-Sq(adj) = 5.5%

Analysis of Variance

Source        DF      SS       MS       F       P
Regression     1    16401   16401.4  27.20   0.000
Error        449   270773     603.1
Total        450   287174
```

Regression Analysis: ht versus no. sibs

```
The regression equation is
ht = 133.3 + 2.932 no. sibs

R-Sq = 5.1%    R-Sq(adj) = 4.9%

Analysis of Variance

Source        DF      SS       MS       F       P
Regression     1    14650   14650.2  24.19   0.000
Error        448   271288     605.6
Total        449   285938
```

Regression Analysis: ht versus chronic medical conditions

```
The regression equation is
ht = 144.3 + 14.50 1

R-Sq = 2.2%    R-Sq(adj) = 2.0%

Analysis of Variance

Source        DF      SS       MS       F       P
Regression     1     6430   6429.72  10.28   0.001
Error        449   280744     625.27
Total        450   287174
```

Table C4.8.4 Female CL/P fitted line regression analysis of independent variables relationship with height

Polynomial Regression Analysis: HT versus AGE

```
The regression equation is
ht = 74.83 + 6.281 age - 0.1150 age**2

R-Sq = 82.4%   R-Sq(adj) = 82.3%

Analysis of Variance

Source        DF      SS       MS        F       P
Regression     2   111731   55865.5   703.59   0.000
Error        301    23900      79.4
Total        303   135631

Sequential Analysis of Variance

Source     DF       SS       F        P
Linear      1   69164.6   314.26   0.000
Quadratic   1   42566.4   536.09   0.000
```

Polynomial Regression Analysis: HT versus AGE at palate op

```
The regression equation is
ht = 131.7 + 1.605 Age op palate - 0.03138 Age op palate**2

R-Sq = 7.2%   R-Sq(adj) = 6.5%

Analysis of Variance

Source        DF      SS       MS        F       P
Regression     2     7557   3778.62   10.59   0.000
Error        275    98090    356.69
Total        277   105648

Sequential Analysis of Variance

Source     DF       SS       F       P
Linear      1   5684.16   15.69   0.000
Quadratic   1   1873.09    5.25   0.023
```

Regression Analysis: HT versus Urban/rural

```
The regression equation is
ht = 139.4 + 2.254 Rural =0 urban = 1

R-Sq = 0.2%   R-Sq(adj) = 0.0%

Analysis of Variance

Source        DF      SS        MS        F       P
Regression     1      248    247.780   0.55    0.458
Error        302   135383    448.288
Total        303   135631
```

APPENDIX C

PAGE 2. Table C4.8.4 Female CL/P fitted line regression analysis of independent variables relationship with height

Regression Analysis: HT versus FOG

```
The regression equation is
ht = 130.9 + 3.217 FOG
```

```
R-Sq = 0.6%   R-Sq(adj) = 0.3%
```

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	823	822.577	1.84	0.176
Error	302	134808	446.385		
Total	303	135631			

Regression Analysis: HT versus MED_COND

```
The regression equation is
HT = 119.6 + 2.960 MED_COND
```

```
R-Sq = 0.1%   R-Sq(adj) = 0.0%
```

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	1002	1001.56	0.89	0.346
Error	1581	1780568	1126.23		
Total	1582	1781569			

Regression Analysis: HT versus CONSAN
```
The regression equation is
HT = 119.3 + 0.452 CONSAN
```

```
R-Sq = 0.0%   R-Sq(adj) = 0.0%
```

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	95	95.36	0.08	0.771
Error	1581	1781474	1126.80		
Total	1582	1781569			

Regression Analysis: HT versus total sibs
```
The regression equation is
ht = 137.0 - 0.7058 N sibs
```

```
R-Sq = 0.5%   R-Sq(adj) = 0.1%
```
Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	618	617.816	1.38	0.241
Error	302	135013	447.063		
Total	303	135631			

Table C4.8.2.5 Males with CL/P and British SDS regression analysis

Best Subsets Regression: B SDS_Height versus age, Age op palate

```
Response is B SDS_Height
405 cases used, 46 LIP cases contain missing values
                                          R
                                          U       D       s
                                        a P R F C e C     i
                              Mallows   g A U O E a O F   b
Vars  R-Sq  R-Sq(adj)  C-p        S     e L L G D f N H   s
  1    8.7     8.5     37.5    1.0174                      X
  1    5.5     5.3     52.6    1.0348    X
  2   11.8    11.4     24.6    1.0011                    X X
  2   11.0    10.6     28.3    1.0054        X             X
  3   14.2    13.6     15.0    0.98838       X           X X
  3   13.9    13.3     16.6    0.99028    X              X X
  4   16.0    15.2      8.4    0.97916    X   X          X X
  4   15.0    14.1     13.4    0.98524        X X        X X
  5   17.1    16.0      5.5    0.97445    X   X X        X X
  5   16.9    15.8      6.4    0.97554    X   X   X      X X
  6   17.4    16.2      5.8    0.97350    X   X X X      X X
  6   17.3    16.0      6.5    0.97438  X X   X X        X X
  7   17.6    16.1      7.0    0.97371  X X   X X X      X X
  7   17.6    16.1      7.1    0.97388    X X X X X      X X
  8   17.7    16.1      8.3    0.97415  X X X X X X      X X
  8   17.7    16.0      8.7    0.97462  X X   X X X X X X
  9   17.8    15.9     10.0    0.97501  X X X X X X X X X
```

Regression Analysis: B SDS_Height versus Age op palate, FOG, ...

```
402 cases used, 46 cases contain missing values


The regression equation is
B SDS_Height = - 1.03 - 0.0249 Age op palate - 0.294 FOG - 0.131
urti + CED
                + 0.527 family history NO=1 - 0.139 N sibs

402 cases used, 46 cases contain missing values

Predictor                   Coef    SE Coef       T      P   VIF
Constant                 -1.0332     0.3050   -3.39  0.001
Age op palate          -0.024929   0.007948   -3.14  0.002   1.1
FOG                     -0.29438    0.09043    -3.26  0.001   1.0
urti + CED              -0.13130    0.05962    -2.20  0.028   1.0
family history NO=1      0.5271     0.1476      3.57  0.000   1.0
N sibs                  -0.13942    0.02731    -5.11  0.000   1.1

R-Sq = 17.1%   R-Sq(adj) = 16.0%

PRESS = 386.634   R-Sq(pred) = 14.72%
```

PAGE 2. Table C4.8.2.5 Males with CL/P and British SDS regression analysis

```
Analysis of Variance
Source             DF       SS       MS       F       P
Regression          6   78.351   13.059   13.75   0.000
Residual Error    395  375.016    0.949
  Lack of Fit     390  367.707    0.943    0.64   0.827
  Pure Error        5    7.309    1.462
Total             401  453.367
```

Continuation of Regression Analysis: B SDS_Height versus Age op palate, FOG, ...

```
189 rows with no replicates

Source             DF   Seq SS
Age op palate       1   25.035
FOG                 1   11.190
urti + CED          1    7.636
family history NO=1 1    8.730
N sibs              1   24.755

Unusual Observations:
21 x R observations with a large standardized residual.
2 x X observations whose X value gives it large influence.
Durbin-Watson statistic = 1.556 (acceptable)
```

Regression Analysis: B SDS_Height versus Age op palate

```
The regression equation is
B SDS_Height = - 1.756 - 0.03865 Age at palate surgery

R-Sq = 5.6%    R-Sq(adj) = 5.3%

Source      DF      SS       MS       F       P
Regression   1   25.273   25.2730   23.64   0.000
```

Regression Analysis: B SDS_Height versus FOG

```
The regression equation is
B SDS_Height = - 0.9279 - 0.3989 FOG

R-Sq = 4.2%    R-Sq(adj) = 4.0%

Analysis of Variance
Source      DF      SS       MS       F       P
Regression   1   21.043   21.0432   19.45   0.000
```

Regression Analysis: B SDS_Height versus urti + CED

```
The regression equation is
B SDS_Height = - 1.938 - 0.1542 urti + CED

R-Sq = 1.4%    R-Sq(adj) = 1.1%

Source      DF      SS       MS       F       P
Regression   1    6.843   6.84278   6.14   0.014
```

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PAGE 3. Table C4.8.2.5 Males with CL/P and British SDS regression analysis

Regression Analysis: B SDS_Height versus family history NO=1
```
The regression equation is
B SDS_Height = - 2.478 + 0.4263 family history NO=1


R-Sq = 1.7%   R-Sq(adj) = 1.5%


Source       DF       SS       MS      F      P
Regression    1     8.632   8.63246   7.78   0.006
```

Continuation of Regression Analysis: B SDS_Height versus Age op palate, FOG, ...

Regression Analysis: B SDS_Height versus N sibs
```
The regression equation is
B SDS_Height = - 1.458 - 0.1325 N sibs

R-Sq = 5.8%   R-Sq(adj) = 5.6%

Source       DF        SS        MS       F       P
Regression    1     29.215   29.2152   27.44   0.000
```

Table C4.8.6 Females with CL/P and British SDS regression analysis

Best Subsets Regression: B SDS_Height versus age, Age op palate, ...

```
Response is B SDS_Height

278 cases used, 26 LIP cases contain missing values

                                      R
                                      U          D        s
                                 a    P    R    F    C    e    C    i
                                 g    A    U    O    E    a    O    F    b
             Mallows             e    L    L    G    D    f    N    H    s
Vars  R-Sq  R-Sq(adj)    C-p       S
  1    9.0     8.7      17.1   1.0488                                      X
  1    5.1     4.8      29.4   1.0710   X
  2   11.4    10.8      11.4   1.0367        X                            X
  2   10.1     9.5      15.6   1.0443   X                                 X
  3   12.8    11.8       9.1   1.0306   X    X                           X
  3   12.4    11.4      10.5   1.0331   X    X                           X
  4   15.1    13.9       3.6   1.0185   X    X    X                      X
  4   13.2    11.9       9.8   1.0300   X    X              X            X
  5   15.5    13.9       4.6   1.0184   X    X    X                 X    X
  5   15.4    13.8       4.8   1.0187   X    X    X         X            X
  6   16.0    14.1       5.0   1.0171   X    X    X         X    X       X
  6   15.7    13.8       5.8   1.0187   X    X    X         X         X  X
  7   16.3    14.1       6.0   1.0172   X    X    X         X    X    X  X
  7   16.0    13.8       6.9   1.0190   X    X    X         X    X  X    X
  8   16.3    13.8       8.0   1.0191   X    X    X    X    X    X    X  X
  8   16.3    13.8       8.0   1.0191   X    X    X         X    X  X  X  X
  9   16.3    13.5      10.0   1.0210   X    X    X    X    X    X  X  X  X
```

Regression Analysis: B SDS_Height versus age, Age op palate, ...

```
The regression equation is
B SDS_Height = - 1.58 + 0.0290 age - 0.0475 Age op palate
               + 0.440 urban = 1 + 0.0910 urti + CED - 0.139 N
sibs

278 cases used, 26 cases contain missing values

Predictor                Coef   SE Coef      T       P   VIF
Constant              -1.5805    0.1841  -8.59   0.000
age                   0.02901   0.01036   2.80   0.005   1.5
Age op palate        -0.04749   0.01446  -3.28   0.001   1.7
Rural =0 urban = 1     0.4398    0.1494   2.94   0.004   1.0
urti + CED            0.09104   0.09841   0.93   0.356   1.0
N sibs               -0.13896   0.03465  -4.01   0.000   1.3

S = 1.01872   R-Sq = 15.4%   R-Sq(adj) = 13.8%
```

PAGE 2. Table C4.8.6 Females with CL/P and British SDS regression analysis

Regression Analysis: B SDS_Height versus age, Age op palate, ...

```
The regression equation is
B SDS_Height = - 1.47 + 0.0241 age - 0.0565 Age op palate
               + 0.437 urban - 0.130 N sibs


267 cases used, 26 cases contain missing values

Predictor                 Coef  SE Coef       T      P  VIF
Constant               -1.4687   0.1945   -7.55  0.000
age                    0.02409  0.01081    2.23  0.027  1.3
Age op palate         -0.05645  0.01541   -3.66  0.000  1.5
Rural =0 urban = 1      0.4374   0.1540    2.84  0.005  1.0
N sibs                -0.12982  0.03815   -3.40  0.001  1.2


R-Sq = 13.2%   R-Sq(adj) = 11.9%


PRESS = 284.451   R-Sq(pred) = 9.79%


Analysis of Variance

Source              DF       SS      MS     F      P
Regression           4   41.580  10.395  9.95  0.000
Residual Error     262  273.741   1.045
Total              266  315.321


No replicates.
Cannot do pure error test.

Source             DF  Seq SS
age                 1   0.278
Age op palate       1  21.701
Rural =0 urban = 1  1   7.501
N sibs              1  12.100

Unusual Observations

11 x R observations with a large standardized residual.
5 x X observations whose X value gives it large influence.

Durbin-Watson statistic = 1.57204
```

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PAGE 3. Table C4.8.6 Females with CL/P and British SDS regression analysis

Regression Analysis: B SDS_Height versus age

```
The regression equation is
B SDS_Height = - 1.781 - 0.005135 age
```

R-Sq = 0.1%   R-Sq(adj) = 0.0%

Source	DF	SS	MS	F	P
Regression	1	0.385	0.38537	0.32	0.573

Regression Analysis: B SDS_Height versus Age op palate

```
The regression equation is
B SDS_Height = - 1.515 - 0.05332 Age op palate
```

R-Sq = 5.9%   R-Sq(adj) = 5.5%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	18.466	18.4662	16.48	0.000

Regression Analysis: B SDS_Height versus Rural =0 urban = 1

```
The regression equation is
B SDS_Height = - 1.919 + 0.2848 Rural =0 urban = 1
```

R-Sq = 1.1%   R-Sq(adj) = 0.7%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	3.772	3.77201	3.14	0.077

Regression Analysis: B SDS_Height versus N sibs

```
The regression equation is
B SDS_Height = - 1.241 - 0.1589 N sibs
```

R-Sq = 6.7%   R-Sq(adj) = 6.4%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	1	23.787	23.7867	21.01	0.000

APPENDIX C

Table C4.9.3.1 SL Reference Polynomial Regression Analysis: (Age - TW3 RUS Bone Age) vs Chronological Age.

(i) Male SL Reference (CA-BA) versus CA

The regression equation is
TW3 RUS bone age = 1.73 - 0.54 Age Male Reference + 0.02 Age Male Reference**2

R-Sq = 83.5%   R-Sq(adj) = 75.2%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	0.86	0.43	10.12	0.03
Error	4	0.17	0.04		
Total	6	1.03			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.11	0.57	0.49
Quadratic	1	0.76	17.76	0.01

(ii) Female SL Reference (CA-BA) versus CA

The regression equation is
Age – TW3 Bone Age = 1.853 - 0.7103 Age Female Reference + 0.03573 Age Female Reference**2

R-Sq = 95.2%   R-Sq(adj) = 92.8%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	2.93	1.46	39.65	0.002
Error	4	0.15	0.04		
Total	6	3.07			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	2.12	11.14	0.02
Quadratic	1	0.80	21.80	0.01

APPENDIX C

Table C4.9.3.2 CL/P Polynomial Regression Analysis: (Chronological Age (CA) -
TW3 RUS Bone Age (BA)) vs CA

(iii) Male CL/P (CA-BA) versus CA
The regression equation is
Age - TW3 RUS bone age = 2.73 - 0.63 Age Male Cleft + 0.02 Age Male Cleft **2

R-Sq = 71.0%   R-Sq(adj) = 56.5%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	1.23	0.61	4.90	0.08
Error	4	0.50	0.13		
Total	6	1.73			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.51	2.01	0.2
Quadratic	1	0.40	5.73	0.08

(iv) Female CL/P (CA-BA) versus CA

The regression equation is
CA-BA = 5.835 - 1.590 Age + 0.08293 Age**2

R-Sq = 76.5%   R-Sq(adj) = 68.7%

Analysis of Variance

Source	DF	SS	MS	F	P
Regression	2	3.68268	1.84134	9.77	0.013
Error	6	1.13061	0.18843		
Total	8	4.81329			

Sequential Analysis of Variance

Source	DF	SS	F	P
Linear	1	0.35532	0.56	0.479
Quadratic	1	3.32736	17.66	0.006