

Fetal and Infant Encephalisation

by

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A thesis submitted for the degree of Doctor of Philosophy (Ph.D.)

at University College London, University of London.

2002

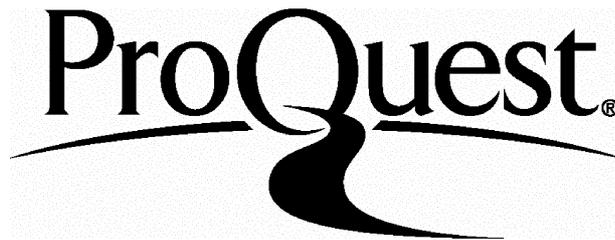
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ABSTRACT

This thesis examines the relationship between growth, nutritional status, body composition and encephalisation in healthy fetuses and infants up to one year-of-age. It also compares human fetal brain and body growth patterns to those of baboons, rhesus monkeys and common marmosets, and assesses whether sex differences in encephalisation are present in these species during early life.

A longitudinal *in vivo* study was undertaken where ultrasound measures of fetal biometry and anthropometric measures of infant biometry provided the basis for quantifying encephalisation and growth. Head circumference in early life was used as a proxy for brain size. In humans, skinfold thickness measures provided an index of nutritional status. The impact of maternal size, nutritional status and life history parameters were also considered in light of human offspring encephalisation, and the relationship between placenta weight and placental notching and offspring encephalisation was assessed. The effects on offspring encephalisation of maternal smoking and alcohol use during pregnancy were also examined and the implications of encephalisation for maternal-fetal conflict theory were considered. The relationship between the relative size of the brain and that of the other major organs was examined using fetal autopsy organ weight measures.

The results demonstrated that intraspecific variation in encephalisation was marked in early life. At this time encephalisation was phenotypically flexible, with encephalisation SD scores undergoing regression to the mean over time. Upward or downward centile shifting in encephalisation related to previous head circumference size and growth. When 'catch up' growth in head circumference occurred, corresponding 'catch down' growth in body length occurred, characterising a trade-off in periodic increased growth between the brain and body. Encephalised neonates tended to be generally well-nourished with high fat and lean tissue deposits and relatively large non-brain organs. Human mothers who produced encephalised offspring had relatively large placentas with few placental notches. Maternal nutritional status further explained a significant but small amount of the variation in offspring encephalisation. Maternal smoking was shown to correlate with

decreased neonatal encephalisation and maternal alcohol use was shown to correlate with decreased head circumference growth.

Human fetal and infant males had relatively larger head circumferences than females (after controlling for body length differences between the sexes), with the degree of sexual dimorphism increasing over time. Non-human primate fetal encephalisation sexual dimorphism was also present but of a very low magnitude. The metabolic costs associated with human fetal and infant encephalisation sexual dimorphism were calculated to be low and did not represent a major additional energetic burden to the fetus or mother.

Human fetal brain growth differed from that of baboons, rhesus monkeys and marmosets in being extended during both the hyperplastic and hypertrophic growth periods. Like the non-human primates, fetal brain growth began to slow *in utero*, but this occurred later in gestation in humans. Data from the literature showed that humans, cetaceans and pinnipeds differed from vertebrates in general in their increased body fatness which was associated with increased encephalisation.

The findings of this thesis are also discussed within the context of evolutionary biology.

ACKNOWLEDGEMENTS

I am deeply grateful to my two supervisors without whom I would not have been able to produce this thesis. Dr. Jonathan Wells (Institute of Child Health, UCL) oversaw aspects of body composition, growth and energetics. Prof. Leslie Aiello (Department of Anthropology, UCL) oversaw aspects of primate evolution and encephalisation. My sincerest thanks to both of them for their unerring patience, guidance, and multiple readings and corrections to the manuscript.

The statistical methods used here were formulated with the invaluable help of Prof. Timothy Cole who provided solutions to, at times, what felt like methodological conundrums. I am indebted to him for his help and advice.

I have been extremely fortunate in being able to study data that was painstakingly collected by a number of researchers. Without these data, this project could not have been carried out.

Drs. Michael Geary and Peter Hindmarsh and Prof. Charles Rodeck very kindly allowed me to analyse the data collected as part of their study on fetal and infant growth. The study was undertaken at University College London Hospitals under the Department of Obstetrics and Gynecology and the Center for Paediatric Endocrinology. This data has been crucial for this thesis and I am greatly indebted to them. Peter Hindmarsh also spent a good deal of time with me, explaining the significance of the measures taken as part of the study, and some of their implications for growth.

Many thanks to Dr. Alice Tarantal at the California National Primate Research Center for providing me with data on fetal and infant biometric measures in rhesus monkeys. My thanks too for hosting me at the center and providing me with countless crucial papers on growth and a demonstration of ultrasound measurement in her subjects.

Sincere thanks to Drs. Karen Rice and Michelle Leland at the Southwest Foundation for Biomedical Research. Drs. Rice and Leland provided me with a wealth of ultrasound data on baboon fetuses. My gratitude extends also to Dr. Ann-Kathrin Oerke at the German

Primate Center who shared her ultrasound and anthropometric data in common marmosets.

I am also very grateful to Dr. Michael Fishbein of the Department of Pathology at UCLA (University of California Los Angeles), who granted me access to the autopsy records compiled by the hospital. These data provided the basis for a major analysis in this thesis.

During the course of my Ph.D., many people provided advise and guidance, while others provided much needed moral support. My thanks go to Robin Dunbar, Roger Gorski, Steve Gould, Mark Hanson, Louise Humphrey, Elizabeth Isaacs, Nathan Jeffrey, Cathy Key, Margaret Lawson, Alan Lucas, Andrew Prentice, Jaroslav Stark, Simon Strickland, Volker Summer, Peter Thoroughgood, Jane Williams and John Wyatt. I am also very grateful to my family and friends for their constant encouragement and support.

I have been very fortunate in receiving an Overseas Research Studentship and a first-year departmental bursary from the Anthropology department at UCL. I also received a travel grant from University College London to support my data collection at UCLA and the CNPRC. I must express my sincerest gratitude to my father who provided a great deal of financial support during my Ph.D. Without his help I could not have completed a doctorate.

Finally, thank you to everyone at the MRC Childhood Nutrition Research Center at the Institute of Child Health and to Jonathan Wells, in particular, for making me so welcome within the group, and helping to make my Ph.D. such an enjoyable experience.

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CHAPTER 1

Introduction

1.1) Aims of thesis

The purpose of this thesis is to (1) quantify encephalisation in the living fetus and infant up to one year-of-age, (2) relate encephalisation to fetal and infant growth patterns, (3) relate encephalisation to maternal factors and (4) relate encephalisation to differential tissue investment within the fetus and infant. Maternal factors include body size, indices of nutritional status in early pregnancy, placenta weight, number of notches within the placenta, age, parity, socio-economic status, alcohol use and smoking during pregnancy.

The underlying premise of the thesis is that energy for encephalisation may be met by the mother or by the fetus or infant itself and that conflict over energy resources between mother, placenta and fetus may impact offspring encephalisation. To this end estimates of maternal fat and lean tissue deposits provide indirect proxies for energy availability for the fetus, and placenta weights provide a proxy for efficiency of energy transfer to the fetus. The fetus or infant may provide additional energy for encephalisation via trade-offs within its own physiological systems. The relationship between the relative size of the fetal brain and that of other major organs is assessed in order to determine whether energy for encephalisation may be met by reducing energy availability to other organs. Additionally, the relationship between encephalisation and somatic growth rate is assessed in order to determine whether additional energy for encephalisation may be met by reducing growth in the non-brain body, in order to divert energy to brain tissue.

Encephalisation within the context of this thesis has no bearing on 'intelligence' but rather reflects brain size relative to body size.

Although much work has been carried out on encephalisation in mammals, and primates in particular, the majority of these studies have focused on comparative cross-sectional data in adults. Relatively little is known of the changing patterns of

encephalisation with growth or the intra-specific variation in encephalisation during ontogeny. This thesis seeks to provide further insights into the way in which brains and bodies grow in encephalised and non-encephalised individuals. To that end, it undertakes a longitudinal *in vivo* study of fetal and infant growth using ultrasound sonography and anthropometry.

A better understanding of the energetic implications for encephalisation during growth would be useful for determining the impact of growth faltering and malnutrition on relative brain size as well as the impact of maternal nutritional stress on offspring encephalisation. Persistent deficits in encephalised brain growth may also serve as a useful indicator for severe growth faltering.

1.2) Brief outline of chapter 1

Chapter 1 is divided into two main sections. The first section deals with the encephalisation quotient - how it is quantified and what it measures. It also compares levels of encephalisation between primates and vertebrates in general, and between humans and non-human primate species. Data from the literature are used to describe the relationships between brain weight and body weight at different taxonomic levels and ages. The author does not impose her own selection criteria to these data, but uses the measures compiled in the relevant publications.

The second section of the chapter explores the energetic costs of encephalisation in the adult and neonate and follows with a brief description of the content of the thesis.

SECTION I: Encephalisation

1.3) The encephalisation quotient

It has long been recognised that large bodied animals have large brains but that a large body is not necessarily associated with a large brain in relative terms. Jerison (1973)

first defined the degree to which observed and expected brain size (scaled to body size) differs as the encephalisation quotient (EQ): the ratio of actual brain size to expected brain size for living mammals using the formula:

$$(1) \quad EQ = 0.12 * (BoW)^{0.667}$$

where EQ = encephalisation quotient and BoW = body weight in grams given by Jerison (1973) based on mammalian data.

Although Jerison established the basis for this work, more recent analyses using larger samples, better distributions of species and arguably more appropriate line fitting techniques have shown that a scaling coefficient of 0.75 better describes the allometric relationship between brain weight and body weight in mammals (Bauchot 1978, Eisenberg 1981, Armstrong 1982, Hofman 1982, Martin 1982, 1983). For example, Martin's (1983) equation states that:

$$(2) \quad \text{Log}_{10} (BrW) = 0.76 \text{Log}_{10} (BoW) + 1.77$$

where BrW = brain weight in milligrams and BoW = body weight in grams.

Traditionally, residual brain weight (a reflection of EQ) is calculated by subtracting observed brain weight measures from estimated brain weight measures (calculated from a predictive equation). The residual values for a given species vary according to the taxonomic level of analysis and the nature of the sample since exponent values determined at lower taxonomic levels, tend to be lower largely as a result of reduced variation around the expected regression line (Holloway and Post 1982). Likewise, the nature of the species included in the sample affects the best-fit regression line through the data, and hence, the equation describing the regression. As a result, the deviation of a species from the 'average' line (its residual value) is largely a function of the sample to which it is compared.

Where evolutionary trends in encephalisation are of interest, phylogenetic relatedness between species may be taken into account, using Harvey and Pagel's (1991) method

of 'independent contrasts'. This method differentiates between traits passed from a common ancestor to descendent species, as opposed to those that have evolved independently in a species. The methods produce contrasts controlling for phylogenetic relatedness of, for example, brain and body weights, which may be entered into regression analysis much the same as absolute data would be. The slope of the model would, however, differ from that derived from absolute brain and body sizes. Because differences in encephalisation between humans and extant species are of interest here, rather than evolutionary trends, independent contrasts are not utilised.

By considering brain size after controlling for body size, it becomes possible to assess brain size more accurately in sexually dimorphic species as well as across species. For example, using data on brain and body weights collected by Quirling (1950), primate encephalisation can be assessed relative to that of other vertebrate orders.

1.4) Primate encephalisation relative to other vertebrates

In Figure 1.1, \log_{10} -transformed vertebrate brain weights are plotted against body weights across eight orders including birds, bony fish, elasmobranch fish, reptiles, rodents, ungulates, cetaceans and primates. Table 1.1 lists the order-specific least squares slopes derived from these data, using linear regression. Least squares linear regression is used to determine the slopes and corresponding residuals. The residuals represent the degree to which a data point deviates from the mean regression line (see Sokal and Rohlf 1997).

The Quirling (1950) data show that primates and cetaceans have the largest brains for their body size relative to the vertebrates in the sample, and the human (marked with an asterix) has a significantly larger brain than expected for a primate of its body weight. The human in this sample was large, with a body weight of 78.5kg. Based on the primate predictive equation (slope and intercepts taken from Table 1.1), this human has a predicted brain weight of 774g, while its actual brain weight is 1540g. Based on the primates in this sample, the human has a brain almost twice as large as expected for a primate of comparable body weight.

This study is based on general methods employed in similar studies in mammals. Jerison (1973), Martin (1982, 1983) and Harvey (1988), for example, showed similar patterns in order-specific encephalisation.

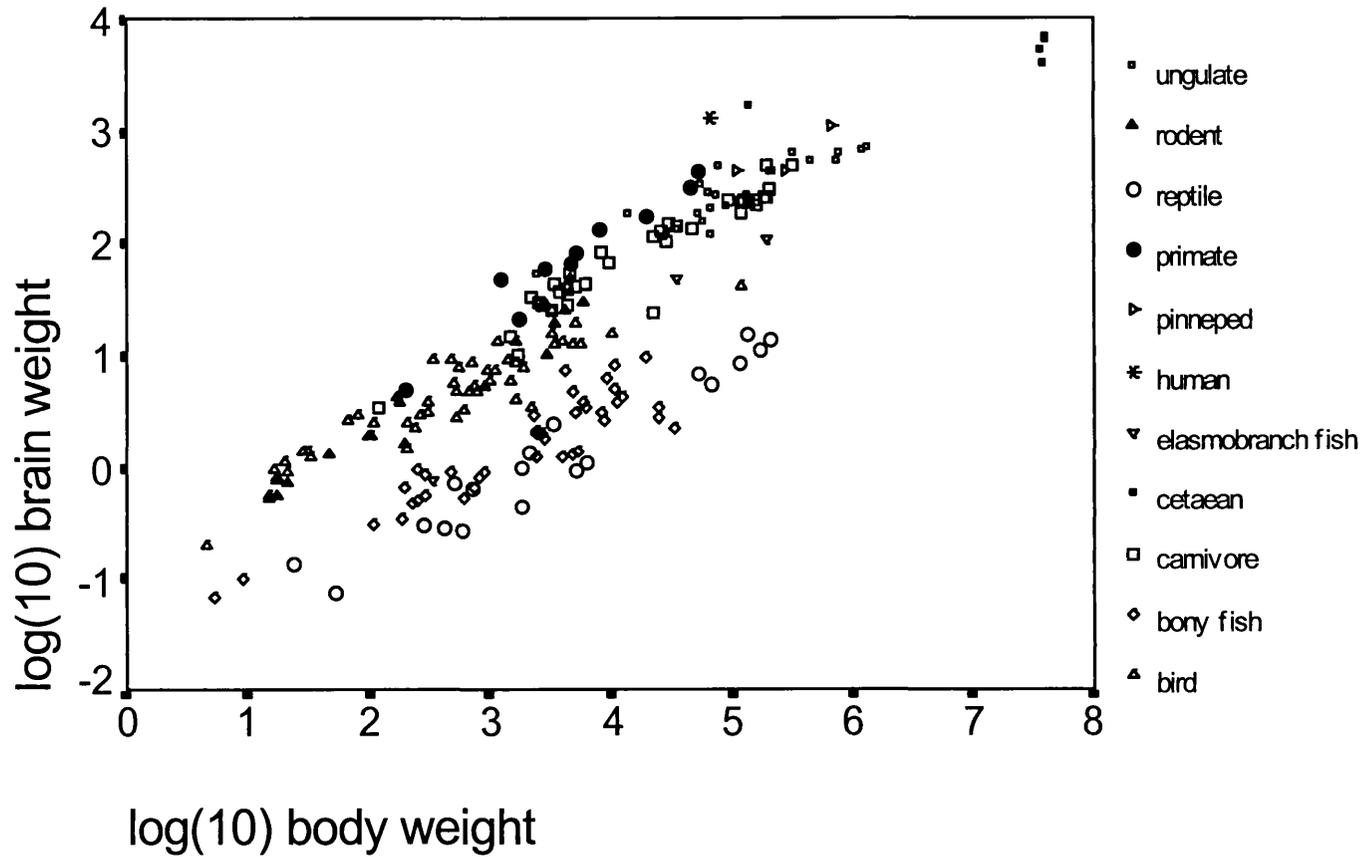


Figure 1.1 Data taken from Quirling (1950). \log_{10} -transformed brain weight in grams plotted against \log_{10} -transformed body weight in grams for species from a variety of vertebrate orders.

Table 1.1 Order-specific least squares regressions calculated from brain weight and body weight data in vertebrates

Order	n	Intercept	Slope	SE	r²	P
ungulate	24	0.141	0.458	0.145	0.836	0.000
bird	52	-0.685	0.500	0.173	0.869	0.000
bony fish	40	-1.484	0.511	0.204	0.833	0.000
reptile	19	-1.914	0.570	0.182	0.937	0.000
carnivore	35	-0.557	0.579	0.149	0.917	0.000
rodent	14	-1.056	0.686	0.179	0.939	0.000
primate ¹	10	-0.884	0.748	0.149	0.942	0.000
primate ²	11	-1.121	0.820	0.180	0.935	0.000

Based on values from Quirling (1950). Weights in grams. Cetaceans and Elasmobranch fish are excluded due to inadequate sample sizes for regression analysis. r² = regression coefficient. SE = standard error, n = number of species represented, P = probability based on bivariate correlation with two-tailed significance of 95%. Primate¹ = primates excluding human, primate² = primates including human.

1.5) Human encephalisation relative to other primates

However, as noted, a predictive equation is largely a function of the species included in the sample. In a larger database of primate brain and body weights, compiled by Stephan et al. (1985), human brain weight and body weight can be assessed relative to 26 other anthropoid (haplorhine) primates, including humans, and 17 prosimian (strepsirhine) primates. It should be noted that in this database, a species is often represented by multiple individuals and no reference to sex is given. *Tarsius syrichta* is excluded from this analysis as it is debatable whether or not its taxonomic affinity lies with the haplorhines or strepsirhines (Dene et al. 1976, Stephan 1984, Joffe and Dunbar 1998).

Figure 1.2 is a scatterplot of \log_{10} -transformed brain weight plotted against body weight in primates and shows that there is a clear grade-shift between these two infra-orders in terms of their relationship between brain and body weight, as documented by other workers (Martin and Harvey 1985, Martin 1989a,b). Although haplorhine and strepsirhine slopes are very similar, the intercepts for those slopes differ, with the strepsirhine intercept below that of the haplorhines (see equations 3 and 4). The two slopes differ significantly. These grade-shifts have clear implications for the calculation of residuals. When fitting a haplorhine-specific and strepsirhine-specific regression to the primates in the Stephan et al. (1985) database, it is possible to calculate brain size residuals from the infra-order-specific regression line. Table 1.2 lists the infra-order specific residuals calculated from these data. Human relative brain size is assessed relative to haplorhine primates alone as our species clearly falls most closely within this grade.

Figure 1.3 shows \log_{10} -transformed brain weights plotted against body weights for the haplorhine primates measured by Stephan et al (1985). Humans and a number of other species are labeled. The least squares linear regression equations (including and excluding humans) are also given (see equations 5 and 6).

There is some debate as to which regression technique should be applied to data for the purposes of calculating residuals. For example, Aiello (1992) suggests that a

reduced major axis regression be used, while Martin (1983) recommends the major axis regression. Falk et al. (1999) on the other hand, used least squares linear regression to describe the relationship between brain size and body weight, and Trinkaus and Hilton (1996) argue for its use when predicting one variable from another. Following Dean et al. (1999) and Trinkaus and Hilton (1996), least squares linear regression is used here.

According to Sokal and Rohlf (1997) least squares regression allows for the calculation of residuals from a mean regression line, where the sum of the squared deviations (calculated as a vertical line from the data point to the line) is as small as possible, and where measurement error associated with the independent variable is relatively low. In contrast, the major axis model assumes that measurement error is greater on the x-axis, while the reduced major axis model assumes that the error is even on both axes, and of a very low order (Ricker 1973, Rayner 1985).

Figure 1.3 shows that humans have a markedly positive residual (+0.39) relative to the other anthropoid primates in the sample. Table 1.2 lists the species-specific residuals calculated from strepsirhine and haplorhine regressions, and shows that *Miopithecus talapoin*, *Saimiri sciurus*, *Cebus* sp. and *Lagothrix lagothricha* are also notably encephalised for primates of their body size. Corresponding EQ values based on the mammalian regression given by Martin (1983) are also listed. Resulting encephalisation values differ depending on the regression used.

In this regression analysis, the chimpanzee is not encephalised relative to the other anthropoids in the sample. Rather, its brain weight lies on the regression line. This contradicts other studies (Jerison 1973, Martin 1983) and is likely an artifact of the individual used in the Stephan et al. (1985) sample rather than the species as a whole.

The above regressions show that there is variation in relative brain size among both haplorhine primates (sd = 0.13, n = 26) and strepsirhine primates (sd = 0.12, n = 17). A number of workers have attributed this variation in relative brain size to adaptations arising from variation in social demands (Byrne and Whiten 1988, Dunbar 1992, Aiello and Dunbar 1993, Joffe 1997, Joffe and Dunbar 1998) as well as variation in

ecological/foraging demands (Milton 1979, 1988; Parker and Gibson 1979, Clutton-Brock and Harvey 1980, Gibson 1986, MacNab and Eisenberg 1989, Barton and Purvis 1994, Barton 1996, Barton and Dunbar 1997). These authors argue that varying levels of social complexity and/or foraging complexity have placed differential selection pressures on species for encephalisation. Reader and Laland (2002), in contrast argue that increased brain size has evolved in response to innovation, social intelligence and tool use.

For example, Dunbar (1992) argued that neocortex size and group size are correlated in primates, with highly social primates having relatively large neocortices - the part of the brain associated with abstract thought, foreplanning and association formation. He suggested that the complex nature of primate social interactions was the selection pressure for increased neocortex size, largely in response to the cognitive demands of maintaining social cohesion in large groups in which individuals must monitor complex triadic relationships.

Keverne et al. (1996) found that the neocortex is under the control of the maternal genome and the authors suggested that increased neocortex size, therefore, evolved in matrilineal primate societies, associated with complex hierarchical relationships.

In contrast, Clutton-Brock and Harvey (1980) showed that brain weight is correlated with diet and home range in primates. The authors argued that increased relative brain weight in frugivores, over folivores, is associated with increased cognitive demands of monitoring a widely dispersed and ephemeral food resources (i.e. fruit). Barton (1996) showed similar findings in assessing the relationship between neocortex size and behavioral ecology in primates.

Parker and Gibson (1977) and Gibson (1986) have argued that ecological selection pressures, particularly the cognitively complex task of extractive foraging of embedded food resources, has been the driving force behind increased brain weight in primates.

Reader and Laland (2002), rather than arguing for a social versus ecological intelligence model, have suggested that these social and ecological cognitive processes are not mutually exclusive but interact to produce innovative behaviors, the basis for increased brain size selection in primates, with both social and ecological benefits. The authors cite tool use as an outcome of these cognitive processes.

Much of the work on the social intelligence hypothesis and the ecological intelligence hypothesis, however, is based on cross-sectional data and indirect measures of social and ecological intelligence. Moreover, there is disagreement as to the functional correlates of relative brain size. For example, Deacon (1997) has argued that in non-human primates, encephalisation does not reflect increased brain size, but rather reduced body size (dwarfism) over evolutionary time.

In summary, encephalisation is a measure of brain size relative to body size. There may be some disagreement as to whether encephalisation in non-human primates has evolved in response to increased brain size or decreased body size, but most authors agree that a combination of social and ecological selection pressures have favored encephalisation in primates.

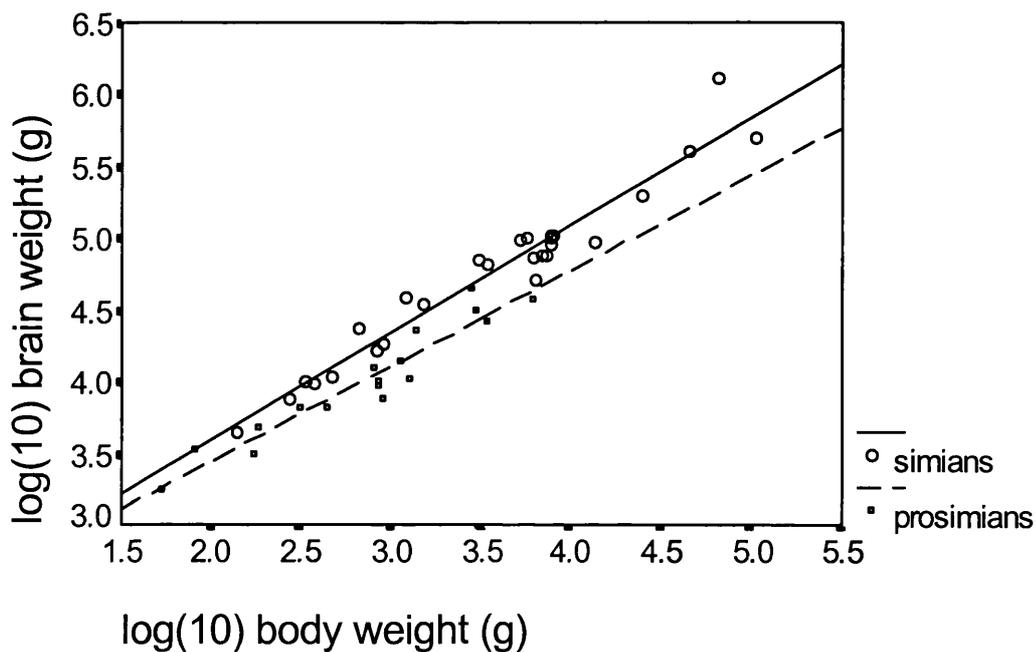


Figure 1.2 Scatterplot showing grade-shift between strepsirhine and haplorhine primates in \log_{10} -transformed brain weight plotted against body weight. Data taken from Stephan et al. (1985).

The least squares linear regression equation for prosimians is:

$$(3) \quad \log_{10} \text{ brain weight (grams)} = 0.664 * \log_{10} \text{ body weight (grams)} + 2.1$$

$$(r^2 = 0.916, \text{SE} = 0.120, n = 17, P = <0.0001)$$

for simians:

$$(4) \quad \log_{10} \text{ brain weight (grams)} = 0.706 * \log_{10} \text{ body weight (grams)} + 2.2$$

$$(r^2 = 0.959, \text{SE} = 0.107, n = 26, P = <0.0001)$$

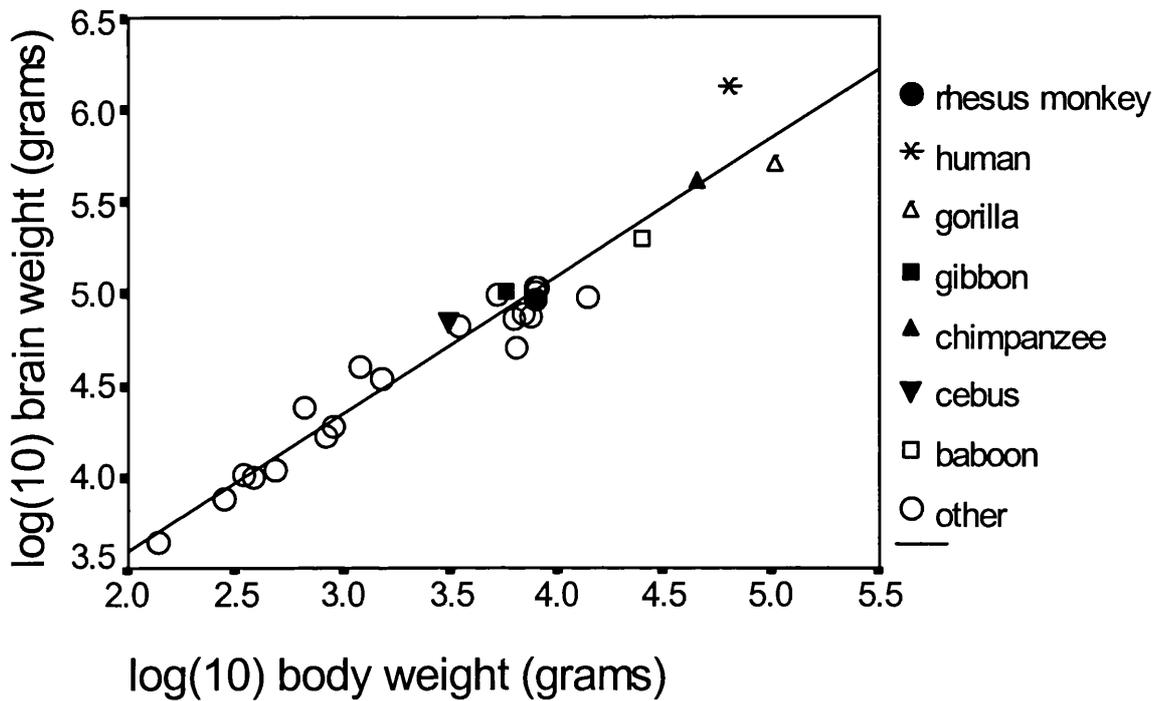


Figure 1.3 Data taken from Stephan et al. (1985). Log₁₀-transformed brain weight plotted against log₁₀-transformed body weight for haplorhine primates. A least squares linear regression is fitted to the data and a predictive equation is calculated. The predictive equation is based on non-human primates. Brain size residuals are then calculated by subtracting observed brain weights from predicted brain weights.

The least squares linear regression equation including humans is:

$$(5) \quad \log_{10} \text{ brain weight (grams)} = 0.749 * \log_{10} \text{ body weight (grams)} + 2.1$$

$(r^2 = 0.945, SE = 0.138, N = 27, P = <0.0001)$

excluding humans:

$$(6) \quad \log_{10} \text{ brain weight (grams)} = 0.706 * \log_{10} \text{ body weight (grams)} + 2.23$$

$(r^2 = 0.959, SE = 0.107, N = 26, P = <0.0001)$

Table 1.2. Residual brain weight measures and encephalisation quotients (EQ) calculated from infra-order specific regression equations

Strepsirhines	Residual	EQ*	Haplorhines	Residual	EQ*
<i>Cheirogaleus major</i>	-0.05	0.07	<i>Callithrix jacchus</i>	-0.03	0.94
<i>Cheirogaleus medius</i>	-0.11	0.03	<i>Cebuella pygmaea</i>	-0.02	0.95
<i>Microcebus murinus</i>	-0.02	0.01	<i>Sanguinus oedipus</i>	-0.01	0.98
<i>Lepilemur ruficaudatus</i>	-0.20	0.11	<i>Sanguinus tamarin</i>	+0.04	1.10
<i>Lemur fulvus</i>	+0.16	0.15	<i>Callimico goeldii</i>	-0.05	0.90
<i>Varecia variegata</i>	+0.07	0.27	<i>Aotus trivirgatus</i>	-0.04	0.91
<i>Avahi laniger</i>	-0.16	0.14	<i>Callicebus moloch</i>	-0.02	0.95
<i>Avahi occidentalis</i>	-0.08	0.11	<i>Pithecia monachus</i>	+0.07	1.18
<i>Propithecus verreauxi</i>	-0.04	0.31	<i>Alouatta sp.</i>	-0.24	0.57
<i>Indri indri</i>	-0.06	0.47	<i>Ateles geoffroyi</i>	0.00	1.00
<i>Daubentonia</i>	+0.25	0.26	<i>Lagothrix</i>	+0.12	1.31
<i>madagascariensis</i>			<i>lagothricha</i>		
<i>Loris tardigradus</i>	+0.04	0.05	<i>Cebus sp.</i>	+0.14	1.37
<i>Nycticebus coucang</i>	+0.05	0.10	<i>Saimiri sciurus</i>	+0.18	1.53
<i>Perodictus potto</i>	0.00	0.13	<i>Macaca mulatta</i>	-0.06	0.88
<i>Galago crassicaudatus</i>	-0.05	0.11	<i>Cercocebus</i>	-0.01	0.97
			<i>albigena</i>		
<i>Galago demidoff</i>	+0.14	0.02	<i>Papio anubis</i>	-0.11	0.77
<i>Galago senegalensis</i>	+0.06	0.03	<i>Cercopithecus</i>	-0.08	0.84
			<i>ascanius</i>		
			<i>Cercopithecus mitis</i>	+0.08	1.20
			<i>Miopithecus</i>	+0.21	1.61
			<i>talapoin</i>		
			<i>Erythrocebus patas</i>	+0.01	1.02
			<i>Pygathrix nemaeus</i>	-0.12	0.75
			<i>Nasalis larvatus</i>	-0.23	0.58
			<i>Procolobus badius</i>	-0.10	0.80
			<i>Hylobates lar</i>	+0.09	1.23
			<i>Gorilla gorilla</i>	-0.20	0.63
			<i>Pan troglodytes</i>	-0.01	0.97
			<i>Homo sapiens</i>	+0.39	2.44

Residuals calculated from strepsirhine-specific and haplorhine-specific regressions. Notably encephalised individuals are highlighted. Raw data taken from Stephan et al. (1985).

* EQ is calculated using Martin's (1983) equation for predicting EQ from body weight in mammals (see equation 2).

SECTION II: Metabolic costs

1.6) Energetic costs of encephalisation

Having a brain almost twice as large as an 'average' primate of comparable body size has very clear energetic implications for our species. Brain tissue is one of the most metabolically active tissues in the body. While weighing less than 2% of adult body mass, the brain utilizes over roughly 21-23% of total basal energy requirements in the human adult (Kety 1957, Armstrong 1985, Holliday 1986, Aiello and Wheeler 1995). Tables 1.3 and 1.4 lists organ sizes and metabolic rates in the adult as well as glucose substrate requirements.

Basal metabolic rate (BMR) is defined in a number of ways. The definition includes, "the respiratory rate of a resting animal, normally measured by oxygen demand". It is also defined as, "the 'background respiration rate, as required for unavoidable muscle contractions (e.g. heart), growth, temperature maintenance, etc.'" (Thain and Hickman 1995) or, "the stable rate of energy metabolism measured in mammals and birds under conditions of minimal environmental and physiological stress, after fasting has temporarily halted digestion and absorptive processes" (Eckert and Randall 1983). In humans, this usually involves fasting, but not starving, a thermoneutral environment, being awake but not active and receiving no previous stimulants (e.g. smoking or alcohol) (see for example, Coward et al. 1984).

Since the mass-specific basal metabolic rate of brain tissue is approximately 296 kcal/kg/day¹ (Holliday 1971), this translates into an average increased basal energy requirement of about 308 kcal/day in direct response to encephalisation in the adult.

¹ Normally, metabolic activity of an organ is expressed in terms of oxygen consumption (VO₂), as milliliters of O₂/100 gm organ weight/minute. In order to compare organ metabolic activity to BMR, VO₂ is converted to OMR (organ metabolic rate), expressed in terms of kcal/kg organ weight (OW)/day at 4.9 kilocalories/L oxygen utilized for the organs [assuming an RQ (respiratory quotient) of 0.9 for the organs or using 4.7 kilocalories/L oxygen utilized for muscle (assuming a RQ of 0.7) Holliday (1971)]. RQ is the ratio of the volume of CO₂ expired to the volume of O₂ consumed within a given time (Eckert and Randall 1983).

Leonard and Robertson (1992, 1994) have shown that humans require about 3.5 times the amount of energy to maintain their brains, than do anthropoid primates of comparable absolute body weight.

In early life, the relative metabolic cost of the brain is even greater. This is principally because the developing brain comprises a greater proportion of total body mass, and hence, basal metabolic rate. In the fetus and infant the brain comprises between 9.5 and 17% of body mass and utilises between 50-60% of metabolic energy (Holliday 1971, Elia 1992). This is significantly higher than in the adult where only ~2% of body mass is accounted for by brain mass. Table 1.4 lists the relative size and metabolic rate of the brain at different stages of growth and shows that the relative cost of brain tissue in early life is significantly greater than during later stages of life.

Strikingly, during infancy, 75% of the combined weight of the major organs is comprised of brain (Holliday 1986) as compared to approximately 39% in the adult male². Elia (1992) shows that from birth to old age, the relative proportion of the brain to total body mass decreases from about 12% to 2%, far exceeding the decrease in size and relative reduction in metabolic cost of the liver, kidneys and heart as well as adipose tissue and muscle (see Tables 1.5 and 1.6).

² Calculated from organ mass values reported by Brozek and Grande (1955).

Table 1.3. Organ metabolic rate and organ size in adult humans: relationship to basal metabolic rate

Component	Weight (kg)	VO₂ (ml/minute/100 gm)	OMR (kcal/day)	OMR/BMR* (%)
1. Brain	1.4	4.2	414	23.3
2. Liver	1.6	4.1	464	26.1
3. Heart	0.3	8.2	182	10.2
4. Kidney	0.3	5.5	116	7.1
Total 1-4	3.6	-	1177	66.7
5. Skeletal muscle	28.3	0.3	500	28.1
Total 1-5	31.9		1677	94.2

Taken from Holliday (1986)

VO₂ = volume of oxygen utilised, expressed in ml per minute per 100g of brain tissue

OMR = organ metabolic rate

BMR = basal metabolic rate

*BMR for a 70 kg male, given by Talbot (1938)

Table 1.4. Human brain size and energy requirement relative to body weight and BMR at different stages of growth

body weight (kg)	brain weight (g)	brain wt/body wt (%)	brain MR kcal/day per 100g	BMR kcal/day	BrMR/ BMR (%)	glucose³ needed g/day	glucose needed g/kg/day
1.1	190	17	-	41	-	-	-
3.5	475	14	140	161	87	35	10
5.5	650	12	192	300	64	48	8.5
11	1045	10	311	590	53	78	7.0
19 (5 yrs)	1235	6.5	367	830	44	92	5.0
31	1350	4.4	400	1160	34	100	3.0
50	1360	2.7	403	1480	27	101	2.0
70	1400	2.0	414	1800	23	103	1.5

Taken from Holliday (1986). BrMR/BMR = brain metabolic rate/basal metabolic rate.

wt = weight, BrMr = brain metabolic rate

³ It should be noted that there is some evidence to suggest that cerebral glucose metabolism varies across grey matter structures (cortex, subcortical grey matter and brainstem nuclei) in the rhesus monkey (Shapiro et al. 1978), suggesting that when total brain metabolism is estimated for humans, brain structure sizes and specific metabolic rates should ideally be considered.

Table 1.5 Percentage contribution of various organs to the body weight of man

Age (yr)	Brain/wt %	Liver/wt %	Kidneys/wt %	Heart/wt %	sum/wt %	Muscle/wt %
Birth	12.2	4.5	0.8	0.7	18.2	21.3
1-5	8.3	3.5	0.5	0.6	12.9	-
6-10	6.7	3.1	0.5	0.6	10.9	-
11-15	3.7	2.6	0.5	0.5	7.3	36.2
16-20	2.6	2.6	0.5	0.5	6.2	-
21-30	2.2	2.5	0.5	0.5	5.7	45.2

Taken from Elia (1992), based on Korenchevsky (1961).

Wt = weight, yr = year, sum = brain, liver, kidneys and heart weights.

Table 1.6 Contribution of different organs and tissues to body weight and basal metabolic rate in the reference male, reference female, and an infant

	Tissue or organ weight (kg)			Tissue or organ weight (% body weight)			Metabolic rate			
	male	female	infant	male	female	infant	OMR % total	male	female	infant
Liver	1.8	1.4	0.26	2.6	2.4	3.5	200	21	21	14
Brain	1.4	1.2	0.71	2.0	2.1	9.5	240	20	21	44
Heart	0.3	0.2	0.04	0.5	0.4	0.5	440	9	8	4
Kidneys	0.3	0.3	0.05	0.4	0.5	0.7	440	8	9	6
Muscle	28.0	17.0	1.88	40.0	29.3	25.0	13	22	16	6
Adipose tissue	15.0	19.0	1.50	21.4	32.8	20.0	4.5	4	6	2
Other	23.2	18.9	3.06	33.1	32.6	40.7	12	16	19	24
Total								Metabolic Rate (kcal/day)		
	70.0	58.0	7.5	100	100	100		1680	1340	390

Taken from Elia (1992)

Tissue and organ weights for reference male and female adults from Snyder et al. (1975)

Infant = 0.5 years old

Other = bone, skin, intestines, glands etc.

OMR = organ metabolic rate (kcal/kg/day)

1.6a) Fetal and infant encephalisation

When comparing relative brain size among fetal and infant primates, Count (1947) first showed that humans are encephalised throughout ontogeny. In addition, Martin (1983) documented a consistent pattern for fetal and neonatal encephalisation in primates, where brain size (scaled to body size) is significantly larger in primates as compared to other mammals during this period, with primates lying along a separate and higher grade. Encephalisation in humans in early life has strong implications for energetics as early life marks the period where the costs of the brain, in relative terms, are greatest, and where at least some of these costs must be met by the mother.

Using data from Harvey et al. (1987), \log_{10} -transformed brain weight is plotted against body weight in 25 neonatal primate species including humans (see Figure 1.4). The least squares residuals are calculated from the regression line and indicate that humans are amongst the most encephalised of the neonatal primates. Table 1.7 lists the resulting residuals.

Of the anthropoid neonatal primates in the sample, humans have one of the largest brain weight residuals (+0.126) compared with, for example, the orangutan (+0.032), gorilla (+0.077), chimpanzee (-0.098) and marmoset (+0.097). In this sample, the pig-tailed macaque (*Macaca nemestrina*) and black-handed spider monkey (*Ateles geoffroyi*) are also highly encephalised at birth. Among the strepsirrhines, the lesser bushbaby (*galago senegalensis*) is the most encephalised prosimian.

This regression analysis suggests that relative to other primate neonates of comparable body weight, humans have brains roughly 87.5 grams larger than expected at birth, about twice that of the average neonatal primate brain. Based on these estimates, the expected brain weight for a non-encephalised human is 297 g.

The human neonate cited by Harvey et al. (1987) weighed 3.3 kg and had a brain weight of 384 g (about 12% of total body mass). A reduction of 87.5 g would result in a 'non-encephalised' neonate with a brain weight of 297 g, representing only 9% of

total body mass. According to Holliday's (1986) values cited in table 1.3, an increase of 26 kcal/day is associated with the metabolic costs of this level of encephalisation.

Thus, encephalisation in the human neonate requires roughly a 6.5% increase in the brain's metabolic energy to maintain the additional 87.5 g of that tissue associated with the human level of neonatal encephalisation. Butte (1996) estimates that a newborn requires a total of about 124 kcal/kg/day to meet its basal metabolic, physical activity, thermogenic, growth and energy loss requirements. Based on these estimates, a 3.3 kg baby would require a daily total of about 409 kcal. The 26 kcal/day increased cost associated with encephalisation translates into about 6.3 % of that daily requirement.

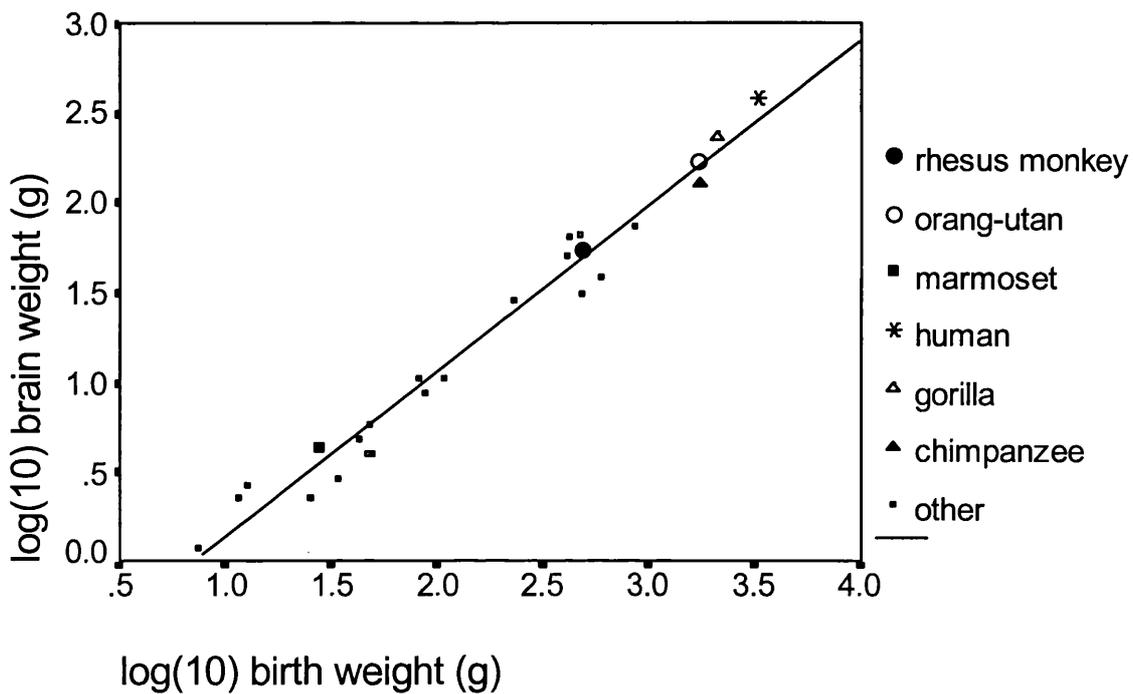


Figure 1.4. Data taken from Harvey et al. (1987). Log_{10} -transformed neonatal brain weight plotted against log_{10} -transformed neonatal body weight for primates.

The least squares equation describing this relationship is as follows:

(7) $\text{Log}_{10}(\text{neonatal brain weight in grams}) = 0.92 * \text{Log}_{10}(\text{neonatal body weight in grams}) - 0.79$
 $(r^2 = 0.971, \text{SE} = 0.291, n = 25, P = <0.0001)$

Table 1.7 Least squares residuals derived from plotting log₁₀-transformed brain weight against body weight in primate neonates

Strepsirhines	Residual	Haplorhines	Residual
<i>Lemur catta</i>	-0.062	<i>Callithrix jacchus</i>	+0.097
<i>Lemur fulvus</i>	+0.055	<i>Sanguinus oedipus</i>	-0.030
<i>varecia variegatus</i>	-0.061	<i>Callimico goeldii</i>	-0.004
<i>Lepilemur mustelinus</i>	-0.168	<i>Cebus capuchinus</i>	+0.072
<i>Loris tardigradus</i>	+0.202	<i>Alouatta palliata.</i>	-0.197
<i>Nycticebus coucang</i>	-0.171	<i>Ateles geoffroyi</i>	+0.168
<i>Arctocebus calabarensis</i>	-0.143	<i>Macaca mulatta</i>	+0.050
<i>Galago crassicaudatus</i>	-0.155	<i>Macaca nemestrina</i>	+0.140
<i>Galago demidoff</i>	+0.061	<i>papio cynocephalus</i>	-0.050
<i>Galago senegalensis</i>	+0.172	<i>Colobus polykomos</i>	-0.188
		<i>Hylobates lar</i>	+0.077
		<i>Pongo pygmaeus</i>	+0.032
		<i>Pan troglodytes</i>	-0.098
		<i>Gorilla gorilla</i>	+0.077
		human	+0.126

Residuals calculated from strepsirhine-specific and haplorhine-specific regressions in neonates. Notably encephalised individuals are highlighted.

1.7) Implications of encephalisation for this thesis

Since encephalisation in early human life poses a significant energetic burden to the growing fetus and infant, over evolutionary time, adaptations are assumed to have arisen to help support this demand. The purpose of this thesis is to examine whether the additional costs of encephalisation are met by the mother's energy supply, or rather through body composition changes or growth rate changes within the fetus and infant itself. In order to answer this question several tasks are undertaken here.

First, encephalisation is quantified in the living fetus and infant and changes in encephalisation over time are measured in order to determine patterns of encephalisation during ontogeny. Second, encephalisation is assessed relative to brain and body growth in general, and that of other metabolically expensive organs in order to determine whether encephalisation is influenced by growth and the size of other metabolically expensive organs. Third, the relationship between encephalisation and maternal variables reflecting energy supply are assessed in order to determine whether maternal energy supply is associated with offspring encephalisation.

1.8) The first law of thermodynamics

The central premise of this thesis is based on the 'first law of thermodynamics'. According to Von Helmholtz (1847), regardless of all processes in an isolated system, the energy of that system remains constant. The principles of this law imply that energy within any system cannot be created or destroyed, only redistributed in different forms. In humans, the system in question is the body and energy leaving and entering that system changes proportionately as a function of the energy stored within the system. Furthermore, the conversion of energy from one form to another within the system (i.e. the body) does not alter the total energy content of that system (Hess 1838). Therefore, energy metabolism is the overall balance between energy intake, expenditure and storage.

During pregnancy the system in question includes the mother, placenta and fetus and according to the first law of thermodynamics, the total energy content of the system is a product of energy entering the system via maternal energy intake (food) and energy stored within her body, as well as the energy expended through, thermoregulation, physical activity, basal metabolism (including that of the placenta), gravity and excretion. A balance must, therefore, be struck between the amount of maternal energy entering and leaving this system and the increased amounts of energy storage associated with fetal encephalisation, while still maintaining an appropriate energy intake given body temperature and basal metabolism.

A brief summary of the subsequent chapters in the thesis follows. These chapters include an examination of different aspects of energy balance in the human mother and offspring as it relates to brain and body maintenance, growth, body composition and encephalisation.

1.9) Summary of contents of subsequent chapters

In chapter 2, patterns and associated metabolic costs of human body growth are examined and compared with those of other primates. Similarly, chapter 3 examines the patterns of brain growth in human fetuses and infants and compares those to other primates. In addition, the costs of brain growth are quantified in chapter 3 and patterns of brain size dimorphism are described.

Chapter 4 deals with the relationship between size, growth and encephalisation in the human fetus and infant, as well as the relationship between encephalisation and somatic growth rates. It also examines the relationship between neonatal nutritional status and encephalisation and growth.

In chapter 5, maternal factors influencing offspring growth and encephalisation are examined. These include maternal body size, placenta size as well as life-history and demographic factors and indices of nutritional status. The effects on offspring

encephalisation of maternal alcohol use and smoking during pregnancy are also examined.

Chapter 6 deals with the relationship between encephalisation and the relative size of other non-brain organs in the human fetus. It tests the hypothesis that there is a trade-off between brain and non-brain organ growth.

Chapter 7 is the final chapter of the thesis and includes the conclusions and a broader discussion of findings in light of life history theory, maternal-fetal conflict theory, the Trivers-Willard Hypothesis and evidence for a functional relationship between encephalisation and 'intelligence'.

CHAPTER 2

Patterns of fetal and infant body growth

2.1) Aims of chapter

This chapter deals with general patterns of growth in fetal and infant life. It also includes a comparison of growth between humans and non-human primates and describes the data used to quantify growth in this thesis.

The chapter is divided into 3 main sections. The first includes a description of growth in fetal and infant life. Here changes in the body's chemical composition during growth are discussed and sex differences in growth velocity are discussed, as are factors which influence growth. The costs of growth in the fetus and infant are also shown.

In the next section, established methods for quantifying growth are discussed and the data used in the thesis are described. These include fetal ultrasound and infant anthropometric measures in humans, rhesus monkeys, baboons and common marmosets. The methods used in the thesis for quantifying growth are described in detail.

In the final section of the chapter, growth and growth velocity curves are constructed and sex differences assessed. In addition, human and non-human primate growth curves are compared, after controlling for gestation length differences between species. Finally, the degree of variability in growth trajectories between individuals is investigated.

SECTION I : Fetal and infant growth

2.2) Body growth

Growth is the result of a complex pattern of genetic, hormonal and environmental influences. Here, general patterns of growth in the fetus and infant are described.

2.2a) Fetal growth

During the course of 280 days of gestation, the human zygote increases in weight by a factor of several billion. From a single cell of about 1/10 of a millimeter, the complex organism develops. The first major developmental period begins during the first post-conception week with the formation and implantation of the blastocyst which consists of about 100 cells. The embryonic period occurs during the second week and lasts until about 56 post-conception days. Gastrulation (laying down of germ layers) and the formulation of the neurula (neural plate and neural tube) occur during this period, followed by differentiation of the embryo. After the completion of embryo metamorphosis, the fetal period begins and lasts from about 56 post-conception days to term. This period is marked by a very high rate of growth compared to that of the child, due largely to the rate of cell division and the fact that the proportion of cells undergoing division decreases with increasing age (Tanner 1989). Between 56-70 days after conception, the eyelids form, the gut is withdrawn into the fetus and the external genitalia differentiate.

In the second stage of fetal development, lasting from 70-140 days, the eyelids become sealed, the vertebral column starts to ossify and hair follicles are formed. The final stage of the fetal period occupies the entire second half of gestation (140-280 post-conception days), during which the fetus increases in weight from about 45 to 3500 grams. This period is one of growth and maturation of function (Southgate and Hay 1976).

During the first trimester, crown-heel length doubles approximately every 10 days from 6 to 10 gestation weeks. During this time, growth is linear and velocity increases by ~1.4 mm/week (Meire 1986).

Growth in biparietal diameter is almost linear throughout the first two trimesters of pregnancy, but during the third trimester there is a progressive reduction in biparietal diameter growth. The same is true of head volume which undergoes a marked decrease in growth velocity during the last trimester, most significant at 30 gestation

weeks. This sudden and significant slowing down of head growth does not appear to be due to placental insufficiency as abdominal growth is not affected in the same way (Meire 1986).

Briend (1979) suggested that brain growth in late gestation slows down in order to allow for passage through the birth canal in upright humans. He postulated that the pressure of the fetal head in the maternal pelvis produces growth reduction by impairing uterine blood supply. However, there is no clear physiological evidence to support his case. No reduction in uterine blood supply has been detected with modern Doppler methods in late pregnancy (Meire 1986). Therefore, it appears that the slowing down in brain growth after 30 gestation weeks may be a natural ontogenetic phenomenon in humans.

Abdominal circumference growth is similar to that of the biparietal diameter, although its reduction in late gestation is much less marked than that of the biparietal diameter. Abdominal growth velocity increases rapidly until about 30 gestation weeks, after which, in synchronism with head circumference, it slows down. At no time is the trend in abdominal circumference growth velocity negative (Meire 1986). This slight reduction in abdominal circumference growth in late pregnancy is probably due to uterine restriction (Meire 1981, Dobbing and Sands 1978, Tanner 1978).

During the last 10 weeks of intrauterine growth, the fetus lays down fat both subcutaneously and deep in the body (Catalano et al. 1998). Most of the fetal weight gain up to about 26 post-menstruation weeks is, however, due to protein accretion (Tanner 1989).

2.2b) Changes in chemical composition during fetal growth

The literature describing the chemical composition of the human fetus is far more comprehensive than at any other age. Zeigler et al. (1976) summarised body composition values for human fetuses and constructed a reference fetus of 'average' body composition. For gestational ages 24 through 40 weeks, the authors included

data on water, lipid, protein and major mineral composition. The authors showed that concentrations of water, sodium and chloride per unit of body weight decrease with increasing gestational age, while concentrations of protein, lipid, calcium, phosphorus, magnesium and potassium increase with age. Ziegler et al. (1976) then used estimates of body composition as a function of age and weight gain to determine daily increments in these body components. Table 2.1 lists the weekly increment in water, protein, lipid, minerals, carbohydrates and other undetermined body constituents in the reference fetus.

These values reveal that during the last 4 months of pregnancy, the fetus is comprised of 79, 74, 69.9 and 62.5 % water, respectively. The fetus, therefore, undergoes a steady decrease in water content. During the same period, the fetus is comprised of 7.8, 11.4, 13.9 and 19.8% lipid. An increase in protein also occurs during this period when the fetus is comprised of 10.8, 12.2, 13.3 and 13.9% protein.

Table 2.1 Weekly increment in water, lipid, protein and carbohydrates and other undetermined body constituents

age interval (weeks)	water (g)	protein (g)	lipid (g)	other (g)
24-25	82.1	10.9	4.7	2.3
25-26	79.6	10.6	7.6	2.3
26-27	78.5	10.8	8.4	2.3
27-28	77.5	11.1	9.1	2.3
28-29	76.1	11.5	10.1	2.3
29-30	74.5	12.0	11.1	2.4
30-31	73.3	12.4	11.8	2.5
31-32	72.2	12.7	12.4	2.6
32-33	71.2	13.1	13.1	2.7
33-34	70.5	13.2	13.4	2.8
34-35	69.5	13.4	14.1	3.0
35-36	68.7	13.5	14.8	3.1
36-37	67.6	13.5	15.6	3.3
37-38	64.7	13.8	18.0	3.5
38-39	59.7	14.2	22.1	4.0
39-40	51.7	14.6	28.9	4.8

Taken from Ziegler et al. (1976)

Other includes: mineral, carbohydrate and DNA

When considering the rate of protein and lipid deposition in the fetus, Widdowson and Spray (1951) showed that protein deposition is most rapid before the fetus reaches a weight of 1 kg, thereafter, the rate of deposition decreases slowly. The rate of fat synthesis in early fetal life is very low and appears to be confined to the synthesis of structural lipids involved in cell membranes and related structures. However, by the middle of gestation, the proportion of fat in the body tissues increases in an exponential manner. Dugdale (1975) showed that fat and lean tissue deposition is cyclical in nature, with early and mid-fetal life marked by lean tissue deposition. Nearer term fat deposition is, however, favored and predominates during the first few months of postnatal life. The fact that both fetal tissue solids and fat increase differentially and markedly during the third stage of gestation and infancy has clear implications for the nutritional requirements of the developing fetus (Southgate 1976).

2.2c) Infant growth

During the first year of postnatal life, body length increases by about 50% of birth values. During this time growth is episodic, increasing at times by about 0.5 to 2.5 cm in a few days or remaining stagnant for some time (Sinclair and Dangerfield 1998). Average weight at birth is 3.4 kg but is more variable than that of length. In the first two days of life, neonates generally lose up to 6.5% of their birth weight (due to the energetic costs of thermoregulation, respiration and gravity), which is completely recovered by 7 to 8 postnatal days (Fritz et al. 1985, Amit et al. 1993). Weight velocity increase is highest shortly after birth, slowing down markedly thereafter. During the first year of life, weight reaches about 3 times that at birth and 4 times that at birth by the end of the second year, thereafter slowing down. Body length follows a similar growth pattern to body weight (Sinclair and Dangerfield 1998), although there are subtle differences in when peak growth rate is achieved.

A large number of studies have described head growth in the infant. These include studies by Meredith (1971), Fujimura and Seryu (1977), Brandt (1976), Fescina and Martell (1983), Borysławski (1988), Tsuzaki et al. (1990), Cabana et al. (1993) and Guihard-Costa and Larroche (1992) amongst others.

Head circumference velocity peaks at about 31 gestation weeks (Brandt 1976, Fujimura and Seryu 1977), at about the same time as does brain weight (Cheek 1975). Head circumference growth then slows down steadily during the last 9 weeks of gestation, rising abruptly following birth. In fact, maximum head growth velocity is attained shortly after birth, perhaps in response to release from uterine restriction at birth (Fujimura and Seryu 1977). Shortly thereafter, velocity decelerates to about 2.4 cm per week. By one year-of-age, head circumference velocity is only about 0.2 cm per week (Brandt 1976).

It should be noted that although growth is often described in terms of smoothed growth curves, normal soft tissue growth fluctuates during development and progresses in cyclicities and pulsilities, with periodic spurts and troughs in growth (Bogin 1998, Hartman et al. 1993). It is not unusual for mini growth spurts to occur from week to week in lower leg length, for example (Hermanussen 1988) or as a function of season (Bogin 1998). This is due principally to fluctuations in growth hormone release (Hartman et al. 1993).

2.2d) Changes in chemical composition during infant growth

Like the fetus, growth in the infant is accompanied by changes in the body's chemical composition. Fomon (1966) and Fomon et al. (1982) have described these changes in chemical composition in the infant during the first year of life by establishing reference values for infant body composition. Infant chemical composition values were based on individual tissues.

These measures are listed in Tables 2.2 and 2.3 and show that together minerals, carbohydrates and non-protein nitrogenous compounds comprise about 2.5% of body mass in the infant throughout the first year of life. Clearly, water comprises a much smaller percentage of postnatal rather than prenatal body mass, while protein and fat comprise a greater proportion, particularly in the case of protein after 6 postnatal months. When the ratio of protein weight to water weight is calculated for the skeletal

muscle, adipose tissue, skin, bone, liver and heart, there are clear changes in the composition of these components during infant growth as shown in Table 2.3.

Protein content of skeletal muscle approaches that of the adult value by about 4 to 7 months of age. Adipose tissue, on the other hand, exceeds that of the adult during infancy, while skin protein composition is approximately that of the adult by 3 to 6 months. The protein composition of neonatal bone, liver and heart in the first year of life, on the other hand, is relatively low. It should be noted that extracellular fluid decreases rapidly during the early months of life (Cheek 1961) while fat-free adipose tissue and skeletal muscle change relatively little in water content during this period (Fomon 1966). By about 4 postnatal months, the chemical maturation of fat-free tissue (in terms of water content) is 25% that of the adult value, and 50% of the adult value by about 12 months. Thus, changes in the body composition with growth relate to underlying changes in the proportions of protein, lipid and water content.

Table 2.2 Body composition of the reference male infant

Age (mo)	weight (kg)	Percentage composition (g/100g)				fat-free body mass	
		Whole body				water	protein
		water	protein	lipid	other*		
birth	3.50	75.1	11.4	11.0	2.5	84.3	12.8
2	5.45	63.7	11.4	22.4	2.5	82.0	14.7
4	7.00	60.2	11.4	25.9	2.5	81.0	15.4
6	8.28	59.9	12.3	25.3	2.5	80.0	16.5
8	9.08	59.6	13.1	24.8	2.5	79.2	17.4
10	9.82	59.3	13.7	24.5	2.5	78.5	18.1
12	10.50	59.0	14.6	23.9	2.5	77.5	19.4

*includes minerals, carbohydrate and non-protein nitrogenous compounds

Table 2.3 Ratio of protein weight to water weight in a number of body components

tissue	Ratio weight of protein to weight of water		
	neonate	infant	adult
skeletal muscle	0.16	0.23 (4-7 months)	0.27
adipose	0.11	0.14 (2-9 months)	0.05
skin	0.20	0.51 (3-6 months)	0.48
bone	0.27	0.30 (2-4.5 months)	1.10
liver	0.18	0.20 (4-7 months)	0.25
heart	0.15	0.16 (5-7 months)	0.17

Taken from Fomon (1966) who used mean values given by Widdowson and Dickerson (1960) for the skin, bone, liver, heart, Dickerson and Widdowson (1960) for the skeletal muscle and Baker (1969) for the adipose tissue.

Adult values based on individuals between 16-86 years of age

Butte et al. (2000), in an updated body composition reference, showed that males have significantly more potassium than do females. Increased potassium is generally associated with decreased nitrogen balance in response catabolising protein during energy stress (Blackburn and Loper 1992: 362). The fact that male infants have relatively more potassium than females may imply that they undergo a greater degree of protein catabolism perhaps in response to their decreased fat stores, relative to females. Bone mineral content and total body water are also higher in boys, with the difference between the sexes generally increasing with age.

2.3) Sex differences in growth patterns

A number of components differ in their growth between the sexes. Fatness, size and shape differ between males and females. Subcutaneous fat begins to be laid down in the last trimester of pregnancy (from about 34 post-menstruation weeks) and peaks at about 9 postnatal months. Male neonates display a greater proportion of centralised fat, while females display a greater proportion of peripheral fat (Cameron, 1998). Full-term females are, on average, about 140 g lighter than males at birth (Sinclair and Dangerfield 1998). Girls, however, generally grow relatively faster than boys, reaching 50% of their adult height at about 1.75 years while boys reach their adult height midpoint at about 2 years (Tanner 1989). The difference in growth rate starts about half way through the fetal period when the skeleton is about 3 weeks more advanced in females (Tanner 1989). By birth, girls are about 4 to 6 weeks more mature than boys in terms of skeletal growth. Although boys are slightly larger than girls at birth, the difference is small and remains so until puberty.

Differences in body shape between the sexes begin *in utero*. For example, during the fetal period males have longer forearms relative to the upper arm than do females. This difference becomes more exaggerated as development progresses. This differs from leg length sexual dimorphism, where longer leg length relative to height in males is associated with a delayed growth spurt (Tanner 1986, Johnston 1998). Between birth and about 10 years of age, males and females are fairly similar in terms of their body lengths and sitting heights. Males are, however, slightly heavier and taller, but

differ in their fat/lean tissue ratio, having proportionately more lean tissue than females (Wells 2000).

2.4) Influences on growth and body composition in fetal life

Growth is largely the outcome of many genetic, hormonal, nutritional and environmental factors. It is particularly difficult to tease out the relative roles played by each of these components in growth as they often work in concert. Here some of the major factors influencing growth in general are summarised and those influences which have a stronger influence either during the fetal or infancy periods are discussed.

2.4a) Genetic and hormonal factors

Genetic factors play a crucial rôle in growth from the point of conception through to maturation. In humans, height and weight are highly correlated with parental height and weight (Tanner 1978, Byard et al. 1993). Indeed, body size and shape, deposition of fat and patterns of growth are more strongly influenced by genetics than external factors (Mueller 1986, Tanner 1989, Hauspie et al. 1994, Sinclair and Dangerfield 1998). Growth tempo, for example, is highly influenced by that of the parents, where late maturing parents tend to have late maturing offspring (Tanner 1989). However, the genetic control of growth rate appears to be independent of the genetic control of final adult size and shape (Tanner 1989). Body composition is also directly influenced by the genome. For example, Sparks (1984) has shown that genetic factors have a stronger relationship with lean (fat-free) body mass, whereas uterine environment correlates better with fetal fat mass. Genes are clearly important in determining the differences between male and female patterns of growth (Bailey and Garn 1986). Interestingly, the advanced skeletal maturation of girls over boys has been attributed to a retarding action of the genes on the Y chromosome of the male (Sinclair and Dangerfield 1998).

Hormones, largely under the control of the genes, also have a strong influence on growth. The pars intermedia of the pituitary, in particular, plays an important role in prenatal growth due to its involvement in the production of growth-stimulating androgens. After birth, the interaction of pituitary growth hormone and the insulin-like growth factors regulate linear growth. Thyroid hormones (thyroxine and triiodothyronine) regulate the rates of skeletal, brain and dental maturation and insulin derived from the pancreas regulates changes in cell size (hypertrophy) (Johnston 1998, Sinclair and Dangerfield 1998). After the first year of life, polypeptide growth hormone (hGH) becomes the predominant controller for the overall rate of growth and development by maintaining the rate of protein synthesis and fat breakdown for use as energy. Insulin-like growth factors or somatomedins and insulin also stimulate protein synthesis and depress protein breakdown when necessary. Also important regulators of growth are the steroids produced by the adrenal glands. At low levels, oestrogens stimulate growth and glucocorticoids activate cell division.

It has been well established that growth patterns vary significantly across ethnic groups, in response to genetic variation, and also in response to environmental effects. A number of parameters are particularly varied: fetal weight and the growth rate of the abdominal circumference (Meire and Farrant 1981, Parker et al. 1982), whole body bone mineral content, relative lean mass, height, ratio of bone mineral content to height, fat mass (Nelson and Barondess 1997), triceps and subscapular skinfold thicknesses, sitting height (Hamill et al. 1973, Malina et al. 1974, Norgan 1999, Eveleth and Tanner 1990) and growth rate (Sinclair and Dangerfield 1998). It is difficult to clearly differentiate between genetic and environmental effects in this context, and it is likely that both are factors in ethnic variation in growth patterns.

In addition to genetic influences, a number of maternal factors influence fetal growth. These include the mother's nutritional status, the health of her placenta and her parity, age and lifestyle.

2.4b) Maternal influences on fetal growth

Maternal nutritional status has a strong effect on fetal growth as demonstrated during the Dutch famine of 1944-1945. Here nutritional deprivation in women during early pregnancy resulted in a higher rate of prematurity and low birth weight, while nutritional deprivation in late gestation resulted in about a 9% reduction in fetal weight but not length (Stein and Susser 1975, see also Catalano et al. 1998). In addition, Antonov (1947) has shown that during the 1942 siege of Leningrad, where maternal nutrition was inadequate prior to conception, a reduction in neonatal birth weight resulted.

It is known that a number of additional maternal factors have an effect on offspring birth weight. For example, maternal pregravid weight (Eastman and Jackson 1968), maternal weight gain during pregnancy (Humphreys 1954, Abrams and Laros 1986), and maternal parity and age (where increased parity and age are associated with an increase in offspring birth weight) (McKeown and Gibson 1951, Thompson et al. 1968, Seidman et al. 1988). Parity is associated with a mean 100-150 gram increase in subsequent pregnancies, however, the added effect of parity on birth weight is diminished with increasing parity (Thompson et al. 1968).

In addition to maternal nutritional status, parity and age, maternal smoking and alcohol use influence fetal growth. Cigarette smoking and alcohol intake during pregnancy are associated with abnormal growth in length, weight and head circumference as well as teratogenic effects on the developing brain (Abel 1984, Chiriboga, 1993, Landzelius 1998, Schell 1998). Diminished lean body mass in the neonate occurs as a result maternal cigarette smoking. In general, the negative effects on growth are dose-dependent and result from impaired fetal oxygenation. This hypoxia results in intra-uterine growth retardation which leads to a proportionate decrease in weight and length. Interestingly, smoking during pregnancy is not associated with a reduction in placental weight (Wilson 1971), but rather with a decrease in placental uptake and transport of nutrients (Goldberg 1998b).

The placenta plays a central role in fetal growth. Humans have a hemochorial, rather than epitheliochorial placenta. As such, the placenta gains direct access to maternal circulation by invading the uterine vasculature. Placenta weight is associated with several factors, reflecting the nutritional status of the mother and affecting that of the fetus. Small placenta weight, for example, is associated with low maternal pregravid weight and low pregnancy weight gain. These factors are associated with low maternal gestational blood volume expansion and, therefore, low blood flow from the uterus to the placenta. Consequently, the major risk associated with small placenta weight is fetal growth retardation (Gluckman and Liggins 1984) and low birth weight (Alexander 1964, Owens et al. 1986). Small placentas are also associated with increased frequency of stillbirth, mental retardation and fetal malformation. Unusually high placenta weight, in contrast, is often associated with maternal diabetes mellitus, severe maternal anemia, fetal anemia, villous edema and a number of associated disorders such as fetal hypoxia and neonatal respiratory distress (Owens and Robinson 1988). Placental notching results in decreased uterine blood flow and is associated with intrauterine growth retardation and increased incidence of pre-eclampsia (Bower et al. 1993, Antsaklis et al. 2000, Aquilina et al. 2000).

Generally, large neonates have large placentas (Thompson et al. 1969), however, if maternal iron deficiency occurs, then neonatal birthweight tends to be relatively lower given present placental weight (Godfrey et al. 1991).

The placenta does not only have a direct effect on fetal nutrition and growth, it also directly affects maternal physiology, by releasing hormones directly into the maternal blood supply (Dennefors et al. 1982). Human placental lactogen (hPL), for example, enters the maternal blood stream and acts to subvert normal responses to human growth hormone (hGH), thereby increasing the supply of nutrients to the fetus (Haig 1993).

Because maternal factors have a strong bearing on fetal growth, it is important, for the purposes of this thesis, to evaluate the relationship between these maternal factors and offspring brain size, growth and encephalisation. In chapter 5 the relationships between maternal nutritional status, age, parity, socio-economic status, cigarette and

alcohol use, as well as placenta weight are evaluated in relation to offspring size, growth and encephalisation.

The developing fetus requires energy from the mother in order to grow. Conflict between mother and fetus is predicted to arise over energy resources, particularly during later gestation, when the placenta is large and maternal fat and protein stores are increased. Maternal-fetal conflict arises due to the different selection pressures acting on the fetal and maternal genotype. Because the fetus shares only 50% of the mother's genes, her inclusive fitness and that of the fetus differ. The fetus is predicted to always attempt to obtain more energy than the mother is selected to give. This may have an impact either on her future reproductive potential, or on her probability of survival into the future (Trivers 1974, Moore and Haig 1991, Haig 1993).

Maternal-fetal conflict theory is particularly interesting in light of fetal encephalisation, since increased fetal brain tissue is assumed to be associated with increased maternal-fetal conflict over energy. This phenomenon is explored in detail in chapter 5 where the relationship between fetal encephalisation and maternal indices reflecting energy availability to the mother are assessed (e.g. measures of maternal nutritional status, fat tissue and lean tissue).

2.5) Influences on infant growth

A number of factors influence growth during infancy, including nutrition, illness and disease, socio-economic status, physical activity, external temperature, altitude and seasonality.

2.5a) Nutrition

There is much evidence suggesting that malnutrition delays growth, however, providing the episode is not overly acute and long-lasting and does not occur during a critical period of development, catch up growth generally occurs (Norgan 2000).

Chronic undernourishment in childhood, on the other hand, generally results in smaller adult size. The tempo of growth is generally affected first by slowing down (Tanner 1989), thus adult size is usually affected by undernutrition. Leg length relative to trunk length may also be affected (Billewicz et al. 1983). Barker et al. (1997) have shown that body composition may also be affected by early undernutrition where low birth weight is associated with increased centralisation in fat deposition in adolescence. Similarly, Yajnik (2000) has shown that early malnutrition is associated with preserved fat but depleted lean tissue deposition. In addition, Leitch (1951) and Victora and Barros (2001) argue that low birth weight and early malnutrition with subsequent 'catch up' growth may result in stunting and obesity (depending on the timing of 'catch up' growth).

Infant nutritional status may be influenced by feeding mode (Dewey et al. 1993), having further implications for growth. Neonatal growth rate in mammals is highly correlated with the composition (amounts of protein and ash) of the mother's milk (Forbes 1983). Growth factors⁴ and hormones found in breast-milk become absorbed in neonatal circulation and affect the growth of tissues such as the gastrointestinal epithelium. Breast milk, on average, provides between 70-80 kcal/100 ml (Macy and Kelly 1961, McCance and Widdowson 1967, Fomon 1974) and has a relatively high concentration of fat in the form of lipoprotein cholesterol (4.2 g/100 ml of breast-milk according to the DHSS 1988). Of this, about 58 kcal/100 ml is utilised by the infant (Lucas and Davies 1990). The amount of fat in the infant's diet is a major determinant of energy availability and hence growth rate, and it is also correlated with the level of vitamins in the diet.

In addition, infants receive long-chain polyunsaturated fatty acids such as arachidonic and docosahexanoic acids through breast-milk. These long chain fatty acids are crucial for development of the central nervous system and are particularly important for humans who have relatively large brains compared to mammals of comparable body size (Horrobin 1998). Prentice and Collinson (2000) also suggest that the higher

⁴ Growth factors found in breast milk include: Epidermal growth factor, transforming growth factor α insulin, insulin-like growth factor I and II, insulin-like-growth-factor-binding globulins 1,2 and 4.

concentration of long-chain fatty acids in breast-milk (over formula) may explain why thymus size (measured sonographically) is generally larger in breast-fed infants rather than formula fed infants. The authors suggest that increased thymic size and corresponding autoimmunity would be in line with the reported immunological effects of breast-feeding. In addition, iron, in the form of lactoferrin (Binns 1998a) and sodium, which stimulates cell proliferation and protein synthesis, are easily absorbed from breast-milk.

However, by the age of 4-6 months, breast-milk no longer provides sufficient energy to support infant growth. At this stage, additional weaning food may be required in order to meet nutritional demands (Binns 1998a). The WHO, however, now advises that breastfeeding continue to 6 months.

2.5b) Illness and disease

Infection has a strong impact on nutritional status since it is associated with reduced appetite and digestive losses (Scrimshaw et al 1968, Briend 1998, Ulijaszek 2000). The prevalence of diarrhea in developing countries, in particular, has led researchers to argue that it may have a very strong influence on growth retardation (Rowland et al. 1977). More recent work, however, has suggested that 'catch up' growth following infection occurs and does not require excessive amounts of increased energy intake (Lutter et al. 1992), nor is there any clear evidence for reduced food intake or loss of micronutrients and protein in the stool (Lutter et al. 1992, Dickin et al. 1990, Briend 1998). However, tuberculosis, kidney disease, cerebral palsy and cystic fibrosis all have effects on growth similar to those of malnutrition, while asthma is associated with a delay in puberty. In asthmatic children, final height is, however, usually within normal range (Sinclair and Dangerfield 1998).

2.5c) Socio-economic status

Nutritional status is often associated with socio-economic status and social status has a strong influence on growth and maturation. For example, children from higher social strata tend to be taller than those from lower strata. They also mature earlier, attaining puberty sooner. Menarchal age is another parameter which reflects social status influences. It increases with increasing number of children in the family and with decreasing levels of parental education (Sinclair and Dangerfield 1998). Likewise, secular trends in stature (particularly due to increases in leg length) and accelerated maturation in 20th (and 21st) century industrialised societies reflect the overall improvement in nutrition and reduction in morbidity in these societies (Eveleth and Tanner 1990, Bielicki 1999).

2.5d) Environmental factors

In addition to the social environment, the geographical environment may influence growth. For example, altitude has a strong effect on growth rate and body size. Children living at high altitudes tend to grow more slowly and are smaller than those living at lower altitudes. This is the result of generalised hypoxia, resulting from low oxygen pressure in the atmosphere. Although the body does increase its lung capacity and the production of red blood cells in an attempt to increase oxygen transport from the lungs to the tissues (Greska 1990), this cannot fully counter the effects of low oxygen pressure (Sinclair and Dangerfield 1998). A large number of studies have been carried out amongst high altitude populations documenting these growth processes which result in reduced adult stature (Pawson 1977, Frisancho 1978, Beall 1981). High altitude also affects prenatal growth where reduced oxygen delivery to the fetus results in a mean reduction in birth weight of about 400 grams in high altitude neonates (Frisancho 1993, Moore 1990).

Temperature and seasonality also influence growth. Fujimura and Seryu (1977) have shown that exposure to sub-thermoneutral temperature is associated with retardation of head growth in early life. In addition, it has been hypothesised that heat stress may have an adverse affect on growth in early life (Wells 2000, 2001). Based on the findings of Bergmann (1847) and Allen (1877), it is well accepted that surface area to

body mass ratio has a strong influence on heat loss capacity. In hot and humid environments, surface area to body mass is generally greater than in temperate environments, allowing for more efficient heat loss. Wells (2000) pointed out that adult stature is the product of previous growth and is largely varied in response to environmental rather than genetic factors (Habicht et al. 1974). In populations with significant heat stress, pregnant women tend to produce low birth weight neonates (Wells and Cole 2002). Wells (2002) argued that adaptations to heat stress include reduced body size and fatness, low pregnancy weight gain and an associated reduction in basal heat production. In addition, decreased placenta weight occurs in animals exposed to heat stress and may give rise to fetal growth retardation. Wells (2002) argued that this growth retardation may be adaptive in that it increases the surface area: mass ratio, thereby increasing heat dissipation in both the mother and fetus whilst also reducing heat production. He argued, therefore, that reduced growth in early life may be an adaptive, phenotypic response to heat stress.

Likewise, Sinclair and Dangerfield (1989) have argued that changes in temperature, sunlight exposure and rainfall (seasonality) tend to be associated with changes in food availability and nutritional stress, while sunlight exposure is also associated with vitamin D3 availability for synthesis for bone growth (Sinclair and Dangerfield 1998). In addition, seasonality has a strong influence on growth rates. For example, Xu et al. (2001) have shown in a sample of 4128 infants aged 1-24 months in Shanghai, China that growth is faster in height in spring and summer, and faster in weight and BMI in autumn and winter, with the seasonal effect on weight gain and length gain largely independent. Xu and colleagues found that the mean length value at 1 month of age was about 2.0 cm higher in infants born in spring and summer than in those born in autumn and winter. At 24 months of age this difference was reduced to about 0.7 cm. Thus longitudinal growth is fastest during the warm months and children tend to fill out during the cooler months.

Since nutritional status is central to infant growth, later in this chapter the relationship between infant nutritional status and the size and growth of the body and brain is assessed.

2.6) Energetic costs of growth

One of the primary factors determining the rate of growth is the amount of energy available to the individual. Energy is required for the synthesis of new tissue and is deposited within the tissue. Lean and adipose tissues store different densities of energy. Per gram of lean tissue, about 1.4 kcal are stored, while per gram of adipose tissue, about 8.5kcal are stored (Jackson et al 1977, Jackson and Wootton 1990).

The costs of growth not only include the energy content of new tissues but also the costs of synthesising those tissues. The energetic cost of synthesising fat is 2.38 kcal for each 1 kcal deposited, while the cost of synthesising protein is 1.17 kcal for each 1 kcal deposited (Roberts and Young 1988).

2.6a) Costs of growth in infancy

Table 2.4 lists the estimated energy costs of growth during the first year of life and differentiates between the costs of depositing lean and fat tissue. These values are compiled by Butte (1996) and are based on Fomon et al.'s (1982) values reported for rates of weight gain and rates of fat and protein deposition.

These estimates show that the rate of weight gain decreases with age, as does the energy cost of growth per kilogram of weight gained. During the first three months of life, growth requires between 30-42 kcal/kg/day. This cost is reduced to about 4 kcal/kg/day by 1 year of age. In contrast, protein deposition remains fairly constant during the first year while fat deposition decreases gradually. The associated costs of depositing fat exceed those of depositing lean tissue, due to the higher energy content of fat.

During the fetal period, the costs of growth are influenced by different rates of protein and fat deposition. Prior to mid-gestation, significant amounts of fat deposition do not

occur (Widdowson and Spray 1951, Dugdate 1975), since growth is largely due to protein deposition.

After birth, the estimated overall cost of growth is 4.8 kcal/g of tissue (Butte et al. 1989). As a percent of total energy requirements, growth utilises between 35% at 1 month and 3% at 1 year-of-age (based on total energy requirement values given by Butte et al. 1989). Wells and Davies (1998) have shown that after determining the costs of fat and protein storage and synthesis, the costs of growth in infancy range from about 204 kcal/day at 6 weeks to about 48 kcal/day at 1 year-of-age. Growth in early life, therefore, imposes a significant energetic impact on the individual.

2.6b) Modeling the costs of growth in the fetus

The costs of fetal growth are estimated by calculating the increments in body weight, fat and protein from about 24 gestation weeks to term. These values are given by Ziegler et al. (1976) and are cross-sectional. Estimated costs are calculated using Roberts and Young's (1988) values for the costs of fat and protein synthesis and deposition (fat = 9.25 kcal/g and protein = 5.65 kcal/g). Table 2.5 lists the estimated costs of fetal growth from 24 gestation weeks to term.

These estimates show that the costs of depositing and synthesizing fat increase rapidly near term while the costs of depositing and synthesising protein increase more gradually. Near term, the average cost of growth is about 53 kcal/kg/day, almost 30% greater than at 24 gestation weeks. Fetal growth costs, therefore, increase during gestation, reaching their zenith near term and then gradually decrease as shown by Butte (1996).

Table 2.4 Energy costs of growth during infancy

age	weight	weight	fat deposition		protein deposition		fat	protein	total cost of	
(months)	(kg)	gain	g/day	kcal/day	g/day	kcal/day	synthesis	synthesis	energy	growth
		(g/day)					(kcal/day)	(kcal/day)	kcal/day	kcal/kg/day
Boys:										
0-1	3.80	29	6	56	4	21	10	29	115	30
1-2	4.75	35	14	130	4	20	23	27	201	42
2-3	6.60	30	13	119	3	17	21	23	181	32
3-4	6.35	21	8	77	2	13	14	18	121	19
4-5	7.00	17	6	51	2	11	9	16	87	12
5-6	7.55	15	4	38	2	11	7	16	72	9
6-9	8.50	13	2	17	2	11	3	16	46	5
9-12	9.70	11	1	9	2	10	2	14	35	4
Girls:										
0-1	3.60	26	6	52	3	19	9	26	105	29
1-2	4.35	29	13	118	3	16	21	22	177	41
2-3	5.05	24	10	93	3	15	16	20	145	29
3-4	5.70	19	7	68	2	12	12	16	108	19
4-5	6.35	16	6	55	2	11	10	15	90	14
5-6	6.95	15	5	45	2	11	8	15	79	11
6-9	7.97	11	2	16	2	10	3	14	43	5
9-12	9.05	10	1	11	2	10	2	13	36	4

From Butte (1996)

Table 2.5 Estimated costs of fetal growth

age (GW)	weight (g)	weight gain (g/day)*	fat gain g/day	deposition‡ kcal/day	protein gain g/day	deposition‡ kcal/day	fat synthesis† (kcal/day)	protein synthesis† (kcal/day)	cost of growth (kcal/day)	cost of growth kcal/kg/ day
24-27	578									
28-31	1181	21.5	1.82	16.8	2.0	11.3	3	16	47.1	39.9
32-35	1735	19.8	1.86	17.2	2.3	13	3	18	51.2	29.5
36-39	2633	32.1	7.26	67.2	4.5	25.4	11	35	138.6	52.6
40-42	3104	22.4	0.0	-	3.0	16.7	-	23	39.7	12.8

GW = gestation weeks

based on values given by Ziegler et al. (1976) for 22 fetuses

*increase in weight between measurement periods divided by 28 and by 21 at gestation week period 40-42

‡deposition costs = fat = 9.25 kcal/g and protein = 5.65 kcal/g (Roberts and Young 1988)

†synthesis costs = protein = 2.38 kcal/g and fat = 1.17 kcal/g (Roberts and Young 1988) calculated by multiplying 0.17 by kcal deposited for fat and 1.38 by kcal deposited for protein

2.7) Human growth in comparison to non-human primate growth

Gompertz or logistic curves are often used to describe the human growth curve (Laird 1965, Zeger and Harlow 1987, German et al. 1994, Humphrey 1998, Luecke et al. 1999). The Gompertz model (Gompertz 1825) was first proposed in 1825 as a law of human mortality showing that, 'the average exhaustion of a man's power to avoid death is such that at the end of equal infinitely small intervals of time, he loses equal proportions of his remaining power to oppose destruction'. The model was later applied as a growth model by Sewell Wright in 1926. The Gompertz model is sigmoid in nature and is of the form:

$$(7) \quad d\log y/dt = (dy/dt)/y = \alpha e^{-kt}$$

where $d\log y$ is the rate of change in relative size (y), as a function of time (t), α is the intrinsic growth rate and k is the rate of decay, t = time (age). The exponent (e) is usually fixed at 1 or is variable. The Gompertz curve has two asymptotes, an upper and lower, and is asymmetric about its inflection point which is closer to the lower rather than upper asymptote.

The logistic model was first proposed by Verhulst (1838) as a model describing growth in the chemistry of cells. It was later applied to growth modeling by Robertson (1923). The logistic model also has a lower and upper asymptote but, unlike, the Gompertz model, it is symmetric around the inflection point. The model is of the form:

$$(8) \quad d\log y/dt = \alpha(1-y/k)$$

where α is the initial growth rate and k is the upper limit of growth, dt = change in age (time), y = size.

Human growth includes a high growth rate immediately after birth followed by rapid deceleration until three years of age. A period of slower deceleration in growth rate then occurs until puberty where there is a marked growth spurt, occurring earlier in females. Growth decelerates thereafter.

It has long been recognised that humans are an altricial species and growth is prolonged in comparison to other mammals (Schultz 1956, Gould 1977), yet the biological mechanisms underlying the delay in maturation are still debated. Some researchers argue that all developmental stages are prolonged (Schultz 1956, Gavan and Swindler 1966) while others argue that specific developmental stages are prolonged (Periera and Altmann 1985, Watts 1986). Laird (1967) and Bogin (1997), on the other hand, argue that a childhood period is inserted into the human growth process, thereby delaying maturity. Gavan and Swindler (1966), in contrast, argue that a pubertal growth spurt is inserted into the human growth curve. Regardless, it is clear that growth is relatively slow in humans and maturation relatively delayed when compared to other mammals.

The primate order is generally associated with slow growth compared to other mammals, perhaps due to the energetic demands of having a big brain and long lifespan (Charnov 1993a,b; Shea 1998). Most non-human primates are precocial, however, the variation in species' growth curves are marked. For example, as a function of age, Callitrichid growth may be described by a decelerating exponential curve. The lemur and gorilla growth curves, on the other hand, are described by a sigmoid curve. Macaque growth is described as linear, while human and chimpanzee growth curves are both complex. In the case of humans, they are often described as asymptotic (Kirkwood 1985, Shea 1998).

The adolescent growth spurt found in humans is not found in all primate species. For example, the common marmoset (*Callithrix jacchus*) has no growth spurt (Neubert et al. 1988), nor does the female baboon (*Papio papio*). The male baboon does undergo a pronounced growth spurt at 5 years of age. In contrast, both male and female colobus monkeys (*Colobus guereza*) undergo weight growth spurts, although the female growth spurt occurs earlier than that of the male and to a lesser degree (Shea 1998). Male mandrills also undergo a subadult growth spurt which is more dramatic in males than females (Setchell et al. 2001). There is also evidence for a slight adolescent growth spurt in the rhesus monkey for weight and sitting height (Tanner 1962, Ulijaszek 2002). Growth studies on the squirrel monkey (Kaack et al. 1979) and howler monkey (Malinow et al. 1966) show no indication of a growth spurt.

Iwamoto (1998), however, found evidence for a weight growth spurt in chimpanzees, at about 1 year-of age and then again at about 7 ½ years. However, using longitudinal data, Gavan and Swindler (1966) and Gavan (1971) failed to show an adolescent growth spurt in linear dimensions in the chimpanzee.

The rate of growth, or growth velocity varies between primates. Generally, folivorous primates display more rapid growth than frugivorous and omnivorous primates of comparable body size, perhaps due to reduced competition for resources. The accelerated growth rates found in marmosets and tamarins, on the other hand, are associated with their rapid reproductive turnover rather than diet (Leigh 1994).

Gavan and Swindler (1966) showed that rhesus monkey growth rate exceeds that of the chimpanzee immediately following birth, but is comparable to that of the chimpanzee by 1 ½ years. Humans grow at the same rate as chimpanzees up until puberty, when humans undergo the growth spurt.

Not only does the rate of growth vary amongst primates, but the duration of growth to sexual maturity also varies, both *in utero* and postnatally. Table 2.6 lists the proportion of total lifespan spent as a fetus, infant, juvenile and adult in 17 primate species, including humans. These values are taken from Joffe (1997) and are based on life-history data published by Clutton-Brock and Harvey (1985), Napier and Napier (1985), Harvey et al. (1987). Figures 2.1 to 2.3 are bar graphs depicting these data in the prosimians, simians and apes in the sample.

It must be noted, however, that these data are not derived from primary sources but are compiled by the aforementioned authors. They do not, therefore, include the thesis author's own selection criteria. By their very nature they are 'noisy' data, collected by a number of observers, under differing conditions, with different selection criteria. In addition, they are often mean values for a species and may not reference sex. They are, however, used here merely to highlight the stark contrast between these human and non-human primate life-history parameters.

Table 2.6 Proportion of lifespan spent as an infant, juvenile and adult in primates

species	fetal	infancy	juvenile	adult	% life spent growing
prosimians:					
<i>Microcebus murinus</i>	0.011	0.007	0.044	0.949	5
<i>Lemur fulvus</i>	0.010	0.012	0.015	0.973	3
<i>Perodicticus potto</i>	0.053	0.041	0.119	0.787	21
<i>Galago crassicaudatus</i>	0.025	0.016	0.050	0.933	7
<i>Galago demidoff</i>	0.022	0.009	0.039	0.952	5
<i>Galago senegalensis</i>	0.021	0.013	0.022	0.965	4
simians:					
<i>Callithrix jacchus</i>	0.034	0.014	0.069	0.917	8
<i>Cebuella pygmaea</i>	0.037	0.025	0.175	0.800	20
<i>Callimico goeldii</i>	0.029	0.020	0.059	0.921	8
<i>Alouatta palliata</i>	0.039	0.133	0.156	0.712	29
<i>Cercocebus albigena</i>	0.023	0.027	0.163	0.810	19
<i>Miopithecus talapoin</i>	0.020	0.022	0.157	0.821	18
apes:					
<i>Hylobates lar</i>	0.018	0.063	0.222	0.714	29
<i>Gorilla gorilla</i>	0.018	0.110	0.055	0.835	17
<i>Pan troglodytes</i>	0.014	0.090	0.131	0.779	22
<i>Homo sapiens</i>	0.012	0.033	0.242	0.725	28+

from Joffe (1997)

% life spent growing = total lifespan (including gestation) minus adulthood period
 humans continue to grow following sexual maturity

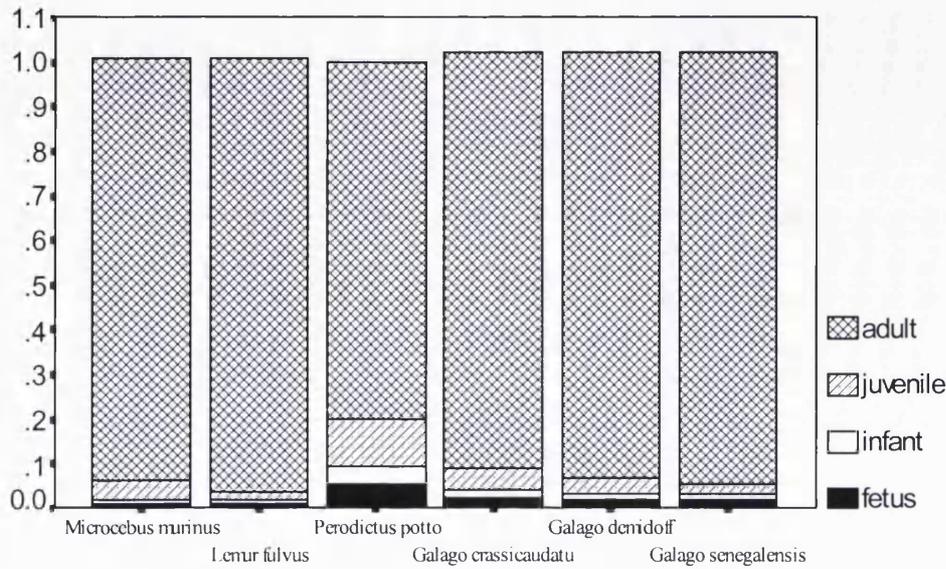


Figure 2.1 Bar graph of fetal, infancy, juvenile and adulthood periods as a proportion of total lifespan in prosimians. Taken from Joffe (1997), based on data provided by Clutton-Brock and Harvey (1985), Napier and Napier (1985), Harvey et al. (1987).

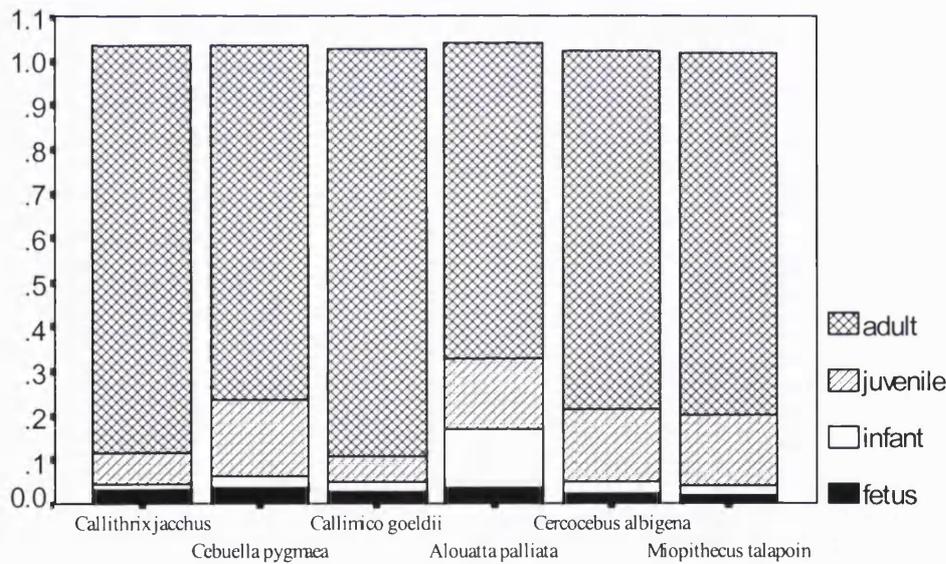


Figure 2.2 Bar graph of fetal, infancy, juvenile and adulthood periods as a proportion of total lifespan in simians. Taken from Joffe (1997), based on data provided by Clutton-Brock and Harvey (1985), Napier and Napier (1985), Harvey et al. (1987).

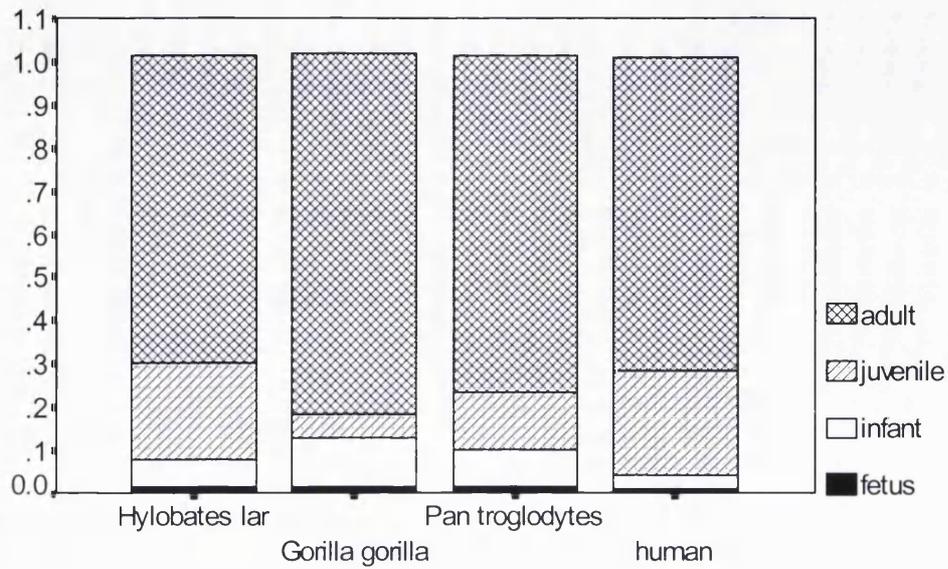


Figure 2.3 Bar graph of fetal, infancy, juvenile and adulthood periods as a proportion of total lifespan in apes, including humans. Taken from Joffe (1997), based on data provided by Clutton-Brock and Harvey (1985), Napier and Napier (1985), Harvey et al. (1987).

Humans spend about 28% of their lives growing to sexual maturity. This is not, however, uncommon. Several other primate species spend over 1/5th of their lives growing to sexual maturity, including a prosimian species, *Perodicticus potto*. The potto's fetal, infancy and juvenile periods are all proportionately longer than the other prosimians in the sample. Similarly, *Alouatta palliata* spends almost 30% of its life growing to sexual maturity, in its case, having an extended infancy period relative to the other monkeys in the sample. The proportion of time that humans spend as fetuses, infants and juveniles is remarkably similar to that of *Hylobates lar*, when controlling for lifespan differences.

No statistically significant relationship between body weight and the percent of life spent growing to sexual maturity was found for prosimians and simians+apes analysed separately and for the total sample. Figure 2.4 is a scatterplot of the percent of life spent growing plotted against body weight (in females). The plot demonstrates that no clear relationship exists between these two parameters. Nor was any statistically significant relationship found between the percent of life spent growing and with encephalisation. This is demonstrated in Figure 2.5 which is a scatterplot between percent of life spent growing and encephalisation values. In Figures 2.5 there is no statistically significant relationship between variables on the x- and y-axes.

Thus, even when considering our size and relative brain size, humans do not appear to differ significantly from other anthropoid primates in the proportion of life spent growing to sexual maturity, we differ rather in continuing to grow following sexual maturity (the pubertal growth spurt) and in the way in which that growth time is divided: into fetal, infancy, childhood and adult periods. Joffe (1997) has shown that humans have an extended juvenile period compared to other primates after controlling for phylogenetic relatedness.

Life history theory predicts that in species with high mortality rates, selection will favor rapid growth and early reproduction. In species with low mortality rates, growth may be slow and delayed reproduction may follow (Charnov 1990, 1993a). Slow growth results in an extended sub-adulthood period when social and ecological skills may be acquired. Acquisition of knowledge about social rank, dominance,

reconciliation, alliance formation, as well as fighting and sexual skills are all acquired during sub-adulthood, as are foraging skills (Mori 1974, Levy 1979, Watts 1988, Cords and Aureli 1993, De Waal 1993, Watts and Pusey 1993, Janson and van Schaik 1993). In addition, Janson and van Schaik (1993) have argued that the slowing down of growth in primates is adaptive in that it is associated with reduced competition during adolescence.

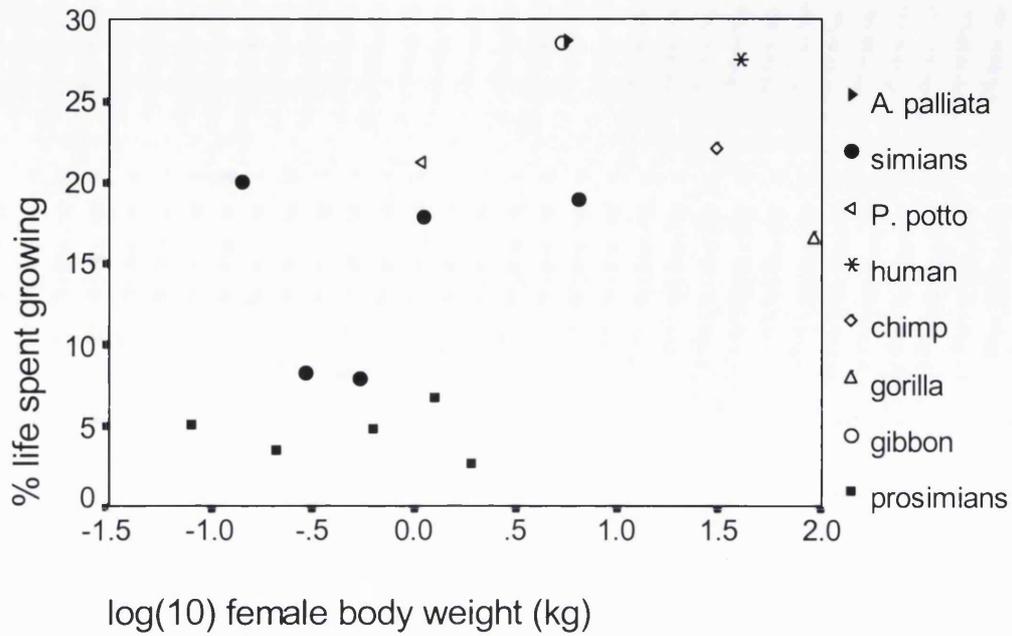


Figure 2.4 Scatterplot of the percent of life spent growing plotted against log₁₀-transformed adult female body weight (kg).

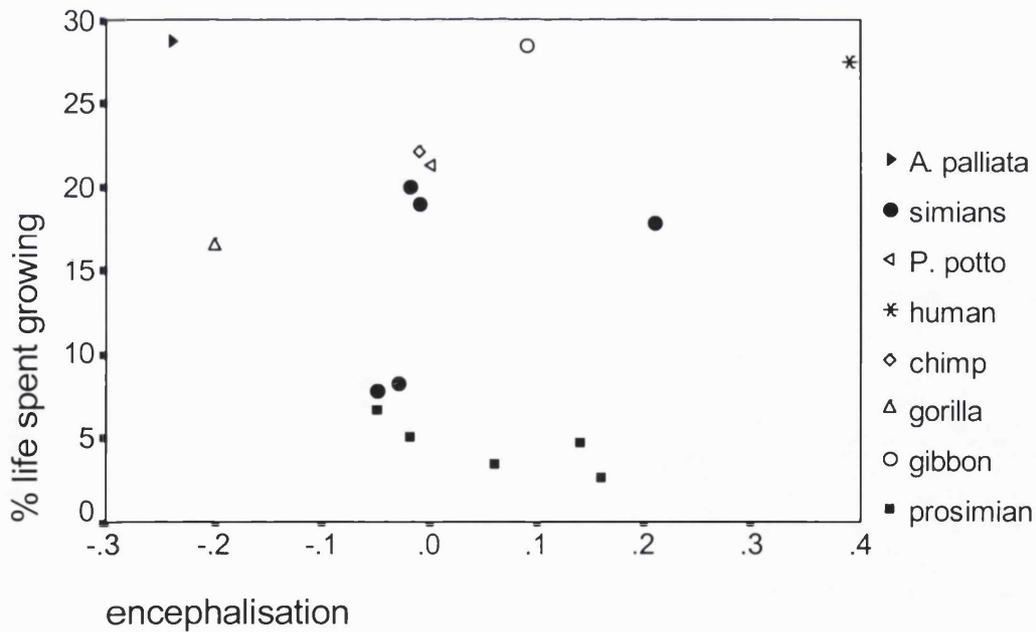


Figure 2.5 Scatterplot of the percent of life spent growing plotted against brain weight residuals taken from Table 1.2. Residuals are strepsirhine and catarrhine-specific and are calculated by plotting log₁₀-transformed brain weight against body weight.

A number of studies on non-human primate fetal growth have also been carried out. For example, Kerr et al. (1969) and Kerr et al. (1972) quantified growth in the rhesus macaque (*Macaca mulatta*) and Tarantal and Hendrickx (1988) quantified growth in the crab-eating macaque (*Macaca fascicularis*). Tame et al. (1998) quantified fetal baboon growth in the second half of pregnancy and Seier et al. (2000) assessed growth in the vervet monkey (*Cercopithecus aethiops*). Corradini et al. (1998) studied prenatal growth in the capuchin monkey (*Cebus apella*).

Together, these studies show that fetal head circumference and femur length growth trajectories differ in that the femur growth trajectory approaches a linear line, while the head circumference trajectory is curvilinear, with growth slowing down prior to birth.

While many more studies have been published on postnatal growth in non-human primates, growth is generally described as the change in weight over time. Few studies include measures of both head circumference and body growth, with the exception of Kaack et al. (1979) for squirrel monkeys (*Saimiri sciureus*), Zlámalová et al. (1995) for rhesus monkeys (*Macaca mulatta*) and Scheffler and Kerr (1975) for the stump-tailed macaque (*Macaca arctoides*). However, because few authors publish the measurements of the animals, it is not possible to directly compare the growth trajectories of these species. While some researchers do measure the width of the head or the breadth of the head, others may only report head circumference measures.

This points to a fundamental problem in that standards have not been established for measuring and reporting specific biometric components in primate species. This means that researchers cannot rely on standard biometric indices being reported in published studies representing different species, which then may be of little use for quantifying cross-species differences in specific aspects of growth.

SECTION II: Quantifying growth

2.8) Previous work quantifying human growth

Between 1759 and 1777, Count Philibert de Montbeillard undertook a longitudinal study of his son's growth from birth to 18 years-of-age. He measured height and calculated height gain as a function of age. For the first time, the existence of a pubertal growth spurt, as well as seasonal changes in growth rate, were established. In many ways, de Montbeillard's study has set in motion centuries of careful auxological study in an attempt to quantify and describe the complex nature of human growth.

A great many studies have been undertaken on normal growth during early life (see for example, Tanner and Whitehouse 1959, Schultz et al. 1961, Meredith 1971, Brenner et al. 1976, Roberts and Thomson 1976, Meire 1981, Deter et al. 1982, Forbes 1983, Fescina and Martell 1983, Falkner and Tanner 1986, Meire 1986, Tanner 1986, Yudkin et al. 1987, Cole et al. 1990, Eveleth and Tanner 1990, Guihard-Costa and Larroche 1992, Cabana et al. 1993, Altman and Chitty 1994a,b,c,d; Guihard-Costa and Larroche 1995, Bertino et al. 1996, Sinclair and Dangerfield 1998, Ulijaszek et al. 1998, Wright et al. 2002), and in preterm infants (Gairdner and Pearson 1971, Lucas et al. 1986).

A number of these are of particular interest here as they quantify growth during the fetal and infancy periods and provide the methodological basis for quantifying size and growth in this thesis.

2.8a) Fetal growth references

Kurmanavicius et al. (1999a,b) published growth reference charts for fetal abdominal circumference, femur length and head circumference between 12 to 42 gestation weeks using ultrasound. These charts are based on 6557 pregnancies and resulted in a total of 5462 head circumference measures, 5807 abdominal circumference measures and 5860 femur length measures. Small-for-date babies as well as premature babies were, however, included in the sample. The authors expressed size as a function of age in percentiles and SD scores. SD scores are calculated as the difference between the observed value and the mean value (from the fitted line) divided by the standard

deviation of the fitted line. This is common practice in growth referencing and allows size to be compared at different developmental periods.

Although Kurmanavicius et al. (1999a,b) were able to quantify changes in head size and body size (abdominal circumference and femur length), controlling for changes in age, they did not quantify the relationship between head and body size, nor did they scale for body size affects on head size, both of which are important for quantifying encephalisation.

The same is true of Altman and Chitty (1994a,b,c,d,) in a study of 644 fetuses, also using ultrasound. The authors successfully established a growth reference for fetuses from 12 to 42 weeks for head size, femur length and abdominal measurements. Unlike Kurmanavicius et al. (1999a,b), they divided the references into 5 centiles (3rd, 10th, 50th, 90th and 97th), rather than 4.

Other authors have undertaken similar ultrasound studies. For example, Guihard-Costa and Larroche (1995) undertook an extensive study of 4507 fetuses between 16 and 34 gestation weeks in order to establish reliable normative values for growth and size. They measured femur length, abdominal transverse diameter, biparietal diameter, fronto-occipital diameter, cerebellar transverse diameter and outer orbital diameter.

The authors established centile curves representing the 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of the distributions. Guihard-Costa and Larrouche then used the longitudinal data to establish growth velocities by dividing the length of pregnancy into 3 or 4 week intervals and performing age-specific linear regression analyses. The resulting slope value of the regression line corresponded to the growth rate of each time interval. Centile curves were then fitted to these velocity curves which were then smoothed. This allowed for individual's growth rates to be compared to that of the sample population and to be expressed as a centile.

The value of these reference charts is that a given individual's size (or growth velocity in the case of Guihard-Costa and Larrouche 1995) can be compared to that of the population from which the charts were derived. Thus, an individual's head

circumference or femur length, for example, can be expressed as an SD score. A low SD score would be indicative of small size, while changes in SD over time would reflect 'catch-up' or 'catch down' growth in the head. By separating out males and females and constructing sex-specific growth curves (see Deter et al. 1982), it is also possible to control for size dimorphism effects and thus compare growth between individuals of different sexes.

For the purposes of quantifying brain size, body size, growth and encephalisation in this thesis, growth reference charts are constructed, but unlike those cited previously, they exclude premature birth and take sex, age and body size differences between individuals into account. These methods will be outlined in detail later in the thesis.

2.8b) Infant growth references

Countless studies have been undertaken to construct growth references during infancy for height, supine length, weight, head circumference, growth tempo, height velocity, weight velocity, sitting height as a function of stature and triceps and subscapular skinfold thickness. The most exhaustive studies were undertaken by J.M. Tanner and colleagues from the mid 1900s, and up to 1990 were used as a gold standard for referencing growth (Tanner 1952, Tanner et al. 1966, Tanner and Whitehouse 1973, Tanner and Whitehouse 1975, Tanner and Whitehouse 1976). These measures were collected as part of a national survey on growth in British children.

However, following the work of Cole et al. (1998) and Wright et al. (2002), it is now recommended that the British 1990 charts be used for referencing growth in British children as these take the secular trend in increased height into account. The British 1990 standards are based on a combination of 17 national surveys and include references for breast-fed infants versus formula fed infants, body mass index (weight in kilograms / height in meters²), and all of the other standard biometric measures taken as part of previous surveys, including height, supine length, weight, head circumference, skinfold thickness, height and weight velocity, and body mass index, among others (Cole 1990, Cole 1993, Cole et al. 1995, Cole et al. 1997, Cole et al. 1998). In addition, thrive lines for the lower 5th centile in weight gain can also be

assessed with these charts in order to determine whether growth faltering is occurring (Cole 1997).

The thrive lines take into account the tendency for regression to the mean in weight as small children will speed up growth (increase SD) and large children will slow down growth (decrease SD) as part of normal 'catch up' and 'catch down' growth (Altigani et al. 1989, Wright et al. 1994a,b, Brandt 1998, Wright et al. 1998). Individuals whose size measures persist in falling below the 5th centile thrive lines are, therefore, not catching up in growth as expected. This is indicative of growth faltering.

The thrive index is a measure of the discrepancy between a child's predicted and actual growth and is helpful in assessing whether children are gaining weight at normal or below average rates. Wright et al. (1994) constructed a growth reference with centiles reflecting the thrive index, for use in assessing the rate of weight gain in children up to 2 years of age.

Like the growth references constructed for fetal growth measurement, these infancy charts do not take the relationship between head circumference and body size into account. Rather, they illustrate changes in size as a function of age. Since the body and head (brain) grow at different rates, both age and the relationship between these variables are controlled for when constructing a growth reference for relative brain size (encephalisation) in this thesis. These methods will be described in detail in chapter 4.

2.9) Methods for measuring size

2.9a) Fetal size measures

Here fetal growth is assessed with the use of biometric measures derived from ultrasound sonography. Ultrasound has been used to assess intra-uterine fetal growth for over 30 years and has formed the basis for numerous fetal growth references. This technique allows for accurate biometric measurement of the living fetus, which in turn allows for more precise gestation length estimation.

Ultrasonography provides an image of a slice of the body by directing a narrow beam of high frequency sound waves (over 20,000 Hz) into the body and recording the manner in which sound is reflected from internal structures and contours of the fetal organs or bones. The ultrasound process involves placing a hand held transducer against the skin of the abdomen. The transducer contains piezoelectric crystals which change with electrical energy into high frequency sound waves. The sound beam is directed into the region of interest and then reflected back toward the transducer at interfaces between tissues of different acoustic impedances (which is determined by the physical density of the tissue and the velocity of sound). As the acoustic impedance mismatch between two tissues increases at any given interface, the reflected sound (echo) becomes stronger. Upon its return to the transducer, the echo is converted to electric signals which are then analysed by a computer to produce the ultrasound images from the internal structures and contours of the fetal organs or bones (Novelline 1997). The acoustic impedance for biological materials differ and are listed in Table 2.7.

The accuracy with which echographical measurements are taken is generally very good, within ~1mm (Guihard-Costa and Larrouche 1995). The ability to directly measure fetal weight and volume ultrasonically are, however, poor as the ultrasound method allows only for accurate linear measurement. The anatomical landmarks listed in Table 2.8 can be detected using ultrasound at different developmental ages.

The following structures can be measured accurately after 12 post-conception weeks (Meire 1998):

biparietal diameter	other limb bone lengths	kidney
head circumference	scapula	spleen
occipito-frontal diameter	foot length	stomach
cephalic index	orbital diameter	bowel
abdominal circumference	interocular distance	ear length
femur length	cerebellum	

Table 2.7 Acoustic impedance values

Material	Acoustic impedance $10^6 \text{ kg}^{-2} \text{ s}^{-1}$
bone	7.80
liver	1.65
kidney	1.62
blood	1.61
fat	1.38
lung	0.26

For biological materials given by McDicken (1981)

Table 2.8 Age at which anatomical landmarks can be detected using ultrasound

Anatomical landmark	Gestation age (weeks)
gestational sac	4-5
secondary yolk sac	5
embryonic pole	5
heart beat	5-6
tail remnant	7
limb buds	8
fetal movements	8-9
physiological bowel herniation	8-10
kidneys	10
mineralisation (long bones)	10
calvarium (calcified)	10-11
face	10-11
stomach	10-11
digits	11
4 chamber view of heart	11-12
bladder	11-12
diaphragm	12
genitalia	12-13

Given by Cullen and Hobbins (1993:22)

A number of biometric indices, however, can be used to estimate body weight and gestation age accurately in the fetus. For example, abdominal circumference is most commonly used to estimate fetal weight (Campbell and Wilkin 1975, Higginbottom et al. 1975, Poll and Vasby 1979) and to assess intra uterine growth (Campbell and Thoms 1977, Sabbagha 1978, De Vore and Platt 1987, Meiri 1981, Little and Campbell 1982). Generally, abdominal circumference provides an estimate with an accuracy of about 90% (Meire 1986). Gestation length is commonly estimated from femur length (Hadlock et al. 1984) and biparietal diameter, prior to 20 gestation weeks, and is generally accurate within 5 days. Where gestation length has not been assessed prior to the third trimester, a ratio of abdominal circumference to femur length can be used to predict gestation length fairly accurately (Hadlock et al. 1983).

Head size is commonly measured during ultrasound. Occipito-frontal diameter or head circumference is measured along the occipito-bregmatic plane in order to reflect head size independently of head shape (Doubilet and Greenes 1984). After Campbell and Thoms (1977) and Hansmann (1978), the established anatomic reference plane for the concurrent measurement of the biparietal diameter, occipito-frontal diameter and head circumference is at the level where the continuous midline echo is broken by the cavum septum.

Measurements of the biparietal diameter are made from the fetal skull skin to the fetal skull skin at the level of the parietal. The occipito-frontal diameter is measured in the same plane between the leading edge of the frontal bone and the outer border of the occiput. Head circumference is then estimated from the measurement of the occipito-frontal diameter and biparietal diameter using the formula for an ellipse:

$$(9) \quad HC = 3.14 \sqrt{(BPD^2 + OFD^2)}/2$$

HC = head circumference, BPD = biparietal diameter, OFD = occipito-frontal diameter in millimeters

The ratio of BPD to AC is also useful for assessing intrauterine growth restriction where the abdominal circumference is significantly smaller than expected for head

circumference. Other abnormalities such as Down's syndrome may also be assessed from the cephalic index: the ratio of occipito-frontal diameter to biparietal diameter (Buttery 1979).

Figures 2.6 and 2.7 are examples of ultrasound images used to derive size measures for the fetal head and femur length.

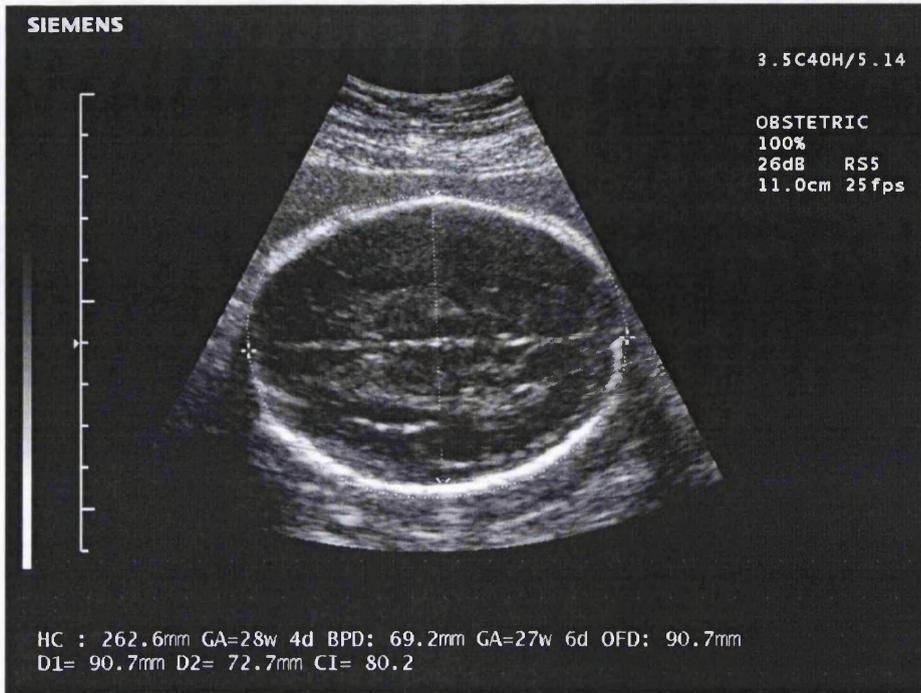


Figure 2.6. Ultrasound showing fetal head circumference, occipito-frontal diameter and bi-parietal diameter. Taken from (www.siemensultrasound.com)



Figure 2.7. Ultrasound showing femur length measurement. Taken from Dr. Joe Woo's web page (www.ob-ultrasound.net)

2.9b) Infant size measures

After birth physical anthropometric measures can be used to assess growth. The most widely taken anthropometric measure is weight. Length is another global measure and provides valuable information about growth. Together weight and length do not accurately describe growth of a particular segment or underlying tissue, they provide, rather a reference for generalised growth. Other anthropometric data can be used to study the growth of different regions of the body or different body segments, e.g. crown-rump length, leg length, arm length and trunk length. They can also be used to describe body proportions and their changes during growth by evaluating changes over time in body size parameters or by comparing size at a specific time, relative to a reference population.

Measurement error can, however, arise from imprecision and inaccuracy (Ulijaszek 1998, Ulijaszek and Kerr 1999). Non-nutritional factors may influence the reproducibility of the measurement. For example, length may vary across the day as a function of the compression of the spinal column. Instrument error and inexperience can also result in unreliable measures. Therefore, it is essential that all anthropometrists follow a precise protocol when measuring biometric parameters. Weiner and Lourie (1969) provide detailed methods for accurate anthropometric measurement.

In this thesis, several analyses relating to size, growth and encephalisation in the fetus and infant are undertaken. The data used in these studies are described in this chapter. In addition, the data are used, in this chapter, to illustrate general patterns of growth in the fetus and infant human and to compare these to rhesus monkey, baboon and common marmoset patterns of growth.

2.10) The data

2.10a) Human data

Data for fetal and infant humans were obtained from a longitudinal study undertaken by researchers based at University College London Hospital and Middlesex Hospital. The study was carried out by Dr. Peter Hindmarsh, Dr. Michael Geary and Prof. Charles Rodeck who allowed the author access to part of the study's data collected between 1996 and 1999. The study was funded by Children Nationwide, The British Heart Foundation and Pharmacia-Upjohn.

These data include biometric measures obtained during both the fetal period (using ultrasound) and the first year of life (using standard anthropometry). Fetal ultrasound scans were taken at three regular intervals during pregnancy: at first visit (at 12 -14 gestation weeks, on average), at roughly 18-20 weeks (second trimester) and between 30-34 weeks (third trimester). Either an Acuson 128/Xpi, ATL HDI3000 or a ATL HD19 ultrasound machine was used (depending on the time of scan). Each machine had a 5 Mhz curvilinear transducer and both of these machines provided compatible data. Post-conception age at each scan and sex were recorded and gestation age was calculated from the last menstruation unless ultrasound measurements at the first ultrasound (crown rump length and biparietal diameter) yielded dates which differed by more than 7 days. If so, then gestation age was calculated using these measures. All biometric measures were taken three times and the mean value was then recorded. All ultrasound scans were performed by trained and experienced radiographers or specialists in Fetal Medicine. The coefficient of variation of the ultrasound measures was no more than 1% at the 20 week ultrasound scan.

In addition, infant gestational age at delivery, body length, body weight, mid-arm circumference, subscapular skinfold thickness and triceps skinfold thickness were taken at birth. They were taken three times and a mean value reported. Birth weight was measured using electronic self-calibrating scales (Seca, U.K.). Head circumference was measured using a metal tape and skinfold thickness was measured with skinfold calipers (Holtain Limited, Crymych, U.K.). The coefficient of variation of the measurement error for body length was 0.15% based on 10 infants each measured 5 times by 3 observers.

Generally the measurement error associated with circumferences is less than that of the skinfolds (Bray et al. 1978). Intrameasurer technical errors for the mid-arm circumference range from 0.1 to 0.4 mm according to Lohman, et al. (1988), based on several published studies. According to Lohman (1981) and Wilmore and Behnke (1969), the measurement error associated with the subscapular skinfold thickness ranges from 0.88 to 1.16 mm. Measurement error in the triceps skinfold generally increases with age and level of fatness. Intermeasurer technical errors, based on several studies, range between 0.8 to 1.89 mm (Lohman et al. 1988). Additional error may arise from variations in skin thickness and sub-cutaneous edema (Keys and Brozek 1953) leading to variations in skin compression. Error may then arise from the duration of caliper application prior to taking the measurement (see for example, Brans et al. 1974).

Subdural space variation, scalp edema and scalp thickness variation contribute to the error involved in measuring head circumference, as does different measurement technique, such as measuring the head circumference along different planes (Cooke et al. 1977). However, measurement error associated with head circumference tends to be relatively low. Guihard-Costa and Larroche (1995) suggest that the error in head circumference measurement is about 5mm.

Because of fetal position it was not always possible to take head measures. Unfortunately, head circumference measures at booking (first ultrasound) were taken successfully in only 24 individuals, significantly reducing first trimester measures for this parameter. A total of 245 individuals have a full compliment of ultrasound scans and postnatal anthropometric measures - from the second trimester through to one year of age. Sample sizes for each fetal and infant parameter are listed in Table 2.9 as well as the percentage of the total sample for which biometric measures were successfully taken prenatally and postnatally. Both head circumference and femur (prenatally) or body length (postnatally) were measured 5,474 times. Of these, males represented 49.9% of the sample.

Table 2.9 Percent of total sample for which prenatal and postnatal measures were taken and sample sizes for each measure, as a function of fetal sex

fetal variables	% sample	number of males	number of females
<i>Ultrasound 1</i>			
head circumference	1.5	12	8
femur length	15.0	124	113
biparietal diameter	38.2	297	334
abdominal circumference	2.2	15	22
<i>Ultrasound 2</i>			
head circumference	90.8	749	704
femur length	89.6	739	690
biparietal diameter	95.7	748	831
abdominal circumference	95.5	748	827
<i>Ultrasound 3</i>			
head circumference	73.2	604	568
femur length	82.6	681	652
biparietal diameter	73.8	604	613
abdominal circumference	83.8	681	701
<i>Birth</i>			
head circumference	90.1	743	701
crown-rump length	69.6	585	563
body length	89.3	737	698
body weight	93.0	767	716
triceps skinfold	84.6	698	646
subscapular skinfold	84.4	696	648
MUAC	81.6	699	648
gestation at delivery	93.0	767	717
<i>6 post-natal months</i>			
head circumference	58.8	485	440
body length	58.8	485	440
body weight	55.6	481	436
<i>1 year</i>			
head circumference	20.6	170	181
body length	20.5	169	181
body weight	21.3	170	181

MUAC = mid upper arm circumference

During the first year of life, standard anthropometric measures were taken at three general age periods: birth, 6 months and at 1 year. In the neonate and infant, postnatal head circumference measures were taken with a metal tape measure, as the maximum perimeter of the head with the tape passing across glabella (Meredith 1971). Anthropometric measures taken included: weight, height, triceps skinfold thickness and sub-scapular skinfold thickness. All measures were taken by an experienced midwife or paediatric clinical worker according to the standards described by Weiner and Lourie (1969) and Lohman et al. (1988). Unfortunately, sample size reduced from about 1650 individuals at birth to about 925 at 6 months and about 350 at 1 year-of-age. Sample sizes for each measure and the percent of the total sample measured are listed in Table 2.9.

All mothers in the sample were Caucasian. If a significant abnormality was found, the woman and baby were excluded from the study. The sample, therefore, represents a normal healthy Caucasian urban population undergoing regular antenatal care. It does not, therefore, necessarily represent a national reference which includes multiple ethnicities, rural and urban-living women and low-birth-weight and premature babies.

Tables 2.10 and 2.11 list the descriptive statistics for fetal and infant measures, respectively. These include the mean, standard deviation and sample size for each biometric measure taken at different measurement periods.

Table 2.10 Descriptive statistics for fetuses in the total sample at ultrasounds 2 and 3

fetal variable	n	mean	sd
<i>ultrasound 2</i>			
gestation age (weeks)	1584	20.2	1.0
femur length (mm)	1551	32.6	2.9
biparietal diameter (mm)	1579	49.4	3.7
head circumference (mm)	1579	178	12
abdominal circumference (mm)	1575	156	13
<i>ultrasound 3</i>			
gestation age (weeks)	1383	32.2	1.2
femur length (mm)	1382	62.0	3.2
biparietal diameter (mm)	1217	84.5	4.2
head circumference (mm)	1217	300	14
abdominal circumference (mm)	1382	287	18

n = sample size, sd = standard deviation

Table 2.11 Descriptive statistics for neonates and infants in the total sample

variable	n	mean	sd
<i>birth</i>			
gestation age (weeks)	1484	39.4	1.7
body weight (kg)	1484	3.40	0.54
body length (cm)	1435	50.0	2.5
crown-rump length (cm)	1271	5.4	3.2
head circumference (cm)	1444	34.5	1.6
triceps skinfold (mm)	1344	5.8	1.5
subscapular skinfold (mm)	1344	5.3	1.6
MUAC (mm)	1347	10.4	1.1
<i>6 months</i>			
age (weeks)	878	25.6	1.5
body weight (kg)	930	8.15	4.66
body length (cm)	930	67.3	2.8
head circumference (cm)	928	43.6	1.3
<i>12 months</i>			
age (weeks)	353	52.1	0.9
body weight (kg)	351	9.85	1.69
body length (cm)	350	75.7	2.9
head circumference (cm)	351	46.5	1.4

n = sample size, sd = standard deviation

MUAC = mid-upper arm circumference

However, a number of exclusion criteria were introduced for the purposes of this thesis. Because this is a study of 'normal' growth and encephalisation, babies born prior to 37 gestation weeks were excluded on the grounds of prematurity and potential associated growth abnormalities. In addition, because ages within the different measurement periods vary, individuals measured more than 4 weeks on either side of the mean age for that measurement period were excluded. The grounds for their exclusion being that significant differences in size and growth are expected and it is not reasonable to compare a fetus of 3 months to a fetus of 5 months, for example, even if they both were included in the second postnatal measurement period.

Further exclusion criteria were based on maternal factors. Mothers entered the study at first ultrasound and were measured once, at booking. The duration in pregnancy at booking, however, differed between women with some entering at 6 gestation weeks and others as late as 20 gestation weeks. Maternal measures were, therefore, influenced by when the mothers joined the study. This introduces several problems since mothers are at different stages of pregnancy when measured.

Firstly, the reasons for undergoing a first ultrasound early or late may be associated with factors such as, for example, illness, fertility issues, lifestyle issues or obesity. Secondly, changes in body composition are associated with increasing gestation age so that mothers booked at, for example, 8 and 20 gestation weeks differ in terms of their metabolism, fat and lean tissue patterning (Seitchik 1960, Bronstein et al. 1996, Prentice et al. 1996).

Since the relationship between maternal factors and offspring size, growth and encephalisation are evaluated here, and because mothers were measured only once (at booking), variation in gestation age at measurement is a potential confound. This is dealt with by excluding mothers from the sample who were measured prior to 9 gestation weeks or after 16 gestation weeks. This was because the mothers in this sample showed the least variation in skinfold thickness (fatness) between 9 and 16 gestation weeks. The maternal exclusion criteria are discussed in more detail in chapter 5.

Table 2.12 lists the frequency of measures and percent of the total samples for which data are available, after excluding the mothers who were measured overly early or late, the premature babies, and those individuals measured outside of 4 weeks of the mean measurement periods. Tables 2.13 lists the descriptive statistics for each measure for males and females in this reduced sample. Table 2.14 lists the results of independent samples t-tests where the means between males and females are compared. These show significant sexual dimorphism in a number of size components.

Although about 400 individuals are lost from the dataset after applying the exclusion criteria, the reduced sample does not differ significantly from the original sample. Table 2.15 lists the results of independent samples t-tests where the means between the original and reduced datasets are compared. Where a statistically significant difference is found, the mean difference is less than 1mm (with the exception of body length at 1 year).

Table 2.12 Frequency of measures for fetal and infant variables in the reduced sample as a percent of the total sample by infant sex

fetal variable	% total sample	males	females
<i>Ultrasound 2</i>			
head circumference	77.3	656	620
femur length	76.1	647	608
biparietal diameter	77.3	655	620
abdominal circumference	77.2	656	618
<i>Ultrasound 3</i>			
head circumference	63.0	538	502
femur length	71.8	605	580
biparietal diameter	63.0	538	502
abdominal circumference	71.8	605	580
<i>Birth</i>			
body weight	77.0	652	619
body length	75.2	634	607
crown-rump length	72.9	534	517
head circumference	75.6	637	610
triceps skinfold	70.2	596	562
subscapular skinfold	70.1	594	563
MUAC	70.4	598	564
gestation at delivery (weeks)	77.0	652	619
<i>6 post-natal months</i>			
body weight	45.2	393	352
body length	45.1	393	351
head circumference	45.2	393	352
<i>1 year</i>			
body weight	15.2	110	140
body length	15.1	109	140
head circumference	15.1	109	140

Reduced sample includes individuals whose mothers were booked between 9-16 gestation weeks and whose offspring were measured within 4 weeks of the mean age for the measurement period, and born after 36 gestation weeks

MUAC = mid-upper arm circumference

Table 2.13 Descriptive statistics in reduced sample

variable	males			females		
	n	mean	sd	n	mean	sd
<i>Ultrasound 2</i>						
gestation age (weeks)	657	20.2*	0.8	621	20.2*	0.9
femur length (mm)	647	32.6*	2.5	608	32.5*	2.5
biparietal diameter (mm)	655	50.1*	3.0	620	48.8*	3.0
head circumference (mm)	656	179*	10	620	176	10
abdominal circumference (mm)	656	158*	11	618	155*	11
<i>Ultrasound 3</i>						
gestation age (weeks)	593	32.3*	1.2	580	32.3*	1.2
femur length (mm)	605	61.9*	3.0	580	62.2*	3.3
biparietal diameter (mm)	538	85.1*	3.9	502	83.9*	4.4
head circumference (mm)	538	302	13	502	298	15
abdominal circumference (mm)	538	288	17	580	286	18
<i>birth</i>						
gestation age (weeks)	588	39.7*	1.3	619	39.5*	1.4
body weight (kg)	652	3.51	0.35	619	3.40	0.50
body length (cm)	634	50.5	2.6	607	49.7*	2.3
crown-rump length (cm)	553	5.4	1.7	517	5.4	1.7
head circumference (cm)	637	34.9*	1.5	610	34.20*	1.4
triceps skinfold (mm)	596	5.7*	1.6	562	5.8*	1.5
subscapular skinfold (mm)	594	5.2*	1.6	563	5.5*	1.6
MUAC (mm)	598	10.5*	1.0	563	10.4*	1.1
<i>6 months</i>						
age (weeks)	393	25.4*	1.1	352	25.4*	1.2
body weight (kg)	393	8.10	1.0	352	8.18*	0.68
body length (cm)	393	68.0	2.3	351	66.3	2.9
head circumference (cm)	393	44.1	1.7	351	42.9	1.2
<i>12 months</i>						
age (weeks)	111	52.0	-	141	52.0	-
body weight (kg)	147	9.9*	1.9	140	9.7*	1.7
body length (cm)	146	76.5	2.8	140	74.7	2.7
head circumference (cm)	146	47.0	1.1	140	45.9	1.3

n = sample size, sd = standard deviation, MUAC = mid-upper arm circumference

*normally distributed as determined by using a Kolmogorov-Smirnoff test

age at 12 months = 52 weeks for all infants

Table 2.14 Results of independent samples t-tests comparing variable means between the sexes in the reduced fetal sample

fetal variable	mean difference¹	P	CI of difference
<i>Ultrasound 2</i>			
abdominal circumference (mm)	3.2	0.000	1.8, 4.5
biparietal diameter (mm)	1.4	0.000	1.0, 1.7
head circumference (mm)	4.1	0.000	2.8, 5.3
femur length (mm)	0.2	0.284	-0.1, 0.5
<i>Ultrasound 3</i>			
abdominal circumference (mm)	2.3	0.028	0.2, 4.3
biparietal diameter (mm)	1.2	0.000	0.7, 1.7
head circumference (mm)	4.0	0.000	2.3, 5.7
femur length (mm)	-0.3	0.138	-0.6, 0.1
<i>Birth</i>			
body length (cm)	0.8	0.000	0.5, 1.1
body weight (kg)	0.1	0.000	0.1, 0.2
head circumference (cm)	0.7	0.000	0.5, 0.8
crown-rump length (cm)	0.2	0.845	-0.2, 0.2
triceps skinfold (mm)	-0.1	0.439	-0.2, 0.1
subscapular skinfold (mm)	-0.2	0.014	-0.4, -0.0
MUAC (mm)	0.2	0.008	0.0, 0.3
gestation age (weeks)	0.2	0.110	-0.0, 0.3
placenta weight (g)	16.0	0.047	0.2, 31.7
<i>6 months</i>			
body length (cm)	1.9	0.000	1.5, 2.2
body weight (kg)	-0.1	0.713	-0.8, 0.5
head circumference (cm)	1.1	0.000	9.7, 12.9
<i>12 months</i>			
body length (cm)	1.7	0.000	1.1, 2.3
body weight (kg)	0.2	0.323	-0.2, 0.6
head circumference (cm)	1.1	0.000	0.9, 1.4

P = probability based on a two-tailed bivariate Pearson's correlation with a confidence interval (CI) of 95%, MUAC = mid-upper arm circumference

Reduced sample includes individuals whose mothers were booked between 9-16 gestation weeks and who themselves were measured within 4 weeks of the mean age for the measurement period, and born after 36 gestation weeks.

¹ positive value indicates that males are larger while a negative value indicates that females are larger

Table 2.15 Results of independent sample t-tests comparing the difference between variable means of the total sample and the reduced prenatal sample

variable	mean difference ¹	P	CI of difference
<i>Ultrasound 2</i>			
abdominal circumference (mm)	-1.0	0.326	-2.9, 1.0
biparietal diameter (mm)	-0.6	0.040	-1.1, -0.0
head circumference (mm)	-1.1	0.257	-2.9, 0.8
femur length (mm)	-0.6	0.009	-1.0, -0.1
<i>Ultrasound 3</i>			
abdominal circumference (mm)	-0.6	0.719	-3.5, 2.4
biparietal diameter (mm)	-0.2	0.649	-0.9, 0.6
head circumference (mm)	0.9	0.506	-1.6, 3.3
femur length (mm)	-0.1	0.684	-0.6, 0.4
<i>Birth</i>			
body length (cm)	-0.3	0.172	-0.7, 0.1
body weight (kg)	-0.0	0.469	-0.1, 0.1
head circumference (cm)	-0.2	0.181	-0.4, 0.1
crown-rump length (cm)	0.5	0.903	-0.7, 0.8
triceps skinfold (mm)	0.2	0.215	-0.1, 0.4
subscapular skinfold (mm)	0.0	0.834	-0.2, 0.3
MUAC (mm)	0.0	0.996	-0.2, 0.2
gestation age (weeks)	-0.2	0.074	-0.5, 0.0
placenta weight (g)	4.8	0.679	-18.0, 27.6
<i>6 months</i>			
body length (cm)	0.6	0.831	-0.5, 0.6
body weight (kg)	-0.3	0.522	-1.3, 0.6
head circumference (cm)	0.2	0.285	-0.1, 0.4
<i>12 months</i>			
body length (cm)	1.0	0.025	0.1, 1.9
body weight (kg)	0.5	0.074	-0.0, 1.0
head circumference (cm)	0.4	0.080	-0.1, 0.8

P = probability based on a two-tailed bivariate Pearson's correlation with a confidence interval (CI) of 95%, MUAC = mid-upper arm circumference
 Reduced sample includes individuals whose mothers were booked between 9-16 gestation weeks and who themselves were measured within 4 weeks of the mean age for the measurement period, and born after 36 gestation weeks
¹ positive value indicates that the total sample is larger while a negative value indicates that the reduced sample is larger

2.10b) Non-human primate data

i) Rhesus macaque data

The rhesus macaque (*Macaca mulatta*) data analysed here were collected by Dr. Alice Tarantal at the California National Primate Research Center at the University of California, Davis. A total of 482 individuals had both fetal head circumference and femur length measures taken ultrasonically, of which 52% were male. Measures were taken longitudinally between 60 days and term (165 days). In addition, anthropometric measures of head circumference and femur length at birth and during infancy were taken for 242 individuals, of which 49% were male.

Postnatal femur length measures were taken, using calipers, from the greater trochanter to the patella. See Tarantal and Gargosky (1995) and Tarantal and Hendrickx, (1988) for a detailed description of these data.

Tables 2.16 lists the descriptive statistics for the maternal rhesus monkeys who produced offspring in the sample. Table 2.17 lists the descriptive statistics for fetal head circumference and femur lengths for fetuses. It also lists descriptive statistics for infants up to 370 post-conception days (i.e. up to about 6 post-natal months). Tables 2.18 and 2.19 list the descriptive statistics for the head circumference and femur lengths of males and females separately. Fetuses are divided into 3 groups, by trimester. Infants are divided into groups of roughly 6 weeks in order to illustrate changes in mean size over time.

Table 2.16 Descriptive statistics for rhesus monkey mothers

	n	mean	sd
age in months	876	9.1	3.1
weight (kg)	876	6.8	1.4
parity	876	3.9	2.5

n = sample size, sd = standard deviation

Table 2.17 Descriptive statistics for rhesus monkey fetuses

variable	n	mean	sd
<i>second trimester (56-110 days)</i>			
femur length (mm)	338	17.6	7.9
biparietal diameter (mm)	338	29.3	7.5
head circumference (mm)	260	111	29
<i>third trimester (110-165 days)</i>			
femur length (mm)	342	42.5	8.3
biparietal diameter (mm)	342	47.4	3.3
head circumference (mm)	277	176	14

Mean age in days in second trimester (79, sd = 14), third trimester (131, sd = 15)

n = sample size, sd = standard deviation

Table 2.18 Means, standard deviations and sample sizes for head circumference in males and females in the rhesus monkey sample

age (days)	mean age	age sd	Males			Females		
			n	mean HC (mm)	sd	n	mean HC (mm)	sd
<i>fetuses</i>								
60 - 99	76	12	85	95	20	79	92	20
100 - 139	116	11	105	155	14	95	151	14
140 - 179	155	12	113	188	13	111	187	12
<i>infants</i>								
180 - 219	190	6	29	211	7	34	208	6
220 - 259	235	15	25	220	5	19	218	4
260 - 299	280	0	5	227	8	4	224	3
300 - 339	310	0	4	233	9	4	227	4
340 - 370	355	16	3	232	2	3	232	2

Average gestation length is 165 days. Males and females have equal mean ages in each age category.

HC = head circumference, n = sample size, sd = standard deviation

Table 2.19 Means, standard deviations and sample sizes for femur length in males and females in the rhesus monkey sample

age (days)	mean age	age sd	Males			Females		
			n	mean FL (mm)	sd	n	mean FL (mm)	sd
<i>fetuses</i>								
60 - 99	76	12	120	14	5	112	13	5
100 - 139	116	11	112	31	5	108	31	5
140 - 179	155	12	136	49	9	144	50	10
<i>infants</i>								
180 - 219	190	6	29	67	3	34	68	4
220 - 259	235	15	25	77	4	19	77	5
260 - 299	280	0	5	87	4	4	84	1
300 - 339	310	0	4	93	5	4	87	3
340 - 370	355	16	3	94	6	3	94	2

Average gestation length is 165 days. Sexes have equal mean ages in each age category.

FL = femur length, n = sample size, sd = standard deviation

ii) Baboon data

Ultrasound head circumference and femur length measures were collected for baboon species by Drs. Karen Rice and Michelle Leland at the Southwest Foundation for Biomedical Research, Texas. The baboon species included: Hamadryas, Olive, Yellow, Chacma, Sacred and Guinea baboons. A total number of 2,677 individuals had both head circumference and femur length measures taken prenatally between 30 and 180 gestation days. Of these, 569 were sexed with males comprising 53% of the sample. The dataset consists of both cross-sectional and longitudinal data. Table 2.20 lists the descriptive statistics for the baboon mothers in the sample. Table 2.21 lists the descriptive statistics for baboon fetuses. Tables 2.22 and 2.23 lists the descriptive statistics for head circumference and femur lengths, respectively, in males and females separately. Due to a lack of identifying data, longitudinal growth within each individual could not be assessed in baboons.

Table 2.20 Descriptive statistics for baboon mothers in sample

variable	n	mean	sd
maternal age (yrs)	5373	10.4	3.9
weight (kg)	55	17.4	2.8
parity	1049	1.9	1.6
gestation age at scan (days)	5839	105	38
gestation age at delivery (days)	1044	153	30

n = sample size (includes a number of multiple births), sd = standard deviation

Baboon species are categorised in groups, some of which are overlapping. It is therefore, not possible to ascribe each individual to a specific species.

Table 2.21 Descriptive statistics for fetal baboons

fetal variable	n	mean	sd
<i>first trimester</i> (1-62 days)			
femur length (mm)	3	5.3	2.1
biparietal diameter (mm)	497	7.8	2.5
fronto-occipital diameter (mm)	471	9.4	3.2
head circumference (mm)	19	43	11.2
<i>second trimester</i> (63 - 123 days)			
femur length (mm)	2110	22.9	10.6
biparietal diameter (mm)	3824	32.2	9.8
fronto-occipital diameter (mm)	3823	41.0	18.2
head circumference (mm)	2114	116	36
<i>third trimester</i> (123-185 days)			
femur length (mm)	268	47.6	7.4
biparietal diameter (mm)	1168	50.3	3.4
fronto-occipital diameter (mm)	1164	66.5	5.4
head circumference (mm)	271	189	16

Mean age at first trimester (60, sd = 0.00), second trimester (92, sd = 21) and third trimester (150, sd = 24)

n = sample size, sd = standard deviation

Table 2.22 Means, standard deviations and sample sizes for head circumference in males and females in the fetal baboon sample

head circumference (mm)	Males			Females		
	n	mean	sd	n	mean	sd
30 - 69 days	48	22	34	58	13	28
70 - 109 days	190	81	49	164	75	48
110 - 149 days	192	86	85	199	77	83
150 - 189 days	52	176	82	47	162	87
190 - 229 days	.	.	.	2	213	6

Average gestation length is 185 days. Sexes have equal mean ages for each age interval.

n = sample size, sd = standard deviation

Mean age between 30-69 days = 60, sd = 0.0,

between 70-109 days = 84, sd = 11, between 110-149 days = 125, sd = 11, between 150 - 189 days = 163, sd = 13, between 190-229 days = 206, sd = 13.

Table 2.23 Means, standard deviations and sample sizes for femur length in males and females in the fetal baboon sample

femur length (mm)	Males			Females		
	n	mean	sd	n	mean	sd
30 - 69 days	15	10	2	11	10	1
70 - 109 days	149	19	8	124	18	7
110 - 149 days	98	38	4	92	39	5
150 - 189 days	44	61	3	39	60	7
190 - 229 days	.	.	.	2	64	1

Average gestation length is 185 days. Sexes have equal mean ages for each age interval.

n = sample size, sd = standard deviation

Mean age between 30-69 days = 60, sd = 0.0,

between 70-109 days = 84, sd = 11, between 110-149 days = 125, sd = 11, between 150 - 189 days = 163, sd = 13, between 190-229 days = 206, sd = 13.

iii) Common marmoset data

Fetal ultrasound and neonatal anthropometric measures for the Common marmoset (*Callithrix jacchus*) were taken by Dr. Ann-Kathrin Oerke at the Deutsches Primatenzentrum, Göttingen. Fetal ultrasound measures were derived from a total of 8 pregnancies resulting in 19 offspring. Four pregnancies resulted in triplets, three in twins and 1 in a singleton. Multiple pregnancies prevented the sexing and longitudinal measurement of individuals and the small size of fetal femurs prevented accurate measurement of femur size *in utero*.

A total of 69 neonates, produced in 30 pregnancies, were measured for both head circumference and body weight. Femur lengths could not be measured accurately at birth due to the very small size of the neonate. Body weight measures were, however, taken. Tables 2.24 lists the descriptive statistics for fetal marmosets mothers whose offspring are in the sample. Tables 2.25 and 2.26 list the descriptive statistics for the fetal and neonatal marmosets in the sample.

Table 2.24 Descriptive statistics for marmoset mothers in sample

maternal variables	n	mean	sd
age in months	8	37	9
parity	8	1.5	0.9
gestation age at scan (days)	196	112	20
gestation age at delivery (days)	19	143	1

n = sample size, sd = standard deviation

Table 2.25 Descriptive statistics for fetal marmosets

fetal variable	n	mean	sd
<i>second trimester (49-96 days)</i>			
biparietal diameter (mm)	58	9.7	2.0
fronto-occipital diameter (mm)	58	12.3	2.8
head circumference (mm)	55	36.1	7.2
head area (cm ²)	55	1.0	0.4
cranial volume (cm ³)	55	0.1	0.5
<i>third trimester (97-145 days)</i>			
biparietal diameter (mm)	133	15.7	2.2
fronto-occipital diameter (mm)	133	22.8	4.1
head circumference (mm)	122	65.0	11.6
head area (cm ²)	116	2.7	0.7
cranial volume (cm ³)	113	4.0	1.6

n = sample size, sd = standard deviation

*Individuals were measured multiple times, sex could not be determined due to multiple pregnancies. Mean age in second trimester (89, sd = 5), in third trimester (122, sd = 15).

Table 2.26 Means, standard deviations and sample sizes for male and female marmoset neonates

variable	Males			Females		
	n	mean	sd	n	mean	sd
birth weight (g)	27	29.0	4.0	45	30.5	4.4
head circumference (mm)	25	85.0	4.6	44	86.4	5.4

n = sample size, sd = standard deviation

Average gestation length is 145 days.

2.11) Models for quantifying growth

2.11a) The LMS method and standard deviation scores

In this thesis, for both the fetal and infancy periods, growth is measured by constructing growth references (see section 2.6) for ultrasound and anthropometric measures and deriving standard deviation scores for individuals from these references. The methods outlined by Cole (1990, 1993) for constructing these references are adopted here as they are used in the construction of the national growth references and are widely accepted.

First, males and females are separated and sex-specific growth references are constructed in order to control for size and growth differences between the sexes. Size measures are then plotted against ages in order to express size as a function of age. Next, the distribution is normalised using a Box-Cox transformation of the data series. The Box-Cox transformation estimates the best transformation to normality through an iterative procedure where the conditional variables include the sum of the natural log-transformed variates, the variance of the transformed Y values and the sample size and degrees of freedom. This is done using customised software by fitting a smoothed curve (known as the L curve) to the distribution. The L curve stretches the tail of the distribution and smoothes the curve in the direction which best normalises the data.

Next, a smoothed 'average' or median curve is fitted to the data and this is known as the M curve, the curve which describes median size at given ages. Finally, a third curve, known as the S curve is fitted. The S curve is the smoothed curve of the measurement's coefficient of variation as it changes with age. This curve serves to take into account the variation in measures around the median, and can be used both the help control for excessive variation or to take variation into account when calculating the best-fit model. This is important where sample sizes differ significantly at different ages as variation in the deviation of measures around the

median curve may increase with increasing sample size. The process of applying these three curves to a distribution of data is referred to as using the LMS method.

Once the best-fit LMS curve is applied to the data, age-specific L, M and S values for each data point are derived from the curves and standard deviation scores for each measure as a function of age are calculated using the following formula:

$$(10) \quad \text{SD score} = (X - \text{mean}_X) / (\text{sd}_X)$$

where X is the anthropometric measure, and sd is the standard deviation

The resulting SD scores largely correct for skewness and have a mean of 0 and a standard deviation of 1. They are both age-independent and sex-independent as both age and sex are controlled for by calculating SD scores as a function of age and by calculating SD scores for males and females separately.

In addition to calculating SD scores, the LMS method may be used to construct centiles which are also useful for assessing size and growth. Figure 2.8 is an example of a body length reference derived using the LMS method. Here, as an example, length at birth in males is plotted against gestation age at delivery. After fitting the L, M and S curves to the data, the 97th, 90th, 75th, 50th, 25th, 10th and 3rd centiles are constructed.

In this model, the S curve is forced through the average coefficient of variation in order to minimise the bias of sample size differences at different ages. The resulting centiles are thus constructed from a sex-specific, normally distributed curve with a constant S value. The L, M and S values associated with each individual data point may then be used to calculate an age-independent SD score. Individuals whose body length falls below the 2nd centile are considered growth retarded or very small-for-gestation-age, while those at the 50th centile are considered average. Figure 2.9 shows the SD score for each data point derived from the LMS model in Figure 2.8.

The Cole and Green (1992) Child Growth Foundation growth norm program is used here to create these growth references using the LMS method, and to derive SD scores for head circumference, femur lengths and body lengths as a function of age.

Data on age and size are entered into the program and plotted along the x and y axes, respectively. Limits for the variation in the corresponding L, M and S curves are then set by the user by varying the degrees of freedom for each curve. A measure of deviance is given each time a model is fitted and improvements in the fit of the model with changing degrees of freedom is assessed by changes in the deviance score. Curves may vary from a constant (linear), spline or complex curve by increasing the degrees of freedom. The program then fits the best L, M and S curves to the data distribution given the constraints set by the user. Centiles and corresponding SD scores are calculated by the program using the SD score equation cited previously in equation 10.

For males and females separately, LMS curves were calculated for the following fetal and infant biometric measures:

ultrasound 2:	birth:	6 months:
femur length	body length	body length
head circumference	head circumference	head circumference
	body weight	body weight
ultrasound 3:	Benn index	BMI
femur length	subscapular skinfold thickness	
head circumference	triceps skinfold thickness	12 months:
	estimated mid-arm muscle area ⁵	body length
	estimated mid-arm fat area	head circumference
		body weight
		BMI

These L, M and S values were then used to calculate age- and sex-specific SD scores for each of the above measures, as well as maternal measures which are described in chapter 5.

⁵ Estimated mid-arm muscle and fat area (mm²) are calculated from equations given by Shaw and Lawson (2001) and described in further detail in chapter 4.

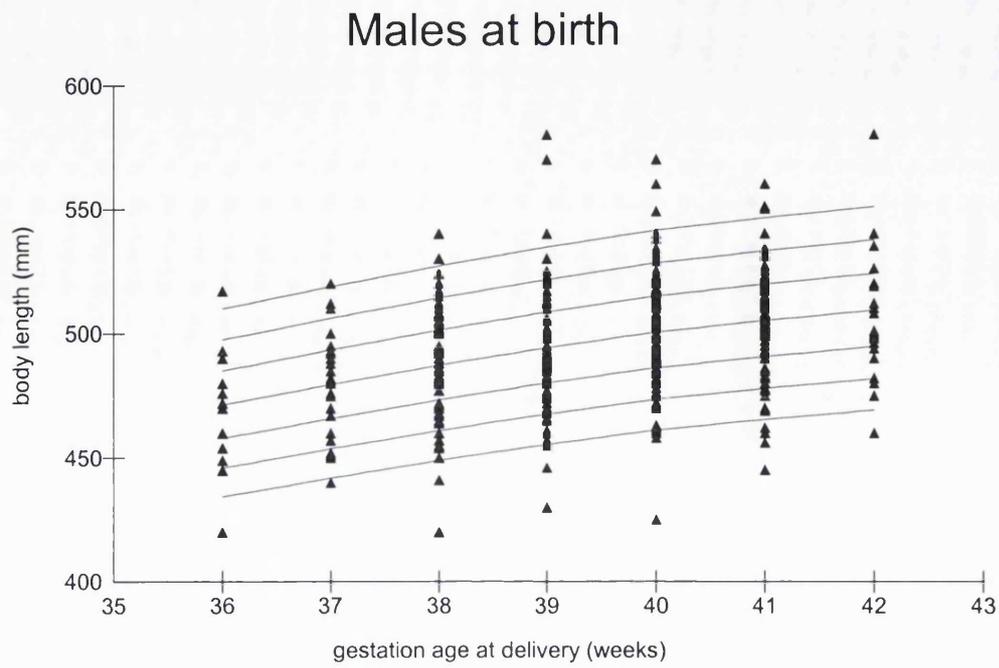


Figure 2.8 LMS curve with centiles describing body length for age in human male neonates

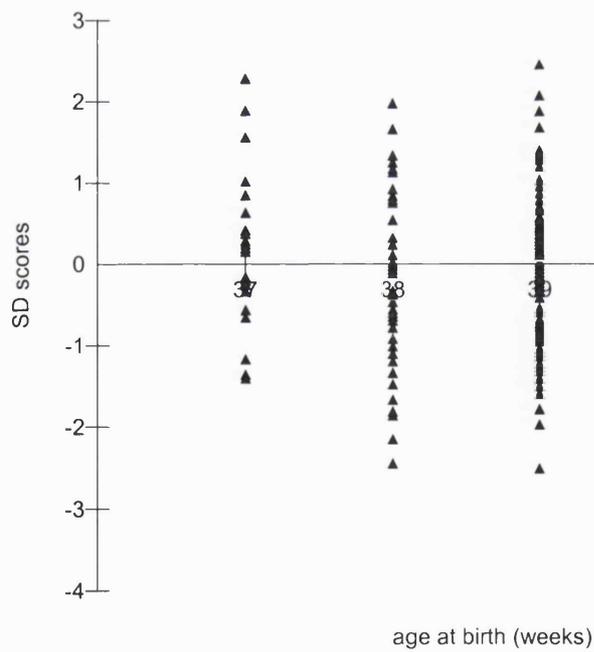


Figure 2.9 SD scores derived from LMS curve for body length in human male neonates

SECTION III: Growth and growth velocity curves

Using the fetal and infant ultrasound and anthropometric data collected at the University College London Hospitals described in section 2.8a, general patterns of fetal and infant growth are described. Growth and growth velocity curves for body length and the head circumference, are constructed and growth patterns between the sexes are compared. In addition, these curves are compared to those of the rhesus monkeys, baboons and marmosets described in sections 2.8(b-d).

2.12) The human fetal and infant growth curve

The growth curves are established here by plotting both body length and head circumference (in mm) against age (in weeks) and fitting non-linear curves through the data. Figure 2.10 shows the body length and head circumference growth curves from about 15 gestation weeks through to 1 year-of-age.

These curves suggest that both body length and head circumference increase rapidly until birth and then slow down. Head growth slows down more rapidly following birth than does body length, however, the head does continue to grow postnatally. Both the body length and head circumference curves asymptote prior to birth, however, the head asymptotes about 7 weeks earlier than does body length. Head and body length trajectories differ throughout the period described. The allometric relationship between head and body size, therefore, changes with age, approaching isometry in very early life.

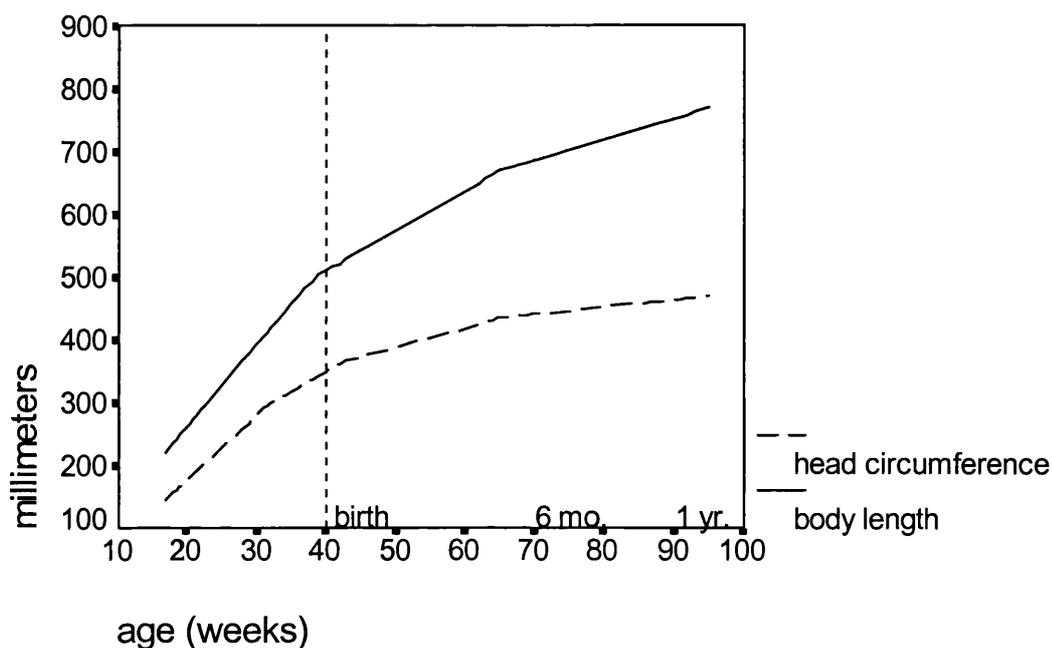


Figure 2.10 Human fetal and infant body length and head circumference growth curves. Fetal body lengths estimated from femur lengths using Fazekas and Kósa's (1978) predictive equation.

The curve describing the relationship between fetal and infant head circumference (up to 1 year-of-age) and age is:

$$(11) \quad \text{head circumference (mm)} = -47.7 + 13.2 * \text{age} - 0.09 * \text{age}^2$$

$(r^2 = 0.974, SE = 15.5, n = 5355, P = <0.0001)$
age in weeks

The curve describing the relationship between fetal and infant body length (up to 1 year-of-age) and age is:

$$(12) \quad \text{body length (mm)} = -82.9 + 19.3 * \text{age} - 0.11 * \text{age}^2$$

$(r^2 = 0.985, SE = 25.9, n = 5718, P = <0.0001)$
age in weeks

2.12a) Human growth velocity

Growth velocity is expressed here as the increase in millimeters per week in body length and in head circumference between measurement periods, scaled to the time interval between those measurement periods.

Table 2.27 lists the average body length and head circumference growth velocities at each measurement period and the changes in velocity between measurement periods. Figure 2.11 shows an overlay scatterplot of head circumference growth velocity relative to body length growth velocity, as a function of age. Although growth cycles or pulses cannot be quantified at this level of analysis, the growth velocity curves show clear distinctions between the average rate of head circumference and body growth during the fetal period and first year of life.

Figure 2.11 shows that the rate of body length growth decreases rapidly during the last trimester of pregnancy. Head circumference growth rate also decreases during the last trimester of pregnancy, but less rapidly than body length. The difference between head circumference growth rate at the beginning and end of the last two months of pregnancy is about 3.4 mm/week, while the difference in body length growth rate is about 8.5 mm/week during the same period. The last trimester is a period when brain growth rate exceeds that of body length growth rate. This is in agreement with the growth velocity curves established by Guihard-Costa and Larrouche (1995) which demonstrate this phenomenon clearly, where femur length growth velocity decreases earlier and more rapidly than does biparietal diameter growth velocity. A small increase in growth rate occurs after birth, leveling off after about 4 postnatal months.

Table 2.27 Means, standard deviations and sample sizes for human head circumference and body length growth velocities (mm/week)

age	measure	n	mean	sd	Δ
ultrasounds 2 - 3	age (weeks)	1324	32.2	1.2	
	head circumference (mm)	1188	10.3	1.1	-
	estimated body length (mm)	1324	15.9	1.5	-
ultrasound 3 - birth	age (weeks)	1290	40.0	1.4	
	head circumference (mm)	1290	6.4	2.5	-3.8
	body length (mm)	1145	7.4	1.0	-8.5
birth - 6 months	age (weeks)	861	25.4	1.1	
	head circumference (mm)	860	3.5	0.6	-2.9
	body length (mm)	861	6.7	1.0	-0.7
6 months - 1 year	age (weeks)	203	52.0	0.0	
	head circumference (mm)	203	1.1	0.3	-2.4
	body length (mm)	203	3.2	0.9	-3.5

GW = gestation weeks, sd = standard deviation, n = sample size, Δ = change in velocity from preceding longitudinal measures, taking time between measures into account. All measures expressed in millimeters for continuity between prenatal and postnatal periods

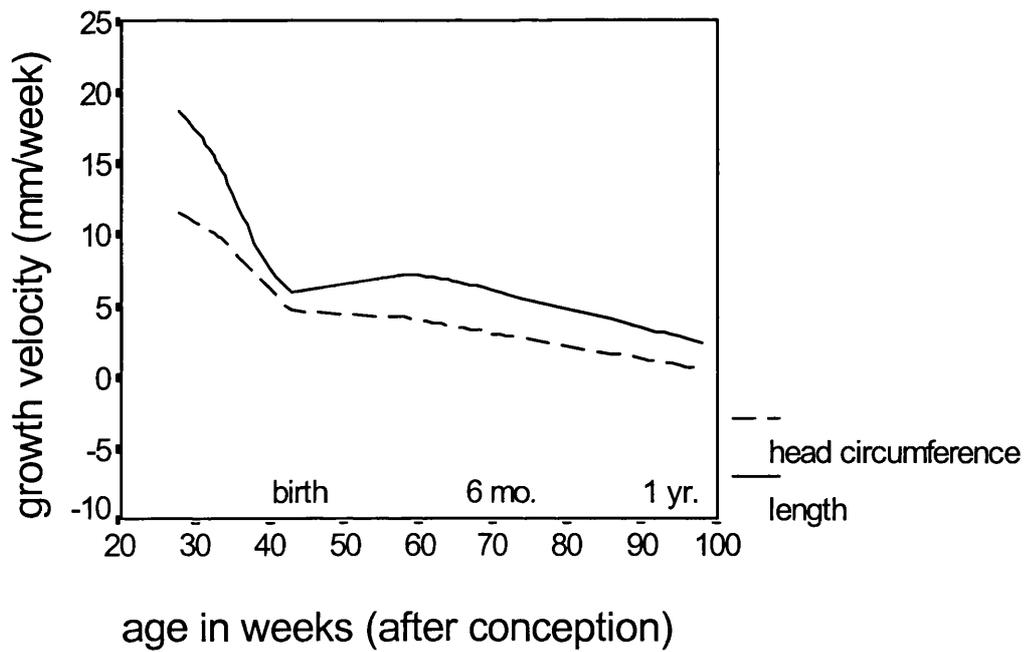


Figure 2.11 Growth velocity curves for head circumference and for body length as a function of age. Velocity is expressed in millimeters per week, scaled to time interval between measurements. A Lowess curve through the mean is applied to the data.

Following birth, body length undergoes a growth spurt. The body length growth spurt peak is reached at about 5 post-natal months, after which time growth in both the body length and head circumference decreases significantly. By one year of age, the head circumference grows by about 1.1 mm/week, while body length grows by about 3.20 mm/week. The head circumference growth velocity at this period is only 11% that of the velocity at about 32 gestation weeks. In contrast, the body length growth velocity is about 20% that of the 32 gestation weeks velocity. Thus, post-natal growth in body length exceeds that of the head circumference significantly.

These patterns of body length and head circumference growth are consistent with other studies utilizing ultrasound and anthropometric data, including those of Meredith (1971), Meire (1981), Fescina and Martell (1983) and Guihard-Costa and Larroche (1995), which show a significant decrease in head circumference and body length growth velocity during the last 2 months of pregnancy. Head circumference and body length growth slow between 30 gestation weeks and 1 year-of-life, with marked body length increase after birth through to about 4.5 months of age, thereafter slowing down again.

2.12b) Sex differences in growth curves

Although the human fetus and infant show a sex difference in weight, with males being larger than females (Hall 1981), in the University College London Hospitals data there is no statistically significant difference between males and females in terms of growth velocity and the inflection points on growth curves. This is not totally unexpected as other studies utilizing ultrasound data find no clear differences between the sexes in these parameters (Deter et al. 1982, Guihard-Costa and Larroche, 1995).

The lack of a significant difference between males and females in terms of head circumference and body length increment rate is illustrated in Figures 2.12 and 2.13

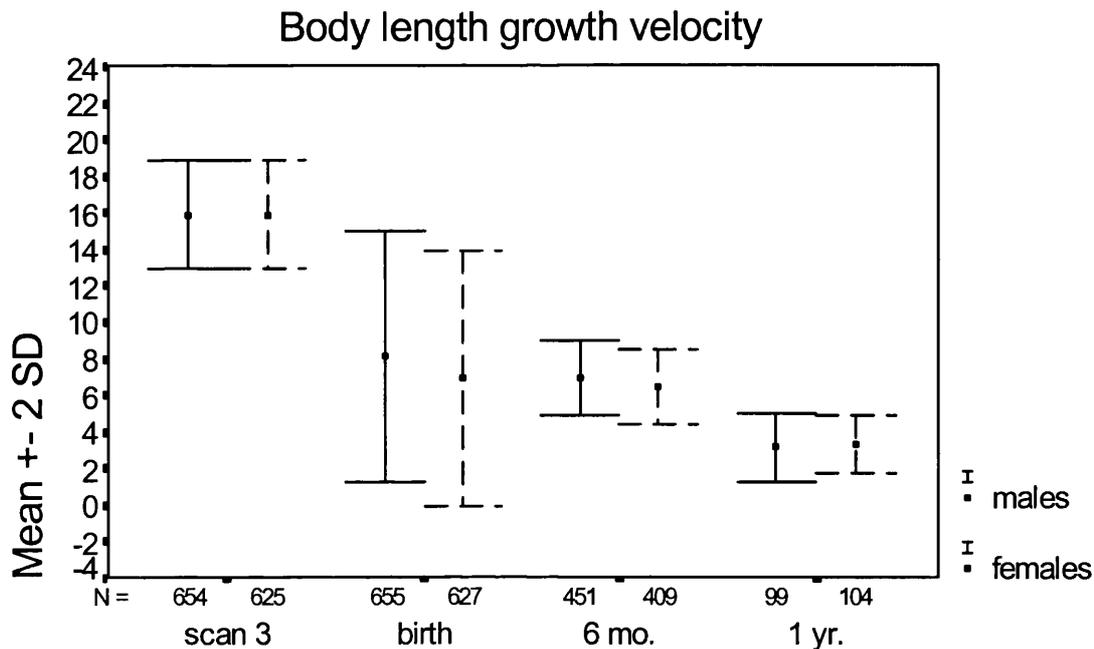


Figure 2.12 Human sex-specific means with error bars (+ or - 2 sd) illustrating body length growth velocity at different measurement periods. There is no statistically significant difference between average male and female velocities. Growth velocity decreases as a function of age and is most variable between ± 32 gestation weeks and birth.

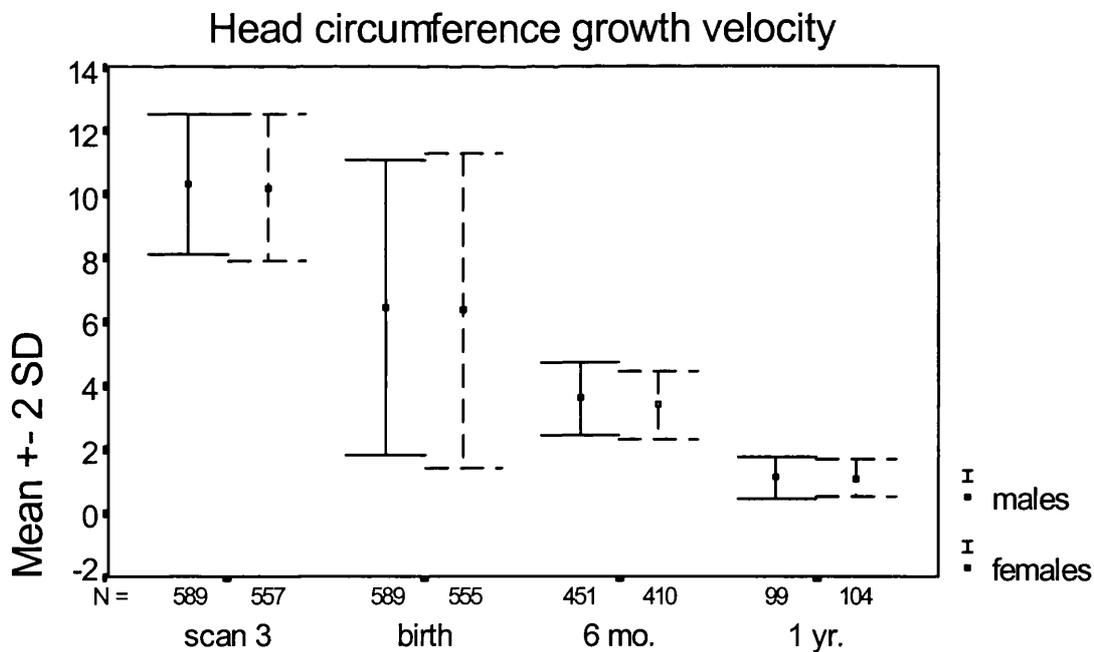


Figure 2.13 Human sex-specific means with error bars (+ or - 2 sd) showing sex-specific head circumference growth velocity at different measurement periods. There is no statistically significant difference between average male and female velocities. Growth velocity decreases as a function of age and is most variable between ± 32 gestation weeks and birth.

Female head circumference growth velocity decreased after birth at a slightly faster rate than in males, but the difference is non-significant. Body length growth velocity in females also decreased slightly more rapidly than in males from about 35 gestation weeks, however, this difference too is not statistically significant. See Table 2.28 for results of independent samples t-tests comparing measurement-specific sex differences in growth velocities.

In both males and females, prenatal growth exceeds that of postnatal growth. This difference is, however, greater for the head circumference. On average, 75% of head circumference at 1 year was already attained at birth, compared with 66% of 1 year body length. At ultrasound 2 (~2nd trimester) 64% of head circumference at 1 year was attained while 59% of 1 year body length was attained. At ultrasound 3 (~3rd trimester) 38% of 1 year head circumference was attained, compared with 34% of 1-year body length. There was, however, no statistically significant differences between the sexes in these parameters. These values reflect the fact that, as a proportion of size at one year, head circumference growth exceeds that of body length growth throughout the fetal period for both males and females and to a similar degree in both sexes.

The results in Table 2.28 show that there is no statistically significant difference between growth rates for the head circumference and body length in males and females.

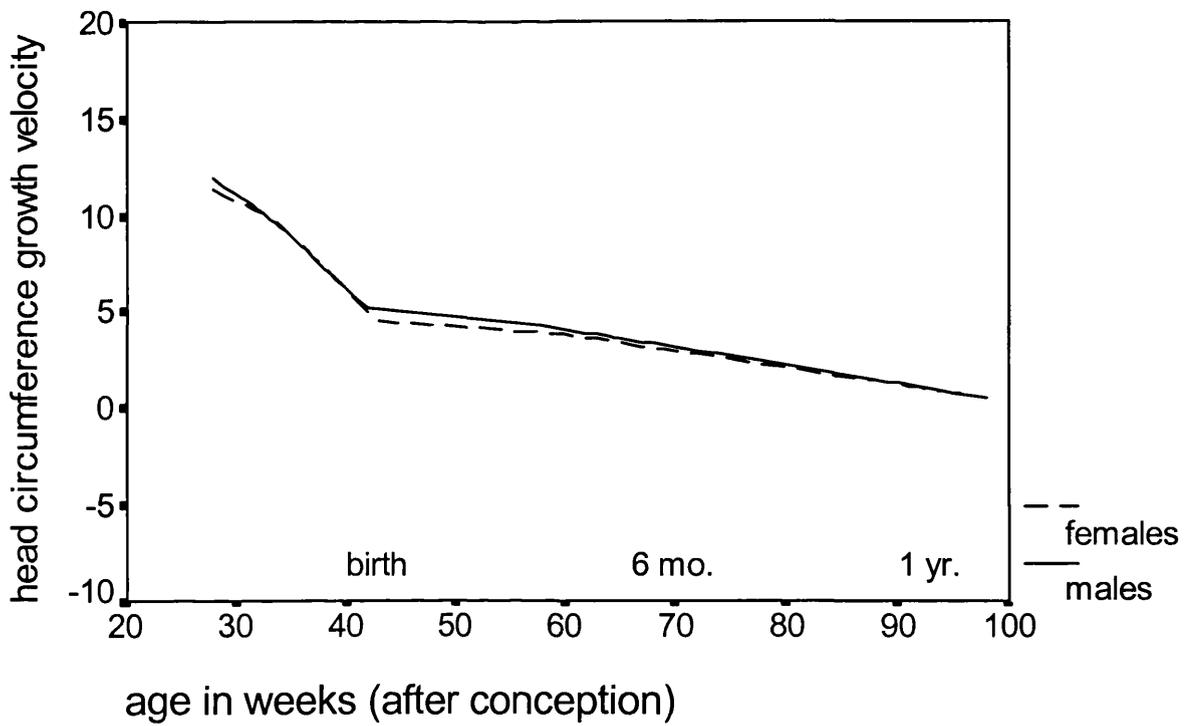


Figure 2.14 Sex-specific fetal and infant head circumference growth velocity curves, derived by fitting Lowess curves through the mean.

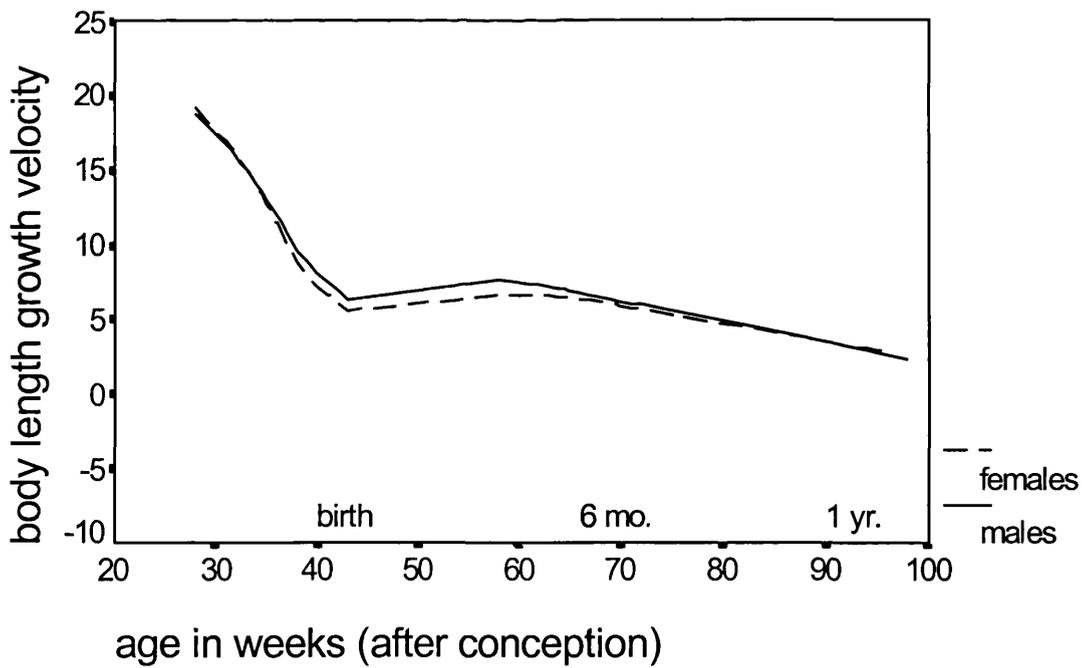


Figure 2.15 Sex-specific fetal and infant body length growth velocity curves, derived by fitting Lowess curves through the mean.

Table 2.28 Results of independent samples t-tests, comparing measurement-specific growth velocities between the sexes in humans

measurement	growth velocity mm/week	n females	n males	mean* difference	P
ultrasound 3	head circumference:	557	589	0.1	0.426
	body length [^] :	626	654	-0.0	0.783
birth	head circumference:	556	589	0.1	0.260
	body length:	633	657	1.3	0.233
6 months	head circumference:	410	451	0.2	0.240
	body length:	409	451	0.4	0.673
1 year	head circumference:	104	99	0.0	0.133
	body length:	104	99	-0.1	0.785

Growth velocity is the increment in size between measurement periods scaled to the time difference between those measurement periods. P = probability, F = F score, n = sample size

*A negative value indicates that females are larger than males

[^] estimated from femur length using Fazekas and Kósa (1978)

All measures expressed in millimeters/week for continuity between prenatal and postnatal periods

2.13) Non human primate fetal growth curves

2.13a) Rhesus macaque

Figure 2.16 is a growth velocity curve of head circumference (in mm) and femur length (in mm) as a function of gestation age (in days) in fetal rhesus monkeys. Figure 2.17 is the same curve in postnatal rhesus monkeys. The growth curves are derived by fitting a nonlinear regression curve through the data. The resulting equations follow the figures.

During the fetal period, head circumference grows more rapidly than femur length and the curve describing head circumference growth asymptotes about 20 days prior to that of the femur length. Postnatally, head circumference growth continues rapidly for the first 50 days and then slows down, while femur length continues to increase linearly.

Like humans, rhesus monkey femur and head circumference growth begins to slow down prior to birth. In addition, head circumference in the rhesus monkey continues to increase for almost 2 months after birth. Rhesus monkey femur length growth, however, differs from body length growth in humans in that it is linear. In humans, the body length growth curve is curvilinear and the prenatal body length growth trajectory is steeper than the postnatal trajectory. In rhesus monkeys, this is not the case.

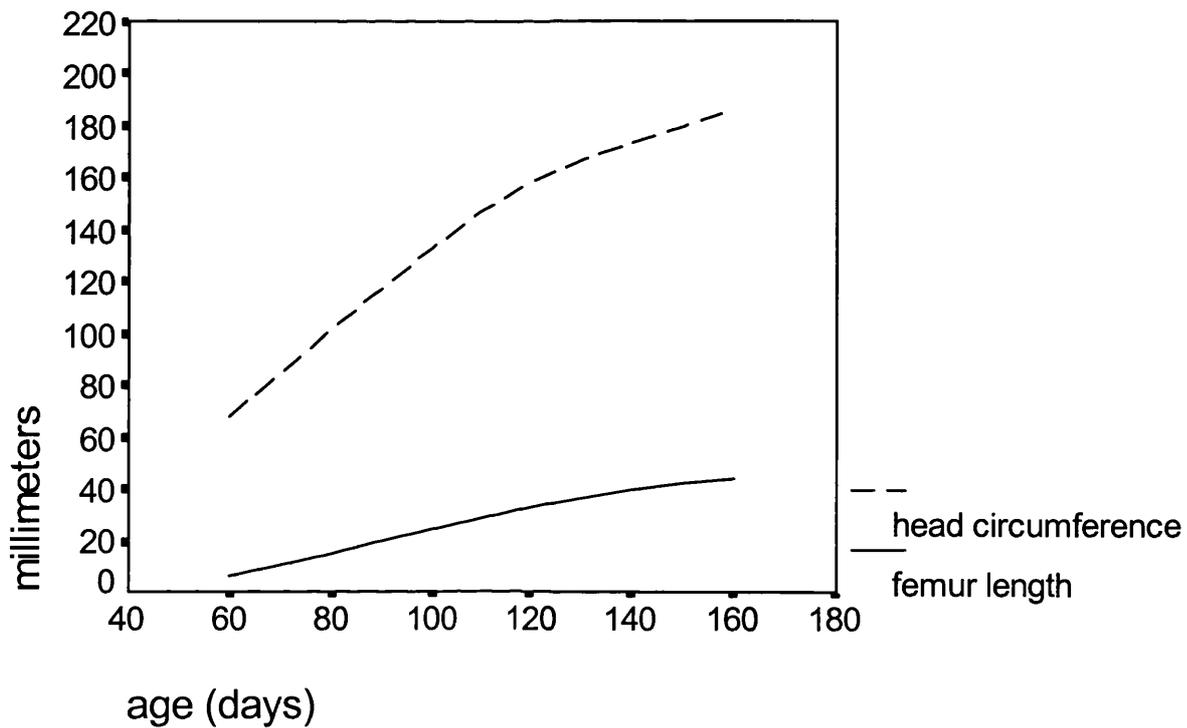


Figure 2.16 Prenatal head circumference and femur length growth curves in rhesus monkeys

The curve describing the relationship between fetal head circumference and age is:

(13)
$$\text{head circumference (mm)} = -89 + 3.1 * \text{age} - 0.01 * \text{age}^2$$

$$(r^2 = 0.970, \text{SE} = 9.6, n = 481, P = <0.0001)$$
age in days

The curve describing the relationship between fetal femur length and age is:

(14)
$$\text{femur length (mm)} = -30 + 0.67 * \text{age} - 0.001 * \text{days}^2$$

$$(r^2 = 0.984, \text{SE} = 9.6, n = 624, P = <0.0001)$$
age in days

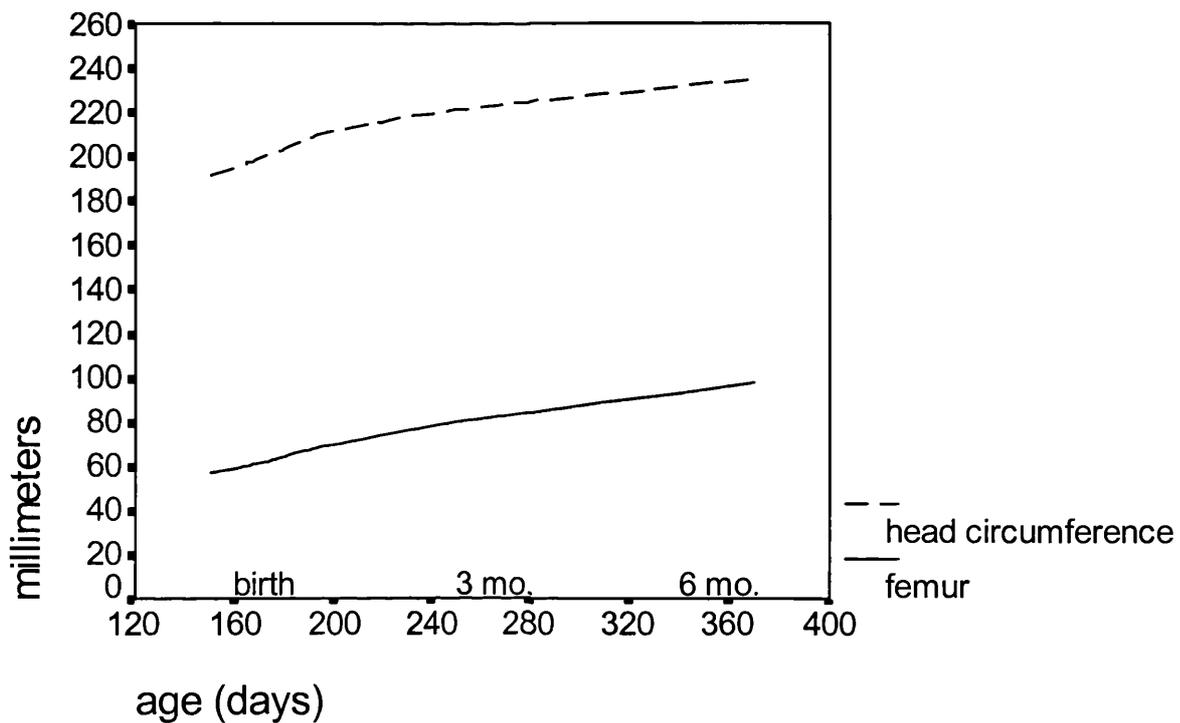


Figure 2.17 Postnatal head circumference and femur length growth curves in rhesus monkeys

The curve describing the relationship between infant head circumference and age is:

(15) head circumference (mm) = $108 + 0.72 * \text{age} - 0.001 * \text{age}^2$
 ($r^2 = 0.806$, SE = 6.5, n = 242, P = <0.0001)
 age in days

The curve describing the relationship between infant femur length and age is:

(16) femur length (mm) = $3 + 0.43 * \text{age} - 0.001 * \text{age}^2$
 ($r^2 = 0.913$, SE = 3.51, n = 244, P = <0.0001)
 age in days

2.13b) Baboons

Figure 2.18 includes the head circumference and femur length growth curves for fetal baboons. Like rhesus monkeys, baboon fetal femur length growth approaches a linear line, however, the head circumference curve is distinctly nonlinear. In baboons, fetal head circumference growth is rapid up to about 118 days, at which time the curve begins to asymptote. While head growth slows down prior to birth, this is not the case for femur length which continues to increase exponentially.

2.13c) Common marmoset

Because femur length measures were not available for the marmosets, and because fetal marmosets could not be sexed (due to multiple pregnancies), the growth curve for fetal head circumference alone is constructed here. Figure 2.19 shows the growth curve in fetal head circumference.

Head growth in the common marmoset is relatively linear compared to the growth curves of humans, rhesus monkeys and baboons. Rather than increasing rapidly during gestation and slowing down near to birth, marmoset head circumference appears to grow at a relatively constant rate throughout gestation, although it does slow down somewhat before birth. This differs markedly from the other primates (humans, rhesus monkeys and baboons) which have growth curves with clearer inflection points prior to birth.

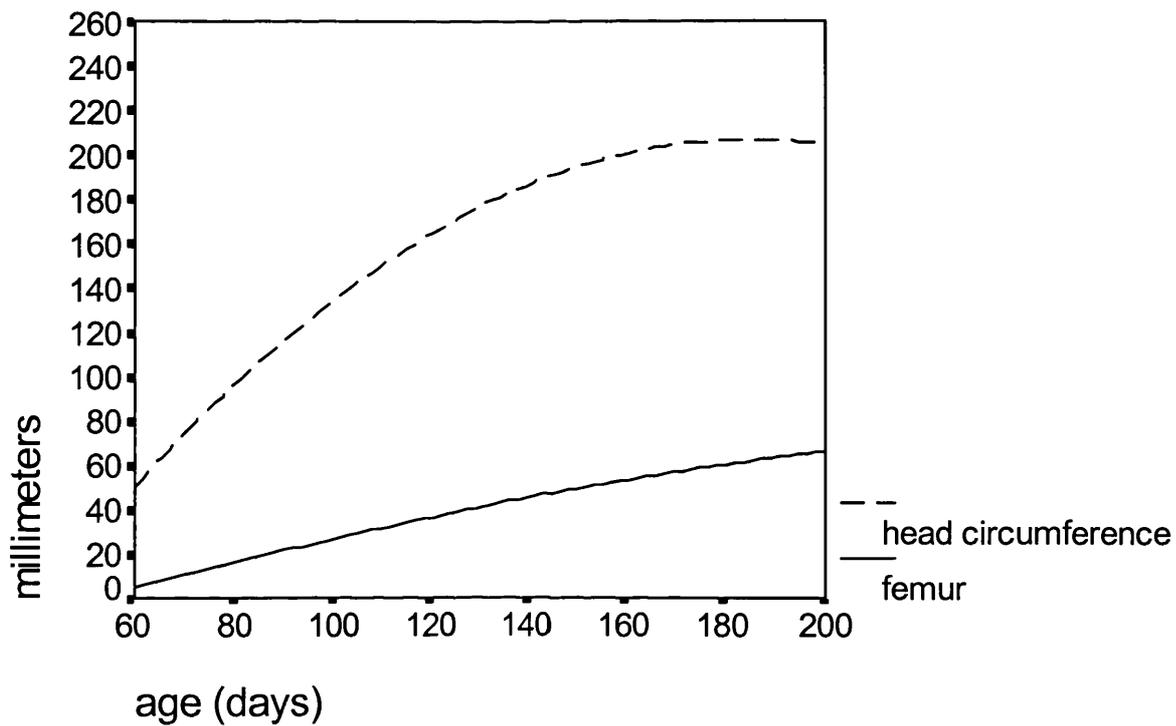


Figure 2.18 Head circumference and femur length growth curves in fetal baboons

The curve describing the relationship between fetal head circumference and age is:

(17) head circumference (mm) = $-136 + 3.7 * \text{age} - 0.01 * \text{age}^2$
 ($r^2 = 0.999$, SE = 7.4, n = 2359, P < 0.0001)
 age in days

The curve describing the relationship between fetal femur length and age is:

(18) femur length (mm) = $-34 + 0.72 * \text{age} - 0.001 * \text{days}^2$
 ($r^2 = 0.999$, SE = 1.1, n = 2352, P < 0.0001)
 age in days

2.14) Comparison of human and non-human primate fetal growth curves

In order to directly compare fetal growth trajectories between humans, baboons and rhesus monkeys, ages are expressed as a percentage of total gestation length, which is 280 days in humans, 180 days in baboons and 165 days in rhesus monkeys. Although birth does not occur at the same point between conception and final size in these species, it is used here as a timepoint at which to assess size. Figures 2.20 and 2.21 are scatterplots of femur lengths and head circumferences plotted against percent of gestation length in fetuses of the three species.

These figures show that the human head circumference growth curve (Figure 2.21) differs more starkly to those of the baboons and rhesus monkeys, than does the human femur length growth curve (Figure 2.20). The human head circumference growth curve approaches linearity while those of the other primates are clearly curvilinear (see equations 23 - 25). The human, baboon and rhesus monkey femur length growth curves, on the other hand, are very similar (see equations 20 - 22), with the exception of the intercepts, which for humans is higher. The human head circumference growth curve is, thus, distinct in that it levels off more slowly than in the baboons and rhesus monkeys. Thus, during later gestation, head circumference growth in humans exceeds that of baboons and rhesus monkeys.

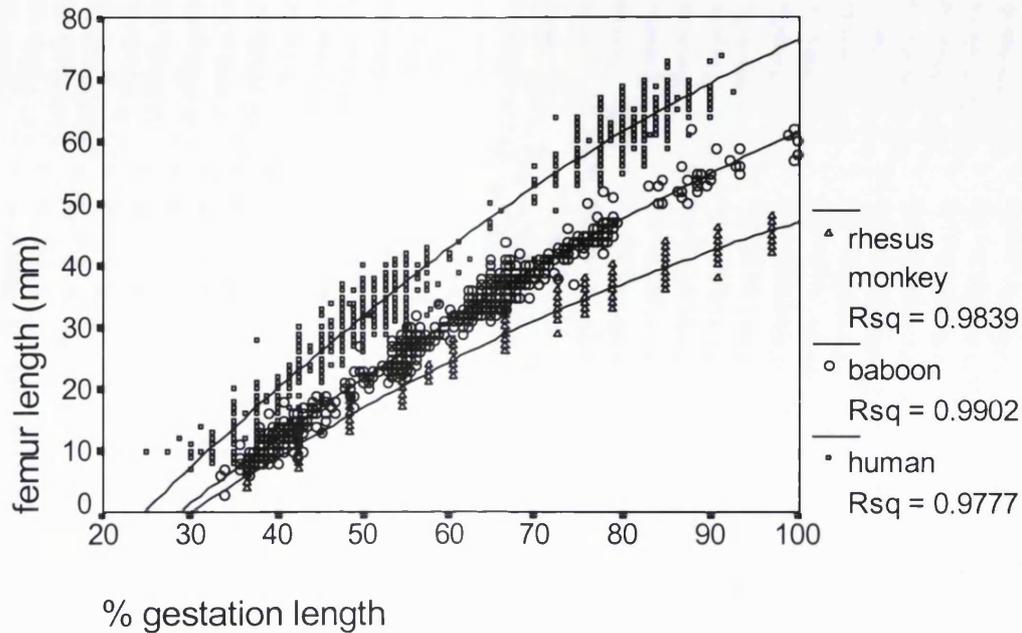


Figure 2.20 Comparative femur length growth trajectories, as a function of percent gestation length, between humans, baboons and rhesus monkey fetuses.

The curve describing the relationship between fetal femur length and percent of gestation length in humans:

$$(20) \quad \text{femur length (mm)} = -37.0 + 1.6 * \% \text{ gestation} - 0.005 * (\% \text{ gestation})^2$$

$$(r^2 = 0.990, n = 3188, P < 0.0001)$$

The curve describing the relationship between fetal femur length and percent of gestation length in baboons:

$$(21) \quad \text{femur length (mm)} = -33.2 + 1.3 * \% \text{ gestation} - 0.003 * (\% \text{ gestation})^2$$

$$(r^2 = 0.980, n = 2344, P < 0.0001)$$

The curve describing the relationship between fetal femur length and percent of gestation length in rhesus monkeys:

$$(22) \quad \text{femur length (mm)} = -30.0 + 1.1 * \% \text{ gestation} - 0.003 * (\% \text{ gestation})^2$$

$$(r^2 = 0.970, n = 622, P < 0.0001)$$

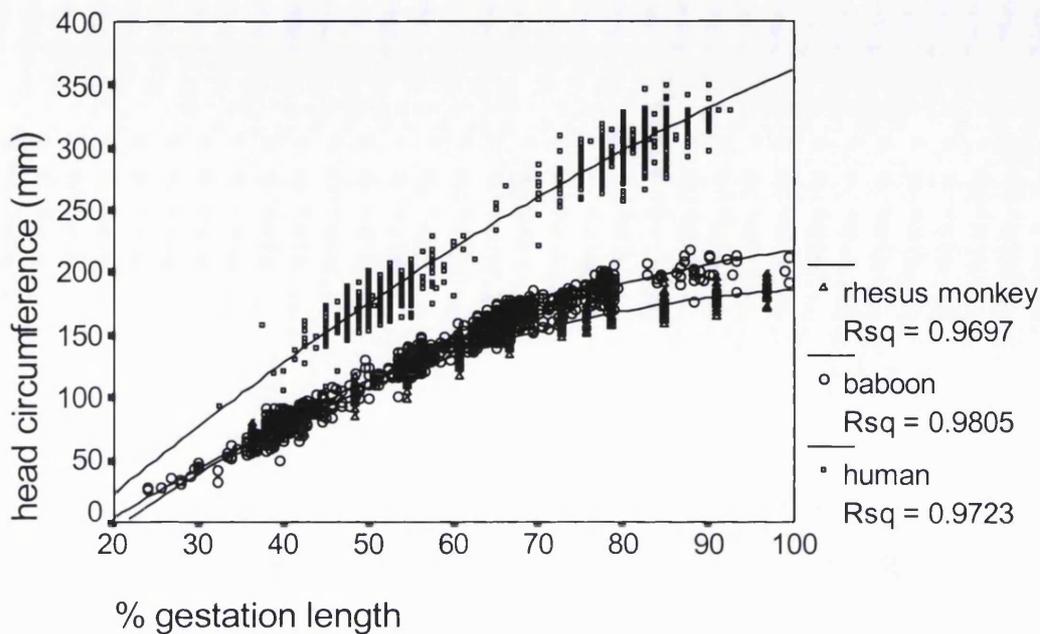


Figure 2.21. Comparative head circumference growth trajectories, as a function of percent gestation length, between humans, baboons and rhesus monkey fetuses.

The curve describing the relationship between fetal head circumference and percent of gestation length in humans:

$$(23) \quad \text{head circumference (mm)} = -96.0 + 6.3 * \% \text{ gestation} - 0.02 * (\% \text{ gestation})^2$$

$$(r^2 = 0.972, n = 2814, P < 0.0001)$$

The curve describing the relationship between fetal head circumference and percent of gestation length in baboons:

$$(24) \quad \text{head circumference (mm)} = -109.5 + 5.7 * \% \text{ gestation} - 0.02 * (\% \text{ gestation})^2$$

$$(r^2 = 0.981, n = 2367, P < 0.0001)$$

The curve describing the relationship between fetal head circumference and percent of gestation length in rhesus monkeys:

$$(25) \quad \text{head circumference (mm)} = -88.8 + 5.1 * \% \text{ gestation} - 0.02 * (\% \text{ gestation})^2$$

$$(r^2 = 0.970, n = 479, P < 0.0001)$$

2.15) Non-human primate growth velocities

Growth velocities could not be determined for the baboons due to the lack of identifying information for each individual. Nor could they be determined for the common marmosets as multiple pregnancies and the shifting position of fetuses made identifying the same individual between measures impossible. They are, therefore, shown for rhesus monkeys only.

As in the case of the humans, the growth velocities were calculated by dividing the difference between two size measures by the time elapsed between those measures. Figure 2.22 is a velocity curve for femur and head circumference as a function of age in the rhesus monkey.

In the rhesus monkeys, the velocity of femur growth remains fairly constant throughout fetal and early postnatal life. Head circumference, in contrast, undergoes a marked decrease in growth velocity up to about 145 gestation days, at which time it begins to level out. From this point through to infancy, head circumference growth velocity continues to decrease until reaching a fairly constant rate of increase by about 205 postnatal days. Rates of head and femur growth, therefore, differ markedly in the rhesus monkey. Like humans, head circumference velocity decreases in later gestation, however, in the rhesus monkey, velocity decrease occurs significantly earlier than in humans.

2.15a) Sex differences in non-human primate growth velocities

Figures 2.23 and 2.24 show that there are no clear differences between male and female growth velocities in the head circumference and femur length in rhesus macaques. Independent samples-tests comparing mean growth velocities within each trimester also show no statistically significant differences between male and female rhesus monkeys in terms of growth velocity (see Table 2.29).

2.16) Variation in growth trajectories

Longitudinal measures of head circumference and femur length growth allow for the assessment of intra-species variation in growth trajectories. In humans, there is marked variation in the head circumference and body length growth trajectories. Figures 2.25 and 2.26 show this variation in head circumference and body length growth trajectories between 6 randomly chosen individuals. It is clear that growth varies markedly between individuals and highlights the problems arising from predicting a mean growth trajectory from cross-sectional data.

2.17) Discussion

Fujimura and Seryu (1977) showed that head circumference growth velocity *in utero* peaks at about 31 gestation weeks in humans and then slows down until birth. Shortly after birth, head circumference growth velocity then peaks and continues to slow down thereafter. The results in Figure 2.11 of this chapter showed that head circumference growth velocity in the study sample population decreased during the late stages of pregnancy, from about 30 gestation weeks. After birth, a slight increase in head circumference growth velocity was evident, and gradual slowing down then followed. The peak in head circumference growth velocity at birth was not as marked as in Fujimura and Seryu's (1977) study, however. Fujimura and Seryu (1977) used cross-sectional data to examine pre- and postnatal head circumference growth velocity curves. This may, in part explain the different levels of velocity peak after birth. In addition, the study sample population included longitudinal measures taken at birth and then 6 and 12 months, while Fujimura and Seryu (1977) included cross-sectional measures for head circumference in daily increments from birth to 140 days.

The additional results in this chapter suggest that the head circumference and femur or body length growth curves differ in humans, rhesus monkeys and baboons, with head circumference growth velocity *in utero* exceeding that of the femur length. In addition, no statistically significant differences were found between growth velocities in males and females in both the head circumference and femur length. Between

species differences in growth trajectories were found for the head circumference, where human head circumference growth exceeded that of the rhesus monkey and baboon during the last third of gestation. Femur length growth trajectories, in contrast, did not differ significantly between the species, after considering body size differences between humans, rhesus monkeys and baboons.

The paucity of published data on comparative longitudinal growth in fetal primates makes it difficult to assess these findings in the context of existing research. Seier et al. (2000) have used ultrasound to measure fetal vervet monkeys longitudinally *in utero* (*Cercopithecus aethiops*). Unfortunately, they did not publish the fetal measures or growth curves. Longitudinal growth studies on fetal macaque species are by far the most common (see for example, Tarantal and Hendrickx 1988a,b; Conrad et al. 1995), and this is true also of postnatal longitudinal studies on growth in weight and length. Although growth in many more species has been studied postnatally, the macaques still predominate since they are used most regularly in biomedical research. Table 2.30 lists some examples of published studies on prenatal and postnatal growth in non-human primates.

This points to the need for more longitudinal measurement of growth in other primate species, and in apes in particular, in order to make the comparative study of growth and variation in growth more feasible and reliable. Presently, we rely on existing cross-sectional data which are inadequate for accurately assessing growth and give no indication of intra-specific variation in growth trajectories. Individual growth trajectories vary markedly between individuals as shown in Figures 2.35 and 2.36, and cross-sectional methods cannot take this variation into account. An additional problem is that authors tend not to publish their measures, making it impossible to quantify cross-species differences in growth.

Deacon (2002) has argued that human brain/body growth *in utero* parallels that of other anthropoid primates. Clearly this is not in agreement with the findings of this chapter. Here the growth trajectories between head circumference and femur length differed in humans, compared with the other primates.

Comparisons in the head circumference growth between humans, rhesus monkeys, baboons and common marmosets are examined in chapter 3.

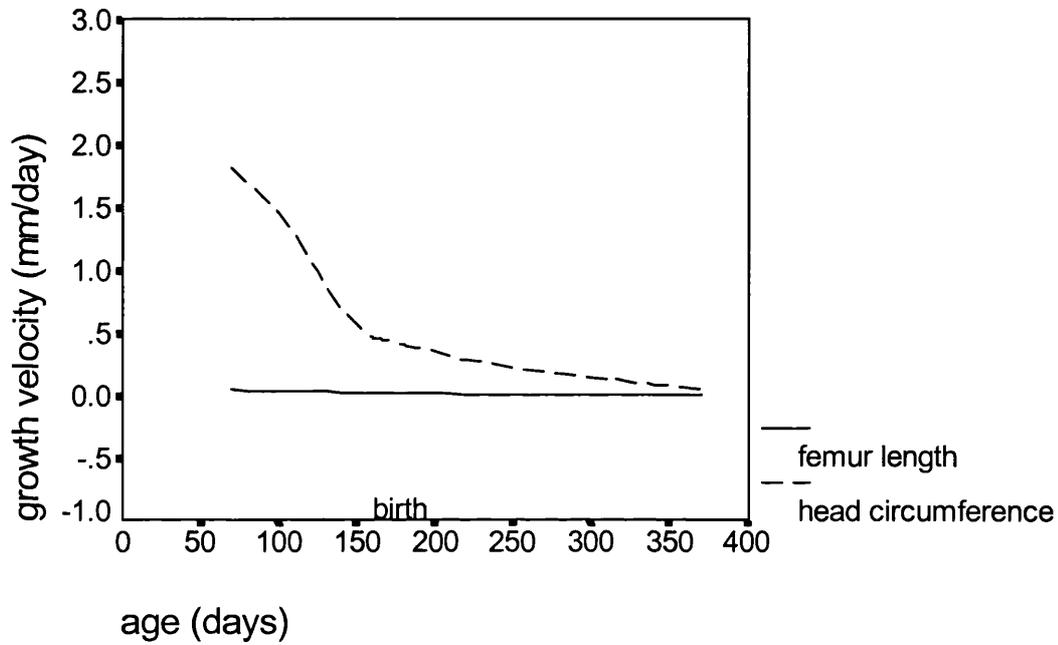


Figure 2.22 Head circumference and femur length growth velocity in fetal and infant rhesus monkeys, derived by fitting a Lowess curve through the mean. Age = post-conception days.

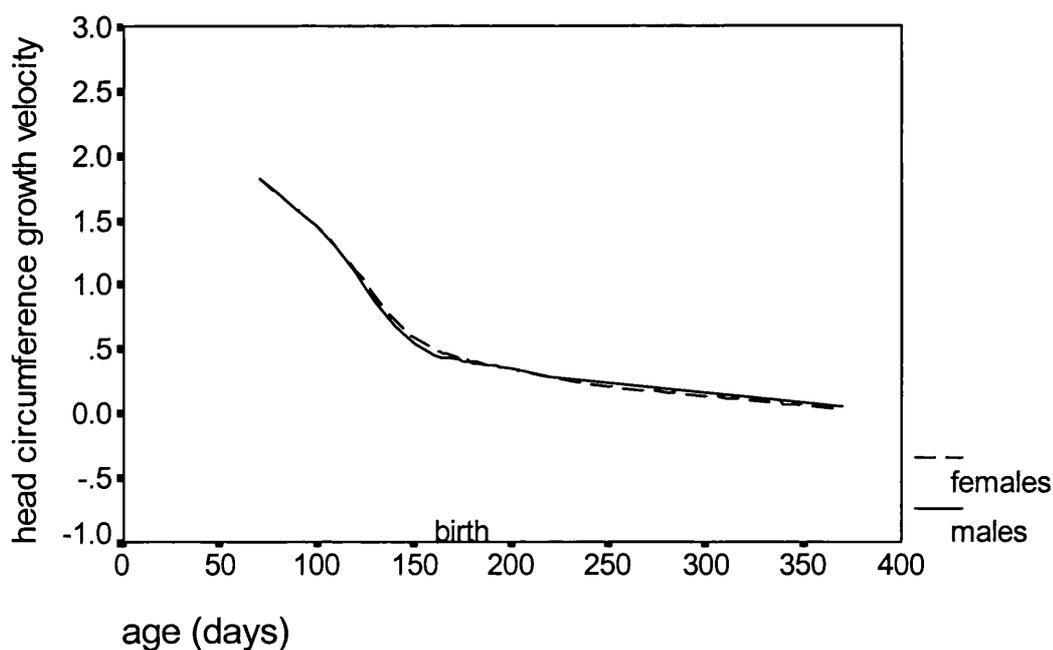


Figure 2.23 Head circumference growth velocity in male and female rhesus monkeys, derived by fitting a Lowess curve through the mean. Age = post-conception days.

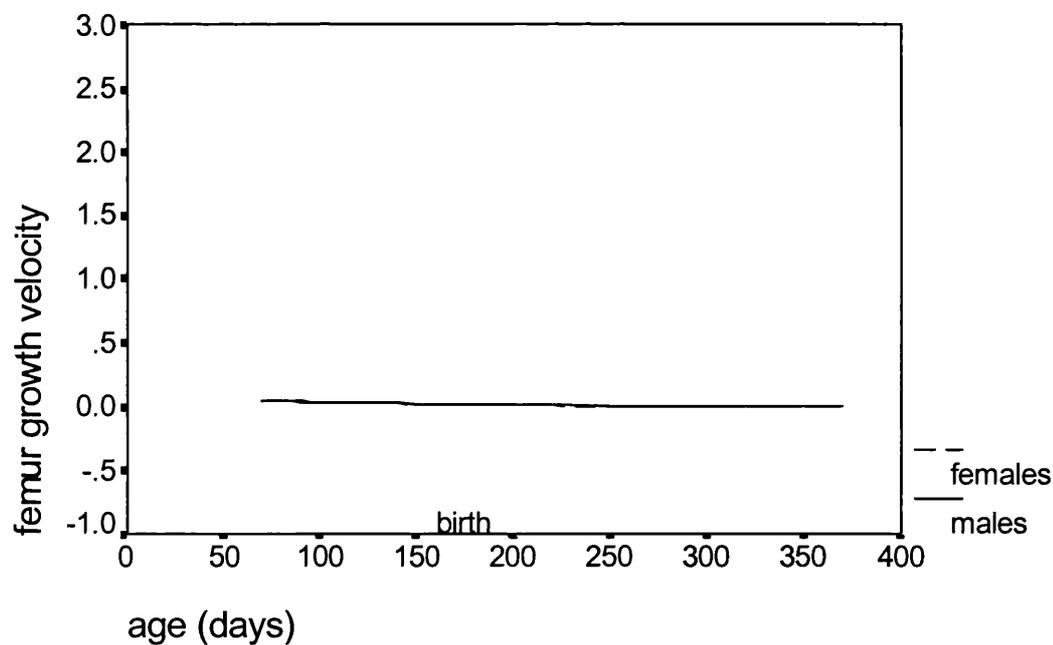


Figure 2.24 Femur length growth velocity in male and female rhesus monkeys, derived by fitting a Lowess curve through the mean. Age = post-conception days.

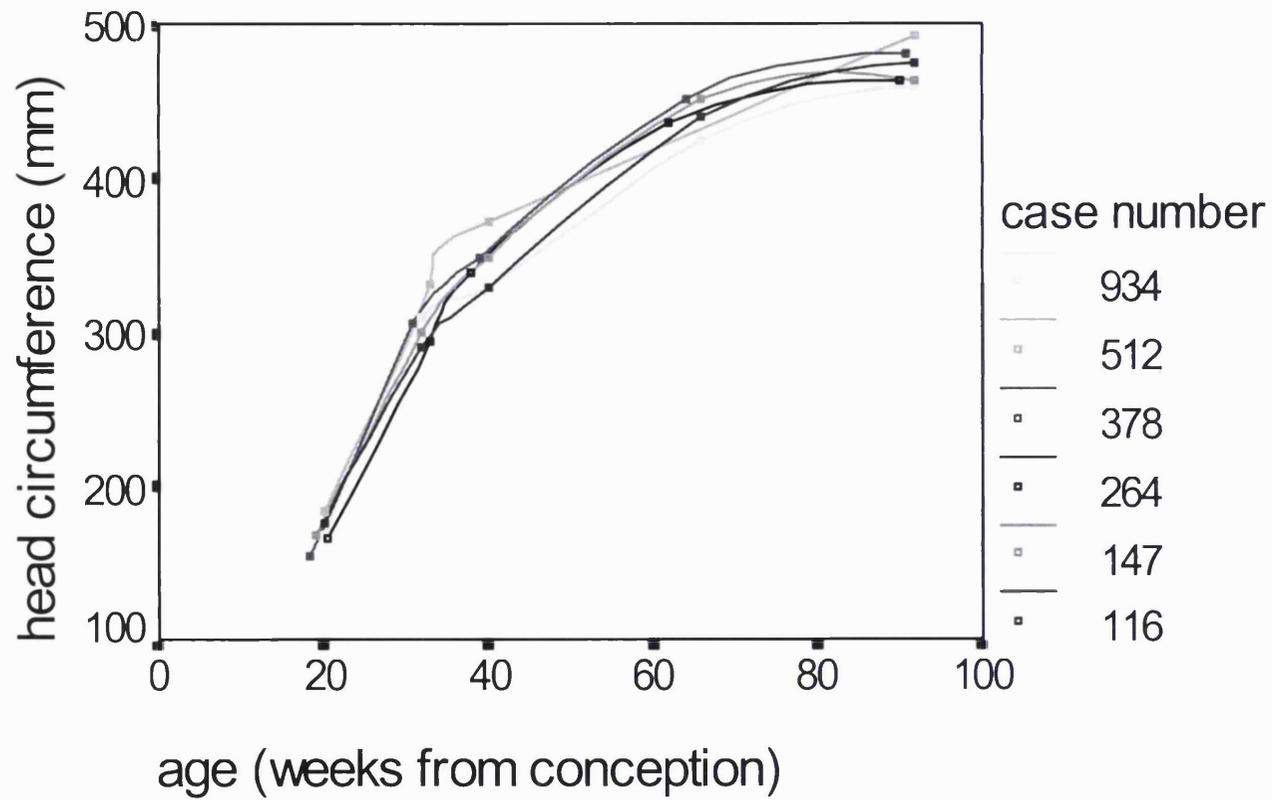


Figure 2.25 Human head circumference growth trajectories for six randomly chosen individuals illustrating intra-specific variation. Lowest curves fitted through data.

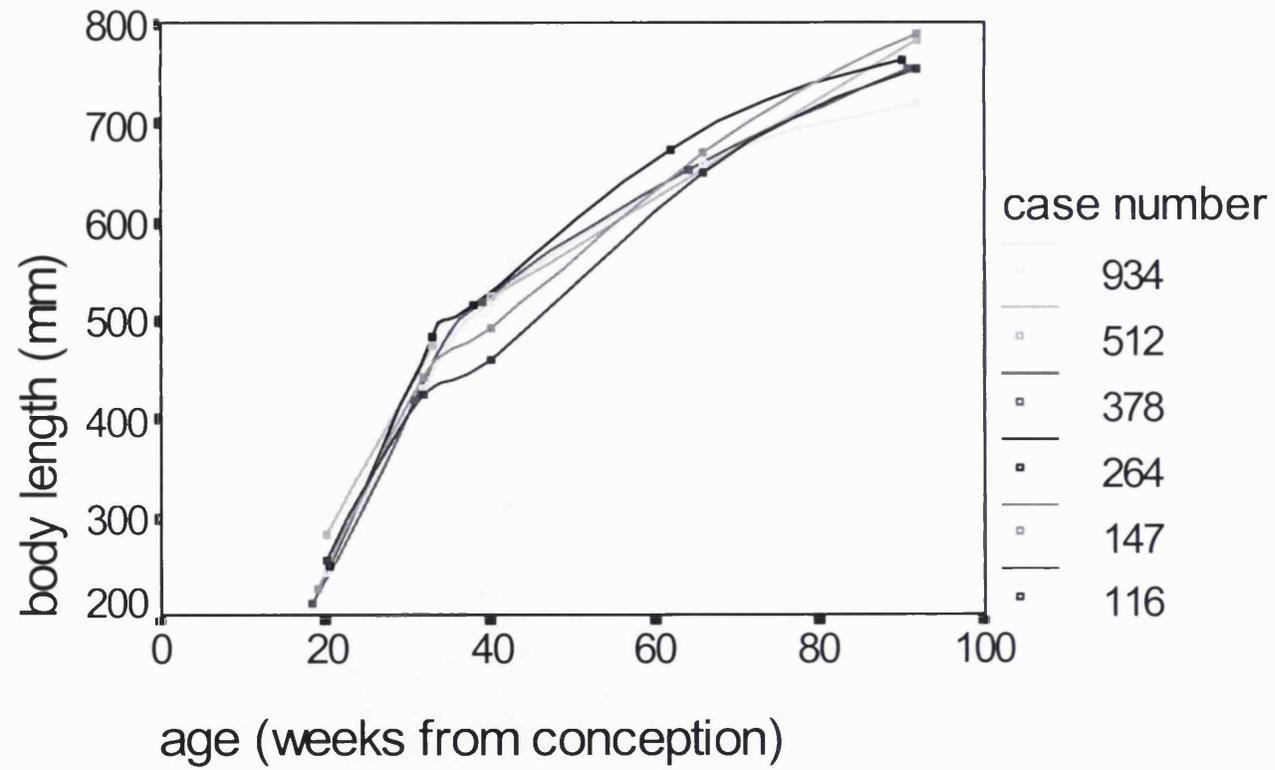


Figure 2.26 Human body length growth trajectories for six randomly chosen individuals illustrating intra-specific variation. Lowess curves fitted through data.

Table 2.29 Results of independent samples t-tests comparing rhesus monkey male and female growth velocities

trimester	mean difference (mm/day)	P
<i>head circumference velocity</i>		
2 nd trimester	0.03	0.669
3 rd trimester	-0.01	0.909
infancy	-0.01	0.885
<i>femur length velocity</i>		
2 nd trimester	0.00	0.785
3 rd trimester	0.00	0.887
infancy	-0.03	0.734

P = probability based on a two-tailed test of significance with a confidence limit of 95%

Table 2.30 Examples of studies on prenatal and postnatal longitudinal growth in non-human primates

common name	species	source
<i>Prenatal studies:</i>		
vervet monkey	<i>Cercopithecus aethiops</i>	Seier et al. (2000)
rhesus monkey	<i>Macaca mulatta</i>	Tarantal and Hendrickx (1988b)
crab-eating macaque	<i>Macaca fascicularis</i>	Tarantal and Hendrickx (1988a)
pig-tailed macaque	<i>Macaca nemestrina</i>	Conrad et al. (1995)
<i>Postnatal studies:</i>		
savannah baboon	<i>Papio cynocephalus</i>	Glassman et al. (1984), Coelho (1985)
squirrel monkey	<i>Saimiri sciureus</i>	Kaack et al. (1979)
patas monkey	<i>Erythrocebus patas</i>	Sly et al. (1978)
cebus monkey	<i>Cebus albifrons</i>	Fleagle and Samonds (1975)
marmoset	<i>Callithrix jacchus</i>	Neubert et al. (1988)
rhesus monkey	<i>Macaca mulatta</i>	Jacobson and Windle (1960), Kerr et al. (1969), Saxton and Lotz (1990), Schwart and Kemnitz (1992)
crab-eating monkey	<i>Macaca fascicularis</i>	Varavudhi et al. (1989)
stump-tailed macaque	<i>Macaca arctoides</i>	Scheffler and Kerr (1975)
pig-tailed macaque	<i>Macaca nemestrina</i>	Sirriani et al. (1975)
mandrill	<i>mandrillus sphinx</i>	Setchell et al. (2001)
chimpanzee	<i>Pan troglodytes</i>	Gavan (1953) and Smith et al. (1975)

CHAPTER 3

Patterns of fetal and infant brain growth

3.1) Aims of chapter

This chapter focuses on fetal and infant brain growth (in absolute terms), its associated costs and how human brain growth in early life differs from that of other non-human primates. Here, head circumference is used as an index of brain size. The chapter is divided into 2 main sections.

The first section deals with brain growth in general. First, brain growth and changes in the brain's chemical composition are described and the associated costs of brain growth are estimated. The relationship between body fatness and increases in brain size is also assessed by comparing the relationship between body fatness and relative brain size across vertebrate species.

In the second section of the chapter, previous work quantifying brain growth is described and methods for comparing brain growth between species are given. Gestation ages between humans and rhesus monkeys, baboons and common marmosets are standardised and Gompertz curves are fitted to the head circumference data (relative to age). Cross-species comparisons are then made by assessing differences in inflections points along the curves and differences in early head circumference size (as a proportion of size attained at birth). The relationship between brain and body growth, gestation length, and the length of hyperplastic and hypertrophic brain growth stages are then considered in light of these cross-species differences.

SECTION I: The brain in early life

3.2) Brain growth

The brain is comprised of non-regenerative tissue. Growth occurs via a combination of increase in cell number (hyperplasia) and increase in the size of component cells (hypertrophy). Initially cell division and increase in cell number predominate, followed later by an increase in cell size (Enesco and Leblond 1962, Winick and Noble 1965). Since the DNA content per diploid nucleus is constant within any one species, tissue DNA content is used as a measure of growth in cell number and reflects the extent of DNA synthesis that takes place during growth in the formation of diploid cell units. In contrast, growth in cell size or mass is assessed by calculating a ratio of either weight:DNA or protein:DNA per unit weight of tissue (Winick and Noble 1965, Winick 1968). Since weight is affected by dehydration, protein content is most often used as an estimate of cell size (Brasel and Gruen 1986).

The brain reaches its full complement of DNA early in postnatal life, unlike, for example, skeletal muscle which does not reach adult values until after adolescence. Indeed, total brain DNA continues to increase to at least 1 year-of-age and perhaps beyond 18 months (Winick and Rosso 1969). Brain growth is completed by about 4 postnatal years, although myelination continues through to about 20 years-of-life (Herschowitz 1988).

The most formative work on comparative cellular brain growth has come from studies of Winick (1968), Howard et al. (1969), Dobbing (1970) and Dobbing and Sands (1970, 1973). Together, their findings characterize human brain growth as a rapid activity due, primarily, to surges in brain cell number, cell size, synaptic connectivity and myelination during ontogeny. For a detailed description of structural brain development see Appendix, endnotes (1).

Dobbing's (1981) findings reveal that although there is a single growth spurt in brain weight, which peaks shortly after birth, there are two distinct growth spurts in brain cell number (see also Dobbing and Smart 1974). The first spurt occurs between 10-18 gestation weeks and extends through to the 5th or 6th gestation month. During this time rapid neuronal multiplication takes place as well as differentiation of non-

dividing neurons. For example, in a 3 week period, DNA content rises nearly 10-fold in the cerebrum (Howard et al. 1969). Interestingly, the human pattern of brain growth is similar to that of the rat and pig which also undergo a brain growth spurt shortly before birth and during early postnatal life (Dobbing 1976).

The second growth spurt is associated with a period of glial cell (non-conductive nerve cell) multiplication corresponding with the increase in brain weight, dendrite development, and synaptogenesis. Glial cell division is largely a postnatal event, peaking at about 3 months. Total brain DNA increase plateaus at about 18 postnatal months after which time cell size increase continues (Brasel and Gruen 1986 after Dobbing 1981). Like brain weight, cholesterol accumulation in the brain, an index of myelination, is marked by a single growth spurt (Dobbing 1970). Myelination begins prenatally in humans (at about 25 gestation weeks) and reaches peak velocity from birth to 1 year before turning to slow myelination which extends into adulthood (Davison and Dobbing 1966, Herschowitz 1988).

A further indication of early rapid brain growth comes in the form of gyri and sulci. The gyri are convolutions on the surface of the grey matter of the cerebral cortex, while the sulci are furrows. These develop from about 24 gestation weeks, reflecting the increasing surface area of the brain during development. A particularly marked increase in fissures and convolutions occurs between 28 and 30 gestation weeks, highlighting a profound spurt in brain growth and size increase (Dorovini-Zis and Dolman 1977).

While cortical thickness, in general, increases sporadically through to adulthood (perhaps due to remodeling of dendritic patterns), neuronal density increase is most rapid during prenatal life, plummeting around birth after which time it levels off almost completely (Rabinowicz 1986). Similarly, blood vessel density is closely associated with cerebral blood flow and metabolic demand. In the cerebral cortex, subcortical white matter, deep white matter, putamen and basis pontis, vessel density increases markedly during the middle to late fetal period and after birth (Miyawaki et al. 1998).

Clearly prenatal and early postnatal life are marked by a period of rapid and significant increase in brain size associated with a significant metabolic turnover. Indeed, from the seventh month of gestation into infancy, basal metabolic rate (BMR) increases more rapidly than either body weight or the sum of organ weights (Holliday 1971). This may suggest that hypertrophy, glial cell development, myelination, synaptogenesis and neuron development are metabolically costly. For example, Abrams et al. (1997) have shown that myelination, during late gestation, is associated with increases in local cerebral protein synthesis - associated specifically with the inclusion of the amino acid leucine (1CPS) into cerebral protein.

Protein synthesis is not the only crucial element for the growing brain. Particularly important for the human brain are long-chain unsaturated fatty acids, synthesised by two proteins: arachidonic acid and docosahexaenoic acid. These phospholipids comprise about 20% of the dry adult brain and play a crucial role in maintaining the structure of the membranes of the brain, both between and within neurons (Horrobin 1998).

There is some suggestion that the conflict between mother and fetus over long-chain fatty acids is, in fact, won by the fetus who parasitises maternal long-chain fatty acid supplies during pregnancy. A longitudinal Magnetic Resonance Imaging Study conducted by Holdcroft et al. (1997), reveals that the maternal brain atrophies during normal pregnancy, returning to normal weight by 6 postpartum months. These investigators report a small degree of atrophy in all segments of the brain equally during the pregnancy scan and thereafter. Unfortunately, brain size measures are not reported by Holdcroft et al. (1997) and the study included only 8 women. It is thought that this reversible cerebral atrophy reflects the loss of long chain fatty acids in the mother's brain in order to accommodate the needs for phospholipids in the growing fetal brain (see for example Horrobin 1998, Aiello et al 1999). Further histological study in this area is, however, needed as it is unclear whether this atrophy is associated with dehydration in the brain, or with lipid or cerebral spinal fluid loss. Furthermore, subjective ratings for the degree of atrophy seen are used by these investigators.

Adequate energy supply is crucial for normal brain growth. The fetal brain is particularly vulnerable during development when an assault can result in long-term and permanent cognitive deficit. The timing of the assault has a direct bearing on whether permanent deficits will result. The most critical period is that of the brain growth spurt, occurring at roughly 25 gestation weeks in humans, and the period directly preceding it when brain growth is achieved via hyperplasia (cell division). During this period, in particular, environmental, maternal and genetic factors can have serious and permanent effects as a result of reduced cell number development. These factors may include hypothyroidism, x-radiation and the inborn errors of metabolism, as well as undernutrition. In this scenario, 'catch-up potential' is not possible as cells grow by increasing in cell number rather than size. Only in the later stages of brain development when brain growth is largely an hypertrophic event (cell size increase) can 'catch-up growth' occur (Winick and Noble 1966, Dobbing 1970), as it does generally in preterm babies (Brandt 1976).

Langley-Evans and Langley-Evans (in press) have shown that micronutrient intake at specific gestation periods influence brain size at birth. In the first trimester, intakes of vitamin E, iron and folate were correlated with neonatal head circumference. Vitamin E in the third trimester was also correlated with neonatal head circumference.

Energetic stress at critical brain development periods is highly deleterious to the individual and may result in microcephaly and/or long-term cognitive or motor deficit (see Winick and Noble 1966, Barker 1994, Lucas et al. 1996), as well as somatic stunting (Dobbing 1976). These critical brain growth periods, along with increases in brain size, therefore, place a considerable demand for a stable, uncompromised energy source during the fetal and early infancy period (particularly during the growth spurt).

Where energy stress is evident, a number of physiological adaptations may take place which help to buffer the brain by diverting energy to the brain from other systems. This process is often referred to as 'brain sparing'.

3.3) Brain sparing

Unlike other organs (such as the liver, heart, and kidney), the brain cannot adapt to malnutrition by decreasing in size and metabolic requirement (Holliday 1986). Brain function and size are conserved, rather, through a physiological system that is 'flexible' and complex.

A significant proportion of the energy our bodies utilize during infancy is for accumulating and storing fats and proteins for potential energy (Spady et al. 1976). Energy invested in brain growth, on the other hand, cannot be stored. There are no fuel reserves in the form of either glycogen or triglycerols within the brain. The brain uses glucose exclusively as substrate and is dependent on a constant supply of that fuel (Kennedy and Solokoff 1957). Therefore, brain metabolism is critically dependent on the concentration of glucose in the blood (requiring a constant blood glucose level of about 80 mg/100 ml) in the adult (Lehninger 1975). If blood glucose levels fall to about 40 mg/100 ml, symptoms of brain dysfunction appear. At 20 mg/100 ml, coma is induced. Moreover, the relative amount of glucose needed during infancy is significantly higher than in the adult since brain metabolism forms a larger fraction of BMR during this period (Holliday 1971, Cornblath and Schwartz 1976). This 'vulnerability' poses a very serious threat to the individual organism.

During starvation, once liver glycogen is depleted, blood glucose is manufactured from other body sources in order to meet the needs of the brain. For example, body proteins normally performing important functions are sacrificed in order to maintain the blood sugar level. During gluconeogenesis in the liver, protein is broken down to form pyruvate or other intermediates of the tricarboxylic acid cycle in order to yield glucose. Digestive enzymes, followed by liver enzymes are lost first, to be followed by muscle proteins. Lipolysis and gluconeogenesis occur by utilising amino acids and glycerol as substrate (Cahill et al. 1966, Owen et al. 1967). When protein stores begin to decline, the brain acquires the ability to utilize blood ketone bodies (in particular D- β -Hydroxybutyrate produced during fatty acid oxidation in the liver) (Owen et al. 1967). Hence, body fat stores are broken down to slow down protein degradation.

This switch to ketone-body metabolism has no effect on mental capacity but is directly responsible for brain conservation during periods of starvation or malnutrition (Owen et al. 1967).

The physiological 'flexibility' driven by the brain's need for substrate, along with phenotypic flexibility of other organs during starvation, hints at the possibility that brain energy requirements may also drive phenotypic change in other metabolically costly organs, a possibility further explored in chapter 6. This may be the case, not only in adults, but also in growing individuals. This is evident in the fetal 'brain sparing' effect, observed antenatally using Doppler ultrasonography technologies.

Using this technology, flow velocity waveforms are recorded from the umbilical artery and from the cerebral artery in the fetus. The ratio of umbilical to cerebral blood flow is the pulsatility index, which is used to assess the magnitude of uterine blood flow to the brain. 'Brain sparing' is a mechanism which helps to prevent fetal brain hypoxia by preferentially shunting blood to the brain from the rest of the body. It is shown to occur as a compensatory mechanism involving hemodynamic redistribution. This preferential shunting occurs above a tolerance limit of 0.72 on the pulsatility index and is associated with significant growth retardation in the fetus (Scherjon et al. 1993) as well as maternal hemorrhage (Calvert et al. 1990) and impaired utero-placental oxygen flow and fetal hypoxia (Peeters et al. 1979, Bilardo et al. 1989). Evidently, the brain's requirements over-ride those of the other organs during periods of acute uterine stress.

A number of studies have documented a 'brain sparing effect'. For example, in severely underfed immature rats Dobbing and Widdowson (1965) showed that brain sparing takes place, resulting in a high brain:body weight ratio while body weight reaches only $\frac{1}{4}$ its normal value. Controlled protein deprivation studies carried out on rhesus monkeys also show that fetal brain parameters such as DNA, RNA, phospholipids, cholesterol and protein are unaffected (Cheek et al. 1976) and there is no effect on infant brain/body weight (Riopelle 1985) other than in the most extreme cases of deprivation. Here it is likely that brain conservation, at the expense of

somatic growth, predominates. Indeed, among the organs, brain growth is least affected by somatic growth rate and poor nutrition (Holliday 1986). In the adult, Dobbing (1976) notes that slow starvation, unto death, has no effect on brain weight or on the chemical composition of the whole brain.

3.4) Fatness and brain size

Because the storage of fat and, to a lesser degree, protein potentially provide a buffer for the brain, Kuzawa (1998) has argued that increased neonatal adiposity in our species may have accompanied our encephalisation. In addition, Aiello and Wells (in press) argue that increased fatness in humans may provide a buffer against seasonality, specifically, given the poor ability of reproducing females to cope with energy stress. Humans are one of the fattest mammals at birth, depositing significant quantities of fat *in utero*. The average neonate is comprised of about 14% fat at birth (Widdowson and Dickerson 1960), exceeding other mammals including seals. A newborn baby's fat content may supply up to 304 weeks in energy requirements, while other mammals are lean at birth (Girard and Ferre 1982).

Few published body composition data are, however, available for neonatal vertebrates, but it is possible to compare the relative fatness of human adults to that of other vertebrates. If, indeed, increased fatness is associated with encephalisation in our species, relative to less encephalised vertebrates, one would expect humans to have relatively more fat.

Cross-sectional body composition data were collected from the literature for 130 vertebrates, of which 113 had data on both body weight and fat. From these data, the percent of the body mass comprised of fat was calculated. Tables A.1(a-k) in the appendix list the body weights, sample sizes from which the values were calculated and the percent fat for each species, divided into tables according to order or infra-

order. They also list the sources from which data were taken. These data were derived using a number of different techniques including: whole carcass analysis, total body water measurement and Magnetic Resonance Imaging. For a detailed description of body composition measuring techniques see Appendix, Endnotes (2).

Several values are cited for humans including a reference male, female and pregnant and lactating females from different countries. Species values are expressed as mean values. Generally, males and females were pooled where sexual dimorphism in fat mass was not significant. Where values were cited for different times of the year, a mean value was calculated. Unfortunately, not all of the species for which data were available were wild-living species. This is true of the jaguar, tiger and lion specimens as well as the primates in this sample. The baboon, however, is noted as wild-feeding. Leigh (1994) showed that weight between captive and wild adult anthropoid primates is highly correlated. On average, males are less than 3 kg heavier in captivity and females are less than 1.5 kg heavier in captivity. It is reasonable to assume, therefore, that fat as a percentage of total body weight is slightly elevated in these captive specimens.

Average species body sizes were taken from Silva and Downing (1995) when not given by the authors. This did not have a bearing on the adiposity values as they were cited by the authors as fat as a percent of body mass. These include Lynch and Wellington (1963), Pearson (1963), Bamford (1970), Tarasoff (1974), Walike et al. (1977), Pond (1985), Hilderbrand et al. (1988), Buskirk and Harlow (1989), Holand (1992), Parker et al. (1993), Ryg et al. (1990), Wirminghouse and Perrin (1993).

Table 3.1 lists the order-specific mean body fat values. Here, humans are separated from other primates in the sample. Along with humans, cetaceans, pinnipeds and chiropterans have the greatest fatness with more than 20% of body weight comprised of fat. However, all but one of the bats in the sample were hibernating at measurement and were likely, therefore, to have increased fat stores and reduced energy expenditure. In humans, increased fatness cannot be explained by modern

lifestyle as Frisch (1987) has shown that the human female requires at least 18% body fat for normal function.

Since cetaceans and pinnipeds, along with humans, are notably encephalised mammals, these results warrant further investigation into the relationship between body fatness and encephalisation. Ideally, data for the same individual should be used and animals should all be measured prior to hibernation (if applicable), reproduction, and seasonal nutritional stress. In addition, brain weights and body fat measures should be collected within the same individual.

For the purposes of Kuzawa (1998) and Aiello and Wells (in press) arguments and this thesis, these results suggest that humans (particularly females) are relatively fat, and it is, therefore plausible that this aspect of our body composition may have evolved in response to encephalisation. Unfortunately, corresponding brain weight data were unavailable for the majority of the species in the vertebrate body fatness dataset, so that the relationship between encephalisation and body fatness could not be directly assessed here. These results are, therefore, only preliminary and further analysis is required for confirmation. The direct relationship between body fatness and brain size should be assessed in mammals in general, and primates in particular.

3.5) Changes in brain chemical composition during growth

Like the rest of the body, the brain undergoes chemical maturation throughout ontogeny, gradually becoming less hydrated and comprised of proportionately more protein (Schultz et al. 1961, Svennerholm and Vanier 1972, Dobbing and Sands 1973). At 20-22 gestation weeks, water comprises about 92.2% of the brain. At birth the brain is 89.7% water and 77.4% water in the adult (Widdowson & Dickerson 1960). On the other hand, the protein (DNA) and fat (cholesterol) content of the brain increases with fetal age as shown in Table 3.2 which lists cerebrum chemical composition values from Dobbing and Sands (1973).

Table 3.1 Order-specific means for fat as a percent of body weight

Order	n	mean % fat	sd	cv
Aves	46	8.9	7.8	87.3
Rodentia	16	15.6	12.2	78.4
Carnovora	19	12.6	7.5	59.7
Chiroptera	4	21.4	9.1	42.3
Artiodactyla & Perrisodactyla	18	17.5	9.9	56.5
Marsupia	12	14.0	8.8	62.5
Cetacea	3	25.2	3.8	15.0
Pinnipedia	8	28.8	10.5	36.6
Primates (excluding humans)	10	13.5	10.4	76.7
Humans (NPNL)	7	22.8	6.1	26.9

n = sample size, sd = standard deviation, NPNL = non-pregnant and non-lactating,
cv = coefficient of variation

Table 3.2 Water, cholesterol and deoxyribonucleic acid content in the cerebrum

age (weeks)	cerebrum mass (g)	water (g/kg)	cholesterol (g/kg)	DNA (μmol)
Fetuses:				
10-13	0.61 - 1.95	911	2.88 - 3.86	7.73 - 23.5
16	11.4	911	3.62	106
17	16.5	908	3.49	159
18	21.7	909	4.10	196
19	31.1	915	4.24	251
21	51.7	894	4.92	348
27	104	915	5.51	393
30	140	897	5.94	474
33	218	904	5.87	651
38	330	887	7.27	698
40	336	887	7.44	656
Children:				
1	402	884	7.32	662
6	435	881	9.00	717
13	522	868	9.83	882
26	765	851	11.93	1042
43	767	830	13.38	1261
61	863	822	15.84	1660
104	996	821	16.10	1317

Taken from Dobbing and Sands (1973). DNA is estimated from phosphorus content. The small reduction in cholesterol content at 33 gestation weeks is likely an artifact of the brain used at that time.

3.6) Modeling energetic costs of brain growth

Changes in the chemical composition of the brain are important in terms of assessing the energetic costs of brain growth. Because water is metabolically inactive, changes in water content within the brain must be taken into account when estimating the costs of age-specific increases in brain weight. Equally, relative increases in protein and fat within the brain must also be considered in light of the different metabolic costs of depositing and synthesising fat and protein.

Water, fat and protein weight in the brain was estimated using Dobbing and Sands (1973) data listed in Table 3.2. Since the cerebrum comprises just under 90% of total brain weight in the adult (calculated from values given by Stephan et al. 1981), a constant rate of hydration between the cerebrum and total brain was assumed when calculating total brain hydration values. It is reasonable to apply the adult value to the sub-adults as Duara et al. (1984) have shown that rates of brain oxidative metabolism in humans do not vary with age.

Table 3.3 lists the estimated weights of water, cholesterol and protein in the cerebrum in the fetus and child and the percent of those constituents to total cerebrum weight. We know that the costs of depositing fat and protein are 9.25 kcal/g and 5.65 kcal/g, respectively (Roberts and Young 1988). It is, therefore possible to assess the costs associated with brain growth, controlling for changes in chemical composition.

Table 3.4 lists the increments in the metabolically active part of the cerebrum during the fetal and infancy periods and the growth in brain fat (cholesterol) and protein (DNA) specifically. It also lists the estimated weekly metabolic costs for brain growth. First, the weekly increments in 'non-water' brain tissue were calculated using estimates of brain water content and weekly brain tissue increase from Dobbing and Sands (1973). Second, the weekly increments in fat and protein were calculated and

finally the costs associated with fat and protein deposition were estimated using Roberts and Young's (1988) estimates for the cost of depositing fat and protein.

According to the estimates from Table 3.4, from 16 to 40 gestation weeks, the absolute cost of growing metabolically active cerebral tissue is 15.5 kcal. If we assume that total brain weight is about 10% more than cerebral weight (Stephan et al. 1981), an additional 1.6 kcal may be added to this estimate. The additional costs of fetal protein and fat synthesis are about 6 kcal for this amount of growth. Thus, from 16 to 40 gestation weeks, about 23 kcal are utilised for brain growth specifically. From birth to 2 years of age, about 1,068 kcal are utilised for brain growth plus roughly 390 kcal for protein and fat synthesis. The remaining energetic cost associated with the brain is, therefore, linked to brain maintenance (basal metabolism) which is significant (~240 kcal/kg/day). The brain's basal metabolic requirement is about 96 kcal/day in a neonate with a brain weight of 400 grams. Brain growth *per se*, does not, therefore, appear to impose significant costs to the fetus and infants. Rather maintaining that metabolically highly active tissue seems to pose the major energetic cost.

Table 3.3 Estimated weight of water, cholesterol and protein in the cerebrum

age weeks	cerebrum mass (g)	water (g)	% water	cholesterol (g)	% cholesterol	protein (g)*	% protein
Fetuses:							
16	11.4	10.4	91.1	0.04	0.35	0.97	8.5
17	16.5	15.0	90.8	0.06	0.36	1.46	8.9
18	21.7	19.7	90.9	0.09	0.41	1.88	8.7
19	31.1	28.5	91.5	0.13	0.42	2.51	8.1
21	51.7	46.2	89.4	0.25	0.48	5.23	10.1
27	104	95.2	91.5	0.57	0.55	8.27	8.0
30	140	126	89.7	0.83	0.59	13.6	9.7
33	218	197	90.4	1.28	0.59	19.7	9.0
38	330	293	88.7	2.40	0.73	34.9	10.6
40	336	298	88.7	2.50	0.74	35.5	10.6
Children:							
1	402	355	88.4	2.94	0.73	43.7	10.9
6	435	383	88.1	3.92	0.90	47.8	11.0
13	522	453	86.8	5.13	0.98	63.8	12.2
26	765	651	85.1	9.13	1.19	105	14
43	767	637	83.0	10.3	1.34	120	16
61	863	709	82.2	13.7	1.58	140	16
2 years	996	818	82.1	16.0	1.61	162	16

Calculated from cerebrum water, cholesterol and DNA values reported by Dobbing and Sands (1973). GW = gestation week

* calculated as the difference between cerebral weight and the sum of water and cholesterol weights

Table 3.4 Estimated weekly costs for brain growth

age weeks	increase in cerebrum (g/week)	increase in metabolically active tissue* (g/week)	increase in fat (g)	increase in protein (g)	†metabolic cost of brain growth g/ week
Fetuses:					
16-17	5.1	0.47	0.002	0.042	0.25
17-18	5.2	0.47	0.002	0.041	0.25
18-19	9.4	0.80	0.003	0.065	0.40
19-21	10.3	1.09	0.005	0.110	0.67
21-27	8.7	0.74	0.004	0.059	0.37
27-30	12	1.24	0.007	0.120	0.75
30-33	12.7	1.22	0.007	0.110	0.69
33-38	22.4	2.53	0.018	0.267	1.68
38-40	3.0	0.34	0.003	0.036	0.23
Children:					
1-6	5.5	0.65	0.006	0.072	0.46
6-13	12.4	1.64	0.016	0.200	1.28
13-26	18.7	2.79	0.033	0.383	2.47
26-43	0.12	0.02	0.000	0.003	0.02
43-61	5.3	0.94	0.015	0.152	1.00
61-104	3.1	0.55	0.009	0.090	0.59

*metabolically active tissue = cerebrum weight - water weight (g)

† sum of the cost of fat and protein at 9.25 kcal/g and 5.65 kcal/g

SECTION II: Quantifying and comparing brain growth across species

3.7) Previous work quantifying brain growth

3.7a) Brain growth in humans

Dobbing and Sands (1973, 1978) constructed brain growth curves using brain weights and biparietal occipito-frontal diameters during the last trimester of gestation and the first 2 years of postnatal life. They showed that both brain weight and head circumference growth velocities peak prior to birth and decrease dramatically thereafter. Dobbing and Sands (1978) showed that head circumference and brain weight growth and velocity curves differ, however, in that the head circumference growth spurt occurs at about 30 gestation weeks, while the brain weight spurt occurs about 6 weeks later. In addition, head circumference growth velocity after birth decreases more rapidly than that of the brain.

Although Dobbing and Sands (1973, 1978) constructed growth curves for the brain and head circumference, they did not express changes in size relative to age as SD scores. Nor did they take sex and body size into account in any way, so that only absolute changes in brain size over time could be described.

In contrast, Brandt (1976) expressed growth in head circumference after birth to 18 months as SD scores as a function of age. She also separated the sexes and constructed sex-specific head circumference growth and velocity curves. Although Brandt did not take the effects of body size into account when constructing these curves, he did compare the head circumference curves of small-for-gestation age neonates, appropriate-for-gestation age neonates, preterm babies, term babies and

monozygotic twins. He, therefore, went one step further than Dobbing and Sands by introducing the need for quantify intra-specific variation in head circumference growth.

Meire (1986) constructed a fetal growth reference for the biparietal diameter from about 13 gestation weeks to term, thus allowing individual BPD measures to be plotted against a 'normal' curve in order to assess head growth over time. Unfortunately, he did not publish the head circumference growth curve, nor did he establish sex-specific curves for the biparietal diameter.

Deter et al. (1982) constructed separate growth curves for male and female fetuses and expressed biparietal and head circumference diameters as SD scores. In addition, they showed that by plotting the ratio of head circumference to abdominal circumference against age, marked variability is present. Unfortunately, the authors did not construct growth curves for the biparietal diameter: abdominal circumference ratio.

Guihard-Costa and Larroche (1995) constructed growth curves for the head circumference and biparietal diameter (using ultrasound) and fresh brain weight (from autopsy materials) and establishing the 5th, 10th, 25th, 75th, 90th and 95th centiles. They also established growth velocity curves for these parameters and showed the presence of sexual dimorphism in these parameters. Guihard-Costa and Larrouche (1995) then went one step further by plotting brain and body weight, biparietal diameter and abdominal circumference and biparietal diameter and femur length, from autopsy materials. Unfortunately, the authors did not provide a means for quantifying the relationships between these variables, but only published a scatterplot depicting the relationships. In addition, they did not construct sex-specific growth curves even though they showed the presence of sexual dimorphism in these variables.

In sum, a number of studies have been undertaken to quantify growth in the brain and head. These studies do not, however, take body size into account when quantifying changes in brain or head size or growth velocity. Ideally, sex-specific growth curves yielding SD scores should be established, and growth curves for relative head and brain size constructed in order to control for the allometric relationship between the head and body. Even though Guihard-Costa and Larroche (1995) acknowledge this relationship, they do not provide a method for quantifying growth and velocity in relative brain size.

3.7b) Non-human primate fetal brain growth

The use of non-human primates in biomedical research has led to an increase in the quantification of normal fetal growth, using ultrasound. Head circumference or biparietal diameter measures are routinely measured during ultrasound and used as a proxy for brain size and a number of papers describing head growth have been published. Unfortunately, most of these are carried out in macaques, so that comparative analyses are generally confined to just a few species, for example the pig-tailed macaque (*Macaca nemestrina*), the crab-eating macaque (*Macaca fascicularis*) and the rhesus macaque (*Macaca mulatta*) (see Tarantal and Hendrickx 1988a,b and Conrad et al. 1995). Corradini et al. (1998) have published ultrasound measures in capuchin monkeys (*Cebus appella*).

In all of these species, head growth is curvilinear, slowing down in later gestation. In the macaques, this occurs at roughly 115 gestation days, while in cebus monkeys, at about 103 gestation days. By birth, macaques and cebus monkeys have head circumferences that are roughly the same size (~175mm).

3.8) Methods for comparing brain growth between species

Head circumference is considered a good and reliable indicator of brain weight (Cooke et al. 1977, Fujimura and Seryu 1977, Epstein and Epstein 1978, Gilles et al. 1983) and intracranial volume (Bray et al. 1969, Buda et al. 1975) during the prenatal

period and the first year-of-life (Bray et al. 1969, Dobbing 1970). Head growth and brain development during the first two years of life are closely related (Bray et al. 1969, Winick and Rosso 1969, Dobbing 1970).

The linear relationship between postmortem brain weight and head circumference for appropriate-for-age infants (ranging in age from 18 to 43 gestation weeks) is described by the relationship where:

$$(26) \quad \log_{10} BW = 3.003 * \log_{10} OFC - 2.0306$$

BW = brain weight in grams and OFC = occipito-frontal head circumference in centimeters. (R = 0.981, SE = 0.097, N = 422) (Cooke et al. 1977)⁶.

As noted, head circumference can be accurately measured in the fetus using ultrasound. It is also routinely measured postnatally with a tape measure, as the maximum perimeter of the head with the tape passing across glabella (Meredith 1971). Unlike ultrasound, this measure includes the thickness of the scalp which at term is about 8 to 10 mm (Fescina and Ucieda 1980, Fescina and Martell 1983).

In order to compare brain growth across species, head circumference data described in chapter 2 for humans, baboons, rhesus monkeys and common marmosets are used and comparative growth curves are constructed. Here Gompertz curves are fitted to these data in order to describe growth. The Gompertz curve is used as it provides a good fit to the data since the growth curves tend to inflect closer to the lower asymptote (see chapter 2 for further details on the Gompertz curve). Because gestation lengths differ among the species, they are standardised by expressing age as a function of the percent of total gestation length for each species (see chapter 2, section 2.9b).

⁶ The authors also give equations for predicting brain weight from head circumference in males only, females only, and small for gestation age infants.

In addition, growth curve inflection points are calculated by fitting a linear regression line along the slope of the curve (from the intercept) and calculating the exact point along the x- and y- axes where the Gompertz curve deviates from the linear regression line. This is done by marking the point where the two lines first deviate.

3.9) Fetal head circumference growth curves

Figures 3.1a through 3.4a show scatterplots of \log_e -transformed head circumference plotted against standardised gestation length (percent of total gestation) in fetal humans, baboons, rhesus monkeys and common marmosets. Figures 3.1b through 3.4b show the gestation length standardised species-specific curves derived by fitting a nonlinear Gompertz curve to the fetal measures of head circumference plotted against age using the formula given in chapter 2 (equation 7).

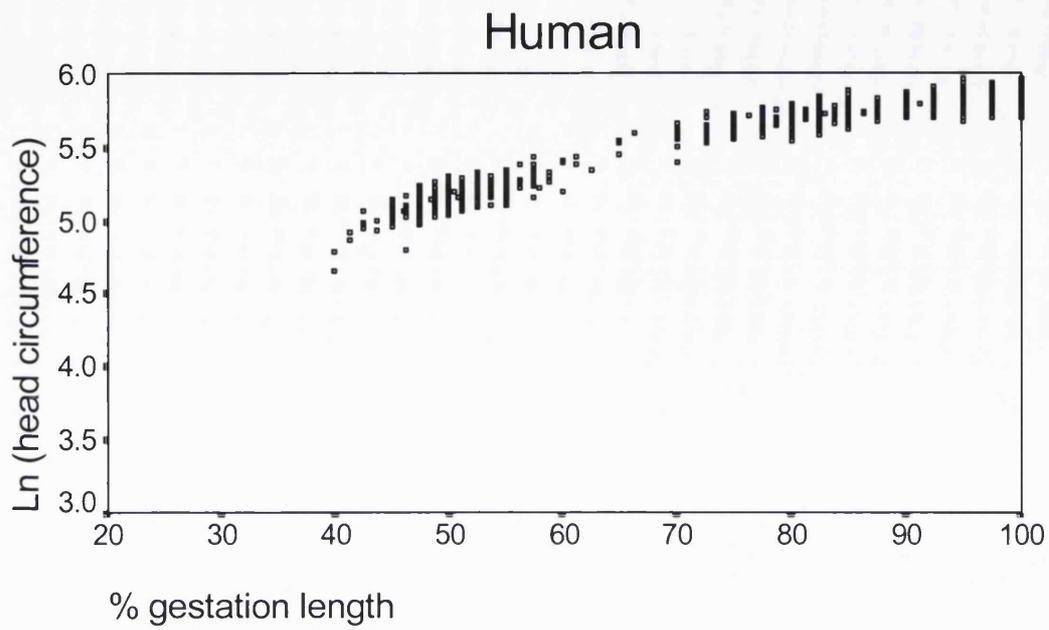


Figure 3.1a Scatterplot of \log_e -transformed head circumference measures plotted against percent gestation length for human fetuses. Data from the University College Hospital fetal and infant growth study.

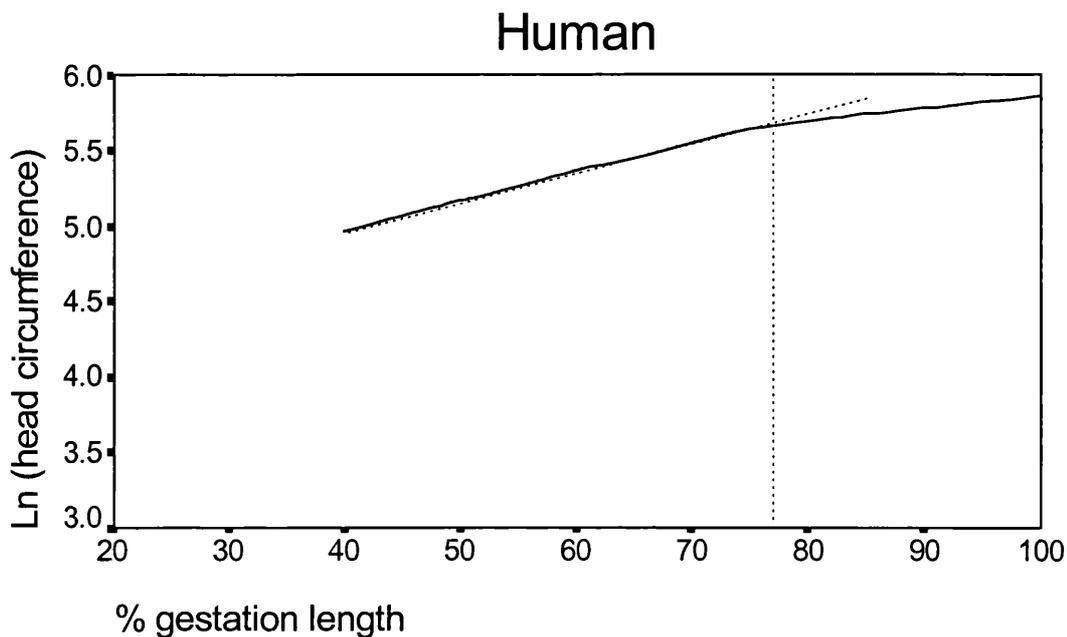


Figure 3.1b. Fetal head circumference growth curve in humans. Data taken from the UCL Hospitals fetal and infant growth study. The point where the two dotted lines meet marks the point of inflection along the curve. This occurs at about 216 gestation days, 64 days prior to birth. This decrease in head circumference growth occurs at 77% of standardised gestation length.

An asymptotic Gompertz curve of the form $y = c + a * \text{EXP}(-\text{EXP}(-b*(x-m)))$ describes the relationship between head circumference and % gestation length, where the best-fit regression is:

(27) $\text{Ln}(\text{head circumference in mm}) = 4.88 + 1.062 * \text{EXP}(-\text{EXP}(0.134 * (\text{Ln}(\text{age in days}) - 22.06)))$.
 The SE of: $c = 0.028$, $a = 0.033$, $b = 0.003$, $m = 0.346$.
 $(r^2 = 0.978, n = 3844, P < 0.0001)$.

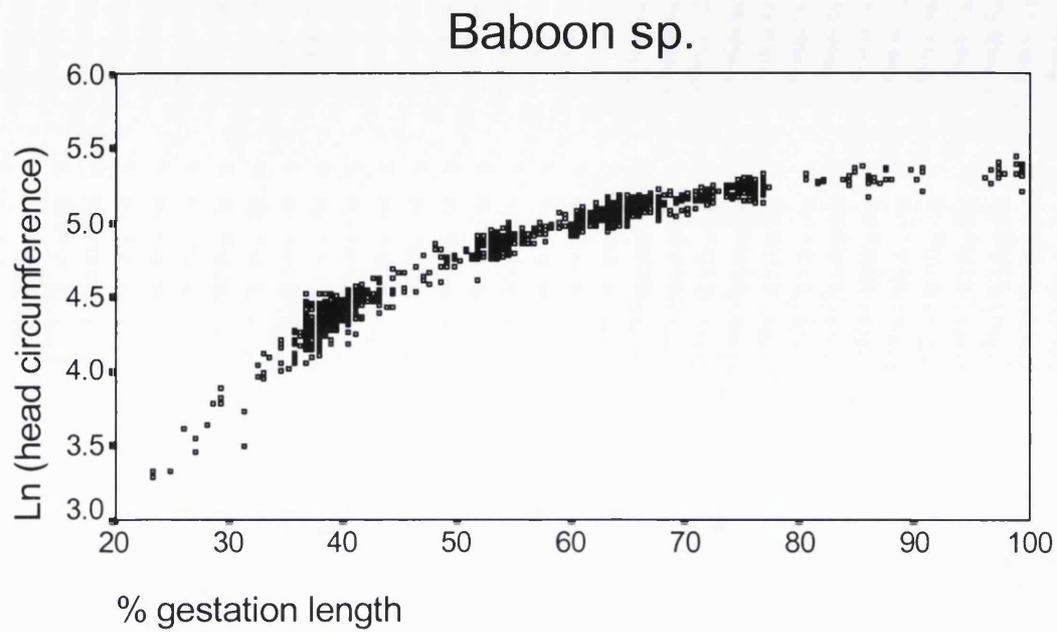


Figure 3.2a Scatterplot of \log_e -transformed head circumference plotted against percent gestation length for baboons.

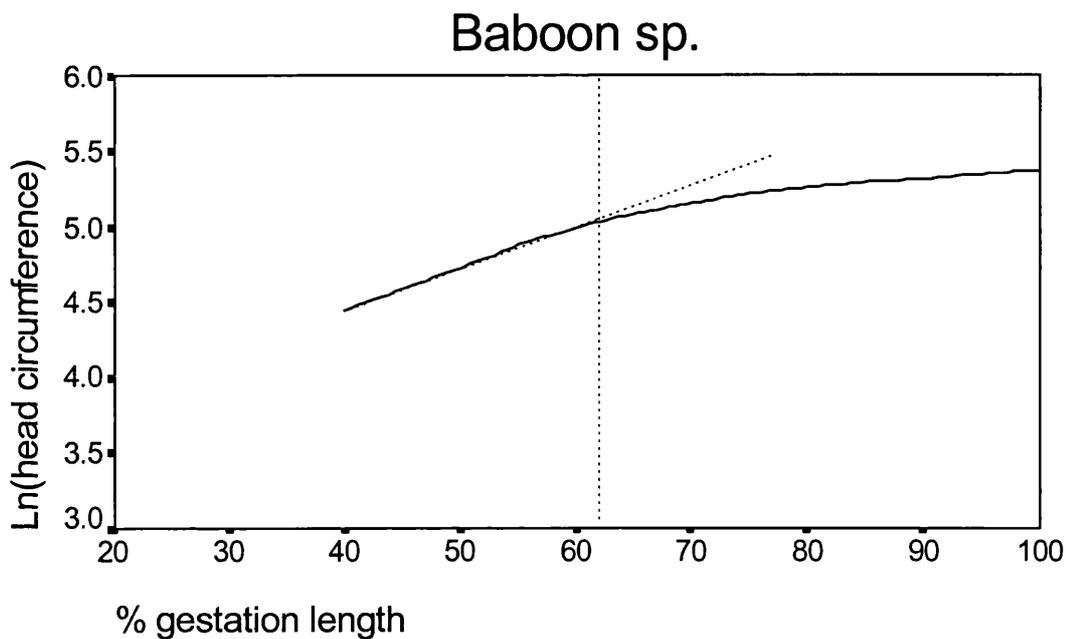


Figure 3.2b Fetal head circumference growth curve in *Papio sp.*. Data provided by Drs. Karen Rice and Michelle Leland (Southwest Foundation for Biomedical Research). The point where the two dotted lines meet marks the point of inflection along the curve. This occurs at about 115 gestation days, a full 70 days prior to birth. This decrease in head circumference growth occurs at 62% of standardised gestation length.

An asymptotic Gompertz curve of the form $y = c + a * \text{EXP}(-\text{EXP}(-b*(x-m)))$ describes the relationship between the head circumference and % gestation length in baboons, where the best-fit regression is:

(28) $\text{Ln}(\text{head circumference in mm}) = 0+5.424*\text{EXP}(-\text{EXP}(0.026*(\text{Ln}(\text{age in days})-12.757)))$.
 The SE of: $c = 0.945$, $a = 0.938$, $b = 0.0005$, $m = 8.553$.
 $(r^2 = 0.984, n = 2690, P < 0.0001)$.

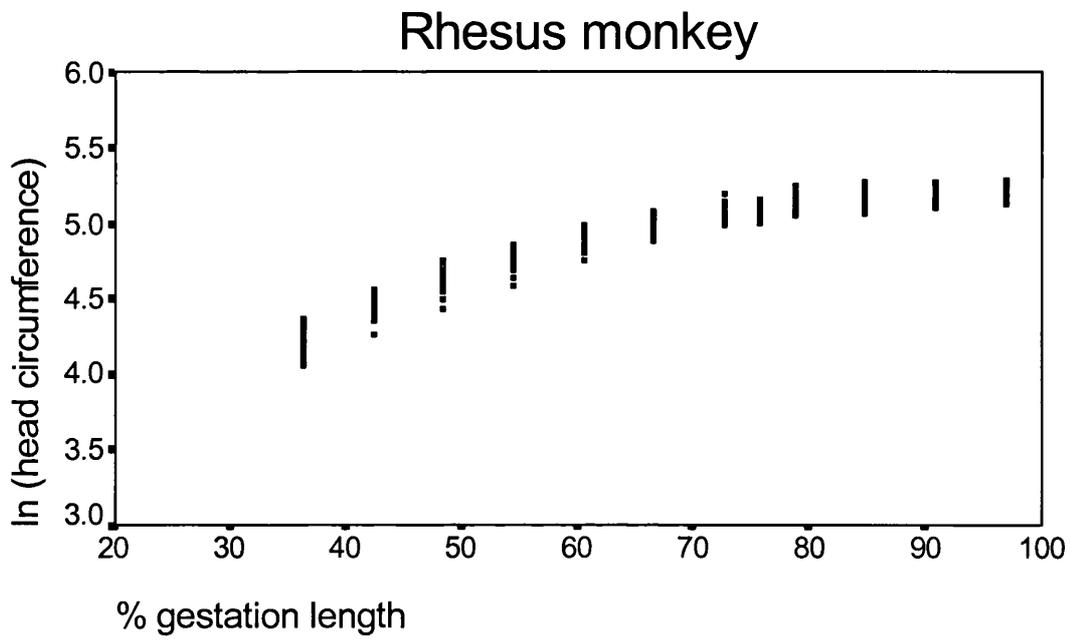


Figure 3.3a Scatterplot of \log_e -transformed head circumference measures plotted against percent gestation length for rhesus monkeys.

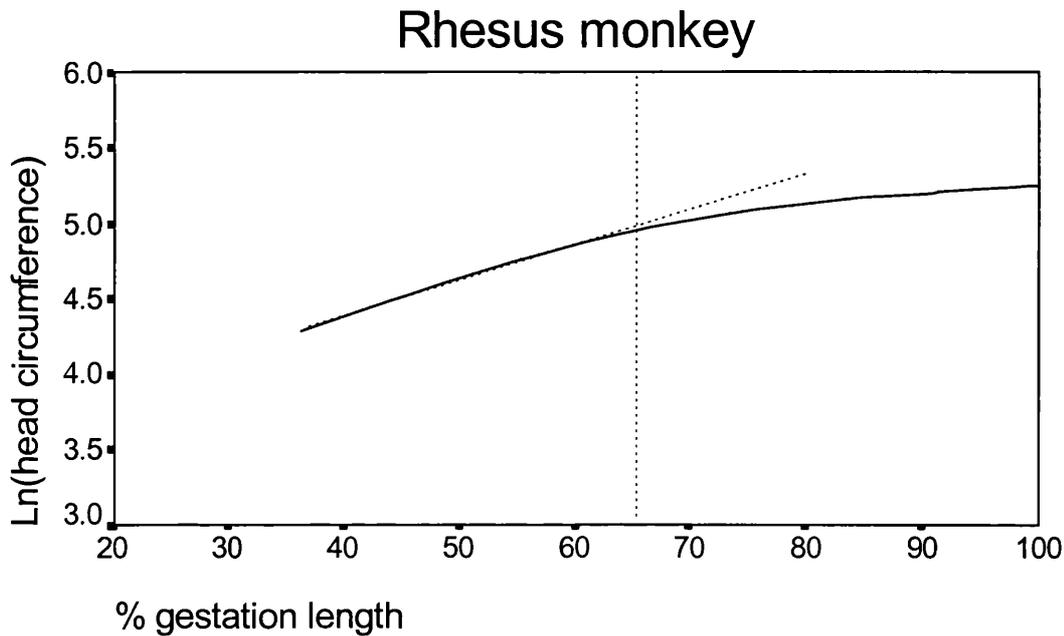


Figure 3.3b Fetal head circumference growth curve in *Macaca mulatta*. Data provided by Dr. Alice Tarantal (California National Primate Research Center). The point where the two dotted lines meet marks the point of inflection along the curve. This occurs at about 109 gestation days, 56 days prior to birth. This decrease in head circumference growth occurs at 66% of standardised gestation length.

An asymptotic Gompertz curve of the form $y = c + a * \text{EXP}(-\text{EXP}(-b*(x-m)))$ describes the relationship between head circumference and % gestation length in rhesus monkeys, where the best-fit regression is:

(29) $\text{Ln}(\text{head circumference in mm}) = 0 + 2.580 * \text{EXP}(-\text{EXP}(0.030 * (\text{Ln}(\text{age in days}) - 39.455)))$.
 The SE of: $c = 0.818, a = 0.834, b = 0.003, m = 15.242$.
 $(r^2 = 0.974, n = 481, P < 0.0001)$.

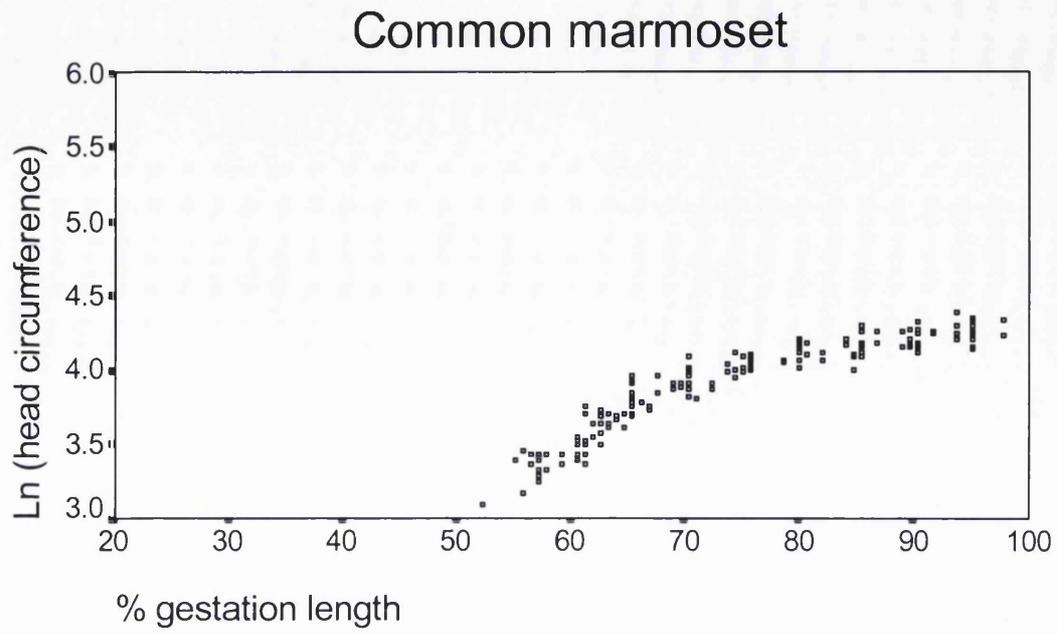


Figure 3.4a Scatterplot of \log_e -transformed head circumference measures plotted against percent gestation length in marmosets.

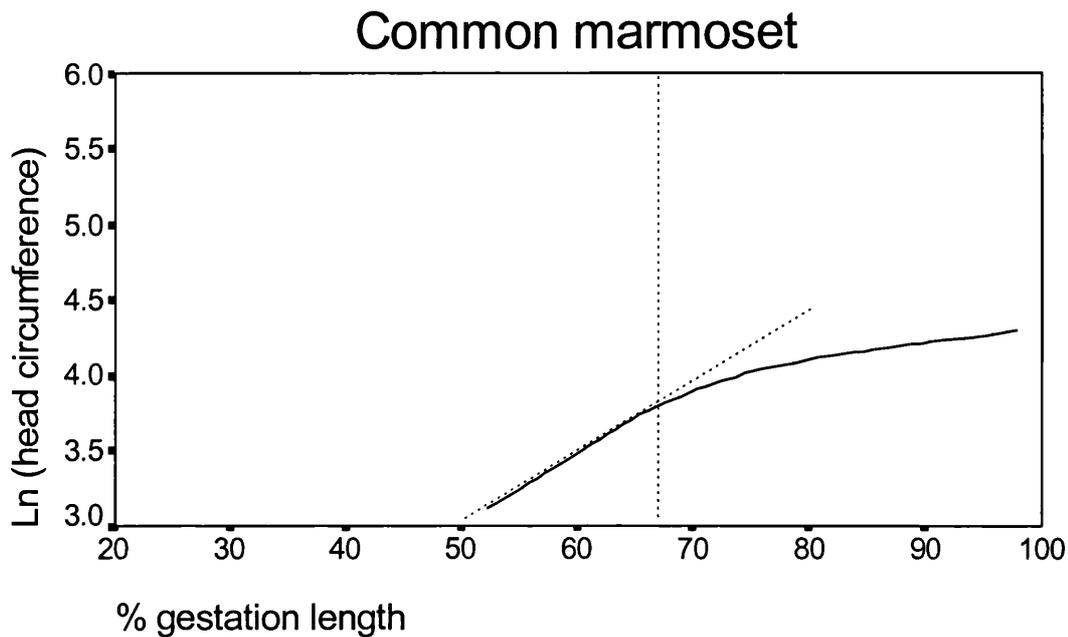


Figure 3.4b Fetal head circumference growth curve in *Callithrix jacchus*. Data provided by Dr. Ann-Kathrin Oerke (Deutsches Primatenzentrum). The point where the two dotted lines meet marks the point of inflection along the curve. This occurs at about 99 gestation days, 46 days prior to birth. This decrease in head circumference growth occurs at 68% of standardised gestation length.

An asymptotic Gompertz curve of the form $y = c + a * \text{EXP}(-\text{EXP}(-b*(x-m)))$ describes the relationship between head circumference and % gestation length in marmosets, where the best-fit regression is:

(30) $\text{Ln}(\text{head circumference in mm}) = 0 + 4.359 * \text{EXP}(-\text{EXP}(0.046 * (\text{Ln}(\text{age in days}) - 53.527)))$.
 The SE of: $c = 7.833$, $a = 7.879$, $b = 0.012$, $m = 51.232$.
 $(r^2 = 0.936, n = 161, P < 0.0001)$.

As shown in Figures 3.1b through 3.4b, inflection occurs at 62% of standardised gestation length in baboons, at 66% of standardised gestation length in rhesus monkeys and at 68% of standardised gestation length in common marmosets. In contrast, human head circumference inflection occurs later in humans, at 77% of gestation length, scaling for gestation length differences between species.

Three possibilities arise from this finding: 1) the period of exponential brain growth in humans is extended relative to baboons, rhesus monkeys and marmosets, 2) the period of exponential somatic growth, in general, is extended and body size allometry drives the inflection point in head circumference. In this scenario, head circumference growth should track body length growth and coincide with body length inflection points. 3) gestation length is about 12% shorter in humans than expected [i.e. the difference between the average anthropoid inflection points (baboon and rhesus monkey) and the human inflection point as a percent of gestation length].

3.10) Delayed inflection in human head circumference growth curve

These possibilities are examined here theoretically.

3.10a) Possible hypertrophic brain growth effects

1: Is the period of exponential brain growth in humans extended relative to baboons, rhesus monkeys and marmosets?

Unfortunately very few comparative analyses of primate fetal brain growth have been undertaken. The majority of this work is traditionally carried out on rodents. Where primate analysis is undertaken it usually includes rhesus monkeys. Therefore, it is difficult to assess whether human brain tissue growth rates differ significantly from those of other non-human primates. We do know, however, that as a percent of adult brain weight, humans undergo a significant proportion of brain growth *ex utero*. This differs from the rhesus monkey which undergoes most of its brain growth *in utero*. This difference may suggest that the later inflection point along the human head

circumference growth curve reflects a generalised extension in brain growth. Simply put, humans may grow their brains for an extended period across both hyperplastic and hypertrophic stages. This would be consistent with the view that adult encephalisation (brain for body size) in humans is largely the result of differences in ontogenetic brain growth patterns relative to body growth patterns (Deacon 1990).

In fact, when comparing the relative amounts of growth in the head circumference, as a function of standardised gestation length, humans do appear to differ from baboons and rhesus monkeys in attaining a greater proportion of birth head circumference earlier in gestation, and slightly less between 50-75% of gestation length (see Figure 3.5).

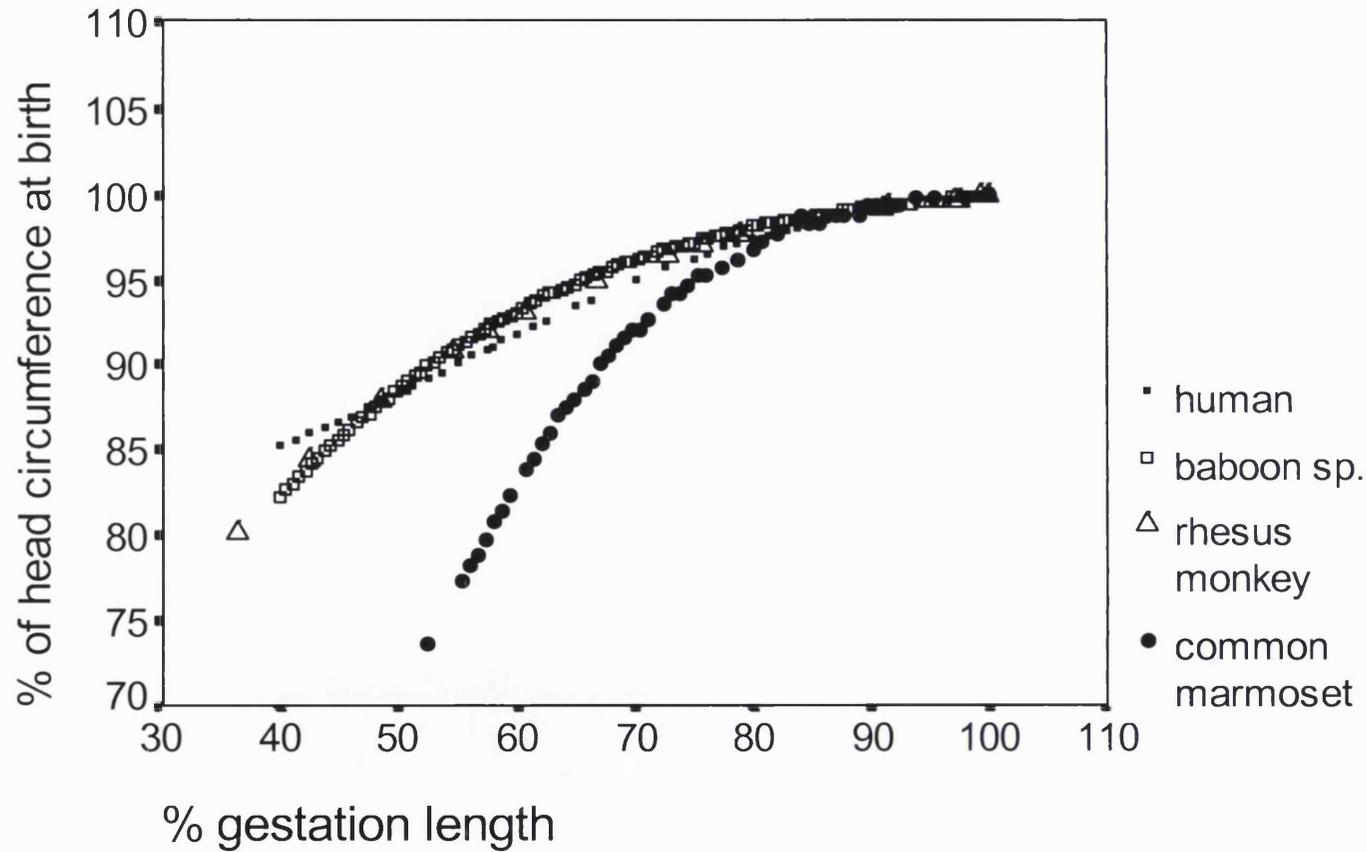


Figure 3.5 Species-specific head circumference (as a percent of head circumference at birth) against standardised gestation length. By 40% of gestation length, percent birth head circumference in humans is about 5% greater than rhesus monkeys and about 2% greater than in baboons. Marmoset head circumference at 50% of gestation is only about 70% of that at birth.

From Figure 3.5 it could be argued that the products of early head circumference growth during the first 2/5 of gestation differ between these anthropoid species. Humans acquire 85% of total birth head circumference by 40% of the gestation period. Rhesus monkeys acquire about 80% and baboons 83% of birth head circumference by 40% of gestation length.

Humans are more altricial than rhesus monkeys, baboons and marmosets. Increased early head circumference (as a percentage of birth head circumference) in humans is, therefore, not likely to stem from a shift in developmental maturity toward birth, since this scenario would be consistent with a more precocial species. Rather, early hyperplastic brain growth may be accelerated/extended in humans.

3.10b) Possible allometric effects

2: Do body size allometry and somatic growth account for the late head circumference growth curve inflection point in humans?

When a Gompertz curve is fitted to \log_e -transformed body length measures (as a function of % gestation length) for humans, the resulting curve differs from that of the head circumference growth curve. This can be seen when comparing the derived constants from the predictive equations below.

Body length growth curve:

(31) $\text{Ln}(\text{length in mm}) = 1.180 + 5.383 * \text{EXP}(- \text{EXP}(0.064 * (\text{Ln}(\text{age in weeks}) - 4.097)))$.
 The SE of: $c = 1.902$, $a = 1.906$, $b = 0.002$, $m = 6.862$.
 $(r^2 = 0.979, n = 5237, P < 0.0001)$.

Head circumference growth curve:

(32) $\text{Ln}(\text{head circumference in mm}) = 2.094 + 4.020 * \text{EXP}(- \text{EXP}(0.072 * (\text{Ln}(\text{age in weeks}) - 1.645)))$.
 The SE of: $c = 0.895$, $a = 0.897$, $b = 0.002$, $m = 3.976$.

($r^2 = 0.984$, $n = 5110$, $P < 0.0001$).

This difference in growth curve between the head circumference and body length growth curves is also illustrated in chapter 2, Figure 2.10. These Figures show that brain growth, through to 1 year-of-age, does not track somatic growth directly, and that the late inflection point for head circumference is not a function of generalised body growth.

However, size differences between the head circumference and body length must be standardised in order to directly compare growth trajectories. This is done by expressing fetal size as a percentage of size at 1 year-of-age and plotting it against percent of gestation length (see Figure 3.6).

After taking size differences between the head circumference and body length into account, the relationship between head circumference and body length standardised size differs from that in Figure 2.10. The slopes describing the relationships between standardised head circumference and percent of gestation and standardised body length and percent of gestation are very similar. In contrast, the intercepts differ. Throughout gestation, fetuses grow a greater proportion of their head circumference at 1 year than they do body length. On average, fetal head circumference is about 5% (of 1 year size) greater. Thus, head circumference growth does track body length growth but the rate of head circumference growth is greater.

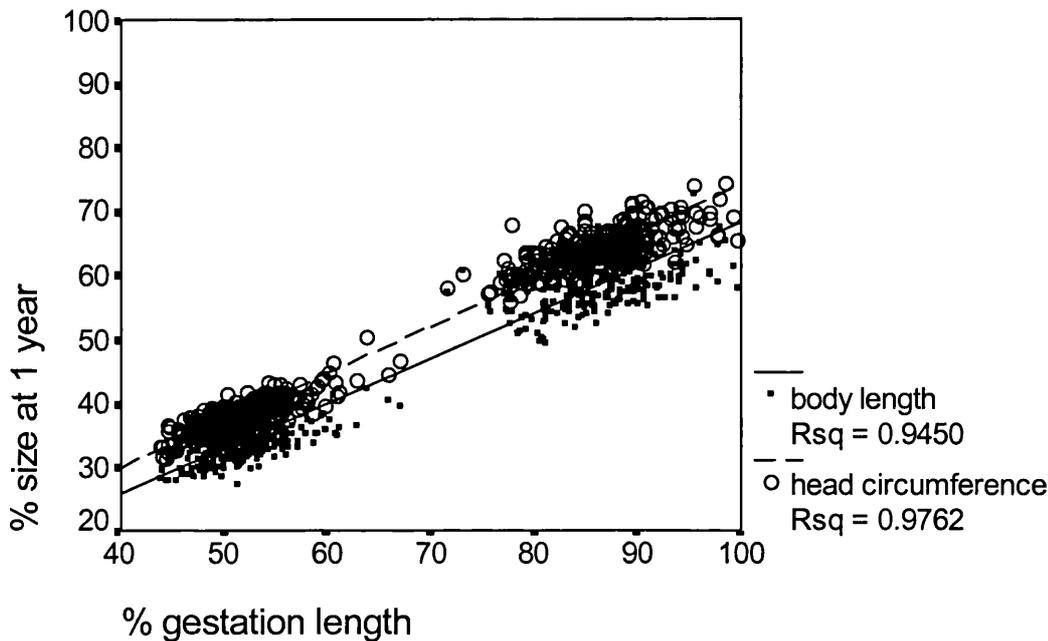


Figure 3.6 Percent of human head circumference size at 1 year plotted against percent of body length size at 1 year, using the UCL Hospitals data.

The least squares linear regressions describing these relationships are as follows:

percent of body length at 1 year

$$(33) \quad \% \text{ BL} = -2.36 + 0.706 * \% \text{ gestation} \\ (r^2 = 0.945, \text{ SE} = 3.03, n = 607, P < 0.0001)$$

where % BL = percent of 1 year body length size attained and % gestation = percent of gestation length at measurement

percent of head circumference at 1 year

$$(34) \quad \% \text{ HC} = 0.643 + 0.735 * \% \text{ gestation} \\ (r^2 = 0.975, \text{ SE} = 2.08, n = 615, P < 0.0001)$$

where % HC = percent of 1 year head circumference size attained and % gestation = percent of gestation length at measurement

3.10c) Possible gestation length effects

3: Is gestation length reduced by ~ 12% in humans?

Although human neonates are less precocial than other primates⁷, we know that gestation is actually extended in humans, due primarily to encephalisation in our species and the slow rate of brain tissue development (Harvey et al. 1987). The extent of gestation prolongation can be assessed by predicting the expected gestation length for a female of our body weight and then subtracting that value from the observed human gestation length.

Data on adult female body weight and gestation length across haplorhine primates are taken from Harvey et al. (1987). In Figure 6.7 \log_e -transformed gestation length (in days) is plotted against \log_e -transformed female body weight (in kg) across 52 primate species.

⁷ Secondary altriciality in humans is associated with the restrictions on *in utero* brain growth arising from a narrow pelvis associated with bipedalism (Leutenegger 1982)

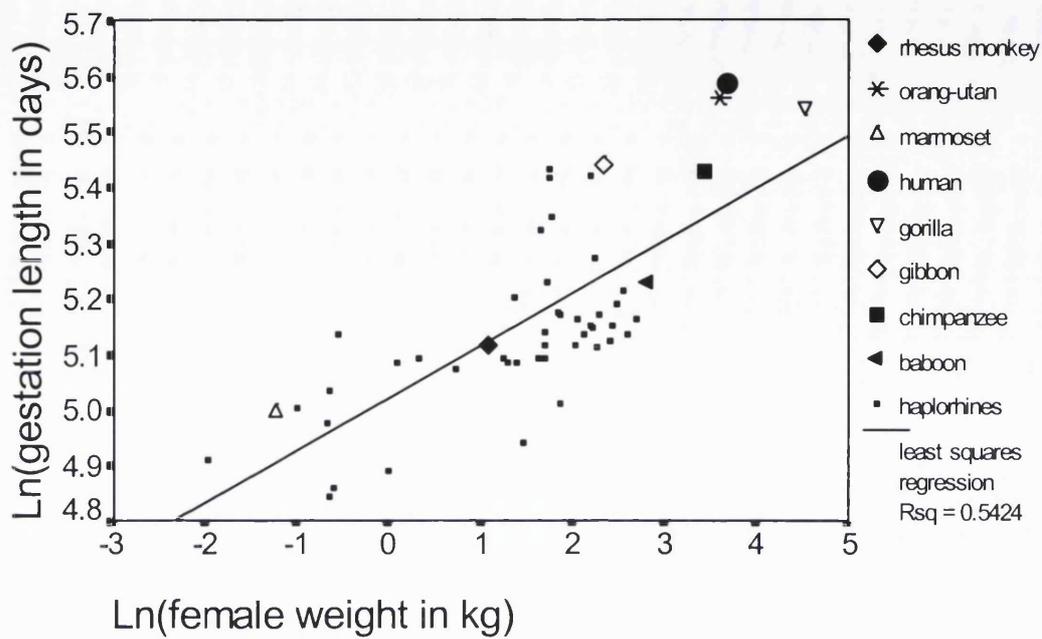


Figure 3.7 \log_e -transformed gestation length plotted against \log_e -transformed female body weight in haplorhine primates. Data taken from Harvey et al. (1987). The least squares regression equation is:

(35)
$$\text{Ln}(\text{gestation length}) = 5.021 + 0.094 * \text{Ln}(\text{female weight})$$

$$(r^2 = 0.542, n = 52, SE = 0.117, P < 0.0001)$$

Based on a haplorhine regression, using Harvey et al.'s gestation length value of 267 days, humans have a predicted gestation length of 214 days. Based on this regression we have a gestation length 20% longer than expected for a female haplorhine primate of comparable body weight.

Rather than gestation being reduced in humans by ~12%, it is prolonged by 19.7%, while the regression analysis suggests that baboons and rhesus monkeys are fairly average in terms of gestation length for body size. In humans, reduced gestation length cannot explain the relatively greater head circumference size attained (as a function of % gestation length), or delayed head circumference inflection, as gestation is actually longer in humans than predicted based on adult female body size.

Together, the above three analyses suggest that delayed inflection in the fetal head circumference growth curve in humans is a) not a direct product of body:brain allometry and somatic growth curve inflection b) not a function of gestation length reduction relative to other haplorhines - in fact gestation length is extended in humans by about 20% c) rather, it may be associated with rapid early brain growth velocity or an extension in hyperplastic brain growth as suggested by the greater proportion of birth head circumference attained in early gestation in humans relative to baboons, rhesus monkeys and common marmosets.

This view is consistent with that of Finlay and Darlington (1995) who argue that an extended period of neurogenesis in humans may account for the larger size of brain structures compared to those of other primates, bats and insectivores. Prolonged hyperplastic growth in the human brain may therefore explain both the larger relative size of the human brain and the delayed inflection in the human fetal brain growth trajectory.

In sum, human patterns of brain growth and size ontogeny do differ from those of the baboon, rhesus monkey and common marmoset. In addition to the slower leveling off of the head circumference growth curve shown in chapter 3, Figure 3.5, head circumference growth in humans differs in that it reaches a 3-5% greater size than that of rhesus monkeys and baboons in early gestation. Head circumference growth also

begins to slow down later than in rhesus monkeys, baboons and common marmosets. The human head circumference growth curve inflects at 77% of total gestation length, while that of the baboon inflects at 62%, the rhesus monkey at 66% and the common marmoset at 68%. The extension in human brain growth relative to these non-human primates appears to include both the early (hyperplastic) and later (hypertrophic) stages of brain growth. However, early increases in cell number (hyperplastic growth) translate into increased brain size due to the hypertrophy of these existing cells in later development. Thus, the key difference in human brain growth may be that hyperplastic growth is extended, resulting in greater brain size in humans compared to baboons, rhesus monkeys and marmosets.

3.11) Discussion

These results contradict findings based on cross-sectional data by Deacon (1997, 2002) who argued that human brain growth rates *in utero* do not deviate from those of other anthropoid primates. The findings in this chapter, however, suggest that human brain growth *in utero* does in fact differ from that of baboons, macaques and marmosets. Human hyperplastic and hypertrophic growth both appear to be extended and fetal head circumference growth velocity slows later in humans than in the other species examined here, after controlling for gestation length differences. The hypothesised increase in hyperplastic brain growth is consistent with Deacon's (2000) argument that early localised developmental changes in the brain, in either mitosis or cell segmentation may relate to increased human encephalisation.

Differences in gestation length between the species cannot explain the prolongation of rapid human brain growth, shown here, as humans do not have a short gestation length compared to non-human primates of comparable body size. To the contrary, we actually have a relatively longer gestation length than predicted for our body size.

The most likely explanation for these contradictory findings is the nature of the data. Longitudinal measures of size allow for intra-specific variation to be taken into

account when assessing growth. Cross-sectional data, on the other hand, are simply mean values which do not take variation into account and are often inaccurately dated.

The findings in this chapter also contradict those of Martin (1983) who argues, using cross-sectional data, that rhesus monkey brain growth slows down markedly after birth, while human brain growth slows down after 1 year-of-age. These results suggest that brain growth slows down appreciably *in utero* in humans, rather than during infancy, as argued by Martin (1983). However, this slowing down does occur later than in the rhesus monkey, baboon and marmoset. These results do not dispute the fact that brain growth continues in humans into childhood, they simply show that brain growth slows down markedly earlier than previously thought, where the growth curve inflects during the late fetal period.

From an energetic point of view, the last trimester is a costly period in which fetal growth and maternal weight gain are high (Strauss and Dietz 1999) and fat deposition begins in the fetus (Catalano et al. 1998). The relative slowing down of brain growth may be crucial for energy balance during this period.

CHAPTER 4

Fetal and infant size, growth and encephalisation

4.1) Aims of chapter

As shown in chapters 1 and 3, encephalisation is a costly adaptation in energetic terms. Body growth itself is costly (see chapter 2) and may be in direct conflict with the encephalised brain. However, brain sparing (see chapter 3) occurs during energy stress where energy is preferentially diverted to the brain.

Foley and Lee (1991) argued that over evolutionary time, a relative reduction in growth rate may have evolved in order to ‘divert’ energy to the brain in encephalised species, and in particular, humans. They argued that, in part, the costs of the brain impose a constraint on growth and development rates in humans.

It is not clear whether encephalisation in the fetus and infant is associated with reduced non-brain body growth, or increased energy availability to the fetus or infant, as a means for supporting the increased brain tissue.

In this chapter, three main hypotheses are tested. These include the ‘Reduced Growth Hypothesis’, the ‘Nutrition Hypothesis’, and the ‘Brain Size Sexual Dimorphism Hypothesis’. The predictions of these hypotheses are as follows:

4.2) Hypotheses tested in chapter

‘Reduced Growth Hypothesis’:

Encephalised fetuses and infants will have reduced growth in body length, compared with less encephalised fetuses and infants. A trade-off between body length growth and brain growth is predicted here.

‘Nutrition Hypothesis’:

Encephalised fetuses and infants will have increased nutritional status, compared with less encephalised fetuses and infants. Increased investment in all fetal tissues is predicted to relate to encephalisation here.

In section II of the chapter, the 'Brain Size Sexual Dimorphism Hypothesis' will be tested. This hypothesis predicts that male fetuses and infants will be more encephalised than females.

Because encephalisation is comprised of a head circumference and body length component, it is important to determine how these two components each contribute to encephalisation. For example, does having a big head determine encephalisation, or rather, having a small body?

In addition, it will also be assessed whether 'catch up' and 'catch down' growth occur in the fetuses and infants and whether it is associated with nutritional status, body size or encephalisation. It will also be determined whether encephalisation itself undergoes 'catch up' and 'catch down' growth and whether this is associated with changes in head circumference or changes in body length.

The chapter is divided into three sections. The first deals with the relationships between size, growth, nutrition and encephalisation. The second deals with encephalisation sexual dimorphism. Section 3 estimates the energetic costs of sexual dimorphism in encephalisation.

SECTION I: Size, growth, nutritional status and encephalisation

4.3) Methods

In order to test these hypotheses, size, encephalisation, growth and nutritional status must be quantified in the fetus and infant. In addition, 'catch up' and 'catch down' growth must be quantified, as must sexual dimorphism in encephalisation.

The fetal and infant data described in chapter 2 are used here to test these hypotheses. Femur length, body length and head circumference were expressed as SD scores which controlled for age- and sex-effects (see chapters 2 and 3), using the LMS method. These SD scores are used here as indices of size.

4.3a) Quantifying encephalisation in the fetus and infant

Traditionally, measures of relative brain size (encephalisation) are calculated by regressing brain weight measures against body weight or length measures and calculating a residual from the 'mean' regression line (see Stephan 1972, Jerison 1973, Gould 1975, Passingham 1975, Jerison 1977, Szarski 1980, Martin 1981, Armstrong and Falk 1982). However, when dealing with ontogenetic data, there are a number of problems with using this method to calculate residual brain size measures (an index of encephalisation). This is principally due to the inability of the regression model to control for several confounding factors. These include the differences between brain and body growth rates and the influence of age, sex and size allometry. In order to quantify encephalisation during ontogeny, an encephalisation index that reflects the change in brain size, independent of body size influences is essential. In addition, a method that quantifies the change in encephalisation over time is required.

Throughout ontogeny the human head becomes proportionately reduced relative to the body while the postnatal skeleton becomes proportionately enlarged relative to the head (Stratz 1909). While, in absolute terms, both the head and body are growing, in relative terms, the head/body ratio is actually decreasing so that relative brain size (to body size) decreases over time.

In growing individuals, therefore, a ratio of brain to body size does not yield a measure of brain size increase over time (growth) controlling for the effects of body size allometry and body size increase. It merely reflects the change in shape between these two parameters over time (see also Tanner 1949, Healy and Tanner 1981, Passingham 1982, Heusner 1985). This is largely an artifact of the different rates of growth between the body and the brain, with brain growth exceeding body growth

during early development and, as Cabana et al. (1993) have shown, reaching its adult size significantly earlier than the body.

Regressing head circumference measures against body length measures⁸ and calculating residuals from the regression line will not yield an index of brain size increase scaled to body size. This is principally because residuals calculated in this way do not control for growth rate differences between the brain and body. For example, a positive residual reflects a case where an individual's body length is growing more slowly than his/her brain size at a given time. The residual does not yield any information about the individual's brain size independent of body size allometric influences, but rather reflects differences body and brain growth trajectories.

Likewise, regressing brain size measures against age does not solve the problem because brain size residuals calculated from age do not control for ontogenetic brain:body allometry. This is principally because the brain:body relationship approaches isometry during the early stages of development (see chapter 2, Figure 2.10) when a residual head circumference measure on age is still highly correlated with a residual body length measure on age.

In addition to the influences of body size on brain size, body and brain growth rate differences and the effects of age and sex need to be controlled for.

All of these issues highlight the inadequacy of traditional regression models for quantifying encephalisation during ontogeny. For the purposes of this study it is essential to calculate a relative brain size measure that reflects both brain growth (i.e. size increase) as well as a size index independent of body size, age and sex effects. Therefore, in order to quantify encephalisation during growth, the sex- and age-specific head circumference SD scores, femur length SD scores (in the fetus) and body

⁸ Here body length (height) rather than weight is used as a measure of body size for two reasons. Firstly, it is not possible to measure fetal body weight directly *in vivo* so that a fetal and infant body weight trajectory cannot be calculated. Secondly, body weight, as opposed to height, is far less conservative in the face of environmental stress (e.g. illness, undernutrition), while in the short term, height remains relatively constant (Yajnik 2000).

length SD scores (in the infant) described in chapter 2 are used to derive an index of encephalisation.

i) Encephalisation SD scores

To briefly reiterate, these SD scores were calculated using the LMS method (see chapter 2, section 2.9) where sex-specific size measures were plotted against age and smoothed L, M and S curves were applied to the data, using the Cole and Green (1998) Growth Reference program. From these curves, sex and age-specific SD scores were calculated. In order to control for the effects of head circumference:body length allometry as well as the difference in growth rate and growth trajectories between the head circumference and body length, ‘conditional’ SD scores were then calculated as follows:

Head circumference SD scores from each measurement period were plotted against femur (in the fetus) or body length (in the infant) SD scores. At this point male and female SD scores were pooled together as they were already sex-specific. The distributions were normalised using the LMS method and the smoothed L, M and S curves were derived. For each SD score on the x-axis (i.e. femur length or body length SD scores), a corresponding L, M and S value for each head circumference SD score on the Y-axis was derived and used in the equation to calculate an SD score (see chapter 2, equation 10). This SD score is termed a ‘conditional’ SD score because it takes another SD score into account - in this case the femur or body length SD score.

Figures 4.1 and 4.2 provide an example of the calculation of the ‘conditional’ SD scores in neonates. Figure 4.1 is a scatterplot of neonatal head circumference SD scores plotted against body length SD scores (described in chapter 2). These SD scores controlled for both sex and age effects. Smoothed L, M, and S curves were fitted through the data and SD scores calculated. Figure 4.2 is a scatterplot of these ‘conditional’ SD scores plotted against age.

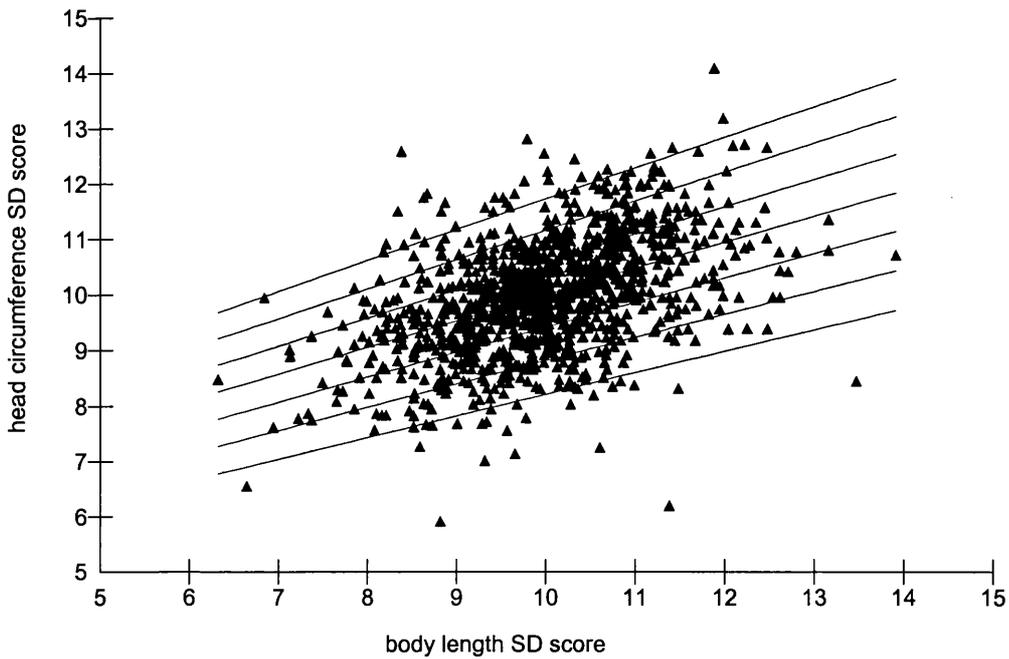


Figure 4.1 LMS curve of neonatal head circumference SD scores plotted against body length SD scores with derived centiles. X- and Y-scales have a value of +10 added as the Cole and Green (1998) program cannot accept negative values. Each SD score is, therefore, 10 units lower than that on the scale. This does not effect the calculation of the 'conditional' SD score.

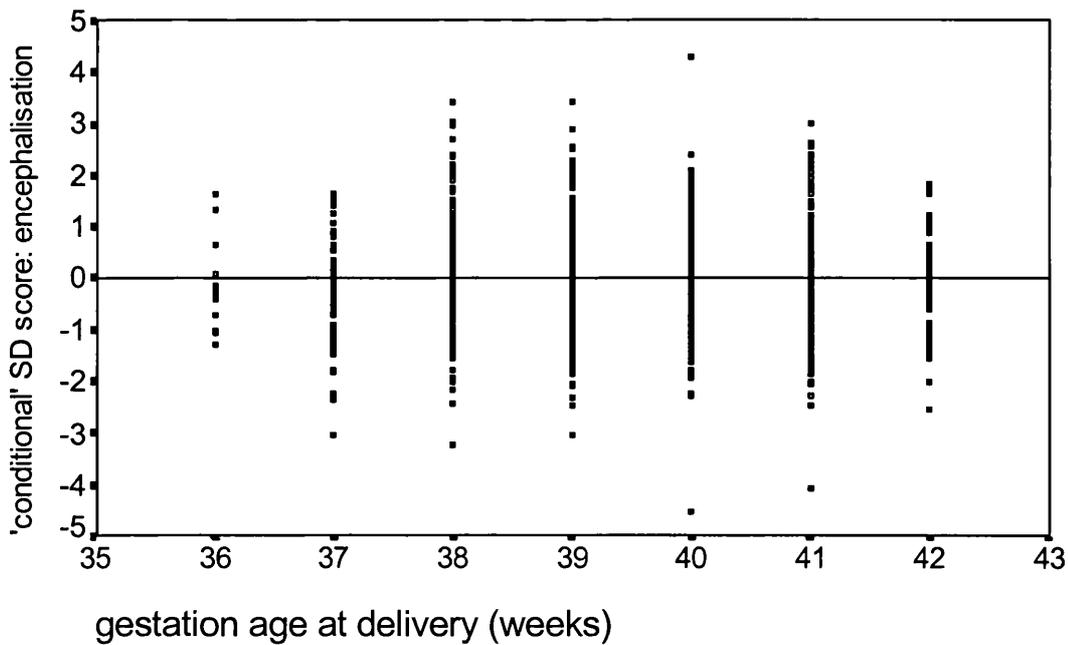


Figure 4.2 Encephalisation SD scores plotted against gestation age at delivery (in weeks) in neonates.

4.3b) Quantifying growth in the fetus and infant

i) Change in SD score

Growth can be assessed by quantifying the change (Δ) in SD score between measurement periods. This is simply the difference between SD scores. These SD scores already control for age differences between measures, so no further control for the age interval between measures is required. The change in SD scores for femur length, body length, head circumference and encephalisation SD scores represent growth in these variables. A negative value represents a case where an individual's size over time decreases relative to the sample population, while a positive value represents a case where an individual's size over time increases relative to the sample population.

ii) Thrive in growth

Thrive in growth is a means for assessing growth independent of initial size-effects. The tendency for the SD scores to regress to the mean by centile shifting is well established (see chapter 2). Individuals in the lowest centiles tend to shift upward toward the mean while those in the highest centiles tend to shift downward over time (Altigani et al. 1989, Wright et al. 1994a,b, Brandt 1998, Wright et al. 1998).

Cole (1997) defined failure to thrive in individuals who fell below the 5th percentile in weight gain, and showed that by including the 5th percentile cutoff as thrive lines on growth reference charts, marginal growth could be assessed. Similarly, Wright et al. (1994a) defined the thrive index as the difference between the observed and predicted change in weight SD score over time. The authors defined a positive value as evidence for thrive in weight gain and a negative value as evidence for failure to thrive.

Here, an index of thrive in head circumference, femur length, body length and encephalisation is calculated in order to control for expected 'catch up' and 'catch down' growth. The thrive index, thus, gives a measure of growth independent of that expected based on initial size.

Thrive in growth is quantified by plotting Δ SD scores (between measurement periods) against size at the initial measurement period. These SD scores already control for sex- and age- effects. For example, between birth and 6 months, the difference in body length SD score is calculated and plotted against body length at birth. Next, the LMS method is used (see chapter 2) and 'conditional' SD are calculated. These SD scores are conditional because they not only control for age and sex, but also for initial size. First, smoothed L, M and S curves are fitted through the data. Next, L, M and S constants are derived from the curves and these are used to calculate SD scores (see equation 10).

iii) 'Catch up' and 'catch down' growth

'Catch up and 'catch down' growth may be assessed by determining whether an individual's size SD score changes substantially over time. A scenario where an individual falls within the lower 10% of the sample population in terms of size SD at birth, but falls within the 75th centile by 6 months, is a clear example of 'catch up' growth. 'Catch up' growth may be best illustrated by plotting size SD scores for the smallest individuals and determining whether they shift centiles upward. 'Catch down' growth in contrast may be illustrated by plotting the size SD scores of the largest individuals (e.g. within the 90th centile) and determining whether they shift centiles downward toward the mean.

4.3c) Quantifying nutritional status in the neonate

Nutritional status in the neonate and infant is routinely assessed by calculating either a Benn index (Benn 1971, Cole et al. 1997) or body mass index (Davies and Lucas

1989b) as a means for assessing weight-for-height. This measure, however, tells nothing of the proportions of fat, lean tissue and water comprising weight. Increased body mass index, is however, usually associated with increased fatness in children since the variation in lean mass is about 2/3 that of fat (Wells 2000).

i) Benn index

Cole et al. (1997) have suggested that the Benn index (Benn 1971), of the general form $\text{weight}/\text{height}^n$ [where the power n is calculated from the data to ensure zero correlation between the index and height, (height expressed in cm and weight expressed in grams)] yields an accurate index of weight-for-height in neonates. According to Cole et al. (1997), calculating the best birth $\text{weight}/\text{height}^n$ index assumes that birth weight, after adjustment, is uncorrelated with height.

In other words, on average, birth weight should be proportional to height^n . In order to calculate the Benn index, \log_e -transformed birth weight is regressed against \log_e -transformed height and the resulting regression coefficient equals the power n value to be used in the calculation of the Benn index. Cole et al. (1997) calculated an average regression coefficient of 2.64 for 999 neonates between the ages of 33 to 43 gestation weeks at delivery. They also showed that males and females do not differ significantly in the relationship between weight and height at birth.

The average regression coefficient of 2.64 calculated by Cole et al. (1997) was used here to determine the Benn index for the neonates in this study. The resulting variation in the index due to body length (height) was minimal (see Table 4.1), as shown using the Wells et al. (2002) equation:

$$(36) \quad \% \text{ variation due to body length} = (1 - \sqrt{1-r^2}) * 100$$

Body mass index, in contrast is a more appropriate measure for assessing nutritional status in infants (Cole et al. 1997), using Quetelet's formula of $\text{weight}/\text{height}^2$

(Garrow and Webster 1985, Davies and Lucas 1989a). Table 4.1 shows that the variation in BMI explained by body length is minimal.

ii) Skinfold thickness

Measures of neonatal and infant skinfold thickness are used as indices of body subcutaneous fat deposition, fat patterning and nutritional status in the neonate and infant (Cameron 1998, Norgan 1998). Skinfold thickness measures also yield information about the distribution of fat, i.e. the relative amount of centralised (subscapular) as opposed to peripheral (triceps) fat⁹. In addition, a ratio of subscapular fat to triceps fat gives an indication of central to limb fat distribution. Subscapular skinfold thickness is a measure of subcutaneous adipose tissue and skin thickness on the posterior aspect of the torso. It is an important measure of nutritional status (Lohman et al. 1988). Triceps skinfold thickness is closely correlated with percentage of body fat and is useful in assessing fat distribution (Lohman et al. 1988). Subscapular and triceps skinfold thicknesses were measured in the neonates in the study and are used as a means for assessing fatness.

Mid-upper arm circumference (MUAC) measures were also taken in neonates. These provide an index of body energy stores and protein mass (Lohman et al. 1988). Mid-upper arm circumference along with skinfolds allow for estimation of mid-arm muscle area as a means for assessing leanness in neonates and mid-arm fat area as a means for assessing fatness in neonates. Unfortunately, skinfolds and mid-arm circumferences were taken only once, after birth, so that changes in nutritional status cannot be assessed here.

Mid-arm muscle and fat areas were estimated using the following equations cited by Shaw and Lawson (2001):

⁹ It should be noted that only about 1-2% of fat is comprised of brown rather than white adipose tissue. Brown fat functions to release heat in neonatal mammals (Thain and Hickman 1994).

$$(37) \quad \text{mid-arm muscle area (mm}^2\text{)} = \frac{(\text{MAC} - (\pi * \text{TSF}))^2}{(4 * \pi)}$$

where MAC = mid arm circumference in mm²

TSF = triceps skinfold thickness in mm

$$(38) \quad \text{mid-arm fat area (mm}^2\text{)} = \frac{\text{TSF} * \text{MAC}^2}{2} - \frac{\pi * (\text{TSF})^2}{4}$$

where TSF = triceps skinfold thickness in mm

MAC = mid-arm circumference in mm

Descriptive statistics for skinfolds and mid-upper arm circumferences were given in chapter 2 (Table 2.13). Table 4.2 lists the descriptive statistics for neonatal males and females separately for the Benn index, estimated mid-arm muscle and fat areas and for infant body mass indices (at 6 and 12 months).

iii) Nutritional status SD scores

The Benn index, skinfolds, mid-upper arm circumference, and mid-arm fat and lean tissue areas are expressed as SD scores, as a function of age, using the LMS method (see chapter 2). First, for males and females separately, the variables were plotted against age and smoothed L, M and S curves were fitted to the data distributions. The derived L, M and S constants were then used to calculate age-specific SD scores. In addition, a ratio of the SD score for subscapular skinfold thickness to triceps skinfold thickness is used as a means for quantifying central to limb fat distribution. Examples of LMS models for deriving subscapular skinfold SD scores in female neonates are given in Figures 4.3 and 4.4.

Table 4.1 Variation in Benn index (at birth) and BMI (at 6 and 12 months) explained by body length

age	r ²	n	% variation due to body length
gestation at delivery (weeks)			
36	0.152	17	4.8
37	0.182	73	9.6
38	0.049	165	2.5
39	0.098	266	5.0
40	0.074	359	3.8
41	0.145	288	7.5
42	0.121	66	6.2
postnatal age (weeks)			
23	0.190	19	10.0
24	0.010	145	0.5
25	0.018	210	0.9
26	0.005	276	0.2
27	0.004	52	0.2
28	0.000	34	0.0
52	0.002	244	0.1

Benn index (at birth) = weight (grams)/ height (cm)ⁿ using Cole et al's. average regression coefficient of 2.64

BMI (from 23 gestation weeks on) = weight (grams) / height (cm)²

% variation due to body length = $1 - \sqrt{1-r^2} * 100$ (Wells et al. in press)

r² values derived from Benn index at birth and BMI at 6 and 12 months measurement periods regressed against height at those times

Table 4.2 Descriptive statistics for estimated nutritional status variables

Outcome variable	males			females		
	n	mean	sd	n	mean	sd
<i>birth</i>						
Benn index (kg/m ^{2.64})	628	21.3	2.4	606	21.3	2.4
mid-arm muscle area (mm ²)	590	740	329	561	683*	320
mid-arm fat area (mm ²)	590	302	125	561	294	118
<i>6 months</i>						
BMI (kg/m ²)	390	17.5	1.7	346	17.8*	1.7
<i>12 months</i>						
BMI (kg/m ²)	105	17.4	1.3	139	17.1	1.5

n = sample size, sd = standard deviation

* sexes differ significantly based on independent samples t-test

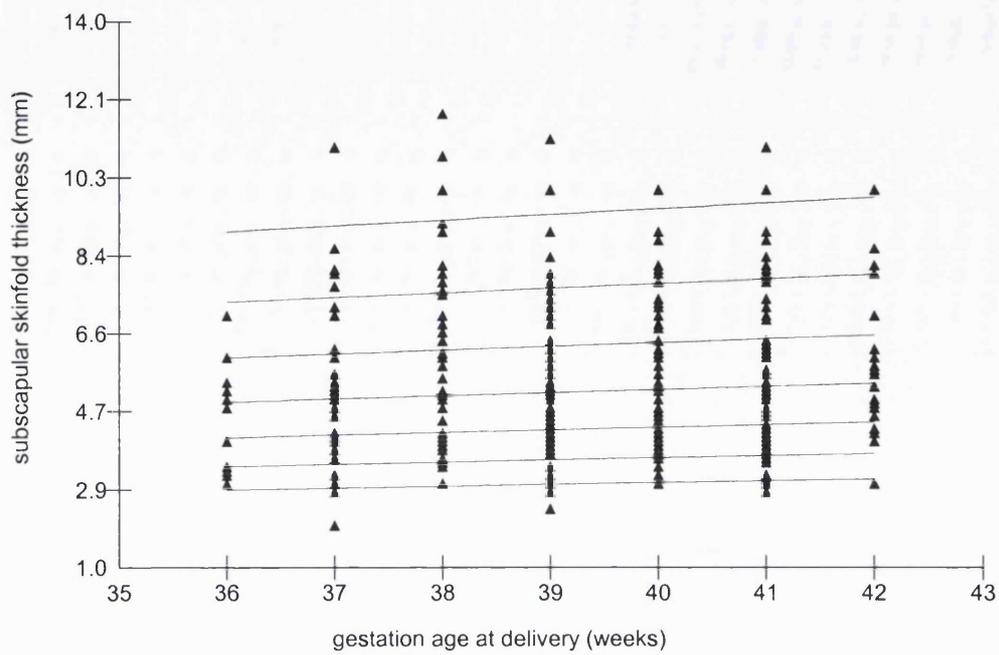


Figure 4.3 LMS - model and centiles derived from subscapular skinfold thickness plotted against age for females at birth.

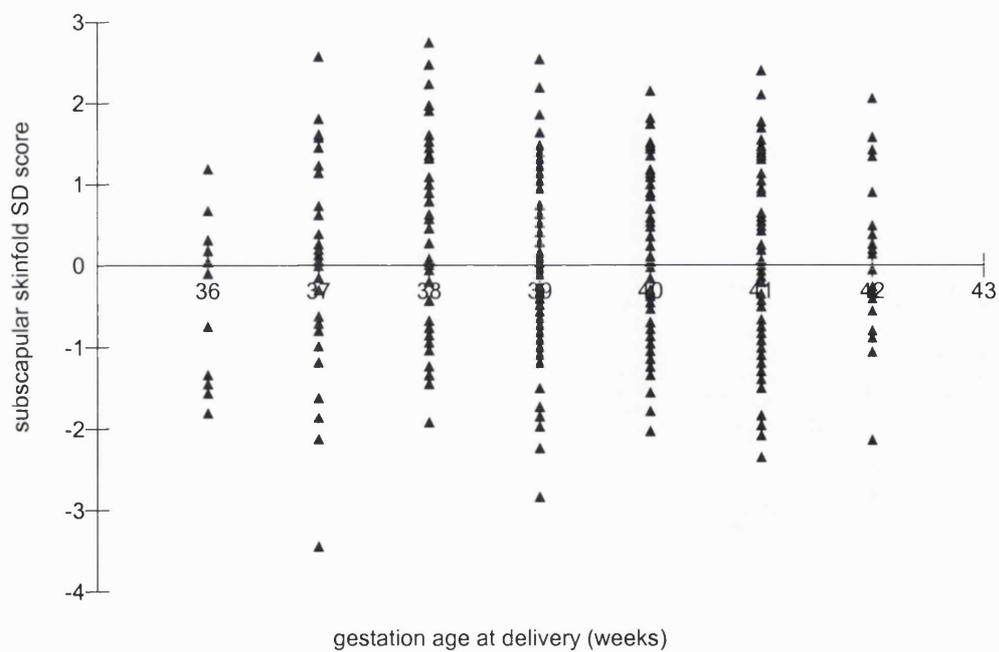


Figure 4.4 SD scores for female subscapular skinfold SD score at birth plotted against age

4.3d) Statistical tests

Two-tailed bivariate correlations with confidence limits set at 95% are used here to determine whether size, growth and encephalisation SD scores are significantly related. In addition, multiple regression is used to determine which variables explain a significant amount of the variation in encephalisation SD scores. Independent samples t-tests (with confidence limits of 95%) are used to determine whether statistically significant differences are found between variable means.

4.3e) Tertiles

Data are also described in terms of tertiles, where SD scores are ranked and divided into 3 equal-numbered groups. Each of these groups is then further sub-divided into 3 groups, yielding a total of 9 categories. Here the database is divided into tertiles based on body length SD scores at each measurement period. These 3 categories of length SD scores represent short, medium and tall individuals. Each size category is then sub-divided into 3 rankings of head circumference size (SD score), so that short babies are divided into groups of short and small head circumference, short and medium head circumference and short and large head circumference. The same is performed for the medium and tall baby categories which are divided into small, medium and large head circumference babies. The result is a 9-cell table, with roughly equal sample sizes in each cell, listing the mean values and standard deviations for variables as they relate to each cell. The descriptive statistics for these rankings are as follows:

Body length SD at birth (n = 1234) 411 per rank

rank 1 body length: (1-411) mean = -1.07 sd = 0.57

Head circumference SD score at birth (n = 411) 137 per rank

1: (1-137) mean = -1.53 sd = 0.52

2: (138-274) mean = -0.50 sd = 0.22

3: (275-411) mean = 0.45 sd = 0.53

rank 2 body length: (412-823) mean = -0.01 sd = 0.24

Head circumference SD score at birth

1: (1-137) mean = -0.87 sd = 0.45

2: (138-274) mean = -0.03 sd = 0.16

3: (275-411) mean = 0.87 sd = 0.51

rank 3 body length: (824-1234) mean = 1.08 sd = 0.56

Head circumference SD score at birth

1: (1-137) mean = -0.48 sd = 0.58

2: (138-274) mean = 0.55 sd = 0.26

3: (275-411) mean = 1.57 sd = 0.49

The tertiles are given in section 4.4b of the results section.

4.4) Results

4.4a) Size and encephalisation

Figures 4.5 and 4.6 show that large neonates (after controlling for age and sex-effects) may be both encephalised and non-encephalised. Equally, small neonates may be both encephalised or non-encephalised. This is the case for all of the measurement periods in the study.

In addition, figures 4.7 (a-j) show that encephalisation is related to increases or decreases in head circumference rather than body length. Here fetuses and infants are divided into two groups - those who fall below the 10th percentile in encephalisation SD score and those who fall above the 90th centile in encephalisation SD score. These two groups, therefore, include the least and most encephalised individuals in the sample population. Mean head circumference and femur (in fetuses) or body length (in infants) SD scores and + or - 2 sd are plotted for males and females separately. In all cases, low encephalisation is related to a decrease in head circumference SD and not an increase in femur or body length SD. In contrast, high encephalisation is related to an increase in head circumference SD and not a decrease in femur or body length SD. Paired-samples t-tests reveal that at all measurement periods, mean femur or body length SD scores differ significantly from mean head circumference SD scores, within the 90th and 10th centile groups.

Body size alone does not, therefore, explain neonatal encephalisation. However, it is possible that some other aspects of morphology, such as growth rate and nutritional status do.

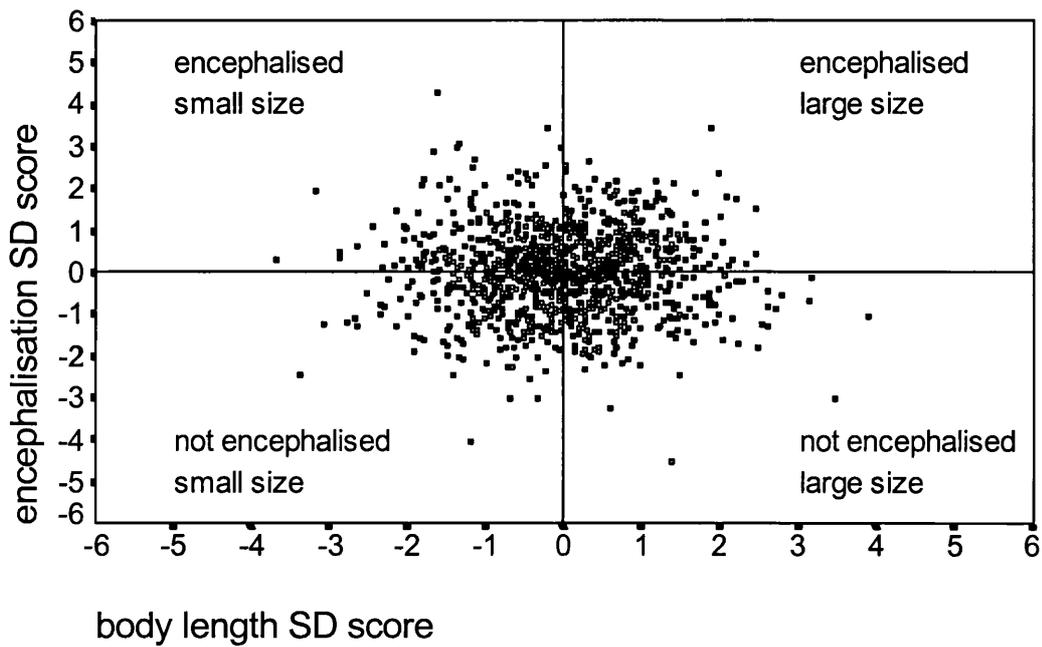


Figure 4.5 Scatterplot of encephalisation SD scores plotted against body length SD scores at birth.

There is no statistically significant relationship between body length and encephalisation SD scores, as expected due to the inclusion of body length SD in the calculation of the encephalisation SD.

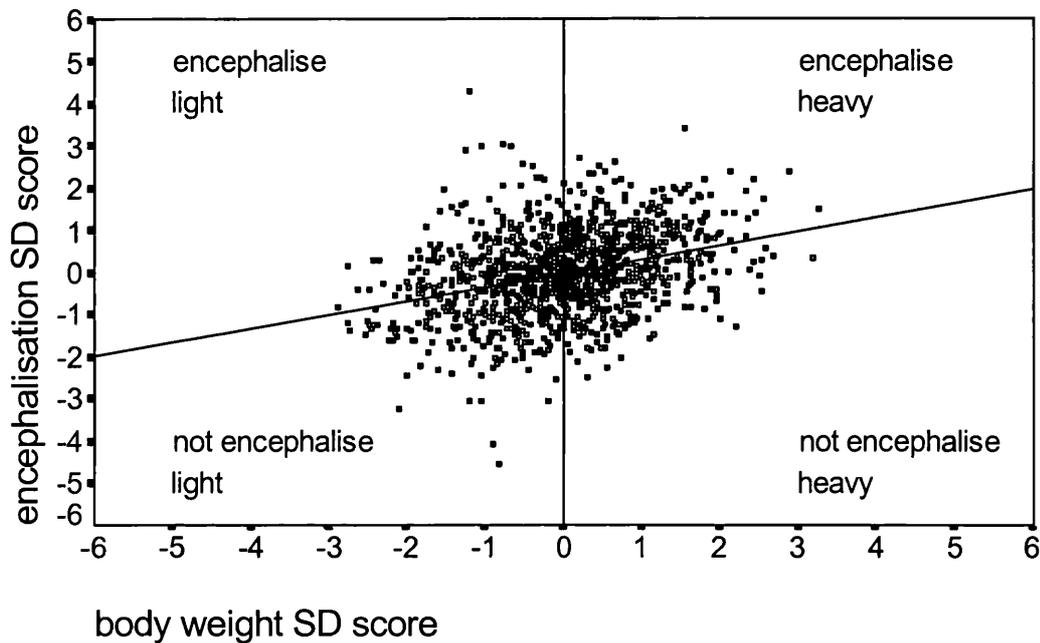


Figure 4.6 Scatterplot of encephalisation SD scores plotted against body weight SD scores at birth. Both heavy and light neonates may be encephalised or non-encephalised, but there is a trend toward increased encephalisation with increased body weight.

The least squares linear regression equations describing this relationship in the neonate is as follows:

(39) $\text{encephalisation SD score} = 0.00 * \text{SD body weight SD score} + 0.33$
 $r^2 = 0.110, \text{SE} = 0.944, n = 1233, P = 0.000$

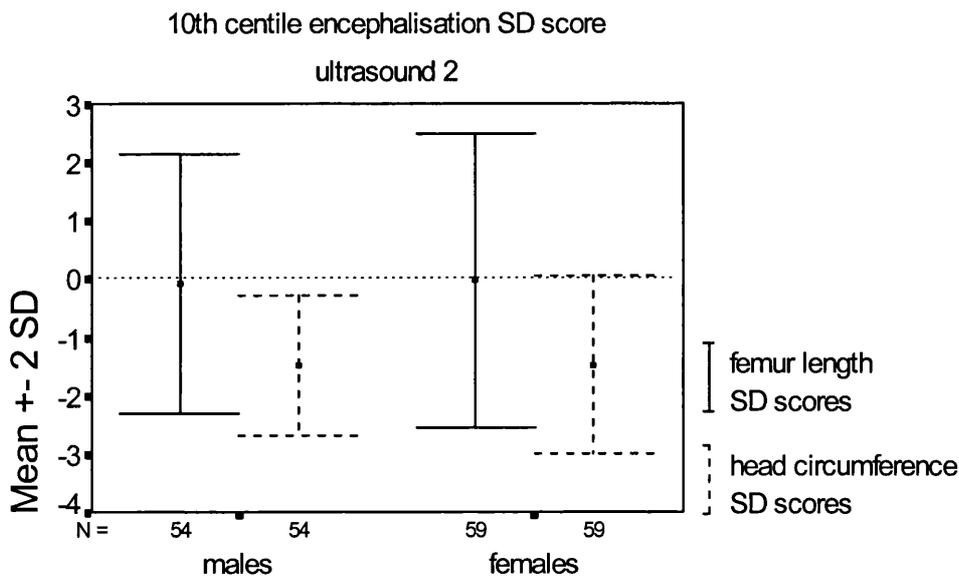


Figure 4.7a Mean SD score with error bars showing + or - 2 sd for fetuses at ultrasound 2 who fell below the 10th percentile in terms of encephalisation SD score

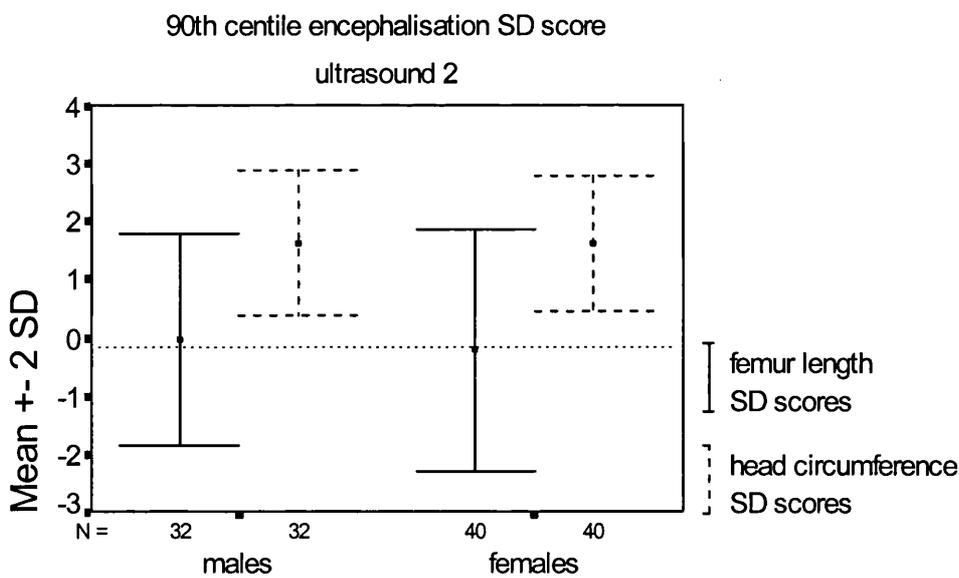


Figure 4.7b Mean SD score with error bars showing + or - 2 sd for fetuses at ultrasound 2 who fell above the 90th percentile in terms of encephalisation SD score

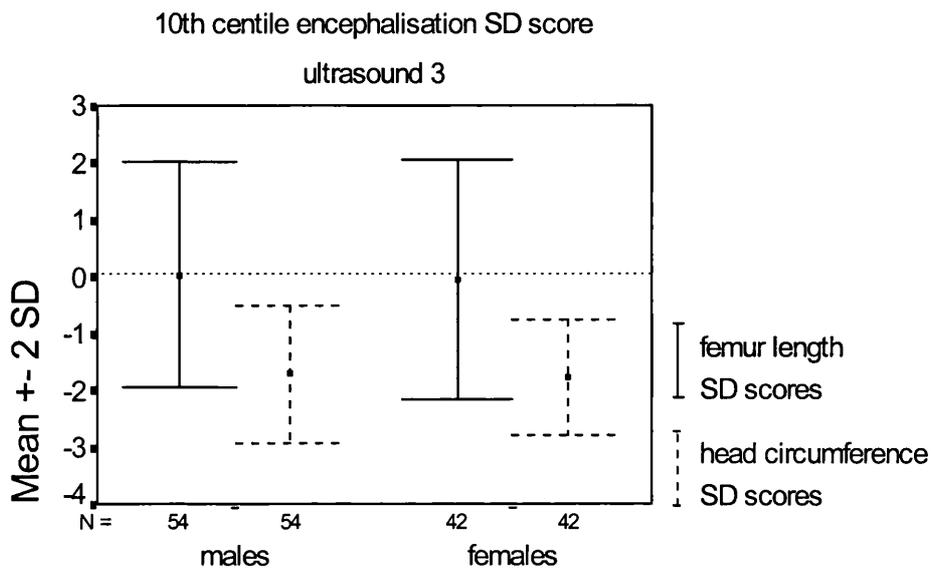


Figure 4.7c Mean SD score with error bars showing + or - 2 sd for fetuses at ultrasound 3 who fell below the 10th percentile in terms of encephalisation SD score

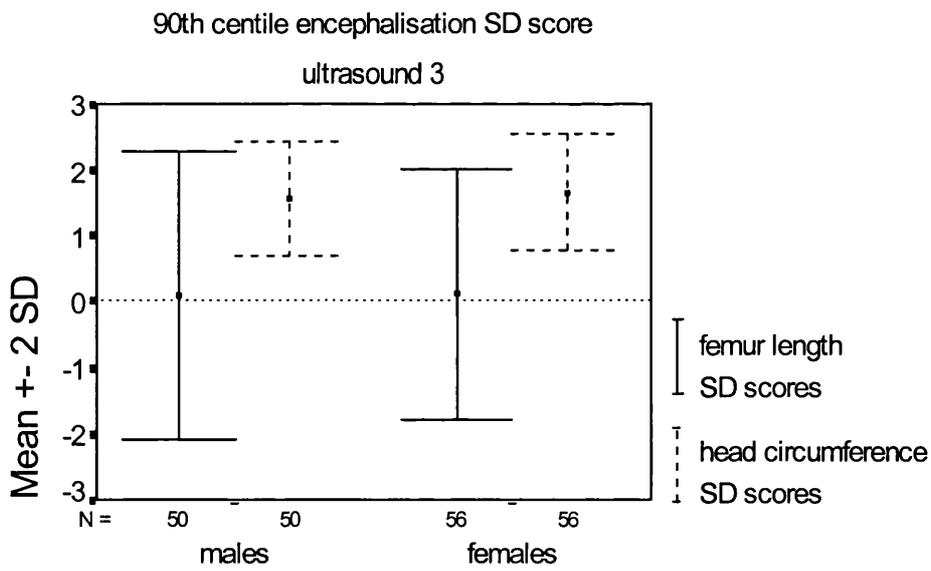


Figure 4.7d Mean SD score with error bars showing + or - 2 sd for fetuses at ultrasound 3 who fell above the 90th percentile in terms of encephalisation SD score

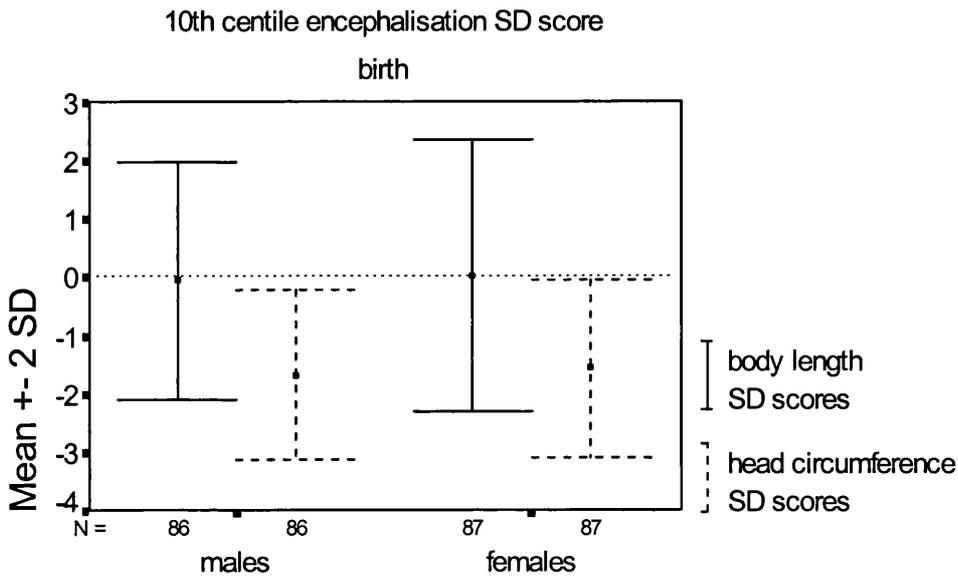


Figure 4.7e Mean SD score with error bars showing + or - 2 sd for neonates at birth who fell below the 10th percentile in terms of encephalisation SD score

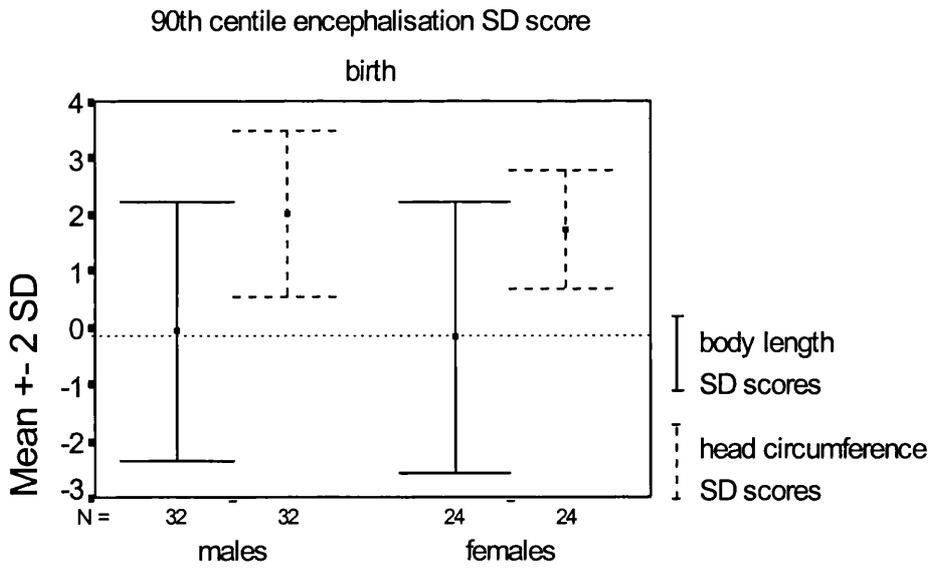


Figure 4.7f Mean SD score with error bars showing + or - 2 sd for neonates at birth who fell above the 90th percentile in terms of encephalisation SD score

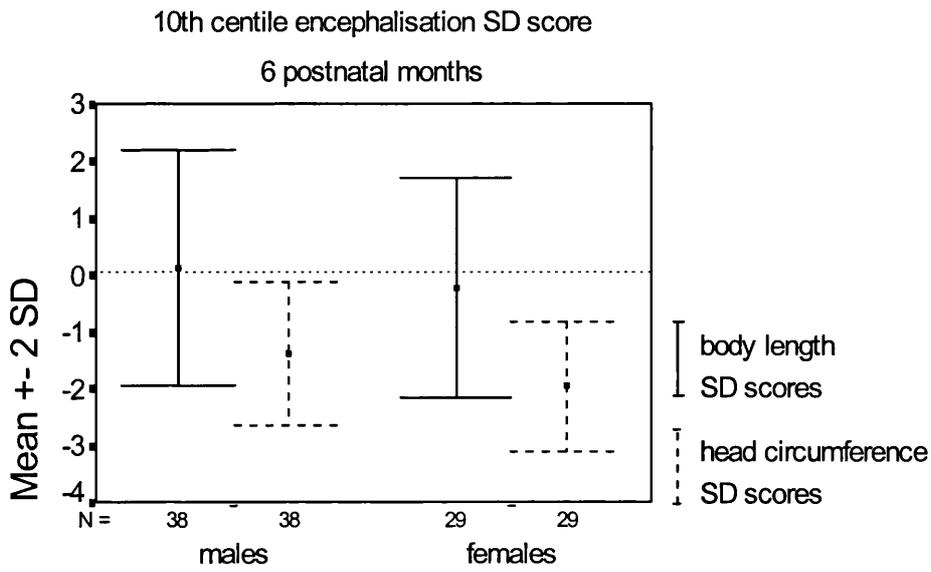


Figure 4.7g Mean SD score with error bars showing + or - 2 sd for neonates at birth who fell above the 90th percentile in terms of encephalisation SD score

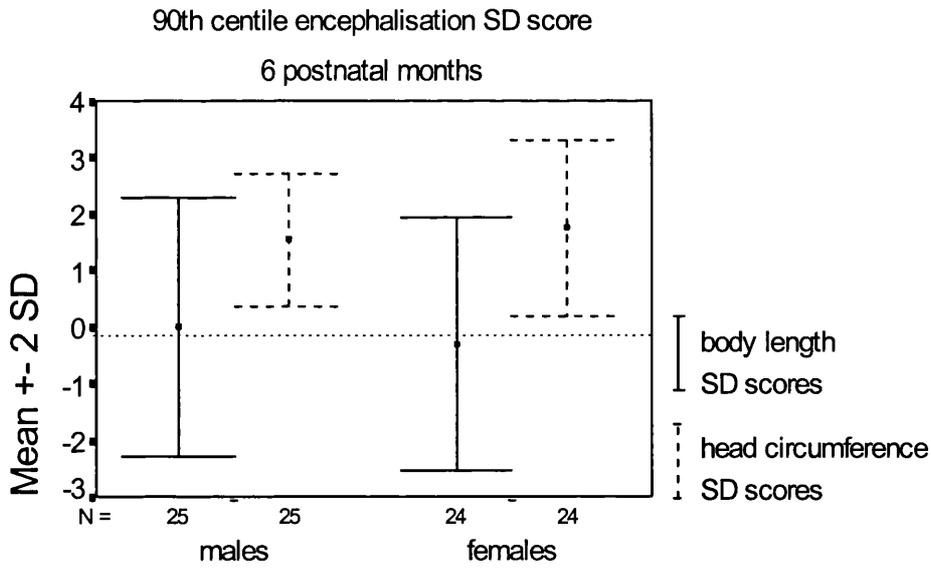


Figure 4.7h Mean SD score with error bars showing + or - 2 sd for infants at 6 months who fell above the 90th percentile in terms of encephalisation SD score

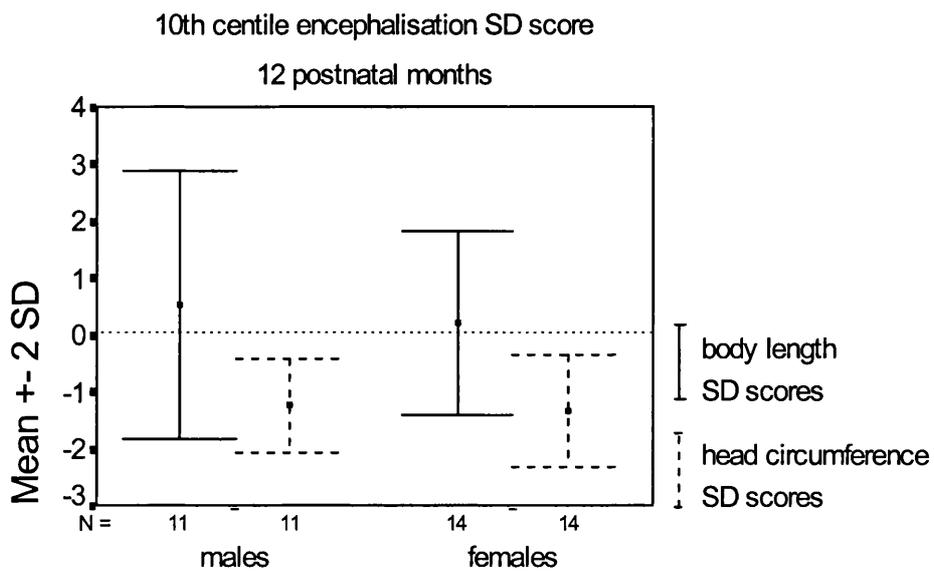


Figure 4.7i Mean SD score with error bars showing + or - 2 sd for infants at 12 months who fell below the 10th percentile in terms of encephalisation SD score

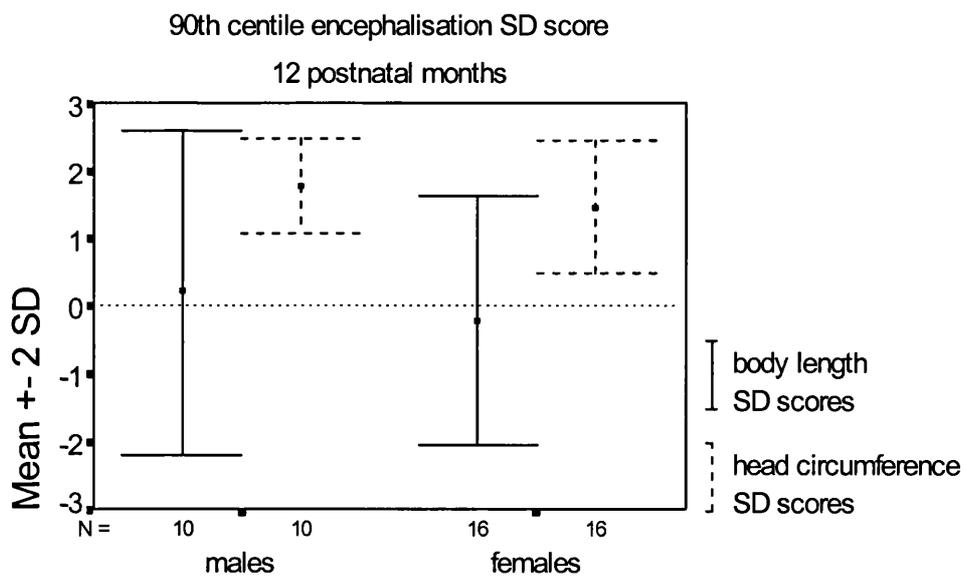


Figure 4.7j Mean SD score with error bars showing + or - 2 sd for infants at 12 months who fell above the 90th percentile in terms of encephalisation SD score

4.4b) Growth and encephalisation

First, the relationship between encephalisation and growth indices are described in terms of body length and head circumference tertiles (see Tables 4.3 to 4.5). Mean values are reported first and sd values are listed beneath in parentheses.

i) Body length growth and encephalisation

Table 4.3 shows that short infants (body length SD tertile 1) undergo the greatest positive change (i.e. increase) in body length SD score between birth and 6 months, but that encephalisation (i.e. head circumference SD tertile relative to body length SD tertile) has little affect. An equivalent but negative change occurs in the tall infants. Whether the small infants were encephalised for their size or not, they underwent 'catch up' growth (i.e. an increase in body length SD score). In contrast, the tall babies underwent 'catch down' growth while the average babies remained so. Thus, body length growth is not associated with encephalisation *per se*.

ii) Head circumference growth and encephalisation

Table 4.4 shows that, regardless of body length, encephalised babies undergo 'catch down' growth in head circumference (i.e. negative SD) while non-encephalised babies undergo 'catch up growth' in head circumference (i.e. increase in SD score between birth and 6 months).

Head circumference growth indices rather than body length growth indices, therefore appear to relate directly to encephalisation. For example, average-sized infants with small head circumferences for their bodies tend to catch up in head circumference while body length remains fairly constant. In contrast, small but encephalised infants tend to catch up in body length but may actually decrease in head circumference SD.

iii) Thrive in growth and encephalisation

After taking initial body length and head circumference into account and thereby controlling for the tendency to regress to the mean (i.e. undergo 'catch up' or 'catch down' growth), the relationship between encephalisation and growth is less clear. Tables 4.6 and 4.7 show that mean thrive in body length and thrive in head circumference SD scores in each of the 9 tertile cells vary far less than in the previous Tables (4.3 to 4.5).

This may suggest that encephalisation is flexible and driven largely by the tendency of the infant to regress to the mean in terms of size SD score (i.e. catch up and catch down growth). Changes in encephalisation, therefore, relate to 'catch up' and 'catch down' growth in head circumference (see Table 4.5), where small headed-babies, regardless of body length, undergo an increase in encephalisation SD score due to catch up growth in the head circumference.

A multiple regression shows that head circumference Δ SD between ultrasound 3 and birth explains about 25% of the variation in encephalisation SD score at birth. Adding Δ body length between ultrasound 3 and birth to the model explains a further 4 % of the variation.

These results support the 'Reduced Growth Hypothesis' in that they show that head circumference growth rather than body length growth drives encephalisation. Encephalised neonates undergo increased head circumference growth, while non-encephalised neonates undergo decreased head circumference growth.

Table 4.3 Mean and standard deviation for change in body length SD score (between birth and 6 months) relative to body length and head circumference SD score tertiles at birth

	3	+0.76 (0.99)	+0.06 (1.03)	-0.57 (0.99)
head circumference	2	+0.51 (0.82)	+0.03 (0.91)	-0.60 (1.03)
SD score at birth	1	+0.60 (1.12)	-0.10 (0.90)	-0.78 (1.02)
		1	2	3
		body length at birth SD score		

Table 4.4 Mean and standard deviation for change in head circumference SD score (between birth and 6 months) relative to body length and head circumference SD score tertiles at birth

	3	-0.25 (0.91)	-0.51 (1.01)	-0.71 (0.93)
head circumference	2	+0.21 (0.88)	-0.05 (0.92)	-0.23 (0.92)
SD score at birth	1	+0.87 (0.88)	+0.47 (0.94)	+0.27 (1.11)
		1	2	3
		body length at birth SD score		

Table 4.5 Mean and standard deviation for change in encephalisation SD score (between birth and 6 months) relative to body length and head circumference SD score tertiles at birth

head circumference SD score at birth	3	-0.75 (1.10)	-0.61 (1.07)	-0.43 (1.01)
	2	-0.05 (0.98)	-0.07 (0.91)	+0.09 (0.92)
	1	+0.68 (0.96)	+0.59 (1.09)	+0.70 (1.15)
		1	2	3
		body length at birth SD score		

Table 4.6 Mean and standard deviation for thrive in body length (between birth and 6 months) relative to body length and head circumference SD score tertiles at birth

head circumference SD score at birth	3	0.21 (0.97)	0.08 (1.08)	0.20 (1.00)
	2	-0.16 (0.79)	0.04 (0.99)	0.05 (1.04)
	1	-0.08 (1.08)	-0.12 (0.95)	-0.19 (1.04)
		1	2	3
		body length at birth SD score		

Table 4.7 Mean and standard deviation for thrive in head circumference (between birth and 6 months) relative to body length and head circumference SD score tertiles at birth

	3	-0.02 (0.92)	-0.05 (1.04)	0.13 (1.04)
head circumference	2	-0.09 (0.95)	-0.08 (1.00)	0.07 (1.01)
SD score at birth	1	0.07 (0.98)	-0.04 (0.98)	0.00 (1.12)
		1	2	3
		body length at birth SD score		

Table 4.8 lists the mean change in SD for head circumference and body length between each measurement period, as a function of encephalisation percentile. It also lists the changes in SD scores in the subsequent measurement period. These descriptives show that amongst highly encephalised individuals (i.e. 90th percentile: ≥ 1.82 SD), preceding head circumference growth (i.e. Δ head circumference SD score) is positive while preceding body length growth (i.e. Δ body length SD score) is negative. In other words, body length growth slows down in relative terms while head circumference growth increases amongst highly encephalised individuals.

In the subsequent measurement period, regression to the mean occurs, where a previously low SD score (in the head circumference or body length) is followed by an increase in SD score, and previously high SD scores are followed by a decrease in SD score. However, in the subsequent period of measurement, the trade-off in growth between the head and length is still present.

The difference in head circumference and body length growth is significant. Paired-samples t-tests reveal that the differences in the mean change in SD score between head circumference and body length SD scores are significantly different for both the 90th and 10th centiles.

Amongst the least encephalised individuals (i.e. 10th percentile: ≤ -1.3 SD), preceding head circumference growth (i.e. Δ head circumference SD score) is negative while preceding body length growth (i.e. Δ body length SD score) is positive. Here, body length growth increases in relative terms while head circumference growth decreases. It thus appears that head circumference and body length do not grow at the same rates but actually offset one another. While head circumference growth rate increases, body length growth rate decreases, each taking it's turn to 'catch up' while the other 'catches down' (see Table 4.8).

Encephalisation, therefore, appears to be driven, at least in part, by 'catch up' growth in head circumference (the brain), the energetic costs of which may be offset by the concomitant relative reduction in linear body growth rates.

Table 4.8 Mean change in SD score as a function of the 90th and 10th centiles and change in SD in subsequent measurement period (in terms of encephalisation index) at beginning of given measurement periods

measurement period	≥ 90 th centile				≤ 10 th centile			
	mean Δ hc SD score	mean Δ fl/bl SD score	subsequent mean Δ hc SD score	subsequent mean Δ fl/bl* SD score	mean Δ hc SD Score	mean Δ fl / bl SD Score	subsequent mean Δ hc SD Score	subsequent mean Δ fl / bl SD Score
ultrasounds 2 - 3	+1.36	-0.27	-0.06	+0.12	-1.50	-0.03	-0.04	-0.11
ultrasound 3 - birth	+0.87	-0.16	-0.14	-0.05	-1.03	+0.02	0.00	+0.12
birth - 6 months	+0.98	-0.30	-0.01	+0.16	-0.92	+0.18	-0.13	+0.04
6 - 12 months	+0.28	-0.36	-	-	-0.34	+0.21	-	-

Δ femur length (fl) prenatally and Δ body length (bl) postnatally, Δ = change in SD score between listed measurement period and the period preceding it. For example, mean 90th centile in Δ head circumference (hc) at birth is the mean change in head circumference SD score between ultrasound 3 and birth for the top 10% of the sample.

Subsequent mean Δ SD score is the change in SD score in the following measurement period.

Mean Δ head circumference and Δ femur/body length differ significantly based on paired-samples t-tests for both the 90th and 10th centiles subsequent

4.4c) Nutritional status and size, growth and encephalisation

i) Nutritional status and size

Table 4.9 lists the results of bivariate correlations between nutritional status variable SD scores at birth and head circumference and body length SD scores. The results show that well-nourished neonates are generally large neonates, both in terms of their body lengths and head circumferences. In addition, neonates with relatively large heads have reduced skinfold ratios (i.e. increased limb fat relative to centralised fat). This is likely associated with good nutritional status generally, as Barker et al. (1997) have shown that increased birth weight is associated with later increased peripheral fat distribution. Yajnik (2000) has also shown that centralised fatness (subscapular skinfold thickness) is preserved during malnutrition, so that increased peripheral fatness reflects good nutritional status.

ii) Nutritional status and growth

Table 4.10a and 4.10b lists the results of bivariate correlations between neonatal nutritional status (SD scores) and measures of growth. Table 4.10a lists the results of the correlations between change in head circumference and body length SD score (i.e. relative growth) between birth and 6 months, and the neonatal nutritional status SD scores. Here fat and lean index SD scores are inversely correlated with growth indice SD scores, suggesting that significant 'catch down' growth occurs in well-nourished neonates. At birth, well-nourished neonates have relatively large head circumferences and body lengths which then regress to the mean in subsequent months.

Table 4.10b lists the results of correlations between thrive in growth SD scores for the head circumference and body length (between birth and 6 months) and neonatal nutritional status SD scores. The results show that variables reflecting fat and muscle at birth are not significantly correlated with subsequent thrive in head circumference and body length growth (between birth and 6 months). This suggests that after

controlling for initial size effects at birth, subsequent growth is not influenced by fat and muscle content in the neonate.

Table 4.9 Results of correlations between neonatal nutritional status SD scores and head circumference and body length SD at birth

variable SD score	head circumference SD		body length SD	
	n	R	n	R
Benn index	1233	0.20*	.	.
subscapular skinfold	1150	0.28*	1151	0.31*
triceps skinfold	1151	0.27*	1151	0.31*
subscapular : triceps ratio	1148	-0.07‡	1148	-0.03
estimated mid-arm fat area	1151	0.41*	1151	0.41*
estimated mid-arm muscle area	1151	0.40*	1151	0.34*

n = sample size, R = correlation coefficient, SD = standard deviation score, based on a two-tailed bivariate correlation with a confidence limit of 95%
Body length is not correlated with Benn index here as it is used in the calculation of this index

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$

Table 4.10a Results of correlations between neonatal nutritional status SD scores and change in (Δ) head circumference and body length SD between birth and 6 months

variable SD score	Δ head circumference SD		Δ body length SD	
	n	R	n	R
Benn index	725	-0.03	.	.
subscapular skinfold	685	-0.12†	684	-0.13#
triceps skinfold	687	-0.15*	686	-0.19*
subscapular : triceps skinfolds	685	0.05	684	0.01
estimated mid-arm fat area	687	-0.20*	686	-0.22*
estimated mid-arm muscle area	687	-0.16*	686	-0.12#

n = sample size, R = correlation coefficient, SD = standard deviation score, based on a two-tailed bivariate correlation with a confidence limit of 95%
Body length is not correlated with Benn index here as it is used in the calculation of this index

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$

Table 4.10b Results of correlations between neonatal nutritional index SD scores and thrive in head circumference SD between birth and 6 months

variable SD score	thrive in head circumference		thrive in body length	
	n	R	n	R
Benn index	725	0.05	.	.
subscapular skinfold	685	0.00	684	0.03
triceps skinfold	687	-0.03	686	-0.05
subscapular : triceps skinfolds	684	-0.02	685	-0.01
estimated mid-arm fat area	687	-0.01	686	-0.02
estimated mid-arm muscle area	687	0.02	686	0.04

n = sample size, R = correlation coefficient

Body length is not correlated with Benn index here as it is used in the calculation of this index

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$

based on a two-tailed bivariate correlation with a confidence limit of 95%

iii) Nutritional status and encephalisation

Table 4.11 lists the results of bivariate correlations between neonatal nutritional status SD scores and neonatal encephalisation SD as well as change in encephalisation SD between birth and 6 months. The results show that neonatal nutritional status, fatness and leanness are significantly and positively correlated with encephalisation SD scores, so that encephalised neonates tend also to be generally well-nourished. In addition, fat distribution is correlated with encephalisation at birth, where encephalised neonates tend to have increased limb fatness relative to centralised fatness. Changes in encephalisation between birth and 6 months are, in contrast, inversely correlated with nutritional status SD scores at birth. Well-nourished neonates tend to be encephalised at birth and undergo ‘catch down’ growth in encephalisation subsequently.

These results are largely in keeping with the ‘Nutrition Hypothesis’ where it was argued that well-nourished individuals will be more encephalised than poorly-nourished individuals. However, good nutritional status is also associated with a relative decrease in subsequent encephalisation as part of the tendency for encephalisation to regress to the mean.

Table 4.11 Results of correlations between neonatal nutritional index SD scores and a) neonatal encephalisation SD b) change in (Δ) encephalisation SD between birth and 6 months

variable SD score	encephalisation SD		Δ encephalisation SD	
	n	R	n	R
Benn index	1233	0.39*	724	-0.22*
subscapular skinfold	1150	0.16*	684	-0.05
triceps skinfold	1151	0.14*	686	-0.05
subscapular : triceps skinfolds	1148	-0.07‡	684	0.04
estimated mid-arm fat area	1151	0.25*	686	-0.09‡
estimated mid-arm muscle area	1151	0.28*	686	-0.09‡

n = sample size, R = correlation coefficient, SD = standard deviation score

Body length is not correlated with Benn index here as it is used in the calculation of this index

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$

based on a two-tailed bivariate correlation with a confidence limit of 95%

4.4d) Body length and head circumference effects on encephalisation

In order to separate out the statistical effects of head circumference and body length as they relate to these neonatal variables, a multiple regression is used where an interaction variable is introduced into the model. The interaction is the product of, for example, head circumference and body length SD scores and is entered into the model along with head circumference and body length SD scores as the independent variables. Neonatal nutritional and growth index SD scores are then entered as the dependent variables. If the interaction variable contributes significantly to explaining the variation in the dependent variable, then the regression coefficient for head circumference changes as the regression coefficient for body length changes, meaning that the two variables do not relate separately to the dependent variable (T. Cole, pers. comm.).

Table 4.12a lists the results of the multiple regressions where the dependent variable is head circumference SD score at birth. The independent variables include neonatal estimated mid-arm muscle area SD scores, subscapular and triceps skinfold SD scores. Each nutritional status SD score along with body length SD and the interaction variable between that nutritional status variable and body length were entered into the multiple regression model as independent variables.

The results show the neonatal nutritional variable SD scores, along with body length SD explain between 27-32% of the variation in head circumference SD score. The nutritional variable SD scores (estimated mid-arm muscle area SD score and subscapular and triceps skinfold SD scores) contribute significantly to the models, while the interaction variables do not. Body length SD score alone explains 22.3% of the variation in head circumference SD score. Mid-arm muscle SD score explains an additional 9.4% of the variation, while the skinfold SD scores explain an additional 5% of the variation each.

Nutritional status appears to be associated with encephalisation. A multiple linear regression reveals that mid-arm muscle area, triceps and subscapular skinfold SD scores together explain 8.35% of the variation in neonatal encephalisation SD, with

mid-arm muscle area and triceps skinfold SD scores contributing most to the model (see Table 4.12b). Neonatal mid-arm muscle area SD scores also contribute significantly to explaining the variance in change in encephalisation (between birth and 6 months). However, less than 1% of the variation in the dependent variable is explained by neonatal nutritional status SD scores (see Table 4.12b).

Table 4.12c lists the results of multiple regressions where indices of growth in the body and head as well as encephalisation are entered as the dependent variables and head circumference and body length SD scores as well as the interaction between head circumference and body length SD scores are entered as the independent variables. Growth indices are calculated as the difference in SD score between measurement periods.

The results show that both body length and head circumference SD scores explain between 27-33% of the variation in growth indices. In all cases, neonatal head circumference contributes significantly to the model while the interaction variable does not.

The fact that the interaction variables do not contribute to the models suggests that the head circumference and body length are functionally distinct, in terms of relating to growth indices. This suggests that head circumference (brain) and body length growth are two related but ultimately separate phenomena, undergoing 'catch up' and 'catch down' growth at separate times, in part, in response to previous growth and size.

Table 4.12a Results of linear multiple regression analyses where neonatal body length SD score, nutritional status variable SD scores and the interaction between these variables explain the variation in neonatal head circumference SD score

independent variable	coefficient t	SE	P	Total r ² (%)
constant	0.011	0.025	0.675	31.7
body length SD	0.432	0.027	0.000	
mid-arm muscle SD	0.265	0.026	0.000	
interaction	0.033	0.023	0.157	
constant	0.037	0.026	0.163	27.5
body length SD	0.478	0.027	0.000	
subscapular skinfold SD	0.134	0.026	0.000	
interaction	-0.035	0.025	0.172	
constant	0.025	0.026	0.343	27.0
body length SD	0.478	0.027	0.000	
triceps skinfold SD	0.124	0.026	0.000	
interaction	0.006	0.025	0.809	

Interaction variable = interaction between body length SD score and nutritional status variable SD score (e.g. body length SD score * subscapular skinfold thickness SD score)

SE = standard error, P = probability based on a 95% confidence limit, r² = regression coefficient

Table 4.12b Results of multiple regression analysis where neonatal nutritional status SD scores are the independent variables and explain 1) the variation in encephalisation SD scores at birth and 2) change in encephalisation SD scores between birth and 6 months

independent variable	coefficient t	SE	P	Total r ² (%)
1) constant	0.022	0.028	0.432	8.3
subscapular skinfold SD	0.020	0.041	0.623	
triceps skinfold SD	0.069	0.040	0.083	
mid-arm muscle area SD	0.254	0.030	0.000	
2) constant	-0.004	0.043	0.918	0.10
subscapular skinfold SD	0.006	0.063	0.929	
triceps skinfold SD	-0.046	0.062	0.452	
mid-arm muscle area SD	-0.010	0.046	0.033	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

Table 4.12c Results of linear multiple regression analyses where neonatal body length SD score, head circumference SD score and the interaction between the two explain the variation in growth index SD scores between birth and 6 months

independent variable	dependent variable	coefficient t	SE	P	Total r ² (%)
Δ encephalisation SD					
constant		-0.012	0.038	0.749	33.3
body length SD		0.465	0.041	0.000	
head circumference SD		-0.751	0.040	0.000	
interaction		0.059	0.036	0.101	
Δ head circumference SD					
constant		0.00	0.036	0.997	26.9
body length SD		0.056	0.040	0.155	
head circumference SD		-0.580	0.038	0.000	
interaction		0.022	0.034	0.511	
Δ body length SD					
constant		-0.002	0.038	0.960	30.3
body length SD		-0.704	0.041	0.000	
head circumference SD		0.165	0.040	0.000	
interaction		-0.001	0.035	0.972	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

Interaction variable = interaction between body length SD score and head circumference SD score (body length SD score * head circumference SD score)

Δ = change in SD score between birth and 6 postnatal months

4.4e) Changes in encephalisation during growth

Together these results demonstrate that encephalisation is not a fixed entity, but changes as ‘catch up’ and ‘catch down’ growth occur. If head circumference SD is large at a given period, it tends to shift centiles downward toward the mean, while body length shifts centiles upward. In this way, relative increases and decreases in encephalisation are ‘pulsatile’ in nature. By desynchronising ‘catch up’ growth in the head with that of linear growth, energy may be temporarily diverted to head (brain) growth.

Figures 4.8 to 4.15 are examples of ‘catch up’ and ‘catch down’ growth in encephalisation during the fetal and infancy periods up to 1 year-of-age, for those individuals within the sample below the 10th percentile, or above the 90th percentile at a given measurement period (i.e. highly encephalised or least encephalised). Only those individuals with measurements taken at all measurement periods were included in this analysis.

At fetal, neonatal and infant measurement periods, those individuals who were highly encephalised initially (i.e. fell above the upper 90th percentile in SD score), underwent regression to the mean subsequently (i.e. ‘catch down’ growth), while those who were least encephalised (i.e. below the 10th percentile in SD score) underwent ‘catch up’ growth. Figures 4.16(a and b) are 2 randomly chosen examples of individual encephalisation SD scores plotted against age, showing the tendency to regress to the mean in encephalisation SD score.

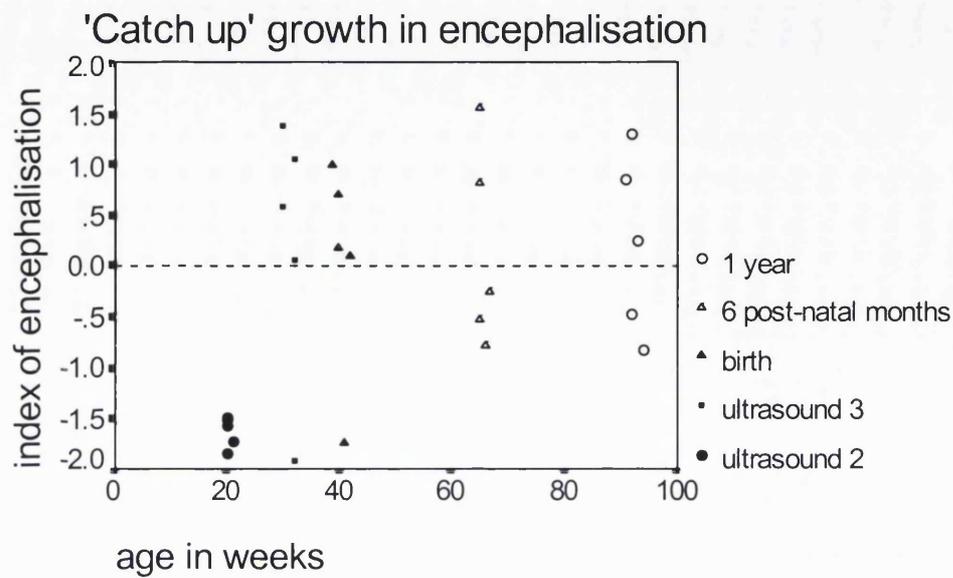


Figure 4.8 Encephalisation SD score plotted against age in post-conception weeks for individuals below the 10th percentile at ultrasound 2, in terms of encephalisation SD score

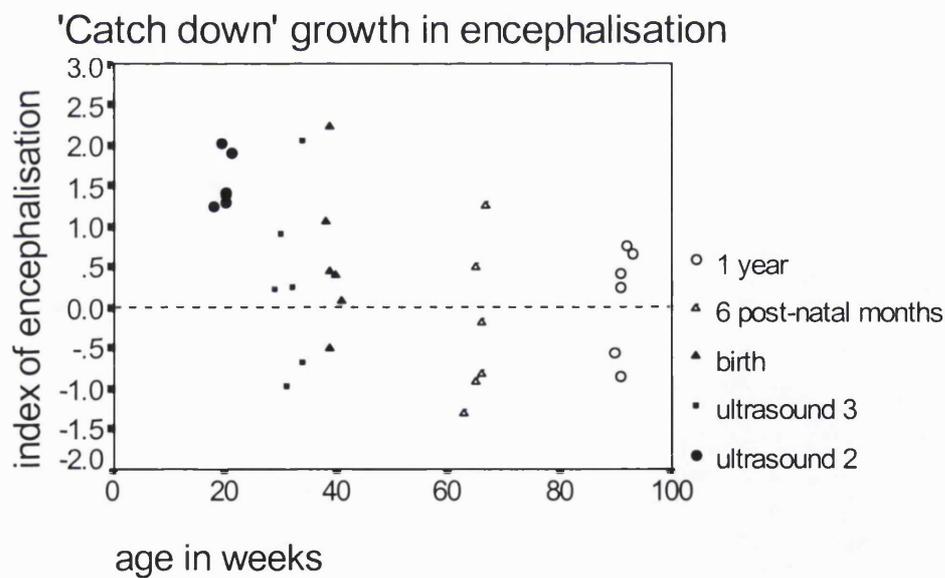


Figure 4.9 Encephalisation SD score plotted against age in post-conception weeks for individuals above the 90th percentile at ultrasound 2, in terms of encephalisation SD score

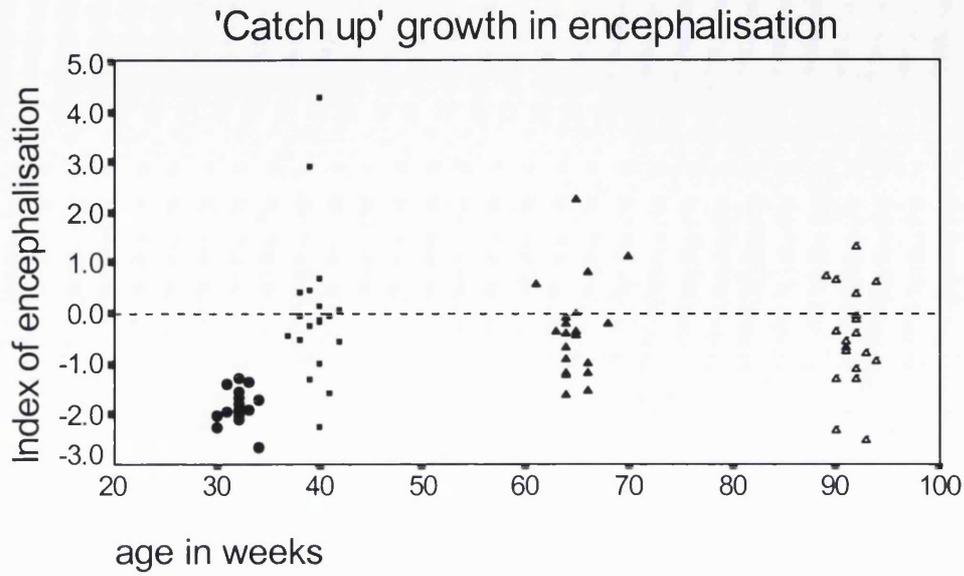


Figure 4.10 Encephalisation SD score plotted against age in post-conception weeks for individuals below the 10th percentile at ultrasound 3, in terms of encephalisation SD score

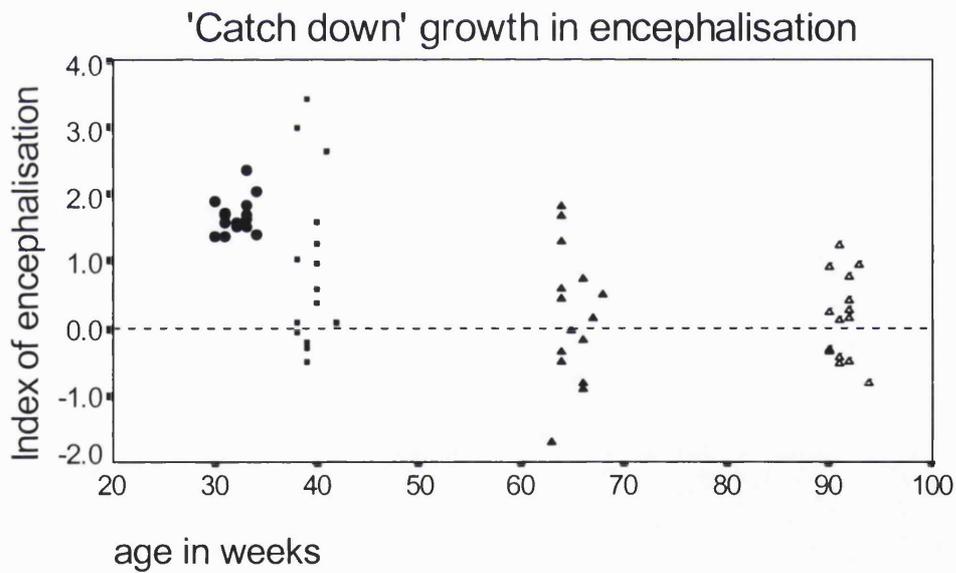


Figure 4.11 Encephalisation SD score plotted against age in post-conception weeks for individuals above the 90th percentile at ultrasound 3, in terms of encephalisation SD score

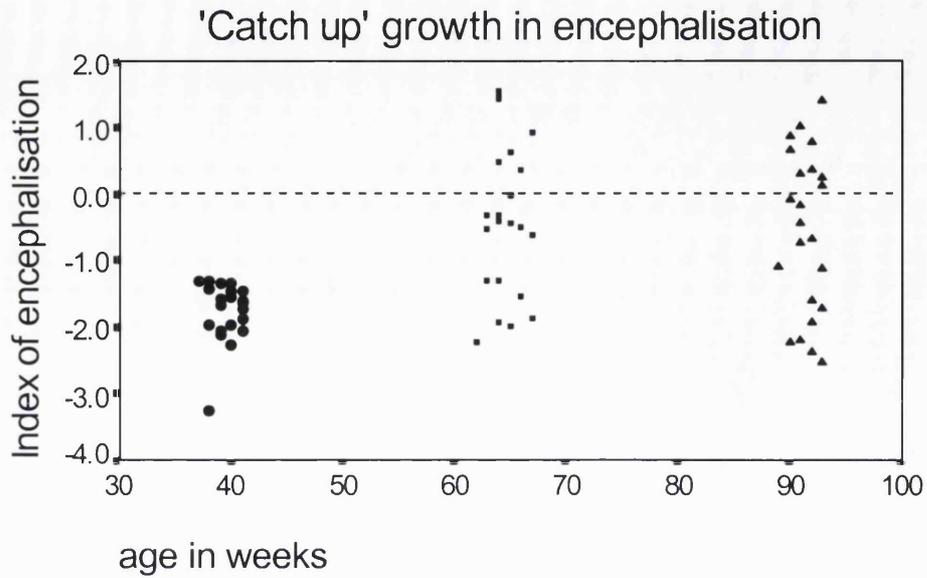


Figure 4.12 Encephalisation SD score plotted against age in post-conception weeks for individuals below the 10th percentile at birth, in terms of encephalisation SD score

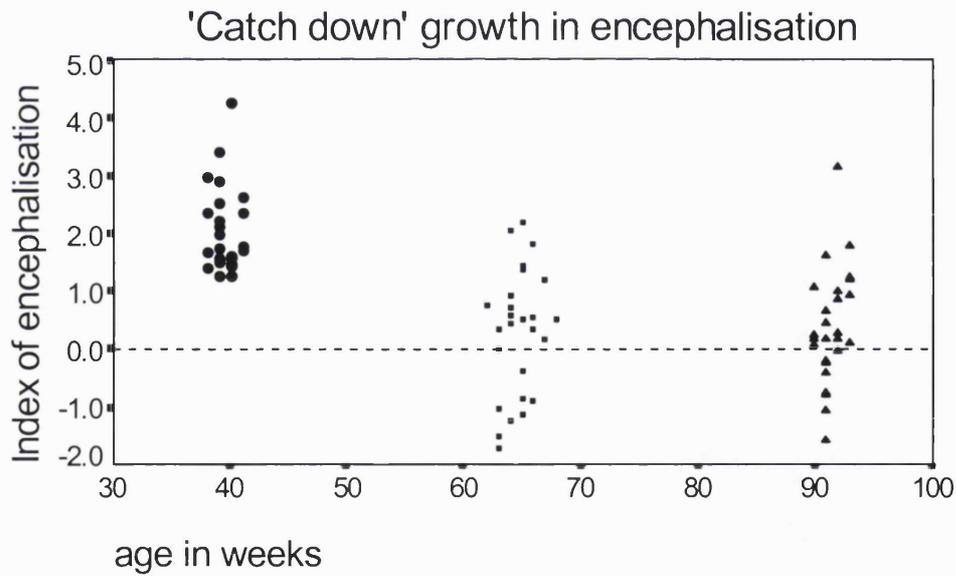


Figure 4.13 Encephalisation SD score plotted against age in post-conception weeks for individuals above the 90th percentile at birth, in terms of encephalisation SD score

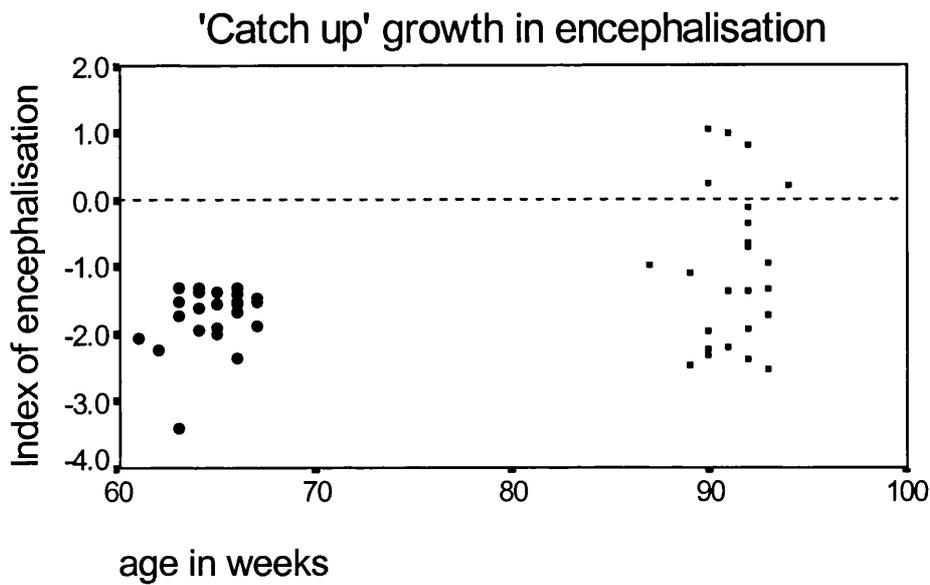


Figure 4.14 Encephalisation SD score plotted against age in post-conception weeks for individuals below the 10th percentile at 6 post-natal months, in terms of encephalisation SD score

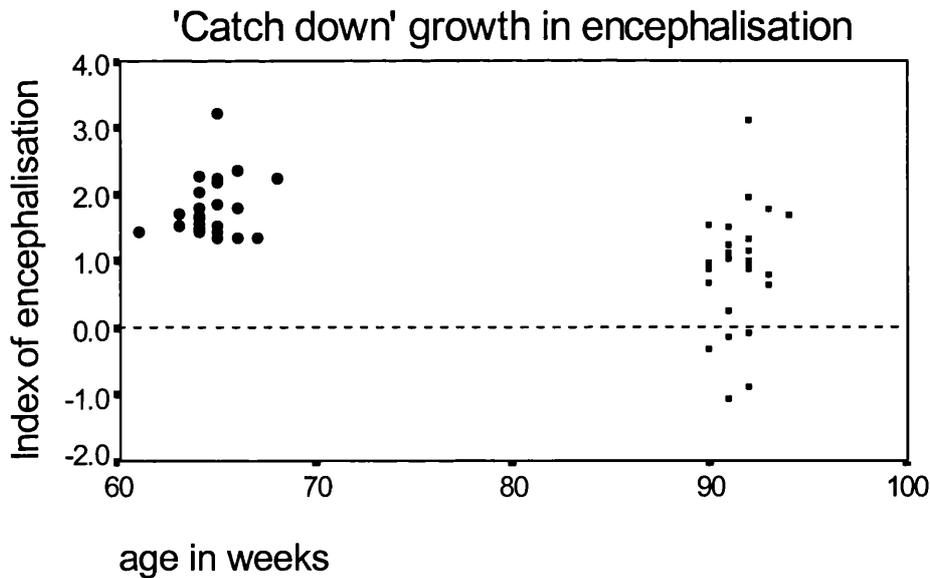


Figure 4.15 Encephalisation SD score plotted against age in post-conception weeks for individuals above the 90th percentile at 6 post-natal months, in terms of encephalisation SD score

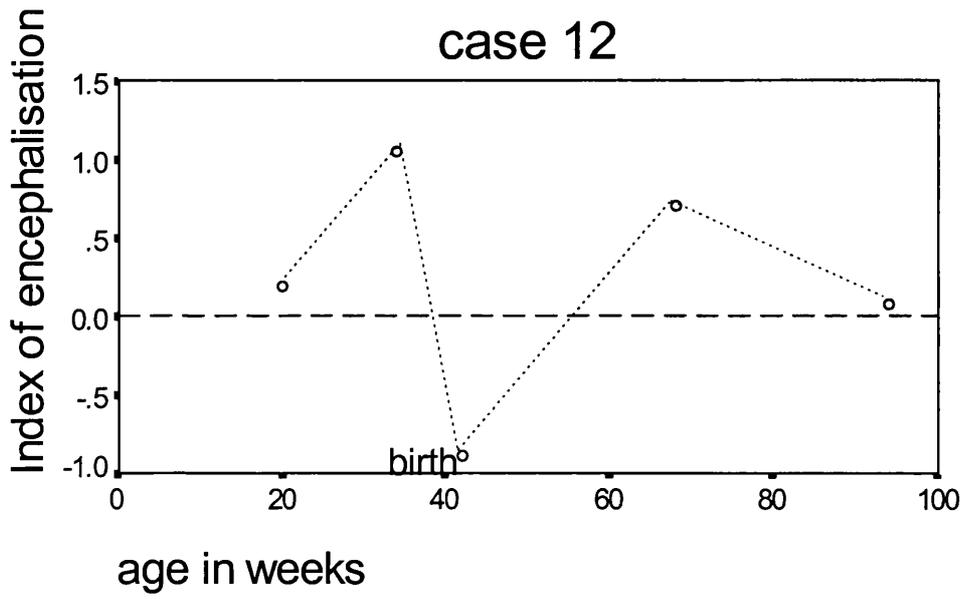


Figure 4.16a Encephalisation SD score plotted against age in post-conception weeks for case number 12

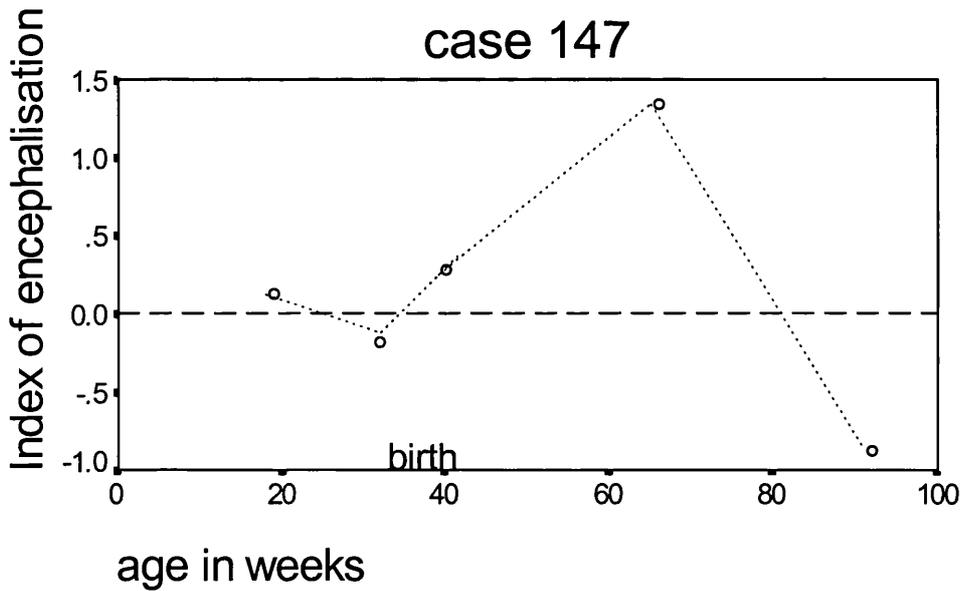


Figure 4.16b Encephalisation SD score plotted against age in post-conception weeks for case number 147

Table 4.13 lists the results of bivariate correlations between change in encephalisation SD scores (i.e. relative growth) at a given period and subsequent change in (Δ) encephalisation SD. The results show that there is an inverse correlation between Δ encephalisation SD and that in the period immediately thereafter. Once again, this suggests that changes in encephalisation are 'pulsatile' in nature, slowing down after a period of relative increase and speeding up thereafter.

Table 4.13 Results of bivariate correlations where change in encephalisation index at initial age (in italics) and subsequent ages (in column 1) are correlated

Δ Encephalisation index	n	R	P
<i>scan 2 to 3</i>			
scan 3 - birth	923	-0.43	0.000
birth - 6 months	560	-0.03	0.506
6 -12 months	164	0.01	0.901
<i>scan 3 - birth</i>			
birth - 6 months	590	-0.48	0.000
6 - 12 months	166	0.05	0.531
<i>birth - 6 months</i>			
6-12	218	-0.42	0.000

R = correlation coefficient, n = sample size, P = probability based on a confidence limit of 95%

4.5) Discussion

These results show that encephalisation occurs in fetuses and infants of all body sizes, and that intra-specific encephalisation is highly variable during early life. In addition, encephalisation is a consequence of previous head (brain) and body growth. The level of encephalisation at a given measurement period is largely determined by previous size and 'catch up' and 'catch down' growth in the head and body.

The results further suggest that encephalisation is highly 'flexible' in early life and that non-encephalised individuals may 'catch up' in encephalisation subsequently and may go on to regress to the mean.

These results are interesting in terms of adult encephalisation because they suggest that levels of adult encephalisation may not necessarily be pre-determined in early life, but may be influenced by early growth faltering due to poor nutrition or illness, for example. Since early malnutrition may or may not be followed by 'catch up' growth in the body (depending on the timing of stress or continued presence of nutritional stress), changing proportions between head and body will influence later encephalisation. In addition, these results suggest that energy stress during hypertrophic brain growth may not necessarily result in low levels of encephalisation later on due to the tendency for 'catch up' growth in encephalisation. Clearly, the different ontogenic schedules of brain and body growth (i.e. cessation of brain size growth at about 7 years and cessation of body length growth in young adulthood) influence final levels of encephalisation, attained after the adolescent growth spurt.

As shown in chapter 2, there are multiple factors which influence growth in early life. Since growth is the crucial factor in determining levels of encephalisation, we cannot assume that encephalisation is entirely determined by the genome. Malnutrition, disease, the environment in which an individual grows up are all likely to influence growth and hence encephalisation.

It is particularly interesting that the ratio of subscapular to triceps skinfold thickness (SD scores) is significantly correlated with encephalisation (SD scores) at birth. Here

the relationship is inverse, where increased centralised fat is associated with reduced encephalisation in the neonate. Increased centralised fat deposition is associated with intrauterine malnutrition (Leitch 1951, Law et al. 1992, Strauss 1997, Whitaker and Dietz 1998, Yajnik 2000), where muscle and abdominal viscera are generally reduced while subcutaneous fat is preserved. This suggests that maternal nutrition may have a direct affect on encephalisation. This will be assessed in detail in chapter 5.

The results in this chapter section provided positive findings for both the 'Reduced Growth Hypothesis' and the 'Nutrition Hypothesis'. Encephalised fetuses and infants were generally well-nourished, with increased fat and lean tissues. In addition, positive changes in head circumference SD score over time were associated with reduced changes in body length SD score over time, indicating an energy trade-off between the brain and rest of the body. In no circumstance did both head circumference and body length increase at the same time.

Cycles of growth rate increase alternating between head circumference and body length were found, with strong evidence for 'catch up' and 'catch down' growth alternating between the head and body length. Encephalisation itself was subject to 'catch up' and 'catch down' growth, suggesting that the tendency to regress to the mean occurs in relative brain size in all fetuses and infants during growth. This may suggest that there is an upper limit beyond which encephalisation is no longer adaptive, perhaps due to the mother's inability to meet the associated energetic costs.

These findings provide support for Foley and Lee's (1991) hypothesis, where they argued that the costs of encephalisation in humans may be offset by reduced somatic growth rate. The fetuses and infants in this sample who were highly encephalised did tend to slow down body length growth rate while increasing head circumference growth rate. Those who did not slow down their body length growth were not encephalised at the subsequent measurement period.

SECTION II: Sex-differences in encephalisation

4.6) Brain size sexual dimorphism

An absolute difference in brain size between males and females has been documented since at least 1861 (Broca 1861). Ankney (1992), using autopsy data on adults (Ho et al. 1980a,b) showed that sex differences persist in brain size after controlling for the effects of body size. These sex differences also exist in relative cranial size in East Asian, European and African samples (Rushton 1994). Sex differences in relative brain size in the living individual have also been found using MRI (Gur et al. 1991, Willerman 1991, Andreasen 1993, Filipek et al. 1994, Pfefferbaum et al. 1994, Harvey et al. 1994, Resnick 1995, Blatter et al. 1995). Falk et al. (1999) also demonstrated that relative brain size is subject to sexual dimorphism in adult rhesus macaques and humans. Based on postmortem data, both species display similar levels of sexual dimorphism in relative brain size with males having brains about 8% (in rhesus monkeys) to 10% (in humans) larger than females. Herndon et al. (1999), have also documented brain size sexual dimorphism in chimpanzees from necropsy records of individuals between birth to 59.4 years of age. However, these authors show that brain weight declines with age in chimpanzees. This is also the case for humans.

Dekaban and Sadowsky (1978) and Hartmann et al. (1994) reported a trend toward lower brain weight with increasing age in humans, with an increase in the rate of decline at about 50 years. In general, brains of 70-80 year-olds weigh about 7% less than those of 20 year-olds of comparable body weight (Pakkenberg and Voigt 1964, Chrzanowska and Beben 1973, Dekaban and Sadowsky 1978, Hartmann et al. 1994). From age 26 to 80, brain mass declines by about 2 g per year (Ho et al. 1980a,b). This loss in brain mass is largely due to the loss of neuronal somata, neurophil or white matter (Herndon et al. 1999) and water (Dobbing and Sands 1973). MRI studies show that an overall decrease in brain volume following the late teens is associated with the replacement of gray matter with cerebrospinal fluid (Gur et al. 1991, Jernigan et al. 1991, Resnick 1995). As a result, variations in the rates of brain weight loss and age make accurate assessment of adult brain weight sexual dimorphism problematic. This

is particularly true for women since levels of brain weight loss may be higher in association with estrogen depletion during the menopause (Namba and Sokoloff 1984, Nehlig et al. 1985, Maki and Resnick 2001)

Evidence for brain size sexual dimorphism has also been found in infants. Jensen and Johnson (1994), found that male children aged 4 to 7 years, had relatively larger head circumferences than females after controlling for body size and racial differences. Sexual dimorphism, between 7 to 17 years, was also found in relative cranial capacity (Lynn 1993, Rushton and Osborne 1995). Similar results were found from autopsy materials in the early months of life, where brain weights were matched by stature (Pakkenberg and Voigt 1964, Dekaban and Sadowsky 1978, Voigt and Pakkenberg 1983).

Autopsy materials are, however, subject to a number of influences which may alter brain/body weight relationships in the individual. First, many people presented for autopsy are generally ill or have died as a result of trauma. Body wasting is common in subjects following long-term illness. In addition, levels of dehydration and edema may be marked in individuals as a function of illness or the time elapsed between death and autopsy. Moreover, the time delay between death and autopsy may influence the degree of brain autolysis, impacting on brain weight. Hypoxia may also have an effect on brain weight as it often results in brain hematoma and engorgement, while blood loss may also influence brain weight. Ideally, brain and body size relationships should be assessed in the young living subject and relative brain size should be calculated as a function of body length, rather than body weight as length tends to be influenced less by environmental insult (Tanner 1978). In addition, unlike length, weight is comprised of several different functional tissues and highly variable fat stores.

4.7) The Fetal/Infant Brain Size Sexual Dimorphism Hypothesis

Deacon (1989) argues that relative brain size (encephalisation) in the adult is the product of brain/body growth patterns throughout ontogeny. It would follow then that

adult brain size sexual dimorphism should reflect brain size sexual dimorphism throughout ontogeny. Here brain/body size relationships in fetal and young infant human and non-human primates are assessed in order to determine if brain size sexual dimorphism is present throughout ontogeny. This is referred to as the ‘Brain size sexual dimorphism hypothesis’ and predicts that males will be more encephalised than females during the fetal and infancy periods.

The species assessed here include humans, rhesus monkeys, baboons and marmosets. The implications for fetal and infant brain size sexual dimorphism are then discussed in light of its energetic costs.

4.8) Methods for quantifying brain size sexual dimorphism in the fetus and infant

The human fetal and infant head circumference and femur and body length data described in chapter 2 are used here to test this hypothesis. In addition, the rhesus monkey, baboon and marmoset head circumference and femur length data described in chapter 3 are used for comparative analysis. Head circumference is used as an index of brain weight (after Cooke et al. 1977, Fujimura and Seryu 1977, Epstein and Epstein 1978, McLennan et al. 1983) and femur length is used as an index of body length in humans. According to Fazekas and Kósa (1978) fetal body length can be estimated from femur length using the following equation where,

$$(40) \quad \text{Total body length} = \text{femur length (cm)} * 6.44 + 4.51$$

Fazekas and Kósa’s measures are based on skeletal materials and include only the femoral diaphyses and can, therefore, be reliably used to estimate body length from the ultrasound femur measures which also include only the ossified diaphyseal portion of the femur.

4.8a) Statistical tests

Biometric measures for head circumference and femur or body length were analysed using regression analysis. Data were normalised by natural log-transformation. Least squares residuals were calculated from best-fit regression lines in order to assess whether relative head circumference dimorphism exists after controlling for femur or body length differences between the sexes. Two-tail bivariate correlations with confidence limits set at 95% were used to determine statistical significance between the variables. Pooled sex and sex-specific regression equations at each measurement period are given. In addition, independent samples t-tests were used to evaluate whether statistically significant levels of head circumference dimorphism were found.

4.8b) Quantifying the effects of sex on fetal and infant encephalisation

In order to evaluate the magnitude of the effect of sex on relative head circumference independently of head and length growth differences, a multiple regression analysis was performed, assessing the variance in head circumference as a function of body length and the interaction between body length and sex. A dummy variable was established whereby values of 0 and 1 were assigned to males and females, respectively. The dummy variable was then multiplied against femur lengths (in the fetus) or body lengths (in the neonate and infant) and then \log_e -transformed, thus representing the interaction between sex and length. The \log_e -transformed length and interaction variables were then entered into a multiple regression model as independent variables with head circumference entered as the dependent variable. The difference in the resulting r^2 values with and without the interaction variable entered into the equation represents the relative influence of sex alone in explaining the variation in head circumference.

This approach to quantifying the effects of sex on the overall variation in relative head circumference is useful when assessing ontogenetic data as it precludes the need to control for body growth differences between the sexes at specific ages and developmental periods.

4.9) Results

4.9a) Human head circumference sexual dimorphism

During the fetal and infancy periods, from about 16 gestation weeks through to 1 year-of-age, males have relatively larger head circumferences than females, after controlling for femur and body length sexual dimorphism. However, although statistically significant, differences in relative head circumference between the sexes is of a low order.

Figures 4.17(a-d) show scatterplots describing the relationship between \log_e -transformed human head circumference and femur length or body length at different measurement periods and the pooled sex and sex-specific regressions describing those relationships.

Table 4.14 lists the results of the multiple regression analysis where the r^2 values for \log_e -transformed values are given. The percent of the variance explained by sex alone is calculated as the difference between r^2 values for body length and the interaction between sex and body length obtained via a multiple regression.

The effect of sex on relative head circumference during the fetal period is of the order of about 2.5%. This drops to 1.3% at birth, rising to 6.7% at 6 postnatal months and 8.4% at 1 year. In this sample, the effects of sex on relative head circumference are, in general, greater *ex utero* than during the fetal period.

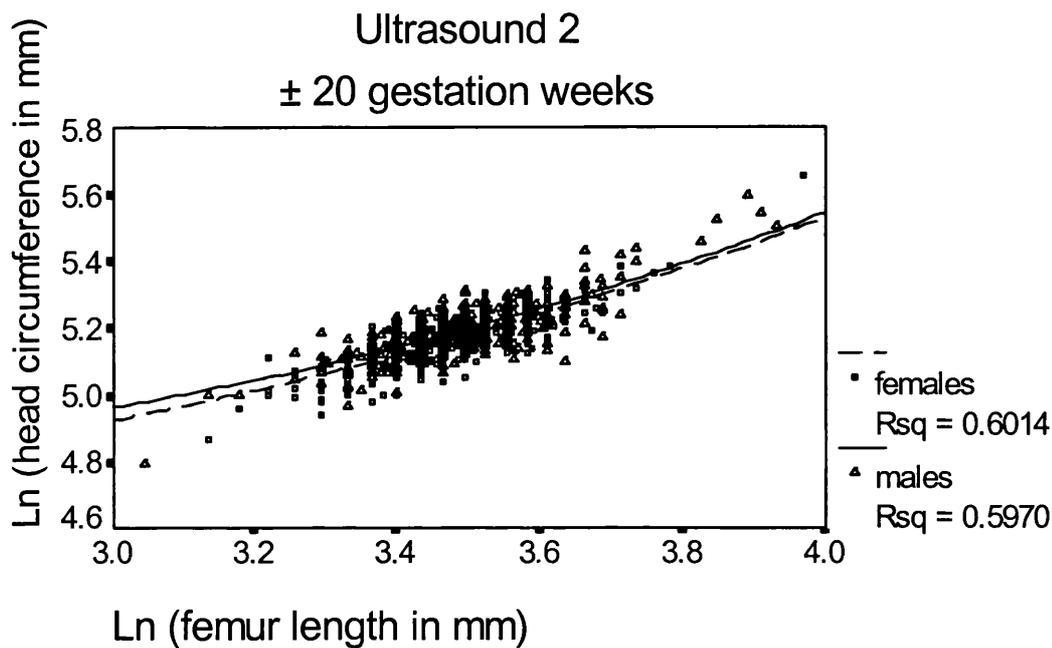


Figure 4.17a. Log_e-transformed human fetal head circumference plotted against femur length at ultrasound 2 (16-28 gestation weeks).

Fetuses (~16-28 gestation weeks)

Pooled sexes:

(41)
$$\text{Ln (head circumference)} = 3.583 + 0.321 * \text{Ln (femur length)} + 0.040 * \text{Ln (femur length)}^2$$

$$(r^2 = 0.599, \text{SE} = n = 1546, F = 1152.02, P < 0.0001)$$
 SE of mean predictions = 0.001

Males:

(42)
$$\text{Ln (head circumference)} = 5.985 - 1.029 * \text{Ln (femur length)} + 0.230 * \text{Ln (femur length)}^2$$

$$(r^2 = 0.597, n = 738, F = 544.31, P < 0.0001)$$
 SE of mean predictions = 0.002

Females:

(43)
$$\text{Ln (head circumference)} = 5.475 - 0.774 * \text{Ln (femur length)} + 0.197 * \text{Ln (femur length)}^2$$

$$(r^2 = 0.601, n = 689, F = 517.47, P < 0.0001)$$
 SE of mean predictions = 0.002

An independent samples t-test reveals that the difference in head circumference residuals between male and female fetuses at this time is statistically significant (mean difference = 0.0202, SE of difference = 0.002, n = 1487, P < 0.0001).

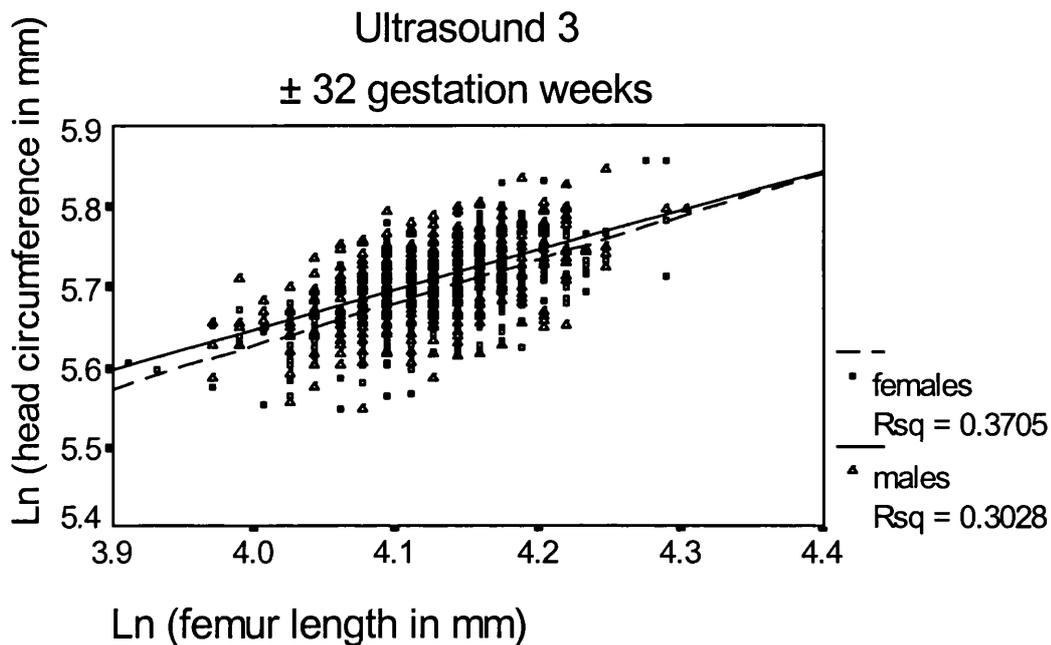


Figure 4.17b. Log_e-transformed human fetal head circumference plotted against femur length at ultrasound 3 (28-37 gestation weeks).

Fetuses (~28-36 gestation weeks)

Pooled sexes:

(44)
$$\text{Ln (head circumference)} = 3.598 + 0.510 * \text{Ln (femur length)}$$

$$(r^2 = 0.333, \text{SE} = 0.039, n = 1217, F = 606.527, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

Males:

(45)
$$\text{Ln (head circumference)} = 3.683 + 0.491 * \text{Ln (femur length)}$$

$$(r^2 = 0.303, \text{SE} = 0.037, n = 604, F = 261.46, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

Females:

(46)
$$\text{Ln (head circumference)} = 3.491 + 0.534 * \text{Ln (femur length)}$$

$$(r^2 = 0.371, \text{SE} = 0.039, n = 568, F = 333.15, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female fetuses at this time is statistically significant (mean difference = 0.015, SE of difference = 0.002, n = 1172, P < 0.0001).

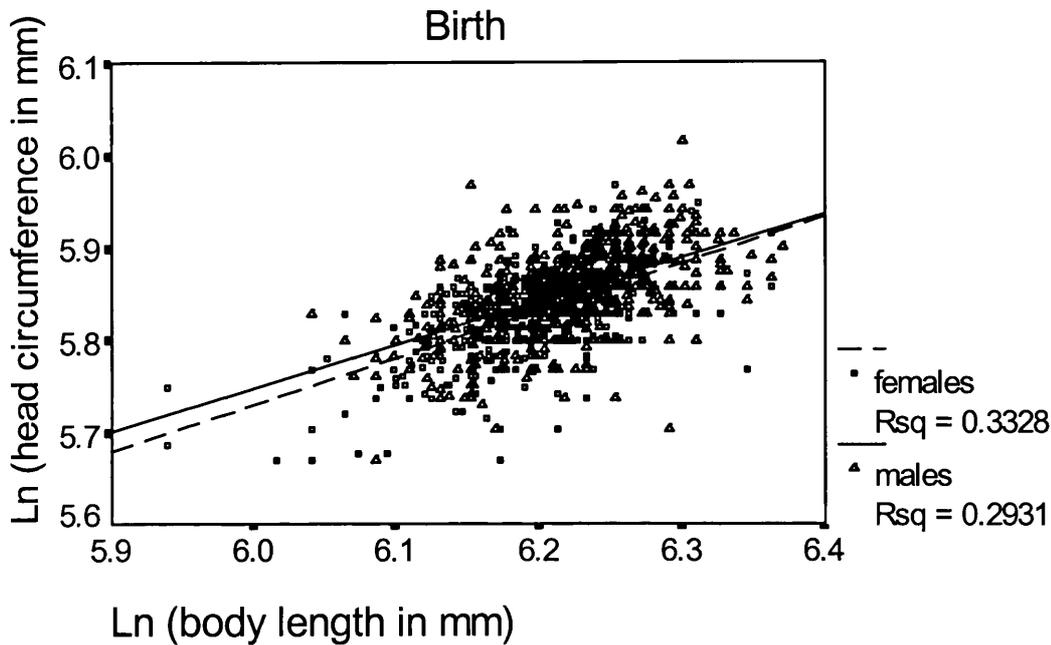


Figure 4.17c. Log_e-transformed human neonatal head circumference plotted against body length at birth.

Neonates

Pooled sexes:

(47)
$$\text{Ln (head circumference)} = 2.723 + 0.502 * \text{Ln (body length)}$$

$$(r^2 = 0.328, \text{SE} = 0.037, n = 1434, F = 698.802, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.001$$

Males:

(48)
$$\text{Ln (head circumference)} = 2.947 + 0.467 * \text{Ln (body length)}$$

$$(r^2 = 0.293, \text{SE} = 0.037, n = 736, F = 304.41, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

Females:

(49)
$$\text{Ln (head circumference)} = 2.691 + 0.507 * \text{Ln (body length)}$$

$$(r^2 = 0.333, \text{SE} = 0.036, n = 698, F = 347.24, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female neonates is statistically significant (mean difference = 0.010, SE of difference = 0.002, n = 1434, P < 0.0001).

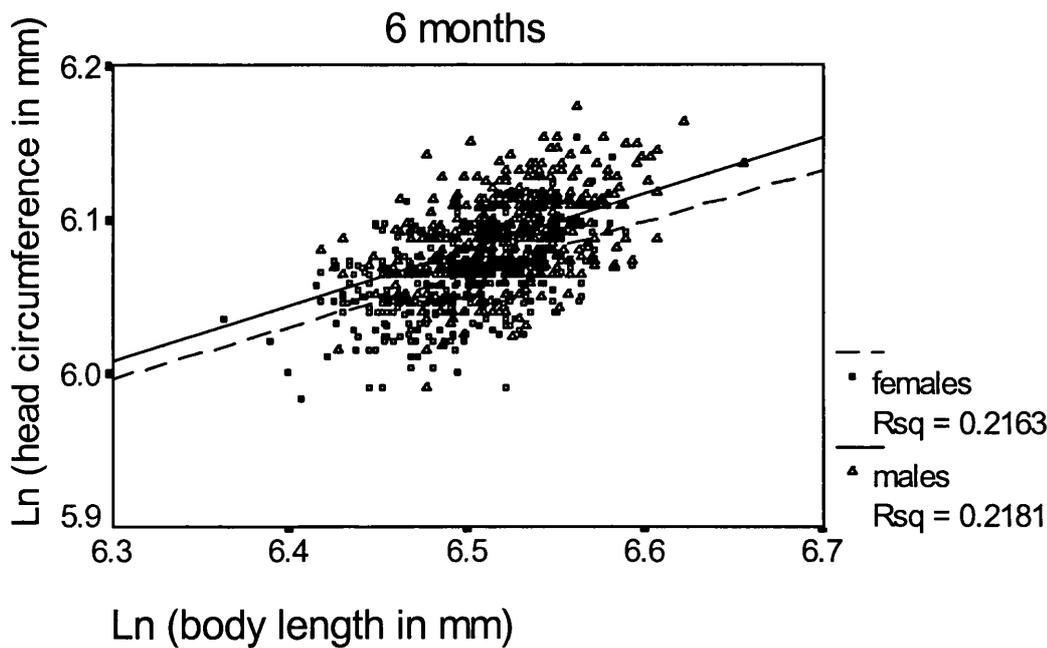


Figure 4.17d Log_e-transformed human head circumference plotted against body length at 6 postnatal months.

Infants (~6 postnatal months)

Pooled sexes:

(50) $\text{Ln}(\text{head circumference}) = 3.301 + 0.426 * \text{Ln}(\text{body length})$
 $(r^2 = 0.295, \text{SE} = 0.025, n = 926, F = 387.518, P < 0.0001)$
 SE of mean predictions = 0.001

Males:

(51) $\text{Ln}(\text{head circumference}) = 3.714 + 0.364 * \text{Ln}(\text{body length})$
 $(r^2 = 0.218, \text{SE} = 0.024, n = 485, F = 134.71, P < 0.0001)$
 SE of mean predictions = 0.002

Females:

(52) $\text{Ln}(\text{head circumference}) = 3.868 + 0.338 * \text{Ln}(\text{body length})$
 $(r^2 = 0.216, \text{SE} = 0.024, n = 436, F = 119.77, P < 0.0001)$
 SE of mean predictions = 0.002

An independent samples t-test reveals that the difference in head circumference residuals between male and female infants at this time is statistically significant (mean difference = 0.0234, SE of difference = 0.007, n = 921, P < 0.0001).

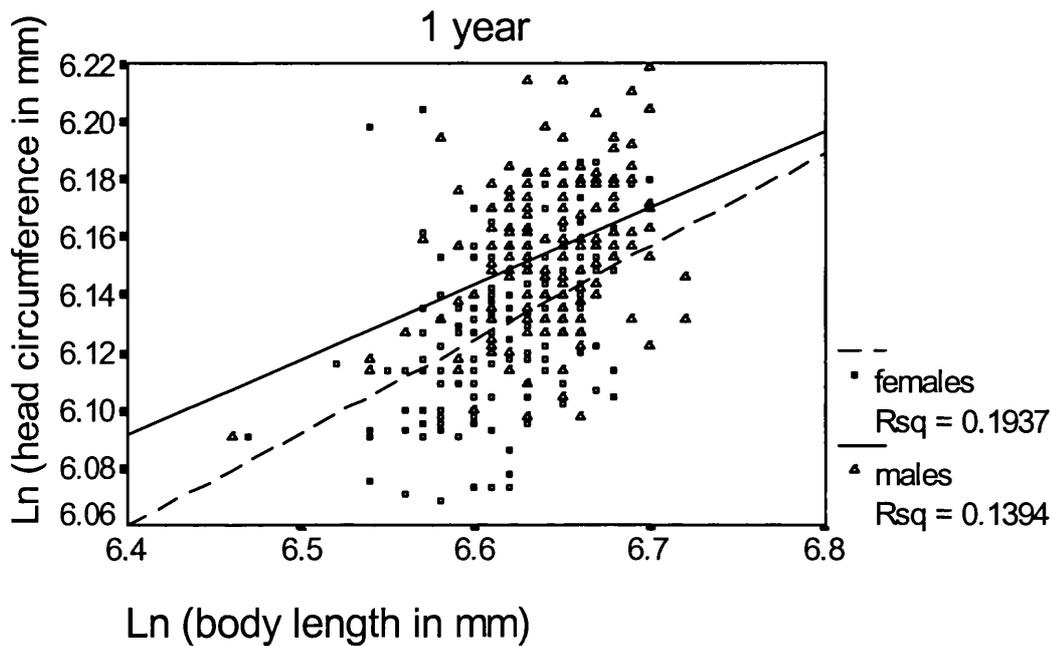


Figure 4.17e Log_e-transformed human head circumference plotted against body length at 6 postnatal months.

Infants (~12 postnatal months)

Pooled sexes:

(53)
$$\text{Ln (head circumference)} = 3.714 + 0.366 * \text{Ln (body length)}$$

$$(r^2 = 0.235, \text{SE} = 0.025, n = 350, F = 107.11, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

Males:

(54)
$$\text{Ln (head circumference)} = 4.413 + 0.262 * \text{Ln (body length)}$$

$$(r^2 = 0.139, \text{SE} = 0.023, n = 169, F = 27.06, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.002$$

Females:

(55)
$$\text{Ln (head circumference)} = 3.998 + 0.322 * \text{Ln (body length)}$$

$$(r^2 = 0.194, \text{SE} = 0.024, n = 181, F = 42.99, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.0024$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female infants at this time is statistically significant (mean difference = 0.0234, SE = 0.007, n = 921, P < 0.0001).

Table 4.14 Results of multiple regression analysis: Human sample

Measurement	n	body length r^2	P body length	sex interaction r^2	P sex interaction	% influence*
fetal scan 2	1427	0.583	<0.0001	0.607	<0.0001	2.4
fetal scan 3	1172	0.326	<0.0001	0.351	<0.0001	2.5
birth	1434	0.328	<0.0001	0.341	<0.0001	1.3
6 months	921	0.295	<0.0001	0.362	<0.0001	6.7
1 year	350	0.235	<0.0001	0.319	<0.0001	8.4

*Percent influence = difference between r^2 values for body length and r^2 values for the interaction between body length and sex, derived from a stepwise regression where head circumference is the dependent variable. These values reflect the influence of sex on the variation in relative head circumference.

r^2 = regression coefficient, P = probability based on 95% confidence limit, a = constant, b = slope.

4.9b) Rhesus macaque head circumference sexual dimorphism

During the fetal and infancy period, there is evidence for head circumference sexual dimorphism in the rhesus monkeys in this sample. Male rhesus monkeys have relatively larger head circumferences than females of comparable femur length, however, while statistically significant, the level of dimorphism is very low (< 1%). In addition, the relationships between head circumference and femur length in the sexes vary markedly.

Figures 4.18a and b describe the linear relationships between head circumference and femur length in males and females during the fetal and infancy periods. The regression equations for pooled sexes, males and females are listed. Table 4.15 gives the results of the multiple regression analysis where the r^2 values for \log_e -transformed values are given. The percent of the variance explained by sex alone is calculated as the difference between r^2 values for body length and the interaction between sex and body length obtained via a stepwise regression.

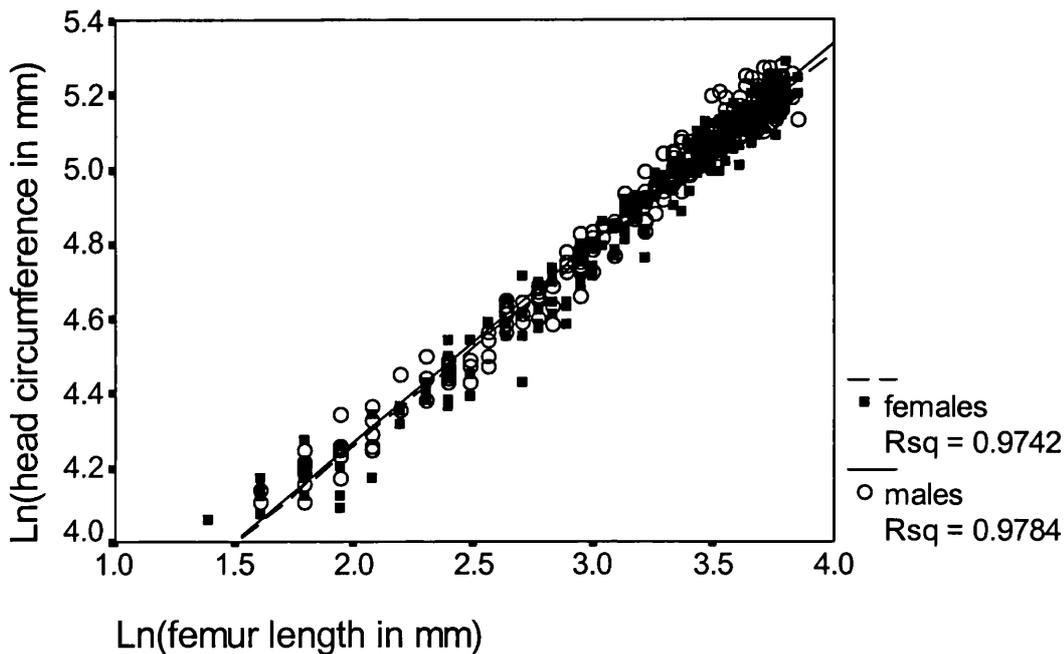


Figure 4.18a. Log_e-transformed head circumference plotted against femur length in fetal rhesus monkeys.

Linear curves describing the relationship between head circumference and femur length

Pooled sexes during the fetal period yield a least squares linear regression of the form:

$$(56) \quad \begin{aligned} \text{Ln (HC in mm)} &= 3.2 + 0.531 * \text{Ln (FL in mm)} \\ (r^2 = 0.976, n = 480, SE = 0.049, P < 0.0001) \\ \text{SE of mean predictions} &= 0.013 \end{aligned}$$

Males:

$$(57) \quad \begin{aligned} \text{Ln (HC in mm)} &= 3.2 + 0.535 * \text{Ln (FL in mm)} + 0.020 \\ (r^2 = 0.978, n = 251, SE = 0.044, P < 0.0001) \\ \text{SE of mean predictions} &= 0.018 \end{aligned}$$

Females:

$$(58) \quad \begin{aligned} \text{Ln (HC in mm)} &= 3.21 + 0.527 * \text{Ln (FL in mm)} \\ (r^2 = 0.976, n = 228, SE = 0.051, P < 0.0001) \\ \text{SE of mean predictions} &= 0.019 \end{aligned}$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female fetuses is statistically significant (mean difference = 0.019, F = 1.770, SE of difference = 0.005, n = 482, P < 0.0001).

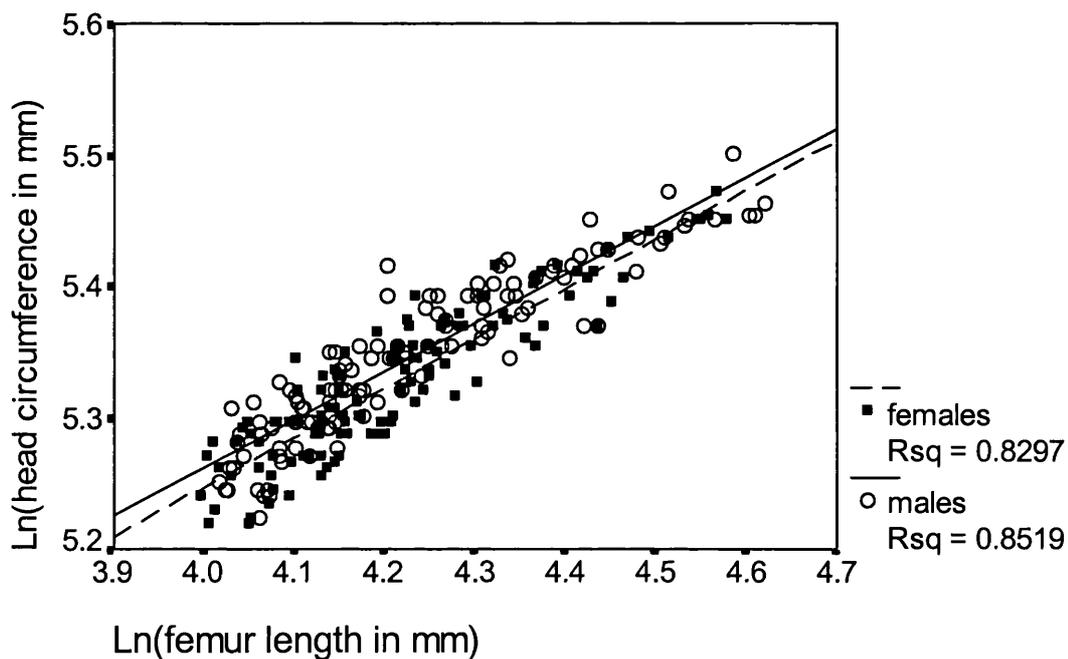


Figure 4.18b. Log_e-transformed head circumference plotted against femur length in infant rhesus monkeys between birth and 1 year of age.

Least squares linear regression equations describing the relationship between head circumference and femur length

Pooled sexes during the first year of life:

(59) $\text{Ln}(\text{HC in mm}) = 3.77 + 0.372 * \text{Ln}(\text{FL in mm})$
 $(r^2 = 0.832, n = 242, \text{SE} = 0.025, P < 0.0001)$
 SE of mean predictions = 0.004

Males:

(60) $\text{Ln}(\text{HC in mm}) = 3.80 + 0.366 * \text{Ln}(\text{FL in mm})$
 $(r^2 = 0.850, n = 119, \text{SE} = 0.024, P < 0.0001)$
 SE of mean predictions = 0.005

Females:

(61) $\text{Ln}(\text{HC in mm}) = 3.75 + 0.376 * \text{Ln}(\text{FL in mm})$
 $(r^2 = 0.830, n = 123, \text{SE} = 0.024, P < 0.0001)$
 SE of mean predictions = 0.003

An independent samples t-test reveals that the difference in rhesus monkey head circumference residuals between males and females is statistically significant (mean difference = 0.014, $F = 3.15$, SE of difference = 0.003, $n = 242$, $P < 0.0001$).

Table 4.15 Results of multiple regression analysis: Rhesus monkey sample

Measurement	n	femur length	sex interaction	% influence
fetus (60-160 days)	481	0.977	0.976	0.10
infant (0 to 205 days)	123	0.834	0.831	0.30

n = sample size

r^2 values derived from multiple regression analysis, where head circumference is the independent variable. Percent influence = difference between r^2 values for body length and r^2 values for the interaction between body length and sex, derived from a stepwise regression. These values reflect the influence of sex on the variation in relative head circumference.

4.9c) Baboon head circumference sexual dimorphism

These data show that male baboons have relatively larger head circumferences than females during the fetal period, however, although statistically significant, like the rhesus monkey, the level of dimorphism is very low - < 1% (see Figure 4.19). Table 4.16 lists the results of the baboon multiple regression analysis where the r^2 values for \log_e -transformed values are given.

4.9d) Marmoset brain size sexual dimorphism

Because fetal femur lengths and sexes are not available in the common marmosets, prenatal brain size sexual dimorphism could not be assessed. The relationship between neonatal head circumference and body weight could, however, be examined. These data show that there is no significant correlation between birth weight and head circumference in the Common marmoset (see Figure 4.20). In addition, there is no evidence for neonatal head circumference sexual dimorphism when controlling for the effects of body weight (see equations 61-63).

Overall, the results of this analysis suggest that brain size sexual dimorphism is of a low order in the fetus and infant. In humans the influence of sex in explaining the variation in head circumference (independently of body length) is of the order of about 2.5-8% in the fetus and infant and of the order of about 0.1% to 0.3% in the rhesus monkey fetus and infant and 0.2% in the baboon fetus.

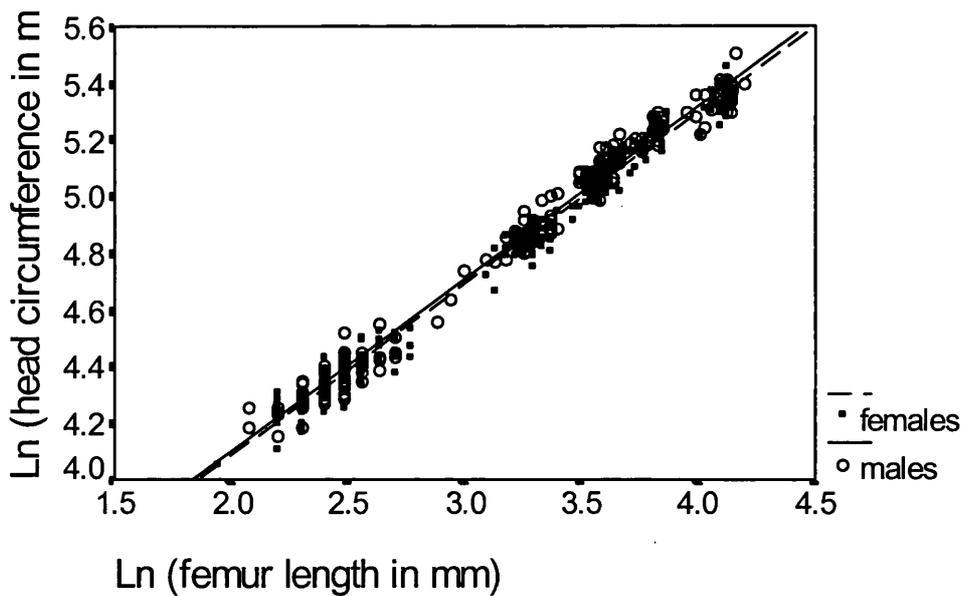


Figure 4.19 Log_e-transformed head circumference plotted against femur length femur length in fetal baboons.

Pooled sexes:

(62)
$$\text{Ln (HC in mm)} = 2.86 + 0.61 * \text{Ln (FL in mm)}$$

$$(r^2 = 0.983, \text{SE} = 0.050, n = 2664, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.050$$

Males:

(63)
$$\text{Ln (HC in mm)} = 2.90 + 0.604 * \text{Ln (FL in mm)}$$

$$(r^2 = 0.985, \text{SE} = 0.018, n = 304, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.004$$

Females:

(64)
$$\text{Ln (HC in mm)} = 2.87 + 0.606 * \text{Ln (FL in mm)}$$

$$(r^2 = 0.984, \text{SE} = 0.048, n = 265, P < 0.0001)$$

$$\text{SE of mean predictions} = 0.048$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female fetuses is statistically significant (mean difference = 0.021, F = 0.642, SE of difference = 0.004, N = 569, P < 0.0001).

Table 4.16 Results of multiple regression analysis: Baboon sample

Measurement	n	femur length	sex interaction	% influence
fetus	265	0.982	0.984	0.20

n = sample size

r^2 values derived from multiple regression analysis, where head circumference is the independent variable. Percent influence = difference between r^2 values for body length and r^2 values for the interaction between body length and sex, derived from a stepwise regression. These values reflect the influence of sex on the variation in relative head circumference.

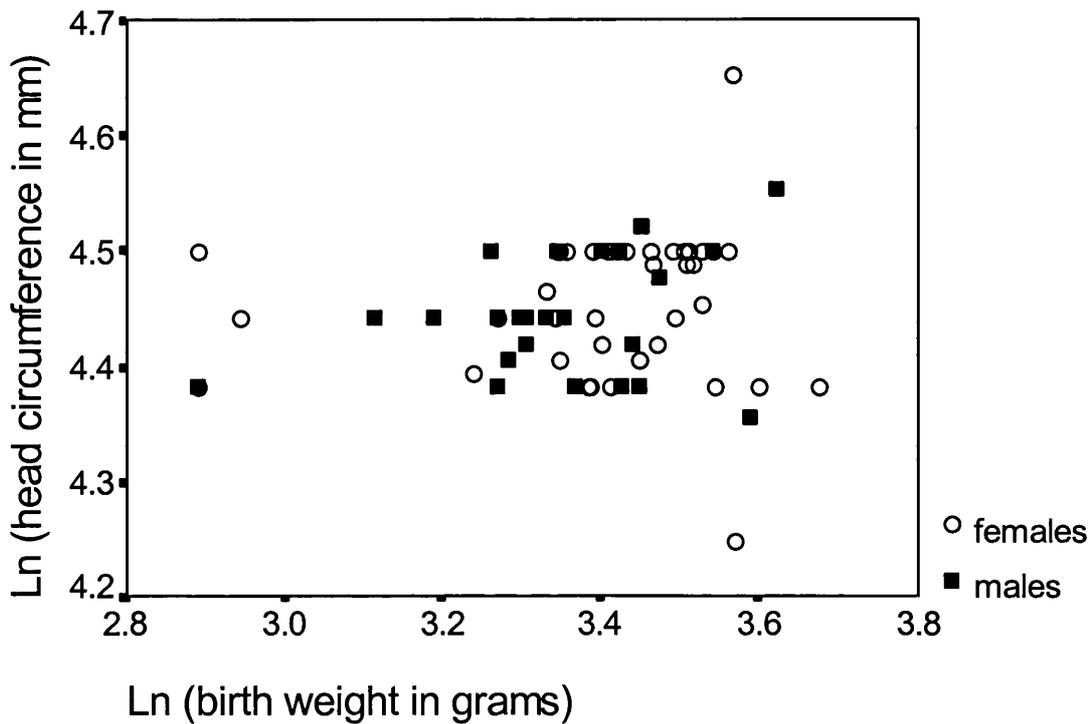


Figure 4.20 Log_e-transformed head circumference plotted against birth weight in the neonatal Common marmoset.

Pooled sexes:

(65)
$$\text{Ln (HC in mm)} = 4.28 + 0.52 * \text{Ln(BW in grams)}$$

$$(r^2 = 0.020, \text{SE} = 0.060, n = 69, P = 0.250)$$

$$\text{SE of mean predictions} = 0.2$$

$$\text{BW} = \text{body weight at birth}$$

Males:

(66)
$$\text{Ln (HC in mm)} = 4.120 + 0.095 * \text{Ln (BW in grams)}$$

$$(r^2 = 0.073, \text{SE} = 0.052, n = 25, P = 0.191)$$

$$\text{SE of mean predictions} = 0.12$$

Females:

(67)
$$\text{Ln (HC in mm)} = 4.38 + 0.023 * \text{Ln (BW in grams)}$$

$$(r^2 = 0.004, \text{SE} = 0.064, n = 44, P = 0.695)$$

$$\text{SE of mean predictions} = 0.12$$

An independent samples t-test reveals that the difference in head circumference residuals between male and female neonates is not statistically significant in the marmosets in this sample (mean difference = -0.013, F = 0.480, SE of difference = 0.015, n = 69, P = 0.403).

In sum, using multiple regression analysis it was shown that in humans the impact of sex alone in explaining the variation in relative head circumference increases with age, from about 2.5% at about 20 gestation weeks to about 8% at 1 year-of-age. The level of head circumference sexual dimorphism is of a lower order in Rhesus macaque fetuses and infants up to one year-of-age. In this species only about 0.1% of the variation in head circumference prenatally is explained by sex alone. Postnatally sex alone explains about 0.3% of the variation. In baboon fetuses the level of head circumference sexual dimorphism is also of a very low order with sex explaining about 0.2% of the variation in head circumference. No evidence for brain size sexual dimorphism was found in the neonatal common marmoset.

Although the human fetus and infant show a clear sex difference in weight, with males being heavier than females at birth (Hall 1981), there is no statistically significant difference between males and females in terms of both length and head circumference growth velocity in the human fetus and infant sample assessed here (see Table 2.23).

The authors of other studies utilizing ultrasound data also find no clear differences between the sexes in these parameters (Deter et al. 1982, Guihard-Costa and Larroche, 1995). Evidence for growth rate variation between the sexes is also lacking in the rhesus monkey (see Figures 3.1 and 3.2) and Coelho (1985) has shown that male and female baboons do not differ significantly in body length at birth. Sex differences in growth velocity do not, therefore, explain the sexual dimorphism found in head circumference in humans, rhesus monkeys and baboons (Tame et al. 1998).

4.10) Discussion

Clear evidence for head circumference sexual dimorphism was found here in the fetus and infant, although of a smaller magnitude prenatally. This is not consistent with Martin's (1986) assertion that, "...despite the marked sexual difference in adult brain weight...there is no difference in mean brain weight at birth [between males and

females]. Accordingly, sexual dimorphism in adult human brain weight must be achieved in the course of postnatal growth”.

Although of a low order, head circumference sexual dimorphism was found in the fetuses studied here. Generally, relative head circumference sexual dimorphism increased with age, presumably reaching its zenith at maturity as suggested by the difference in the amount of brain dimorphism between the adult and fetus/infant. Adult human males have brains about 10% larger than those of females (Dekaban 1978, Ho et al. 1980a,b; Filipek et al. 1994, Pfefferbaum et al. 1994, Blatter et al. 1995) and adult male rhesus monkeys have brains about 8% larger than those of females (Falk et al. 1999). Thus, the influence of sex in explaining the variance in head circumference differs markedly between the fetus, infant and the adult.

The gradual increase with age in brain size dimorphism between the sexes points to the likelihood that initial sex differences may occur during the hyperplastic period of brain growth and increase as a function of hypertrophic growth. This suggestion is in agreement with Finlay and Darlington (1995). It is not clear from brain weight or head circumference data, however, whether males have proportionately larger brains than females or whether one or more specific brain components is larger in males, accounting for larger total brain weight or head circumference.

There is strong evidence suggesting that male and female brains differ in terms of component volumetric patterning. In 13-37 week fetuses, de Lacoste et al. (1991) have shown that males and females exhibit volumetric asymmetries in the prefrontal and striate-extrastriate cortical areas. These striate-extrastriate asymmetries are more pronounced in male rather than female fetuses and are at least two-fold greater in males. Moreover, these authors show that accelerated development of the right hemisphere and/or delayed development of the left hemisphere appears to be more prevalent in male rather than female cerebra.

In addition, sex differences in left/right asymmetries of cortical thickness in visual cortex has been found in several mammalian species (Diamond et al. 1981, Stewart and Kolb 1988). In female fetuses, the right and left hemispheres appear to develop at

about the same rate whereas in male fetuses, the right hemisphere shows accelerated growth and a greater proportion of cerebro-spinal fluid and white matter (Gur et al. 1999). Geschwind and Galaburda (1984, 1987) have suggested that testosterone may lead to more rapid growth of the right hemisphere or may, alternatively, retard the growth of the left hemisphere in males.

Reiss et al. (1996) argue that gender associated differences in brain size may be related to gender differences in cortical neuronal density. The authors found that in the MRIs of children aged 5 to 17 years of age total cerebral volume is about 10% larger in males compared with females, with increased cortical gray matter in males explaining this gender difference.

Regardless of the nature of brain size sexual dimorphism, it is clear that the metabolic costs associated with maintaining brain tissue are high. An increase in brain tissue associated with sexual dimorphism may translate into a significant increase in energetic requirements for the fetus and infant.

SECTION III: The energetic costs of encephalisation sexual dimorphism

4.11) Modeling the metabolic costs of encephalisation sexual dimorphism

In order to understand the energetic implications for brain size sexual dimorphism in the fetus and infant, the costs of mass-specific brain tissue must be quantified. However, simply calculating mass-specific metabolic rate estimates from total brain weight and total brain metabolic rate do not yield an accurate measure of the metabolic cost of brain tissue during ontogeny. This is because the brain undergoes chemical maturation during development. This issue was discussed at length in chapter 3, section 3.3, where it was shown that water comprises about 90-92% of the brain's weight in early life. Based on Dobbing and Sands (1973) reported values for water content in the brain, the estimated costs associated with increased relative brain size in males are modeled. These estimates are listed in Table 4.17.

This model shows that the additional costs of brain size sexual dimorphism in the fetus are negligible (less than 1 kcal/day). At 6 postnatal months, the metabolic cost rises to 12 kcal per day (3.1% of total daily energy requirements). The relatively larger brain of the male does not, therefore, appear to impose a significant additional energetic demand on the fetus or infant during early life.

In summary, the findings in this chapter suggest that encephalisation in early life is associated with general nutritional status. Neonates who were encephalised tended also to have increased fat and lean tissue deposits. It was also shown that encephalisation relates to previous growth, and 'catch up' and 'catch down' growth, in particular. A trade-off in head versus body growth was shown to relate to encephalisation, where increased head circumference SD score (over time) was generally accompanied by a concomitant decrease in body length SD score, and hence, resulted in increased encephalisation. Changes in encephalisation over time, therefore, reflect underlying cyclical changes in head and body growth.

In addition, it was shown that during ontogeny head circumference sexual dimorphism is present in humans, rhesus monkeys and baboons. The degree of head circumference sexual dimorphism increases with age and in humans explains 1.3% of the variation in head circumference (independent of body length effects) at birth, 7.6% at 6 months and 8.4% at 1 year. In contrast, less than 1% of the variation in head circumference in rhesus monkeys and baboons is explained by sex. The estimated metabolic costs associated with this level of human brain size sexual dimorphism amount to less than 1kcal/day prenatally and no more than 12 kcal/day at 6 postnatal months. This is about 3% of daily energy requirements.

Table 4.17 Estimates of daily metabolic costs of metabolically active brain tissue

Age	% brain [^] metabolically active	% brain size sexual dimorphism	brain weight (grams)	metabolically active brain tissue (grams)	daily* cost of active tissue (kcal/day)	daily costs of dimorph. (kcal/day)
19 GW	8.5	2.4	< 49	< 4.2	6.7	0.16
33 GW	9.6	2.5	217	20.8	33.6	0.84
40 GW	11.3	1.3	356	40.2	64.8	0.84
6 months	14.9	6.7	762	114	183	12.3

Fetal brain weights taken from Sung and Singer (1988)

Infant brain weights taken from Schultz et al. (1962)

[^] calculated from Dobbing and Sands' (1973) values for cerebrum hydration (brain weight - % water weight)

*assuming a cost of 1.611 kcal/g of brain/day based on a 6-month-old reference child with a brain weight of 713 grams, a metabolic cost of 171.12 kcal/day (Elia 1992), and an estimate of 85.1% brain water content.

GW = gestation age in weeks, dimorph. = dimorphism

CHAPTER 5

Maternal correlates of fetal and infant size, growth and encephalisation

5.1) Aims of chapter

In this chapter, the relationship between maternal variables and offspring encephalisation, size, growth and nutritional status are assessed. The maternal variables examined here include indices of maternal size (height), nutritional status in early pregnancy (skinfolts and estimated mid-arm muscle and fat areas), placenta weight and the number of notches in the placenta at delivery as well as maternal age, parity, socioeconomic status and alcohol and cigarette use.

The chapter is divided into four sections. The first section describes the physiological changes that occur in the female body during pregnancy and relates how these changes are adaptive in light of maternal-fetal conflict over energy resources during pregnancy. Section 2 is a methodology section where the maternal data are described and the statistical methods for quantifying maternal size and nutritional status are described. Here the statistical tests used to test two main hypothesis are described.

5.2) Hypotheses tested in chapter

These hypotheses include the ‘Maternal Nutritional Status Hypothesis’ and the ‘Placenta Hypothesis’. The predictions of these hypotheses are as follows:

‘Maternal Nutritional Status Hypothesis’:

Well-nourished mothers will produce encephalised offspring

‘Placenta Hypothesis’:

Increased placenta weight and decreased placental notching (associated with impaired blood flow) are associated with increased neonatal encephalisation

These hypotheses are described in further detail at the end of section one. Section 3 of the chapter includes the results of the analyses and section 4 focuses on R.D. Martin's (1983) 'Maternal Energy Hypothesis'. Here, the assumptions underlying the hypothesis are examined and questioned and the hypothesis is critiqued in light of the findings in this thesis.

SECTION I: Maternal adaptations to pregnancy

5.3) Physiological adaptations to pregnancy

During pregnancy, the woman undergoes a number of physiological adaptations which influence her body composition, metabolism and general nutritional status. These occur in order to increase the efficiency of maternal physiological systems. Adaptations take place in the hematologic and hemostatic systems, the cardiovascular and respiratory systems, the renal, gastrointestinal and hepatic systems, as well as changes in metabolism and thermoregulation.

5.3a) Hematologic changes

Circulating blood volume in the pregnant woman increases by about 30 - 50% during pregnancy (Pritchard 1965, Chesley 1972, Peck and Arais 1979, Brinkman 1984) while plasma volume increases by 30-60% (Pritchard 1965, Chesley 1972, Peck and Arais 1979, Bentley 1985, Hytten 1985). Increased plasma volume is associated with changes in the vasculature of the uterus, breasts, muscles, kidneys and skin as well as hemodilution and a net decrease in red blood cell volume as well as total circulating plasma proteins (Blackburn and Loper 1992). In contrast, pregnancy red blood cell

(RBC) volume increases by about 18% (250 ml) in women (Hyttén 1985, Kelton and Cruickshank 1988).

Increased blood and plasma volumes are highly adaptive in that they enhance maternal-fetal exchange of gases and nutrients. They help to meet the demands of the enlarged uterus and the hypertrophied vascular system, while maintaining normal systemic blood pressure. They also help accommodate blood loss at delivery, which can account for over half of red blood cell volume (Chesley 1972).

Increased plasma volume is positively correlated with placental mass, neonatal birth weight and fetal growth (Bentley 1985, Hyttén 1985). In addition, increased blood volume protects the woman from impaired venous return and hypotension, particularly during the third trimester when a significant volume of fluid may be held within the venous system of the lower extremities. A reduction in blood viscosity during the third trimester helps to conserve maternal energy resources by allowing cardiac effort reduction (Chesley 1972). Finally, increased blood volume plays an important role in thermoregulation during pregnancy. Cutaneous blood flow increase, (between 4 -7 fold), occurs during pregnancy and assists in heat dissipation through the skin (Chesley 1972, Pritchard 1975, Peck and Arais 1979, Bassell and Marx 1981, Bentley 1985, Kelton and Cruickshank 1988).

5.3b) Cardiovascular changes

Major changes during pregnancy occur in maternal heart rate, blood volume, stroke volume, cardiac output, systemic vascular resistance and pulmonary vascular resistance (Walsh 1988). Cardiac output is one of the most significant hemodynamic changes that occurs during pregnancy. It is the product of heart rate and stroke volume and increases most rapidly during the embryonic period where stroke volume increases rapidly over heart rate. By 8 gestation weeks, cardiac output increases by 1 L/min, or 22% above non-pregnant values. By 24 gestation weeks this increase rises to 57% above non-pregnancy values and elevated levels are maintained throughout

pregnancy (Capeless and Clapp 1989, Robson et al. 1989), although reduced in relative terms after 24 weeks gestation (Ueland et al. 1969, Quilligan 1982).

Significantly, the increase in cardiac output is not related to the metabolic requirements of the mother or fetus, nor is it related to the increase in body mass (Romen et al. 1991). This is principally because at the time the increase occurs, the fetus is relatively small. Later in gestation when the fetus is larger, there is a relative decline in maternal cardiac output, associated with a decline in stroke volume following the compression of the inferior vena cava by the uterus. Cardiac output is reduced in later gestation even though there is a concomitant increase in maternal oxygen consumption in response to the metabolic needs of the fetus, maternal heart and respiratory muscles (Blackburn and Loper 1992).

Heart size also increases during pregnancy. Hypervolemia results in changes in cardiac silhouette, chamber size and pressures, in part due to positional displacement following uterus growth and displacement of the diaphragm (Blackburn and Loper 1992).

5.3c) Respiratory changes

Major physiological changes occur in the maternal respiratory system during pregnancy (Mescher et al. 1975, DeSwiet 1984). These changes are principally in response to increased maternal, fetal and placental metabolic requirements. Adequate oxygenation is achieved via increased respiratory efficiency in the woman. An increase in air volume in the order of about 50% is attained by shifting breathing from the abdomen to the thoracic region (Weinberger and Weiss 1982, Bassell and Marx 1984). This occurs in response to displacement of the diaphragm and the flaring of the lower ribs when the uterus becomes enlarged. The resulting increase in intra-abdominal pressure serves to increase lung volume (Weinberger and Weiss 1982, Bassell and Marx 1984, Cruikshank and Hays 1986). The most notable period of lung volume increase occurs when a 4 cm elevation of the diaphragm changes the configuration of the chest (Weinberger and Weiss 1982, Bassell and Marx 1984).

This takes place in the middle of the second trimester (Turner et al. 1980, Cruikshank and Hays 1986). In addition, oxygen consumption increases with gestation age, partly in response to the increased work associated with carrying a greater load (Ueland et al. 1973, DeSwiet 1984, Alexander 1984) and in order to protect the fetus from the risk of hypoxia (Ueland et al. 1973, Knuttgen and Emerson 1974).

A number of authors have found that oxygen consumption may actually remain unchanged or may decrease during exercise (Guzman and Caplan 1970, Ueland et al. 1973, Knuttgen and Emerson 1974, Artal et al. 1986) due to increased respiratory efficiency.

5.3d) Renal changes

The kidneys play a key role in the woman's physiology in that they regulate water and electrolyte balance, vitamin D activity, arterial blood pressure, erythrocyte production as well as gluconeogenesis. They are also responsible for excretion of metabolic waste products (Vander 1985, Blackburn and Loper 1992). The kidneys also play a role in sodium retention and undergo an increase in cellular volume during pregnancy.

Hydronephrosis and dilation of the renal pelvis and ureters occurs in about 80% of pregnant women, beginning in the first trimester and becoming even more prominent after 20 gestation weeks (Bailey and Rolleston 1971, Bay and Ferris 1979, Freed 1981, Rowe et al. 1981, Beydoun 1985). Increases in ureter volume may be as great as 25 times non-pregnancy values (Freed 1981) and are accompanied by changes in renal hemodynamics, fluid and electrolyte balance and glomerular filtration (Blackburn and Loper 1992).

Overall mean kidney length increases by 1 - 2 cm during pregnancy as a consequence of increased renal blood flow and vascular volume (Blackburn and Loper 1992). By the end of the first trimester, renal blood flow increases by 35-60%, later decreasing until term (Lindheimer and Katz 1975, Brinkman and Meldrum 1979, Rowe et al. 1981, Davison 1987). Renal plasma flow, on the other hand, increases by about 60%

of non-pregnancy values by mid-gestation and then decreases to about a 40% increase over non-pregnancy values at term (Sims and Krantz 1958, Stewart and Jose 1985, Davison 1985).

5.3e) Gastrointestinal changes

Changes in the gastrointestinal system during pregnancy are mainly due to mechanical forces such as the pressure from the growing uterus, as well as hormonal influences, notably that of progesterone. As a result, gastric motility is reduced during pregnancy, thus allowing for enhancement of nutrient absorption. Although maternal food consumption increases by about 15 - 20% during early pregnancy, this increase in caloric intake does not influence gastrointestinal basal metabolism (Rosso 1987, Blackburn and Lee 1992).

5.3f) Hepatic changes

During pregnancy, the liver is displaced markedly by the growing uterus. Although blood flow to the liver is not greatly altered compared to non-pregnancy values, mild to moderate hepatomegaly does occur. This is the case even though there is a proportionate decrease in cardiac output reaching the liver during pregnancy, in the margin of 28 - 35%, and due to increased cardiac blood flow to the placenta (Klion and Wolke 1985).

In addition to hepatomegaly during pregnancy, increased fat and glycogen storage as well as variations in hepatic cell size have been reported in biopsy materials (Ingeslev and Teilum 1945).

Thus, during pregnancy, organ hypertrophy occurs in response to increased blood flow and increased metabolic demands of the fetus, as well as the increased carrying costs of the pregnant body. The heart, lungs and kidneys increase in size and in efficiency during a period when it is crucial for the energetic demands of the fetus to be met.

In response, maternal metabolic changes occur during pregnancy and are crucial for the protection of the mother and the promotion of fetal growth and development. They serve to increase fuel conservation in the mother while freeing up glucose, amino acids and free fatty acids to the fetus.

5.3g) Metabolic changes

Metabolism is the totality of chemical reactions in the body functioning to maintain: a) plasma glucose levels b) an optimal source of glycogen as an emergency fuel c) an optimal supply of protein for enzymatic mechanisms of metabolism and muscular mobility as well as conversion of excess protein to fat and release of nitrogen in urine and to d) conserve protein and fat during periods of caloric scarcity (Pitkin 1983, Hare 1989).

During pregnancy major alterations in metabolic processes, mediated endocrinologically, arise in order to allow the mother to provide adequate nutrients to the fetus for growth and development as well as adequate stores of energy and substrates needed during the transition to extra-uterine life. At the same time, maternal metabolic requirements associated with the increased physiologic demands of pregnancy must be met and energy and substrate stores provided to meet the demands of pregnancy, labour and lactation (Baird 1986, Herrera 2000). Invariably maternal-fetal metabolic demands are in conflict and alterations in maternal metabolic processes may have significant effects on both maternal and fetal health (Kretchmer et al. 1985). Haig (1993) discusses this aspect of maternal-fetal-conflict in some detail, arguing that mother and fetus actively compete for resources by manipulating both maternal and fetal as well as placental systems.

Pregnancy is primarily an anabolic state in which food intake and appetite increase while activity decreases. About 3.5 kg of fat are deposited and about 900 g of new protein synthesised by mother, fetus and placenta. The overall energetic cost of pregnancy is estimated at 75 000 to 85 000 kcal (Kretchmer et al. 1985, Baird 1986).

Anabolic aspects of pregnancy are greatest during the first half of pregnancy when increased fat deposition and increased blood volume in the woman lead to weight gain. During the second half of pregnancy, however, the woman's metabolic status becomes more catabolic as fat stores are used, insulin resistance increases and serum glucose falls. Weight gain during this period is primarily due to the growing fetus and placenta (Knopp et al. 1979, Hare 1989).

Table 5.1 lists the changes in chemical composition (from Prentice et al. 1996) during pregnancy and the associated energetic costs arising from those changes. The fetus comprises about 19% of the total costs of pregnancy. The placenta contributes less than 2% of the cost, while the cost of the amniotic fluid is negligible (0.05%). Changes in maternal body structures also contribute to the costs of pregnancy. For example, the enlarged breasts comprise almost 2% of the metabolic costs, increased blood volume comprises about 3% and the enlarged uterus also contributes about 3%. However, increased fat storage during pregnancy comprises the greatest cost at about 72% of total pregnancy metabolic costs.

Although the combined cost of the fetus and placenta is just over 20% of the total costs of pregnancy, maternal metabolic processes are greatly influenced by the fetus and placenta which themselves biosynthesise hormones and also become an additional site for the metabolism of maternal hormones. Many of these changes are aimed at providing additional glucose and amino acids to the fetus for growth and development. Most notably, human placental lactogen (hPL), estrogen and progesterone alter glucose utilisation and insulin action and alter lipid and protein metabolism as well as increasing the uptake of glucose and amino acids for transfer to the fetus. At the same time they provide an alternate energy substrate for maternal homeostasis in the form of free fatty acids (Blackburn and Loper 1992, Herrera 2000).

Changes in the way in which carbohydrates, proteins and fats are metabolised by the mother also promote transference of energy to the fetus (Herrera 2000).

i) Carbohydrate metabolism

Changes in carbohydrate metabolism during pregnancy are largely controlled by progesterone, estrogen, cortisol and human placental lactogen (hPL). Together, these hormones reduce maternal utilisation of glucose and increase glucose availability to the fetus (Waisman and Kerr 1965, Baird 1986, Weiss 1988, Hollingsworth and Moore 1989, Herrera 2000). As pregnancy progresses, peripheral glucose utilisation by the mother decreases as insulin resistance increases, thus reducing maternal glucose utilisation and freeing it up for the growing fetus (Hare 1989). In fact, blood glucose levels are, on average, 10 to 20% lower in pregnant versus non-pregnant women, while plasma glucose levels fall by about 15 to 20 mg/dl in pregnant women, often leading to ketosis (Waisman and Kerr 1965, Blackburn and Loper 1992). In addition, a reduction in insulin extraction by the maternal liver may also contribute to increased levels of insulin availability to the fetus (Baird 1986). Fetal glucose availability is further enhanced by the effects of progesterone and estrogen in the mother which act to augment insulin secretion and plasma cortisol levels which in turn stimulate insulin production (Hollingsworth and Moore 1989).

Lind and Aspillaga (1988) have shown that women reset their homeostatic controls at a lower level during pregnancy by reducing blood glucose levels (throughout gestation) and increasing insulin levels during the third trimester, when fetal growth is at a maximum. This influences carbohydrate metabolism by elevating both glucose and insulin levels for a relatively longer time (compared to non-pregnancy) following a meal in late pregnancy. This increases energy supply to the rapidly growing fetus and is associated with increased birthweight (Tallarigo et al. 1986).

ii) Protein metabolism

During pregnancy serum amino acid and serum protein levels are reduced due to increased placental uptake, increased insulin levels, hepatic diversion of amino acids for gluconeogenesis and transfer of amino acids to the fetus liver for glucose formation (Blackburn and Loper 1992). Changes in protein metabolism during early

and late pregnancy differ markedly. In the first half of pregnancy maternal protein storage increases while during the second half of pregnancy, stored protein is broken down to provide an alternate source of energy for the fetus (Naismith and Morgan 1976, Naismith 1980, 1981; Page et al. 1981).

iii) Fat metabolism

Like carbohydrate and protein metabolism, lipid metabolism undergoes marked changes during pregnancy (Cooney and Newsholme 1982, Baird 1986, Herrera 2000). During the first two trimesters, there is an increase in fat storage and triglyceride synthesis, accompanied by increased lipogenesis and suppressed lipolysis. This anabolic phase is mediated, once again, by progesterone and cortisol. It is during this period that fat utilisation is enhanced as suggested by the increased occurrence of ketogenesis after fasting (Page et al. 1981). The third trimester, however, is characterised by an equal occurrence of lipogenesis and lipolysis. These later increased levels of lipolysis are driven by increasing levels of hPL (human placental lactogen). At the same time, increased oxidation of free fatty acids in the maternal liver frees up energy but also increases the risk of maternal ketosis. Fat mobilisation during this period is crucial in serving as an alternative fuel for the mother, allowing her to conserve glucose for the fetus and for the maintenance of her own central nervous system (Waisman and Kerr 1965, Page et al. 1981, Baird 1986).

Changes in fat metabolism are accompanied by morphological and functional changes in adipocytes. Cell hypertrophy accommodates increased fat storage during the first two trimesters, while a decrease in glucose transport, glucose oxidation and lipogenesis occurs during the last trimester (Waisman and Kerr 1965). In addition, there is a temporary and reversible increase in the number of insulin receptors on the adipocytes during the first half of pregnancy (Baird 1986).

In addition, general increased metabolic efficiency has been found in a nutritionally stressed Gambian population, where basal metabolic rate actually decreases during

pregnancy as an 'energy sparing' mechanism (Lawrence et al. 1987, Heini et al. 1992, Poppitt et al. 1993).

These changes in metabolism, along with physiological adaptations in the major systems of the body all serve to increase maternal efficiency and thus, free-up additional energy for the growing fetus.

Coombs et al. (1992) and Catalano et al. (1998), have shown that maternal metabolism has a direct effect on fetal growth and body composition. By studying the long-term alterations in glucose metabolism during pregnancy, these authors found that fetal birth weight and accretion of adipose tissue was influenced by maternal glucose metabolism.

5.4) Maternal influences on offspring size and growth

In addition to maternal metabolism, a number of maternal factors influence fetal growth. These were discussed in chapter 2 and included maternal nutrition, placenta weight, age and parity, cigarette smoking and alcohol use. In this chapter, the relationship between these maternal factors and the size, growth and encephalisation of the fetuses and infants is examined.

Table 5.1 Change in body composition during pregnancy

Site	Weight gain (g)				Energy cost (kcal)		
	Protein	Fat	Water	Total	Protein	Fat	Total
Fetus	440	440	2414	3294	3050	4837	7887
Placenta	100	4	540	644	693	44	737
Amniotic fluid	3	0	792	795	21	0	21
Uterus	166	4	800	970	1151	44	1195
Breasts	81	12	304	397	561	132	693
Blood	135	20	1287	1442	936	220	1156
Water	0	0	1496	1496	0	0	0
Subtotal	925	480	7633	9038	6411	5277	11689
Fat stores	67	2676	602	3345	464	29421	29885
Total	992	3156	8235	12383	6876	34698	41574

Taken from Prentice et al. (1996)

5.4a) Maternal Nutrition Hypothesis

Previous studies have shown that maternal nutritional status relates to a number of neonatal size indices, including: birth weight, crown-heel length, head circumference, chest circumference, abdominal circumference, arm circumference, thigh circumference, arm length, femur length, sub-scapular skinfold thickness, thigh skinfold thickness and triceps skinfold thickness (Garn and Pesick 1982, Anderson et al. 1984, Abrams and Laros 1986, Briend 1985, Neggers et al. 1995). Although much work has been done illustrating the effects of maternal physiology and anthropometry on offspring size and nutrition, little is known about the impact of maternal factors on offspring encephalisation (i.e. relative brain size) and change in encephalisation over time. Clearly, the amount of energy made available to the fetus by the mother is a crucial factor in the growth and development of that fetus as a whole.

Here, it is hypothesised that the increased energetic demands of encephalisation in the fetus are met by increased energetic input from the mother. As such, well-nourished women will produce encephalised fetuses while undernourished women will produce non-encephalised fetuses.

In order to test this hypothesis, the relationships between indices of maternal nutritional status and offspring encephalisation and growth in encephalisation are examined.

5.4b) Placenta Hypothesis

In addition to testing the 'Maternal Nutrition Hypothesis', the relationship between placenta weight and the number of placental notches and offspring encephalisation is examined. Placental factors may impede or augment energy transfer from the mother to the fetus and may, thus, influence fetal encephalisation. Increased placental notching is associated with decreased blood flow to the fetus (Antsaklis et al. 2000) and may be associated with intrauterine growth restriction (Bower et al. 1993, Aquilina et al. 2000). The size of the placenta has implications for nutrient transfer to

the fetus. Increased placenta size is associated with increased placental surface area which influences the amount of and rate of diffusion of nutrients and hormones to the fetus (Blackburn and Loper 1992). The placenta also competes with the fetus for energy resources, particularly during later pregnancy, and thus, may actually decrease energy availability to the fetus for encephalisation and growth in encephalisation.

Here it is hypothesised that increased placenta weight and decreased placental notching are associated with increased encephalisation in the fetus, due to increased blood and nutrient transfer to the fetus. In contrast, increased placental notching (blood flow impairment) and overly large placenta weights are associated with reduced encephalisation and growth in encephalisation (due to the increased energy use by the overly large placenta).

SECTION II: Methodology

5.5) Maternal data

The mothers of fetuses and infants measured as part of the UCL hospitals study are analysed here. Placenta weight (in grams) and the number of notches in the placenta (associated with decreased uterine blood flow) were taken at birth. In addition, a number of biometric, life history, demographic and lifestyle measures were taken at first visit. These included age, parity (number of pregnancies past 24 gestation weeks), weight, height, subscapular skinfold and triceps skinfold, average number of cigarettes smoked per day and units of alcohol consumed per week during pregnancy. Maternal height was measured with a stadiometer (Holtain Limited, Crymych, U.K.) and weight was measured using Seca scales (CMS Weighing Equipment Limited, London, U.K.).

According to Goldberg (1991), increased maternal parity is associated with increased age, socioeconomic status and reduced smoking as well as increased centralised fat storage.

Table 5.2 lists the proportion of the sample for which maternal measures were taken and the proportion of sons and daughters produced. Tables 5.3 and 5.4 list the descriptive statistics for the maternal variables.

The mothers in the sample were all Caucasian and lived in London and were all considered to be healthy. Women in the study were generally well-nourished. According to Garrow and Webster's (1985) index of fatness, these women, on average, were close to the upper limit of the desirable range in the Quetelet index. The mean BMI was 23.7 with an upper limit of 25 and the distribution was skewed toward the right (i.e. increasing BMI). According to the Garrow and Webster (1985) index of fatness, Grade I obesity includes body mass indices between 25.0 to 29.9. In the study population, 297 women were classified as Grade I on this obesity scale. In contrast, 26 women had a BMI $\leq 18.5 \text{ kg/m}^2$, which is considered to be indicative of clinical malnutrition (Ferro-Luzzi and James 1996, James et al. 2001).

Although these women were between 9-16 weeks pregnant at measurement, early pregnancy weight gain is only about 0.65 kg during the first 10 weeks of pregnancy (Hyttén 1991). In an average woman with a BMI of 24.0 kg/m^2 and a height of 1.65 m, this translates into an estimated BMI increase of only 0.3 kg/m^2 during the first 10 weeks of pregnancy. In addition, Sidebottom et al. (2001) have shown that triceps and subscapular skinfold thicknesses do not increase significantly until about 18 gestation weeks.

As noted in chapter 2, exclusion criteria were introduced here. Offspring who were born prior to 36 gestation weeks were excluded on the grounds of prematurity and offspring measured more than 4 weeks on either side of the mean age at the measurement period were excluded. In addition, mothers who entered the study before 9 gestation weeks and after 16 gestation weeks were excluded due to the influence of duration of pregnancy on body composition.

Figures 5.1 to 5.3 show that in this sample, prior to 9 gestation weeks and after 16 gestation weeks, mean weight, body mass index and subscapular skinfold thickness

differs from that of the rest of the sample. From 9-16 gestation weeks, means for these variables remain fairly constant, and thus, gestation age differences during this period do not contribute to much variation in weight, BMI and skinfold thickness. Therefore, those mothers who were measured between 9-16 gestation weeks and whose offspring were born after 36 gestation weeks and were measured within 4 weeks of the mean age at ultrasounds 2 and 3, birth, 6 and 12 months, were retained in the study sample. Thus, early bookers and late bookers were excluded on the grounds that the early bookers may have entered the study early due to unusual external circumstances, while the late bookers were excluded principally due to their increased weight and body composition change.

Tables 5.5 lists the proportion of the total sample for which maternal measures in this 'reduced' sample were available. Tables 5.6 through 5.8 list the descriptive statistics for the mothers in the 'reduced' sample.

Independent samples t-tests show that the 'reduced' sample does not differ significantly from the total sample, and, therefore, represents the total sample of women measured as part of the study. The results of the independent samples t-tests are listed in Table 5.9. An independent samples Mann-Whitney U test was used to determine whether the maternal descriptive measures (including number of cigarettes smoked, socio-economic status and marital status) differed between women included in the study sample and those women excluded from the study. The Mann-Whitney U test is a nonparametric version of the t-test, and determines whether two samples are likely to come from the same population, based on the sum of category ranks (Sokal and Rohlf (1997). No statistically significant differences were found between the reduced and excluded samples (cigarettes: $P = 0.530$, socio-economic status: $P = 0.114$, marital status: $P = 0.730$).

Table 5.10 lists the estimated variables reflecting maternal nutritional status. These include the mid-arm muscle and fat areas, as well as the body mass index (BMI).

Table 5.2 Percent of maternal sample for which measures were taken and sample sizes for each measure, as a function of offspring sex

Maternal variables	% sample	males	females
maternal age	93.0	767	717
marital status	89.9	767	717
socio-economic group	89.9	767	717
parity	93.0	767	717
maternal weight	86.1	710	678
maternal height	92.9	766	714
maternal subscapular skinfold	91.3	753	702
maternal triceps skinfold	91.3	753	702
maternal mid-arm circumference	88.2	753	702
maternal BMI	83.8	709	674
cigarette consumption	93.0	767	717
alcohol consumption	93.0	767	717
placenta weight at birth	81.6	673	627

BMI = body mass index

All maternal measures taken at booking. Total number of mothers were 1650. Socio-economic status was determined from age at which full-time education was completed, marital status, occupation, and partner's occupation and social class assignment was made using the classification of the United Kingdom Office of Population Census and Statistics (Standard Occupational Classification Volume 3. OPCS 1991).

Table 5.3 Descriptive statistics for maternal variables

maternal variable	n	mean	sd
<i>life history</i>			
age (yrs)	1650	30.8	5.6
parity	1650	0.08*	1.2
<i>size & weight-for-height</i>			
height (cm)	1644	164.5	6.8
weight (kg)	1548	64.0	11.4
BMI	1542	23.7	4.2
<i>fat indices</i>			
triceps skinfold (mm)	1616	18.7	6.4
subscapular skinfold (mm)	1617	15.8	6.9
<i>lean tissue indices</i>			
MUAC (cm)	1617	2.6	0.3
<i>placental indices</i>			
weight (g)	1300	665	135
number of notches	1378	0.2	0.6
<i>gestational indices</i>			
gestation at booking (weeks)	1649	12.9	2.6
gestation age at delivery (weeks)	1484	39.4	1.7
<i>lifestyle indices</i>			
alcohol (# units/week)	1650	1.6	3.5
<i>offspring sex ratio</i>			
males/females	767/717	1484	

All maternal variables taken at booking, placenta weight (g) taken at delivery

* parity: 0 (53%), 1 (27%), 2 (10%), 3 (6%), 4 (2%), 5+ (2%)

n = sample size, sd = standard deviation, BMI = body mass index

Table 5.4 Descriptive maternal variable sample sizes and percent of total sample (n=1650)

cigarettes per day	ex-smoker	0	1-9	10-20	21+
	148 (9.0%)	1188 (72.0%)	160 (9.7%)	120 (7.3%)	34 (2.1%)
marital status	married	single	divorced	widowed	other
	917 (55.6%)	693 (42.0%)	17 (1.0%)	2 (0.12%)	21 (1.3%)
socio-economic group	5	4	3	2	1
	224 (13.6%)	688 (41.7%)	355 (21.5%)	206 (12.5%)	177 (10.7%)

socio-economic group : 5 (lowest), 1 (highest)

Socio-economic status was determined from age at which full-time education was completed, marital status, occupation, and partner's occupation and social class assignment was made using the classification of the United Kingdom Office of Population Census and Statistics (Standard Occupational Classification Volume 3. OPCS 1991).

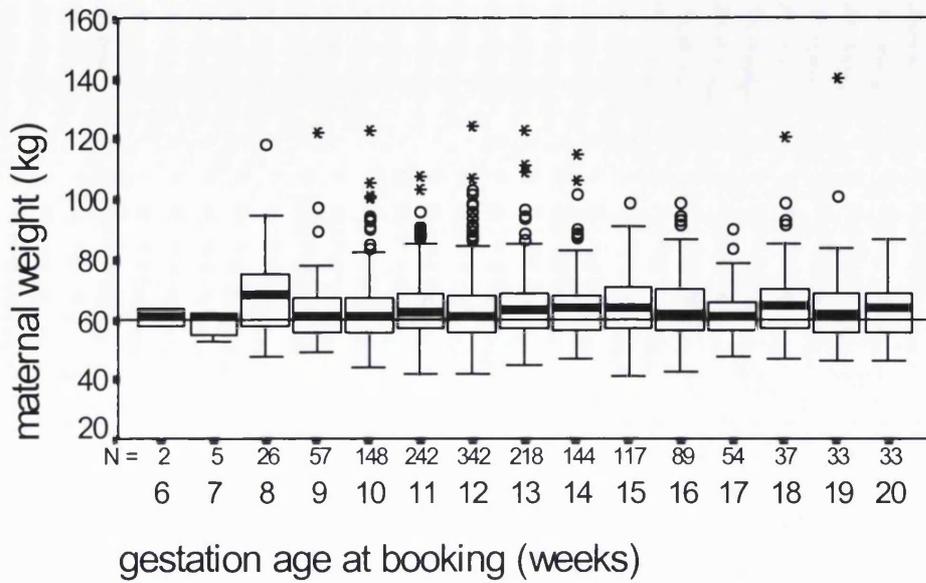


Figure 5.1 Box plot showing mean maternal weight at booking, with outliers (open circles) and extreme cases (*). Mothers booked between 9 - 16 gestation weeks were included in the reduced sample.

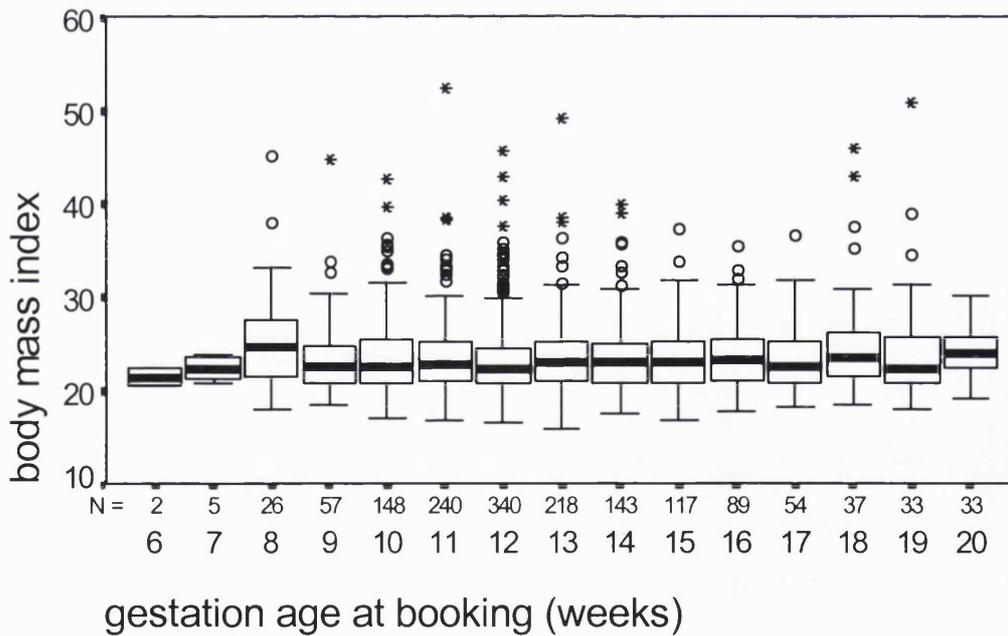


Figure 5.2 Box plot showing mean maternal body mass index (kg/m^2) at booking, with outliers (open circles) and extreme cases (*). Mothers booked between 9 - 16 gestation weeks were included in the reduced sample.

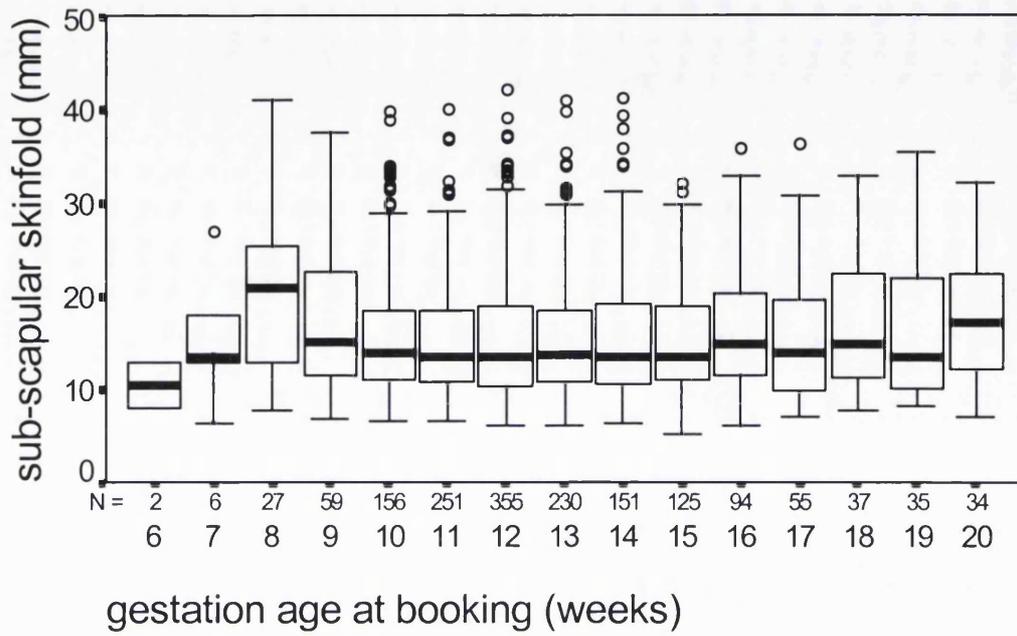


Figure 5.3 Box plot showing mean maternal sub-scapular skinfold thickness at booking, with outliers (open circles). Mothers booked between 9 - 16 gestation weeks were included in the reduced sample.

Table 5.5 Frequency of measures for maternal variables in the reduced sample as a percent of the total sample by infant sex

maternal variable	% total sample	males	females
<i>life history</i>			
age	81.7	674	633
parity	78.6	674	633
<i>size and weight-for-height</i>			
height	80.9	673	631
weight	78.6	623	599
BMI	78.6	622	595
<i>fat indices</i>			
triceps skinfold	80.2	662	622
subscapular skinfold	80.2	662	622
<i>lean tissue indices</i>			
MUAC	77.8	662	622
<i>placental indices</i>			
weight	67.8	575	543
<i>lifestyle indices</i>			
cigarettes/day	81.7	674	633
alcohol units/week	76.8	674	633
<i>demographic indices</i>			
marital status	81.7	674	633
socio-economic group	81.7	674	633

reduced sample includes individuals whose mothers were booked between 9-16 gestation weeks and whose measurements were taken within 4 weeks of the mean measurement time

All maternal variables taken at booking

n = sample size, sd = standard deviation, BMI = body mass index, MUAC = mid-upper arm circumference

Table 5.6 Descriptive statistics for mothers included in the reduced sample (gestation at booking between 9-16 weeks) and those excluded

maternal variable	included			excluded (< 9 GW)			excluded (> 16 GW)		
	n	mean	sd	n	mean	sd	n	mean	sd
<i>life history</i>									
age (yrs)	1293	30.9	5.6	35	29.4	4.9	167	30.1	6.3
parity	1293	0.8	1.2	35	1.3	1.4	167	1.1	1.6
<i>size & weight-for-height</i>									
weight (kg)	1211	63.8	11.1	35	163.4	6.1	166	163.5	7.2
height (cm)	1289	164.7	6.7	33	67.2	14.6	157	64.5	12.8
BMI (kg/m ²)	1206	23.6	4.1	33	25.1	5.6	157	24.2	5.0
<i>fat indices</i>									
triceps skinfold (mm)	1267	18.6	6.3	35	21.3	7.3	161	18.5	6.3
subscapular skinfold (mm)	1268	15.6	6.8	35	19.0	8.6	161	16.6	7.1
<i>lean tissue indices</i>									
MUAC (mm)	1268	26.1	3.1	35	26.9	3.7	161	25.9	3.0
<i>placental indices</i>									
weight (g)	1027	665	138	27	645	112	126	675	128
notches	1222	0.2	0.6	27	0.1	0.4	129	0.2	0.6
<i>gestational indices</i>									
gestation at booking (weeks)	1307	39.5	1.7	35	7.7	0.6	167	18.3	1.2
gestation at delivery (weeks)	1293	12.3	1.5	32	39.5	1.5	145	39.1	1.9
<i>lifestyle indices</i>									
alcohol (units/week)	1293	1.7	3.6	35	0.5	1.4	167	0.9	2.2
<i>offspring sex ratio</i>									
males/females	1307	674/633		32	14/18		145	79/66	

All maternal measures taken at booking, placenta weight (g) taken at delivery, n = sample size, sd = standard deviation, BMI = body mass index, MUAC = mid-upper arm circumference.

Table 5.7 Descriptive maternal variable sample sizes and percent of total sample for the reduced sample (gestation at booking between 9-16 weeks only, measured within 4 weeks of mean measurement age and born no earlier than 37 gestation weeks)

cigarettes per day:	ex-smoker	0	1-9	10-20	21+
	132 (10.2%)	1045 (80.8%)	134 (10.4%)	108 (8.4%)	28 (2.2%)
marital status:	married	single	divorced	widowed	other
	800 (61.9%)	615 (47.6%)	14 (1.1%)	2 (0.2%)	16 (1.2%)
socio-economic group :	5	4	3	2	1
	201 (15.6%)	606 (46.9%)	311 (24.1%)	180 (13.9%)	149 (11.5%)
socio-economic group : 5 (lowest), 1 (highest)					

Table 5.8 Descriptive maternal variable sample sizes and percent of total sample for excluded mothers (gestation at booking between 9-16 weeks only, measured within 4 weeks of mean measurement age and born no earlier than 37 gestation weeks)

maternal variable		< 9 GW					> 16 GW				
		ex-smoker	0	1-9	10-20	21+	ex-smoker	0	1-9	10-20	21+
cigarettes per day:	1	24	4	4	2	15	118	22	8	4	
		(2.9%)	(68.6%)	(11.4%)	(11.4%)	(5.7%)	(9.0%)	(70.7%)	(13.2%)	(4.8%)	(2.4%)
marital status:	married	single	divorced	widowed	other	married	single	divorced	widowed	other	
	21	11	2	0	1	95	67	1	0	4	
		(60.0%)	(31.4%)	(5.71%)		(2.9%)	(56.9%)	(40.1%)	(0.6%)		(2.4%)
socio-economic group :	5	4	3	2	1	5	4	3	2	1	
	3	8	12	7	5	19	74	32	19	23	
		(8.6%)	(22.9%)	(34.3%)	(11.4%)	(14.3%)	(11.4%)	(44.3%)	(19.2%)	(11.4%)	(13.8%)

socio-economic group : 5 (lowest), 1 (highest)

GW = gestation weeks

Mann-Whitney U tests revealed that the above variables in the women 'excluded' from the study did not differ significantly from those of the women included in the study.

Table 5.9 Results of independent samples t-tests comparing the means of maternal variables from mothers in the reduced sample with sons and with daughters

maternal variable	mean difference ¹	P	CI of difference
<i>life history</i>			
age (yrs)	0.01	0.965	-0.63, 0.66
parity	0.02	0.830	-0.12, 0.15
<i>size and weight-for-height</i>			
height (cm)	0.2	0.611	-0.6, 1.0
weight (kg)	-0.3	0.678	-1.6, 1.1
BMI (kg/m ²)	-0.2	0.492	-0.7, 0.3
<i>fat indices</i>			
triceps skinfold (mm)	-0.1	0.712	-0.9, 0.6
subscapular skinfold (mm)	-0.3	0.520	-1.1, 0.5
<i>lean tissue indices</i>			
MUAC (cm)	-0.1	0.618	-0.5, 0.3
<i>placental indices</i>			
placenta weight (grams)	15.8	0.067	-1.1, 32.6
placental notches	0.01	0.807	-0.06, 0.08
<i>gestational indices</i>			
gestation at booking (weeks)	0.0	0.990	0.0
<i>lifestyle indices</i>			
alcohol (# units/week)	0.3	0.149	-0.1, 0.7

All maternal measures taken at booking, placental measures taken at birth

¹ positive value indicates that males are larger while a negative value indicates that females are larger

BMI = body mass index, MUAC = mid-upper arm circumference (mm)

P = probability based on a two-tailed Pearson's bivariate correlation with a confidence interval of 95%, CI = confidence interval

negative mean difference are associated with mothers producing daughters.

Table 5.10 Descriptive statistics for calculated maternal variables

maternal variable	n	mean	sd
mid-arm muscle area (cm ²)	1420	33.9	2.0
mid-arm fat area (cm ²)	1420	6.6	4.0

sd = standard deviation, n = sample size

area (mm²) estimated using equations given by Shaw and Lawson (2001)

5.6) Indices of maternal nutritional status

Nutritional status is a global index of whether an individual is overweight, underweight or of relatively normal weight. Nutritional status can be assessed indirectly. For example, weight-for-height is a good indicator of nutritional status in humans (Brandt 1988). The body mass index or Quetelet index is often used to define weight-for-height in the adult. The formula is expressed as $\text{weight}/\text{height}^2$ (weight in kg and height in meters). As in the Benn index in infants described in chapter 4, the body mass index (BMI) yields no information about the relative proportions of fat, lean tissue or water comprising weight. Additional anthropometric indices reflect nutritional status. Mid-arm circumference reflects protein reserves in humans (Jelliffe 1966), while triceps skinfold thickness reflects energy reserves (Frisancho 1981). In addition, fat distribution may be assessed by calculating a ratio of central to limb fatness (i.e. subscapular to triceps skinfold thickness ratio) (see for example Barker et al. 1997).

Here, maternal nutritional status is assessed using measures of weight and height to calculate BMI, subscapular and triceps skinfold thickness as a means for assessing fatness and for estimating mid-arm fat area. In addition, mid-arm circumference is used as a means for assessing lean tissue and for estimating mid-arm muscle area.

Mid-arm muscle and fat areas are estimated using the predictive equation cited by Shaw and Lawson (2001) and given in chapter 4, equations 37 and 38.

5.7) Quantifying maternal size and nutritional status

Because mothers were measured at different stages of pregnancy, gestational differences between the women in the sample must be controlled for. A women's weight at 9 gestation weeks, for example, will be significantly less than that at 16 gestation weeks, as will her fatness. In order to standardise for gestation age, the LMS method described in chapter 2 is used here and SD scores for size and nutritional indices are calculated.

By using the LMS method, distributions are normalised and size variables are expressed as an SD score relative to gestational age. The L, M and S values for maternal variables are listed in Tables A.13 through A.15 in the appendix.

First, the maternal variable was plotted against gestation age at measurement. Next, smoothed L, M and S curves were fitted through the data. Gestation age-specific L, M and S values for each women were then derived and used to calculate an SD score (as per equation 10). This procedure was undertaken for maternal weight, height, BMI, skinfold thicknesses and estimated fat and muscle areas. A ratio of subscapular to triceps skinfold SD scores was used as an index of fat distribution. Placenta weights at delivery were not expressed as SD scores here because maternal weight measures at delivery were not available in this sample. In addition, the placenta is correlated with a number of variables (both maternal and neonatal) and there is no *a priori* reason to express placenta weight as a function of maternal size rather than neonatal size, for example. Placenta weight, was therefore, left as an absolute value.

Measures of offspring encephalisation (encephalisation SD scores) and growth (change in SD scores between measurement periods and thrive SD scores) were described in chapter 4 and are analysed here in relation to maternal SD scores reflecting size and nutritional status, and placental variables.

5.8) Statistical tests

In order to determine whether there is a relationship between maternal variables and offspring size, growth, nutritional status and encephalisation, the following statistical tests are used.

First, two-tailed bivariate correlations with confidence limits set at 95% are used to determine whether a statistically significant correlation between maternal and offspring variables exists. Partial correlations controlling for maternal height and age are used where these variables are confounders. Multiple regression is used to

determine whether maternal size or nutritional variables explain the variation in offspring encephalisation.

The multiple regressions are undertaken in two stages. First maternal nutritional status SD scores are entered into a multiple regression model as independent variables and offspring encephalisation SD scores are entered as the dependent variable. This is done in order to determine whether maternal nutritional status explains a significant amount of the variation in offspring encephalisation.

Because encephalisation is comprised of body length and head circumference SD scores, a second multiple regression is undertaken where maternal nutritional status SD scores and offspring body length SD scores are entered as the independent variables, along with an interaction variable (see chapter 4, section 4.3) calculated as the product of maternal and offspring body length SD scores, while offspring head circumference SD score is entered as the dependent variable. This multiple regression is carried out in order to determine whether maternal nutritional status SD scores, or simply offspring size (body length SD scores) alone explains the variation in offspring head circumference SD scores. The maternal nutritional status variables include maternal skinfolds and mid-arm muscle area SD scores, as well as placenta weight at delivery.

Should maternal nutritional status and placenta weight variables contribute significantly to the model, then they are statistically significantly related to offspring head circumference SD scores, independently of the effects of offspring body length SD scores. If the interaction variables do not contribute significantly to the model, then the relationship between maternal nutritional variables and offspring body length SD scores relate independently to offspring head circumference SD scores.

Multiple regression is also used to determine whether maternal size or nutritional status explains the variation in offspring growth indices and in offspring nutritional status indices. These growth and nutritional status indices were described in detail in chapter 4. Growth indices include growth in head circumference, body length and encephalisation, calculated as the difference in SD scores between measurement

periods. Indices reflecting thrive in growth were also calculated. These are SD scores which control for initial size effects.

Finally, both maternal and neonatal size and nutritional status variables are entered into a multiple regression in order to determine which contribute significantly to explaining the variation in neonatal encephalisation SD scores. The offspring nutritional status variables were described in chapter 4 and include neonatal Benn index, skinfolds and estimated mid-arm muscle area SD scores.

In addition to correlations and multiple regression analysis, tertiles are used to describe the associations between maternal variable and offspring variable SD scores. See chapter 4 section 4.4e for further details on tertiles. In this chapter, tertiles are based on maternal variables where SD scores are ranked and divided into three groups, representing small, medium and large sizes for the maternal variable in question. Tertiles are computed for five maternal variables. These include a) maternal height SD scores b) maternal BMI SD scores c) maternal estimated mid-arm muscle area SD scores d) maternal subscapular skinfold thickness SD scores and e) triceps skinfold thickness SD scores.

Within each of these three size groups, offspring body length SD scores are ranked and sub-divided into three groups reflecting short, medium and tall individuals. A 9-celled table results, where different offspring sizes correspond to different maternal variable sizes. Mean and sd values for offspring head circumference SD scores are then given in relation to each of the 9 cells.

A principal components analysis, with a varimax rotation, is then carried out in order to determine which maternal and which neonatal variables load on the same factor as offspring encephalisation SD scores. The principal components procedure is used as it determines which variables form coherent subsets that are relatively independent of one another. Factors are produced which contain variables correlated with one another but largely independent of other subsets of variables. The size of the loading on each factor reflects the extent of the relationship between each variable and each factor. These factors are normally assumed to reflect underlying processes that have

created correlations among variables. The varimax rotation maximizes the variance of factor loadings by making high loadings higher and low ones lower for each factor, thereby simplifying the interpretation of the factors in the analysis. It does so, however, without changing their underlying mathematical properties.

SECTION III: Results

5.9) Results of analyses

5.9a) Relationship between maternal nutrition and offspring size and encephalisation

Table 5.11 lists the results of the bivariate correlations where maternal variable SD scores and skinfold ratios were correlated with femur length, head circumference and encephalisation SD scores in the fetus at ultrasounds 2 and 3. This analysis shows that maternal size and nutritional status SD scores (i.e. BMI, skinfolds and estimated mid-arm muscle areas) are significantly correlated with fetal size (femur length and head circumference SD scores). In contrast, maternal nutritional status variable SD scores and skinfold ratio are not significantly correlated with fetal encephalisation SD scores. Maternal height SD does, however, correlate with fetal encephalisation SD at ultrasound 3. Thus, while maternal size and nutritional status are correlated with fetal size, maternal nutritional status is not significantly correlated with fetal encephalisation.

Table 5.11 Results of bivariate correlations where maternal variable SD scores at booking are correlated with fetal size variable SD scores at ultrasounds 2 and 3

fetal variable:	fl(sc2) n = 1154- 1231	hc(sc2) n = 1170- 1252	EI(sc2) n = 1152- 1229	fl(sc3) n = 1093- 1173	hc(sc3) n = 958- 1031	EI (sc3) n = 958- 1027
R:						
maternal variable:						
height	0.11*	0.08†	0.02	0.25*	0.20*	0.13*
weight	0.12*	0.02	-0.05	0.22*	0.11*	0.05
BMI	0.06‡	-0.03	-0.06‡	0.10#	0.01	-0.02
subscapular skinfold	0.09†	0.01	-0.04	0.12*	0.01	-0.03
triceps skinfold	0.09†	0.02	-0.03	0.15*	0.06	0.02
mid-arm muscle area	0.09†	0.01	-0.05	0.14*	0.03	-0.01
skinfold ratio	-0.022	-0.033	-0.023	-0.019	-0.035	-0.032

A two-tailed Pearson's bivariate correlation with a confidence limit of 95% is used
R = correlation coefficient, BMI = body mass index, n = sample size, sc2 = ultrasound 2, sc3 = ultrasound 3, fl = femur length SD score, hc = head circumference SD score, skinfold ratio = subscapular : triceps skinfold SD score

* = P≤0.0001, # = P≤0.001, † = P≤0.01, ‡ = P≤0.05 probability based on a confidence interval of 95%

However, maternal height and skinfolds are themselves significantly correlated. It is, therefore, necessary to control for the covariance between height and nutritional status variable SD scores when undertaking this bivariate correlation analysis. A partial correlation (controlling for maternal height SD scores) between maternal nutritional variable SD scores and fetal encephalisation SD scores was thus undertaken, the results of which are listed in Table 5.12.

The results of the partial correlations analysis between maternal nutritional status variable SD scores and fetal encephalisation SD scores (listed in Table 5.12) show that even after controlling for maternal height SD scores, maternal nutritional status variables are significantly correlated with fetal femur length but not with head circumference or encephalisation SD scores. The skinfold ratio is not significantly correlated with any of the fetal variables.

Table 5.12 Results of partial correlations where maternal variable SD scores at booking are correlated with fetal size variable SD scores at ultrasounds 2 and 3, controlling for maternal body length SD score

fetal variable:	fl(sc2) n = 1138	hc(sc2) n = 1159	EI(sc2) n = 1136	fl(sc3) n = 1084	hc(sc3) n = 951	EI (sc3) n = 951
R:						
maternal variable:						
weight	0.08†	-0.01	-0.06	0.15*	0.06	0.02
subscapular skinfold	0.11*	0.02	-0.04	0.15*	0.02	-0.03
triceps skinfold	0.09†	0.01	-0.04	0.15*	0.05	0.01
mid-arm muscle area	0.09†	0.01	-0.05	0.14*	0.01	-0.03
skinfold ratio	0.002	-0.015	-0.019	-0.004	-0.027	-0.026

A two-tailed partial correlation with a confidence limit of 95% is used

R = correlation coefficient, n = sample size, sc2 = ultrasound 2, sc3 = ultrasound 3, fl = femur length SD score, hc = head circumference SD score, EI = encephalisation SD score, skinfold ratio = subscapular : triceps skinfold SD score

= P≤0.0001, # = P≤0.001, † = P≤0.01, ‡ = P≤0.05 probability based on a confidence interval of 95%

The same analyses were carried out for the infants in the sample. Table 5.13 lists the results of the bivariate correlation where maternal size and nutritional status variable SD scores were correlated with neonatal and infant body length, head circumference and encephalisation SD scores.

These results show that at birth and 6 months, maternal size and nutrition SD scores are significantly correlated with offspring body length, head circumference and encephalisation. Body mass index SD scores are, however, not correlated with offspring body length SD scores. By 12 months, maternal height SD scores are correlated with infant body length and head circumference SD scores alone. Encephalisation is not significantly correlated with maternal variables at this time.

Thus, unlike the fetus, the young infant's encephalisation SD score is correlated with maternal size and nutritional status SD scores. The lack of a significant relationship at 12 months may be due to the reduced sample size at this time rather than due to the lack of a biological relationship, as such.

After controlling for the co-variance between maternal height and nutritional status variable SD scores, these relationships remain largely unchanged in the neonate. Table 5.14 lists the results of the partial correlations between maternal nutritional status variable SD scores and offspring encephalisation SD scores, where maternal height SD scores are controlled for.

These results show that neonatal encephalisation SD scores are still significantly correlated with maternal nutritional status variable SD scores. By 6 months, however, only the maternal triceps skinfold thickness SD score is correlated with infant size and encephalisation. By 12 months, no significant relationships are found. The lack of a significant correlation during the early fetal period may not be wholly surprising given that this sample population is generally well-nourished and healthy. It is possible that energy stress in the early stages of pregnancy may result in a correlation between maternal nutritional status and fetal encephalisation in an energetically stressed population. This, however, remains to be studied.

Table 5.13 Results of bivariate correlations where maternal variable SD scores at booking are correlated with postnatal size variable SD scores at birth, 6 and 12 months

infant variable:	bl(0) n = 1147- 1231	hc(0) n = 1153- 1237	EI(0) n = 1146- 1233	bl(6) n = 694- 737	hc(6) n = 691- 738	EI (6) n = 694- 737	bl(12) n = 245- 249	hc(12) n = 245- 247	EI (12) n = 245- 247
R:									
maternal variable:									
height	0.22*	0.16*	0.06‡	0.33*	0.23*	0.10†	0.37*	0.22*	0.11
weight	0.16*	0.20*	0.14*	0.17*	0.19*	0.13*	0.12	0.11	0.07
BMI	0.05	0.13*	0.12*	0.03	0.08‡	0.09‡	-0.07	-0.01	0.01
subscapular skinfold	0.08†	0.08†	0.04	-0.04	0.04	0.06	-0.01	-0.01	-0.02
triceps skinfold	0.12*	0.15*	0.10*	0.08‡	0.12#	0.10†	-0.01	0.01	0.01
mid-arm muscle area	0.08†	0.12*	0.09#	0.05	0.09‡	0.08‡	-0.04	-0.05	-0.04

A two-tailed Pearson's bivariate correlation with a confidence limit of 95% is used, R = correlation coefficient, n = sample size, 0 = birth, 6 = 6 months, 12 = 12 months

bl = body length SD score, hc = head circumference SD score, EI = encephalisation index (SD score)

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a confidence limit of 95%

Table 5.14 Results of partial correlations where maternal variable SD scores at booking are correlated with postnatal size variable SD scores at birth, 6 and 12 months, controlling for maternal body length SD score

infant variable:	bl(0) n = 1137	hc(0) n = 1143	EI(0) n = 1136	bl(6) n = 683	hc(6) n = 684	EI (6) n = 683	bl(12) n = 241	hc(12) n = 241	EI (12) n = 241
maternal variable:	R:								
weight	0.09#	0.15*	0.13*	0.05	0.12†	0.11†	-0.03	0.03	0.04
subscapular skinfold	0.11*	0.09†	0.04	-0.01	0.04	0.05	0.03	0.01	-0.01
triceps skinfold	0.12*	0.15*	0.10#	0.06	0.11‡	0.09‡	-0.01	0.01	0.01
mid-arm muscle area	0.07‡	0.12*	0.09†	0.03	0.07	0.07	-0.06	-0.06	-0.05

A two-tailed partial correlation with a confidence limit of 95% is used

R = correlation coefficient, n = sample size, 0 = birth, 6 = 6 months, 12 = 12 months, bl = body length SD score, hc = head circumference SD score, EI = encephalisation index (SD score)

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a 95% confidence interval

Tables 5.15 and 5.16 list the results of the multiple regression analyses for fetuses and infants, where SD scores for maternal height, skinfolds and estimated mid-arm muscle area explain the variation in offspring encephalisation SD scores. No one variable explained a significant proportion of the variance in fetal encephalisation at ultrasound 2. The total amount of variation explained by the model was 0.3% ultrasound 2. At ultrasound 3, only maternal height SD scores contributed significantly to explaining the variation in fetal encephalisation. However, the total model explained 1.9% of the variation. At birth, preliminary investigation showed that maternal height, triceps skinfold thickness and mid-arm muscle area SD scores, explained a significant amount of the variation in neonatal encephalisation SD score, when entered separately into a regression model. These variables were entered into the multiple regression and together explained 1.7% of the variation in neonatal encephalisation SD scores. At 6 months, preliminary investigation showed that maternal height, triceps and subscapular skinfolds and mid-arm muscle area SD scores explained a significant amount of the variation in encephalisation SD scores at 6 months, when entered independently into a regression model. All these variables were entered into a multiple regression and together explained 2% of the variation in encephalisation SD scores at 6 months. At 12 months, maternal size and nutritional status variable SD scores together explained 1.7% of the variation in infant encephalisation SD scores at 12 months. No one variable, however, explained a significant amount of the variation in encephalisation SD scores at 12 months.

Thus, only a very small percentage of the total variation in offspring encephalisation is explained by maternal size and nutritional status in early pregnancy. Maternal triceps skinfold thickness SD score contributes significantly to the model in explaining the variation in neonatal encephalisation SD score. At 6 months, maternal height SD score contributes significantly to the model in explaining the variation in infant encephalisation SD score at 6 postnatal months.

Maternal size and nutritional status, however, explain a greater proportion of the variation in offspring body size measures. Maternal height SD scores, triceps and subscapular skinfold SD scores and estimated mid-arm muscle area SD scores together explain 7% of the variation in neonatal body length SD scores.

Table 5.15 Results of linear multiple regression analyses for the relationship between maternal height SD score and maternal nutritional status variable SD scores (independent variables) and fetal encephalisation SD score (dependent variable)

Independent variables	coefficient	SE	P	Total r² (%)
<i>Ultrasound 2</i>				
constant	-0.006	0.029	0.825	0.3
maternal height	0.180	0.029	0.540	
maternal triceps skinfold	-0.010	0.041	0.804	
maternal subscapular skinfold	0.006	0.042	0.883	
maternal mid-arm muscle area	-0.048	0.040	0.227	
<i>Ultrasound 3</i>				
constant	0.006	0.031	0.853	1.9
maternal height	0.129	0.033	<0.001	
maternal subscapular skinfold	-0.039	0.044	0.377	
maternal triceps skinfold	0.063	0.046	0.169	
maternal mid-arm muscle area	-0.032	0.043	0.452	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

Dependent variable is encephalisation SD score, maternal variables are SD scores

Table 5.16 Results of linear multiple regression analyses for the relationship between maternal height SD score and maternal nutritional status variable SD scores (independent variables) and in infant encephalisation SD score (dependent variable)

Independent variables	coefficient	SE	P	Total r² (%)
<i>birth</i>				
constant	-0.005	0.029	0.862	1.5
maternal height	0.053	0.029	0.068	
maternal triceps skinfold	0.077	0.037	0.039	
maternal mid-arm muscle area	0.043	0.037	0.248	
<i>6 months</i>				
constant	0.005	0.037	0.899	2.0
maternal height	0.10	0.038	0.008	
maternal subscapular skinfold	0.016	0.053	0.766	
maternal triceps skinfold	0.081	0.054	0.132	
maternal mid-arm muscle area	0.015	0.052	0.777	
<i>12 months</i>				
constant	-0.004	0.066	0.956	1.7
maternal height	0.108	0.063	0.086	
maternal subscapular skinfold	-0.006	0.092	0.952	
maternal triceps skinfold	0.079	0.103	0.443	
maternal mid-arm muscle area	-0.097	0.089	0.278	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

Dependent variable is encephalisation SD score, maternal variables are SD scores

5.9b) Relationship between maternal nutritional status and offspring growth

As in the case for maternal size, maternal nutritional status in relation to offspring encephalisation is assessed using bivariate correlations. Tables 5.17 and 5.18 list the results of the bivariate correlations between maternal nutritional status variable SD scores and offspring growth in body length, head circumference and encephalisation (i.e. change in SD scores between measurement periods). Between ultrasounds 2 and 3, maternal height SD scores are significantly and positively correlated with head circumference and encephalisation growth indices. Maternal weight SD scores, in contrast, are correlated with femur length growth indices alone. None of the maternal nutritional status SD scores are significantly correlated with fetal growth indices at this time.

Between ultrasound 3 and birth, however, a number of maternal nutritional status variable SD scores are significantly correlated with change in fetal head circumference and encephalisation SD scores. These include the BMI, subscapular and triceps skinfolds and estimated mid-arm muscle area SD scores. Maternal height SD scores are also correlated with growth in encephalisation at this time.

Thus, in early pregnancy (ultrasounds 2-3), maternal nutritional status is not associated with fetal growth. In later pregnancy, however, it is associated with well-nourished mothers producing offspring who undergo increased change in SD score between measurement periods in the head and encephalisation alone. Notably, femur length growth is not associated with maternal nutritional status at this time. Once again, this may highlight the importance of maternal nutrition for offspring growth in later pregnancy, when energy stress increases.

From birth to 6 months of age, maternal height SD scores are correlated with infant body length and head circumference growth indices. Maternal height, at this time, is not correlated with infant growth in encephalisation, however. Of the nutritional status indices, only maternal subscapular skinfold thickness SD scores are correlated with infant growth in encephalisation during this period. In contrast, maternal BMI

SD scores are correlated with infant growth in encephalisation between 6 and 12 months. No other maternal variables are correlated with infant growth at this time.

Table 5.17 Results of bivariate correlations where maternal variable SD scores at booking are correlated with prenatal growth variables

offspring variable:	Δfl (sc2-sc3) n = 1036- 1105	Δhc (sc2-sc3) n = 928- 991	ΔEI (sc2-sc3) n = 899- 967	Δbl (sc3-0) n = 1037- 1112	Δhc (sc3-0) n = 916- 987	ΔEI (sc3-0) n = 908- 979
R:						
maternal variable:						
height	0.12	0.09†	0.09†	-0.02	-0.05	-0.07‡
weight	0.08†	0.06	0.07	-0.04	0.06	0.05
BMI	0.03	0.02	0.02	-0.03	0.10†	0.10†
subscapular skinfold	0.02	-0.02	0.00	-0.04	0.08‡	0.07‡
triceps skinfold	0.04	0.03	0.05	-0.02	0.08‡	0.06‡
mid-arm muscle area	0.04	0.02	0.04	-0.04	0.07‡	0.07‡

n = sample size, Δfl = change in femur length SD score, Δhc = change in head circumference SD score, ΔEI = change in encephalisation index (SD score), sc = ultrasound scan

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a Pearson's bivariate correlation with a confidence limit of 95%

Table 5.18 Results of bivariate correlations where maternal variable SD scores at booking are correlated with postnatal growth variables

infant	Δ bl(0-6)	Δ hc(0-6)	Δ EI(0-6)	Δ bl(6-12)	Δ hc(6-12)	Δ EI (6-12)
variable:	n = 677- 722	n = 678- 723	n = 676- 721	n = 219- 222	n = 219- 222	n = 219- 222
R:						
maternal variable:						
height	0.09‡	0.08‡	0.04	0.01	0.06	0.11
weight	0.03	0.07	0.06	0.05	-0.06	-0.07
BMI	-0.01	0.04	0.04	0.03	-0.12	-0.14‡
subscapular skinfold	-0.08	0.03	0.08‡	0.01	-0.01	-0.02
triceps skinfold	-0.03	0.01	0.03	-0.06	-0.06	-0.04
mid-arm muscle area	0.00	0.04	0.05	0.02	-0.10	-0.11

R = correlation coefficient, n = sample size, BMI = body mass index

Δ = change, bl = body length SD score, hc = head circumference SD score, EI = encephalisation SD score, 0 = birth, 6 = 6 months, 12 = 12 months, sc = ultrasound scan

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a Pearson's bivariate correlation with a confidence limit of 95%

Table 5.19 lists the results of the multiple regression analysis, where maternal height and nutritional status variable SD scores explain some of the variation in offspring encephalisation growth indices (i.e. change in encephalisation SD score between measurement periods). Maternal height explains a significant amount of the variation in Δ encephalisation between ultrasounds 2 and 3 and ultrasound 3 and birth, and is just below significance in explaining the variation in Δ encephalisation between birth and 6 months.

Between ultrasounds 2 and 3, maternal size and nutrition variables explain about 1.2% of the variation in fetal encephalisation growth, with maternal height contributing significantly to the model. Between ultrasound 3 and birth, maternal variables explain about 1.1% of the variation and between birth and 6 months, maternal height and nutrition variables explain 1.1% of the variation in offspring encephalisation growth, with maternal sub-scapular skinfold thickness contributing significantly to the model. Between 6 and 12 months, maternal size and nutrition variables explain about 3% of the variation in infant encephalisation growth.

Table 5.19 Results of linear multiple regression analyses where maternal height SD scores and maternal nutritional status variable SD scores explain the variation in offspring change in encephalisation SD score (Δ) between measurement periods

dependent variable: Δ encephalisation SD	independent variable	coefficient	SE	P	Total r^2 (%)
between ultrasounds 2 - 3	constant	0.020	0.041	0.636	1.2
	maternal height	0.109	0.043	0.011	
	maternal subscapular skinfold	-0.064	0.059	0.275	
	maternal triceps skinfold	0.087	0.061	0.150	
	maternal mid-arm muscle area	0.023	0.056	0.680	
between ultrasound 3 -birth	constant	-0.007	0.037	0.842	1.1
	maternal height	-0.085	0.038	0.027	
	maternal subscapular skinfold	0.016	0.052	0.751	
	maternal triceps skinfold	0.021	0.053	0.689	
	maternal mid-arm muscle area	0.064	0.050	0.204	
between birth - 6 months	constant	0.034	0.043	0.430	1.1
	maternal height	0.073	0.044	0.097	
	maternal subscapular skinfold	0.134	0.061	0.030	
	maternal triceps skinfold	-0.062	0.062	0.319	
	maternal mid-arm muscle area	0.011	0.060	0.856	
between 6 - 12 months	constant	-0.052	0.057	0.361	2.9
	maternal height	0.098	0.054	0.071	
	maternal subscapular skinfold	0.066	0.079	0.401	
	maternal triceps skinfold	-0.003	0.088	0.972	
	maternal mid-arm muscle area	-0.138	0.076	0.071	

r^2 = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

Δ encephalisation SD = difference in encephalisation SD score between measurement periods, maternal variables are SD scores

Similarly, thrive in growth is assessed in relation to maternal size and nutrition indices. See chapter 2, section 2 for details on calculating thrive SD scores. Table 5.20 lists the results of bivariate correlations, showing that maternal height and nutritional status variable SD scores are significantly correlated with offspring thrive in head circumference and change in encephalisation between ultrasound 3 and birth. In addition, they show that postnatal thrive in head circumference growth and maternal nutritional status SD scores are positively correlated.

Table 5.20 Results of bivariate correlations where maternal variable SD scores are correlated with offspring thrive in growth SD scores

offspring variable:	thrive in body length	thrive in head circumference	thrive in EI
	ultrasound 3 - birth n = 1094-1111	ultrasound 3 - birth n = 973-987	ultrasound 3 - birth n = 963-978
maternal variable:	R:		
height	0.15*	0.06‡	0.02
subscapular skinfold	0.05	0.10†	0.08‡
triceps skinfold	0.08†	0.13*	0.11#
mid-arm muscle area	0.04	0.10#	0.10†
	birth - 6 months n = 711-722	birth - 6 months n = 712-723	birth - 6 months n = 710-721
height	0.27*	0.18*	0.09‡
subscapular skinfold	-0.06	0.04	0.07
triceps skinfold	0.05	0.08‡	0.07
mid-arm muscle area	0.04	0.08‡	0.07

EI = encephalisation index, thrive = SD score derived by plotting the change in size SD score between two measurement periods against the size SD score at the initial measurement period using the LMS method

A two-tailed Pearson's bivariate correlation with a confidence of limit of 95% is used where * = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$

Tables 5.21 through 5.23 list the results of multiple regression analyses examining the relationship between maternal height and nutritional status variable SD scores and the variation in offspring thrive in body length (Table 5.21), head circumference (Table 5.22) and encephalisation (Table 5.23) SD scores between ultrasound 3 and birth and between birth and 6 postnatal months.

These results show that maternal height explains a small but significant proportion of the variation in thrive in body length between ultrasound 2 and birth and between birth and 6 postnatal months. Maternal height also explains a significant amount of the variation in thrive in head circumference between ultrasound 3 and birth (where it is just below significance) and between birth and 6 postnatal months (where it is highly significant). It also explains a significant proportion of thrive in encephalisation between birth and 6 months.

Maternal subscapular skinfold thickness SD scores contribute significantly to explaining the variation in thrive in body length between birth and 6 postnatal months. Maternal triceps skinfold thickness SD scores also contribute significantly to explaining the variation in thrive in body length between ultrasound 3 and birth. It also explains a significant proportion of the variation in thrive in head circumference SD score between ultrasound 3 and birth.

In late pregnancy (between ultrasound 3 and birth), maternal variables explain about 3% of the variation in fetal thrive in body length growth. Maternal height and triceps skinfold thickness SD scores contribute significantly to the model at this time. Maternal variables also explain about 2% of the variation in the thrive in head circumference growth between ultrasound 3 and birth. At this time, maternal triceps skinfold thickness SD scores contribute significantly to the model. The variation in the thrive in encephalisation during this period is explained by maternal variables as well. However, less than 1.5% of thrive in encephalisation growth is explained by maternal height and nutritional status.

Between birth and 6 months, about 8% of the variation in body length thrive is explained by maternal height and nutritional status. However, only height contributes

significantly to the model at this time. About 4% of the variation in head circumference thrive is explained by maternal variables, with maternal height contributing significantly to the model. Thrive in encephalisation between birth and 6 months is also associated with maternal variables. However, only 1.7% of the variation in encephalisation thrive at this time is explained by maternal nutritional status variables, with height alone contributing significantly to the model. Maternal nutritional status, therefore explains only a very small proportion of the thrive in growth in this sample. Maternal height, rather, explains a significant amount of the variation in offspring thrive in growth, including that of encephalisation.

Thus, a positive finding for the 'Maternal Nutrition Hypothesis' appears to be found in the neonate, however, less than 1.5% of the total variation in neonatal encephalisation is explained by maternal nutritional status as measured at booking. In earlier fetal life and in later infancy maternal nutritional status is not significantly correlated with fetal encephalisation. Similarly growth in encephalisation is clearly associated with maternal nutritional status between ultrasound 3 and birth, however, only about 1% of the variation in encephalisation growth is explained by maternal nutritional status. Maternal sub-scapular skinfold thickness explains most of this variation, perhaps indicating that centralised maternal fatness plays a more important role than peripheral fatness in relation to fetal encephalisation growth in later pregnancy. Sidebottom et al. (2001) have shown that centralised fat deposition during pregnancy is associated with pre-pregnancy BMI. In addition, Neggers et al. (1995), Brown et al. (2002) and Wells et al. (in press) have shown that pre-pregnancy nutritional status and weight are more important to fetal growth than is maternal gestational nutrition and weight gain. The relationship between centralised fatness and offspring encephalisation may thus stem from the relationship with maternal pre-pregnancy nutritional status. In contrast to maternal fatness, thrive in body length and head circumference growth is largely related to maternal height rather than nutritional status.

It is unfortunate that the women in this study were not measured in later pregnancy. Because pregnancy weight gain could not be assessed here it is not possible to assess nutritional status in later pregnancy. However, maternal nutritional status at

conception has been shown to better predict offspring size and body composition at birth than does weight gain (Barker 1998, Wells et al. in press). The results in this chapter suggest that mothers who are nutritionally well-nourished in early pregnancy, go on to produce encephalised neonates.

Table 5.21 Results of linear multiple regression analyses describing the relationship between maternal height SD score and maternal nutritional status variable SD scores (independent variables) and offspring thrive in body length growth (dependent variable)

dependent variable: thrive in body length SD	independent variable	coefficient	SE	P	Total r² (%)
between ultrasound 3 -birth	constant	0.009	0.030	0.770	3.1
	maternal height	0.162	0.031	0.000	
	maternal subscapular skinfold	0.039	0.042	0.360	
	maternal triceps skinfold	0.086	0.043	0.047	
	maternal mid-arm muscle area	-0.046	0.041	0.266	
between birth - 6 months	constant	-0.015	0.036	0.675	7.8
	maternal height	0.248	0.037	0.000	
	maternal subscapular skinfold	-0.121	0.052	0.019	
	maternal triceps skinfold	0.100	0.052	0.057	
	maternal mid-arm muscle area	0.026	0.051	0.602	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

thrive in body length SD scores are calculated using the LMS method and control for initial body length SD score, maternal variables are SD scores

fetal body length at ultrasound 3 is estimated from femur length using Fazekas and Kósa's (1978) equation given in equation 40

Table 5.22 Results of linear multiple regression analyses describing the relationship between maternal height SD score and maternal nutritional status variable SD scores (independent variables) and offspring thrive in head circumference growth (dependent variable)

dependent variable: thrive in head circumference SD	independent variable	coefficient	SE	P	Total r² (%)
between ultrasound 3 -birth	constant	0.001	0.032	0.965	2.2
	maternal height	0.065	0.033	0.051	
	maternal subscapular skinfold	0.025	0.045	0.577	
	maternal triceps skinfold	0.101	0.046	0.030	
	maternal mid-arm muscle area	0.022	0.044	0.617	
between birth - 6 months	constant	0.003	0.037	0.941	4.1
	maternal height	0.184	0.038	0.000	
	maternal subscapular skinfold	0.008	0.053	0.876	
	maternal triceps skinfold	0.059	0.053	0.268	
	maternal mid-arm muscle area	0.027	0.052	0.601	

r^2 = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

thrive in head circumference SD scores are calculated using the LMS method and control for initial head circumference SD score

maternal variables are SD scores

Table 5.23 Results of linear multiple regression analyses describing the relationship between maternal height SD score and maternal nutritional status variable SD scores (independent variables) and offspring thrive in encephalisation growth (dependent variable)

dependent variable: thrive in encephalisation SD	independent variable	coefficient	SE	P	Total r² (%)
between ultrasound 3 -birth	constant	-0.002	0.032	0.950	1.4
	maternal height	0.019	0.033	0.570	
	maternal subscapular skinfold	0.004	0.045	0.936	
	maternal triceps skinfold	0.077	0.047	0.098	
	maternal mid-arm muscle area	0.047	0.044	0.284	
between birth - 6 months	constant	0.009	0.037	0.817	1.7
	maternal height	0.105	0.038	0.006	
	maternal subscapular skinfold	0.057	0.053	0.288	
	maternal triceps skinfold	0.023	0.054	0.668	
	maternal mid-arm muscle area	0.016	0.52	0.758	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

thrive in encephalisation SD scores are calculated using the LMS method and control for initial encephalisation SD score
maternal variables are SD scores

5.9c) Relationship between placental variables and offspring encephalisation and growth in encephalisation

Table 5.24 lists the results of bivariate correlations between placental weight and the number of placental notches and offspring size and growth. These results show that placenta weight is positively correlated with neonatal body length, head circumference and encephalisation SD scores. In addition, placenta weight is correlated with change in body length and head circumference SD scores (i.e. growth between ultrasound 3 and birth). The number of placental notches, in contrast is inversely correlated with head circumference and encephalisation SD scores, but not with growth indices.

Because maternal height is significantly correlated with placenta weight, a partial correlation, controlling for maternal height SD scores, was undertaken. The results of this analysis are listed in Table 5.25 and show that after controlling for the effects of maternal height (size), placenta weight is positively and significantly correlated with neonatal size, encephalisation, nutritional status and growth in body length and head circumference. It is not, however, correlated with growth in encephalisation.

Placental notching is correlated with maternal age, where young mothers tend to have more placental notches. Maternal age was, therefore, controlled for by performing a partial correlation. Here the number of placental notches was correlated with neonatal variable SD scores, after controlling for maternal age. Table 2.25 lists the results where notching is inversely correlated with neonatal head circumference, encephalisation, Benn index and estimated mid-arm muscle area. In addition, growth in encephalisation (i.e. change in encephalisation SD score between ultrasound 3 and birth) is inversely correlated with the number of placenta notches.

Thus, women with large placentas (for their size) tend to have neonates which are large, encephalised, well-nourished and who grow their bodies and heads relatively quickly. Women with many placental notches (after controlling for their age), in contrast, tend to have small-headed neonates with reduced muscle and fatness and reduced growth in encephalisation. Women with overly large placentas at delivery

(i.e. in the 90th centile: ≥ 839 g) also tend to have encephalised neonates. A bivariate correlation between placenta weight above the 90th centile and neonatal encephalisation SD scores was significantly correlated ($R = 0.187$, $n = 116$, $P = 0.045$), as was a partial correlation controlling for maternal height SD scores ($R = 0.191$, $n = 112$, $P = 0.042$).

These results provide evidence for the 'placenta hypothesis', in that large placentas (i.e. increased energy transfer to the fetus) are associated with encephalised offspring, while increased placental notching (impaired placental efficiency) is associated with reduced encephalisation and growth in encephalisation. Contrary to the predictions of the 'Placenta Hypothesis', however, having an overly large placenta does not appear to constrain offspring encephalisation (see figure 5.4).

Table 5.24 Results of bivariate correlations between maternal variables and neonatal SD scores for body length, head circumference, encephalisation indices and the change in those indices between ultrasound 3 and birth

neonatal variable	bl(0) n = 1096-1234	hc(0) n = 1099-1240	EI(0) n = 1096-1233	Δ bl(sc3-0) n = 998-1114	Δ hc(sc3-0) n = 883-989	Δ EI(sc3-0) n = 878-980
R:						
Maternal variable						
<i>Demographic indices:</i>						
age	0.11*	0.14*	0.10*	0.02	0.04	0.02
parity	0.09†	0.07‡	0.03	0.06‡	0.10#	0.06‡
socio-economic status	0.10#	0.11*	0.08†	-0.02	-0.05	-0.04
<i>Lifestyle indices:</i>						
alcohol	0.01	0.01	0.01	0.01	-0.09†	-0.08‡
cigarettes smoked	-0.12*	-0.12*	-0.08†	0.02	-0.01	0.01
<i>Placental indices:</i>						
weight at delivery	0.40*	0.38*	0.22*	0.16*	0.13*	0.02
notches at delivery	-0.05	-0.10#	-0.09†	0.01	-0.01	-0.01

Maternal variables are not SD scores, socio-economic status: values between 1 - 5 in increasing order of income bracket variables are absolute values (not SD scores).

body length SD score (bl), head circumference SD score (hc), encephalisation SD score (EI) at birth (0)

Δ = change in SD score between ultrasound 3 (sc3) and birth

Descriptive statistics listed include R (correlation coefficient), n = sample size. Two-tailed test of significance with a confidence limit of 95% based on a Pearson's bivariate correlation.

* = P≤0.0001, # = P≤0.001, † = P≤0.01, ‡ = P≤0.05

Table 5.25 Results of partial correlations between neonatal variable SD scores and placenta weight at delivery, controlling for maternal body length SD scores and placental notching, controlling for maternal age

neonatal variable	placenta weight		notches	
	n	R	n	R
<i>birth</i>				n = 903
body length	1118	0.37*	1090	-0.04
weight	1118	0.61*	1105	-0.11*
head circumference	1122	0.37*	1093	-0.09†
encephalisation	1117	0.21*	1090	-0.08†
Benn index	1118	0.33*	1090	-0.11*
subscapular skinfold	1044	0.30*	1045	-0.03
triceps skinfold	1045	0.30*	1046	-0.05
mid-arm muscle area	1045	0.39*	1046	-0.08‡
<i>scan 3 - birth</i>				
Δ body length	1106	0.16*	993	0.01
Δ head circumference	981	0.14*	878	0.00
Δ encephalisation	972	0.03	874	-0.01

n = sample size, R = regression coefficient, Δ = change in SD between measurement periods score between measurement periods

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a two-tailed partial correlation with a confidence limit of 95%

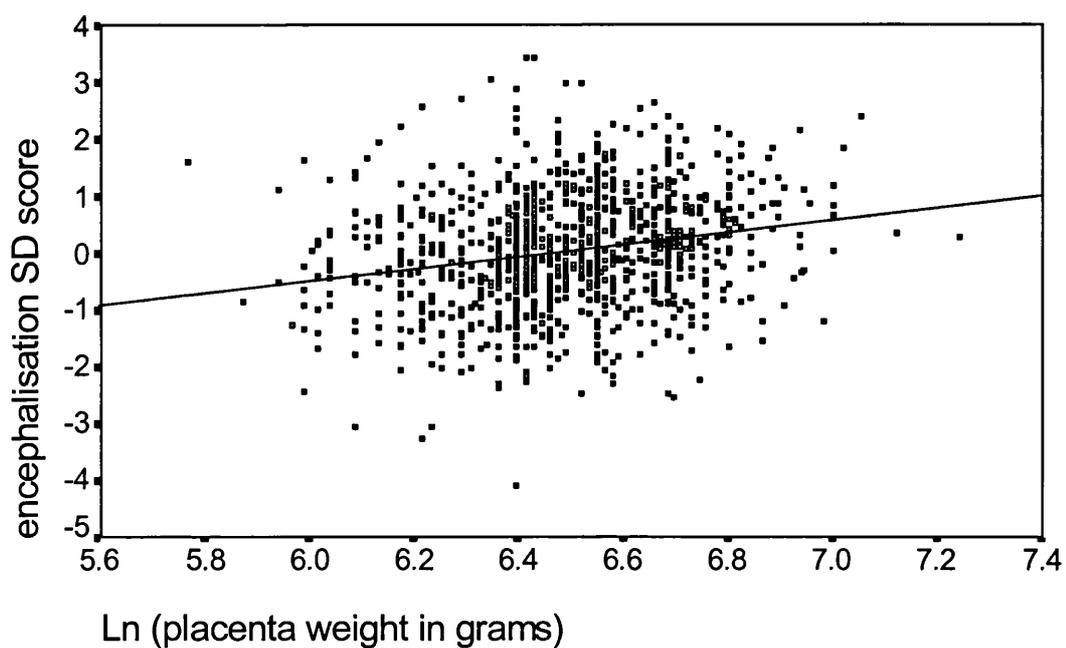


Figure 5.4 Encephalisation SD scores at birth plotted against \log_e -transformed placenta weight measures at delivery

The least squares linear regression equation describing this relationship is as follows:

(68) $\text{Encephalisation SD score} = -6.9 + 1.1 * \text{Ln (placenta weight in grams)}$
 $(r^2 = 0.05, \text{SE} = 0.96, n = 1096, P < 0.0001)$

Maternal size, nutrition and the placenta are not the only factors associated with offspring encephalisation. Table 5.26 lists the results of a number of additional maternal variables as they correlate with neonatal encephalisation, size and growth indices. These include maternal age, parity, socioeconomic status, alcohol and cigarette use.

Neonatal size is positively correlated with maternal age, parity and socioeconomic status, and inversely correlated with maternal cigarette use. Older mothers with increased parity and increased socioeconomic status, therefore, produce larger encephalised offspring, with the exception of those who smoke. Increased cigarette use is associated with smaller neonates and less encephalised neonates. In terms of growth, maternal age has no significant effect on neonatal growth, however increased parity is associated with increased neonatal growth in body length, head circumference and encephalisation. In contrast, alcohol use is associated with reduced growth in head circumference and encephalisation between ultrasound 3 and birth.

The relationships between alcohol use and smoking on offspring encephalisation may be influenced by a number of confounding variables. In the UCL Hospitals data, for example, increased alcohol use is correlated with increased maternal age ($R = 0.134$, $n = 1650$, $P = 0.000$), low maternal socioeconomic status, ($R = 0.185$, $n = 1650$, $P = 0.000$), low estimated mid-arm fat area (-0.067 , $n = 1420$, $P = 0.012$), low estimated mid arm muscle area ($R = -0.068$, $n = 1420$, $P = 0.011$) and low placenta weight ($R = -0.067$, $n = 1300$, $P = 0.016$). Equally, increased smoking is correlated with decreased maternal age ($R = -0.225$, $n = 1650$, $P = 0.000$) and high socioeconomic status ($R = -0.331$, $n = 1650$, $P = 0.000$).

Table 5.26 Results of partial correlations (controlling for maternal age) between maternal variables and neonatal SD scores for body length, head circumference, encephalisation indices and the change in those indices between ultrasound 3 and birth

neonatal variable	bl(0) n = 875-977	hc(0) n = 875-977	EI(0) n = 875-977	Δ bl(sc3-0) n = 875-977	Δ hc(sc3-0) n = 875-977	Δ EI(sc3-0) n = 875-977
R:						
Maternal variable						
<i>Demographic indices:</i>						
parity	0.08‡	0.07‡	0.03	0.06‡	0.10†	0.06
marital status						
socio-economic status	0.03	0.04	0.03	-0.03	-0.07‡	-0.06
<i>Lifestyle indices:</i>						
alcohol	-0.01	-0.03	-0.02	-0.01	-0.09†	-0.08‡
cigarettes smoked	-0.09†	-0.08‡	-0.04	0.01	0.01	0.01
<i>Placental indices:</i>						
weight at delivery	0.40*	0.37*	0.20*	0.16*	0.13*	0.02
notches at delivery	-0.03	-0.08‡	-0.07‡	0.02	0.00	-0.01

Descriptive statistics listed include R (correlation coefficient), n = sample size

0 = birth, sc3 = ultrasound 3, bl = femur length SD score, hc = head circumference SD score, EI = encephalisation SD score, Δ change in SD score between measurement periods

* = $P \leq 0.0001$, # = $P \leq 0.001$, † = $P \leq 0.01$, ‡ = $P \leq 0.05$ probability based on a two-tailed test of significance with a confidence limit of 95% is used.

When controlling for the covariance between maternal age and parity, these correlations remain fairly constant. Increased parity (independent of maternal age) is associated with large, heavy and fatter neonates, but not necessarily more encephalised neonates. Table 5.27 lists the results of bivariate correlations between maternal parity and these offspring variable.

Thus, neonatal size and nutritional status is largely associated with maternal size, and to a lesser degree, parity and socio-economic status. Maternal nutritional status, on the other the other hand, is statistically significantly associated with offspring encephalisation and growth.

Table 5.27 Results of bivariate correlations between maternal parity and offspring variable SD scores and partial correlations between those variables (controlling for maternal age)

neonatal variable SD score	n	R ₁	r ²
weight	1264	0.14*	0.12*
body length	1234	0.09†	0.07‡
head circumference	1240	0.07‡	0.04
encephalisation	1233	0.32	0.01
subscapular skinfold	1150	0.16*	0.14*
triceps skinfold	1151	0.12*	0.10*
mid-arm muscle area	1151	0.07‡	0.06

n = sample size, R₁ = correlation coefficient for bivariate correlation, r² = correlation coefficient for partial correlation

* = P≤0.0001, # = P≤0.001, † = P≤0.01, ‡ = P≤0.05 probability with a confidence limit of 95%

A multiple regression was carried out in order to determine the relative contributions of placenta weight, maternal height SD and maternal estimated mid-arm fat area and muscle area SD scores in explaining the variation in neonatal encephalisation SD score. Placenta weight and maternal triceps skinfold thickness SD scores were found to contribute significantly to the model. This appears to support the previous finding that maternal nutritional status (triceps skinfold thickness) is associated with offspring encephalisation, rather than her size, and that placenta weight influences offspring encephalisation (see Table 28).

Table 5.28 Results of multiple regression where maternal variables explain the variation in neonatal encephalisation SD score

Independent variable	coefficient	SE	P	r² (%)
constant	-0.968	0.152	0.000	6.3
placenta weight (kg)	1.490	0.222	0.000	
maternal height SD	0.026	0.030	0.383	
maternal subscapular skinfold SD	-0.070	0.041	0.089	
maternal triceps skinfold SD	0.108	0.043	0.013	
maternal mid-arm muscle area SD	0.058	0.042	0.160	

r² = regression coefficient, SE = standard error, P = probability based on a confidence limit of 95%

maternal variables (excluding placenta weight) are SD scores
variables in bold contributed significantly to the model

5.10) Tertiles

Table 5.28 lists the tertiles as they relate to maternal height SD scores. Tables 5.29 to 5.33 lists the tertiles as they relate to the maternal nutritional status variables and Table 5.34 lists the tertiles as they relate to maternal subscapular : triceps skinfold SD score ratio.

All the tertile tables show that neonatal head circumference SD scores increase with neonatal body length SD scores. This is expected since large neonates tend to have large heads. However, maternal variables also have an influence on neonatal head circumference SD scores.

Table 5.29 shows that increasing mothers' height SD score, whether their offspring are short, medium or long, is associated with increasing neonatal head circumference SD scores. Table 5.30 shows that increasing maternal BMI SD scores are associated with increasing neonatal head circumference SD scores in short, medium and long neonates. Similarly, increasing maternal mid-arm muscle area SD scores are also associated with increasing neonatal head circumference SD scores, regardless of neonatal body length SD (Table 5.31). Table 5.32 shows that in medium and long neonates, maternal subscapular skinfold thickness SD scores increase as neonatal head circumference SD scores increase. Maternal triceps skinfold thickness SD scores also increase as neonatal head circumference SD scores increase, in neonates of all body length SD scores (Table 5.33). In contrast, Table 5.34 shows that maternal skinfold ratio does not increase as neonatal head circumference SD scores increase.

Although these tertiles are descriptive and do not illustrate causal relationships between these variables, they do indicate trends between maternal size and nutrition and offspring head circumference SD scores, regardless of offspring body length SD scores. As shown in the multiple regression (see Table 5.15), maternal size and nutritional status explain a significant amount of the variation in offspring encephalisation SD scores at ultrasound 3 and at 6 months.

Table 5.29 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles for (1) neonatal body length (y-axis) and (2) maternal height SD scores (x-axis)

body length SD score at birth	3	+0.25 (0.97)	+0.63 (0.92)	+0.73 (0.92)
	2	-0.18 (0.81)	+0.04 (0.86)	+0.08 (0.81)
	1	-0.66 (0.95)	-0.58 (0.96)	-0.24 (0.81)
		1	2	3
		maternal height SD score	at booking	

Table 5.30 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles for (1) neonatal body length (y-axis) and (2) maternal BMI SD scores (x-axis)

body length SD score at birth	3	+0.34 (1.02)	+0.51 (0.96)	+0.69 (0.92)
	2	-0.07 (0.89)	-0.12 (0.76)	+0.11 (0.78)
	1	-0.64 (0.91)	-0.46 (0.96)	-0.47 (0.90)
		1	2	3
		maternal BMI SD score	at booking	

Table 5.31 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles and (1) neonatal body length (y-axis) and (2) maternal mid-arm muscle area SD scores (x-axis)

body length	3	+0.46 (1.00)	+0.42 (0.96)	+0.73 (0.92)
	2	-0.13 (0.83)	-0.09 (0.74)	+0.15 (0.83)
	1	-0.70 (0.87)	-0.42 (0.95)	-0.44 (0.93)
		1	2	3
		maternal mid-arm muscle area	SD score at booking	

Table 5.32 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles for (1) neonatal body length (y-axis) and (2) maternal subscapular skinfold thickness SD scores (x-axis)

body length	3	+0.42 (0.98)	+0.29 (0.87)	+0.87 (0.94)
	2	-0.12 (0.90)	-0.12 (0.82)	+0.06 (0.82)
	1	-0.57 (0.83)	-0.56 (0.93)	-0.49 (0.97)
		1	2	3
		maternal subscapular skinfold	SD score at booking	

Table 5.33 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles for (1) Neonatal body length (y-axis) and (2) maternal triceps skinfold thickness SD scores (x-axis)

body length	3	+0.28 (0.87)	+0.47 (1.03)	+0.82 (0.93)
	2	-0.11 (0.83)	-0.03 (0.78)	+0.08 (0.88)
	1	-0.61 (0.88)	-0.53 (0.93)	-0.40 (0.91)
SD score at birth		1	2	3
		maternal triceps skinfold	SD score at booking	

Table 5.34 Mean and standard deviation (in parentheses) for neonatal head circumference SD scores according to tertiles for (1) neonatal body length (y-axis) and (2) maternal skinfold ratio (x-axis)

body length	3	+0.40 (0.87)	+0.61 (1.06)	+0.63 (0.92)
	2	-0.09 (0.89)	-0.01 (0.80)	-0.01 (0.80)
	1	-0.45 (0.89)	-0.60 (0.94)	-0.49 (0.92)
SD score at birth		1	2	3
		maternal skinfold SD score	ratio at booking	

maternal skinfold ratio is the ratio between subscapular skinfold and triceps skinfold SD scores

5.11) Relationship between maternal variables and offspring head circumference and body length

Having established that maternal body components associate separately with offspring components (i.e. size, growth, fat and muscle), it is informative to determine whether maternal body components also relate separately to offspring components of encephalisation (i.e. head circumference and body length SD scores).

Following on to the multiple regressions listed in Tables 5.15 and 5.16, Table 5.35 lists the results of multiple regression analyses where neonatal body length SD scores and maternal variables explain the variation in neonatal head circumference SD score. In addition to including neonatal body length and the maternal variable SD scores in the model as independent variables, an interaction variable between neonatal body length and the maternal variable SD scores was included in order to determine whether the two independent variables are functionally related (see chapter 4, section 4.3 for details on the interaction variable).

While the results of Tables 5.15 and 5.16 showed that maternal variables explain a significant proportion of the variation in offspring encephalisation, the results in Table 5.35 show that neonatal body length and maternal variable SD score influences are largely separate from each other in explaining the variation in neonatal head circumference SD.

The interaction variables (between the maternal SD score and offspring body length SD score) did not contribute significantly to the model, while both neonatal body length SD and maternal height, triceps skinfold thickness and mid-arm muscle area SD scores did. Placenta weight also contributed significantly to the model. Neonatal body length SD and maternal variables explained between 23 to 29% of the variation in neonatal head circumference SD scores. The maternal subscapular skinfold thickness SD score did not contribute significantly to the model in explaining the variation in neonatal head circumference SD.

Table 5.35, thus, shows that maternal factors are significantly associated with offspring head circumference SD scores, even after taking into account the impact of body length on head circumference SD scores. However, it must be noted that neonatal body length SD scores explain 22.3 of the variation in neonatal head circumference SD scores when entered alone into a regression model. This suggests that adding the additional maternal variables (height, triceps skinfold thickness and mid-arm muscle area SD scores) improves the model by <1%. Adding placenta weight to the model, on the other hand, improves it by almost 7%. Of the maternal factors, placenta weight, therefore, appears to contribute most to explaining the variation in neonatal head circumference SD scores.

Table 5.35 Results of linear multiple regression analyses describing the relationship between neonatal body length SD score and maternal nutritional status variable SD scores and placenta weight (independent variables) and neonatal head circumference SD score (dependent variable)

independent variable	coefficient	SE	P	r² (%)
constant	0.006	0.026	0.824	22.6
neonatal body length SD	0.458	0.026	0.000	
maternal height SD	0.053	0.026	0.043	
interaction variable	-0.011	0.025	0.651	
constant	-0.006	0.025	0.814	22.6
neonatal body length SD	0.463	0.025	0.000	
maternal subscapular skinfold SD	0.034	0.026	0.182	
interaction variable	0.042	0.024	0.086	
constant	-0.006	0.025	0.813	23.2
neonatal body length SD	0.456	0.026	0.000	
maternal triceps skinfold SD	0.093	0.026	<0.001	
interaction variable	0.019	0.026	0.461	
constant	-0.004	0.025	0.874	23.0
neonatal body length SD	0.463	0.025	0.000	
maternal mid-arm muscle area SD	0.083	0.026	0.001	
interaction variable	0.008	0.025	0.743	
constant	-1.040	0.140	0.000	28.8
neonatal body length SD	0.420	0.118	<0.001	
placenta weight (kg)	1.600	0.207	0.000	
interaction variable	-0.006	0.176	0.972	

r² = regression coefficient, SE = standard error, P = probability based on confidence limit of 95%

5.12) Combined influences of maternal and neonatal variables on neonatal encephalisation

In chapter 4, it was shown that reduced body length growth and increased nutritional status in the neonate was associated with increased encephalisation. In this chapter maternal placental weight and nutritional status were also associated with neonatal encephalisation. A multiple regression was undertaken where both maternal and neonatal indices of size and nutritional status, along with placenta weight were entered as independent variables, while neonatal head circumference SD scores were entered as the dependent variable. This was undertaken in order to determine whether both maternal and neonatal variables explain a significant amount of the variation in neonatal head circumference, when entered into the same model.

The results are listed in Table 5.36 and show that both neonatal body length and placenta weight contribute significantly to the multiple regression model. For every 100 gram increase in placenta weight, head circumference increases by 0.1 SD and for every 1 SD increase in body length, head circumference increases by 0.4 SD. In addition, neonatal estimated mid-arm muscle area SD scores and maternal triceps skinfold thickness SD scores explain a significant amount of the variation in the dependent variable. For every 1 SD increase in maternal triceps skinfold thickness, neonatal head circumference increases by just below 0.1 SD and for every 1 SD increase in maternal estimated mid-arm muscle area, neonatal head circumference increases by 0.03 SD.

This suggests that body size alone does not explain the variation in head circumference SD, but lean tissue (in the neonate) and central fat stores (in the mother) and placenta weight also contribute to the model, together explaining over 35% of the variation in neonatal head circumference SD scores.

Table 5.36 Results of multiple regression describing the relationship between placenta weight, maternal and neonatal SD scores reflecting size and nutritional status (independent variables) and neonatal head circumference SD scores (dependent variable)

variable	coefficient	SE	P
neonatal body length SD	0.351	0.030	0.000
neonatal subscapular SD	0.000	0.038	0.980
neonatal triceps SD	0.048	0.037	0.196
neonatal mid-arm muscle area SD	0.236	0.031	0.000
placenta weight	0.901	0.207	0.000
maternal height SD	0.041	0.026	0.120
maternal subscapular skinfold SD	-0.045	0.036	0.206
maternal triceps SD	0.086	0.037	0.020
maternal mid-arm muscle area SD	0.025	0.036	0.492

regression coefficient $r^2 = 0.351$, $df = 9,1016$, constant = -0.578

SE = standard error, P = probability based on a confidence limit of 95%

In addition to the multiple regression, a principal components analysis was undertaken in order to determine which neonatal and maternal variables load on the same factor as neonatal encephalisation SD scores. The results are listed in Table 5.37 and show that 5 factors are derived. Factor 1 includes maternal indices of nutritional status. Factor 2 includes neonatal indices of lean tissue deposition, encephalisation and placenta weight at delivery. Factor 3 includes neonatal indices of fatness. Factor 4 includes maternal height and factor 5 includes the number of placental notches.

There, thus, appears to be a separate effect of maternal size, maternal nutritional status and placenta weight, with neonatal size and encephalisation outcomes largely associated with placenta weight.

The close association of neonatal nutritional variable SD scores and neonatal encephalisation SD scores may reflect the fact that well-nourished mothers produce neonates who are not only encephalised, but also generally well-nourished. This suggests that where maternal energy is abundant, mothers invest the energy in both the brain and the rest of the body. The relationship between brain size and the other metabolically expensive organs is assessed in chapter 6.

Table 5.37 Results of the principal components analysis

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Maternal mid-arm circumference SD	.94772	.06820	.05562	.06566	.03927
Maternal mid-arm fat area SD	.93948	.07917	.07767	-.00316	-.00284
Maternal mid-arm muscle area SD	.91905	.06586	.04905	.07779	-.04544
Maternal BMI SD	.88330	.08288	.01690	-.12271	-.06148
Maternal weight SD	.83504	.12353	.02312	.39280	-.06088
Maternal triceps skinfold SD	.82833	.07876	.07783	-.04686	.01939
Maternal sub-scapular skinfold SD	.75634	-.02993	.13293	-.16120	.07436
Neonatal mid-arm muscle area SD	.05224	.81118	.28514	.08379	.16575
Neonatal mid-arm circumference SD	.06980	.77069	.47532	.06909	.13506
Birth weight SD	.11532	.73170	.43259	.23106	-.03287
Neonatal Benn index SD	.06155	.69821	.11324	-.05623	-.06409
Neonatal encephalisation SD	.07968	.63780	-.12710	-.1038	-.21615
Placenta weight	.02911	.54203	.24689	.29130	-.07051
Neonatal triceps skinfold SD	.08996	.14540	.91602	-.01438	-.06131
Neonatal sub-scapular skinfold SD	.11594	.21438	.82875	.02066	-.03714
Neonatal mid-arm fat area SD	.09168	.50482	.82634	.02737	.03433
Maternal height SD	-.02422	.09017	.00659	.95114	-.00825
Placental notches	-.03785	-.07463	-.06459	-.02497	.94555

Includes a varimax rotation

5.13) Discussion

The analyses in this chapter suggest that maternal influences on offspring size, nutritional status, growth and encephalisation are evident but small. The results also suggest that different aspects of maternal body composition influence different aspects of offspring body composition. For example, maternal size (height) appears to be largely associated with neonatal size. This relationship is well-established and was first shown by Cawley et al. (1954). Maternal placenta weight and nutritional status appears to be associated with offspring encephalisation and growth (independent of offspring size), however placental weight explains a greater proportion of the variation in offspring encephalisation than do maternal measures of nutritional status.

The relationship between maternal nutritional status and offspring encephalisation is less clear during the fetal period when maternal size (height) was correlated with fetal size and encephalisation but maternal nutritional status was correlated with fetal femur length (SD scores) alone. Unlike maternal height SD scores, maternal nutritional status SD scores explained a very small proportion of the variation in offspring outcomes. It is possible that this low level of significance may have occurred by chance. However, it should be noted that maternal nutritional indices in the second and third trimesters were not available as mothers were measured only once, at booking. Therefore, changes in maternal nutritional status and fetal encephalisation could not be assessed here.

It is possible that maternal nutritional status in the second and third trimesters may relate to fetal indices. Barker (1998), for example, has argued that women tend to store fat during the first half of pregnancy in order to support later fetal fat deposition in the second half of pregnancy. Langley-Evans and Langley-Evans (in press) have also shown that diet in the first and third trimesters of pregnancy influences neonatal ponderal index, head circumference and birth weight, while Strauss and Dietz (1999) have demonstrated that inadequate weight gain during pregnancy is associated with fetal growth retardation. However, the results of some studies contradict these findings. For example, Bhargava (2000), has shown that maternal weight gain during pregnancy has little effect on neonatal birth weight, body length and head

circumference, while maternal pre-pregnancy BMI does. Wells et al. (in press) have also shown that maternal nutritional status at conception is a better predictor of offspring size and body composition at birth than is weight gain during pregnancy.

In addition, it was shown in this chapter that both smoking and alcohol use during pregnancy have an adverse effect on encephalisation and change in encephalisation, respectively. Langley-Evans and Langley-Evans (in press) have shown that alcohol use in the third trimester of pregnancy is associated with reduced placenta weight relative to fetal size. Since it was shown here that placenta weight is correlated with encephalisation, it seems probable that placental insufficiency caused by alcohol use explains decreased encephalisation change in late pregnancy.

Although maternal measures were taken only once, at booking, and changes in nutritional status during pregnancy could not be assessed, studies have tended to show that pre-conceptual nutritional status is more important for offspring birth weight than change in nutritional status during pregnancy, and by inference, energy intake during pregnancy (Wells et al. 2002). It should be noted, however, that maternal weight gain in the first trimester of pregnancy influences newborn birth weight to a greater degree than does weight gain in the second and third trimesters (Wells et al. in press). Due to the unavailability of weight gain data in the study sample, the impact of early pregnancy weight gain on offspring variables could not be assessed. It is possible that the relationship between nutritional status measures in later pregnancy, had they been available, and offspring variables would have differed. Unfortunately this could not be assessed here.

In this study sample, maternal height and neonatal body length were correlated. Whether or not a neonate was encephalised appears to depend, in part, on whether its mother was well-nourished or not (i.e. had above average skinfolds and muscle area SD scores) and had a large or small placenta at delivery. Thus, short but well-nourished women may have produced small but encephalised neonates. Equally tall but undernourished women may have produced medium-large sized neonates but they

were unlikely to be encephalised. Relatively small placenta weight, however, was associated with decreased encephalisation.

In a malnourished population it might have been assumed that energy deficits would restrict brain growth and that, as a result, neonates would be less encephalised than those in the London sample. However, as discussed in the beginning of this chapter, a number of physiological adaptations take place during pregnancy which serve as energy sparing mechanisms. These were shown to exist in a nutritionally stressed Gambian population, for example, where basal metabolism and energy expenditure were reduced (see Poppitt et al. 1993). In addition, brain sparing, discussed in chapter 2, also serves to conserve brain metabolism during periods of nutritional stress.

Thame et al. (1997), in a study of maternal nutrition and birth outcome in Jamaica, showed that nutritionally stressed women produced offspring who were shorter, thinner and had smaller absolute head circumferences than those of well-nourished mothers. However, the head circumference to body length ratio was greater in nutritionally stressed neonates. These findings suggest that increased encephalisation in nutritionally stressed neonates is likely the result of body length growth restriction accompanied by brain sparing.

SECTION IV: Martin's 'Maternal Energy Hypothesis'

The results in this chapter suggest that maternal condition has an impact on offspring encephalisation. In this thesis, nutritional status was assessed using skinfold thickness measures and BMI, controlling for the effects of gestation age on these parameters. Martin (1983) hypothesised that there is a link between maternal basal metabolism and offspring brain size. His hypothesis is examined and critiqued here in light of research on basal metabolism in humans and other vertebrates. In addition, the assumptions underlying the Maternal Energy Hypothesis are evaluated.

5.14) Maternal Energy Hypothesis

Martin (1983, 1996), building on the work of Kestner (1936), Kleiber (1947) and Brody (1945), hypothesised that maternal metabolic turnover determines offspring brain size. He termed this the 'Maternal energy hypothesis' and argued that, "it is the mother's metabolic turnover which, both in direct terms (through the physiology of gestation) and in indirect terms (through the partitioning of resources between maintenance and reproduction), determines the size of the neonate's brain and hence the ultimate size of the adult brain." (Martin 1983: p.14). Martin based his hypothesis on the following findings:

1. "Kleiber's Law" - basal metabolic rate (kcal/day) in mammals and other vertebrates scales to body size with an exponent value approximately 0.75.
2. Brain weight scales to body weight in placental mammals with an exponent value approximately 0.75 (Martin 1981).
3. There is a close relationship between neonatal brain size and gestation period in placental mammals (Sacher and Staffeldt 1974). Indeed, this relationship is stronger than that between gestation period and overall neonatal body size.
4. Neonatal brain size scales isometrically with adult brain size in primates.

Martin interpreted point 3 as, "clear evidence of a particularly intimate connection between gestational processes (including the mother's metabolic capacity) and fetal brain growth." (Martin 1983: p.20). He further argued that the consistency between points 1 and 2 reflects an underlying functional relationship rather than coincidence and that point 4 explains how this functional relationship determines ultimate brain size in the adult primate.

5.15) Problems with assumptions of the hypothesis

5.15a) Maternal BMR

There are a number of problems with these underlying assumptions. For example, the assumption that BMR during pregnancy is constant. Basal metabolic rate (BMR) is loosely defined as, “the respiratory rate of a resting animal, normally measured by oxygen demand. The ‘background’ respiration rate, as required for unavoidable muscle contractions (e.g. heart), growth, temperature maintenance, etc.” (Thain and Hickman 1995) or, “the stable rate of energy metabolism measured in mammals and birds under conditions of minimal environmental and physiological stress, after fasting has temporarily halted digestion and absorptive processes” (Eckert and Randall 1983).

Basal metabolic rate is not a fixed entity but is variable and influenced by several factors, including: undernutrition (Grande et al. 1958), ovulatory status (Solomon *et al.* 1982; Snell *et al.* 1920; Wakeham 1923), growth (Talbot 1938), age, organ mass relative to body mass, organ growth rate (Holliday 1971, 1986; Elia 1992), fat stores (Dulloo and Jacquet 1998, Garby and Lammert 1992), altitude (Lewis et al. 1943, Gill and Pugh 1964, Hannon and Sudman 1973), temperature and season (Gustafson and Benedict 1928, Mason 1934, Thompson et al 1959, Mason and Jacob 1964, Park et al. 1969) disease state (Bose and De, 1934, Elia 1992), and pregnancy and lactation (Khan and Belavady 1973, van Raaij et al. 1989, Heini et al. 1992, Goldberg et al. 1991). BMR changes during pregnancy as body composition changes and as efficiency in energy use increases. This is particularly evident in pregnant women who are nutritionally stressed during pregnancy where BMR actually decreases with gestation (Prentice et al. 1989, Poppitt et al. 1993).

5.15b) BMR and brain and body weight

There is also a problem with assuming that brain weight, body weight and basal metabolic rate are functionally associated. In mammals, brain size is not the only parameter which scales to body size with an exponent value of about 0.75. For

example, the number of adipocytes in the body scale to body mass to an exponent value of 0.74 in predominantly carnivorous species, and 0.78 in predominantly herbivorous nonruminant mammals (Pond and Mattacks 1985). In addition, data from Wedgewood et al. (1953) show that the volume of plasma in the human male body scales to body weight at an exponent value of 0.70. Interstitial fluid scales to an exponent value of 0.72 and extracellular fluid scales to the exponent value of 0.71. Blueweiss et al. (1978) show that the growth rate between independence and maturity scales to body weight with an exponent value of 0.75. Read and Harvey (1989) also show that the same exponent (i.e. $\text{weight}^{0.75}$) is found for total biomass of offspring produced per year. The similarity in slope between these relationships and body size and that of the brain and body size does not necessarily imply a direct functional relationship as indeed, there is no evidence to suggest one between brain size and number of adipocytes, plasma volume, interstitial fluid volume and extracellular fluid volumes in the body.

Indeed, the lack of a functional relationship between BMR and brain size is highlighted by MacNab and Eisenberg (1989) who compiled data on basal metabolic rate and brain size in mammals. However, it must be noted that brain and BMR values in their study were derived from different specimens. Regardless, the authors showed that relative brain size in mammals is independent of BMR, where the habitat of the mammal influences relative brain size, while factors influencing basal metabolic rate include surface-to-volume ratio, body mass and the temperature of the environment in which the mammal lives. The authors did suggest, however, that brain size and BMR scale in a similar manner with respect to body mass, although no functional relationship is evident.

Others authors have also shown that BMR and brain weight are not functionally related. Hafner and Hafner (1984) showed that in rodents (Geomyoidea) adult metabolic capacity and maternal metabolism do not correlate with brain weight or body weight relationships. Nor does egg metabolism in birds scale to the 0.75 power of hatchling brain weight. Furthermore, hatchling brain weight and maternal brain size do not scale isometrically (Bennet and Harvey 1985), suggesting that Martin's assumptions cannot apply to birds and rodents.

There are, moreover, a number of general problems with studies relating BMR to body mass. Most comparative studies of basal metabolic rate [including that of MacNab and Eisenberg (1989)], express BMR as a function of body mass rather than lean body mass. This is true of Brody and Kestner's work as well as Kleiber's (1947) comparative vertebrate study showing that BMR scales to body mass in mammals to the exponent value of 0.75 ('Kleiber's Law'). However, body mass is not an appropriate parameter against which to compare mass-specific basal metabolic rates across species.

Animals of comparable body mass may have markedly different body compositions with markedly different amounts of metabolically active tissue. Water and the extracellular phase,¹⁰ unlike the metabolically active tissues, are essentially metabolically inactive and do not contribute directly to basal metabolic rate, while fat contributes less to BMR than does lean tissue. Fat-free mass, defined as body weight minus body fat, on the other hand, is highly metabolically active, having a metabolic rate in humans of about 1.35 watts/kg (Garby et al. 1988). Fat mass, on the other hand, has a significantly lower metabolic rate of 0.31 watts/kg (Garby et al. 1988). However, body fat, water and extracellular fluids do not contribute significantly to BMR, they do contribute significantly to body mass. This has an important bearing on studies which relate basal metabolic rate to body mass (i.e. lean body mass + fat mass + intercellular fluid mass). It is apparent that lean body mass is the best predictor for basal metabolic rate and is closely tied to body composition (Grande and Keys 1980, Cunningham, 1982, Ravussin and Bogardus 1986, Ravussin et al. 1986, Owen et al. 1987, Garby et al. 1988, Lawrence et al. 1988, Weinsier et al. 1992, Dulloo and Jacquet 1998).

¹⁰ The extracellular phase is comprised of: plasma, interstitial fluid, connective tissue fluid, gastrointestinal fluid, cerebrospinal fluid, and transcellular fluids. Major nutrients are exchanged between the environment and body system through extracellular fluid. Although metabolically inactive, it is important to take into account when calculating energy requirements as a function of body weight, as it contributes significantly to total body weight (Holliday 1986).

5.15c) Body composition variation in vertebrates

Tables A.1(a-k) in the appendix list body weight and percent of weight comprised of fat in mammals and birds. These data were described previously in chapter 3 and illustrate the marked degree of inter-specific variability in body composition in mammals and birds (refer to Table 3.1). This marked variation in body composition (% body fat and % fat-free tissue) makes the estimation of BMR based on body weight alone, a highly questionable practice.

In addition to the marked variation in fat mass, organ mass, muscle mass, bone density and bone mass vary significantly across species. These components of body composition, likewise, have a significant influence on the size and total cost of the metabolically active component of body mass. Analysis of data collected by Quirling (1950) illustrates that the variation in percent body mass comprised of major organs (brain, heart, kidneys, liver, lungs, spleen) is marked. In a total of 33 vertebrate species, on average 7.69% of body mass is comprised of these organs. However, the smallest value is 3.39% (green-winged teal) and the largest is 22.46% (giraffe). The standard deviation is 4.43, 58% of the mean value. Thus, the general relationship may conceal marked differences between species.

This suggests that body mass is an inappropriate measure against which to assess BMR within the context of the Maternal Energy Hypothesis. Moreover, the mammalian regression equation used to estimate BMR from body mass is problematic.

5.15d) Kleiber and Brody's equations

An additional, and perhaps, more problematic premise with Martin's hypothesis is the unquestioning use of Kleiber or Brody's equations for predicting basal metabolic rates in mammalian species. Although both Kleiber and Brody's comparative studies have largely been accepted as defining interspecific BMR:body size allometry in mammals, there are a number of problems with this assumption. As Hayssen and Lacy (1985)

point out, Kleiber's (1961) dataset is based on a very small and unrepresentative subset of mammals. Nine out of the twelve species represented are in fact animals from domestic populations which have been under artificial energetic constraints (or lack thereof). For example, there is evidence to suggest that food intake and growth rate is elevated in domestic animals (Bronson 1984), while relative brain size is lowered (Kruska 1996). Furthermore, Kleiber rounded off the exponent of his allometric equation to 0.75 so that it could be calculated without logarithms. Likewise, Brody's (1945) "mouse-to-elephant" curve utilized the same species as those used by Kleiber, with the addition of two further domestic species and six non-mammalian species (birds). The elephant was not actually used in the derivation of the equation.

Therefore, the practice of applying Brody's 0.73 exponent as a mammalian standard must be called into question as over 23% of the sample is comprised of non-mammalian species as well as being biased by a preponderance (over 57%) of domestic species. Further complicating matters, in both of these studies, data from individual studies were used in the statistical analysis, rather than data from individual species. For example, Kleiber used the domestic rabbit for six of his twenty-six data points.

Clearly, the choice of slope used will have a significant bearing on predicted and residual basal metabolic rates. For example, using Kleiber's 0.75 exponent as opposed to Brody's 0.73 exponent (a relatively small difference) will result in a 15-26% difference in predicted BMR (depending on mass) (Hayssen and Lacy 1985). When one considers the variation in exponent values that arises from using different datasets and different mammalian species to calculate a predictive equation between BMR and body mass, the problem of predicting a biologically meaningful BMR value becomes amplified.

Indeed, Hayssen and Lacy (1985), using a much larger and more evenly distributed mammalian dataset ($n = 293$), found an interspecific mammalian slope significantly different from that of Kleiber. When describing the least squares allometric relationship between mass-specific BMR and body size, they find a slope of -0.3 as

opposed to Kleiber's slope (for mass-specific BMR and body size) of -0.25. When considering their primate data alone ($n = 10$), the resulting slope is -0.363, significantly different to Kleiber's even when taking sample size differences into account.

Hayssen and Lacy (1985) showed that although there is a general negative trend between body weight and BMR across all mammalian orders, the slopes vary significantly as a function of phylogeny. This is also shown by Blaxter (1989). Here, the slopes derived from Hayssen and Lacy's (1985) analysis are listed for each order separately and the slopes describing the relationship between body weight and brain weight from data compiled by Quirling (1950) are listed. It is clear that there is no relationship between the slopes describing body weight and BMR and body weight and brain weight (see Table 5.38) at this phylogenetic level.

5.16) Discussion

There is no clear evidence to suggest that a functional relationship exists between the slopes describing body mass and BMR and body mass and brain mass as posited by Martin (1981, 1983, 1996). Indeed, at the order rather than class level of analysis, there is no relationship between these parameters. Moreover, the basis for predicting BMR based on body mass alone is flawed. In addition to these methodological issues, the functional relationship between lean body mass and BMR during pregnancy may differ from that during the non-pregnant, non-lactating state, where, as noted, BMR in an energetically stressed woman is likely to decline, when taking changes in body composition into account.

In this thesis, maternal BMR was not assessed directly. However, it was shown that both maternal fat tissue and lean tissue components of the body (i.e. skinfolds and mid-arm muscle and fat areas) were correlated with offspring encephalisation. Since the relationship between fat tissue and fat-free tissue in relation to BMR differ, the results do not point toward a direct relationship between BMR and encephalisation.

There is, therefore, no clear evidence for maternal BMR relating functionally to offspring brain size. However, this issue can be resolved by examining the relationship between maternal BMR during pregnancy and offspring relative brain size directly. There are a number of studies where maternal BMR during different stages of pregnancy was determined (for example, Mason and Jacob 1964, Lawrence et al. 1988, Goldberg et al. 1991, Poppitt et al. 1993, Bronstein et al. 1995). It would be informative to study the relationship between those maternal BMR values and the brain sizes of their offspring at birth. As shown here, head circumference and body length may be used to calculate an encephalisation SD score. Both head circumference and body length are routinely measured at birth, although not necessarily with accuracy.

Table 5.38 Relationship between slopes describing body weight and basal metabolic rate and body weight and brain weight in mammals

Order	n	r ²	Body:BMR slope	n	r ²	Body:Brain slope
Primates (excl. humans)	10	0.44	0.25	10	0.94	0.77
Rodentia	122	0.67	0.33	14	0.94	0.71
Carnivora	18	0.63	0.26	36	0.92	0.67
Artiodactyla	12	0.52	0.20	26	0.84	0.51

slopes describing body weight and basal metabolic rate from Hayssen and Lacy (1985)
slopes describing body weight and brain weight calculated from data in Quirling (1950)

n = sample size, r² = regression coefficient

CHAPTER 6

Relationship of encephalisation to the relative size of other organs

6.1) Aims of chapter

This chapter deals with the relationship between the size of the fetal brain and that of the other organs. As shown in chapter 1, Table 1.3, in addition to the brain, the liver, heart and kidneys also contribute significantly to basal metabolism. Since increased brain size in encephalised fetuses is related to increased metabolic costs associated with maintaining the extra brain tissue, it is important to determine whether the non-brain organs decrease in size in order to offset the extra metabolic costs of encephalisation, or whether they increase in size as the brain increases.

The chapter is divided into 3 main sections. The first section uses published data on organ weights in human and rhesus monkey fetuses to describe organ growth during gestation. In addition, patterns of organ growth relative to body length are described in order to determine whether relative organ size growth differs between the brain and non-brain organs.

6.2) Hypothesis tested in chapter

The ‘Organ Trade-off Hypothesis’ predicts that encephalised fetuses will have relatively reduced non-brain organ weights in one or more non-brain organs.

In section 2 of the chapter, the data used to test this hypotheses and the methods used to quantify relative organ sizes are described. These methods control for the effects of age, body length, sample size differences and distribution skewness in human fetal organ weights.

Section 3 includes the results and assesses their implications for the ‘Organ Trade-off’ hypothesis.

SECTION I: Organ growth

6.3) Patterns of organ growth in humans

Human organ ontogeny is a complex process. The organs grow at different rates and at different times and may undergo growth spurts at different times and of a different magnitude. The organs also undergo changes in chemical composition at different rates and times, adding to this complexity (Holliday 1971, Brasel and Gruen 1986, Elia 1999).

At birth, the brain weighs about 25% of its adult value. The thymus, at birth, is relatively more mature, weighing 65% of its adult value, while the other organs are relatively immature. The ovaries, testes, thyroid, pancreas, liver, heart, lungs and kidneys, all weigh between 3-9% of their adult values (Elia 1999). The contribution of the organs to body weight generally decreases during development, while the contribution of muscle increases with developmental age.

Schultz et al. (1962) published cross-sectional data taken from autopsy materials in the fetus and infant. They provided mean weights and standard deviations from 5 gestation months through to 1 year-of-age, for a total of 1339 specimens, including the brain, thymus, heart, lungs, liver, spleen, pancreas, adrenal glands and kidneys. Here mean organ weight values from Schultz et al. (1962) are used to illustrate patterns of organ growth from 5 gestation months through to one year-of-age as a function both of age (see Figure 6.1) and body size (see Figure 6.2). Regression equations are given following the graphs.

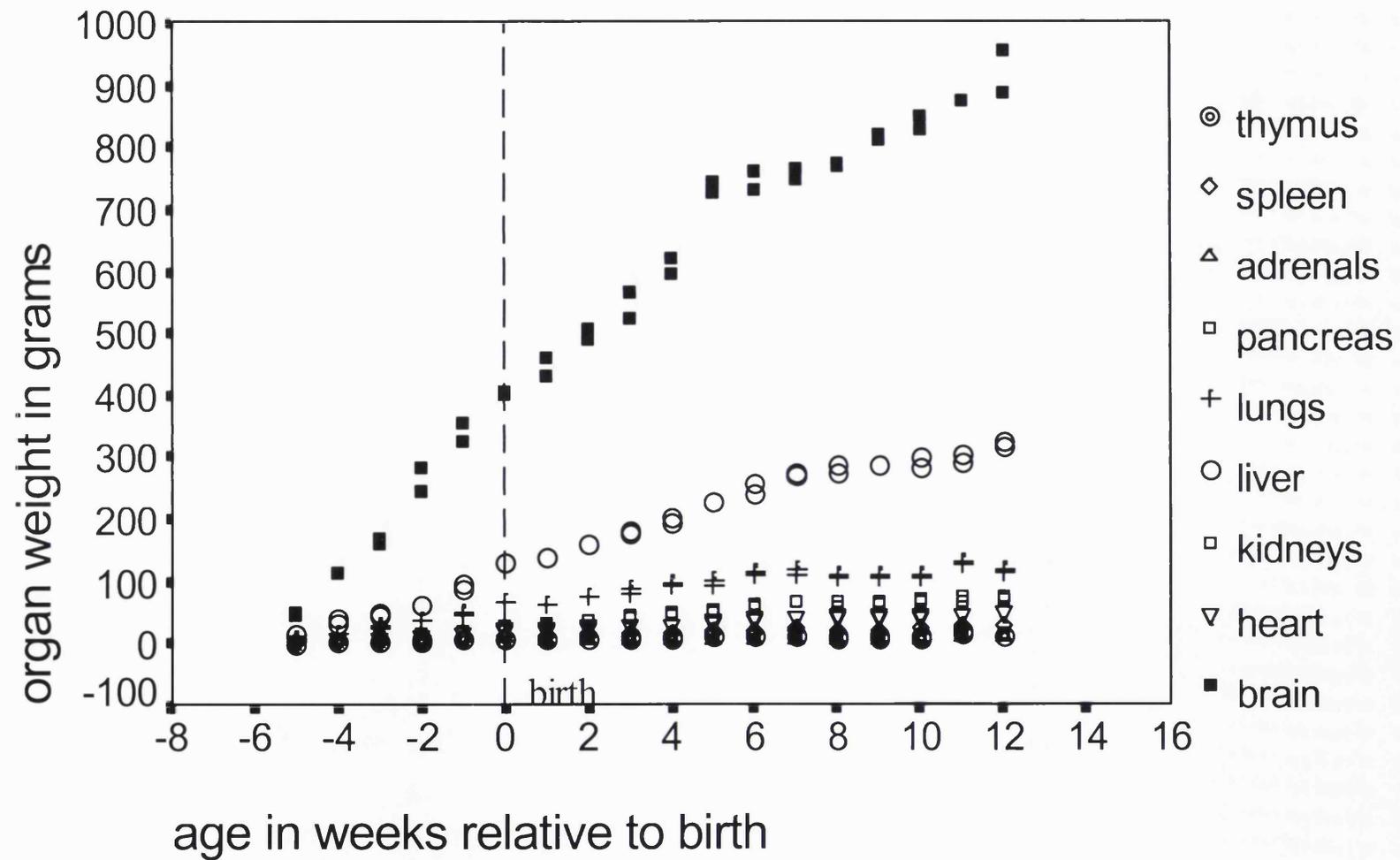


Figure 6.1. Organ weight as a function of age from human fetal and infant autopsy data compiled by (Schultz et al. 1962)

The quadratic regression equation for the organs are as follows, where age is in weeks:

brain:

$$(69) \quad \text{brain weight (grams)} = 396 + 64 * \text{age} - 1.8 * \text{age}^2$$

($r^2 = 0.991$, SE = 51, n = 36, P <0.0001)
age in weeks

heart:

$$(70) \quad \text{heart weight (grams)} = 21 + 3.0 * \text{age} - 0.07 * \text{age}^2$$

($r^2 = 0.987$, SE = 2, n = 36, P <0.0001)
age in weeks

liver:

$$(71) \quad \text{liver weight (grams)} = 124 + 22 * \text{age} - 0.45 * \text{age}^2$$

($r^2 = 0.989$, SE = 15, n = 36, P <0.0001)
age in weeks

lungs:

$$(72) \quad \text{lung weight (grams)} = 61 + 9.4 * \text{age} - 0.39 * \text{age}^2$$

($r^2 = 0.976$, SE = 11, n = 36, P <0.0001)
age in weeks

pancreas:

$$(73) \quad \text{pancreas weight (grams)} = 5.5 + 0.9 * \text{age} - 0.01 * \text{age}^2$$

($r^2 = 0.956$, SE = 1.1, n = 36, P <0.0001)
age in weeks

thymus:

$$(74) \quad \text{thymus weight (grams)} = 7 + 0.8 * \text{age} - 0.03 * \text{age}^2$$

($r^2 = 0.727$, SE = 2.1, n = 36, P <0.0001)
age in weeks

spleen:

$$(75) \quad \text{spleen weight (grams)} = 10 + 1.7 * \text{age} - 0.03 * \text{age}^2$$

($r^2 = 0.968$, SE = 1.7, n = 36, P <0.0001)
age in weeks

adrenals:

$$(76) \quad \text{adrenal weight (grams)} = 4.9 + 0.19 * \text{age} - 0.01 * \text{age}^2$$

($r^2 = 0.376$, SE = 0.9, n = 36, P <0.0001)
age in weeks

kidneys:

$$(77) \quad \text{kidneys (grams)} = 29.6 + 5.12 * \text{age} - 0.11 * \text{age}^2$$

($r^2 = 0.983$, SE = 4.1, n = 36, P <0.0001)
age in weeks

The growth trajectories derived from the Schultz et al. (1962) data and shown in Figure 6.1 illustrate that the brain grows more rapidly than the other organs throughout early development. Growth velocity begins to slow down markedly at about 5 postnatal months when the growth curve begins to asymptote. The liver, although smaller than the brain, tracks brain growth fairly closely, albeit at a slightly slower velocity. This is not surprising given that the liver produces glucose, the brain's substrate (Lehninger 1975). The liver growth curve also asymptotes with inflection occurring at about 6 postnatal months.

Lung weight increases noticeably first at birth in response to the requirements of breathing, while kidney weight increases only at about 5 or 6 postnatal months. This is not surprising given that weaning foods are generally not taken prior to this period and human milk is relatively low in protein and is easily absorbed. The adrenals, pancreas, thymus and spleen change little throughout this period, while the heart tracks lung growth fairly closely. These findings are consistent with those of many other workers as summarised by (Elia 1999).

According to Elia (1999), the reproductive organs also grow slowly throughout early life and approach adult mass rapidly during adolescence. At this stage they grow more rapidly than the body as a whole. The thymus is a particularly interesting organ in terms of its growth. At birth, it is 2/3 of its size during young adulthood. However, the thymus actually decreases in size during adolescence while all of the other organs rapidly increase in size. During later adulthood (20-50 years), thymus size is actually smaller than that of the child and adolescent (Elia 1999). Large thymic size in the infant appears to be a phenotypic response for increased lymphocytes and immunity during early life.

6.4) Patterns of organ growth in rhesus monkeys

Organ weights in fetal rhesus monkeys have also been measured. Kerr et al. (1974) published weights for organs in fetuses and infant. Organ weights for fetal and infant rhesus monkeys up to 1 week-of-age are plotted against age (relative to birth) in Figure 6.2. These data were based on cross-sectional necropsy measures where the sexes were pooled. Sample sizes for the organs at each age varied from 3 to 31 individuals.

The growth trajectories for the rhesus monkey fetus organs (shown in Figure 6.2) are remarkably similar to those of the human (shown in Figure 6.1). Like in humans, the rhesus monkey brain grows far more quickly *in utero* than the other organs. The liver followed by the lungs have the next highest growth rates, while the remaining organs grow at a fairly constant rate. In addition, brain and liver growth begin to slow down prior birth. The equations describing the rhesus monkey organ growth curves are listed below Figure 6.2. Sample sizes are based on mean values reported by Kerr et al. (1974) at given ages. As noted, between 3 to 31 individuals were measured at each age and mean values are based on these individuals.

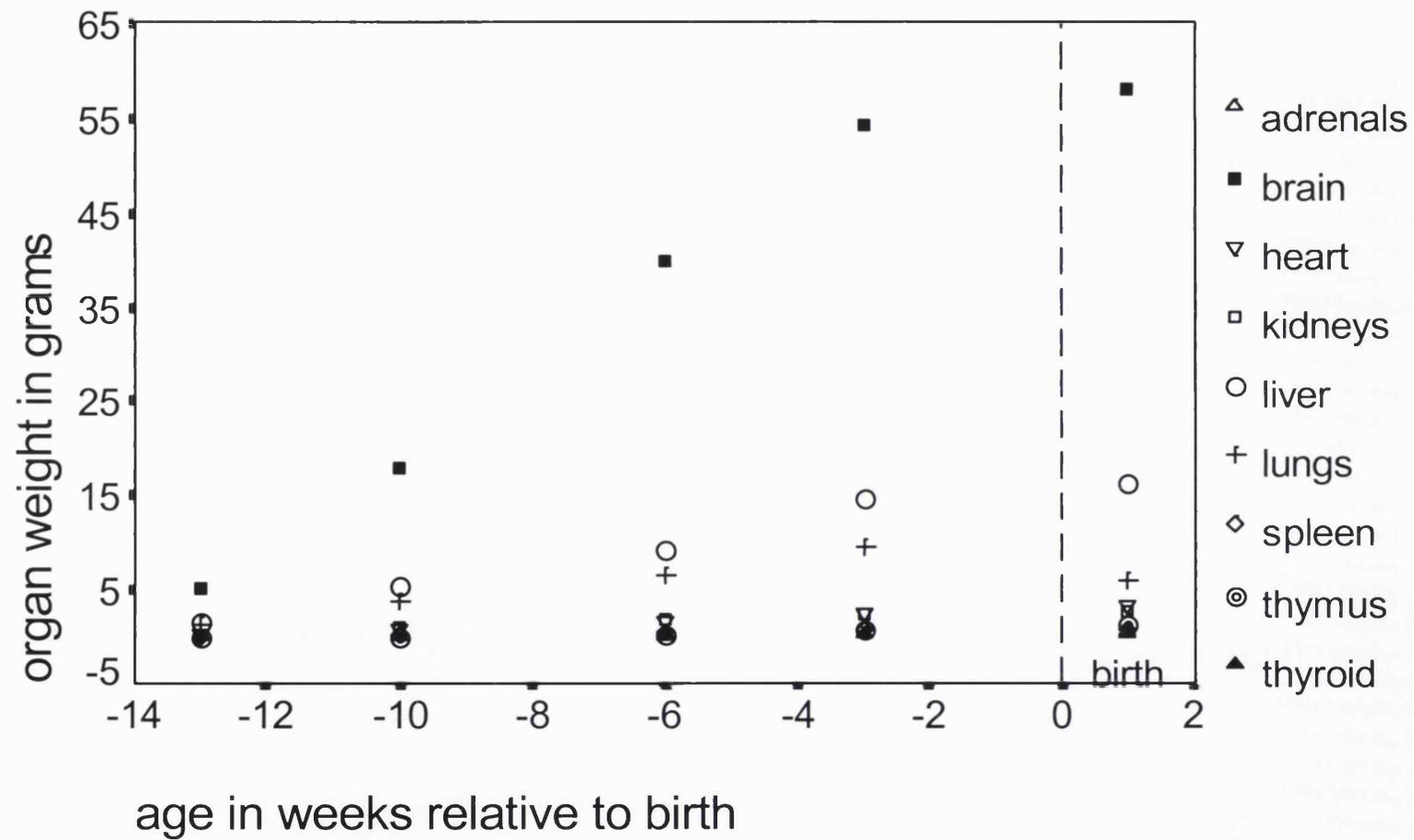


Figure 6.2 Organ weight in rhesus monkeys as a function of age relative to birth from fetal and infant necropsy data compiled by Kerr et al. (1974)

The quadratic regression equation for the organs are as follows, with age in weeks:

brain:

$$(78) \quad \text{brain weight (grams)} = -28.7 + 3.55 * \text{age} + 0.003 * \text{age}^2$$

($r^2 = 0.962$, SE = 5.4, n = 5, P <0.0001)
age in weeks

heart:

$$(79) \quad \text{heart weight (grams)} = -0.38 + 0.003 * \text{age} + 0.01 * \text{age}^2$$

($r^2 = 0.994$, SE = 0.26, n = 35, P <0.0001)
age in weeks

liver:

$$(80) \quad \text{liver weight (grams)} = -5.84 + 0.69 * \text{age} + 0.01 * \text{age}^2$$

($r^2 = 0.979$, SE = 1.13, n = 5, P <0.0001)
age in weeks

lungs:

$$(81) \quad \text{lung weight (grams)} = -9.50 + 1.43 * \text{age} - 0.03 * \text{age}^2$$

($r^2 = 0.846$, SE = 1.95, n = 5, P <0.05)
age in weeks

thymus:

$$(82) \quad \text{thymus weight (grams)} = 0.81 - 0.15 * \text{age} + 0.01 * \text{age}^2$$

($r^2 = 0.998$, SE = 0.2, n = 5, P <0.05)
age in weeks

spleen:

$$(83) \quad \text{spleen weight (grams)} = -0.17 + 0.14 * \text{age} + 0.001 * \text{age}^2$$

($r^2 = 0.989$, SE = 0.6, n = 5, P <0.0001)
age in weeks

adrenals:

$$(84) \quad \text{adrenal weight (grams)} = 0.13 - 0.02 * \text{age} - 0.002 * \text{age}^2$$

($r^2 = 0.949$, SE = 0.08, n = 5, P <0.0001)
age in weeks

kidneys:

$$(85) \quad \text{kidney weight (grams)} = -1.59 + 0.22 * \text{age} - 0.002 * \text{age}^2$$

($r^2 = 0.981$, SE = 0.18, n = 5, P <0.0001)
age in weeks

thyroid:

$$(86) \quad \text{thyroid weight (grams)} = -0.29 + 0.03 * \text{age} - 0.001 * \text{age}^2$$

($r^2 = 0.926$, SE = 0.03, n = 4, P <0.05)
age in weeks

6.5) Relative organ size in human fetuses

In addition to looking at the growth trajectories of the organs, it is informative to compare the relative sizes of the organs. In Figure 6.3, \log_{10} -transformed mean organ weights are plotted against body length and least squares regression equations are given for all organs except the adrenal glands and the thymus. The relationship between these two organs and body length is non-linear and quadratic equations are given for them.

This graph shows that regardless of body size, relative brain weight is consistently greater than that of the other organs, followed by the liver, lungs, kidneys and heart. In addition, with the exception of the adrenal glands, all of the organs' regression lines have very similar slopes (see regression equations following graph), albeit contrasting intercepts. This may indicate that the organs share a fairly consistent allometric relationship with the body.

6.6) Sex differences in human fetal organ weights

There are sex differences in the weights of organs during early life. Males tend to have larger brains and hearts than females. The weights of the kidneys are similar in males and females up to about 1 postnatal month. However, thereafter, they are larger in males (Schultz et al. 1962). These size differences are, however, largely a function of body size sexual dimorphism, with males being larger than females. Upon examination of the least squares residuals calculated from the data in Figure 6.1, no statistically significant differences were found between males and females in terms of their relative organ sizes when performing an independent samples t-test.

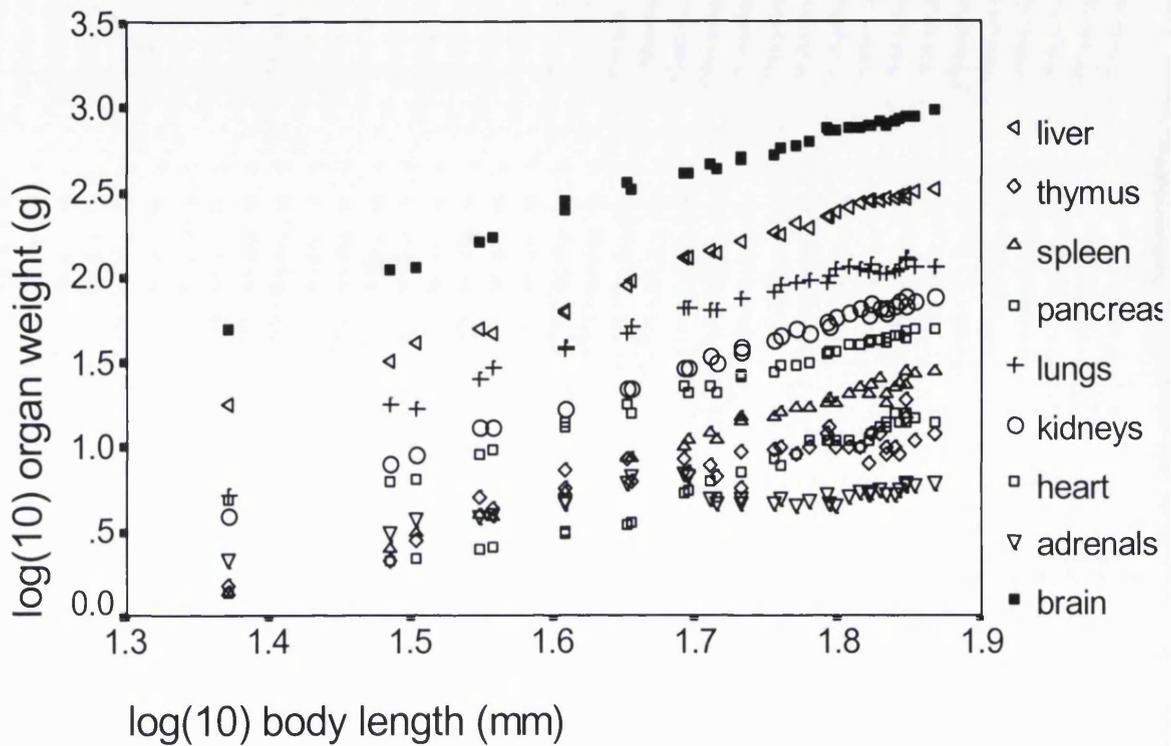


Figure 6.3 Scatterplot of \log_{10} -transformed mean organ weights plotted against body length. Data from Schultz et al (1962).

Least squares linear regression equations are:

brain:

$$(87) \quad \log_{10} \text{ brain weight (g)} = -1.6 + 2.5 * \log_{10} \text{ body length (mm)}$$

$$(r^2 = 0.988, SE = 0.03, n = 36, P < 0.0001)$$

liver:

$$(88) \quad \log_{10} \text{ liver weight (g)} = -2.5 + 2.7 * \log_{10} \text{ body length (mm)}$$

$$(r^2 = 0.994, SE = 0.03, n = 36, P < 0.0001)$$

heart:

$$(89) \quad \log_{10} \text{ heart weight (g)} = -2.5 + 2.3 * \log_{10} \text{ body length (mm)}$$

$$(r^2 = 0.988, SE = 0.03, n = 36, P < 0.0001)$$

kidneys:

$$(90) \quad \log_{10} \text{ kidney weight (g)} = -3.0 + 2.6 * \log_{10} \text{ body length (mm)}$$

$$(r^2 = 0.995, SE = 0.02, n = 36, P < 0.0001)$$

lungs:

$$(91) \quad \log_{10} \text{ lung weight (g)} = -2.4 + 2.5 * \log_{10} \text{ body length (mm)}$$

$$(r^2 = 0.960, SE = 0.06, n = 36, P < 0.0001)$$

pancreas:

$$(92) \quad \log_{10} \text{pancreas weight (g)} = -3.3 + 2.4 * \log_{10} \text{body length (mm)} \\ (r^2 = 0.963, SE = 0.06, n = 36, P < 0.0001)$$

spleen:

$$(93) \quad \log_{10} \text{spleen weight (g)} = -3.5 + 2.7 * \log_{10} \text{body length (mm)} \\ (r^2 = 0.985, SE = 0.04, n = 36, P < 0.0001)$$

Non-linear regression equations are:

thymus:

$$(94) \quad \log_{10} \text{thymus weight (g)} = -8.81 + 9.92 * \log_{10} \text{body length (mm)} - 2.48 * \\ \log_{10} \text{body length (mm)}^2 \\ (r^2 = 0.866, SE = 0.09, n = 36, P < 0.0001)$$

adrenals:

$$(95) \quad \log_{10} \text{adrenal weight (g)} = -6.68 + 8.34 * \log_{10} \text{body length (mm)} - 2.34 * \\ \log_{10} \text{body length (mm)}^2 \\ (r^2 = 0.670, SE = 0.07, n = 36, P < 0.0001)$$

6.7) Relative organ size in rhesus monkey fetuses

Unfortunately, body length measures were not taken in the rhesus monkey necropsy study by Kerr et al. (1974). Body weight was, however, measured. Weight, particularly in autopsy materials, is less reliable than body length as an index of body size, as discussed previously in chapter 4, section 4.4. However, because this is the only available data, albeit problematic, it is used here to provide a comparison between humans and a non-human primate species with regard to the relationships between organ size and body size. Figure 6.4 is a scatterplot of rhesus monkeys organ weights plotted against body size. These graphs show that, as in humans, the slopes describing the relationship between organ weights and body weight are remarkably similar.

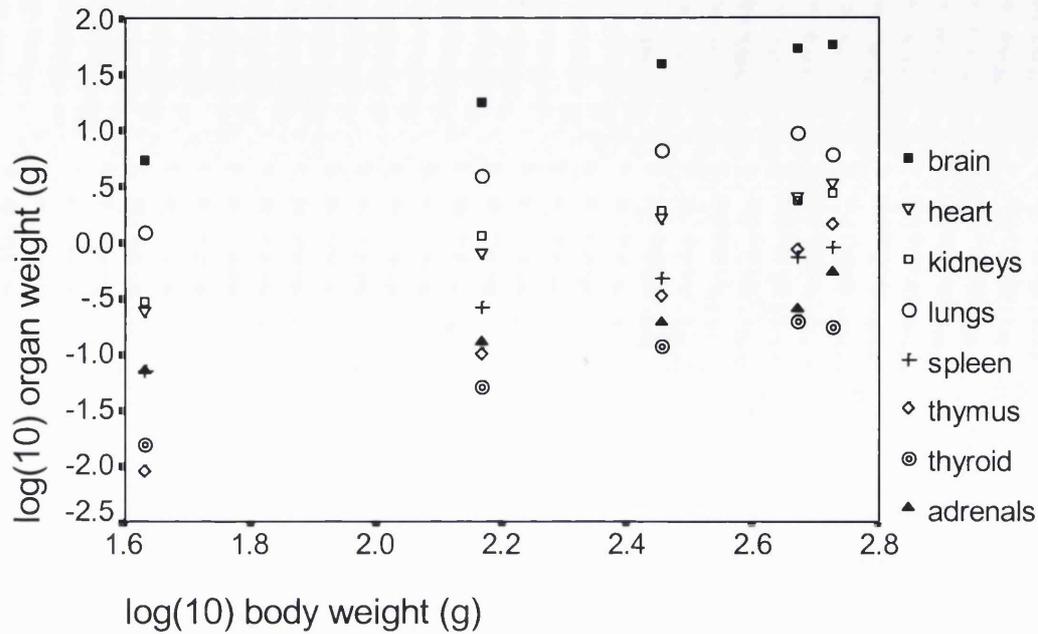


Figure 6.4 Scatterplot of \log_{10} -transformed rhesus monkey organ weights plotted against body weight (g). Data from Kerr et al. (1974).

Least squares linear regression equations are:

brain:

$$(96) \quad \log_{10} \text{ brain weight (g)} = -0.85 + 0.97 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.998, SE = 0.04, n = 5, P < 0.0001)$$

liver:

$$(97) \quad \log_{10} \text{ liver weight (g)} = -1.29 + 0.92 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.999, SE = 0.03, n = 5, P < 0.0001)$$

heart:

$$(98) \quad \log_{10} \text{ heart weight (g)} = -2.14 + 0.96 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.998, SE = 0.04, n = 5, P < 0.0001)$$

kidneys:

$$(99) \quad \log_{10} \text{ kidney weight (g)} = -2.29 + 1.03 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.987, SE = 0.11, n = 5, P < 0.0001)$$

lungs:

$$(100) \quad \log_{10} \text{ lung weight (g)} = -1.47 + 0.90 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.972, SE = 0.14, n = 5, P < 0.0001)$$

throid:

$$(101) \quad \log_{10} \text{ thyroid weight (g)} = -3.45 + 1.01 * \log_{10} \text{ body weight (g)} \\ (r^2 = 0.991, SE = 0.05, n = 5, P < 0.0001)$$

spleen:

$$(102) \quad \log_{10} \text{ spleen weight (g)} = -2.28 + 0.79 * \log_{10} \text{ body weight (g)}$$

($r^2 = 0.979$, SE = 0.11, n = 5, P < 0.0001)

thymus:

$$(103) \quad \log_{10} \text{ thymus weight (g)} = -5.24 + 1.96 * \log_{10} \text{ body weight (g)}$$

($r^2 = 0.997$, SE = 0.05, n = 5, P < 0.0001)

adrenals:

$$(104) \quad \log_{10} \text{ adrenal weight (g)} = -2.34 + 0.69 * \log_{10} \text{ body weight (g)}$$

($r^2 = 0.966$, SE = 0.12, n = 5, P < 0.0001)

6.8) Organ phenotypic flexibility

Non-brain organs are phenotypically flexible. For example, organ weight is highly flexible in response to food quality/availability, reproductive status and, in birds, migratory patterns. For example, caribou (*Rangifer tarandus grownlandicis*) liver and kidney weights vary in response to forage quality and are seasonally highly variable within an individual. In fact, they more than double their weight in the summer months. These changes in organ weights reflect physiological functioning (Adamczewski et al. 1987).

Functional hypertrophy in the liver has also been found in cattle (*Bos taurus*) (Leche 1973) and red deer (*Cervus elaphus*) (Mitchell et al 1976), while seasonal variation in kidney weight has been shown in red deer (Mitchell et al. 1976). In addition, seasonal hypertrophy of the alimentary tract, heart, liver and spleen (accompanied by a reduction in kidney mass) has been found in muskrats (*Ondatra zibethicus*) in response to food quality (Campbell and MacArthur 1998).

Liver and kidney weight, cell number and cell size undergo significant decreases in the wild boar (*Susu scrofa*) in response to long term dietary restriction (Wolkers et al. 1994). Likewise, gonads are highly variable in size with the testes and follicles of birds increasing 100-fold or more during the breeding season and declining to very small sizes in the long periods in-between (Murton and Westwood 1977). Birds also undergo diurnal changes in the fat-free mass of the liver as well as 40-50% decreases in the mass of the liver and intestine before migratory departure (Dolnik and Blyumental 1967).

In response to variation in food and energy demand (e.g. in response to lactation, exercise or temperature), mammals, reptiles and birds also show dramatic changes in gut mass (Fell et al. 1962, Karasov 1996, Piersma et al. 1993). Perhaps the most intriguing example of phenotypic flexibility is that of the Burmese python (*Phyton molurus*). Within 24 hours of consuming a meal, the snake's small intestine more than doubles in mass, while the kidneys and liver undergo a 45% increase in size (Secor and Diamond 1995, see also Piersma and Lindström 1997).

In light of these findings, it is clear that a number of organs (and their relative metabolic costs) are highly plastic and vary in response to energetic or physiological demands. The human liver, heart and kidney also undergo phenotypic change by reducing in size and metabolic turnover in response to nutritional stress (Holliday 1986) and by increasing in size during pregnancy (Rubler et al. 1977, Blackburn and Loper 1992). There is some evidence to suggest that the pancreas also increases in size during pregnancy (van Assche et al. 1978). During malnutrition, the thymus is severely reduced in size (Golden et al. 1977). Brain size, on the other hand, is conserved (see chapter 3). In addition, growth retardation in humans is associated with brain conservation at the expense of the liver (Dawkins 1964).

6.8a) Organ conservation and size decrease during malnutrition

In a study on the effects of malnutrition on organ size in infant rhesus monkeys up to 210 days-of-age, Kerr et al. (1973) found evidence for both a reduction and conservation of organ weights. After taking reduced body weight in malnourished animals into account, the authors found significant reductions in the relative weights of the heart, liver, spleen, thymus, pancreas and muscle. Distended and thin gastrointestinal tracts were also found. In contrast, conservation of brain weight, in particular, and that of the kidneys, lungs, thyroid, adrenal and pituitary glands was evident.

This suggests that energy stress in growing animals is associated with a reduction in the relative size of a number of organs and sparing of others, particularly the brain. Based on studies in rats, Hales and Barker (1992) referred to this phenomenon as the 'Thrifty Phenotype hypothesis', arguing that early protein deprivation causes selective preservation of some organs, such as the brain, at the expense of others, such as the kidneys in rats.

During early human life, when the brain comprises a significant proportion of body weight, brain conservation requires a greater proportion of total energy than in the less

encephalised rhesus monkey or rat. Here, patterns of organ reduction and conservation may differ in response to the increased energetic demands of the human brain.

In this chapter, an hypothesis relating to phenotypic flexibility and brain size conservation is tested. This is referred to as the ‘Organ trade-off hypothesis’.

6.9) Organ trade-off hypothesis

The ‘Organ trade-off hypothesis’ posits that:

Encephalised fetuses will have a relatively reduced weight in one or more major non-brain organs.

Here, the assumption is that encephalisation is associated with a disproportionate amount of energy which is diverted from other organs to the brain in order for it to meet its elevated metabolic requirements. This is largely in line with Hales and Barker’s (1992) ‘Thrifty Phenotype Hypothesis’. It differs, however, from Aiello and Wheelers’ (1995) ‘Expensive Tissue Hypothesis’.

6.10) Aiello and Wheeler’s Expensive Tissue Hypothesis

Aiello and Wheeler (1995) argued that over evolutionary time, the primate order has undergone a change in organ composition, where brain size has increased and gut size has decreased, in relative terms. The authors argue that the corresponding decrease in gut tissue offset the increased costs of encephalisation in the order.

The ‘Organ trade-off hypothesis’ tested here differs from this hypothesis in that it seeks to explain phenotypic changes in organ composition (excluding the gut) within the individual during growth. These changes are driven largely by the survival needs of the individual. Given our species’ present organ composition (i.e. relatively increased brain and decreased gut size compared to mammals of comparable body

size), it attempts to explain phenotypic changes in organ sizes as a mechanism for supporting encephalised brain growth.

SECTION II: Methodology

6.11) Human fetal autopsy data

As discussed previously in chapter 4, autopsy data is by no means ideal for assessing size and growth. However, published ultrasound data on organ sizes in normal living fetuses are not available. The autopsy data used to test these hypotheses are, therefore, limited to only those cases where the fetus appeared 'normal' morphologically and histologically and the results serve as a starting point rather than definitive answer to the questions raised in this chapter.

Data from post-mortem records were collected, including fetal organ weights, sex, body length, and body weight for 400 individuals. These autopsy records were compiled by the Department of Pathology at the University of California Los Angeles which has undertaken these autopsies since 1960. Access to these records was granted by Dr. Michael Fishbein of the Pathology Department (UCLA).

Only data for individuals who were apparently normal were collected, i.e. were not suffering from any clear pathology, congenital anomaly, mental retardation or chromosomal abnormality. Any organs marked by edema, hemorrhage/hematoma or congestion were excluded. Severely autolysed organs were also excluded. Where marked aspiration of amniotic fluid was noted, lung weight data was excluded due to potential weight inflation. Fetuses of diabetic mothers were excluded from the study on the grounds that body size is markedly increased in the offspring of diabetic mothers (Catalano et al. 1998). Fetuses of mothers who were using prescription or recreational drugs during pregnancy were also excluded from the study on the basis

that these may alter glucose transfer and protein and hormone synthesis, resulting in reduced fetal growth and altered placental function (Naeye et al. 1973, Wunderlich et al. 1979, Snyder et al. 1986, Owens and Robinson 1988). These criteria were established in order to limit the database to apparently 'normal' individuals. Head circumference measures are not reported here as there was a strong indication of severe head moulding or maceration in these fetuses.

The number of autopsy cases which could potentially be used in this study was greatly reduced due to the effects of hypoxia on the brain during death. A large percentage of stillbirth and premature deaths and miscarriages result from anoxia, usually occurring in response to strangulation by the umbilical cord during pregnancy or birth, or due to respiratory insufficiency arising from immature lungs or hyaline membrane disease. In these cases, severe congestion of the lungs occurs and panting or grunting of the infant leads to brain hemorrhage, engorgement or congestion. Therefore, those individuals who showed evidence of brain abnormality either at the gross or at the histological level were excluded for the purposes of this study which seeks to consider organ size variation in 'normal' fetuses. It should also be noted that in the majority of cases, the heart and lungs were removed and weighed *en bloc*. Therefore, the combined weight of the heart and lungs is reported. In these cases, the combined weights were collected, but where there is the likelihood of lung tissue congestion or edema, the combined weight (including that of the heart) was excluded. As a result, the potential sample size for the combined weight of lung and heart was reduced.

The resulting organ weight database includes the following sample sizes listed in Table 6.1, where 56.5% of the fetuses were male. There are notably fewer reported weights for the pancreas (n = 15), thyroid gland (n = 41), lungs (n = 54) and heart (n = 86). Data on gut weights were not available. Tables A.11 (a-q) lists the mean weights, standard deviations, and sample sizes for organs, in each week of gestation where there are sufficient data.

Because relative organ sizes are a function of body size, only those individuals with both body size and organ size data could, ultimately, be included in the analyses. Table 6.2 lists the number of individuals for each gestation age group with data on body length. Gestation weeks in bold have fewer than ten individuals with reported body length measures. Body length rather than body weight is used here as post-mortem weight is often influenced by edema and dehydration.

Table 6.1 Sample sizes for fetal autopsy organs weights, body lengths and body weights and numbers from males and females

organ	males	females
brain	225	172
heart and lungs combined	125	101
heart	52	34
lungs	31	23
liver	195	156
kidneys	187	148
spleen	200	145
thymus	140	101
thyroid	25	16
pancreas	10	5
adrenal glands	187	152
body length	219	167
body weight	217	160

Table 6.2 Sample sizes at each gestation week where fetal body length data are available

gestation weeks	n	gestation weeks	n	gestation weeks	n
17	2	27	13	37	5
18	4	28	20	38	9
19	0	29	14	39	3
20	16	30	17	40	43
21	6	31	11	41	1
22	17	32	21	42	2
23	14	33	16	43	1
24	30	34	16	44	1
25	16	35	9		
26	20	36	17		

gestation weeks in bold have fewer than 10 individuals with body length data
n = sample size.

6.12) Quantifying relative organ weights

In order to quantify relative organ weights during fetal growth, the effects of body length as well as distribution skewness and the differences in growth rates between the organs must be controlled for. The LMS method was, therefore, used (see chapter 2, section 2.9). Distributions were normalised by fitting a smoothed L curve through the data. Smoothed M and S curves were also fitted to the data to establish a median curve and to control for the variation in sample sizes at different ages. The L, M and S curves then provided the L, M and S constants for calculating age-specific SD scores (see equation 10).

The resulting L, M and S values for the organs and body length (as a function of age) are listed in Tables A.12 (a-l) in the appendix. The sexes were combined here as independent samples t-tests showed no statistically significant difference between the weights of male and female organs, with the exception of the liver (see Table 6.3). In the case of the liver only, sex-specific SD scores were calculated. The organ weight SD scores are age-specific but do not control for the allometric relationship between the organs and the body as a whole. In order to do this, 'conditional' SD scores were calculated.

'Conditional' SD scores were derived by plotting organ weight SD scores against body length SD scores and fitting the appropriate smoothed L, M and S curves through the data. From the L, M and S values derived from the curves, SD scores were calculated. These are conditional SD scores in that they not only control for age-effects, but also for the effects of body length.

Figures 6.5 to 6.7 are growth references providing an example for the conditional SD scores calculated here. Figure 6.5 is a sex-pooled fetal kidney growth reference (with corresponding 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles) and Figure 6.6 is a body length reference. These two references provide L, M and S constants for each individual which were applied to equation 10 (see chapter 2) in order to calculate organ weight SD scores. The kidney weight and body length SD scores were then used to calculate a 'conditional' SD score. In the example, kidney weight SD scores

were plotted against body length SD scores (see Figure 6.7) and L, M and S curves and constants are derived. The resulting SD scores were then body length-specific and age-specific. These SD scores are used here as relative organ weight indices, so that the relative size of a 16 week kidney, for example, may be compared directly with the relative size of a 38 week kidney, as both age affects and changes in the relationship of the kidney with body length are controlled for.

In the case of the liver, combined male and female SD scores were plotted against body length SD scores in order to derive 'conditional' SD scores. They were combined at this stage because sex effects on size were already controlled for by calculating sex-specific SD scores.

Table 6.3 Results of independent samples t-tests comparing the means of organ weights between males and females

	mean difference	P	CI of difference
age (weeks)	-1.16	0.09	-2.49, 0.18
body length (mm)	-1.27	0.17	-3.10, 0.56
body weight (g)	-98.0	0.34	-299, 103
brain (g)	-12.3	0.35	-38.2, 13.6
heart (g)	-1.91	0.36	-6.06, 2.24
heart + lungs (g)	-5.26	0.10	-11.6, 1.05
lungs (g)	1.86	0.76	-10.3, 14.0
kidney (g)	0.61	0.62	-1.77, 2.98
liver (g)	-9.65	0.05	-19.3, 0.03
spleen (g)	-0.07	0.90	-1.12, 0.99
adrenal glands (g)	-0.21	0.54	-0.89, 0.47
thymus (g)	-0.50	0.44	-1.77, 0.77
thyroid (g)	-0.49	0.07	-1.03, 0.04
pancreas (g)	0.42	0.50	-0.89, 1.73

P = probability based on a confidence limit of 95%. CI = confidence interval
 negative value indicates that female organs are larger than males

Kidneys

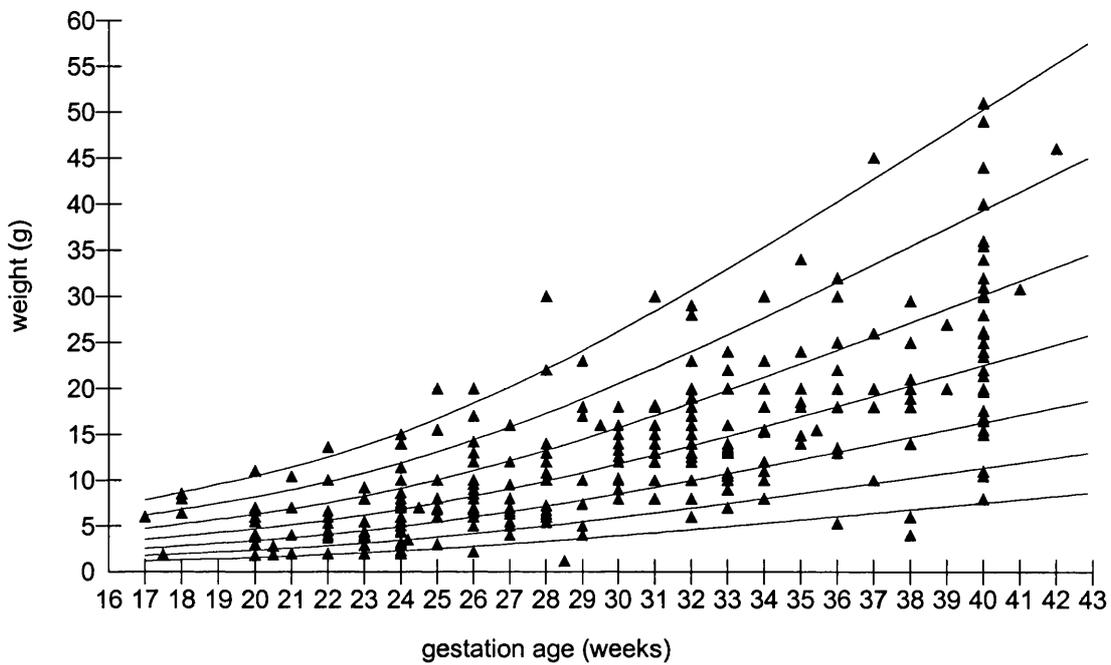


Figure 6.5 LMS-model and centiles derived from plotting autopsy fetal kidney weight against gestation age in weeks

Body length

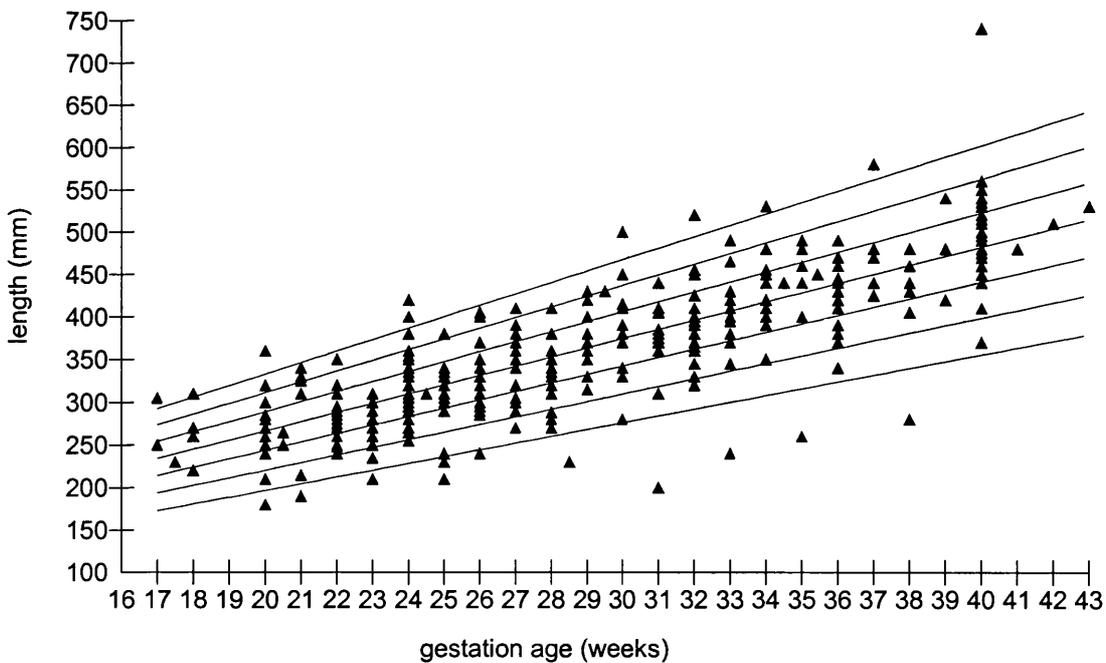


Figure 6.6 LMS-model and centiles derived from plotting autopsy fetal body length against gestation age in weeks

Relative kidney size

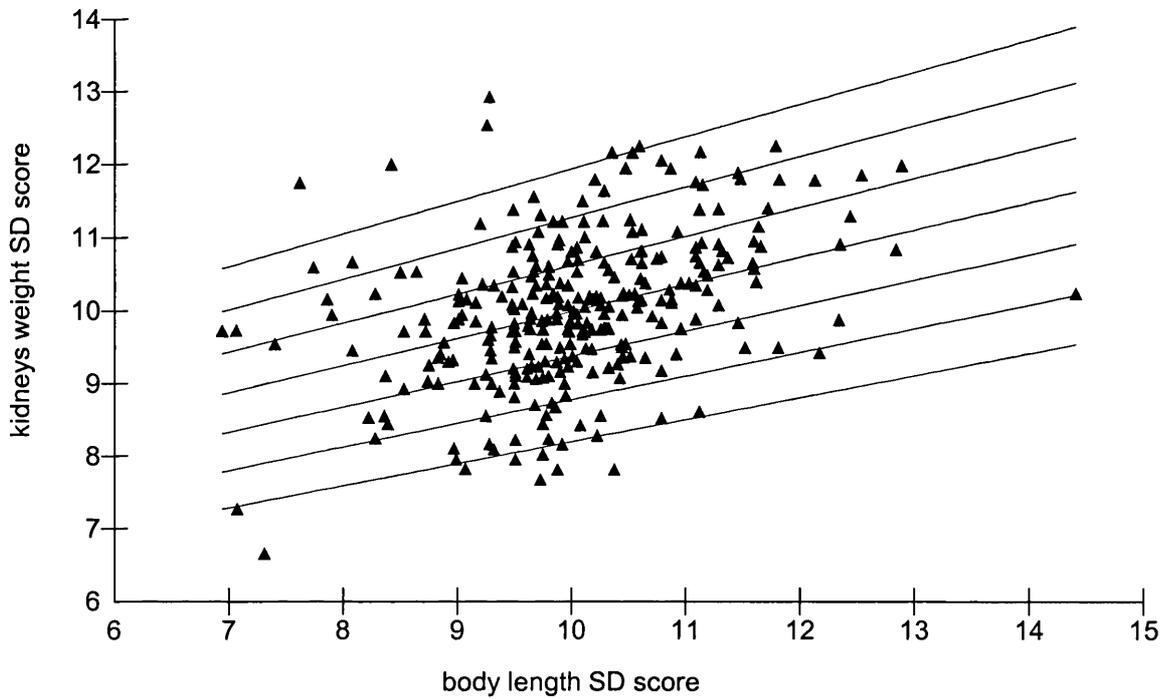


Figure 6.7 LMS-model and centiles derived from plotting kidney weight SD scores against body length SD scores. Resulting 'conditional' SD scores represent relative organ size. A value of +10 was added to each SD score on both the y- and x-axes here as the Cole and Green (1998) LMS Growth Reference Program cannot plot negative values. The resulting conditional SD scores were not affected by this.

6.13) Quantifying a trade-off in size between the brain and other organs

A trade-off in organ sizes may be assessed, by determining whether the relationship between relative brain weight, after controlling for age and body size effects (i.e. 'conditional' SD scores, and that of the other organs is positive or inverse. An inverse relationship between brain weight 'conditional' SD scores and another organ would suggest that brain size increases while the other organ decreases in size. However, if fetuses with relatively small brains have small non-brain organs, or if fetuses with relatively large brains have large non-brain organs, this would be indicative of proportionate growth in all organs.

6.14) Statistical tests

Two-tailed bivariate correlations with confidence limits set at 95% are used to determine whether correlations between brain weight SD scores (controlling for body length SD scores) and those of the other organs are significant.

In addition, the non-brain organ weight (for body length) SD scores are plotted against brain weight (for body length) SD scores and least squares linear regression lines are fitted through the mean. It may, thus, be determined whether a positive or negative relationship exists between the non-brain and brain weight (for body length) SD scores in question.

SECTION III: Results

6.16) Results of analyses

Figures 6.4(a-h) are scatterplots where ‘conditional’ non-brain organ weight SD scores (controlling for age body length SD scores) are plotted against ‘conditional’ brain weight SD scores (controlling for age body length SD scores). The least squares linear regression statistics derived are listed in Table 6.5.

Unfortunately, sample sizes were very small at the tail ends of the distribution, with 0 - 2 individuals having non-brain organ weights in the most encephalised and least encephalised fetuses. However, non-brain organ weight sample sizes were greatly increased corresponding to about -1.5 to +1.5 SD for ‘conditional’ brain weight SD scores. For all of the non-brain organs, positive and significant correlations were found between ‘conditional’ SD scores and brain weight ‘conditional’ SD scores [see Tables 6.4(a-c)], suggesting that encephalised fetuses also have relatively large non-brain organ weights, after controlling for the effects of age and body length.

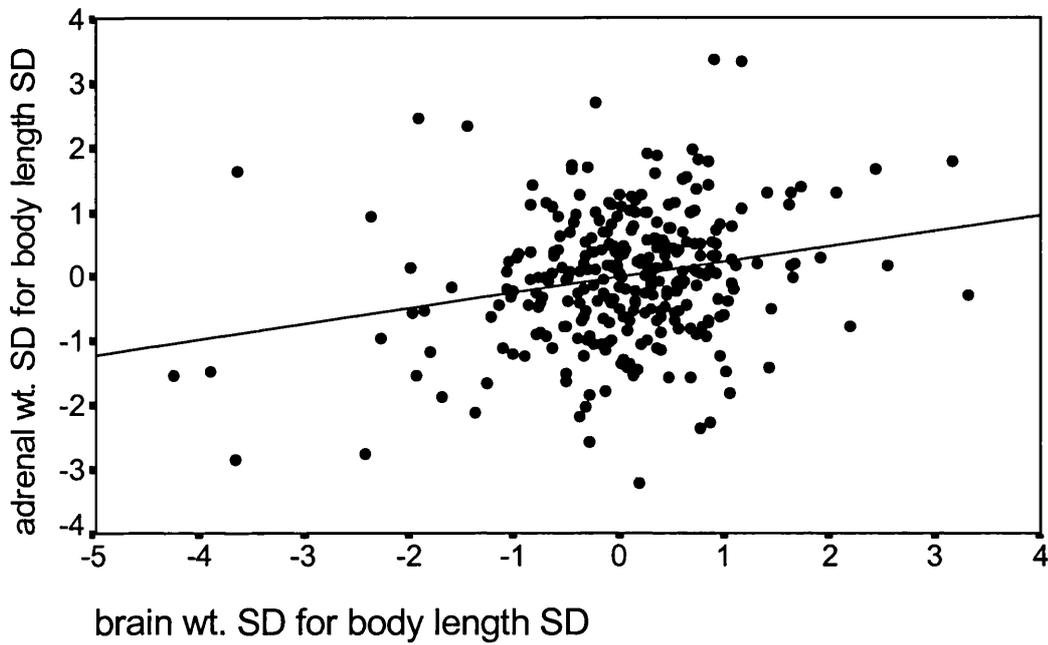


Figure 6.8a Scatterplot of fetal human adrenal weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

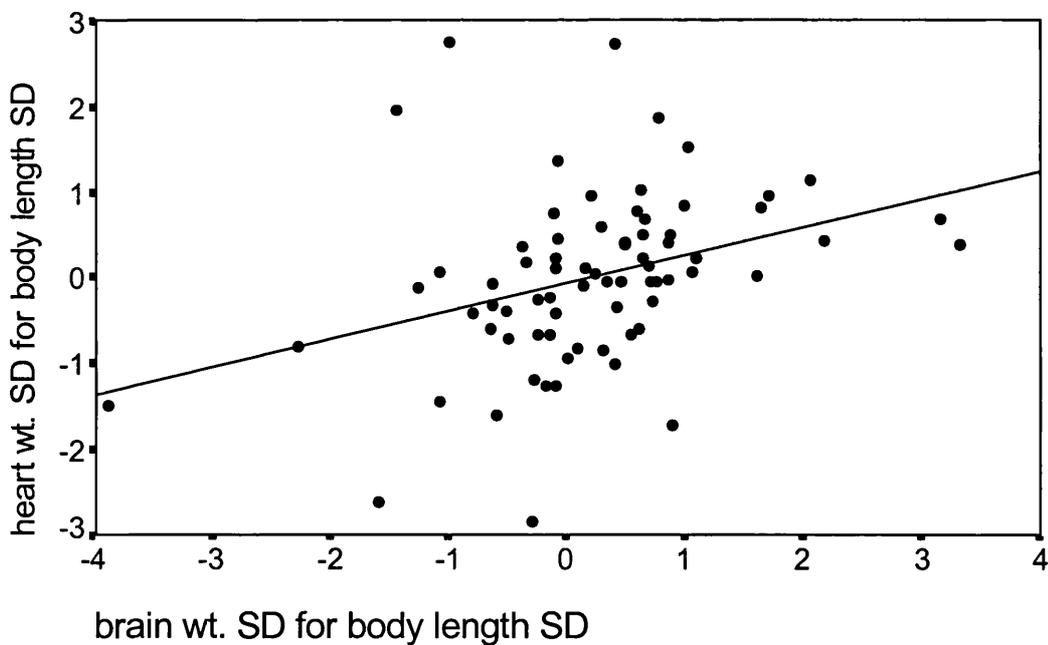


Figure 6.8b Scatterplot of fetal human heart weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

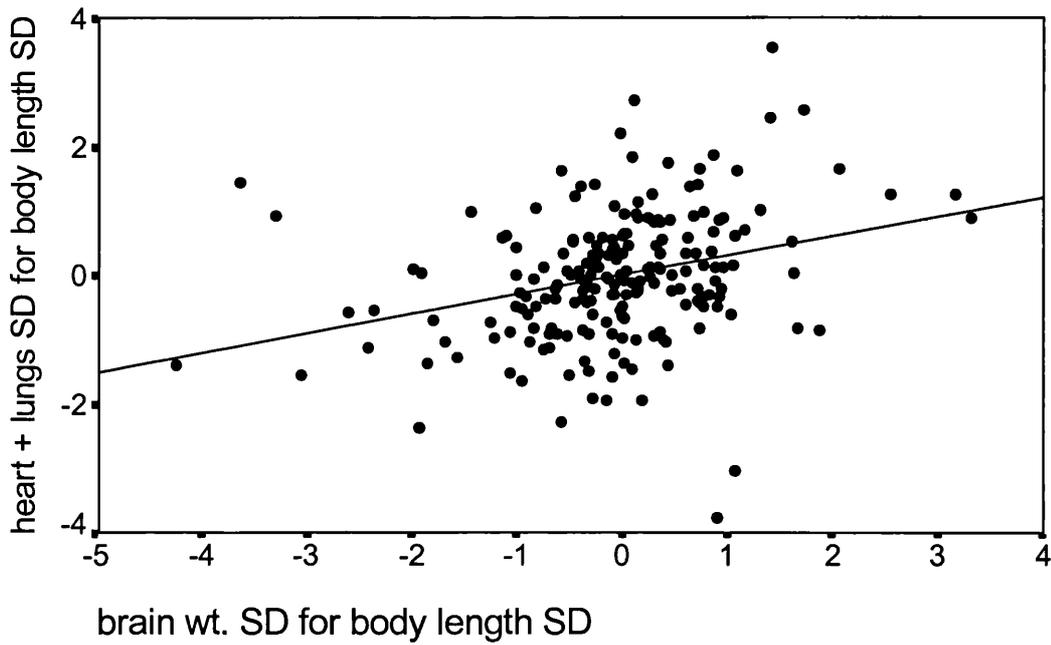


Figure 6.8c Scatterplot of fetal human heart + lungs weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects. ± 2 standard deviations are shown.

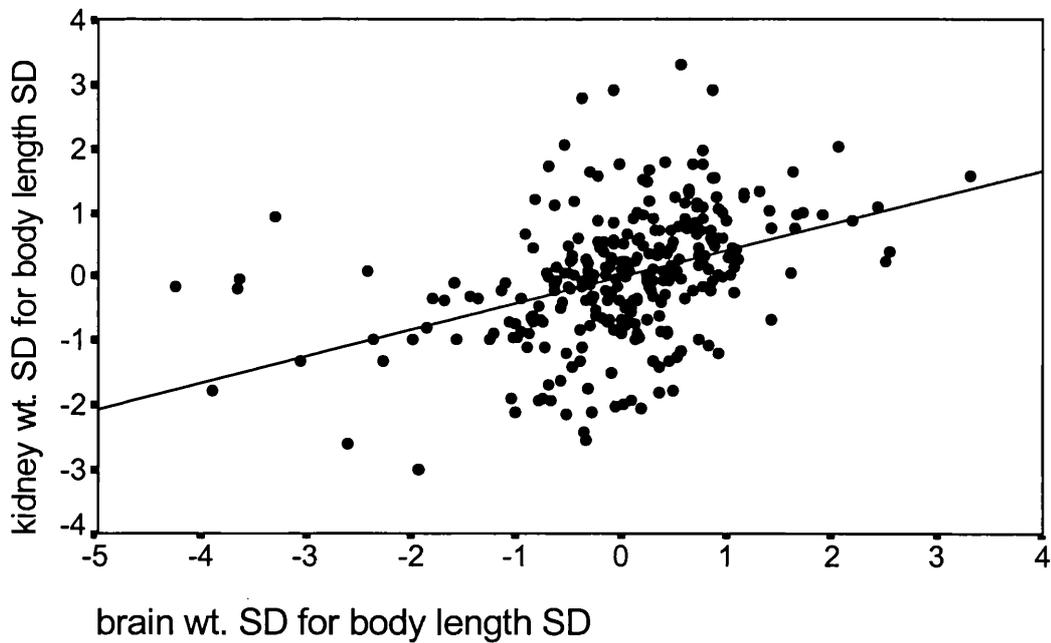


Figure 6.8d Scatterplot of fetal human kidney weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

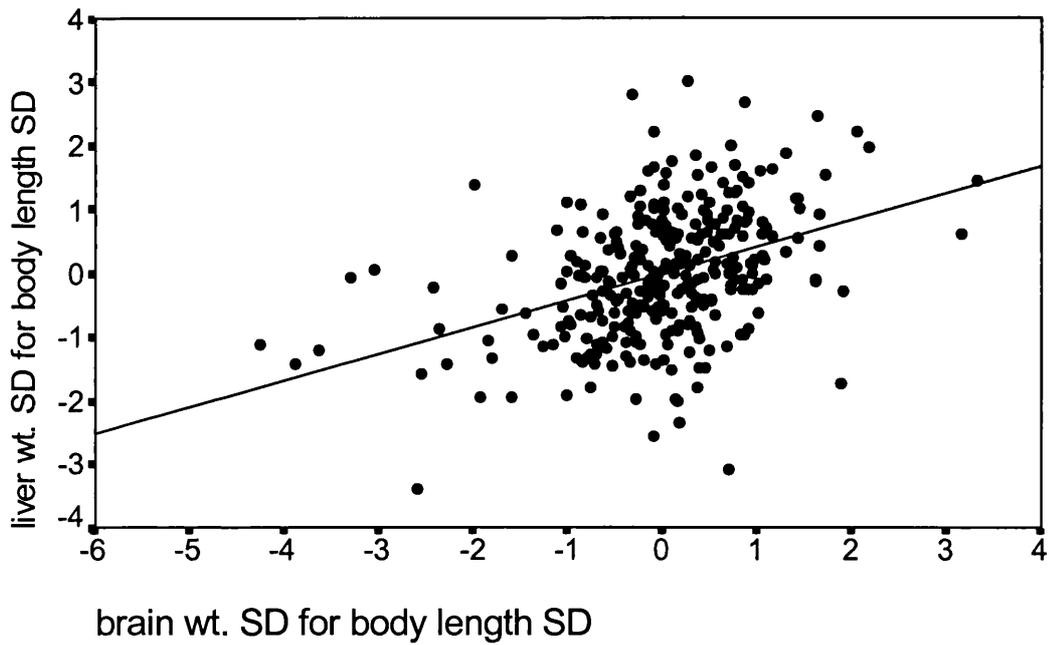


Figure 6.8e Scatterplot of fetal human liver weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

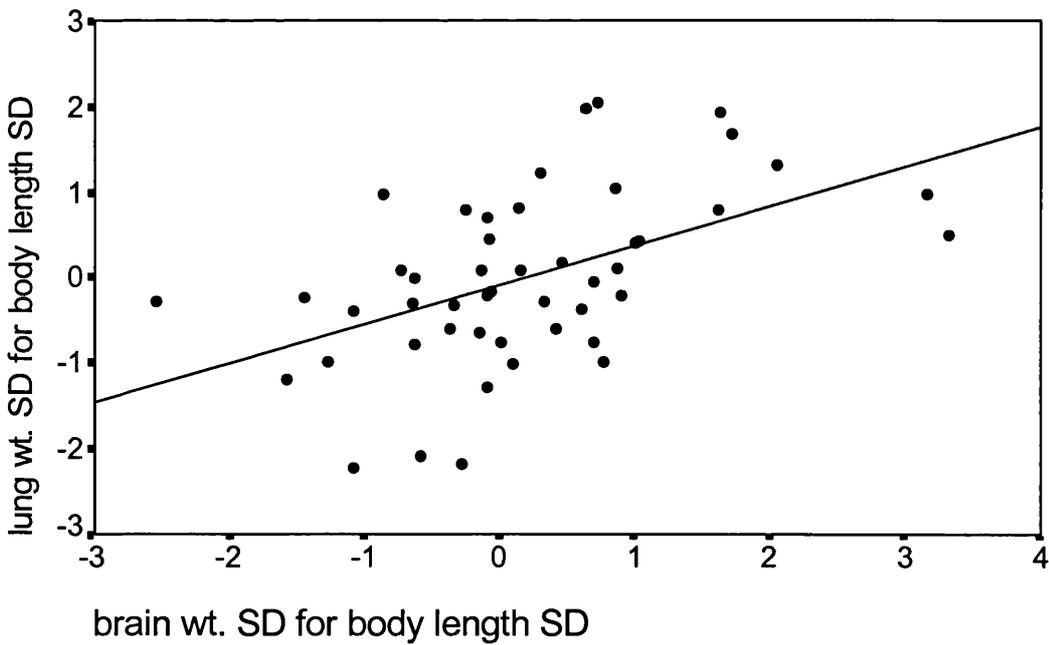


Figure 6.8f Scatterplot of fetal human lung weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

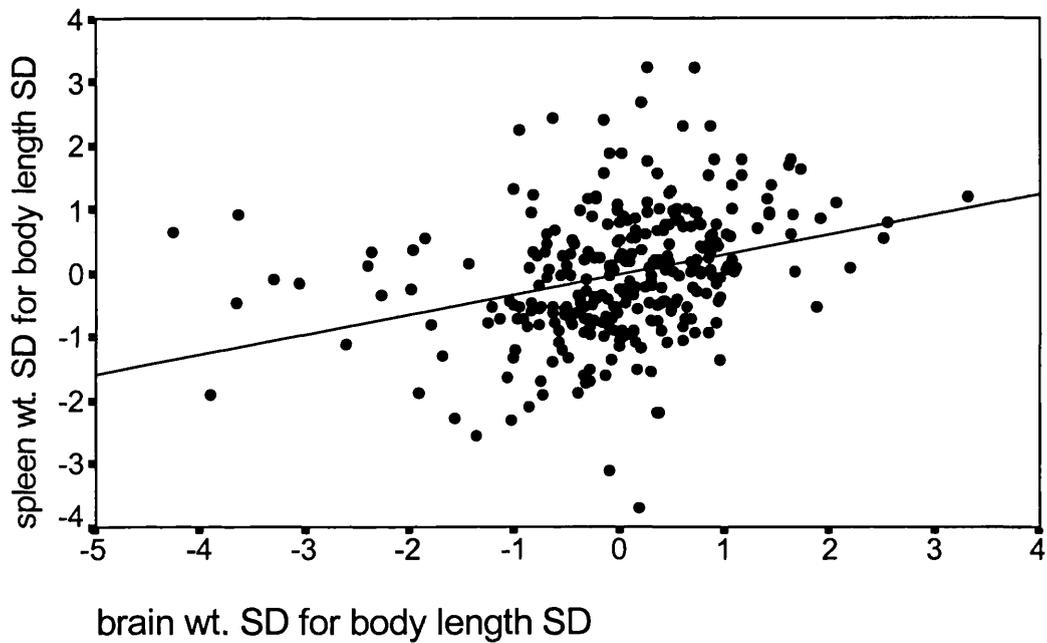


Figure 6.8g Scatterplot of fetal human spleen weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

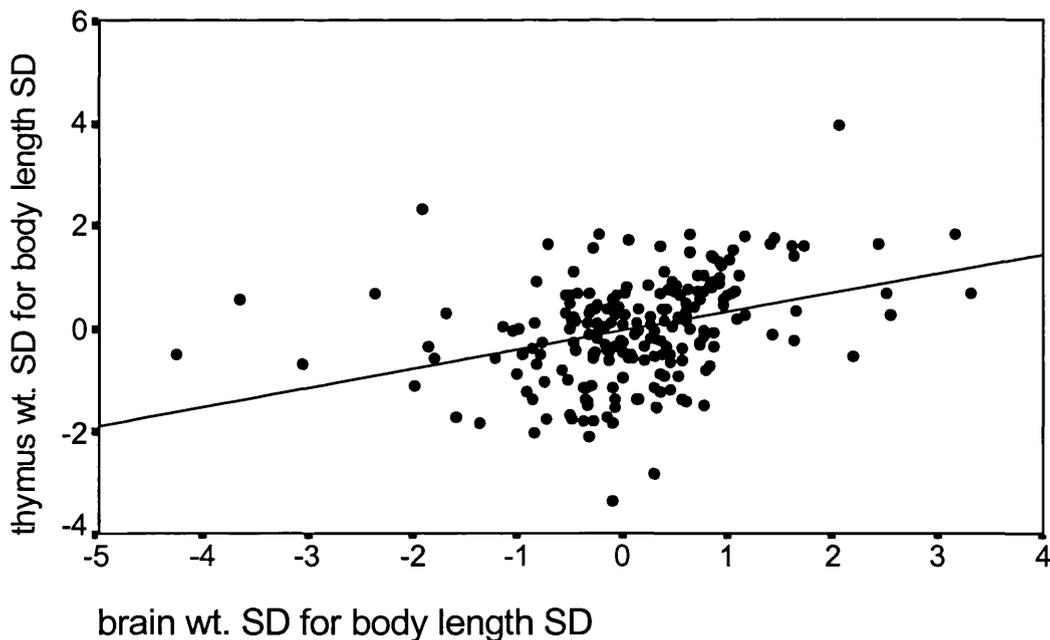


Figure 6.8h Scatterplot of fetal human thymus weight 'conditional' SD scores plotted against brain weight 'conditional' SD scores. 'Conditional' SD scores control for age and for body length SD score effects.

Table 6.4 Results of bivariate correlations between brain weight SD scores (controlling for age and body length SD scores) and those of non-brain organs

Relative organ size (SD score)	n	R	P
adrenal glands	293	0.227	0.000
heart	73	0.348	0.003
heart + lungs combined	204	0.301	0.000
kidneys	291	0.403	0.000
liver	304	0.397	0.000
lungs	48	0.506	0.000
spleen	300	0.308	0.000
thymus	211	0.351	0.000

R = correlation coefficient, P = probability based on 95% confidence limit, n = sample size.

Table 6.5 Least squares linear regression statistics where 'conditional' brain weight SD score is the independent variable and 'conditional' non-brain organ weight SD score is the dependent variable

organ	n	a	error of a	b	error of b	P	r ² %
adrenals	297	-0.012	0.057	0.242	0.060	< 0.001	5.2
heart	73	-0.067	0.113	0.326	0.105	< 0.001	12.1
heart + lungs	204	0.019	0.067	0.299	0.067	< 0.0001	9.1
kidneys	291	-0.001	0.054	0.412	0.055	< 0.0001	16.2
liver	304	-0.002	0.053	0.416	0.055	< 0.0001	15.8
lungs	48	-0.008	0.129	0.461	0.116	< 0.001	25.6
spleen	300	-0.004	0.055	0.315	0.056	< 0.0001	9.5
thymus	211	-0.045	0.065	0.366	0.067	< 0.0001	12.3

n = sample size, P = probability based on 95% confidence limit, r² = regression coefficient, a = constant, b = slope.

6.17) Discussion

These results suggest that in the fetuses, organ weights were fairly proportional. Non-brain organ weight 'conditional' SD scores generally increased as brain weight 'conditional' SD scores increased. Thus, in contradiction to the predictions of the 'Organ Trade-Off Hypothesis', big-brained fetuses tended also to have relatively large non-brain organs (relative to body size). Thus, proportionate investment in organ weight (after controlling for age and body length effects) appears to be the norm.

Generally, as fetuses grow larger brains (in relative terms) they also tend to grow larger non-brain organs. There was, therefore, no clear evidence for a trade-off in size (i.e. inverse relationship) between brain weight and non-brain organ weight 'conditional' SD scores. The absence of data for the gut makes the relationship between relative gut weight and relative brain weight impossible to assess here. The fetal gut, is however, smaller than the heart, kidney, spleen, liver and lungs and is, therefore, not likely to compete directly with the brain over energy resources.

As shown in chapter 5, well-nourished mothers tend to produce encephalised and well-nourished neonates. These neonates tend also to have high levels of both fat tissue and muscle tissue. The results in this chapter suggest that these neonates are also likely to have relatively large non-brain organs. It, therefore, appears that in order to maintain an encephalised fetus, relatively larger organs in general are required. This is not surprising given that, for example, the liver is implicated in sustaining the brain by producing glucose and the heart and lungs are central for oxygenating the brain. The kidneys, on the other hand, help to regulate blood pressure and are also implicated in gluconeogenesis (Eckert and Randall 1983, Blackburn and Loper 1992). Adequate organ size is, therefore, important for sustaining life after birth.

The encephalised fetus, therefore, is one whose mother has invested her energy in fetal organ, fat and lean tissues (relative to its body size). Maternal energy supply, must, thus, be adequate to meet fetal demands.

In an energetically stressed population, where maternal energy is reduced, it is, therefore, likely that women will produce offspring with proportionately reduced body weights and lengths and reduced non-brain organ weights. Brain sparing is likely to result in proportionately large head circumferences. Kerr et al. (1973) showed that in rhesus monkeys, severe protein deprivation in early life was associated with brain, kidney and lung conservation at the expense of the heart, liver, spleen, thymus and pancreas. Hales and Barker (1992), on the other hand, showed that in humans, malnutrition in early life was associated with brain conservation at the expense of the kidneys.

Because the autopsy data analysed here do not represent a malnourished population, they cannot shed further light on the likely patterns of organ conservation and reduction during severe energy stress. In addition, it cannot be dismissed that these were non-viable fetuses for a number of different reasons and although only 'apparently' normal fetuses were included in the study, they cannot define organ growth in a normal and healthy population.

These results are, however, only preliminary. The data used here were 'noisy' and cross-sectional methods were used to study growth, which is highly problematic. Further investigation into the impact of high levels of encephalisation on the relative size of non-brain organs in living individuals is needed before the questions raised in this chapter can be answered with more certainty.

CHAPTER 7

Conclusions and discussion

This thesis has been an attempt to clarify the relationship between maternal factors, early growth and encephalisation. The mother-placenta-fetal system was studied in terms of its impact on offspring encephalisation. The relationship between growth and encephalisation from the second trimester through to 1 year-of-age was also examined.

This study differed from previous work in that it involved a longitudinal *in vivo* study of encephalisation during the fetal and infancy periods. Previous work has mainly focused on cross-sectional data and adult encephalisation.

Some of the results of the thesis were in agreement with previous findings. Others contradicted previous findings, and a number of results provided new information about fetal and infant encephalisation. Contradictions with previous findings may relate to differences arising from cross-sectional and longitudinal measures. Cross-sectional data cannot account for intraspecific variation. As shown in this thesis, intraspecific variation in encephalisation and growth trajectories is marked. The new findings in the thesis are summarised below.

7.1) Summary of findings

1) Fetal growth curve

After standardising for gestation length differences, the human fetal femur length growth curve did not differ significantly from that of the rhesus monkey, baboon and common marmoset. The head circumference growth curve, however did. Human head circumference growth during the fetal period was found to slow down later in gestation compared with the other primates. In addition, a greater proportion of head circumference at one year was found to be attained earlier in humans than in the other

primates. Both hyperplastic and hypertrophic brain growth appears to be extended in humans.

The fact that head circumference growth begins to slow down prior to birth, contradicts findings by Martin (1983, 1989) and Deacon (1990, 1997) who argued that the brain weight to body weight relationship is isometric in humans until some time after birth. Martin and Deacon's data were compiled from several sources and the analyses were based on cross-sectional data, rather than *in vivo* data, as in this thesis. This may, in part, explain these different results.

Deacon (1990, 1997) has argued that human brain growth rates do not differ from other primates, while body growth rates are slower in humans than other primates. In addition, the brain growth period is extended in humans. Deacon suggests that humans have brain growth typical for a primate with a body size of 1,000 lbs., and a body growth pattern similar to that of a chimpanzee.

In this study, fetal femur length growth trajectories did not differ markedly between humans, rhesus monkeys and baboons, while human head circumference trajectories did. This points to a possible disagreement with Deacon's hypothesis, in that longitudinal assessment of fetal body length growth did not differ markedly between humans and the other primates studied. One possible cause for this discrepancy may be Deacon's use of autopsy body weight measures, which are notoriously subject to marked fluctuation between life and death, due to edema, dehydration, autolysis, disease state and so forth.

According to Deacon's assessment of human brain growth, we undergo brain growth in excess of that predicted by our body size. This 'mismatch' between brain and body growth patterns begins in early embryogenesis and culminates in our prolonged postnatal brain growth. Deacon (1989, 1997) argues that humans differ fundamentally from the other primates in that non-human primates are encephalised due to a reduction in body size, rather than an increase in brain size.

Unfortunately very little reliable comparative work has been carried out between fetal brain growth trajectories in primates (using longitudinal data), so that it is not possible to compare these results with those of other workers. These results do suggest that growth curves based on longitudinal rather than cross-sectional data are likely to vary, as pointed out by Israelsohn (1960).

2) Predicted costs of brain growth

The costs of maintaining brain tissue were calculated to far exceed the costs of growing brain tissue (see Holliday 1971, Elia 1992). After controlling for the changes in the chemical composition of the brain during growth, the estimated costs of adding metabolically active brain tissue and the costs of synthesising protein and fat were calculated to amount to 23 kcal from 16-40 gestation weeks, and 1458 kcal from birth to 2 years of age, while the total daily costs of maintaining brain tissue during that time were 414 kcal/day based on Holliday's (1986) estimates.

Foley and Lee (1991) estimated that a 10% increase in energetic costs is associated with encephalisation in our species. According to the brain growth costs estimated in this thesis, the additional costs for encephalisation appear to relate primarily to brain tissue maintenance rather than growth. This view is consistent with that of Kuzawa (1998) who suggested that brain growth alone does not impose a significant cost to the individual since the lipid and protein deposits of the brain comprise only 3% and 6%, respectively, of the total fat and protein deposited by the growing infant during the first year of life.

3) Body fatness and encephalisation

A positive but indirect relationship between body fatness and encephalisation was found in a preliminary analysis including mature vertebrates. Humans, cetaceans and pinnipeds were found to be particularly encephalised and also to have very high levels

of body fat, compared with other vertebrates. Early fat deposition in humans may, therefore, be related to increased encephalisation in our species.

Kuzawa (1998) argued that increased neonatal fatness has been important for sustaining the encephalised human neonate during early postnatal life when the metabolic costs associated with thermoregulation, gravity and breathing increase. These findings are consistent with Kuzawa's (1998) suggestion that increased fatness in our species has been important for encephalisation.

However, increased fatness in humans is also a crucial energy store during disease and weaning. Infection, for example, is associated with a marked increase in basal metabolic rate (Bose and De 1934, Elia 1992). The shift from maternal milk supply to weaned foods is associated with an initial reduction in caloric intake as well as increased gut and kidney metabolic costs associated with the processing of solid foods (1971). Fat stores may also be important during seasonal fluctuations in food availability, and in extreme cases of energy stress, for brain sparing due to the breakdown of fat for use in gluconeogenesis (Owen et al. 1967).

4) Fetal and infant encephalisation

Both large and small fetuses and infants may be encephalised or not. Intraspecific variation in encephalisation during the fetal and infancy periods was found to be marked. Encephalisation resulted in two ways. Both individuals with relatively small bodies and average or large head circumferences, and individuals with relatively large bodies with particularly large heads were encephalised. These individuals may be distinguished by comparing their body length SD scores and head circumference SD scores. These two types of encephalised individuals represent very different energetic loads for the pregnant female, due principally to their body size differences.

Encephalisation during the fetal and infancy periods was not found to be static, but phenotypically flexible. Recent growth largely determined current level of encephalisation. Head circumference and body length rates of growth differed

between measurement periods, and the amount of growth that occurred related to previous size. Relatively short individuals tended to 'catch up' in length, while relatively large-headed individuals underwent relatively less change in head circumference. 'Catch up' growth did not occur in both body length and head circumference at a given time. One component underwent 'catch up' growth while the other component underwent 'catch down' growth, both regressing to the mean. Increased encephalisation at a given time, therefore, related to previous increased head circumference and decreased body length. Reduced encephalisation related to previous increased body length and concomitant decreased head circumference growth.

Encephalisation itself underwent 'catch up' and 'catch down' over time (see Figures 4.7 to 4.15). Fetuses and infants tended to regress to the mean in encephalisation. Previously highly encephalised individuals underwent relatively less change in encephalisation subsequently, while non-encephalised individuals 'caught up' in encephalisation, suggesting that there is an upper limit to encephalisation, beyond which the energetic costs may be too great to support.

5) Neonatal nutritional status and encephalisation

Neonates who were encephalised tended also to be relatively well-nourished. They had relatively increased body fat and lean tissues, as well as relatively high Benn indices. In addition, they had proportionately less centralised fat than non-encephalised neonates. Increased centralised fatness is associated with intrauterine malnutrition (Barker et al. 1997, Yajnik 2000). Encephalised neonates, therefore, appear to be well-nourished neonates during fetal life. In addition, organ composition in fetuses showed a similar pattern. Those fetuses who were encephalised also had proportionately relatively large organs in general.

The author is unaware of any previous work linking nutritional status to encephalisation. The implications for these findings cannot be assessed within the context of previous work.

6) Relative brain size sexual dimorphism in the fetus and infant

Brain size sexual dimorphism (after controlling for body length effects) is found during the fetal and infancy period in humans. Human males were more encephalised than females during both the fetal and infancy periods. However, the degree of sexual dimorphism increased with age. During the fetal period sex explained about 2.5% of the variation in head circumference. At birth, it explained about 1.5% of the variation and 6.7% at 6 months. At 1 year, sex explained 8.4% of the variation in head circumference. The effect of sex in explaining the variation in encephalisation was greater during the first year of postnatal life than during the fetal period.

Brain size sexual dimorphism was also observed in rhesus monkey fetuses and infants and in baboon fetuses. Although statistically significant, it was of a very low order (< 1%). Sexual dimorphism in encephalisation was not, however, observed in the common marmoset.

The metabolic costs associated with encephalisation sexual dimorphism were calculated to be low. After correcting for the metabolically inactive components of brain weight, the additional cost of encephalisation sexual dimorphism to the male was less than 1 kcal/day during the fetal period and no more than 12 kcal/day by 6 months of age. At this time, this would amount to about 3% of daily energy requirements.

Wells and Davies (1998) calculated that, as a percent of daily energy intake at 6 months, BMR comprises about 50% of total daily energy intake, thermogenesis explains the utilisation of an additional 5% and the costs of activity explain an additional 30% of energy intake. The remaining 10% of energy requirements is explained by the energetic cost of growth. The additional 3% of daily energy requirements associated with increased encephalisation in males may, therefore, be met either by increasing food intake by 3%, reducing activity levels by 10%, or reducing growth costs by 30%. BMR and thermoregulation would not be likely

candidates for offsetting these extra costs as these are basic physiological processes necessary for survival. Because male infants are larger than females and have relatively more lean tissue than females, their energy requirements are greater and they are more vulnerable to stress, due to malnutrition and infection, as a result (Wells and Davies 1998).

Butte et al. (1989) has shown that the estimated costs of growth in male and female infants vary with age and are influenced by the relative proportions of fat and lean tissues in males and females. After controlling for fat and lean tissue differences between the sexes, and for the costs of synthesising differing amounts of these tissues, Butte et al. (1996) estimated that the total cost of growth (including tissue deposition and synthesis) differs between the sexes. Between birth and 1 month of age, males utilise 361 kcal/day on growth, while females use 343 kcal/day. Between 5 and 6 months, males use 623 kcal/day and females utilise 608 kcal/day. Males, thus, utilise between an additional 5% (between birth and 1 month) and 2.4% (between 5 and 6 months) of energy for growth.

The additional 12 kcal/day cost of encephalisation dimorphism to the 6 month old male infant comprises less than 2% of the daily cost for growth at this time. The costs for growing an additional 6.7% of brain in male neonates at this time does not contribute significantly to the costs for growth in general. Brain size sexual dimorphism does not appear to be an energetically costly phenomenon in the male infant.

7) Maternal influences on offspring encephalisation

A number of maternal factors (measured in early pregnancy) were associated with offspring encephalisation and growth. These factors had a statistical relationship with offspring growth and encephalisation in later pregnancy. Together, maternal height, nutritional status and placenta weight explained about 6% of the variation in neonatal encephalisation. Maternal condition in early pregnancy was, therefore, a factor in later offspring encephalisation, but in this population explained a relatively small

proportion of the variation in offspring encephalisation. It cannot be discounted that although statistically significant, this low statistical correlation may have resulted from chance. In addition to the effects of placenta weight, placental notching was also inversely correlated with encephalisation. Women with decreased uterine blood flow to the fetus (due to increased placental notching) tended to produce less encephalised offspring, but again, in this population, it had a small effect.

In addition, maternal cigarette smoking was associated with reduced encephalisation in neonates, while maternal alcohol use during pregnancy was associated with reduced head growth and change in encephalisation in late pregnancy. Socioeconomic status also had an effect on growth and change in encephalisation in late pregnancy, where low socioeconomic status was associated with reduced fetal growth and change in encephalisation.

Previous work has shown that maternal smoking and alcohol use during pregnancy has an adverse effect on fetal length, weight and head circumference growth (Landzelius 1998), as well as teratogenic effects on the developing brain (Sexton et al. 1991). Stunting and microcephaly may persist into postnatal life in the offspring of mothers who consumed large quantities of alcohol during pregnancy (Landzelius 1998).

Generally, infants whose mothers smoked during pregnancy tend to be shorter than those of non-smokers (Abel 1984, Landzelius 1998). The fact that offspring of mothers who smoked during pregnancy are less encephalised than those whose mothers did not, suggests that head circumference (brain) growth retardation accompanies relative body stunting in these offspring. Reduced oxygenation to the fetal brain in response to smoking, may negate the possibility for adequate brain sparing in these fetuses.

Maternal as well as offspring nutritional status were associated with offspring encephalisation. Multiple regression analysis showed that the nutritional status of both mother and newborn, along with placenta weight, were statistically associated with 35% of the variation in neonatal encephalisation. Maternal placenta weight and,

to a lesser degree, nutritional status influence offspring growth and nutritional status, and are, therefore, important factors in predicting encephalisation at birth.

8) Relative size of fetal brain and non-brain organs

It was shown that a positive relationship exists between the relative weights of non-brain organs and relative brain weight in the human fetus, after controlling for body length and age-effects. This suggests that there is no direct energy trade-off between the non-brain organs and brain in encephalised fetuses. Together with the findings that encephalisation is associated with increased fatness and lean tissue in early life, these results suggest that energy is proportionately invested within the tissues of the encephalised fetus.

7.2) Implications for the Trivers-Willard Effect

Evolutionary theory predicts that lifetime reproductive success is the same in males and females, since each individual receives genes equally from its mother and father (Fisher 1930). However, reproductive success within the sexes may vary (Trivers and Willard 1972, Clutton-Brock and Harvey 1991), hence the relationship between early parental investment and later offspring return need not necessarily be equal between the sexes (Frank 1990). In a good environment mothers are predicted to maximise their reproductive success by skewing investment toward the more variable sex, in contrast to a poor environment, they are predicted to invest in the less variable sex. In humans, like many mammals, males have greater variability in reproductive success. In deer, for example, a large and strong male is likely to access many mates, while poor quality males may not mate at all (Clutton-Brock 1991). Equally, in humans, one study showed that larger males tend to have more offspring (Pawlowski et al. 2000).

The different inclusive fitness returns of sons and daughters relate to the different costs imposed on the mother for producing males and females, and the likelihood of

offspring reproduction. Although the variation in males' lifetime reproductive potential may be greater than that of females, males are generally more costly to produce than females due to their larger body size, increased growth rates, and relatively increased lean tissue deposits (Fomon 1966, Clarke 1995). That males are more costly to maternal fitness is shown by the fact that red deer, for example, are less likely to breed in the subsequent season if they produced a male in the current season (Clutton-Brock et al. 1986, Clutton-Brock 1991).

In this thesis, it was shown that the fetal and infant male has a larger brain than the female after controlling for body size differences between the sexes. This may, at first, suggest that mothers direct greater investment into fetal male encephalisation. However, as shown in chapter 4, the costs associated with increased male encephalisation are very low during the fetal period, and amount to no more than 1 kcal/day. During the first 6 months of life, while the infant is likely to be breastfed, they are also low, amounting to no more than an additional 12 kcal/day. This comprises an increase in total daily requirements of no more than 3% in males. Given that a big brain is associated with larger vital organs (chapter 6), this direct 3% increase may, in fact, be accompanied by additional indirect increases. According to Butte's (1996) values for total energy requirements in the first 6 months of life, males have an additional average greater cost of 5.8%.

7.3) Male encephalisation as an adaptation

It remains to be shown whether higher levels of encephalisation within males are associated with increased reproductive success. Ankney (1992) and Kolakowski and Malina (1994) have suggested that greater cranial size in males may have evolved in response to the cognitive demands of mens' hunting through improved spatial ability. Lynn (1994), on the other hand, has suggested that the reproductive advantages of social dominance (accompanying increased relative brain size and 'social intelligence') incur the reproductive benefit. Falk et al. (1999) have also suggested that increased encephalisation in males may relate to superior visuo-spatial ability, thus potentially conferring a fitness advantage to males that are more encephalised.

Variation in spatial ability and 'social intelligence' within males is yet to be correlated with relative brain size, or with reproductive success, however.

Functional neuroimaging techniques have shown that visuo-spatial processing activates the dorsolateral prefrontal cortex, dorsal and ventral visual cortical areas as well as the right ventral extrastriate cortex and superior parietal lobule (mainly in the right hemisphere) (Ng et al. 2001). Thus, the parts of the brain believed to be associated with visuo-spatial ability, Brodman's areas 18 and 19, together account for a small proportion of total brain size. This does not, however, discount the possibility that additional tissue is incorporated into the 'visuo-spatial network' of the brain. However, we still do not know whether increased brain size is associated with increased visuo-spatial processing capability directly.

There are two hypotheses, which attempt to explain sex differences in visuo-spatial ability, which are clearly supported by existing data (Halpern 1992). Both of these hypotheses are based on the argument that optimum hormone levels during maturation, rather than brain size, determine lateralisation and spatial ability. Petersen (1976) argues that testosterone is the critical hormone while Nyborg (1884, 1988, 1990) suggests that estradiol is the critical hormone. Both authors agree that although sex differences in visuo-spatial ability have been documented from mid-childhood, visuo-spatial ability improves markedly during adolescence when sex hormone levels are greatly increased.

Visuo-spatial differences between the sexes are not directly related to brain size, however. Halpern (1992: 140-141) cautions that, "there is no evidence to suggest that... smaller brains or that male brains differ in complexity to female brains". Crucially, we do not yet know what comprises the difference in total relative brain size between the sexes. One possibility, yet to be explored, is that male brains may be associated with higher levels of hydration.

Adult males have about 50% more lean body tissue than females (Norgan 1999) and are generally more hydrated as a result (Ellis 1990). About 73% of lean tissue in human adults is comprised of water (Wang et al. 1999). We know that over $\frac{3}{4}$ of the

adult brain is comprised of water and that brain hydration values are not constant but change with age (Widdowson and Dickerson 1960). It is certainly not clear from existing longitudinal MRI studies whether temporary changes in brain size are associated with changes in water, lipid, or protein, for example (see Holdcroft et al. 1997).

Alternatively, increased cerebro-spinal fluid in males (Gur et al. 1999) may explain overall gender differences in relative brain size. It may be that larger individuals (males) require relatively more CSF.

As noted, although female brains are smaller in absolute terms than male brains, neuronal density in female brains is, in fact, higher than in males (Andreasen et al. 1993). This once again calls into question the practice of ascribing function based on size alone.

In addition, the potential statistical influences on brain size dimorphism outcomes must be considered. Body size is comprised of different types and amounts of organs and tissues (bone, fat, lean) and fluids (intercellular and extracellular) in males and females. Present statistical methods for assessing relative brain size cannot adequately control for all of these subunits and their respective allometric affects on brain size. It must at least be acknowledged that present statistical methodological limits may influence these relative size dimorphism outcomes.

Until we can accurately assess whether brain size sexual dimorphism is attributed to a proportional increase in the total size of male brain tissue, or to an increase in one or more specific components (as suggested earlier), or indeed to water, lipid, cerebrospinal fluid or neuronal density differences, a related functional advantage cannot be ascribed, nor can the implications for natural selection be fully assessed.

7.4) Encephalisation and intelligence

In this thesis encephalisation was evaluated simply as a function of the differing proportions of head and body length. There is, however, contradictory evidence regarding the relationship between absolute brain size and intelligence in humans. Some authors argue that there is no link between cognitive ability and brain size, while others argue that there is a relationship between cognition and brain size as well as a number of sub-brain components.

Galton (1888) first attempted to establish a relationship between head size and 'intelligence' scientifically. Using head measures (controlling for age-effects) he found a correlation between estimated head volume and attainment of first-class honors degrees in Cambridge University undergraduate men. Several similar studies followed until the early 20th century when it became unfashionable to ascribe constraints on IQ based on brain size. This was largely in response to the finding that the brains of several distinguished people who bequeathed their bodies to science, were not particularly large or distinguished (see Kuhlenbeck 1978: 636). In the latter part of the century, several studies once again focused on brain size/cognitive correlates, using MRI technology. Their findings appear to support the case for a relationship between brain size and certain aspects of cognitive ability in humans. However, not all investigators agree with this view.

7.4a) Studies in support of a relationship

Flashman et al. (1988), using magnetic resonance imaging, found a statistically significant but weak correlation between whole brain volume and IQ. They also found a positive relationship between full scale IQ and the temporal and frontal regions of the brain. Paradiso et al. (1997) also showed that cerebellar size and IQ were correlated.

Reiss et al. (1996) have shown that gender associated differences in brain size may be related to gender differences in cortical neuronal density. In the MRIs of children aged 5 to 17 years of age total cerebral volume was found to be about 10% larger in males compared with females, with increased cortical gray matter in males explaining this gender difference. The authors showed that IQ in children explained about 15% of the variance in the volume of cortical gray matter in the prefrontal region of the brain.

According to Kimura (1992) and Andreasen et al. (1992) women excel at tasks associated with verbal fluency and retrieval, perceptual speed and motor coordination within personal space. Males, on the other hand, tend to have greater skills in the visuospatial domain and mathematical reasoning. Accordingly, gender differences in brain morphology may be associated with cognitive differences. Andreasen et al. (1992) found that about 12 - 31% of the variance in measures of intelligence were explained by brain size and the size of a number of sub-regions.

The authors derived component volumes from MRI scans, and correlated these with measures of verbal, performance and full-scale IQ. They found a positive correlation between full-scale IQ and intracranial volume, cerebral, temporal lobe, hippocampal and cerebellar volumes, but not with caudate and lateral ventricle volume.

Sex-specific cognitive and brain size differences should not, however, be presumed to reflect differences in 'intelligence' between males and females, as no one cognitive task can be ascribed to overall intelligence. This view is held by a great many researchers who believe that there is no clear relationship between brain size and cognitive ability.

7.4b) Studies negating a relationship

Andreasen et al. (1993) argued that the majority of variance in IQ (intelligence quotient) is explained by the quality rather than quantity of brain tissue. The complexity of the circuitry, dendritic expansion, number of synapses, thickness of

myelin, metabolic efficiency, and efficiency of neurotransmitter production, release and uptake, which facilitate the speed and efficiency of information transfer within the brain. In addition, Schultz (1991), Miller (1994) and Willerman et al. (1994) all argued that the amount of myelination in the brain is related to IQ rather than the amount of brain tissue, *per se*.

According to these findings, size alone cannot be viewed as a cognitive constraint. Females, who have relatively smaller brains than males, have proportionately more gray matter than males. The greater volume of gray matter in female brains is associated with increased efficiency of computational processing of the brain in response to the associated increased nerve cell bodies and dendritic expansion, and greater number of neural connections associated with increased gray matter (Andreasen et al. 1993). Gur (1999) argues that the increased grey matter could compensate for the decreased intracranial space in women.

In addition, no clear association between brain size and intelligence has been found across species (Hahn et al. 1979, MacPhail 1982). As Passingham (1975) points out, the gorilla and orangutan have low encephalisation quotients compared with the chimpanzee, yet there is no evidence to suggest that they are less intelligent. Equally, the talapoin has a higher encephalisation index than that of the chimpanzee, with no evidence suggesting that it is more intelligent. Gibson et al. (2001) concedes that encephalisation measures in primates do not predict performance on the transfer test, which distinguishes simple stimulus-response learning from mental flexibility and changing of tactics to solve a problem. Deacon's (1997) suggestion that encephalisation in primates is not associated with increased intelligence, but with a decrease in body size, is consistent with Gibson's findings.

It cannot, therefore, suffice to argue a general rule based on the fact that humans (and cetaceans) are more encephalised and supposedly more 'intelligent' than other mammals, since there are an equal number of anomalies found in the mammalian literature. For example, the spiny anteater has a relatively larger neocortex than humans, yet there is no evidence suggesting that it is more intelligent (MacPhail 1982).

Humans do appear to differ fundamentally from other primates, according to Deacon (1990, 1997), in being encephalised, not due to reduced body size, but due to extended brain growth, reorganisation and size increase. Deacon (1997) argues that increased brain size in our species is not a reflection of increased intelligence but rather an outcome of prefrontal cortex expansion and brain reorganisation associated with the increased demands of symbolic language.

Until a non-anthropomorphic view of intelligence can be ascribed to non-humans, taking species-specific adaptations into account, any links between brain size and intelligence cannot be objectively assessed across species. Moreover, until some consensus can be reached as to what 'intelligence' means for different species solving very different ecological and social problems, these questions remain in the arena of speculation rather than science.

7.5) Implications for life-history theory

Life-history theory predicts that an organism has a finite amount of energy which it invests in order to maximise its survivability and reproductive success. Accordingly, gestation length, size at birth, weaning age, growth and development, age at sexual maturity and first reproduction, litter size, number of offspring, interbirth interval and age at death vary so as to optimise the organism's inclusive fitness (Hamilton 1974, Stearns 1992).

Life-history theory predicts that a woman will maximise her lifetime reproductive success by differentially investing in her offspring in order to maximise her own inclusive fitness (Trivers 1972). The theory assumes that a female has a finite amount of energy which she invests in her own growth, maintenance, pregnancy, lactation and energy expenditure. Natural selection is assumed to have favored biological mechanisms which achieve an optimal balance between her own survival and fitness needs and the needs of her offspring.

Offspring survival and fitness potential have a bearing on the optimal level of maternal investment in any one offspring. This is because any offspring shares only 50% of her genome and as such constitutes a genetic conflict of interest (Trivers 1974, Haig 1993). Lifetime reproductive success may, therefore, be best served by curtailing or stopping investment in a poorly fetus or infant and saving her energy for future reproduction or for her own survival in times of energy stress (Trivers 1974). This may be in direct opposition with offspring survival strategies and may result in maternal-fetal-conflict.

Clutton-Brock (1991) cites several examples of maternal-fetal conflict in infant and juvenile primates. He argues that infants will attempt to prolong the period of parental care while maternal fitness favors the diversion of energy to reproduction and investment in new young. Infants may adopt several strategies to force mothers to continue their investment. For example, vervet monkeys, baboons, macaques, gorillas and humans engage in frequent suckling in order to prolong maternal anovulation and hence interbirth intervals (Nicolson 1982, Pope et al. 1986, Blurton-Jones and da Costa 1987, Lee 1987, McNeilly 1988, Stewart 1988), thereby maintaining maternal investment levels. Clutton-Brock and Harvey (1976) showed that juvenile rhesus monkeys may actively try and prevent males from copulating with their mothers.

Mothers may respond to offspring attempts at manipulation by attacking offspring (as in coots) or ignoring begging of older young while responding only to younger offspring (as in budgerigars) (Hudson 1979, Horsfall 1984). As Haig (1993) pointed out, genetic conflicts between the fetus and mother during pregnancy also result in maternal-fetal conflict in prenatal life when the fetus attempts to obtain a greater proportion of maternal energy and the mother attempts to curtail fetal investment. An escalation of both maternal and fetal physiological strategies may result, often with detrimental effects, including maternal hypertension, gestational diabetes, fetal hypoxia, fetal ischaemia and growth retardation (Haig 1993).

Life history theory and parent-offspring conflict theory have implications for the findings in this thesis. As shown here, encephalised neonates not only have relatively

large head circumferences (brains) for their body lengths, they also have relatively large non-brain organs, lean and fat tissue deposits and are generally well-nourished. They, therefore, represent the product of greater maternal energetic investment, and are predicted to require similarly high investment subsequently due to their larger body and organ sizes. The study population, however, represents a healthy well-nourished population without energy stress.

In this study there was little evidence for maternal-fetal-conflict. Maternal size (height), explained 0.3% of the variation in neonatal encephalisation, 5% of the variation in neonatal body length and 5% of the variation in birth weight. Placenta weight explained a further 5% of the variation in neonatal encephalisation, a further 14% of the variation in neonatal body length and a further 35% of the variation in birth weight. Maternal protein reserves (mid-arm muscle area) explained a further 1% of the variation in neonatal encephalisation and a further 1.5% of the variation in birth weight. Maternal fatness (triceps skinfold thickness) explained a further 0.3% of the variation in both neonatal encephalisation and body length and a further 1% of the variation in birth weight. This suggests that the well-nourished mothers in this sample tended to invest their energy principally in producing large offspring. Investment in encephalisation appears to be a secondary outcome. This is further supported by the fact that increased maternal parity is associated with increased birth weight and body length. However, as shown in chapter 5, it is not associated with increased encephalisation in the study sample.

Although no indication of maternal-fetal conflict was found, there was evidence for placental-fetal conflict. Placenta weight explained about 5% of the variation in neonatal encephalisation, 14% in neonatal body length and 35% of the variation in birth weight.

This finding is consistent with that of Harding (2001), who argued that maternal nutrition may bear little or no relationship to neonatal size at birth, while fetal nutrition is crucial for fetal growth (as shown in chapter 4, encephalisation). Since

the placenta is integral to nutrient transfer from mother to fetus and is important in metabolism of key nutrients and hormone production, the significant contribution of placental weight in explaining the variation in neonatal size, nutritional status and encephalisation is consistent with Harding's view. This may also explain why maternal nutritional supplementation programs in the developing world have only moderate success in increasing birth weight (Kramer 1993).

Environmental, hormonal, genetic and micronutrient availability may all be factors which help to explain the remaining variation in neonatal encephalisation. These factors were not directly assessed as part of this thesis, but may be important for future study.

Although there was no evidence for maternal-fetal-conflict in the study population, in a nutritionally stressed population, maternal-fetal conflict theory may be more important for explaining the relationship between maternal nutritional status and offspring encephalisation. Given that there is a limit to maternal energy reserves and availability, the encephalised phenotype may be produced via maternal and fetal strategies. Energetic trade-offs may occur between the mother and fetus (i.e. maternal-fetal-conflict), followed by additional energetic trade-offs within the fetus itself (i.e. brain sparing) during severe stress.

In an energy stressed population women are likely to employ energy saving mechanisms, such as those described in a Gambian population by Poppitt et al. (1993). She may reduce basal metabolism (see Dulloo and Jacquet 1998) and energy expenditure and increase her metabolic efficiency (Prentice et al. 1989, Poppitt et al. 1993). If this proves insufficient for meeting fetal energy needs, the fetus may adapt to energy stress by diverting energy resources from other systems to the brain (Dobbing and Widdowson 1965, Cheek et al. 1976, Dobbing 1976, Riopelle 1985, Holliday 1986). Dawkins (1964) and Petry et al. (1997) have shown that a number of non-brain organs may be relatively reduced in nutritionally stressed neonates, while normal brain weight is generally conserved. The fetus may also deposit less lean tissue in favor of increased fat deposition in order to provide itself with an energetic

'safety net' at birth, when fat stores may be broken down to provide energy (Yajnik 2000). The fetus may also manipulate the mother directly in order to gain additional nutrients.

The energetic impact of encephalisation is not the only factor which has impacted human life history. Increased brain size in humans and prolonged brain growth into childhood have a direct impact on life history in their association with an increased sub-adulthood period (Foley and Lee 1991, Deacon 1997). The author has argued elsewhere that human encephalisation, and neocortex expansion in particular, is associated with an increased juvenile period in response to the increased demands of social skill learning prior to reproduction (Joffe 1997). Deacon (1997) suggested that an increased childhood in humans has been an essential part of our brain evolution in that it provided a means for language evolution. According to Deacon, children have reduced capacity for associative learning and short-term memory. They, therefore, acquire language operations quickly and easily and pass this language structure on to subsequent generations with fidelity. He describes childrens' minds as a 'bottleneck' through which language evolved.

Human life history is, therefore, closely associated with the evolution of our brain, its impact on our growth and the energetic costs associated with its maintenance. The inter-relationships between the coevolution of encephalisation and complex sociality and symbolic language are also key factors in human life history patterns.

7.5a) Fetal programming and malnutrition

Maternal inclusive fitness is affected by the potential for her offspring to thrive and reproduce. It may be assumed that the well-nourished, encephalised neonate is more likely to contribute to her inclusive fitness than is the growth retarded neonate. This may be due to the impact of early malnutrition on later health, and presumably reproduction. However, this hypothesis is yet to be directly confirmed by reproductive outcome studies. The current literature on fetal programming may help to explain a potential link between fetal malnutrition and reproductive success.

Programming occurs during critical periods of development when an insult or stimulus permanently alters the endocrine, metabolic and vasculature structure of a particular system and may effect subsequent development and function (Lucas 1991, Barker 1995, 1998). Nutritional programming during the fetal period has been shown to have a significant impact on adult onset diseases including, coronary heart disease and stroke (Barker et al 1993a, Barker et al. 1993b, 1994, 1998), Type-2 non-insulin dependent diabetes (Hales and Barker 1992, Barker et al. 1993c, Petry et al. 1997) and hypertension (Barker et al. 1990). This is referred to as the 'early-origins' hypothesis (see Barker 1992).

Maternal malnutrition at conception is more strongly associated with reduced fetal growth than is maternal condition during pregnancy (Barker 1998). The timing of the intrauterine growth retardation determines which systems are likely to be affected. Once the critical window for development closes, the changes in those systems are imprinted and permanent. Subsequent 'catch up' growth *ex utero* may lead to a 'mismatch' between underlying hormonal and cellular systems and body size (Barker 1994).

The implications of fetal programming for the growth retarded neonate are two-fold. There is now much evidence linking poor-condition to increased morbidity and mortality in babies in the developing world (Victora and Barros 2001). Adequate nourishment, in the absense of disease, is likely to lead to 'catch up' growth in weight, length and head circumference (Brandt 1976, 1988). However, according to the 'early origins' hypothesis, this catch up growth has subsequent implications for adult disease.

Because encephalisation reflects underlying body proportions, changes in encephalisation reflects catch up growth in either body length/weight (i.e. relative reduction in encephalisation) or head circumference (i.e. relative increase in encephalisation). In light of the 'early-origins' hypothesis, regression to the mean in encephalisation, therefore, may not have long-term benefits to the individual, particularly where initially high levels of encephalisation in early life are followed by 'carch down' in encephalisation.

Therefore, the implications of the 'early-origins' hypothesis for a mother's inclusive fitness are that mothers who curtail investment in fetuses in favor of increased postnatal investment are likely to experience a detriment to their inclusive fitness. This is because the 'early-origins' hypothesis predicts that intra-uterine growth faltering in nutritionally stressed populations, followed by 'catch up' growth is associated with adult morbidity and presumably reduced fitness.

According to life history theory, mothers should increase investment in current pregnancies where short-term strategies promote increased inclusive fitness. She should decrease her investment in the fetus only where her immediate survivability or future reproductive prospects promise to increase her inclusive fitness.

7.6) Future directions

The study of growth and encephalisation is clearly in its infancy. This thesis provides new information on strategies for producing encephalised neonates and infants in a well-nourished population. However, it is now important to study these relationships in energy stressed populations in order to improve understanding of the mother's contribution to encephalisation in her offspring.

Measures of maternal energy metabolism will also be important for better understanding the energetic relationship between maternal condition and offspring encephalisation. For example, nitrogen balance and plasma protein levels may be used to assess protein status, while blood glucose levels may indicate glucose availability and metabolism. Basal metabolic rate may be directly assessed using a Douglas Bag, ventilated hood or whole body calorimetry (see Charbonnier et al. 1990). Changes in these parameters, as well as changes in maternal fat and lean body deposits could then be assessed in relation to fetal growth and encephalisation.

Techniques are now available to safely and reliably measure body composition in both mothers and offspring. For example, Dual-energy X-ray absorptiometry (DEXA) is

routinely used to measure bone density (Sartoris and resnick 1989, Fuller et al. 1992b), while whole body air displacement plethysmography (Dewit et al. 2000) is used to estimate body volume. Deuterium dilution is used to calculate total body water and hence lean tissue (Pullicino et al. 1990). Bioelectrical impedance may also be used in this way (see Suzuki et al. 1996). Together these techniques allow for estimates of body density, fat and lean tissues which are far more accurate than estimates based on skinfolds, weight and height measures and water displacement (Durnin and Womersley 1974, Fuller et al. 1992, Chan et al. 1998, Wells et al. 1999).

The relationship between body composition, growth and encephalisation is an important avenue to pursue given that they have strong implications for energy balance in the young individual and mother. In addition, the composition of maternal milk as well as measures of milk output are important to consider in relation to infant encephalisation and changes in encephalisation over time.

Longitudinal assessment of brain growth using Magnetic Resonance Imaging would also be informative in that the brain component composition underlying changes in encephalisation during growth are not yet clearly understood.

Finally, the implications of the 'early origins' hypothesis for adult brain disease should be assessed in light of the evidence for marked 'catch up' in encephalisation in the study population. Barker (1998) has shown that head circumference at birth in relation to birth weight and placental weight is a strong predictor for adult stroke, particularly in men. A low birth weight to head circumference ratio and a low placenta weight to head circumference ratio is associated with an increased incidence of stroke in adult men.

These body proportions reflect encephalisation, where head circumference exceeds body weight. If we assume that body weight reflects size in a similar fashion to body length, then changes in encephalisation over time, therefore, reflect changes in body proportions, where 'catch up' in body weight may be associated with 'catch down' in the head or vice versa.

Potentially, a link between high neonatal encephalisation and subsequent 'catch down' in encephalisation may have implications for adult onset disease, such as stroke and possibly cardiac disease (see Barker et al. 1993b).

APPENDIX

Tables

Table A.1a Body weight and fat as percent of body weight values for birds

Common name	Species	Body mass (kg)	% fat	n
Aves:				
zebra finch	<i>Peophila guttata</i>	.011	5.20	2
Bengalese finch	<i>Lonchura striata</i>	.012	10.00	1
European robin	<i>Erithacus rubecula</i>	.016	12.00	1
great tit	<i>Parus major</i>	.016	9.60	1
house sparrow	<i>Passer domesticus</i>	.024	1.90	1
blackbird	<i>Turdus merula</i>	.067	1.50	2
quail	<i>Coturnix coturnix</i>	.090	10.00	2
ruddy turnstones	<i>Arenaria interpres</i>	.094	5.30	1
	<i>Pluvialis apricarius</i>	.159	19.30	4
collared dove	<i>Streptopelia decaocto</i>	.170	4.40	5
magpie	<i>Pica pica</i>	.178	1.80	1
jackdaw	<i>Corvus monedula</i>	.188	3.60	5
kestrel	<i>Falco</i>	.203	15.60	2
	<i>tinnunculus</i>			
bar-tailed godwit	<i>Limosa lapponica</i>	.240	20.70	8
black-headed gull	<i>Larus ridibundus</i>	.249	2.10	4
paleartic oystercatcher	<i>Haematopus ostralegus</i>	.449	0.60	1
coot	<i>Fulica atra</i>	.474	12.60	2
carrion crow	<i>Corvus corone</i>	.516	4.80	3
tufted duck	<i>Aythya fuligula</i>	.611	14.90	2
mallard	<i>Anas</i>	.741	7.40	7
	<i>platyrhynchos</i>			
herring gull	<i>Larus argentatus</i>	.827	1.90	1
brent goose	<i>Branta</i>	1.25	6.30	1
	<i>bernicla</i>			

source: Daan et al (1990)

Table A.1b Body weight and fat as percent of body weight values for rodents

Common name	Species	Body mass (kg)	% fat	n	Source
Rodentia:					
spiney mouse	<i>Acomys cahirinus</i>	.039	8.50	10	Pond & Mattacks 1985
white mouse		.026	10.00	111	Hayward 1965
deer mouse	<i>Peromyscus</i> genus	.023	24.44	50	Hayward 1965
Four-striped mouse	<i>Rhabdomys pumilio</i>	.042	31.42	109	Wirminghaus and Perrin 1993
Natal multi mammate mouse	<i>Mastomys natalensis</i>	.046	33.92	105	Wirminghaus and Perrin 1993
woodland doormouse	<i>Graphiurus murinus</i>	.021	37.86	26	Wirminghaus and Perrin 1993
woodland mouse	<i>Grammomys dolichurus</i>	.033	29.40	40	Wirminghaus and Perrin 1993
dwarf hamster	<i>Phodopus sungorus</i>	.040	19.95	12	Pond & Mattacks 1985
muskrat	<i>Ondatra zibethicus</i>	.945	4.69	74	Campbell and MacArthur 1998
cotton rat	<i>Sigmodon hispidus</i>	.175	15.65	9	Pond & Mattacks 1985
red-backed vole	<i>Clethrionomys rutilus</i>	.026	3.33	24	Zuercher et al. 1999
prairie vole	<i>Microtus ochrogaster</i>	37.48	4.46	11	Voltura and Wunder 1998
field vole	<i>Microtus agrestis</i>	.022	2.18	32	Meerlo et al. 1997
brown lemming	<i>Lemmus sibiricus</i>	.038	4.00	155	Batzli and Essecks 1992
guinea pig	<i>Cavia porcellus</i>	.905	11.30	10	Pond & Mattacks 1985
gray squirrel	<i>Sciurus carolinensis</i>	.560	7.95	6	Pond & Mattacks 1985

Table A.1c Body weight and fat as percent of body weight values for insectivores

Common name	Species	Body mass (kg)	% fat	n	Source
Insectivora:					
forest shrew	<i>Myosorex varius</i>	.012	30.17	60	Wirminghaus and Perrin 1993
hedgehog	<i>Erinaceus europaeus</i>	.755	8.00	5	Pond & Mattacks 1985

Table A.1d Body weight and fat as percent of body weight values for carnivores

Common name	Species	Body mass (kg)	% fat	n	Source
Carnivora:					
ferret	<i>Mustela putorius</i>	.695	13.75	11	Pond & Mattacks 1985
stoat - laboratory	<i>Mustela erminea</i>	.788	15.83	8	Pond & Ramsay 1992
American marten	<i>Martes americana</i>	1.25	4.20	45	Buskirk & Harlow 1989
ringtail cat	<i>Bassariscus astutus</i>	.752	1.49	8	Chevalier 1989
domestic cat	<i>felis catus</i>	2.66	10.50	5	Pond & Mattacks 1985
dog	<i>Canis</i>	6.04	19.87	.	Harrison et al. 1936 ³
wolverine	<i>Gulo gulo</i>	12.07	4.49	19	Pond et al. 1994
wild otter	<i>Lutra lutra</i>	7.60	3.00	.	Pond 1985
river otter	<i>Lutra canadensis</i>	7.96	12.60	3	Tarasoff 1974
sea otter	<i>Enhydra lutris</i>	19.6	1.80	1	Tarasoff 1974
arctic fox	<i>Alopex lagopus</i>	3.21	15.40	75	Prestrud & Nilssen 1992
badger	<i>Meles meles</i>	9.24	13.30	11	Pond & Mattacks 1985
coyote	<i>Canis latrans</i>	13.00	12.08	27	Huot et al 1995
polar bear	<i>Ursus maritimus</i>	407	17.80	1	Pond et al. 1992
black bear	<i>Ursus americanus</i>	107.7	27.00	8	Hilderbrand et al. 1998
brown bear	<i>Ursus arctos</i>	206	27.40	2	Pond & Ramsay 1992
jaguar	<i>Panthera onca</i>	64	15.00	1	Pond & Ramsay 1992
tiger	<i>Panthera tigris</i>	100	10.00	1	Pond & Ramsay 1992
lion	<i>Panthera leo</i>	165	13.30	1	Pond & Ramsay 1992

Table A.1e Body weight and fat as percent of body weight values for bats

Common name	Species	Body mass (kg)	% fat	n	Source
Chiroptera:					
little brown bat (hibernating)	<i>Myotis lucifugus</i>	.009	20.50	5	O'Farrell et al. 1971
yuma bat (hibernating)	<i>Myotis yumanensis</i>	.007	31.90	8	O'Farrell et al. 1971
fringe-tailed bat (hibernating)	<i>Myotis thysanodes</i>	.010	23.30	9	O'Farrell et al. 1971
evening bat	<i>Nycticeius humeralis</i>	.009	9.92	20	Wilson Baker et al. 1967

Table A.1f Body weight and fat as percent of body weight values for lagomorphs

Common name	Species	Body mass (kg)	% fat	n	Source
Lagomorpha:					
rabbit	<i>Oryctolagus cuniculus</i>	3.14	14.85	5	Pond & Mattacks 1985

Table A.1g Body weight and fat as percent of body weight values for ungulates

Common name	Species	Body mass (kg)	% fat	n	Source
Artiodactyla:					
chinese water deer	<i>Hydropotes inermis</i>	8.30	6.45	4	Pond & Mattacks 1985
mule deer	<i>Odocoileus hemionus</i>	70.6	7.58	119	Torbit et al. 1988, Anderson et al. 1971
European roe deer	<i>Capreolus capreolus</i>	23.5	20.00	43	Holand 1992
black-tailed deer	<i>Odocoileus hemionus sitkensis</i>	55.5	11.07	9	Parker et al. 1993
caribou	<i>Rangifer tarandus groenlandicu</i>	81.0	34.78	79	Adamczewski et al. 1995
reindeer	<i>Rangifer tarandus platyrhynchu</i>	63.1	18.96	5	Reimers et al. 1982
camel	<i>Camelus</i>	520	14.66	3	MacFarlane & Howard 1972 ⁴
muskoxen	<i>Ovibos moschatus</i>	158.3	18.74	11	Adamczewski et al. 1995
moose	<i>Alces alces</i>	431.9	13.22	9	Stephenson et al. 1998
Thompson's gazelle	<i>Gazella thompsonii</i>	24.5	.33	.	Ledger et al 1961
steer	<i>bos</i>	533.38	26.00	.	Pearson 1963
hog	<i>sus</i>	95.8	33.70	20	Lynch & Wellington 1963
Omani sheep	<i>Ovis</i>	22.3	25.08	60	Mahgoub & Lodge 1998
Omani goat	<i>Capra</i>	21.2	15.72	60	Mahgoub & Lodge 1998
Saanen goat	<i>Capra</i>	30.0	32.80	.	Colomer-Rocher et al. 1992
goat	<i>Capra</i>	31.3	6.07	.	Ledger et al 1961
sheep	<i>Ovis</i>	32.2	13.35	.	Palsson 1940
mare	<i>equus</i>	250	17.00	.	Pearson 1963

Table A.1h Body weight and fat as percent of body weight values for marsupials

Common name	Species	Body mass (kg)	% fat	n	Source
Marsupialia:					
brush-tailed possum	<i>Trichosurus vulpecula kerr</i>	2.93	24.06	200	Bamford 1970
long-nosed bandicoot	<i>Perameles nasuta</i>	.972	17.00	6	Hulbert and Dawson 1974
greater bilby	<i>Macrotis lagotis</i>	1.08	24.00	4	Hulbert and Dawson 1974
short-nosed bandicoot	<i>Isoodon macrourus</i>	1.47	24.00	5	Hulbert and Dawson 1974
golden bandicoot	<i>Isoodon aurus</i>	.306	16.67	.	Bradshaw et al. 1994 ¹
koala	<i>Phascolarctos cinereus</i>	6.91	3.26	9	Degabriele et al. 1978 ¹
phascogale	<i>Dasycerus cristicauda</i>	.092	10.98	34	Kennedy and MacFarlane 1971 ²
dunnart	<i>Smithopsis crassicaudata</i>	.019	11.05	8	Kennedy and MacFarlane 1971 ²
Tammar wallaby	<i>Macropus eugenii</i>	6.50	16.71	6	Denny and Dawson 1975
potoroo	<i>Potorous tridactylus tridactyl</i>	1.40	19.43	6	Denny and Dawson 1975
red kangaroo	<i>Macropus rufus</i>	39.4	.92	5	Tribe and Peel 1963
grey kangaroo	<i>Macropus major</i>	21.4	.30	1	Tribe and Peel 1963

Table A.1i Body weight and fat as percent of body weight values for cetaceans

Common name	Species	Body mass (kg)	% fat	n	Source
Cetacea:					
rough-toothed dolphin	<i>Steno bredanensis</i>	133.4	25.60	15	Miyazaki and Perrin 1994
beaked whale	<i>mesoplona</i> genus	1540	21.20	2	Mead 1989
franciscana dolphin	<i>Pontoporia blainvillei</i>	35.4	28.73	1	Brownell Jr. 1989

Table A.1j Body weight and fat as percent of body weight values for pinnipeds

Common name	Species	Body mass (kg)	% fat	n	Source
Pinnipedia:					
ringed seal	<i>Phoca hispida</i>	68.3	41.82	45	Ryg et al 1990
gray seal	<i>Halichoerus grypus</i>	128.1	33.65	12	Pond & Mattacks 1985
crabeater seal	<i>Lobodon carcinophagus</i>	201.4	20.41	7	Bryden and Erickson 1976
fur seal	<i>Arctocephalus gazella</i>	40.6	14.50	5	Arnould et al. 1996
harp seal	<i>Phoca groenlandica</i>	112.3	44.05	8	Beck et al. 1993
Ross seal	<i>Ommatophoca rossi</i>	179	21.82	2	Bryden and Erickson 1976
elephant seal - male	<i>Mirounga leonina</i>	1920	30.53	3	Bryden 1972
elephant seal - female	<i>Mirounga leonina</i>	311.3	23.83	4	Bryden 1972

Table A.1k Body weight and fat as percent of body weight values for primates

Common name	Species	Body mass (kg)	% fat	n	Source
Primates:					
ringtailed lemur	<i>Lemur catta</i>	3.80	20.00	1	Pereira and Pond 1995
collared lemur	<i>Eulemur fulvus</i> <i>collaris</i>	2.22	7.00	1	Pereira and Pond 1995
red-fronted lemur	<i>Eulemur fulvus</i> <i>rufus</i>	1.61	7.00	1	Pereira and Pond 1995
rhesus monkey	<i>Macaca</i> <i>mulatta</i>	7.00	18.30	7	Walker et al. 1984
baboon - wild feeding	<i>Papio sp.</i>	11.9	5.18	16	Altmann et al. 1993
pigtailed macaques	<i>Macaca</i> <i>nemestrina</i>	7.93	12.70	.	Walike et al. 1977
squirrel monkey	<i>Saimiri sciurus</i>	.792	7.21	26	Russo et al. 1980
crab eating macaque	<i>Macaca</i> <i>fascicularis</i>	3.20	38.34	4	Kamis and Latif 1981
gibbon	<i>Hylobates lar</i>	3.85	15.06	3	Kamis and Latif 1981
cebus monkey	<i>cebus albifrons</i>	2.70	4.17	12	Ausman et al. 1982
human - male	<i>Homo sapiens</i>	69.4	14.00	32	Dulloo and Jacquet 1998 ²
human -female reference man	<i>Homo sapiens</i>	53.8	21.30	93	Lawrence et al 1988 ²
reference woman	<i>Homo sapiens</i>	70.0	21.00	.	Snyder et al. 1975
reference woman in Gambia	<i>Homo sapiens</i>	58.0	33.00	.	Snyder et al. 1975
woman in Gambia	<i>Homo sapiens</i>	50.8	19.00	47	Lawrence et al 1988
woman in Scotland	<i>Homo sapiens</i>	56.7	23.6	46	Lawrence et al 1988
pregnant [^] (Scotland)	<i>Homo sapiens</i>	57.0	25.40	91	Lawrence et al 1988
Pregnant [^] (Gambia)	<i>Homo sapiens</i>	50.4	19.40	50	Lawrence et al 1988
Pregnant [^] (Thailand)	<i>Homo sapiens</i>	48.0	24.00	52	Lawrence et al 1988
pregnant* (Cambridge)	<i>Homo sapiens</i>	67.9	29.78	10	Goldberg et al. 1991
NPNL (Cambridge)	<i>Homo sapiens</i>	57.1	27.45	10	Goldberg et al. 1991
lactating (1 mo.)	<i>Homo sapiens</i>	58.9	30.28	10	Goldberg et al. 1991
lactating (2 mo.)	<i>Homo sapiens</i>	58.9	31.05	10	Goldberg et al. 1991
lactating (3 mo.)	<i>Homo sapiens</i>	58.6	31.42	10	Goldberg et al. 1991

% fat = percent of body weight attributed to fat, n = sample size, NPNL = non-pregnant, non-lactating,

[^] gestation ranging between 6-17 weeks, *Pregnancy at 36 gestation weeks

calculated from total body water, where TBW:FFM =

¹ 0.737 (Wang et al. 1999)

² 0.730 (mammalian average from Wang et al. 1999 and Sheng and Huggins 1979)

³ 0.744 (Wang et al. 1999)

⁴ 0.740 (Mac Farlane and Howard 1972)

Table A.2 L, M and S values derived by plotting head circumference against age.
Used to calculate head circumference SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
ultrasound 2:						
18	-	-	-	1.514	160.216	.0446
19	1.525	171.781	.0433	1.514	167.314	.0446
20	1.525	178.047	.0433	1.514	174.401	.0446
21	1.525	184.335	.0433	1.514	181.474	.0446
22	1.525	190.665	.0433	1.514	188.558	.0446
23	-	-	-	1.514	195.651	.0446
ultrasound 3:						
29	2.988	283.296	.0367	.522	275.013	.0374
30	2.988	289.310	.0367	.522	281.904	.0374
31	2.988	295.319	.0367	.522	288.791	.0374
32	2.988	301.313	.0367	.522	295.666	.0374
33	2.988	307.284	.0367	.522	302.527	.0374
34	2.988	313.248	.0367	.522	309.382	.0374
35	2.988	319.212	.0367	.522	316.226	.0374
36	-	-	-	.522	323.062	.0374
birth:						
36	-	-	-	1.763	329.380	.0383
37	.004	337.334	.0410	1.763	333.155	.0383
38	.004	342.197	.0410	1.763	336.930	.0383
39	.004	346.734	.0410	1.763	340.705	.0383
40	.004	350.631	.0410	1.763	344.480	.0383
41	.004	353.570	.0410	1.763	348.255	.0383
42	.004	355.921	.0410	1.763	352.030	.0383
6 months:						
23	.773	437.487	.0258	-.0976	424.708	.0272
24	.773	438.798	.0258	-.0976	426.569	.0272
25	.773	440.108	.0258	-.0976	428.428	.0272
26	.773	441.418	.0258	-.0976	430.279	.0272
27	.773	442.729	.0258	-.0976	432.114	.0272
28	.773	444.039	.0258	-.0976	433.934	.0272
1 year:						
52	-.245	470.364	.2404	-1.993	458.468	.0273

Table A.3a L, M and S values derived by plotting femur length against age. Used to calculate femur length SD scores

gestation age (weeks)	Males			Females		
	L	M	S	L	M	S
ultrasound 2						
18	-	-	-	.0794	28.719	.0614
19	-.9563	30.2693	.0600	.0794	30.432	.0614
20	-.9563	32.0980	.0600	.0794	32.145	.0614
21	-.9563	33.9267	.0600	.0794	33.858	.0614
22	-.9563	35.7553	.0600	.0794	35.571	.0614
23	-	-	-	.0794	37.284	.0614
ultrasound 3:						
29	1.3347	57.134	.0394	-	-	-
30	1.3347	58.646	.0394	-.2506	58.525	.0390
31	1.3347	60.157	.0394	-.2506	60.132	.0390
32	1.3347	61.669	.0394	-.2506	61.735	.0390
33	1.3347	63.181	.0394	-.2506	63.336	.0390
34	1.3347	64.693	.0394	-.2506	64.936	.0390
35	1.3347	66.204	.0394	-.2506	66.535	.0390

Table A.3b L, M and S values derived by plotting body length against age. Used to calculate body length SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	.4985	471.426	.0426
37	-.1185	485.535	.0463	.4985	479.572	.0426
38	-.1185	492.493	.0463	.4985	487.269	.0426
39	-.1185	499.452	.0463	.4985	494.253	.0426
40	-.1185	506.410	.0463	.4985	500.442	.0426
41	-.1185	513.368	.0463	.4985	505.112	.0426
42	-.1185	520.326	.0463	.4985	509.199	.0426
6 months:						
23	-.4548	668.223	.0333	.8900	649.184	.0349
24	-.4548	672.942	.0333	.8900	655.035	.0349
25	-.4548	677.661	.0333	.8900	660.878	.0349
26	-.4548	682.380	.0333	.8900	666.692	.0349
27	-.4548	687.099	.0333	.8900	672.419	.0349
28	-.4548	691.818	.0333	.8900	678.097	.0349
1 year:						
52	3.0926	767.647	.0345	3.4905	748.119	.0357

Table A.4 L, M and S values derived by plotting body weight against age. Used to calculate body weight SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	.9393	2.767	.1317
37	.3267	3.012	.1343	.9393	2.974	.1317
38	.3267	3.214	.1343	.9393	3.162	.1317
39	.3267	3.393	.1343	.9393	3.315	.1317
40	.3267	3.552	.1343	.9393	3.440	.1317
41	.3267	3.687	.1343	.9393	3.535	.1317
42	.3267	3.830	.1343	.9393	3.619	.1317
6 months:						
23	.5327	7.964	.1152	-.3282	7.114	.1141
24	.5327	8.008	.1152	-.3282	7.256	.1141
25	.5327	8.051	.1152	-.3282	7.397	.1141
26	.5327	8.095	.1152	-.3282	7.539	.1141
27	.5327	8.138	.1152	-.3282	7.681	.1141
28	.5327	8.182	.1152	-.3282	7.822	.1141
1 year:						
52	-.4482	10.076	.0986	-.9577	9.4572	.1117

Table A.5 L, M and S values derived by plotting Benn indices against age. Used to calculate Benn index SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
<i>Benn index</i>						
birth:						
36	-	-	-	.761	.108	.116
37	.845	.109	.111	.761	.109	.116
38	.845	.110	.111	.761	.110	.116
39	.845	.111	.111	.761	.111	.116
40	.845	.112	.111	.761	.112	.116
41	.845	.113	.111	.761	.113	.116
42	.845	.114	.111	.761	.114	.116

Table A.6 L, M and S values derived by plotting body mass indices against age. Used to calculate BMI SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
6 months:						
23	.806	1.782	.090	.066	1.693	.088
24	.806	1.767	.090	.066	1.696	.088
25	.806	1.752	.090	.066	1.700	.088
26	.806	1.737	.090	.066	1.702	.088
27	.806	1.723	.090	.066	1.704	.088
28	.806	1.708	.090	.066	1.706	.088
1 year:						
52	-1.627	1.714	0.075	0.730	1.710	0.085

Table A.7 L, M and S values derived by plotting sub-scapular skinfold thickness against age. Used to calculate subscapular skinfold thickness SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	-.1582	4.937	.2867
37	-.3405	4.772	.2821	-.1582	5.011	.2867
38	-.3405	4.835	.2821	-.1582	5.085	.2867
39	-.3405	4.898	.2821	-.1582	5.159	.2867
40	-.3405	4.961	.2821	-.1582	5.234	.2867
41	-.3405	5.025	.2821	-.1582	5.308	.2867
42	-.3405	5.088	.2821	-.1582	5.382	.2867

Table A.8 L, M and S values derived by plotting triceps skinfold thickness against age. Used to calculate triceps skinfold thickness SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	-.0017	5.242	.2535
37	-.2903	5.193	.2621	-.0017	5.350	.2535
38	-.2903	5.297	.2621	-.0017	5.459	.2535
39	-.2903	5.400	.2621	-.0017	5.567	.2535
40	-.2903	5.503	.2621	-.0017	5.675	.2535
41	-.2903	5.607	.2621	-.0017	5.783	.2535
42	-.2903	5.710	.2621	-.0017	5.891	.2535

Table A.9 L, M and S values derived by plotting estimated mid-arm muscle area against age. Used to calculate mid-arm muscle area SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	-.0043	418.221	.4243
37	.5207	591.111	.4252	-.0043	477.468	.4243
38	.5207	636.334	.4252	-.0043	536.714	.4243
39	.5207	681.557	.4252	-.0043	595.960	.4243
40	.5207	726.781	.4252	-.0043	655.206	.4243
41	.5207	772.004	.4252	-.0043	714.453	.4243
42	.5207	817.228	.4252	-.0043	773.699	.4243

Table A.10 L, M and S values derived by plotting estimated mid-arm fat area against age. Used to calculate mid-arm fat area SD scores

age (weeks)	Males			Females		
	L	M	S	L	M	S
birth:						
36	-	-	-	-.0328	211.395	.3745
37	-.1886	239.525	.3759	-.0328	229.382	.3745
38	-.1886	253.371	.3759	-.0328	247.370	.3745
39	-.1886	267.132	.3759	-.0328	265.358	.3745
40	-.1886	280.889	.3759	-.0328	283.345	.3745
41	-.1886	294.576	.3759	-.0328	301.333	.3745
42	-.1886	308.311	.3759	-.0328	319.321	.3745

Table A.11a Descriptive statistics for fetal autopsy measures at 20 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	16	26.8	4.37	thyroid	16	26.8	4.37
weight	16	468.6	146	kidney	16	468.6	146
brain	16	62.3	20.8	liver	16	62.3	20.8
heart + lungs	13	19.2	9.50	spleen	13	19.2	9.50
heart	1	4.30	.	adrenal glands	1	4.30	.
lungs	1	20.4	.	thymus	1	20.4	.

Table A.11b Descriptive statistics for fetal autopsy measures at 22 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	17	28.05	2.92	thyroid	2	0.80	0.28
weight	16	543	221	kidney	12	5.78	3.17
brain	17	69.7	36.0	liver	16	30.9	14.8
heart + lungs	12	20.8	6.68	spleen	13	1.25	0.83
heart	5	8.04	3.19	adrenal glands	14	2.42	1.43
lungs	5	15.87	6.5	thymus	6	5.17	8.76

Table A.11c Descriptive statistics for fetal autopsy measures at 23 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	14	27.8	3.09	thyroid	1	0.60	.
weight	14	545	129	kidney	9	4.64	2.52
brain	14	82.6	44.35	liver	13	28.3	8.86
heart + lungs	14	21.2	7.44	spleen	11	1.11	0.63
heart	2	5.75	1.77	adrenal glands	13	2.98	1.22
lungs	2	20.75	3.18	thymus	10	1.77	1.30

Table A.11d Descriptive statistics for fetal autopsy measures at 24 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	30	31.8	3.95	thyroid	2	0.75	0.35
weight	30	710	264	kidney	26	7.07	3.41
brain	30	102.6	40.9	liver	27	33.3	9.30
heart + lungs	21	25.5	10.5	spleen	27	2.10	2.01
heart	4	9.75	5.25	adrenal glands	25	2.98	1.44
lungs	4	27.10	11.31	thymus	20	2.91	2.63

Table A.11e Descriptive statistics for fetal autopsy measures at 25 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	16	30.2	4.36	thyroid	.	.	.
weight	16	727	191	kidney	13	8.40	4.54
brain	16	104	24.7	liver	14	36.7	15.5
heart + lungs	11	23.9	6.98	spleen	13	1.73	1.62
heart	.	.	.	adrenal glands	14	2.83	1.14
lungs	.	.	.	thymus	8	2.06	0.80

Table A.11f Descriptive statistics for fetal autopsy measures at 26 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	20	32.8	3.97	thyroid	1	0.50	.
weight	20	929	315	kidney	20	9.86	4.81
brain	22	123	36.8	liver	20	41.2	16.6
heart + lungs	12	25.6	6.45	spleen	20	2.27	2.08
heart	7	7.04	2.52	adrenal glands	21	3.13	1.59
lungs	5	17.0	2.83	thymus	12	3.23	2.02

Table A.11g Descriptive statistics for fetal autopsy measures at 27 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	13	34.1	4.19	thyroid	.	.	.
weight	13	826	236	kidney	11	8.13	3.48
brain	13	114	35.9	liver	12	39.4	11.9
heart + lungs	4	38.6	11.0	spleen	12	2.93	4.56
heart	.	.	.	adrenal glands	11	2.78	1.42
lungs	2	21.25	5.30	thymus	8	1.74	1.09

Table A.11h Descriptive statistics for fetal autopsy measures at 28 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	20	33.6	3.39	thyroid	3	1.90	0.53
weight	19	935	265	kidney	16	11.0	6.64
brain	19	132	38.4	liver	16	40.3	15.4
heart + lungs	13	25.1	9.85	spleen	16	2.27	1.42
heart	5	6.36	1.04	adrenal glands	19	3.11	1.18
lungs	4	13.0	4.08	thymus	12	3.04	1.86

Table A.11i Descriptive statistics for fetal autopsy measures at 29 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	14	35.4	9.06	thyroid	1	0.80	.
weight	14	1224	362	kidney	12	10.7	5.88
brain	14	178	55.7	liver	13	44.0	13.8
heart + lungs	7	33.5	16.3	spleen	12	4.06	2.93
heart	5	8.90	4.35	adrenal glands	10	5.05	4.74
lungs	3	24.9	8.82	thymus	6	5.08	3.17

Table A.11j Descriptive statistics for fetal autopsy measures at 30 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	17	38.3	4.85	thyroid	4	0.68	0.38
weight	16	1304	375	kidney	14	12.2	2.88
brain	17	169	51.7	liver	13	52.0	17.7
heart + lungs	9	32.9	9.91	spleen	14	3.14	1.69
heart	2	15.5	10.6	adrenal glands	16	3.49	1.99
lungs	1	22	.	thymus	12	5.13	2.33

Table A.11k Descriptive statistics for fetal autopsy measures at 31 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	11	36.5	3.36	thyroid	1	1.50	.
weight	13	1419	469	kidney	11	15.2	5.80
brain	13	175	64.3	liver	11	54.6	14.8
heart + lungs	7	38.4	18.1	spleen	12	4.15	3.38
heart	4	14.38	9.50	adrenal glands	10	5.28	2.06
lungs	4	26.25	15.46	thymus	6	5.05	3.01

Table A.11l Descriptive statistics for fetal autopsy measures at 32 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	21	40.1	5.29	thyroid	4	1.10	0.27
weight	21	1434	412	kidney	23	15.6	5.73
brain	24	210	83.6	liver	18	69.7	30.9
heart + lungs	5	37.7	11.0	spleen	19	5.37	3.50
heart	8	13.0	6.67	adrenal glands	22	4.61	2.17
lungs	2	26.5	7.07	thymus	14	7.13	4.24

Table A.11m Descriptive statistics for fetal autopsy measures at 33 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	16	39.6	5.45	thyroid	1	1.00	.
weight	15	1699	450	kidney	15	14.4	4.81
brain	16	232	64.2	liver	16	57.2	17.2
heart + lungs	7	42.8	13.1	spleen	15	4.43	1.90
heart	4	11.4	4.96	adrenal glands	14	4.08	2.20
lungs	3	26.6	10.7	thymus	11	5.28	2.88

Table A.11n Descriptive statistics for fetal autopsy measures at 34 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	16	42.9	4.06	thyroid	2	1.45	0.78
weight	16	1732	628	kidney	12	16.9	6.25
brain	16	244	55.5	liver	13	77.4	31.2
heart + lungs	9	53.2	22.1	spleen	15	7.00	4.07
heart	2	10.5	6.36	adrenal glands	11	4.67	2.23
lungs	2	27.0	24.0	thymus	12	5.81	3.16

Table A.11o Descriptive statistics for fetal autopsy measures at 35 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	9	42.8	6.82	thyroid	.	.	.
weight	10	2256	434	kidney	7	20.5	6.81
brain	10	288	60.3	liver	7	90.7	32.1
heart + lungs	3	85.7	44.4	spleen	8	7.03	2.31
heart	.	19.5	2.12	adrenal glands	8	4.89	2.47
lungs	.	.	.	thymus	3	8.00	3.61

Table A.11p Descriptive statistics for fetal autopsy measures at 36 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	17	42.8	4.05	thyroid	3	2.33	1.53
weight	17	2338	417	kidney	15	20.3	7.02
brain	17	277	79.8	liver	16	88.4	34.1
heart + lungs	11	59.2	14.6	spleen	17	8.43	8.59
heart	4	15.13	1.44	adrenal glands	14	6.56	2.44
lungs	2	57.0	9.90	thymus	12	7.30	3.60

Table A.11q Descriptive statistics for fetal autopsy measures at 40 gestation weeks

variable	n	mean	sd	variable	n	mean	sd
length	43	50.2	5.43	thyroid	2	1.85	0.49
weight	39	3105	747	kidney	37	25.9	9.95
brain	43	359	83.5	liver	38	128	43.0
heart + lungs	24	74.1	12.7	spleen	38	10.3	4.71
heart	9	20.9	10.2	adrenal glands	38	8.84	3.25
lungs	5	46.9	8.91	thymus	28	9.06	3.80

Means, standard deviations (sd) and samples sizes (n) derived from pooled sex data.
All distributions are age-specific and normal.

Table A.12a L, M, and S values derived by plotting adrenal gland weight (g) against gestation age. Used to calculate fetal adrenal weight SD scores

Variable & age	L	M	S	Variable & age	L	M	S
adrenal glands							
17	0.31	1.915	0.502	31	0.31	3.976	0.502
18	0.31	1.977	0.502	32	0.31	4.253	0.502
19	0.31	2.049	0.502	33	0.31	4.548	0.502
20	0.31	2.120	0.502	34	0.31	4.862	0.502
21	0.31	2.210	0.502	35	0.31	5.193	0.502
22	0.31	2.315	0.502	36	0.31	5.541	0.502
23	0.31	2.435	0.502	37	0.31	5.900	0.502
24	0.31	2.567	0.502	38	0.31	6.269	0.502
25	0.31	2.713	0.502	39	0.31	6.645	0.502
26	0.31	2.875	0.502	40	0.31	7.024	0.502
27	0.31	3.055	0.502	41	0.31	7.403	0.502
28	0.31	3.256	0.502	42	0.31	7.782	0.502
29	0.31	3.477	0.502	43	0.31	8.159	0.502
30	0.31	3.717	0.502	44	0.31	8.537	0.502

age = gestation weeks

Table A.12b L, M, and S values derived by plotting brain weight (g) against gestation age.
Used to calculate fetal brain weight SD scores

Variable & age	L	M	S	Variable & age	L	M	S
brain							
17	0.16	58.98	0.388	31	0.16	169.7	0.388
18	0.16	61.80	0.388	32	0.16	183.3	0.388
19	0.16	65.07	0.388	33	0.16	197.2	0.388
20	0.16	68.33	0.388	34	0.16	211.3	0.388
21	0.16	72.76	0.388	35	0.16	225.6	0.388
22	0.16	78.23	0.388	36	0.16	240.0	0.388
23	0.16	84.78	0.388	37	0.16	254.5	0.388
24	0.16	92.35	0.388	38	0.16	269.2	0.388
25	0.16	100.9	0.388	39	0.16	283.9	0.388
26	0.16	110.4	0.388	40	0.16	298.6	0.388
27	0.16	120.7	0.388	41	0.16	313.3	0.388
28	0.16	132.0	0.388	42	0.16	328.0	0.388
29	0.16	144.0	0.388	43	0.16	342.8	0.388
30	0.16	156.6	0.388	44	0.157	357.5	0.388

age = gestation weeks

Table A.12c L, M, and S values derived by plotting heart weight (g) against gestation age. Used to calculate fetal heart weight SD scores

variable & age	L	M	S	variable & age	L	M	S
heart							
18	-0.02	3.795	0.491	31	-0.02	10.54	0.491
19	-0.02	4.193	0.491	32	-0.02	11.30	0.491
20	-0.02	4.591	0.491	33	-0.02	12.09	0.491
21	-0.02	5.020	0.491	34	-0.02	12.90	0.491
22	-0.02	5.473	0.491	35	-0.02	13.74	0.491
23	-0.02	5.934	0.491	36	-0.02	14.60	0.491
24	-0.02	6.403	0.491	37	-0.02	15.46	0.491
25	-0.02	6.894	0.491	38	-0.02	16.34	0.491
26	-0.02	7.384	0.491	39	-0.02	17.23	0.491
27	-0.02	7.945	0.491	40	-0.02	18.12	0.491
28	-0.02	8.505	0.491	41	-0.02	19.02	0.491
29	-0.02	9.140	0.491	42	-0.02	19.91	0.491
30	-0.02	9.823	0.491				

age = gestation weeks

Table A.12d L, M, and S values derived by plotting heart and lungs weight (g) against gestation age. Used to calculate fetal heart and lungs weight SD scores

variable & age	L	M	S	variable & age	L	M	S
heart & lungs	combined						
17	0.61	15.11	0.379	31	0.61	38.28	0.379
18	0.61	16.12	0.379	32	0.61	41.03	0.379
19	0.61	17.17	0.379	33	0.61	43.88	0.379
20	0.61	18.22	0.379	34	0.61	46.81	0.379
21	0.61	19.36	0.379	35	0.61	49.80	0.379
22	0.61	20.59	0.379	36	0.61	52.81	0.379
23	0.61	21.92	0.379	37	0.61	55.84	0.379
24	0.61	23.40	0.379	38	0.61	58.89	0.379
25	0.61	25.02	0.379	39	0.61	61.96	0.379
26	0.61	26.80	0.379	40	0.61	65.03	0.379
27	0.61	28.76	0.379	41	0.61	68.10	0.379
28	0.61	30.89	0.379	42	0.61	71.17	0.379
29	0.61	33.19	0.379	43	0.61	74.24	0.379
30	0.61	35.66	0.379	44	0.61	77.31	0.379

age = gestation weeks

Table A.12e L, M, and S values derived by plotting kidney weight (g) against gestation age. Used to calculate fetal kidney weight SD scores

variable & age	L	M	S	variable & age	L	M	S
kidneys							
17	0.33	3.51	0.459	31	0.33	12.74	0.459
18	0.33	3.89	0.459	32	0.33	13.75	0.459
19	0.33	4.28	0.459	33	0.33	14.80	0.459
20	0.33	4.67	0.459	34	0.33	15.86	0.459
21	0.33	5.12	0.459	35	0.33	16.95	0.459
22	0.33	5.61	0.459	36	0.33	18.05	0.459
23	0.33	6.17	0.459	37	0.33	19.16	0.459
24	0.33	6.80	0.459	38	0.33	20.28	0.459
25	0.33	7.49	0.459	39	0.33	21.40	0.459
26	0.33	8.24	0.459	40	0.33	22.53	0.459
27	0.33	9.04	0.459	41	0.33	23.66	0.459
28	0.33	9.90	0.459	42	0.33	24.78	0.459
29	0.33	10.80	0.459	43	0.33	25.91	0.459
30	0.33	11.75	0.459	44	0.33	27.04	0.459

age = gestation weeks

Table A.12f L, M, and S values derived by plotting lungs weight (g) against gestation age. Used to calculate fetal lungs weight SD scores

variable & age	L	M	S	variable & age	L	M	S
lungs							
18	0.42	13.60	0.391	30	0.42	23.50	0.391
19	0.42	14.31	0.391	31	0.42	25.00	0.391
20	0.42	15.02	0.391	32	0.42	26.65	0.391
21	0.42	15.74	0.391	33	0.42	28.43	0.391
22	0.42	16.46	0.391	34	0.42	30.33	0.391
23	0.42	17.18	0.391	35	0.42	32.32	0.391
24	0.42	17.87	0.391	36	0.42	34.32	0.391
25	0.42	18.55	0.391	37	0.42	36.36	0.391
26	0.42	19.23	0.391	38	0.42	38.41	0.391
27	0.42	20.04	0.391	39	0.42	40.47	0.391
28	0.42	21.01	0.391	40	0.42	42.53	0.391
29	0.42	22.16	0.391				

age = gestation weeks

Table A.12g L, M, and S values derived by plotting spleen weight (g) against gestation age. Used to calculate fetal spleen weight SD scores

variable & age	L	M	S	variable & age	L	M	S
spleen							
17	0.00	0.477	0.661	31	0.00	3.506	0.661
18	0.00	0.579	0.661	32	0.00	3.909	0.661
19	0.00	0.686	0.661	33	0.00	4.328	0.661
20	0.00	0.793	0.661	34	0.00	4.760	0.661
21	0.00	0.915	0.661	35	0.00	5.202	0.661
22	0.00	1.053	0.661	36	0.00	5.651	0.661
23	0.00	1.213	0.661	37	0.00	6.105	0.661
24	0.00	1.398	0.661	38	0.00	6.564	0.661
25	0.00	1.610	0.661	39	0.00	7.026	0.661
26	0.00	1.851	0.661	40	0.00	7.490	0.661
27	0.00	2.124	0.661	41	0.00	7.954	0.661
28	0.00	2.428	0.661	42	0.00	8.418	0.661
29	0.00	2.762	0.661	43	0.00	8.882	0.661
30	0.00	3.122	0.661	44	0.00	9.346	0.661

age = gestation weeks

Table A.12h L, M, and S values derived by plotting thymus weight (g) against gestation age. Used to calculate fetal thymus weight SD scores

variable & age	L	M	S	variable & age	L	M	S
thymus							
17	-0.02	1.002	0.644	31	-0.02	4.113	0.644
18	-0.02	1.117	0.644	32	-0.02	4.469	0.644
19	-0.02	1.243	0.644	33	-0.02	4.830	0.644
20	-0.02	1.369	0.644	34	-0.02	5.196	0.644
21	-0.02	1.516	0.644	35	-0.02	5.566	0.644
22	-0.02	1.679	0.644	36	-0.02	5.938	0.644
23	-0.02	1.858	0.644	37	-0.02	6.311	0.644
24	-0.02	2.059	0.644	38	-0.02	6.686	0.644
25	-0.02	2.283	0.644	39	-0.02	7.062	0.644
26	-0.02	2.532	0.644	40	-0.02	7.438	0.644
27	-0.02	2.806	0.644	41	-0.02	7.813	0.644
28	-0.02	3.106	0.644	42	-0.02	8.186	0.644
29	-0.02	3.428	0.644	43	-0.02	8.560	0.644
30	-0.02	3.765	0.644	44	-0.02	8.934	0.644

age = gestation weeks

Table A.12i L, M, and S values derived by plotting body length (mm) against gestation age. Used to calculate fetal body length SD scores

variable & age	L	M	S	variable & age	L	M	S
<i>body length</i>							
17	1.21	234	0.127	31	1.21	385	0.127
18	1.21	245	0.127	32	1.21	396	0.127
19	1.21	256	0.127	33	1.21	407	0.127
20	1.21	267	0.127	34	1.21	417	0.127
21	1.21	277	0.127	35	1.21	428	0.127
22	1.21	288	0.127	36	1.21	439	0.127
23	1.21	299	0.127	37	1.21	450	0.127
24	1.21	310	0.127	38	1.21	461	0.127
25	1.21	321	0.127	39	1.21	471	0.127
26	1.21	331	0.127	40	1.21	482	0.127
27	1.21	342	0.127	41	1.21	493	0.127
28	1.21	353	0.127	42	1.21	504	0.127
29	1.21	364	0.127	43	1.21	514	0.127
30	1.21	374	0.127	44	1.21	525	0.127

age = gestation weeks

Appendix

Endnotes

1. Structural brain development involves a series of interrelated but distinguishable events. These are outlined below, following Herschowitz (1988):

Between 3-4 gestation weeks **Neuronal Induction** occurs. During this time, the neural plate is formed through a series of transformations of the blastocyst ectoderm. The neural plate later gives rise to the entire central nervous system and neural crest (from which much of the peripheral nervous system is derived).

Between 8-25 gestation weeks **Neuroblast Proliferation** takes place. This is the period of primary cell proliferation in the central nervous system. It is most marked from 15 to 25 gestation weeks.

Between 8-34 gestation weeks **Neuronal Migration** occurs. Neurons begin to migrate away from the proliferative zone by making adhesive contacts at their leading edges and then pulling themselves forward to their final topographic destination. In the cerebral cortex the cells that undergo early mitosis end up in the deepest layers of the cortex while those produced later migrate to the superficial layers.

Neuronal Selective Aggregation occurs between 8-34 gestation weeks. This occurs when migrating cells reach their final destination and selectively aggregate to form a nuclear group or cortical layer. The first layer in the cortical plate is present at about 8 gestation weeks. By 12½ gestation weeks a subplate develops which later forms the deeper layers of the cortex (which are fully formed by about 8 gestation months).

From 5 gestation weeks to 4 postnatal years **Neuronal Differentiation and Formation of Specific Patterns of Connection** takes place. Neuronal differentiation comprises the growth of processes and growth cones. These are specialized terminations at which nerve cell processes, axons and dendrites grow. The development of characteristic membrane properties, the adoption of a specific mode of synaptic transmission and the formation of necessary synaptic specializations also takes place during this period. The first synapses are

seen at about 8 gestation weeks above and below the cortical plate. By about 23 gestation weeks, synapses can be seen within the cortical plate. Synaptic density increases from about 11×10^8 synapses/mm³ at birth to about 16.5×10^8 synapses/mm³ at 7 years of age, after which time it begins to decline. Synapses are not morphologically mature before about 6-24 months of life. Periods of synaptic and dendritic development vary very much from region to region and clearly delineated timespans for humans are yet known.

Neuronal Death in the cortex occurs between 2-16 postnatal years and is the natural outcome of early overproduction of neurons. About 40-50% of neurons originally generated die. Death occurs during the time when synaptic connections are being made and each phase of cell death lasts only a few days. The size of the projection area involved usually determines how much cell death will occur.

From 2-16 postnatal years **Selective Synapse Elimination** occurs in order to regulate the number of cells and their distribution in target areas. Synapse elimination is believed to take place in the developing visual cortex in humans. Postnatal cortical development is marked broadly by two phases. In the first phase (from birth to 1 year of age) there is a rapid decline in neural density accompanied by an increase in synaptic density as well as an increase in the number of synapses per neuron. Dendritic growth and expansion of total volume of the cortex also occur. In the second phase (extending from 1 year of age to adolescence) there is a slow decline in neuronal and synaptic density. Dendrites continue to grow, however, there is a decrease in synaptic density associated with these dendrites. It appears that each target cell is initially innervated by more axons than in maturity. These axons progressively confine an increasing number of endings to a smaller number of target cells with a resulting reduction in synapses. This helps to ensure the prompt innervation of cells and it eliminates redundancy.

Myelination occurs between 25 gestation weeks to 20 postnatal years. It is initiated when axons to be myelinated reach a diameter of about 1 μm . The ensheathment of axons by myelin is an important energy saving mechanism and helps to increase nerve conduction velocity, essential for a normal functioning nervous system. In the central nervous system, Oligodendrocytes are responsible for myelination of axons. This process starts at about 25

gestation weeks and reaches its peak velocity from birth to 1 year of age. It continues through to about 20 years of age. See also Bartelmezans and Dekaban (1962), Rodier (1980).

2. Measuring body composition:

A number of non-invasive techniques for measuring body composition are available for use in children and adults. These measure different body compartments such as fat tissue, lean tissue, total body water, total body potassium or body density, for example. They are safe and generally provide reliable and accurate measures. These include hydrodensitometry for measuring body density, whole body air displacement plethysmography for measuring total body volume, total body water using deuterium oxide ($^2\text{H}_2\text{O}$) or oxygen-18 (O^{18}) for estimating lean body tissue, absorptiometry for measuring bone mass, lean body mass and fat mass, Potassium-40 for measuring whole body potassium (^{40}K), magnetic resonance imaging and bioelectrical methods for measuring bone density, fat mass and lean tissue mass.

a) Multi-component models for predicting body composition:

It is generally accepted that a four-component model for assessing body composition by dividing body weight into 4 constituent parts: fat, water, mineral and protein is ideal (Fuller et al. 1992, Wells et al. 1999) and not subject to additional errors arising from the compilation of different techniques (Fuller et al. 1992). Where only biometric data (such as height, weight and skinfold thickness) are available, 2-component models can be used to estimate a number of parameters such as nutritional status in the infant (Brandt 1998, Rolland-Cachera et al. 1982, Cole et al. (1995).

a) Hydrodensitometry:

Underwater weighing is used to determine body density in children over 6 years of age. The density of the body is determined by weighing the body in air and then immersed in water. Corrections are made for the volume of air in the lungs and intestines and for the density of air and water. Using the known values of density of fat (0.9 g/cc) and fat-free mass (1.1 g/cc), fat mass, fat free mass and percent fat can be calculated once body density is measured (Zemel 1998, Westrate and Deurenberg 1989).

Because the chemical composition of the body changes during sub-adulthood, hydrodensitometry must be combined with other body composition methods such as total body water or dual absorptiometry, which greatly improve the accuracy of body composition methods.

b) Whole body air displacement plethysmography:

Total body volume can be measured with the use of a whole body air displacement plethysmograph. By measuring the difference in air volume in the chamber when vacant and when housing the subject, raw body volume can be calculated. Corrections are made for thoracic gas volume and for the air next to the subject's skin. Body density is then calculated as body/volume (kg/litre). Body fat is then predicted using age-specific equations (Dewitt et al. 2000).

This method proves to be more readily accepted by children than hydrodensitometry and provides more precise measures of body composition (Dewitt et al. 2000).

c) Total body water:

Isotope dilution methods are used to estimate total body water in infants and children. The stable isotopes, deuterium oxide ($^2\text{H}_2\text{O}$) or oxygen-18 (O^{18}) are naturally occurring and safe for use. A concentrated dose of the isotope is delivered and after a period of equilibration, the concentration is measured from urine or saliva. Once total body water is established, hydration factors in fat-free mass are used to estimate total body fat-free mass and fat mass as well as percent body fat. The hydration factor for human fat-free mass ranges between about 72 and 81 depending on sex and age (Fomon 1982, Lohman 1992). It is also possible to estimate the extracellular water compartment of the body with the use of sodium bromide. It is estimated that $^2\text{H}_2\text{O}$ overestimates TBW by about 4% while O^{18} overestimates TBW by about 1%. This is because some of the isotope mixes with the non-aqueous part of the body (Zemel 1998).

d) Absorptiometry:

Dual photon absorptiometry (DPA) and dual energy X-ray absorptiometry (DXA) are used to measure bone mass, lean body mass and fat mass. Because these compartments of the body all have different densities, energy beams are lengthened differently allowing for measurement of total body bone, fat and lean tissue. Radiation exposure is extremely low (3.5 mrad) and is therefore safe for use in children. The advantage of this method is that it enables more accurate estimation of fat-free mass by providing estimates of bone mass. (Zemel 1998).

e) Potassium-40:

The body contains a naturally occurring stable isotope of potassium (^{40}K) which emits a strong gamma ray. By placing the subject in a lead shielded room with a gamma ray detector, whole body ^{40}K can be determined. The ^{40}K content of the body represents 0.0118% of total body potassium. This method can therefore be used to estimate total body potassium which is representative of cell mass which itself is highly correlated with fat-free mass (Zemel 1998).

f) Bioelectrical methods:

Because water and electrolytes in the body have electrical properties, these can be measured with a total body electrical conductivity device (TOBEC). The body passes through a low energy electromagnetic coil and alterations in the conductance caused by water and electrolytes are measured. Prediction equations are then used to estimate total body water and fat free mass from these measures. The method is safe, non-invasive and effectively used in children. Likewise, bioelectrical impedance can be used to measure body composition in children. A low energy electrical signal is passed through the body and the impedance (resistance signal) is measured. The resistance signal is then used to estimate body composition with the use of predictive equations. Both of these methods require body composition predictive equations specific to children, however (Zemel 1998).

Chan et al. (1998) have shown that magnetic resonance imaging can also be used to assess body fat volume and percent body fat in children aged 8-12 years. These authors argue that MRI gives a far more accurate estimate of total body fat than does bioelectrical impedance alone.

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