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Evidence of genetic regulation of fetal longitudinal growth

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Abstract

Background: Genetic as well as environmental factors are important determinants of fetal growth but there have been few studies of the influence of paternal factors on fetal growth.
Aim: To study the influence of paternal anthropometry on detailed measurements of offspring at birth.
Design: A prospective cohort study involving biochemistry, and anthropometry, of mothers and fathers at 28 weeks gestation, and detailed anthropometry of children within 24 h of birth.
Subjects: 567 White Caucasian singleton, non-diabetic, full term pregnancies recruited from central Exeter, UK.
Results: Paternal height, but not paternal BMI, was correlated with birth weight ($r=0.19$) and with birth length ($r=0.33$). This was independent of potential confounders and maternal height. All measurements of fetal skeletal growth including crown—rump, knee—heel and head circumference were associated with paternal height. Maternal height showed similar correlations with birth weight ($r=0.18$) and birth length ($r=0.26$). Maternal BMI was correlated with birth weight ($r=0.27$) and birth length ($r=0.15$). In a multifactorial analysis 38% of the variance in fetal height could be explained by gestation, sex, paternal height, maternal height, maternal glucose, maternal BMI, parity and maternal smoking.
Conclusion: Paternal height has an independent influence on size at birth. This predominantly influences length and skeletal growth of the baby. In contrast to

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maternal obesity the degree of paternal obesity does not influence birth weight. This work suggests that there is genetic regulation of skeletal growth while the maternal environment predominantly alters the adiposity of the fetus.

1. Introduction

Genetic as well as environmental factors are important determinants of fetal growth. Studies including fathers can provide information on the nature of these genetic factors but to date studies including fathers have been limited. Strong support for genetic regulation is provided by the correlation of paternal birth weight with offspring birth weight, which remains after correcting for maternal birth weight [1—4].

Paternal anthropometry has been associated with birth weight but the size of this and nature of this association is controversial. Kramer in his review of the determinants of low birth weight in 1987 [5], identifies the association between paternal height and paternal weight with offspring birth weight, but suggests that the influence is minimal, with the sample size weighted magnitude of height effect estimated as 1.6 g/cm, and for weight as 3.3 g/kg. Subsequent studies have reported a greater association with paternal height and birth weight, ranging from 6.8 to 10 g/cm. These associations are present after correction for maternal height [6—8], but frequently corrections were not made for other confounders such as social class. The paternal height studies have been mainly undertaken on Caucasian populations, but similar trends have been noted in the Chinese [9] and Indian [10] populations. Paternal weight was associated with birth weight but this association was lost when adjusted for paternal height in most [6,7], but not all cases [10]. Birth weight is an overall measure of fetal growth and it is uncertain which components of fetal growth are associated with paternal height. A link with skeletal development would seem logical and this was supported by Godfrey and colleagues [11,12] as paternal height was associated with both fetal crown heel length, and bone mineral content. Further studies are needed to confirm this.

Our study aimed to define the relationship of paternal anthropometry and size at birth in normal singleton delivery. We report our results from 567 parents and children who were studied prospectively using research measurements.

2. Research design and methods

The Exeter Family Study of Childhood Health (EFSOCH) was set up to study fetal and early post natal growth, by investigating the role of genes and genetic factors [13] within a normal Caucasian population. This is an ongoing, prospective, community based study, within a specific area of central Exeter, as defined by postcode. The detailed study protocol is available [14]. Ethical approval was given by the North and East Devon local ethics committee [15]. We report data from the first 600 families in this study.

3. Inclusion and exclusion criteria

All white Caucasian families (both partners) living in central Exeter (postcode EX1-4), who were registered on the obstetric database of the Royal Devon and Exeter Hospital, were invited to participate in EFSOCH. Diabetic mothers and multiple pregnancies were excluded. Those families where both the pregnant mother and the father of her child agreed to participate were visited at home when the mother was 28 weeks gestation. Written consent was obtained from both parents prior to any data collection. We obtained; a medical history, a lifestyle questionnaire, detailed anthropometric measurements and a fasting blood sample from both partners.

4. Paternal anthropometric measurements

Anthropometry was measured by one of three specially trained research midwives. Each measurement was taken three times on the non-dominant side, and the mean value was used in analysis.

Inter- and intra-rater reliability studies were undertaken to ensure reproducibility [16]. Inter-rater coefficient of variation (CV) for weight and skeletal measures (height and head circumference) was $<1\%$, and for skinfolds measurements $<5\%$. Intra-rater CVs for all measurements were $<1\%$. Measurements included height (to nearest 0.1 cm

using the Harpenden stadiometer), weight (to nearest 0.1 kg using Tanita electric scales), skinfold measurements taken on the non-dominant side of the body (to the nearest 0.2 mm, using Holtain skinfold calipers), and head, mid-arm, waist and hip circumferences (to nearest 0.1 cm using appropriate sized fibreglass, nonstretching tape).

5. Blood measurements

Fasting venous blood samples were collected in appropriate tubes and spun to separate plasma within 2 h. Haematological, biochemical and hormonal measurements were made on these samples. DNA was extracted from leucocytes and stored for genetic analysis.

6. Socio-economic status (SES)

We assigned Socio-economic status (SES) by Townsend Scores based on Enumeration Districts by postcode [17]. A Townsend score of 0 indicates the average for the UK, with positive scores indicating more deprivation, and negative scores representing more affluence.

7. Gestation

Gestation was calculated from last menstrual period (LMP) in women who had regular periods and were confident of the date of their last period. Where there was doubt about the LMP, or if the ultrasound-dating scan differed from LMP by 10 or more days, gestation was calculated by the "dating scan", done early in pregnancy (12.6 ± 1.6 weeks gestation). Of the 600 pregnancies, 311 were thus dated by LMP, and 289 by ultra sound scan date.

8. Antenatal follow up and delivery details

Following routine antenatal care, the women delivered locally, and delivery details were recorded on the local maternity unit database.

9. Neonatal anthropometry

Babies were measured within 24 h of birth, by one of the three research midwives. Measurements included length (to nearest 0.1 cm using the Harpenden stadiometer), weight was taken from delivery room records (to nearest 0.1 kg, using Soehnle scales), skinfold measurements taken on the left side of the body (to the nearest 0.2 mm, using Holtain skinfold calipers), and head and mid-arm circumference (to nearest 0.1 mm using appropriate sized fibreglass, nonstretching tape.) Inter- and intrarater reliability studies were undertaken to ensure reproducibility. Intra-rater CV for all measurements was $<1\%$. Limits of agreement (mean $\pm$ 2SD) between the research midwives were within ± 1 cm for all measures.

10. Statistics

Data are summarized as means and standard deviations, except where the data were not normally distributed, when they are presented as median and interquartile range. Relationships between parental variables and birth measurements were estimated using partial correlations (Pearson), in all cases adjusting for sex, gestational age and parity. The known potential confounders of SES, maternal glucose and maternal smoking were corrected for independently and together. Multiple linear regression analysis was used to further explore the relationships between parental variables, and birth measures, adjusting for the known potential confounders of maternal glucose, maternal smoking, and parity.

Parental determinants of offspring birth size were also adjusted for the same parameter in the other parent, to correct for the potential effect of assortative mating.

11. Results

11.1. Study cohort (Fig. 1)

Of the 600 couples studied, 5 were excluded as the partner was found to be nonwhite Caucasian, 1 woman was found to be diabetic, 2 families moved away and delivered elsewhere (Fig. 1). There was 1 intrauterine death. 591 live singleton babies were born. 21 babies were born premature (gestation <37 weeks), 2 babies had severe growth problems, and one had cerebral palsy. Thus we report on 567 singleton, full term, healthy babies delivered in the EFSOCH study.

11.2. Characteristics of study population (Table 1)

Mothers were on average 30 years old, weighed 70.3 kg at 28 weeks gestation and were 165 cm

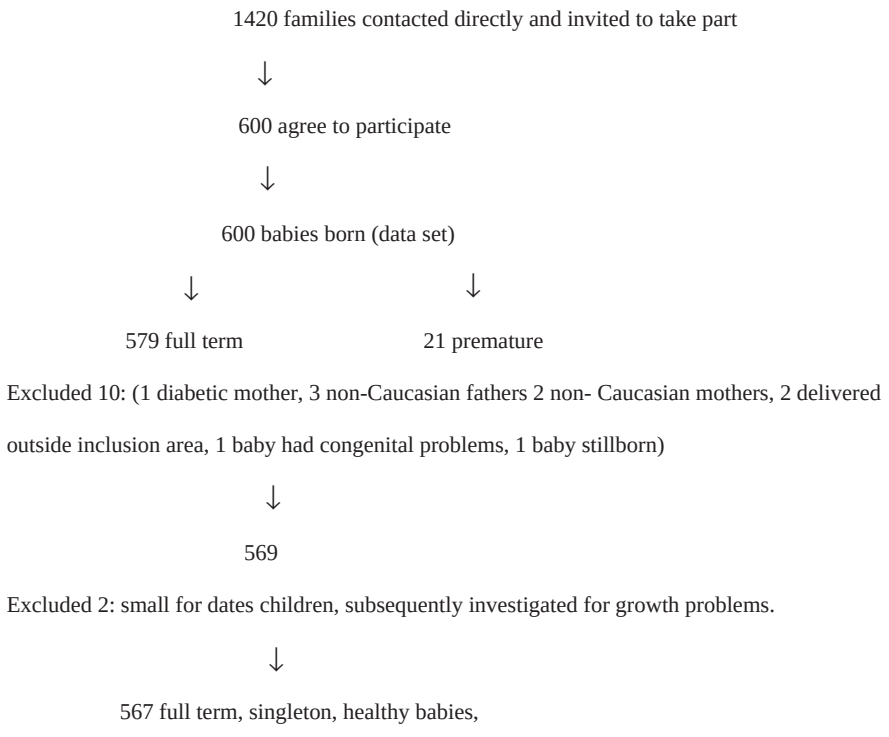

Figure 1 Flow chart showing selection of parents and babies from EFSOCH.

tall (Table 1). Two hundred and sixty six (40%) were primiparous, and 67 (12%) smoked. The fathers were on average 33 years old, weighed 84.7 kg (mean BMI 26.7), were 177.9 cm tall, and 165 (29%) were smokers. The babies were on average born at 40.2 weeks gestation, weighed 3.5 kg, and were 50.3 cm long. Gestation at birth was not related to parental age, BMI, or SES. Gestation at birth was correlated with both birth weight ($r=0.37$, $p<0.001$) and length ($r=0.43$, $p<0.001$).

The median Townsend score for families in EFSOCH was −0.32 (range −6.62 to 8.85).

Table 1 Characteristics of mothers (28 weeks gestation), fathers, and full term babies

	Mean	(SD)	Range	*n*
Mothers				567
Age (years)	30.2	(5.1)	17.0–45.0	
Height (cm)	165.0	(6.4)	145.9–184.6	
Weight (kg)	73.4*	(66.5–82.7)	52.3–127.2	
BMI (kg/m^2)	26.8*	(24.6–30.0)	18.0–47.1	
Fathers				567
Age	32.7	(5.9)	18.0–61.0	
Height (cm)	177.9	(6.7)	157.5–197.0	
Weight (kg)	84.7	(13.4)	51.8–142.0	
BMI (kg/m^2)	26.7	(3.8)	16.8–42.1	
Babies (297 males)				567
Gestation (weeks)	40.2	(1.2)	37.1–42.7	
Length (cm)	50.3	(2.1)	40.4–55.8	
Birthweight (kg)	3.5	(0.5)	1.6–5.0	
Ponderal index (kg/m3)	27.8	(2.6)	21.0–39.9	
Head circumference (cm)	35.3	(1.3)	30.7–40.0	
Mid-arm circumference (cm)	11.1	(0.9)	7.8–14.	
Skin folds:				
Triceps (mm)	5.0*	(1.3)	4.1–5.6	
Sub scapular (mm)	5.0*	(1.2)	4.1–5.9	

* Median and inter quartile range.

11.3. Maternal size and birth weight (Table 2a)

Potential confounding factors were corrected for both individually and together (All) (Table 2a). All maternal measures of size, i.e. weight, height, and BMI, were significantly associated with offspring birth weight ($p<0.001$). Maternal weight was strongly correlated with offspring birth weight ($r=0.31$, $p<0.001$) and remained so after adjustment for SES, smoking, fasting glycaemia and the corresponding paternal variable. Adjusting maternal weight for maternal height slightly reduced the strength of the correlation with birth weight but it remained highly significant ($r=0.26$, $p<0.001$). Birth weight was less strongly correlated with maternal height ($r=0.18$) than BMI ($r=0.27$). The strength of the correlation with BMI (a measure of obesity) was slightly reduced

Table 2a Partial correlations between maternal anthropometry and babies birth weight, adjusting for common confounding factors

Adjusting for	Sex, parity & gestation		SES		Maternal smoking		Maternal glycaemia		Paternal variable		All	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Height	0.18	<0.001	0.18	<0.001	0.19	<0.001	0.20	<0.001	0.15	<0.001	0.18	<0.001
Weight	0.35	<0.001	0.35	<0.001	0.37	<0.001	0.30	<0.001	0.34	<0.001	0.31	<0.001
BMI	0.27	<0.001	0.27	<0.001	0.28	<0.001	0.20	<0.001	0.27	<0.001	0.22	<0.001

Table 2b Partial correlations between maternal anthropometry and babies birth length, adjusting for common confounding factors

Adjusting for	Sex, parity & gestation		SES		Maternal smoking		Maternal glycaemia		Paternal variable		All	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Height	0.26	<0.001	0.26	<0.001	0.27	<0.001	0.27	<0.001	0.22	<0.001	0.24	<0.001
Weight	0.27	<0.001	0.27	<0.001	0.28	<0.001	0.22	<0.001	0.25	<0.001	0.22	<0.001
BMI	0.15	0.001	0.15	<0.001	0.16	<0.001	0.08	0.07	0.15	<0.01	0.10	<0.05

by adjusting for maternal fasting glycaemia ($r=0.20$).

11.4. Maternal size and birth length (Table 2b)

Potential confounding factors were corrected for both individually and together (All) (Table 2b).

All maternal measures of size i.e. weight, height, and BMI were strongly correlated with their offspring birth length ($p<0.001$). Offspring birth length was equally correlated with maternal weight ($r=0.27$, $p<0.001$) and height ($r=0.26$, $p<0.001$). These correlations remained after adjustment for SES, maternal smoking and maternal fasting glycaemia. Adjusting for paternal height only slightly reduced the strength of the maternal height correlation ($r=0.22$, $p<0.001$). The size and strength of the correlation of maternal weight and birth length was reduced when corrected for maternal height. ($r=0.15$, $p=0.001$). Birth length was less strongly associated with maternal BMI ($r=0.15$, $p=0.001$) than maternal height. The correlation of length with BMI was only just significant after adjusting for maternal glycaemia and other potential confounding factors ($r=0.10$, $p<0.05$).

11.5. Paternal size and birth weight (Table 3a)

Potential confounding factors were corrected for both individually and together (All) (Table 3a). Offspring birth weight was similarly correlated with paternal weight ($r=0.19$, $p<0.001$) and height ($r=0.16$,

Table 3a Partial correlations between paternal anthropometry, and babies' birth weight, adjusted for common confounding factors

Adjusting for	Sex, parity & gestation		SES		Maternal smoking		Maternal glycaemia		Maternal variable		All	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Height	0.19	<0.001	0.19	<0.001	0.17	<0.001	0.19	<0.001	0.16	<0.001	0.14	<0.01
Weight	0.16	<0.001	0.17	<0.001	0.15	<0.001	0.15	<0.01	0.12	<0.01	0.12	<0.01
BMI	0.07	0.118	0.07	0.83	0.06	0.128	0.06	0.181	0.04	0.355	0.05	0.301

Table 3b Partial correlations between paternal anthropometry, and baby's birth length, adjusted for common confounding factors

Adjusting for	Sex, parity & gestation		SES		Maternal smoking		Maternal glycaemia		Maternal variable		All	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Height	0.33	<0.001	0.31	<0.001	0.32	<0.001	0.32	<0.001	0.30	<0.001	0.28	<0.001
Weight	0.20	<0.001	0.21	<0.001	0.20	<0.001	0.19	<0.001	0.18	<0.001	0.17	<0.001
BMI	0.05	0.241	0.05	0.217	0.05	0.249	0.04	0.346	0.04	0.423	0.04	0.430

Table 4 Partial correlations between paternal height and child birth measure, controlling for sex, gestation and parity ($N = 514$)

Birth measure	r	p
Length	0.3084	<0.001
Crown/rump	0.2459	<0.001
Knee/heel	0.2436	<0.001
Head circumference	0.1528	<0.001
Arm circumference	0.1157	0.009
Triceps	0.0784	0.075
Sub scapula	−0.0010	0.982
Ponderal index	−0.0939	0.033

$p < 0.001$). These correlations remained after adjustment for SES, maternal smoking and maternal glycaemia, and the corresponding maternal variable. The correlation of paternal weight with offspring birth weight was lost when corrected for paternal height ($r = 0.04$, $p = 0.33$). The size of the magnitude of effect of birth weight with paternal height was 9.3 g/cm. Paternal BMI in contrast to maternal BMI was not associated with offspring birth weight.

11.6. Paternal size and birth length (Table 3b)

Potential confounding factors were corrected for both individually and together (All) Table 3b. Offspring length has a stronger correlation with paternal height ($r = 0.33$ $p < 0.001$) than paternal weight ($r = 0.20$, $p < 0.001$). The correlation with paternal height remained after correction for potential confounding factors and maternal height. The correlation of paternal weight with offspring birth length was lost following adjustment for paternal height ($r = 0.06$, $p = 0.14$). The size of the effect of birth length with paternal height was 0.07 cm/cm. Paternal BMI was not related to offspring length.

11.7. Components of fetal growth associated with paternal height (Table 4)

Measures of fetal skeletal growth were most strongly correlated with paternal height; this included head circumference and arm circumference as well as measures of length (Table 4). The correlation between paternal height and a measure of spinal length (crown—rump length) and limb length (knee—heel) were similar. Measures of fat (skin fold thickness, and ponderal index) were not associated with paternal height.

11.8. Correlations of parental variables (Table 5)

Maternal and paternal age showed the strongest correlation. There were significant, but weak, correlations between maternal and paternal: height, weight, sum of skinfolds, and BMI.

11.9. Multivariate analysis (Table 6)

The independent relationship between paternal size and offspring size was assessed by multiple linear regression analysis with dependent variables of offspring weight and length at birth (Table 5).

The independent variables were: gestational age, offspring sex, parity of mother, SES, maternal smoking, maternal fasting plasma glucose concentration, and appropriate parental size measurements. After gestational age, maternal BMI was the next strongest predictor of offspring birth weight. After gestational age, paternal and maternal heights were equally predictive of offspring birth length. Using this model, and with these independent variables we can explain 34.7% of the variation in offspring birth weight, and 38.3% of the variation of offspring birth length Table 6.

12. Discussion

Our study has clearly shown that paternal anthropometry influences size at birth. The strongest paternal influence on fetal growth is fathers' height and this predominantly influences length and linear growth of the baby. In contrast to maternal obesity the degree of paternal obesity does not influence birth weight. This work suggests that there is genetic regulation of skeletal growth. Our study is consistent with the earlier studies that have also shown that paternal height influences birth weight [5—12]. In our study the magnitude of the effect of paternal height on birth weight was 9.3 g/cm. This influence is independent of maternal height and remains a significant independent determinant of birth weight after removing all potential confounders and maternal influences.

The value of this study lies in the fact that we have used robust methodology, utilizing prospective, research standard anthropometric measures from fathers, and their offspring. Of interest, that

Table 5 Correlations of maternal and paternal variables (maternal pre-pregnancy weight was used in this analysis)

Variable	n	r	r^2	p
Age (years)	567	0.643	0.414	<0.001
Height (cm)	567	0.186	0.345	<0.001
Sum of skinfolds	562	0.158	0.250	<0.001
Weight (kg)	522	0.124	0.154	0.005
BMI wt	522	0.102	0.104	0.019

Table 6 MLRA—baby's birth length and weight, and parental heights and maternal BMI

Regression model	Length				Weight			
	B	Beta	*p*	Rsq	*B*	Beta	*p*	Rsq
Model 1								
Gestation	0.8	0.44	<0.001	0.265	156.6	0.39	<0.001	0.252
Parity	−0.7	−0.15	<0.001		−183.3	−0.19	<0.001	
Sex	−1.1	−0.25	<0.001		−143.5	−0.15	<0.001	
Townsend	0.016	0.03	0.645		9.1	0.06	0.102	
Mat smoking	−0.7	−0.11	0.003		−232.1	−0.16	<0.001	
Mat glucose	1.0	0.17	<0.001		315.0	0.24	<0.001	
Model 2								
Gestation	0.7	0.42	<0.001	0.337	150.8	0.38	<0.001	0.327
Parity	−0.7	−0.16	<0.09		−190.6	−0.19	<0.001	
Sex	−1.1	−0.25	<0.001		−146.3	−0.15	<0.001	
Townsend	0.01	0.02	0.408		5.8	0.04	0.276	
Mat smoking	−0.9	−0.13	<0.001		−267.2	−0.18	<0.001	
Mat Glucose	0.7	0.13	0.001		219.2	0.17	<0.001	
Mat height	0.09	0.26	<0.001		16.4	0.22	<0.001	
Mat BMI	0.06	0.14	<0.001		23.9	0.24	<0.001	
Model 3								
Gestation	0.7	0.42	<0.001	0.383	152.9	0.38	<0.001	0.347
Parity	−0.7	−0.15	<0.001		−186.4	−0.19	<0.001	
Sex	−1.1	−0.26	<0.001		−152.8	−0.16	<0.001	
Townsend	0.005	0.01	0.811		4.9	0.03	0.355	
Mat smoking	−0.7	−0.10	0.004		−246.9	−0.17	<0.001	
Mat glucose	0.7	0.12	0.001		214.5	0.16	<0.001	
Mat height	0.07	0.22	<0.001		14.4	0.19	<0.001	
Mat BMI	0.06	0.14	<0.001		25.1	0.25	<0.001	
Pat height	0.07	0.22	<0.001		9.3	0.13	<0.001	

Model 1 explains the variance in the dependant variables by known independent variables.
Model 2 explains the variance by the addition of maternal anthropometry.
Model 3 explains the variance by the addition of paternal height.

while previous studies have suggested that the increase in fetal weight associated with a centimeter increase in fathers height ranged from 1.6 to 10 g/cm, this robust study is very close to the upper limit at 9.3 g/cm, suggesting that previous studies had underestimated the effect size, in part due to methodological differences. Paternal obesity and paternal weight did not have an impact on birth weight after the influence of paternal height was taken into account.

The other independent genetic factor seen in this study was fetal gender. In our study male infant birth weight was greater then female infant birth weight (3585.5 vs. 3446.0 g, $p<0.001$). We found that the major component of fetal growth that was associated with paternal height was length at birth. The magnitude of the effect is 0.07 cm/cm. More detailed analysis suggested paternal height was associated with both axial (crown—rump) and limb length (knee/heel) skeletal growth, and interestingly, was significantly associated with head and arm circumference. This suggests that the genetic factors reflected in paternal height regulate many aspects of skeletal growth, with no evidence that there was any influence on adiposity. This is in keeping with the study of Godfrey and colleagues who found a relationship between bone mineral content in the new born child and paternal height [5—12], and the study by Catalano and colleagues showing a relationship between paternal height and fetal fat-free mass [18]. Maternal obesity, but not paternal obesity, has a major effect on offspring birth weight.

This is likely to be mediated through the maternal environment by altering maternal glycaemia, maternal triglyceride levels, and maternal insulin resistance. These factors are more likely to alter insulin mediated growth, as maternal glycaemia, and insulin sensitivity are positively correlated with birth weight and cord insulin [19—22]. This study has the advantage that the measurements were of "research standard", and performed prospectively on parents and babies. However, the requirement for families to be white Caucasian and for a father to be recruited into this study does introduce the limitation that the study cannot be considered representative of all pregnancies. The population studied is likely to be of higher socio-economic

status than the population as a whole: we had fewer teenage pregnancies and fewer smokers than the background population admitted to our hospital in this time period. Parental heights are themselves a combination of genetic and environmental factors [23]. These limitations do not affect comparisons within the cohort such as the role of the paternal anthropometry. All studies that have measured the father will have the same inevitable limitation of needing the father to be present and so will have a similar bias.

The vast majority of fetal growth takes place in the last trimester of pregnancy. This is a study based on birth measures, utilizing parental anthropometry, and measures of the intrauterine environment obtained at 28 weeks of gestation. It is inevitable that our study looks predominantly at factors which alter growth in the last trimester. Factors prior to this are important, and may even be crucial in determining the impact of those in the later stages of pregnancy.

Although the finding of parental associations strongly support that genetic influences are altering fetal growth this study can only give indirect information on which physiological processes are affected, and cannot identify the underlying genes involved. Our study shows strong evidence for genetic factors involved in longitudinal and skeletal growth. This would suggest that the mechanism is probably through regulation of the major growth factors in utero: Insulin-like growth factor 1 (IGF1) or Insulin-like growth factor 2 (IGF2) [24]. Increased IGF1 can result in increased skeletal length [24—26]. The molecular genetics of IGF1 and IGF2 are interesting; with evidence of imprinting of IGF2 and surrounding region. There have been recent studies suggesting that fetal size may be altered by genetic variants which may alter the IGF2 gene expression [27,28]. The insulin gene variable number of tandem repeat (INS-VNTR) polymorphism has also been associated with fetal growth in some studies [29,30] but unfortunately these have not been replicated in further larger studies making their significance uncertain [27,31—33]. It is likely that the recent advances in polymorphism identification and the ability to perform rapid, large studies on very large numbers of subjects will greatly assist future studies. This should lead to the future identification of the underlying molecular mechanism of the genetic regulation of early skeletal size.

In conclusion paternal height is an important independent determinant of fetal linear growth. This suggests that there is important genetic regulation of skeletal size while the adiposity of the newborn reflects the maternal intrauterine environment.

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