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Genetic and Environmental Influences on Infant Weight and Weight Change: The Fels Longitudinal Study

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Abstract

Despite significant progress in understanding the mechanisms by which the prenatal/maternal environment can alter development and adult health, genetic influences on normal variation in growth are little understood. This work examines genetic and nongenetic contributions to body weight and weight change during infancy and the relationships between weight change and adult body composition. The dataset included 501 white infants in 164 nuclear and extended families in the Fels Longitudinal Study, each with 10 serial measures of weight from birth to age 3 years and 232 with body composition data in mid-adulthood. Heritability and covariate effects on weight and weight z -score change from birth to 2 years of age were estimated using a maximum likelihood variance decomposition method. Additive genetic effects explained a high proportion of the variance in infant weight status ($h^2 = 0.61$ – 0.95), and change in weight z -score ($h^2 = 0.56$ – 0.82). Covariate effects explained 27% of the phenotypic variance at 0–1 month of age and declined in effect to 6.9% of phenotypic variance by 36 months. Significant sex, gestational age, birth order, birth year, and maternal body mass index effects were also identified. For both sexes, a significant increase in weight z -score (>2 SD units) (upward centile crossing) was associated with greater adulthood stature, fat mass, and percent body fat than decrease or stability in weight z -score. Understanding genetic influences on growth rate in a well-nourished, nutritionally stable population may help us interpret the causes and consequences of centile crossing in nutritionally compromised contexts.

Growth in body size tends to track over time in a “canal” or relatively narrow percentile range (Cameron, 2002; Tanner, 1962; Tanner and Whitehouse, 1980; Waddington, 1957) unless perturbed by environmental stressors. Physical growth has therefore been described as a “target-seeking function” (Tanner, 1986). During infancy, decanalization, or centile crossing, is common with some 40–50% of infants experiencing significant upward or downward shifts in weight and length percentile within the first 2 years of life (Cameron et al., 2003; Ong et al., 2000), which may be a normal aspect of “recovery” of the individual’s genetic growth potential following gestation (Tanner, 1994). It has been recently postulated that this common phenomenon has long-term consequences; individuals born smaller at birth, and particularly those who then experience rapid increases in weight-for-age percentiles during infancy, have significantly higher risk of chronic debilitating diseases later in life, including obesity, diabetes, and coronary heart disease (Barker, 1994; Barker et al., 1989; Cameron et al., 2003; Crowther

et al., 1998, 2000; Eriksson et al., 1999, 2000, 2001, 2002; Ong et al., 2000; Ong and Dunger, 2002, 2004).

Gluckman and Hanson conceptualized cen-tile crossing during infancy, and its long-term effects, as an illustration of a “predictive adaptive response” to the maternal/placental environment (Gluckman and Hanson, 2005). In this conceptual framework, the shaping of the developmental program by the prevailing prenatal environment could be adaptive, in the sense that prenatal predictions are likely to match the postnatal environment, increasing selective fitness. However, if the postnatal environment differs significantly from what was anticipated in utero, then the acquired developmental form may be unable to respond appropriately, possibly leading to altered glucose metabolism, vascular dysfunction, and other maladaptive responses in adult life (Gluckman and Hanson, 2004, 2005).

Using this research framework, there has been significant progress in understanding the subtle mechanisms by which the prenatal/ maternal environment can alter the course of growth and development, and ultimately, adult health (reviewed in Barker, 1994; Gluckman et al., 2005; Gluckman and Hanson, 2004, 2005; Kuzawa, 2005). However, there have been few modern genetic studies of the human developmental program itself (Towne et al., 1993, 2002). Monogenic disorders affecting fetal growth and infant growth have been identified (Ratcliffe, 1981; Roberts, 1986), but genes influencing normal variation in infant growth remain poorly understood. The notion of a “genetic potential to grow” remains more a heuristic device than a focus of research.

This article considers body weight and growth rate during infancy within a genetic epidemiologic framework, in which growth rate is multifactorial, with genetic as well as environmental determinants. In this perspective, the interpretation of slow or rapid growth rate must consider the complex role of genes in interaction with the environment and possibly having pleiotropic effects on other suites of traits such as body composition or chronic disease risk. The adaptive significance of population-level differences in growth rate is not considered here, as it requires the tracking of reproductive success and mortality in a large population as a function of growth rate and nutrient intake.

As an initial step toward understanding the relative contributions of genetic and environmental factors to infant growth rate, we will use the well-characterized Fels Longitudinal Study cohort to (1) estimate the heritability of body weight and weight change from birth to age 3 years, accounting for important environmental covariates; (2) test the hypothesis that the genetic variance of body weight varies over the course of infancy, and differs in males and females; and (3) examine relationships between infant weight change and body composition in adulthood. Understanding the degree of genetic influence on growth rate in a well-nourished, nutritionally stable population may help us to interpret the causes and consequences of centile crossing in more nutritionally compromised contexts.

METHODS

Sample and data

Serial weight measurements were collected from 501 white children ($N = 257$ boys, $N = 244$ girls) in 164 nuclear and extended families enrolled in the Fels Longitudinal Study, born between 1929 and 2004. The Fels Longitudinal Study began in 1929 as a study of the growth and development of children (Roche, 1992). Unlike the other major growth and development studies of its time (e.g., Harvard Growth Study, Berkeley Child Development Study), the Fels Longitudinal Study began collecting familial data from the outset, and continues to do so to this day. The first participants in the Fels Longitudinal Study were randomly ascertained from the greater Dayton, OH area; that is, they were not chosen on the basis of having any particular

condition or risk factor. Since that time, participants have been continuously enrolled at birth as off-spring of existing participants. Our quantitative genetic analysis procedure uses all of the available familial information contained in the Fels Longitudinal Study pedigrees, including a total of 1,704 relative pairings, of which 379 were pairs of first degree relatives, 317 pairs were second degree relatives, and 1,008 pairs were of higher degree relatives.

Gestational age was calculated from maternal report of last menstrual period. Infants were weighed in the hospital at birth (age 0) and then at 1, 3, 6, 9, 12, 18, 24, 30, and 36 months of age at the study center. Weight *z*-scores were calculated at birth, age 6, 12, and 24 months. (Weight *z*-score for each child was calculated as weight minus the sex- and agespecific sample mean weight, divided by sex, and age-specific sample standard deviation). Three different weight *z*-score change variables were calculated by subtracting the weight *z*-score at birth from weight *z*-score at 6, 12, and 24 months. These were used as continuous variables, and we also categorized infants as having “catch-up” and “catch-down” infant growth according to accepted definitions (Cameron et al., 2003; Ong et al., 2000), as those who increased or decreased weight *z*-score more than 0.67 SD units, respectively, between birth and age 6, 12, and 24 months.

Infant feeding was determined using a retrospective questionnaire administered to the mothers. Because of incomplete information on the exact duration of breastfeeding for the majority of participants, responses were coded as “ever breast-fed” or “never breast-fed.”

Body composition measures in adulthood (range: 18–76 years of age) included stature, weight, body mass index (BMI), as well as waist circumference (measured at the iliac crest). Total body fat (TBF) and total body fat-free mass (FFM) were measured using dual energy X-ray absorptiometry (DXA) (Hologic QD4500).

Statistical analysis

Sex differences in study variables were tested using unpaired *t* tests. Phenotypic correlations between important covariates (maternal age, maternal BMI, birth order, year of birth, gestational age, and infant-feeding method) were tested using linear regression models, and only those that were statistically significant ($P < 0.05$) were retained in the genetic analyses. Birth year effects were examined by dividing the infants into three 20–30 year birth cohorts, born 1929–1949 ($N = 208$), 1950–1969 ($N = 169$), and 1970–2004 ($N = 124$). The chi-square goodness-of-fit test (χ^2) was used to test the significance of differences in the prevalence of catch-up and catch-down growth by birth cohort.

We used a maximum-likelihood variance decomposition method for pedigree data (Sequential Oligogenic Linkage Analysis Routines (SOLAR version 2.1.2) (Almasy and Blangero, 1998) to obtain heritability estimates (h^2) of infant weights and weight changes and to test gene-by-age and gene-by-sex interactions. Heritability (expressed as σ_a^2/σ_p^2) is the proportion of the residual phenotypic trait variance after covariate adjustment that is attributable to the effects of genes. Heritability was defined in the narrow sense (proportion of residual variance attributed to the additive effects of genes); nonadditive genetic effects (e.g. dominance effects) were not modeled. The null hypothesis is that the additive genetic variance (σ_a^2) equals zero. Significance was tested by comparing the likelihood of a restricted model in which σ_a^2 was set to zero with the likelihood of a model in which σ_a^2 was estimated, using likelihood ratio tests. Descriptions of these tests, including determination of appropriate degrees of freedom, are provided elsewhere (Almasy and Blangero, 1998).

We used two tests to examine whether or not the same gene or suite of genes influenced variation in infant weight in boys versus girls, and whether or not the same gene or suite of

genes influenced variation in weight at birth versus weight at subsequent ages (Almasy et al., 2001). First, we calculated the additive genetic correlation (ρ_G) between weight in males and weight in females at each age, and the additive genetic correlation (ρ_G) between weight at birth and weight at each subsequent age. An additive genetic correlation of 1.0 or -1.0 indicates complete pleiotropy, an additive genetic correlation of zero between the traits indicates that different genes control both traits, and a genetic correlation between 0.0 and 1.0 or -1.0 indicates incomplete pleiotropy, meaning that the two traits are influenced to some extent by the same genes, but that each trait also has a genetic basis unique from the other. Using the likelihood ratio test, a significantly greater likelihood of the fully estimated model compared to a model where ρ_G is constrained to 0.0 tests the significance of pleiotropy. The squared genetic correlation is an estimate of the proportion of the additive genetic variance in each trait of the pair that is due to the effects of the same gene(s). Second, we tested for the presence of sex and age interaction effects by comparing the likelihood of models in which the additive genetic variances (σ_a^2) for weight were constrained to be the same in boys and girls (or, for age-interactions, at birth and at a later age) to the likelihood of models in which the genetic variances were estimated for each sex (or each age), again using the likelihood ratio test. Significantly greater likelihood of the fully estimated model suggests gene-by-sex or gene-by-age interaction effects, and is another test of pleiotropy. In the case where $\rho_G = 1$, but σ_a^2 is not equal between traits, it is concluded that the same genes are operating, but that the expression of those genes or sets of genes differs between the two traits or groups.

Finally, relationships between weight z-score change (catch-up or catch-down growth) and adulthood BMI and body composition were tested using ANCOVA, adjusting for birth weight, gestational age, and a number of covariates measured in adulthood (age, stature, sports activity, educational attainment, and cigarette smoking).

RESULTS

Sample description

Characteristics of the subjects in this analysis are provided in Table 1. The children in this study were term or near-term births (gestational age ranged from 36–44 weeks). Maternal age ranged from 15 to 46 years of age. Most children in this analysis (~65%) were breastfed, as defined as having been breastfed at least in part for any period of time. Birth order ranged from 1 to 10, with 35% of infants being first-born, 33% being second-born, 16% being third-born, and 16% being fourth-born or higher. In comparison to current U.S. national growth reference data (Ogden et al., 2002), the infants in this analysis were near or slightly below the median for weight for age at birth and at age 2 years. At birth, mean weight of boys was at the 49th and of girls was at the 43rd weight-for-age percentile; at 24 months, mean weight of boys was at the 44th and of girls was at the 40th weight-for-age percentile. As shown in Figure 1, weight was greater in boys than in girls at every age ($P < 0.0001$ for all); boys were 0.21 kg heavier than girls at birth, 0.32 kg heavier than girls at 1 month, and 0.63 kg heavier at 3 months of age. From 6 to 36 months, boys were 0.63–0.78 kg heavier than females. An example of two individual children experiencing catch-up (A) and catch-down growth (B) are also plotted (Figure 1).

Phenotypic associations

We tested the phenotypic relationships between weight from 0–36 months and a number of maternal and infant characteristics to identify critical covariates for the subsequent genetic analyses. Gestational age was positively associated with birth weight (0.11 kg increase in birth weight per week of gestation, $P < 0.0001$) and weight at 3 months of age (0.08 kg increase in weight per week of gestation, $P = 0.001$). Thereafter, gestational age was not associated with weight. At ages 18 and 24 months, higher birth order was marginally associated with lower

weight (0.11–0.13 kg decrease in weight per unit increase in birth order, $P = 0.03$). Maternal age and breastfeeding status were not associated with infant weight at any time point. Prevalence of catch-up growth declined somewhat from 28.9% in Cohort 1 and 32.5% in Cohort 2, to 19.6% in Cohort 3 ($P = 0.02$), while prevalence of catch-down growth increased from 23% in Cohort 1 and 21% in Cohort 2 to 40% in Cohort 3 ($P = 0.0003$).

For a subset of subjects, maternal BMI was available ($N = 383$). The correlation between maternal BMI and infant weight was not significant at birth [$r = 0.06$ (ns) in boys; $r = 0.11$ (ns) in girls] but rose over time [at 36 months, $r = 0.22$ ($P < 0.0001$) in boys; $r = 0.28$ ($P < 0.0001$) in girls]. Correlations tended to be higher in girls than boys (Fig. 2). In linear regression models that also included maternal age, sex, birth order, infant feeding, gestational age, and birth year, maternal BMI added between 1 and 10% to the variance explained in body weight. Because of the reduced sample sizes for maternal BMI, we were unable to include it as a covariate in the genetic analyses.

Heritability of infant weight and weight change z-scores

Heritability estimates for infant body weight were high at all time points, starting at $h^2 = 0.81$ at birth, and falling to $h^2 = 0.6$ – 0.8 from 1 to 18 months, followed by an apparent increase in heritability from 24 to 36 months of age ($h^2 = 0.88$ – 0.95) (Table 2). The change in weight z-score, whether it was calculated from birth to 6 months, birth to 12 months, or birth to 24 months, was also highly heritable. This indicates that after accounting for covariate effects, additive genetic effects account for a very high proportion of the variance for infant weight status and also for change in weight. Total covariate effects explained 27% of the phenotypic variance at 0–1 month of age. Subsequently, the variance explained by covariate effects steadily declined to 6.9% by 36 months. We were able to detect transient gestational age effects on both body weight from 0–6 months and weight change variables, as well as effects of birth year and birth order. More recent birth year was associated with higher weight early in infancy (0–3 months), but lower weight later in infancy (12–30 months), as well as lower weight z-score changes. Higher birth order individuals also tended to experience lower weight change (i.e., they experienced gains in weight z-score less frequently than those with lower birth order).

Age and sex differences in the additive effects of genes

To examine age effects on the genetic influences, we calculated additive genetic correlations between birth weight and subsequent weights, which declined from $\rho_G = 0.91$ at 1 month to $\rho_G = 0.14$ at 36 months of age (Fig. 3). All were significantly different from both 0.0 and 1.0 ($P < 0.05$), indicating partial pleiotropy between weight at birth and weight at later ages. In other words, weight at 1–36 months had some genetic influences in common with weight at birth, and some genetic influences that were unique, but over time, the proportion of shared genetic influences with birth weight dwindled. Similarly, the genetic standard deviations for birth weight and weight at each subsequent age were not equal to one another, which also indicates pleiotropy.

We hypothesized that differences existed between boys and girls in the genetic factors influencing infant weight, or in the magnitude of their effects. For all traits, ρ_G was not significantly different from 1.0, indicating that the same set of genes operated in both males and females to affect weight. However, at 9 months of age, the genetic standard deviation in girls was significantly higher than that in boys ($P = 0.02$), which suggests that there may be a sex difference in the expression or effect of the common set of genes influencing weight at that age. There was no evidence of sex differences in the genes or the expression of genes influencing weight z-score changes.

Catch-up growth and adulthood body composition

In a subset of 232 individuals, we examined the phenotypic relationship between weight change during infancy (categorized as catch-down, no change, or catch-up) and body composition measured approximately 45 years later, at a mean age of 46.8 years of age (Table 3). In both men and women, catch-up growth was associated with greater stature, fat mass, and percent body fat than catch-down growth. Although there was a trend toward greater BMI, abdominal circumference and FFM among those with catch-up infant growth, these contrasts were not statistically significant.

DISCUSSION

Our primary finding was that infant weight and weight change have a strong familial basis, even after consideration of important perinatal factors. Birth weight had a narrow-sense heritability estimate of 81%, and the change in weight z -score from birth to age 2 was also highly heritable (82%). The classic studies by Morton (1955) on Japanese children born between 1945 and 1948 in Nagasaki and Hiroshima and Karn et al. (1957) on children born between 1935 and 1946 in the UK, and also more recent studies in the UK (Baird et al., 2001), Israel (Livshits et al., 2000), the Netherlands (van Dommelen et al., 2004), and Sweden (Clausson et al., 2000) have all suggested that family resemblance in birth weight is more strongly determined by maternal and other shared environmental factors than by the effects of genes. In those studies, heritability ranged from 10 to 40%. However, our results are similar to those of Magnus who reported a strong heritability estimate ($h^2 \sim 0.70$) for birth weight in a large sample of singleton offspring (Magnus, 1984a) and singleton grandchildren (Magnus, 1984b) of Norwegian twins, after accounting for maternal genetic and nongenetic effects. Our results also corroborate two recent reports using the extended pedigree study design and the variance components analytic approach used here. After accounting for the effects of sex and gestational age, the heritability of birth weight (from birth records) was 0.72 ($P < 0.0001$) in a sample of Mexican Americans in the San Antonio Family Heart Study (Arya et al., 2006; Stern et al., 2000). Similarly, Cai et al. (2006) reported a heritability of 0.92 for birth weight in a sample of 1,030 Mexican–American children in the Viva La Familia Study.

Although there is significant disagreement on the relative role of fetal genes, maternal genes, and other environmental factors on birth weight, most studies have shown a significant and/or increasing role for the additive effects of genes on body weight in the months and years following birth (Chen et al., 1990; Towne et al., 2002; van Dommelen et al., 2004). This is in keeping with classic theoretical works on growth and development hypothesizing that early infancy is a period of realignment of the child's growth pattern with their genetic potential (Tanner, 1994; Thompson, 1942; Waddington, 1957). The rapid drop in phenotypic variance explained by measured perinatal effects from birth (~27%) to age 36 months (~7%) in our study, as well as the rise in weight heritability by age 3 years, support the notion that canalization of growth is a genetically driven phenomenon. The genetic propensity to experience catch-up or catch-down weight gain during infancy has not been previously reported to our knowledge. This result again emphasizes the familial influences on postnatal growth patterns.

For most traits, heritability estimates from twins are usually thought to be somewhat inflated by the closely shared environment of twins. In the case of fetal growth and birth weight, however, twin studies may actually give lower heritability estimates than sibling pairs or other study designs. Despite identical genotype, as in the case of monozygotic (MZ) twins, twins are highly *unlikely* to display identical prenatal growth. This is because MZ twins are more likely to have competed for resources in the uterus, the effects of which depend on whether they are mono- or dichorionic, have one or two amniotic sacs, and how they differ in the placement of the umbilical cord in a fused placenta, among other factors (Halvorsen et al., 2006; Loos et

al., 2005). Also, MZ and dizygotic (DZ) twins with intrauterine growth retardation (IUGR) have more than twice the risk of perinatal mortality and morbidity than do singletons with IUGR (Odibo et al., 2005), which suggests the health consequences of growth retardation differ in twins versus singletons. Thus, aspects of the maternal/fetal environment may be particularly important for twins when compared with singletons (Baird et al., 2001), and may therefore explain more of their variance in weight at birth. To better understand the causes and consequences of early growth status and growth rate among the majority of individuals who are singletons, it is perhaps preferable to focus on studies of singleton births.

It is also important to keep in mind that heritability of a trait is a population-specific parameter dependent on the total trait and environmental variances. In contrast to other populations within which the developmental origins of health and disease have been examined, the Fels Longitudinal Study population has been demonstrably stable in terms of growth and maturation over its 75-year history. Average age at menarche was steady at 12.8 years for girls born between 1929 and 1970, with a small decline in age at menarche detected in girls born after 1970 (Demerath et al., 2004b). Similarly, we have seen no secular change in adult stature in the population over time (Demerath et al., 2004a). At this time, 75% of Fels adults have at least some college/university education and the median household income is ~\$60,000 per year. Therefore, compared to other groups, the mothers and infants in the Fels Longitudinal Study have experienced a relatively low degree of nutritional stress. This may have allowed us to observe the genetic influences on birth weight and early infant growth than is possible in other human populations.

Maternal weight gain in pregnancy tends to have little influence on birth weight in industrialized countries, but greater influence in developing countries where most mothers have low body mass (Bakketeig et al., 1979, 1986). Although maternal BMI was unrelated to weight at birth in the Fels Longitudinal Study, its effects increased as the infants grew older, suggesting that maternal BMI was more an indicator of household environment or genetic predisposition to weight gain than a determinant of prenatal growth.

We found evidence of partial pleiotropy, or shared genetic influences, on birth weight and later infant weights, although the impact of shared genetic influences declined over time. These results are similar to those reported by Livshits (1986) and suggest that largely different genes or different patterns of gene expression act to influence weight in early versus later infancy. If growth traits were measured at only a single age, even within the relatively narrow span of 0–3 years, the full picture of genetic influences on infant growth would not be apparent. Localization and identification of specific genes involved in infant growth (through genetic linkage and association studies) may therefore benefit from a longitudinal approach where growth traits measured at multiple serial occasions are considered. Given suggestions that girls are “buffered” from the environment more than boys in infancy (Stinson, 1985), we had expected significant gene-by-sex interaction effects, but evidence for this was minor, which may have been due to insufficient statistical power to estimate sex-specific parameters.

Catch-up growth has been shown to be associated with higher rates of cardiovascular disease (Eriksson et al., 1999; Osmond et al., 1993), obesity (Stettler et al., 2002, 2003), and diabetes (Eriksson et al., 2003), and it has been suggested that these effects might be most apparent in populations where the mismatch between prenatal and postnatal environments is greatest, as in the case of rapidly developing countries (Prentice and Moore, 2005). Yet the impact of lower birth weight (Rogers et al., 2006) and rapid postnatal growth on adiposity (among other chronic disease outcomes) is also widely seen in populations with ostensibly well-nourished mothers (Gluckman et al., 2005). Similarly, in the Fels Longitudinal Study subjects, infant catch-up growth was associated with greater stature and body fatness in adulthood; percent body fat was 25% higher in catch-up versus catch-down males, and 10% higher in catch-up versus catch-

down females. In contrast, adults who had experienced catch-down growth tended to have lower body fat mass than individuals with no significant weight change in infancy. These effects remained significant after adjusting for birth weight, gestational age, adulthood stature, education, physical activity, and tobacco use. Because of the possible *benefits* of downward centile crossing on adiposity in adulthood, a “mismatch” between fetal and postnatal environments (which must also have occurred in the case of catch-down growth) may not completely explain the developmental origins of obesity; rather, rapid postnatal weight gain in particular must be considered as an important independent factor in obesity risk, and research into its causal determinants should be sought.

We found a complex secular trend in infant weight gain, in which individuals born more recently tended to be heavier from birth to 3 months but lighter from 12–30 months compared to individuals born earlier in the study, even after accounting for the familial component. Children born after 1970 had a lower prevalence of catch-up growth (19.6%) and a higher prevalence of catch-down growth (40%) than previous generations. Thus, even in this nutritionally stable population, there may be aspects of the prenatal environment that are improving, such that catch-up growth (and its associations with increased adiposity) may be becoming less common. The prevalence of breastfeeding has also fluctuated over time in the Fels Longitudinal Study (77% ever breast-fed in Cohort 1, 47% in Cohort 2, and 66% in Cohort 3), but since the highest breastfeeding rate was among those in Cohort 1, and the lowest prevalence of catch-up growth occurred in Cohort 3, the two trends do not appear to be concurrent. However, given that our measure of breastfeeding was somewhat crude (ever versus never), we cannot fully explore the relationship between breastfeeding and infant growth over time.

As a quantitative genetic study, this study has interpretive limitations. In particular, the variance we attribute to the additive effects of genes may also include the effects of unmeasured environmental factors that are shared among family members (Stern et al., 2000). These factors may include unmeasured maternal factors and postnatal feeding norms that persist across successive pregnancies, for example, and thus contribute to similarities between siblings in infant weight and weight gain. However, because the genetically related individuals in this study have been reared in large part in different households (i.e., because we include not only siblings, but first and second cousins, avuncular relationships, and so on), and were born across a wide span of time (from pre-World War II to the present), it seems unlikely that shared maternal or postnatal environmental factors account entirely for the high heritabilities that we have observed for infant growth traits. Identification of particular genetic polymorphisms accounting for significant variation in infant weight and weight change would confirm that maternal and household factors do not explain the high heritabilities reported here and in other studies (Arya et al., 2006; Cai et al., 2006). Finally, we have examined infant growth in a genetic epidemiologic context only; while our results suggest that the necessary substrate for genetic adaptation (i.e., genetic variation between individuals) exists for infant growth traits, the adaptive significance of centile crossing in infancy falls outside the scope of the data presented here.

In conclusion, infant weight and weight gain are highly heritable and are also significantly influenced by maternal and other environmental factors such as maternal BMI. Infants with catch-up growth tended to have greater stature, fat mass, and percent body fat in adulthood than infants with catch-down or no significant change in weight status. The strong familiarity of infant growth patterns, alongside their significant impact on adulthood body composition in this nutritionally stable population, suggest that centile crossing during infancy is part of an individual's developmental package stemming from genetic as well as environmental origins.

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Fig. 1.
Weight from 0 to 36 months, Fels longitudinal study, $N = 501$.

Fig. 2. Phenotypic correlations between maternal BMI and offspring weight from 0 to 36 months by sex; $N = 383$, asterisks (*) indicate correlations that are significantly different from 0.0, $P < 0.05$.

Fig. 3.
Sex-adjusted genetic correlations ($\pm$ SE) between weight at birth and subsequent weight measures, Fels longitudinal study, $N = 501$.

TABLE 1

Characteristics of the subjects (mean $\pm$ SD)*

	Boys	Girls
<i>N</i>	257	244
Weight at birth (kg)	3.5 $\pm$ 0.5	3.3 $\pm$ 0.5*
Weight at 24 months (kg)	12.6 $\pm$ 1.4	11.9 $\pm$ 1.3*
Weight change categories (%) ^a		
Catch-up (%)	26.5	28.7
No change (%)	48.3	43.4
Catch-down (%)	25.2	27.9
Birth year	1957 $\pm$ 21	1960 $\pm$ 22
Gestational age (weeks)	39.7 $\pm$ 1.7	39.5 $\pm$ 1.9
Birth order	2.3 $\pm$ 1.5	2.3 $\pm$ 1.4
Maternal age (years)	29.1 $\pm$ 5.8	28.7 $\pm$ 5.6
Maternal BMI (kg/m ²)	24.0 $\pm$ 3.5	22.4 $\pm$ 4.1*
Breastfed (% ever) ^b	67	65

* Girls significantly different from boys, $P < 0.05$.

^aPercent of infants in each of three weight change categories; "catch-up," increase in weight z -score $\geq +0.67$ SD units from 0 to 24 months; "catch-down," decrease in weight z -score ≤ -0.67 SD units from 0 to 24 months; "no change," change in weight z -score > -0.67 and $< +0.67$ from 0 to 24 months.

^b"Ever", ever breast-fed; "never", never breast-fed.

TABLE 2

Heritability of weight and weight change^a in 501 Fels Longitudinal Study infants

	h^2	$\mu \pm SE$	β_{sex}	$\beta_{birthyr}$	$\beta_{gestage}$	$\beta_{birthorder}$	Covariate (%)
Weight, 0 mo	0.81 ± 0.12	3.5 ± 0.5	-0.21	0.003	0.133	— ^b	26.6
Weight, 1 mo	0.61 ± 0.10	4.3 ± 0.5	-0.30	7.2	0.127	—	26.7
Weight, 3 mo	0.67 ± 0.14	6.1 ± 0.7	-0.52	5.9	0.104	—	21.1
Weight, 6 mo	0.77 ± 0.12	8.0 ± 0.8	-0.65	—	0.07	—	16.4
Weight, 9 mo	0.75 ± 0.11	9.3 ± 0.9	-0.73	—	—	—	16.4
Weight, 12 mo	0.65 ± 0.11	10.2 ± 1.0	-0.68	-6.6	—	—	13.7
Weight, 18 mo	0.72 ± 0.11	11.5 ± 1.1	-0.66	-8.3	—	—	10.9
Weight, 24 mo	0.88 ± 0.10	12.7 ± 1.3	-0.66	-6.1	—	—	8.1
Weight, 30 mo	0.89 ± 0.12	13.8 ± 1.4	-0.78	-9.8	—	—	9.6
Weight, 36 mo	0.95 ± 0.10	14.9 ± 1.5	-0.72	—	—	—	6.9
Weight change, 0–6 mo	0.66 ± 0.13	0.05 ± 1.0	—	—	-0.169	-0.08	11.3
Weight change, 0–12 mo	0.55 ± 0.13	0.06 ± 1.1	—	-0.01	-0.230	-0.10	19.4
Weight change, 0–24 mo	0.82 ± 0.12	0.07 ± 1.1	—	-0.01	-0.236	-0.09	19.6

^aWeight change defined as in Table 1.

^bCovariate term not significant ($P > 0.05$).

TABLE 3

Relationship between weight change^a and body composition measured in adulthood: Age-adjusted means ($\pm$ SD), N = 232

	Males			P	Females			P
	Catch-down	No change	Catch-up		Catch-down	No change	Catch-up	
Stature (cm)	177.1 ± 2.2	181.3 ± 1.5	180.0 ± 2.4	0.017	163.0 ± 3.4	164.6 ± 1.8	167.2 ± 2.3	0.013
BMI (kg/m ²)	26.8 ± 1.7	27.5 ± 1.3	28.8 ± 1.8	ns	26.3 ± 26.4	26.5 ± 1.7	28.5 ± 2.1	ns
Abdominal circumference (cm)	97.9 ± 4.8	100.7 ± 3.1	104.4 ± 4.5	ns	91.2 ± 5.6	91.3 ± 4.0	96.0 ± 4.9	ns
Fat free mass (kg)	65.5 ± 2.5	67.0 ± 1.9	68.8 ± 2.6	ns	45.4 ± 2.4	48.1 ± 1.7	48.6 ± 2.1	ns
Fat mass (kg)	17.3 ± 2.7	20.0 ± 2.2	23.8 ± 2.9	0.006	22.6 ± 4.1	26.2 ± 2.7	28.6 ± 3.4	0.06
Percent body Fat (%)	20.3 ± 2.2	22.8 ± 1.6	25.4 ± 2.3	0.006	33.0 ± 2.7	34.4 ± 1.9	36.5 ± 2.4	0.07

^aWeight change defined as in Table 1.