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Characterization of the Infant BMI Peak: Sex Differences, Birth Year Cohort Effects, Association with Concurrent Adiposity, and Heritability

William Johnson^{1,2}, Audrey C. Choh³, Miryoung Lee^{3,4}, Bradford Towne^{3,4}, Stefan A. Czerwinski³, and Ellen W. Demerath^{2,*}

¹MRC Unit for Lifelong Health and Ageing, 33 Bedford Place, London, UK

²MRC Unit for Lifelong Health and Ageing, 33 Bedford Place, London, UK

³Division of Epidemiology, Lifespan Health Research Center, Boonshoft School of Medicine, Wright State University, Dayton, OH, USA

⁴Department of Pediatrics, Boonshoft School of Medicine, Wright State University, Dayton, OH, USA

Abstract

Objectives—To characterize an early trait in the BMI-for-age curve, the infant BMI peak.

Methods—BMI-for-age curves were produced for 747 non-Hispanic, white Fels Longitudinal Study participants, from which individual age (Age_{Peak}) and BMI (BMI_{Peak}) at maximum infant BMI were estimated. Multivariable general linear regression was used to examine the effects of sex and birth year cohort (1929–1950, 1951–1970, and 1971–2010) on Age_{Peak} and BMI_{Peak}, with associations between BMI_{Peak} and concurrent sum of four skinfold thicknesses assessed in a subsample ($N = 155$). Heritability (h^2) of Age_{Peak} and BMI_{Peak} was estimated using maximum-likelihood variance components analysis.

Results—Age_{Peak} occurred at 9 months of age in both sexes, but BMI_{Peak} was 0.4 kg/m² higher for boys than for girls (P -value < 0.001). Infants born between 1971 and 2010 experienced a 1.5 month earlier Age_{Peak} and a 0.35 kg/m² lower BMI_{Peak} than infants born between 1929 and 1950 (P -values < 0.001). Skinfold thickness explained 37% of the variance in BMI_{Peak} in boys and 20% of the variance in girls (p -values < 0.001). Age_{Peak} and BMI_{Peak} were significantly heritable ($h^2 = 0.54$ and 0.75, respectively).

Conclusions—Both Age_{Peak} and BMI_{Peak} decreased over successive birth year cohorts in the Fels Longitudinal Study. Despite a positive association of BMI_{Peak} with concurrent adiposity, Age_{Peak} appears to occur later than does the well-documented peak in infant fat mass and BMI_{Peak} does not capture known sex differences in infant adiposity. Strong heritability of these infant BMI

traits suggests investigation of genetic control, and validation of their relationship to body composition is greatly needed.

Body mass index [BMI = weight (kg)/length or height (m)²] follows a characteristic age-related pattern of change, increasing rapidly after birth to reach a maximum during infancy and then falling to a nadir near 5 years of age, before increasing once again through late childhood and adolescence (Chivers et al., 2009, 2010; Johnson et al., 2012a; Silverwood et al., 2009; Sovio et al., 2011; Wen et al., 2012). The nadir in the BMI-for-age curve marks the onset of the adiposity rebound, a well-characterized trait (Rolland-Cachera et al., 1984, 1987, 2006). Earlier adiposity rebound is associated with greater obesity risk (Chivers et al., 2009; Freedman et al., 2001; Guo et al., 2000; Rolland-Cachera et al., 2006; Williams and Goulding, 2009; Wisemandle et al., 2000), even in the absence of elevated concurrent BMI (Dorosty et al., 2000; Johnson et al., 2012a; Rolland-Cachera et al., 1987; Whitaker et al., 1998; Williams and Dickson, 2002). The infant BMI peak [(characterized by age (Age_{Peak}) and BMI (BMI_{Peak}) at maximum infant BMI)] has received far less attention to date, but may be a useful marker of infant adiposity for large-scale studies with serial weight and length data (Silverwood et al., 2009; Sovio et al., 2011; Wen et al., 2012).

One publication has referred to the infant BMI peak as the “infant adiposity peak” (Sovio et al., 2011), consistent with the terminology of the adiposity rebound. However, where evidence exists showing that characteristics of the adiposity rebound reflect underlying body composition changes (Campbell et al., 2011; Taylor et al., 2004, 2011), such evidence for the infant BMI peak is speculative. Human infants have relatively high body fat at birth and deposit large amounts of white subcutaneous fat following birth, as compared with other species (Pond, 1997). Total body adiposity assessed using criterion body composition methods reach a maximum at ~6 months of age, on average (e.g., Butte et al., 2000; Fomon et al., 1982; and reviewed by Rigo, 2006; Wells, 2010). It is not yet clear, however, whether Age_{Peak} coincides with the timing of the established infant peak in adiposity, or indeed whether BMI_{Peak} strongly correlates with more direct measures of adiposity.

Our research group has recently described secular trends in the BMI-for-age curve of children aged 2–18 years in the Fels Longitudinal study (Johnson et al., 2012a). Shifts in the BMI-for-age curve were apparent starting in children born in the 1970's, a decade that marked the onset of the obesity epidemic in the United States of America (Flegal et al., 1998; Troiano et al., 1995). In our analysis, children born in the most recent birth year cohort (1973–1999) had lower BMI values until the adiposity rebound, but faster BMI gain during adolescence, than children born in earlier birth year cohorts (Johnson et al., 2012a). This finding corroborates other published studies (Deheeger and Rolland-Cachera, 2004; Hughes et al., 1997) that together suggest that a downward secular trend in BMI_{Peak} has occurred in recent generations. It is also possible that a secular trend toward earlier Age_{Peak} has occurred, perhaps anticipating the observed secular trend toward earlier adiposity rebound (Johnson et al., 2012a). The only study to examine this question (Wen et al., 2012) did not observe birth year cohort effects on Age_{Peak} and BMI_{Peak}, perhaps because the infants were all born relatively recently (i.e., after 1980). Longer term secular trends have not been examined.

The BMI is significantly heritable during both childhood and adulthood (Schousboe et al., 2003; Wardle et al., 2008) and our research group has recently shown that the heritability of infant BMI is greatest between 6 and 9 months of age (heritability = 78%; Choh et al., 2011). Given this, the infant BMI peak may be a useful trait for genetic analysis; known genetic variants associated with BMI and obesity in adults tend to associate fairly weakly with birth weight and ponderal index (Andersson et al., 2010) and with later infancy BMI (Choh et al., 2011). In contrast, a recent study using curve fitting to derive Age_{Peak} and BMI_{Peak} found significantly lower BMI_{Peak} in carriers of a high risk genotype for the obesity gene FTO (Sovio et al., 2011). As family based studies with longitudinal infant BMI data are uncommon, heritability estimates for infant BMI peak traits, the first step in determining the genetic basis of human variation, are lacking.

To address these gaps in the literature, this study used data from the Fels Longitudinal Study, the world's longest continuously running family-based study of human physical growth, to provide the first detailed characterization of the infant BMI peak. Our aims were as follows: (1) to describe mixed effects regression models for estimating Age_{Peak} and BMI_{Peak} for individual infants; (2) to test sex differences and secular trends in Age_{Peak} and BMI_{Peak} over an 80 year period of time (1929–2010); (3) to investigate associations between BMI_{Peak} and concurrent skinfold thickness; and (4) to determine the heritability of Age_{Peak} and BMI_{Peak}.

METHODS

Sample

The sample comprised 747 non-Hispanic, white participants (385 boys; 362 girls) in the Fels Longitudinal Study born 1929–2010. The Fels Longitudinal Study has been described in detail elsewhere (Roche, 1992), but in summary began in 1929 as a study of normative child growth and development and continues today as a study of the early life antecedents of chronic diseases of aging. Mother-infant dyads living in Yellow Springs and other towns in southwestern Ohio, USA have been enrolled from 1929 onward. Other family members were also simultaneously enrolled. The 747 participants in the present study were distributed among 200 nuclear and extended families and in total comprised 5,485 relative pairs, of which 720 pairs were of first degree relatives, 686 pairs were of second degree relatives, 809 were of third degree relatives, and 3,265 pairs were of less closely related relatives.

All protocols and informed consent documents were approved by the Wright State University Institutional Review Board. Parents of minors provided written consent for their offspring.

Measurements

Serial weight and recumbent length measurements were collected throughout infancy using standard anthropometric methods (Lohman et al., 1998). In this study, we used data from target assessment ages at birth and at 1, 3, 6, 9, 12, and 18 months of age. BMI was calculated where weight and length were available at the same assessment. Infant triceps, biceps, subscapular, and suprailiac skinfold thickness measurements, initiated in 1984, were

collected using Holtain skinfold calipers (Holtain, Crymch, United Kingdom); Z-scores for triceps and subscapular skinfolds were calculated according to the World Health Organization (WHO) 2006 Child Growth Standard (WHO Multicentre Growth Reference Study Group, 2006). Gestational age at birth and parity were collected from birth records.

Modelling the infant BMI peak

Serial BMI data were used to construct individual BMI-for-age curves, thereby allowing us to identify the infant BMI peak (i.e., Age_{Peak} and BMI_{Peak}) for each individual. Change in BMI was modeled as a cubic regression spline of age (Gasser et al., 1993), specifying five knots at equally spaced quantiles of the age distribution. Other functions, including structural models such as that proposed by Berkey and Reed (1987), cubic and quartic polynomials, and a best fitting fractional polynomial (Long and Ryoo, 2010) were tested but none resulted in a better model fit, as assessed using the Bayesian Information Criteria (Shwartz, 1978).

A mixed effects approach was employed because it allows the user to model simultaneously the individual curves and the sample average curve (Johnson et al., 2012b). Briefly, a mixed effects model comprises fixed effects (equivalent to parameter estimates from general linear regression) and random effects (departures from the fixed effects estimates for any specified level, which in this instance was the individual). In the context of growth modeling, the fixed effects describe the sample average curve, whereas the combination of fixed and random effects produces distinct parameter estimates and thus a distinct curve for each individual. Statistical packages efficiently handle nonconsistently collected data using probability functions to describe the relative likelihood of each random effect occurring at a given point in the observation space (Rabe-Hesketh and Skrondal, 2008). This makes it possible to fit a single model to a sample of individuals with any (nonconsistent) number of serial measurements occurring at non-consistent assessment ages. As the number of serial measurements increases, however, an individual's estimated curve is influenced less by the sample average curve. All models were fit using Stata's (College Station, Texas) linear mixed effects regression command *xtmixed*.

The modeling procedure was stratified by sex and included BMI data between 0.04 and 1.58 years of age, thereby avoiding the period of neonatal weight loss in the first 2 weeks of life (Macdonald et al., 2003). Models were initially applied to all participants ($N = 951$, 49.8% girls) with at least one BMI measurement in our studied age range (Fig. 1). Age_{Peak} and BMI_{Peak} were estimated for each infant at the highest point in their individual BMI-for-age curve; we estimated individual BMI values at 0.02 year (1 week) intervals between 0.08 years (1 month) and 1.5 years (18 months) of age, before selecting the largest value (BMI_{Peak}) and the age at the largest value (Age_{Peak}) for each infant. There was no infant BMI peak in the BMI-for-age curves of 35 (15 boys and 20 girls) infants. The largest predicted BMI values for these infants occurred at 1.5 years of age (i.e., the last age at which we estimated individual BMI values). These infants also had estimated BMI values at 0.08 years of age that were 0.7 kg/m^2 lower than those of infants with an identifiable infant BMI peak ($P\text{-value} < 0.001$), but then demonstrated almost linear BMI change over age to achieve BMI values at 1.5 years of age similar to those for infants with an identifiable infant

BMI peak (P -value = 0.342). Further, there were no significant differences in sex, birth weight, and gestational age between those infants with an identifiable infant BMI peak and those infants without an identifiable infant BMI peak (P -values > 0.25); although there were significant differences in birth year (mean for infants with an identifiable infant BMI peak = 1965; mean for infants without an identifiable infant BMI peak = 1948; P -value < 0.001). Because infants with no identifiable infant BMI peak may have comprised an extreme subgroup with other special defining characteristics (that could not be investigated here owing to the lack of covariate data), the modeling procedure was performed a second time excluding the 273 BMI observations for the 35 infants with no identifiable infant BMI peak. All 916 infants (49.6% girls) in this second run demonstrated an infant BMI peak (Fig. 1).

For boys, the final mixed effects model included 2,672 serial BMI observations on 462 participants with an average of 5.8 per participant (range 1–14) over an average of 1.2 years (range 0.1–1.5) for participants with more than one observation. For girls, the final model included 2,543 serial BMI observations on 454 participants with an average of 5.6 per participant (range 1–42) over an average of 1.2 years (range 0.1–1.5) for participants with more than one observation. Velocity ($\text{kg}/\text{m}^2/\text{year}$) from estimated BMI at age 0.08 years to estimated BMI_{Peak} at Age_{Peak} (hereafter called “Velocity_{Pre-Peak}”), and velocity from BMI_{Peak} at Age_{Peak} to estimated BMI at age 1.5 years (hereafter called “Velocity_{Post-Peak}”), were calculated as change in BMI/change in age. The final mixed effects models included all available BMI data regardless of any constraining criteria such as the number of times an infant had been measured. Because, however, we were interested in characteristics of the individual BMI-for-age curves, an *a priori* decision had been made to only carry forward infant BMI peak traits for further analysis for infants who had a minimum of three serial observations used in the modelling process. This reduced the final sample to 747 infants (385 boys; 362 girls; Fig. 1). Sensitivity analyses were performed to ensure that results did not differ between our sample and other samples based on a different minimal number of serial BMI observations (four serial observations, $N = 692$; five serial observations, and $N = 632$). There were no significant differences (P -values > 0.16) in sex, birth weight, and gestational age between the sample of 747 infants and the remaining infants (i.e., $N = 951 - 747 = 169$) not in the sample but in the starting N of 951; although there were significant differences in birth year (mean for sample = 1961; mean for remaining infants = 1977; P -value < 0.001).

Statistical analysis of sex differences

The sample average BMI-for-age curves of the sample of 747 infants were plotted by sex to illustrate differences in Age_{Peak} and BMI_{Peak} and related traits (e.g., Velocity_{Pre-Peak} and Velocity_{Post-Peak}) between boys and girls. Sex differences in all the infant BMI peak traits and covariates were determined using *t*-tests. In addition, a partial correlation matrix (adjusted for sex) among Age_{Peak} and BMI_{Peak}, Velocity_{Pre-Peak} and Velocity_{Post-Peak}, birth year, birth weight Z-scores according to the WHO 2006 Child Growth Standard (WHO Multicentre Growth Reference Study Group, 2006), and the four skinfold thickness measurements was produced.

Statistical analysis of secular trends

Multivariable general linear regression models were built to investigate secular trends in Age_{Peak} and BMI_{Peak} . The two outcomes were Age_{Peak} and BMI_{Peak} and the exposure was birth year, categorized into three empirical birth year cohorts (birth year cohort one: 1929–1950, $N = 277$, referent; birth year cohort two: 1951–1970, $N = 257$; birth year cohort three: 1971–2010, $N = 213$) based on the distribution of participants according to birth year. Data from the National Health and Nutrition Examination Surveys (NHANES) suggest that significant increases in childhood obesity prevalence were first evident in the USA by the third NHANES (1988–1991) (Troiano et al., 1995). Birth year cohort three in this study, therefore, corresponds to infants born during the current obesity epidemic (i.e., year 1988–17 years = 1971). Birth year cohort one and two comprise infants born before the obesity epidemic. Two sets of regression models were built: the first adjusted for sex, gestational age (centered to mean 39.6 weeks), and parity (categorized as 1, 2, 3, or greater) and the second additionally adjusted for birth weight Z-scores, thereby allowing us to determine whether any secular trends in Age_{Peak} and BMI_{Peak} were driven by increasing size at birth. Models were initially built for boys and girls separately, but because estimates of birth year cohort effects were similar for both sexes, only models for boys and girls combined are presented here. Further, sex interactions with birth year cohort, gestational age, parity, and birth weight Z-scores were tested but were not retained in models because all P -values were nonsignificant (P -value > 0.3). Two degrees-of-freedom Wald tests of the null hypothesis that both birth year cohort estimates (1951–1970 vs. 1929–1950 and 1971–2010 vs. 1929–1950) were equal to zero were used to test for trends across birth year cohorts. Covariate data were missing for some participants (Table 1) so these data were imputed five times using chained equations implemented by the *ice* command in Stata. The imputation model included the four infant BMI peak traits and all covariates. The distributions of the imputed variables were similar to those of the observed data, thereby providing evidence that the missing data were missing at random. The *micombine* command in Stata was used to simultaneously fit the regression models to each of the five imputation sets and estimate single parameter estimates.

A secondary analysis was performed to correctly attribute secular trends in BMI_{Peak} to changes in weight and/or length; each infant's observed (i.e., raw) weight and length (and raw BMI) data closest to their Age_{Peak} were selected and separate ANOVA models for each dimension were used to test for differences between birth year cohorts, with a Bonferroni correction for multiple comparisons. All models were adjusted for sex and the difference between Age_{Peak} and age at the observed weight and length measurements.

In addition, a figure showing secular trends in sample average BMI-for-age curves across the studied age range was produced by sex from additional mixed effects models that included birth year cohort as a main effect (i.e., to test the absolute magnitude of the BMI-for-age curve for one birth year cohort relative to the referent) and as an interaction with the age, age^2 , and age^3 terms in the cubic spline models (i.e., to test the change in the shape of the BMI-for-age curve for one birth year cohort relevant to the referent; Johnson et al., 2012b). These models were applied to BMI data on the sample of 747 infants and were

performed to provide a visual representation of differences in BMI-for-age curves by birth year cohort.

Statistical analysis of associations with concurrent adiposity

Because of the design of the Fels Longitudinal Study, this analysis was restricted to the subsample of infants born after 1983 who had skinfold thickness data (Fig. 1). We initially modeled individual triceps, biceps, subscapular, and suprailiac skinfold thickness-for-age curves using a similar approach to that used to model BMI (data not shown). However, owing to the lack of extensive serial skinfold thickness data, we were not confident in the fit of these models. Instead, for each of the four skinfold thickness sites, we selected a single observation closest (± 0.25 years) to each individual's Age_{Peak} . A sum of four skinfolds variable was calculated for the 155 participants (77 boys; 78 girls) with an observation at each measurement site. Multivariable general linear regression of BMI_{Peak} on sum of four skinfolds was performed to quantify the association between the infant BMI peak and concurrent adiposity. This analysis was stratified by sex because the strength of the association was different for boys compared with girls. Models were adjusted for birth year (to account for any residual secular trend occurring after 1983), gestational age, parity, and the difference between Age_{Peak} and age at the skinfold measurements. As with the secular trend analysis, *micombine* in Stata was used to simultaneously fit the models to each of the five imputation sets and estimate single parameter estimates. The results of this analysis are shown in a plot of the two regression lines (one for boys and one for girls) with 95% confidence intervals. None of the covariate parameters were statistically significant ($P < 0.05$); hence, they are not reported here.

Quantitative genetic analysis of heritability

Maximum-likelihood variance components methods in SOLAR (Almasy and Blangero, 1998) were used to estimate narrow-sense heritabilities of Age_{Peak} , BMI_{Peak} , $\text{Velocity}_{\text{Pre-Peak}}$, and $\text{Velocity}_{\text{Post-Peak}}$. Heritabilities, defined as the proportion of the phenotypic variance attributable to additive genetic effects, were estimated as $h^2 = \sigma^2_G / \sigma^2_P$, where σ^2_G is the additive genetic variance (estimated using the trait covariance matrix across all relative pairings) and σ^2_P is the total phenotypic variance. The variables of interest were inverse normalized to handle residual kurtosis and the models were adjusted for covariate effects of sex, birth year, gestational age, and parity. The models were applied to the five imputation sets and parameter estimates were combined following recommendations from Little and Rubin (2002) to produce single values. Likelihood ratio tests were also combined following recommendations from Li et al. (1991) and Little and Rubin (2002) to test if h^2 estimates were significantly different from zero.

RESULTS

Sex differences

Descriptive statistics for the infant BMI peak traits and covariates are provided by sex in Table 1. According to the WHO 2006 Child Growth Standard, the magnitude of BMI_{Peak} corresponded to a mean Z-score of ~ 0.4 units for both sexes; concurrent triceps and subscapular skinfold thickness were also greater than the WHO 2006 Child Growth

Standard median, thereby indicating greater adiposity in the current sample than in the WHO 2006 Child Growth Standard source sample. Age_{Peak} occurred at ~9 months of age for both boys and girls ($P < 0.05$), but boys had faster Velocity_{Pre-Peak} ($P < 0.001$) and BMI_{Peak} was ~0.4 kg/m² greater for boys than for girls ($P < 0.001$). To illustrate the sex differences, the sample average BMI-for-age curves from the mixed effects models for boys and girls are shown in Figure 2.

Secular trends

Table 2 shows a partial correlation matrix (adjusted for sex) among the key observed variables. Increasing birth year was significantly correlated with earlier Age_{Peak} (coefficient -0.350), with marginal evidence for an association with lower BMI_{Peak} (coefficient -0.073 , P -value = 0.108). Because, however, birth weight Z-scores were positively correlated with birth year (coefficient 0.200) as well as Age_{Peak} and BMI_{Peak} (coefficients 0.262 and 0.164, respectively), we investigated potential mediation of the birth year cohort – infant BMI peak associations by birth weight in regression models in Table 3. Secular trends in decreasing Age_{Peak} and BMI_{Peak} were observed after adjustment for sex, gestational age, and parity, such that infants in the 1971–2010 birth year cohort experienced a 0.122 year earlier Age_{Peak} and a 0.352 kg/m² lower BMI_{Peak} than infants in the 1929–1950 birth year cohort (P -values < 0.001). Parameter estimates retained significance and were largely unaffected after additional adjustment for birth weight Z-scores, thereby providing evidence for secular trends in decreasing Age_{Peak} and BMI_{Peak} independent of birth weight. Figure 3 provides a visual representation of birth year cohort differences in infant BMI-for-age, showing a downward and earlier shift in the curves with more recent birth year cohort.

In a secondary analysis, birth year cohort associations with observed (i.e., raw) weight and length closest to each infant's Age_{Peak} were examined. Both weight and, to a lesser degree, length declined with increasing birth year cohort (Supporting Information Table 1); mean weight declined by ~0.5 kg, or 5% from the first to the third birth year cohort, while mean recumbent length declined by 1.7 cm, or 2%.

Associations with concurrent adiposity

Regression analysis using the sum of four skinfolds showed positive association between BMI_{Peak} and concurrent subcutaneous adiposity after adjustment for birth year, gestational age, and parity (Fig. 4). A 1 mm increase in sum of four skinfold thicknesses was associated with a 0.120 kg/m² increase in BMI_{Peak} in boys and a 0.078 kg/m² increase in girls (P -values < 0.001). The four skinfold thicknesses together explained ~37% of the variance in BMI_{Peak} in boys and 20% of the variance in girls.

Heritability

All of the infant BMI peak traits were significantly heritable (Table 4). Heritability was greatest for BMI_{Peak} ($h^2 = 0.747$; SE = 0.090) and least for Age_{Peak} ($h^2 = 0.541$; SE = 0.094).

DISCUSSION

The infant BMI peak is an identifiable trait demonstrated by the majority of participants in this study (96%) and in other studies (Silverwood et al., 2009; Sovio et al., 2011; Wen et al., 2012). This article provides the first detailed characterization of the infant BMI peak in a sample of non-Hispanic, white infants with ~5,000 serial BMI measurements, including an extensive description of statistical modeling of the serial data using mixed effects regression. Our primary findings were that BMI_{Peak} was lower in girls than in boys; Age_{Peak} and BMI_{Peak} were earlier and lower, respectively, in infants born after 1970 compared with infants born before 1950; BMI_{Peak} was positively but only moderately associated with concurrent skinfold thickness; and all of the infant BMI peak traits were moderately to strongly heritable.

The approach we used to model individual BMI-for-age curves provided a good fit for the data; the overall residual standard deviations (RSD is a measure of average error in the original unit of measurement) were 0.69 kg/m² in the boys' model and 0.64 kg/m² in the girls' model. In addition, scatter plots of model residuals against age showed no evidence of systematic fitting of individual BMI-for-age curves too high or too low across age (data not shown). Three different approaches to modelling infant BMI-for-age curves, with the aim to determine Age_{Peak} and BMI_{Peak}, have been used elsewhere (Silverwood et al., 2009; Sovio et al., 2011; Wen et al., 2012). The first is a cubic polynomial model (Sovio et al., 2011), which is known to perform poorly at the extremities of the data; the second is a eight degree fractional polynomial developed to model BMI from 1 week to 18 years of age (Wen et al., 2012), thereby risking high residual error by having to fit a complex pattern of change over a wide age range; and the third was a penalized cubic spline model (Silverwood et al., 2009), which was unnecessary here because our cubic spline models were developed to avoid over-fitting (by specifying a relatively small number of knots) and thus did not need to be penalized (Gasser et al., 1993).

Age_{Peak} and BMI_{Peak} in this study are similar to two other published estimates, which show that on average Age_{Peak} occurs at ~9 months of age in both sexes and that BMI_{Peak} occurs at ~18 kg/m² in boys and 17.5 kg/m² in girls (Silverwood et al., 2009; Sovio et al., 2011). One study has reported Age_{Peak} to occur at ~7 months of age (Wen et al., 2012), but that study modeled BMI-for-age using a eight degree fractional polynomial, despite pertinent recommendations that even three or four degree models may only be useful on rare occasions (Royston and Sauerbrei, 2008). Systematic fitting of individual BMI-for-age curves too high or too low across age was not investigated by Wen et al. (2012), which may have resulted in inaccurate estimates of Age_{Peak}. Alternatively, there may be true population differences in Age_{Peak}; future studies may help to resolve this question by providing estimates for infants from diverse populations and comparing results using different modeling approaches. Currently, there is no consensus on the best method to model the infant BMI peak, including discussion of the best function, the appropriate age range, and the minimum necessary number and timing of serial measurements.

We observed a significant secular trend toward earlier Age_{Peak} and lower BMI_{Peak}. This somewhat counterintuitive finding is supported by previous work from our group and others

showing secular trends toward lower BMI values in infancy, followed by earlier adiposity rebound, and higher subsequent BMI values (Deheeger and Rolland-Cachera, 2004; Hughes et al., 1997; Johnson et al., 2012a). This study advances this theme by showing that the secular trend toward lower infant BMI values remains after consideration of individual differences in developmental timing in the BMI-for-age curve (i.e., Age_{Peak}). The secular trend toward a somewhat earlier Age_{Peak} fits well with the literature showing acceleration over time in other developmental traits such as age at the adiposity rebound (Johnson et al., 2012a), age at menarche (Anderson et al., 2003; Chumlea et al., 2003), and age at peak height velocity (Aksglaede et al., 2008).

The decrease in BMI_{Peak} over birth year cohorts was attributable to decreases in both weight and length, as we have previously reported in the Fels Longitudinal Study (Johnson et al., 2012c), although the decrease in weight was larger than the decrease in length when expressed as percentages of mean values. Given that infant BMI at any age is a good, but certainly not a perfect, proxy for body adiposity (Rigo, 2006), it should be kept in mind that inter-individual or sample variation in BMI_{Peak} may not reflect variation in weight (or adiposity) alone.

Starting in 1966, a series of infant body composition reference data (based on different objective methods of assessment) have been published (Butte et al., 2000; Fomon, 1966, 1967; Fomon et al., 1982), all of which demonstrated a rapid increase in relative total body adiposity (percent body fat) to reach a maximum at ~6 months, at which age fat-free mass continues to increase robustly and fat deposition slows (Rigo, 2006). In his book, “The evolutionary biology of human body fatness,” Wells (2010) summarizes empirical data from seven studies in western populations to demonstrate that the infant peak in adiposity occurs near 6 months of age. This pattern has been proposed to be an evolutionary adaptation that buffers the large human brain (Kuzawa, 1998) as well as the other rapidly growing organs (Wells, 2012) against nutritional disruption and infection during weaning, a period of increased infant mortality.

In this study, BMI_{Peak} was positively associated with concurrent adiposity, to the extent that correlation coefficients between BMI_{Peak} and four skinfold thickness measurements were not dissimilar to those between the four skinfold thickness measurements themselves. In adjusted regression analyses, however, <40% of the variance in BMI_{Peak} was explained by skinfold thickness, thereby suggesting only a moderate association between BMI_{Peak} and concurrent adiposity. The Fels Longitudinal Study has one of the more extensive infant skinfold thickness assessment schedules compared with other birth cohort studies. Nonetheless, we had insufficient longitudinal skinfold data to model individual curves in adiposity with age and test whether the timing of the infant peak in skinfold thickness is coincident with Age_{Peak}.

Our study and others suggest that Age_{Peak} occurs three months later than would be expected if it were a sole reflection of the well-documented infant peak in adiposity, and we also found that BMI_{Peak} is significantly greater in boys than girls. As sexual dimorphism in body composition is already evident by 1 month of age (Fields et al., 2009), with girls having lower fat-free mass and greater percent body fat than boys, BMI_{Peak} fails to capture sex

differences in early life adiposity. We suspect that the greater BMI_{Peak} of boys compared with girls is attributable to their greater lean mass (de Bruin et al., 1995b). Given its adaptive significance and likely developmental plasticity, as well as its potential as a marker of future obesity, validation studies of BMI_{Peak} against infant peak in adiposity (using air displacement plethysmography or other criterion methods) are clearly needed.

Despite our lack of precise knowledge on relationships of infant BMI with infant body composition, one interesting question that our results raise is “how secular trends toward earlier Age_{Peak} and lower BMI_{Peak} might be interpreted in light of life history theory?” As this study is based upon the systematic examination of successive generations of children within the same families, the secular trends we show are in a sense “adjusted” for any genetic differences across birth year cohorts and therefore strongly support the idea that infant BMI-for-age trajectories can be modified in response to changing environments. As suggested by Kuzawa (1998), rapid fat deposition during early infancy may be a key adaptation to sustain brain and fat-free mass growth during illness under energy-limited conditions. There have been massive reductions in infant mortality in the broader society over the period of the study [(e.g., a 90% reduction from 100/1,000 in 1915 to <10/1,000 in 1997 (MMWR, 1999)], and it is possible that in the absence of continued selection pressure toward rapid adiposity gains, slower growing infants might have survived more frequently in recent generations, and thus constitute a larger proportion of the BMI distribution than in the past. This scenario is, of course, purely speculative. Although we showed that the downward secular trend in BMI_{Peak} was robust to adjustment for birth weight, which increased over time in this study, an alternative explanation is increasing maternal BMI over time, which has previously been shown to be associated with decelerated early growth (Ode et al., 2012).

In addition to demonstrating the plasticity of the infant BMI peak to changes over time in the environment, the present paper also documents (for the first time) the strong heritability of Age_{Peak} and BMI_{Peak}, as well as the rates of BMI-for-age change before and after the infant BMI peak. Our findings fit well with recent publications showing that genetic variants known to influence BMI are also associated with shifts in developmental timing in the BMI-for-age curve (Elks et al., 2012; Sovio et al., 2011). Sovio et al. (2011), for example, found that genetic variants associated with increasing obesity risk at the FTO locus were associated with earlier adiposity rebound (but not with earlier Age_{Peak}). Andersson et al. (2010) found lower BMI_{Peak} in individuals carrying the FTO risk genotype at rs9939609 (AA), but higher BMI later in childhood, again showing that there are complex age-dependent variations in genetic control of BMI, with lower infant BMI being characteristic of individuals at ultimately higher risk of obesity. Our results emphasize the point that while environmental factors are very important in shaping the infant BMI-for-age curve (as shown by the secular trends analysis), the majority of inter-individual variation is nonetheless attributable to genetic factors. It is hoped that through collaborative research across multiple child growth cohorts, new obesity loci may be discovered by targeting traits known to reflect developmental switches or shifts in adipose tissue growth, as may be the case with the infant BMI peak, and by integrating gene-by-environmental interactions into the analysis.

Alternatives and limitations

To account for familial clustering within the Fels Longitudinal Study, we tested mixed effects BMI-for-age curve models that included pedigree as a third level (i.e., measurements within infants within pedigrees). Because, however, this drastically worsened model fit (compared with models that did not account for familial clustering), these three-level models were not considered further. The BMI uses length or height squared when the appropriate power (to create an index that is independent of length or height) is closer to three in infancy (Cole, 1986), therefore we also modeled ponderal index [$PI = \text{weight (kg)}/\text{length (m)}^3$]. The peak in PI was difficult to identify for many infants because it occurred very close to birth (~3 months of age; data not shown) and therefore further investigation of PI peak would require extensive serial data in early infancy (i.e., >5 serial measurements between 0 and 3 months of age), which were not available in this study. It appears that while Age_{Peak} occurs later than the peak in infant adiposity, the peak in infant PI occurs before it. Surprisingly limited evidence exists on the predictive value of PI versus BMI for concurrent adiposity using rigorous methodology (e.g., multicomponent body composition models) in infancy (de Bruin et al., 1995a). Further research is needed before any decision about the best anthropometric index to indicate the peak in infant adiposity can be made.

Birth year cohort differences observed in this study may have been the result of any number of factors that changed over the studied time period (e.g., infant feeding practices, maternal smoking, and maternal alcohol use, etc). Because, however, such factors have not been uniformly assessed over the duration of the Fels Longitudinal Study, it was not possible to explicitly model these factors to determine the particular changes that were responsible for the observed secular trends. Further, this article does not test the relationship of the infant BMI peak traits with later obesity and adiposity; this important topic is the focus of ongoing work. Our select sample of 747 infants was on average born >10 years earlier than the infants not in the sample. This selection bias may be a limitation of our secular trends analysis if the infants not in the sample demonstrated different infant BMI peak characteristics compared with those infants in the sample (with similar birth years). We can, however, be certain that this was not the case because of the nonsignificant differences (P -values > 0.2) in Age_{Peak} and BMI_{Peak} between the sample and the infants not in the sample (who had an identifiable infant BMI peak). A final limitation is that the sample was composed exclusively of non-Hispanic, white infants born in southwestern Ohio, USA, which limits the generalizability of the results to other ethnic groups.

CONCLUSIONS

In this study, we have characterized important aspects of the understudied infancy phase of the BMI-for-age curve. Of the four known studies on this topic using individual growth curve modeling, including this one, three place the infant BMI peak at nine months of age and all find higher values for boys than girls. Novel findings of the present study are a downward shift over time in Age_{Peak} and BMI_{Peak} , a positive but moderate association of BMI_{Peak} with concurrent skinfold thickness, and significant heritability of Age_{Peak} and BMI_{Peak} . Because Age_{Peak} appears to occur later than the infant peak in adiposity and BMI_{Peak} fails to capture known sex differences in infant adiposity, further work is required

to test the relationship of the infant BMI peak to concurrent and later adiposity. Such work will be important to guide the appropriate use of infant BMI in large-scale epidemiologic studies and comparative field studies in which more direct measures of infant body composition are not available.

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WJ analyzed data and performed statistical analysis, wrote article, and designed research. EWD was responsible for project conception, development of overall research plan, and had primary responsibility for final content. ACC, ML, BT, and SAC designed research, interpreted data, and revised manuscript. ACC additionally performed the genetic analysis. All authors provided critical revision for important intellectual content and approved the final version.

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Fig. 1.
Flow diagram showing sample selection and summarizing statistical analyses.

BMI-for-age curves were fitted for boys and girls separately using mixed effects cubic regression splines.

Fig. 2.
Mean BMI-for-age curves showing sex differences in Age-Peak and BMI_{Peak} in 747 Fels Longitudinal Study participants.

BMI-for-age curves were fitted for boys and girls separately using mixed effects cubic regression splines.

Fig. 3.

Mean BMI-for-age curves showing birth year cohort differences in Age_{Peak} and BMI_{Peak} in 747 Fels Longitudinal Study participants.

Results from sex-stratified general linear regressions of BMI_{Peak} on sum of four skinfold thicknesses (triceps, biceps, subscapular, suprailiac). Models were adjusted for birth year, gestational age, parity, and the differences between Age_{Peak} and age at skinfold measurement. Because gestational age was imputed, micombine in Stata was used to apply the models to the five imputation datasets and estimate single parameter estimates.

Fig. 4.

Sex-stratified regression lines and 95% confidence intervals of BMI_{Peak} on sum of four skinfold thicknesses in 155 Fels Longitudinal Study participants.

TABLE 1

Description of the study sample, by sex

	Boys		Girls		Sex difference
	N	Mean (SD) or Median (range)	N	Mean (SD) or Median (range)	
Birth year	385	1958 (1930–2009)	362	1958 (1929–2010)	0.991
Gestational age (weeks) at birth	269	39.56 (1.79)	243	39.65 (1.78)	0.581
Gestational age after imputation ^b	385	39.53 (1.77)	362	39.66 (1.80)	–
Parity	385	2 (1–10)	362	2 (1–9)	0.636
Birth weight Z-score ^{c,d}	262	0.06 (1.08)	232	0.02 (1.09)	0.736
Birth weight Z-score after imputation ^b	385	0.03 (1.10)	362	–0.04 (1.11)	–
Age _{Peak} (years)	385	0.76 (0.14)	362	0.77 (0.11)	0.127
BMI _{Peak} (kg/m ²)	385	17.73 (1.07)	362	17.31 (1.15)	<0.001
BMI _{Peak} (Z-score) ^c	385	0.39 (0.77)	362	0.38 (0.77)	0.772
Velocity _{Pre-Peak} ^e (kg/m ² /year)	385	5.04 (0.86)	362	4.81 (1.06)	0.001
Velocity _{Post-Peak} ^e (kg/m ² /year)	385	–1.36 (0.52)	362	–1.35 (0.57)	0.817
Triceps skinfold Z-score ^{c,f}	83	0.94 (1.17)	83	1.03 (1.07)	0.598
Subscapular skinfold Z-score ^{c,f}	82	0.26 (1.30)	83	0.10 (1.31)	0.421
Sum of four skinfold thicknesses (mm) ^{f,g}	79	30.12 (5.18)	78	30.92 (7.20)	0.422

^a Sex differences were tested using independent samples T-tests for continuous variables and Chi-squared tests for categorical variables.

^b Missing covariate data were imputed five times using ice in Stata. Here, the means over the five imputation runs are presented.

^c Z-scores were calculated according to the WHO 2006 Child Growth Standard.

^d Birth weight was always collected within 0.03 years (i.e., 10 days) of birth.

^e Velocity_{Pre-Peak} was calculated as BMI/ age between BMI at age 0.08 years and BMI_{Peak} at Age_{Peak}, and Velocity_{Post-Peak} was calculated as BMI/ age between BMI_{Peak} at Age_{Peak} and BMI at age 1.5 years.

^f A single skinfold observation (for each measurement site) closest (± 0.25 years) to each individual's Age_{Peak} was selected.

^g Calculated as the sum of triceps, biceps, subscapular, and suprailiac skinfold thickness measurements.

TABLE 2

Partial correlation matrix (adjusted for sex) showing relationships between the infant BMI peak traits, birth year, and concurrent infant adiposity in 747 Fels Longitudinal Study participants

	Age _{Peak} N=747	BMI _{Peak} N=747	Velocity _{Pre-Peak} ^a N=747	Velocity _{Post-Peak} ^a N=747	Birth year ^a N=747	Birth weight Z-score ^b N=494	Triceps skinfold ^c N=166	Biceps skinfold ^c N=161	Subscapular skinfold ^c N=165	Suprailiac skinfold ^c N=157
Partial correlation coefficient (P-value)										
Age _{Peak}	–	0.290 (<0.001)	0.735 (<0.001)	–0.064 (0.154)	–0.350 (<0.001)	0.262 (<0.001)	0.086 (0.316)	0.082 (0.347)	0.048 (0.579)	0.040 (0.649)
BMI _{Peak}		–	0.663 (<0.001)	–0.751 (<0.001)	–0.073 (0.108)	0.164 (<0.001)	0.392 (<0.001)	0.322 (<0.001)	0.508 (<0.001)	0.419 (<0.001)
Velocity _{Pre-Peak}			–	–0.651 (<0.001)	–0.277 (<0.001)	–0.209 (<0.001)	0.274 (0.001)	0.217 (0.012)	0.311 (<0.001)	0.266 (0.002)
Velocity _{Post-Peak}				–	0.041 (0.365)	0.012 (0.787)	–0.362 (<0.001)	–0.264 (0.002)	–0.482 (<0.001)	–0.359 (<0.001)
Birth year					–	0.200 (<0.001)	–0.037 (0.667)	0.050 (0.562)	–0.118 (0.171)	0.275 (0.002)
Birth weight Z-score						–	–0.009 (0.921)	–0.124 (0.154)	–0.032 (0.712)	–0.036 (0.682)
Triceps skinfold							–	0.567 (<0.001)	0.503 (<0.001)	0.417 (<0.001)
Biceps skinfold								–	0.480 (<0.001)	0.489 (<0.001)
Subscapular skinfold									–	0.585 (<0.001)
Suprailiac skinfold										–

^aVelocity_{Pre-Peak} was calculated as BMI/ age between BMI at age 0.08 years and BMI_{Peak} at Age_{Peak}, and Velocity_{Post-Peak} was calculated as BMI/ age between BMI_{Peak} at Age_{Peak} and BMI at age 1.5 years.

^bZ-scores were calculated according to the WHO 2006 Child Growth Standard.

^cA single skinfold observation (for each measurement site) closest (± 0.25 years) to each individual's Age_{Peak} was selected. Partial correlation coefficients involving a skinfold variable were also adjusted for the difference between Age_{Peak} and age at skinfold measurement.

TABLE 3

Birth year cohort effects on infant BMI peak traits in 747 Fels Longitudinal Study participants: estimates from general linear regression models^a

	AgePeak (years)		BMIPeak (kg/m ²)		
	Beta (standard error) P-value				
	Unadjusted for birth weight Z-score	Adjusted for birth weight Z-score	Unadjusted for birth weight Z-score	Adjusted for birth weight Z-score	
Constant	747	0.825 (0.010) <0.001	0.820 (0.010) <0.001	17.938 (0.094) <0.001	17.998 (0.097) <0.001
Sex	747				
Boys (referent)	385 (51.5)	–	–	–	–
Girls	362 (48.5)	0.016 (0.008) 0.050	0.014 (0.008) 0.088	–0.408 (0.080) <0.001	–0.381 (0.081) <0.001
Gestational age (weeks) ^b [imputed]	747	–0.014 (0.003) <0.001	–0.008 (0.004) 0.016	–0.046 (0.026) 0.078	–0.117 (0.029) <0.001
Parity	747				
1	257 (34.4)	–	–	–	–
2	249 (33.3)	–0.021 (0.010) 0.038	–0.018 (0.010) 0.072	–0.020 (0.100) 0.838	–0.059 (0.098) 0.546
3 or greater	241 (32.3)	–0.020 (0.011) 0.061	–0.018 (0.010) 0.078	–0.011 (0.099) 0.911	–0.036 (0.101) 0.724
Birth weight Z-score ^c (imputed)	747		–0.018 (0.005) 0.001		0.252 (0.052) <0.001
Birth year cohort	747				
1929–1950 (referent)	277 (37.1)	–	–	–	–
1951–1970	257 (34.4)	–0.055 (0.010) <0.001	–0.053 (0.0103) <0.001	–0.306 (0.096) 0.001	–0.332 (0.095) <0.001
1971–2010	213 (28.5)	–0.122 (0.010) <0.001	–0.111 (0.011) <0.001	–0.352 (0.101) 0.001	–0.500 (0.105) <0.001
Trend across birth year cohorts ^d	747	<0.001	<0.001	<0.001	<0.001
Total model adjusted R ² range ^e		0.171–0.197	0.185–0.220	0.047–0.052	0.083–0.114

^a *Micombe* in Stata was used to apply the models to the five imputation datasets and estimate single parameter estimates.

^b Gestational age was centered to mean 39.6 weeks.

^c Z-scores were calculated according to the WHO 2006 Child Growth Standard.

^d The P-value for the trend across birth year cohorts is a two degrees-of-freedom Wald test of the null hypothesis that both birth year cohort estimates (1951–1970 vs. 1929–1950 and 1971–2010 vs. 1929–1950) are equal to zero.

Micombe in Stata does not produce a single r-squared value so the range from the models applied to the five imputation datasets is provided.

TABLE 4

Heritability of infant BMI peak traits in 747 Fels Longitudinal Study participants

	Heritability (h^2) ^a		
	h^2 Estimate	Standard error	P-value
Age _{Peak} (years)	0.541	0.094	<0.001
BMI _{Peak} (kg/m ²)	0.747	0.090	<0.001
Velocity _{Pre-Peak} (kg/m ² /year)	0.626	0.094	<0.001
Velocity _{Post-Peak} (kg/m ² /year)	0.488	0.091	<0.001

^aTraits were inverse normalized and heritability estimates were adjusted for sex, birth year, exact age at measurement, gestational age at birth, and parity in quantitative genetic models in SOLAR. The models were applied to the five imputation sets and single parameter estimates were calculated.