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Associations of the infancy body mass index peak with anthropometry and cardiometabolic risk in Mexican adolescents

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Abstract

Background: Early-life growth dynamics are associated with future health. Little is known regarding timing and magnitude of the infancy body mass index (BMI) peak with adiposity and metabolic biomarkers during adolescence.

Aim: Examine associations of the infancy BMI peak with anthropometry and cardiometabolic risk during peripuberty.

Methods: Among 163 ELEMENT participants, we estimated age and magnitude of the infancy BMI peak from eight anthropometric measurements from birth-36 months using Newton's Growth Models, an acceleration-based process model. We examined associations of the infancy milestones with anthropometry and cardiometabolic risk at 8-14 years using linear regression models that accounted for maternal calcium supplementation and age; child's birthweight, sex, and age; and the other infancy milestone.

Results: Median age at the infancy BMI peak was 9.6 months, and median peak BMI was 16.5 kg/m². Later age and larger magnitude of the peak predicted higher BMI z-score, waist circumference, and skinfold thicknesses; i.e., each 1 month of age at peak and each 1 kg/m² of peak BMI corresponded with 0.04 (0.01, 0.07) and 0.33 (0.17, 0.48) units higher BMI z-score, respectively. Later age at peak was also a determinant of worse glycaemia and higher blood pressure.

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Conclusion: Later age and larger magnitude of the infancy BMI peak are associated with higher adiposity at 8-14 years of age. Later age but not magnitude of the BMI peak are related to a worse cardiometabolic profile during peripuberty.

Keywords

postnatal growth; childhood adiposity; metabolic risk; peripuberty; cardiometabolic health; Bayesian stochastic process model; Newton's Growth Model

Introduction

Early growth is a key determinant of cardiovascular and metabolic health. For example, greater weight gain during the first two to three years of life is associated with future risk of obesity (Monteiro and Victora 2005; Jones-Smith et al. 2007; Taveras et al. 2009; Druet et al. 2012; Min et al. 2012; Sacco et al. 2013; Perng, Hajj, et al. 2016), hypertension (Adair and Cole 2003; Belfort et al. 2007; Leunissen et al. 2009; Perng, Rifas-Shiman, et al. 2016), and dysglycaemia (Bhargava et al. 2004). Additionally, some studies indicate highest risk among infants at the lower (Eriksson et al. 1999; Adair and Cole 2003; Fagerberg et al. 2004; Ekelund et al. 2006; Jones-Smith et al. 2007; Fabricius-Bjerre et al. 2011) and upper (Baird et al. 2005) ends of the birth size distribution.

The most common approach for characterising infant growth is use of change in anthropometry between specific ages (Baird et al. 2005; Monteiro and Victora 2005; Jones-Smith et al. 2007; Perng, Hajj, et al. 2016; Perng, Rifas-Shiman, et al. 2016). However, this method assumes homogeneity of development within a population and linearity of growth, both of which can be problematic in light of inter-individual variability in tempo of growth (Li et al. 2007), and non-linear trends in weight and length gain (de Onis M et al. 2004). A more realistic approach is to characterise trajectories using serial anthropometric measurements for individuals within a population. These trajectories may then be used to estimate milestones of growth, such as timing of the infancy body mass index (BMI) peak (Silverwood et al. 2009; Wen et al. 2012) and the adiposity rebound (Guo et al. 2000), that have implications for future health.

Although a wealth of studies have consistently found that earlier age at adiposity rebound predicts future obesity and obesity-related conditions (see reviews (Taylor et al. 2005; Rolland-Cachera and Peneau 2013)), the infancy BMI peak has received far less attention. Understanding how infancy growth dynamics relate to future health is potentially more valuable than hallmarks of growth later in childhood as it permits detection of growth patterns that could be altered by preventive intervention strategies earlier in the life course when phenotypic plasticity is highest (Wells 2014).

To date, published studies on infancy BMI peak have focused on how timing and/or magnitude of this milestone correlate with future overweight/obesity status during early (age 2 to 4 years) (Jensen et al. 2015; Roy et al. 2015; Sun et al. 2017) and mid- to late-childhood (age 5 to 9 years) (Silverwood et al. 2009; Hof et al. 2013; Bornhorst et al. 2017), with only one study that included participants up to 13 years of age (Jones-Smith et al. 2013). A major chasm in current evidence is the paucity of investigations evaluating relations of early

growth with health outcomes during adolescence, a transitional period that may set the stage for long-term metabolic health (Lee 2008). Further, with the exception of two studies – one in Singaporean children that measured blood pressure at age 4 years (Aris et al. 2017) and one in Danish children that assessed blood pressure, insulin, and lipid profile at age 6 years (Marinkovic et al. 2017) – little is known regarding how infancy growth milestones correlate with biomarkers of metabolic risk. Such relationships are important to consider given that excess metabolic risk may be present in non-overweight/obese youth (Lakshmi et al. 2012).

In this study, we used a newly-developed Bayesian stochastic process model to characterise timing and magnitude of the infancy BMI peak, and examine associations of these milestones with anthropometry and biomarkers of cardiometabolic risk during peripuberty among 163 participants of a Mexico City birth cohort.

Methods

Study population

This study included participants of the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) Project, three sequentially-enrolled cohorts of pregnant women recruited from maternity hospitals in Mexico City between 1994 and 2005 (Hu et al. 2006), and followed-up for measurements of offspring weight and length through 36 months of age. In 2010, we re-contacted a subset of the offspring ($n = 250$) who were then 8-14 years of age based on availability of archived prenatal biospecimens to participate in follow-up studies. At research visits that took place in 2011, henceforth referred to as the “peripubertal visit,” the children participated in anthropometric assessments and provided a fasting blood sample. The present analysis excluded 16 participants born before 37 weeks gestation, followed by 27 participants missing data on key covariates. Of the 207 remaining participants, 21.3% ($n = 44$) participants did not exhibit a distinct infancy BMI peak during the first three years of life – a phenomenon that has been observed in a similar proportion of participants (16.6%) in an analysis of nearly 3000 German children (Hof et al. 2013). Figure 1 shows examples of individual BMI trajectories of infants with and without detectable peaks in this population. After excluding the participants with no distinct BMI peak, the final analytical sample comprised 163 participants. The institutional review boards of the Mexico National Institute of Public Health and the University of Michigan approved research protocols.

Exposure: timing and magnitude of the infancy BMI peak

The exposures of interest in the analysis were age at and magnitude of the infancy BMI peak. We estimated these growth milestones from individual BMI trajectories derived from a median of eight serial measurements of weight and length between birth and 36 months of age. We focused on BMI because it is positively correlated with air-displacement plethysmography measured fat mass in infants, and because prospective change in BMI from birth through 4-6 months was shown to be a better proxy for change in directly-measured fat mass and % fat mass than other commonly-used weight- and length-based indices (i.e., weight-for-length and weight-for-age) (Perng et al. 2017).

To create the BMI trajectories, we used Newton's Growth Models (NGMs), an extension of a semi-parametric stochastic velocity model developed by Zhu (Zhu et al. 2011), to simultaneously model three aspects of growth: (1) mean change in BMI, or the BMI growth trajectory; (2) velocity, or rate of change in BMI over time; and (3) acceleration, or the speeding up and slowing down of BMI growth during the observation period. The novel feature of NGMs is the acceleration trajectory – an aspect of growth that may be more relevant to long-term health than change in anthropometry or growth velocity (Singhal 2017). To model acceleration, NGMs capture both long-term change in velocity through the Ornstein-Uhlenbeck (OU) process (i.e., the child's BMI growth velocity pattern across the entire birth-to-36-month observation period), as well as short-term fluctuation in velocity (i.e., oscillations in a child's BMI velocity between study visits) via a Wiener process. Joint modelling of mean change, velocity, and acceleration of BMI growth enables NGMs to capture deviations of each child's BMI trajectory, velocity, and acceleration from the population averages, while also accounting for intra-individual instantaneous changes in each child's growth with respect to his or her overall trajectory. For instance, a child may exhibit an increase in BMI growth velocity from birth to 4 months, reach his BMI peak at 4.5 months, and then experience a decrease in BMI growth velocity for the remainder of the observation period. This trend represents the child's "long-term" velocity trajectory. However, his growth data may show "short-term" deviations from the overall pattern, such as a temporary increase in velocity followed by a minor decrease in velocity, while still following the longer term trajectory. These short-term fluctuations are taken into account by the NGMs and contribute to the estimation of each child's trajectory, rather than being consolidated into the error term, as is the case with other common methods for trajectory analysis (e.g., linear mixed regression, SITAR). To improve estimation of the BMI trajectories, we incorporated sex-specific World Health Organization (WHO) Multi-Center Growth Reference Study data (de Onis M et al. 2004) as a prior for Bayesian inference. We specifically used WHO data to inform the shape of the BMI trajectories, which were then used to derive the velocity and acceleration functions.

After creating the trajectories, we identified the infancy BMI peak as the point on the trajectory when BMI velocity = 0 and when acceleration changed from increasing to decreasing mode. The corresponding age to this point on the trajectory is the age at the infancy BMI peak, and the BMI at this point is the magnitude of the infancy BMI peak (a.k.a. peak BMI). Additional details on NGMs are in the Supplemental Material. The manuscript describing development and implementation of NGMs is currently under revision (Baek J. et al.). The R program package for NGMs can be found online: <http://www.umich.edu/~songlab/software.html#NGM>. Figure 1 shows examples of raw BMI data with the fitted trajectories and estimated peak from individual children exhibiting a range of age of BMI peaks. For subsequent regression analyses, we evaluated the age at infancy BMI peak and the magnitude of the peak (i.e., peak BMI) as continuous variables.

Outcomes: anthropometry and cardiometabolic biomarkers at 8-14 years of age

Anthropometry—At the peripubertal visit, trained research staff measured the children's weight (kg) on a digital scale (BAME Mod 420; Catálogo Médico), height (cm) using a calibrated stadiometer (BAME Mod 420; Catálogo Médico), waist circumference (cm) using

a non-stretchable measuring tape (QM2000; QuickMedical), and the subscapular (SS) and triceps (TR) skinfold thicknesses (mm) using calibrated skin calipers (Lange; Beta Technology) (Lohman et al. 1988). All anthropometric assessments were carried out in duplicate. Because the correlations between the repeated measures were high (Pearson's $R^2 > 0.98$), we used the average of the two values for each indicator in the analysis.

We used weight and height to calculate BMI and height and standardised both as a z-score using the WHO growth reference (de Onis Mercedes et al. 2007). We assessed BMI and height z-score as indicators of overall body size and stature, respectively. We evaluated waist circumference as a proxy for central visceral adiposity, and the SS+TR sum as an indicator subcutaneous adiposity, respectively (Boeke et al. 2013).

Cardiometabolic biomarkers—Using fasting blood collected at the peripubertal visit, we measured serum glucose enzymatically, serum C-peptide using an automated chemiluminescence immunoassay (Immulite 1000, Siemens Medical Solutions), and leptin via a radioimmunoassay (Millipore, Merck). We also quantified serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) using a biochemical analyser (Cobas Mira Plus, Roche Diagnostics), and calculated low-density lipoprotein cholesterol (LDL-C) as: $\text{total cholesterol} - \text{HDL-C} - (\text{Triglycerides}/5)$.

Research staff measured systolic (SBP) and diastolic blood pressure (DBP) five times (mmHg) in the seated position with an automated blood pressure monitor (BpTRU; Coquitlam, BC). Because the intra-class correlation (ICC) between the measurements were high ($\text{ICC}_{\text{SBP}} = 0.95$; $\text{ICC}_{\text{DBP}} = 0.89$), we used the average of the values for the analysis.

In addition to the individual biomarkers, we derived two indices: C-peptide-based insulin resistance (CP-IR) and a metabolic syndrome risk z-score (MetS z-score). We calculated CP-IR using the following equation: $[\text{fasting serum C-peptide} \times \text{fasting serum glucose}]/405$ (Wallace et al. 2004). For the MetS z-score, we calculated the sum of five age- and sex-specific internal z-scores for waist circumference, fasting glucose, fasting C-peptide, triglycerides/HDL-C, and $(\text{SBP} + \text{DBP})/2$. This score is a modification (i.e., use of C-peptide rather than insulin) of a score proposed by Viitasalo et al. (Viitasalo et al. 2014) in a study that examined correlations among the metabolic biomarkers in children and adults, and established its association with incident type 2 diabetes and cardiovascular disease.

Covariates

At enrollment, mothers reported on age, reproductive history, lifestyle habits including smoking during pregnancy, and sociodemographic characteristics like marital status and education level, via an interviewer-administered questionnaire. We extracted birthweight from medical records. During research visits scheduled at 1, 3, 6, and 12 months postpartum, we administered surveys inquiring on breastfeeding status. The women were asked whether they were currently breastfeeding, and if the answer was, “No,” they were then asked when they stopped. We used responses from these surveys to estimate breastfeeding duration and dichotomized the variable as ≥ 6 vs. < 6 months. A paediatrician assessed each child to determine Tanner stage on a scale of 1 (no development) to 5 (full development) for genital (boys) and breast (girls) development. We then dichotomized pubertal status as pre-pubertal

vs. pubertal: boys were classified as pubertal if they received an assessment of Tanner stage >2 for genital development, and girls were classified as pubertal if they received an assessment of Tanner stage >2 for breast development.

Data analysis

We carried out the analysis in three steps. First, we examined associations of unadjusted associations of timing (age at BMI peak) and magnitude of the infancy BMI peak (peak BMI), while weighting all estimates by the number of anthropometric measurements for each participant from birth to 36 months of age.

Next, we introduced key covariates that were associated with the infancy growth milestones in bivariate analysis, and are known determinants of child health based on current literature and our *a priori* knowledge. In the models, we included maternal calcium supplementation (per study design of the original ELEMENT cohorts (Hernandez-Avila et al. 2003; Tellez-Rojo et al. 2004)) and age at enrollment; child's sex, birthweight, and age at the peripubertal visit. Because puberty is associated with body composition and metabolism (Hannon et al. 2006), but could also be a mediator to the relationships of interest, we explored the impact of adjustment for this variable in a separate model to evaluate its impact on the estimates of association. Age at BMI peak was right skewed, so we examined associations of this variable with the peripubertal outcomes after natural log transformation. Because the direction, relative magnitude, and significance of the estimates were similar to non-transformed age at BMI peak, we report results using the original variable for ease of interpretation. We did not note any deviations from normality for peak BMI.

To determine whether the relationships of interest differed by established modifiers to the relationship between infant growth and future health, we tested for interactions with sex, birthweight (continuous in g, as well as ≥ 3160 vs. <3160 g) (Ong 2006), and breastfeeding duration (≥ 6 vs. <6 months) (Jensen et al. 2015). Non-significant interaction terms (P -interaction >0.30) allowed us to evaluate all children together in the analysis.

Finally, we carried out sensitivity analyses. We evaluated the impact of adjusting for additional characteristics known to be associated with adiposity and metabolic health in this cohort, including pubertal status, mother's marital status, education level, age, parity, and smoking habits during pregnancy; and gestational age at delivery. All models met standard assumptions for multivariable linear regression (linearity of relationships between exposure/outcome pairs, homoscedasticity of model error, normality of residuals). Implementation of NGMs was carried out in R software. All other analyses were carried out in SAS version 9.4 (SAS, Cary, NC).

Results

Median age of the participants at the peripubertal research visit was 10.3 years (range: 8.1, 13.8). Median (range) age at infancy BMI peak was 9.6 (6.0-34.8) months. Median (range) of peak BMI was 16.6 (13.5-20.3) kg/m². The two infancy milestones were mildly positively correlated (Pearson's $R = 0.11$). Background characteristics of the study sample are

displayed in Table 1, and descriptive statistics of the peripubertal outcomes are shown in Table 2.

Table 3 presents unadjusted and adjusted associations of age at BMI peak (per 1 month), as well as the magnitude of BMI peak (per 1 kg/m²) with the peripubertal outcomes. Generally speaking, the unadjusted and adjusted models yielded similar estimates. In the multivariable analysis, later age at the infancy BMI peak was associated with higher BMI z-score (0.05 [95% CI: 0.02, 0.08]), waist circumference (0.37 [95% CI: 0.16, 0.59] cm), and SS+TR (0.44 [95% CI: 0.18, 0.70] mm). A later age at BMI peak was also a determinant of worse glycaemia, as indicated by fasting glucose, C-peptide, and CP-IR; higher leptin; higher blood pressure; as well as higher overall metabolic risk according to the MetS z-score (Table 3). We observed similar associations of the magnitude of the infancy BMI peak with the anthropometric outcomes. However, with respect to the cardiometabolic biomarkers, peak BMI was only associated with higher leptin (1.04 [95% CI: 0.01, 2.08] ng/mL per 1 kg/m²) and MetS z-score (0.10 [95% CI: 0.01, 0.18] units per 1 kg/m²). Neither age nor magnitude of the BMI peak was associated with height z-score during peripuberty (Table 3).

Table 4 shows estimates from a single multivariable model where age at BMI peak and the magnitude of the BMI peak were mutually adjusted for each other, in addition to the covariates included in Table 3. Results from this model are similar to those in Table 3, with the exception that the magnitude of the BMI peak was no longer associated with the cardiometabolic biomarkers.

Further adjustment for pubertal status did not change the direction, magnitude, or precision of the estimates (Supplemental Table 1). None of these relationships differed with respect to birthweight, breastfeeding duration, sex, or pubertal status (all *P*-interaction >0.30). Accounting for other known determinants of adiposity and metabolic health (mother's marital status, education level, age, parity, and smoking habits during pregnancy; gestational age at delivery) did not alter the direction, magnitude, or precision of the associations (data not shown; available upon request) and therefore, were not included in final models.

Discussion

In this analysis of 163 mother-child pairs in Mexico City, we applied Newton's Growth Models (NGMs) (Baek J et al. 2017), a novel individual-based trajectory technique that jointly models mean BMI, BMI velocity, and BMI acceleration, to examine associations of timing and magnitude of the infancy BMI peak with anthropometry and cardiometabolic risk during peripuberty. We found that later age at the infancy BMI peak and a larger magnitude of peak are associated with larger body size (BMI z-score) and higher adiposity (waist circumference and skinfold sum) during peripuberty (8-14 years). Additionally, later age at peak was a determinant of cardiometabolic risk during peripuberty, even after accounting for magnitude of the peak.

Comparison of age at BMI peak with other populations

The average age at the infancy BMI peak was 11.9 months, which is later than what has been reported for children in Sweden (~9 months) (Silverwood et al. 2009), the Netherlands

(9.3 months) (Hof et al. 2013), Denmark (8.2 months in boys, 8.7 months in girls) (Jensen et al. 2015), the U.S. (7.2 months in boys, 7.4 months in girls) (Wen et al. 2012), and China (7.6 months) (Sun et al. 2017). Conversely, average peak BMI in this study was 16.5 kg/m², which is lower than estimated values for German (17.5 kg/m²) (Hof et al. 2013), Chinese (18.3 kg/m²) (Sun et al. 2017), and African American infants (18.6 kg/m²) (Roy et al. 2015). The later age and lower magnitude of BMI peak of participants in this study sample could be due to numerous factors, including lower socioeconomic status, higher altitude, relatively high exposure to lead in Mexico City (Schnaas et al. 2004), maternal macronutrient composition (e.g., higher carbohydrate intake), secular trends, and genetics – all of which have potential to impact early growth (Wijlaars et al. 2011; Johnson et al. 2013; Hong et al. 2014; Wang W et al. 2016; Chen LW et al. 2017).

Infancy BMI peak and anthropometry during peripuberty

Early life BMI typically follows a distinct age-related pattern characterised by a rapid increase after birth, followed by attainment of the infancy BMI peak between 7 to 9 months, then falling to a nadir around 5 to 6 years of age, marking the beginning of the adiposity rebound, before increasing again through late childhood/early adolescence (Chivers et al. 2009; Wen et al. 2012). Researchers have consistently found that an earlier adiposity rebound (e.g., younger age at rebound) predicts future obesity (Taylor et al. 2005; Rolland-Cachera et al. 2006), even in the absence of elevated concurrent BMI (Whitaker et al. 1998; Williams and Dickson 2002; Roy et al. 2015). Fewer studies have examined long-term health in relation to the infancy BMI peak, which may permit earlier recognition of growth abnormalities for preventive action.

Our finding that later age and larger magnitude of the BMI peak predicted higher future BMI z-score, waist circumference, skinfold sum aligns with those of other studies utilising individual trajectory techniques (Silverwood et al. 2009; Hof et al. 2013; Jones-Smith et al. 2013; Roy et al. 2015; Sun et al. 2017). For instance, Silverwood et al. (Silverwood et al. 2009) used semi-parametric mixed modelling with penalised splines to model BMI data of 602 Swedish children born between 1987 and 1995. The researchers found that each 1-month increase in age at BMI peak was associated with 0.07 z-scores higher BMI at 5-13 years (Silverwood et al. 2009). Using a similar analytical technique, Hof et al. (Hof et al. 2013) found that each 1-month increment in infancy BMI peak and each 1-kg/m² increase in peak BMI corresponded with ~0.07 units higher BMI z-score at 5-6 years among 2,822 children born between 2003 and 2004 in Amsterdam. In a recent analysis that used polynomial regression with quadratic terms, Sun et al. (Sun et al. 2017) reported that both later age at peak and higher peak BMI predicted odds of overweight at age 2 years among 2,073 children born in Shanghai between 2009 and 2010 (odds ratio per 1 month: 1.35 [95% CI: 1.21, 1.50]; odds ratio per 1 kg/m²: 3.11 [95% CI: 2.64, 3.66]). Using the same analytical approach, Roy et al. found that each 1-month of age at BMI peak and each 1 kg/m² of peak BMI corresponded with 26% (95% CI: 3%, 54%) and 100% (95% CI: 154%, 264%) higher odds of obesity at age 4 years in a cohort of predominantly African American children (*n* = 1,075; born 2003-2010) (Roy et al. 2015). Taken together, the consistency in direction and magnitude of effects reported in the literature across different time periods (e.g., infants born in the 1980s prior to the obesity pandemic vs. post-obesity pandemic in

the early 2000s) and in children of different ethnic groups points toward the importance of infancy growth patterns in the understanding of future risk of obesity-related diseases.

Of note, neither age at BMI peak nor peak BMI were associated with height during peripuberty. While it remains to be elucidated whether this could be due to residual confounding by tempo of maturation, these results suggest that the timing and magnitude of the infancy BMI peak are determinants of future adiposity but not linear growth. Future studies beyond adolescence are warranted to confirm our finding.

Infancy BMI peak and metabolic biomarkers during peripuberty

To date, we are aware of only two published studies that examined associations of the infancy BMI peak with biomarkers of cardiometabolic risk. In the above-mentioned analysis of children in Amsterdam, Hof et al. found that both the timing and magnitude of the infancy BMI peak were positively associated with blood pressure at 5-6 years, and that the relationship was mediated by concurrent BMI (Hof et al. 2013). We observed similar associations in ELEMENT participants. However, we did not adjust for current adiposity because doing so could introduce bias since current weight is likely on the causal pathway between early growth and cardiometabolic health (Tu et al. 2005). In the second study, which was embedded in the Generation R cohort in the Netherlands, Marinkovic et al. found that age at infancy BMI peak, but not the magnitude of the peak, predicted a clustering of metabolic syndrome risk factors defined as having 3 of the following internally-standardized components: central fat mass 75th percentile; systolic or diastolic blood pressure 75th percentile, HDL cholesterol 25th percentile or triglycerides 75th percentile, and insulin 75th percentile (Marinkovic et al. 2017). We similarly found that later age but not magnitude of the peak correlated with a higher metabolic syndrome risk z-score during peripuberty. However, unlike Marinkovic et al.'s reports of no consistent relations of the infancy BMI peak with individual components of the metabolic syndrome, later age at BMI peak in the ELEMENT cohort corresponded with worse glycemia according to higher fasting glucose, C-peptide, and CP-IR; and higher blood pressure. This discrepancy could be due to the fact that our study population is older, and metabolic perturbations likely worsen over time.

In addition to the fact that we were able to examine associations of the infancy BMI peak with a range of cardiometabolic biomarkers, a key novelty of the present study is the fact that we linked early growth to health outcomes during the pubertal transition, which is a sensitive period for development of cardiometabolic disease risk. For example, fasting glucose from late childhood through the end of puberty is directly correlated with glycaemia in adulthood, and is also a strong predictor of type 2 diabetes risk (Wang G et al. 2011). Likewise, high blood pressure is a leading risk factor for atherosclerosis that tracks from late childhood/early adolescence into adulthood (Chen X and Wang 2008), and elevated leptin – an adipocyte-derived peptide hormone that is conventionally considered a consequence of excess adiposity – was recently shown to precede gains in overall and central adiposity accrual in peripubertal youth over 6 years of follow-up (Zhang et al. 2017).

Strengths & limitations

Strengths of this study include the prospective study design, multiple anthropometric assessments during infancy, rich covariate data, assessment of multiple health outcomes during peripuberty (i.e., body fat distribution and multiple cardiometabolic biomarkers), and use of a novel Bayesian trajectory analysis approach. Our study also has some limitations. First, the relatively small sample size may have reduced power to detect significant associations. Second, because ELEMENT is a Hispanic population, our findings may lack generalisability to non-Hispanic populations, especially given the role that genetics may play in growth (Johnson et al. 2013). Finally, we cannot rule out potential misclassification of infants in the categories of infancy BMI peak due to model error; however, analysis of the subset of participants with an observable infancy BMI peak yielded similar results, thereby reducing the possibility of bias in our results.

Conclusions

In this study, we utilised data from a longitudinal study in Mexico, a low- to middle-income setting afflicted by disproportionately high rates of obesity and obesity-related conditions (Food and agriculture organization (FAO) of the United Nations 2013; Rivera et al. 2014), and linked median of eight BMI measurements between birth and 36 months to anthropometry and cardiometabolic risk during peripuberty. We combined these unique data with a novel Bayesian stochastic process model to characterise BMI trajectories based on growth acceleration, which may be more relevant to long-term health than change in anthropometry or growth velocity given the impact of rapid postnatal weight gain and future obesity risk (Singhal 2017). Our primary findings are that later age and larger magnitude of the infancy BMI peak are determinants of higher adiposity during the pubertal transition, and later age at peak is associated with several cardiometabolic biomarkers. These findings are salient as the pubertal transition coincides with establishment of adipocyte quantity (Spalding et al. 2008) and may also be a sensitive period for long-term metabolic risk (Alberga et al. 2012). Accordingly, identifying early life determinants of health during this life stage will direct preventive efforts.

Areas for future inquiry include: (1) use of causal inference techniques to disentangle the extent to which upstream determinants of infant growth that are also risk factors for excess adiposity – e.g., maternal pre-pregnancy obesity and excess gestational weight gain (Perng et al. 2014), gestational diabetes mellitus (Regnault et al. 2013) – are responsible for the observed associations between of age at infancy BMI peak and the peripubertal outcomes; (2) mechanistic studies to determine whether early growth patterns are causally related to future physiology via developmentally-plastic processes like epigenetics, as suggested by Gluckman & Hanson (Gluckman and Hanson 2008)); (3) given that BMI represents a combination of weight and length, the former of which comprises both fat and fat-free mass, it will be important to ascertain which component(s) of BMI drive the associations of interest. These endeavors will not only improve understanding of the relationships explored in this study, but will also provide a platform for future studies to identify determinants of the infancy growth dynamics. Ultimately, these combined efforts have potential to identify viable avenues for early prevention of obesity-related disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
NGM	Newton's growth model
CP-IR	C-peptide insulin resistance

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Figure 1.

Example BMI data and fitted trajectory curve for four ELEMENT participants. Panels (a)-(c) are examples of individuals with detectable BMI peaks, and panel (d) is an example of a participant with no detectable peak and was subsequently excluded from the analysis.

Table 1

Characteristics of 163 ELEMENT participants.

	<u>Mean $\pm$ SD or % (N)</u>
Maternal & perinatal characteristics	
Age at enrollment (years)	27.6 $\pm$ 5.5
Married/cohabiting	72.4% (118)
Maternal education (years)	11.0 $\pm$ 2.9
Parity	
0	34.4 (56)
1-2	58.9% (96)
3	6.8% (11)
Smoked during pregnancy	1.2% (2)
Birthweight (g)	3168.5 $\pm$ 0.4
Gestational age at delivery (weeks)	39.2 $\pm$ 1.1
Breastfeeding 6 months	68.1% (111)
Calcium supplementation	43.0% (89)
Child characteristics at the peripubertal visit	
Male	49.1% (80)
Age (years)	10.3 $\pm$ 1.6
Pubertal status in girls ^a	
Pre-pubertal	66.3% (55)
Pubertal	33.7% (28)
Pubertal status in boys ^a	
Pre-pubertal	53.3% (41)
Pubertal	46.8% (36)

^a Puberty was defined as Tanner stage 3-5 (vs. 1-2) for breast (girls) and testicular (boys) development.

Table 2Mean $\pm$ SD of peripubertal health outcomes among 163 ELEMENT participants.

	All <i>n</i> = 163	Boys <i>n</i> = 80	Girls <i>n</i> = 83
Adiposity			
BMI z-score ^a	0.64 $\pm$ 1.18	0.63 $\pm$ 1.17	0.64 $\pm$ 1.19
Height z-score ^a	-0.28 $\pm$ 0.88	-0.22 $\pm$ 0.81	-0.33 $\pm$ 0.96
Waist circumference (cm)	68.9 $\pm$ 9.9	68.2 $\pm$ 9.5	70.0 $\pm$ 10.4
SS+TR (mm)	26.6 $\pm$ 11.5	24.0 $\pm$ 10.8	29.0 $\pm$ 11.6
Cardiometabolic biomarkers			
Fasting glucose (mg/dL)	86.4 $\pm$ 8.7	86.9 $\pm$ 7.2	85.9 $\pm$ 9.9
C-peptide (ng/mL)	1.7 $\pm$ 1.2	1.5 $\pm$ 1.1	1.8 $\pm$ 1.3
CP-IR ^b	0.37 $\pm$ 0.33	0.33 $\pm$ 0.25	0.40 $\pm$ 0.39
Leptin (ng/mL)	9.9 $\pm$ 7.8	7.3 $\pm$ 6.0	12.4 $\pm$ 8.5
Total cholesterol (mg/dL)	154.9 $\pm$ 27.0	140.2 $\pm$ 27.1	159.3 $\pm$ 26.3
HDL (mg/dL)	59.4 $\pm$ 12.3	60.4 $\pm$ 12.2	58.4 $\pm$ 12.4
LDL (mg/dL)	78.1 $\pm$ 22.9	74.6 $\pm$ 23.6	81.5 $\pm$ 21.7
Triglycerides (mg/dL)	87.0 $\pm$ 44.1	76.3 $\pm$ 38.0	97.4 $\pm$ 47.2
SBP (mmHg)	101.7 $\pm$ 10.2	103.1 $\pm$ 10.5	100.3 $\pm$ 9.8
DBP (mmHg)	65.2 $\pm$ 7.3	65.2 $\pm$ 7.3	65.1 $\pm$ 7.3
MetS z-score ^c	-0.07 $\pm$ 0.62	-0.08 $\pm$ 0.62	-0.07 $\pm$ 0.64

BMI: body mass index; SS: subscapular skinfold; TR: triceps skinfold; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CP-IR: C-peptide based insulin resistance index; MetS z-score: metabolic syndrome risk z-score

^aStandardized according to age- and sex-specific values from the World Health Organization (WHO) growth reference for children 5-19 years

^bCalculated as [fasting serum C-peptide $\times$ fasting serum glucose]/405.

^cCalculated as the average of 5 internally-standardized z-scores for waist circumference, fasting glucose, C-peptide, triglycerides/HDL ratio, and the average of SBP and DBP.

Associations of age and magnitude of the infancy BMI peak with anthropometry and cardiometabolic biomarkers during peripuberty (8-14 years) in 163 ELEMENT participants.

Table 3

	Difference (95% CI) in peripubertal outcomes			
	per 1 month increase in age at BMI peak ^a		per 1 kg/m ² increase in the peak BMI ^d	
	Unadjusted model	Adjusted model ^b	Unadjusted model	Adjusted model ^b
Anthropometry				
BMI z-score ^c	0.03 (0.01, 0.06)	0.05 (0.02, 0.08)	0.40 (0.25, 0.55)	0.37 (0.22, 0.52)
Height z-score ^c	0.02 (-0.00, 0.04)	0.02 (-0.00, 0.04)	-0.01 (-0.13, 0.11)	0.00 (-0.13, 0.12)
Waist circumference (cm)	0.09 (-0.14, 0.31)	0.37 (0.16, 0.59)	1.93 (0.56, 3.30)	1.86 (0.60, 3.12)
SS+TR (mm)	0.23 (-0.02, 0.49)	0.44 (0.18, 0.70)	1.96 (0.39, 3.54)	2.00 (0.48, 3.51)
Cardiometabolic biomarkers				
Fasting glucose (mg/dL)	0.22 (0.04, 0.41)	0.26 (0.05, 0.47)	0.33 (-0.86, 1.51)	0.50 (-0.71, 1.72)
C-peptide (ng/mL)	0.04 (0.01, 0.07)	0.06 (0.03, 0.09)	0.16 (-0.02, 0.33)	0.16 (-0.02, 0.34)
CP-IR ^d	0.01 (0.00, 0.02)	0.02 (0.01, 0.02)	0.05 (-0.00, 0.09)	0.05 (-0.00, 0.10)
Leptin (ng/mL)	0.19 (0.02, 0.37)	0.29 (0.12, 0.47)	0.98 (-0.11, 2.06)	1.04 (0.01, 2.08)
Total cholesterol (mg/dL)	0.41 (-0.18, 1.01)	0.33 (-0.28, 0.95)	2.12 (-1.58, 5.81)	1.37 (-2.17, 4.91)
HDL cholesterol (mg/dL)	-0.17 (-0.44, 0.10)	-0.16 (-0.47, 0.14)	-0.52 (-2.22, 1.19)	-0.79 (-2.53, 0.95)
LDL cholesterol (mg/dL)	0.37 (-0.13, 0.87)	0.30 (-0.22, 0.81)	2.64 (-0.45, 5.75)	2.03 (-0.93, 5.00)
Triglycerides (mg/dL)	1.08 (0.09, 2.07)	1.00 (-0.08, 2.07)	-0.08 (-6.29, 6.14)	0.64 (-5.63, 6.90)
SBP (mmHg)	0.14 (-0.09, 0.37)	0.37 (0.13, 0.60)	1.02 (-0.41, 2.46)	1.10 (-0.25, 2.46)
DBP (mmHg)	0.00 (-0.16, 0.16)	0.14 (-0.02, 0.31)	0.65 (-0.35, 1.65)	0.64 (-0.31, 1.60)
MetRisk z-score ^e	0.02 (0.01, 0.03)	0.04 (0.02, 0.05)	0.10 (0.01, 0.19)	0.10 (0.01, 0.18)

^aEstimates are weighted for the number of anthropometric measurements during infancy.

^bEstimates are weighted for the number of anthropometric measurements during infancy and adjusted for maternal calcium supplementation and age at enrollment; and child's sex, birthweight, and age at the peripubertal visit.

^cAccording to the WHO growth reference for children 5-19 years.

^dCalculated as [fasting serum C-peptide × fasting serum glucose]/405.

^e Calculated as the average of 5 internally-standardized z-scores for waist circumference, fasting glucose, C-peptide, triglycerides/HDL-C ratio, and the average of SBP and DBP.

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Table 4

Associations of mutually-adjusted age at the infancy BMI peak and magnitude of the infancy BMI peak with adiposity and cardiometabolic risk during peripuberty (8-14 years) in 163 ELEMENT participants.

	β (95% CI) in peripubertal outcomes^a	
	per 1 mo age at BMI peak	per 1 kg/m² of peak BMI
Anthropometry		
BMI z-score ^b	0.04 (0.01, 0.07)	0.33 (0.17, 0.48)
Height z-score ^b	0.02 (0.00, 0.04)	−0.02 (−0.15, 0.11)
Waist circumference (cm)	0.32 (0.11, 0.54)	1.51 (0.25, 2.76)
SS+TR (mm)	0.39 (0.13, 0.65)	1.56 (0.06, 3.07)
Cardiometabolic biomarkers		
Fasting glucose (mg/dL)	0.25 (0.04, 0.46)	0.22 (−1.00, 1.44)
C-peptide (ng/mL)	0.05 (0.02, 0.09)	0.10 (−0.08, 0.27)
CP-IRc	0.01 (0.01, 0.02)	0.03 (−0.02, 0.08)
Leptin (ng/mL)	0.27 (0.09, 0.44)	0.74 (−0.28, 1.77)
Total cholesterol (mg/dL)	0.30 (−0.32, 0.92)	1.04 (−2.56, 4.64)
HDL cholesterol (mg/dL)	−0.14 (−0.45, 0.16)	−0.63 (−2.40, 1.14)
LDL cholesterol (mg/dL)	0.24 (−0.28, 0.76)	1.77 (−1.25, 4.78)
Triglycerides (mg/dL)	1.01 (−0.08, 2.11)	−0.49 (−6.81, 5.82)
SBP (mmHg)	0.35 (0.11, 0.58)	0.72 (−0.63, 2.07)
DBP (mmHg)	0.13 (−0.04, 0.29)	0.50 (−0.47, 1.47)
MetRisk z-score ^d	0.03 (0.02, 0.05)	0.06 (−0.02, 0.14)

^aEstimates are weighted for the number of anthropometric measurements during infancy, and adjusted for maternal calcium supplementation and age at enrollment; and child's sex, birthweight, age at the peripubertal visit, and the other infant growth milestone.

^bAccording to the WHO growth reference for children 5-19 years.

^cCalculated as [fasting serum C-peptide × fasting serum glucose]/405.

^dCalculated as the average of 5 internally-standardized z-scores for waist circumference, fasting glucose, C-peptide, triglycerides/HDL-C ratio, and the average of SBP and DBP.