Obesity

BMI Trajectories from Birth to 23 Years by Cardiometabolic Risks in Young Adulthood

Patricia East [1], Erin Delker[1], Estela Blanco[1], Betsy Lozoff[2], Paulina Correa[3], Raquel Burrows [3], and Sheila Gahagan [1]

Objective: The aim of this study was to investigate whether the level, rate, and acceleration of BMI growth differ according to the presence or absence of adult cardiometabolic (CM) risks.

Methods: BMI was measured in 1,000 Chileans at nine time points from birth to 23 years, and metabolic syndrome and its components were assessed at young adulthood. BMI growth was analyzed in the following three developmental periods: birth to 6 months, 6 months to 5 years, and 5 to 23 years.

Results: Individuals with CM risks had a specific constellation of early-life growth (faster growth after infancy, lower BMI decline approaching age 5, absence of a definitive BMI nadir in early childhood, higher 5-year BMI) and distinct young adult growth (larger BMI increases from childhood to young adulthood and lower levels of expected growth deceleration approaching young adulthood). Those with CM risks also attained BMI ≥ 25 at significantly younger ages than those absent risks (metabolic syndrome: 12.3 years vs. 20.1 years; hyperglycemia: 13.1 years vs. 18.9 years; hypertension: 13.2 years vs. 19.4 years; hypertriglyceridemia: 14.3 years vs. 19.5 years; inflammation: 15.9 years vs. 20.6 years).

Conclusions: Larger and faster increases in BMI and a failure of BMI growth to decline or decelerate at specific developmental periods distinguished individuals who would and would not have adult CM risks.

Obesity (2020) **28**, 813-821.

Study Importance

What is already known?

- Large increases in body mass and overweight/obesity relate to poor cardiometabolic outcomes.

What does this study add?

- This study analyzed body mass at nine time points from birth to age 23 years in 1,000 Chileans and found that individuals with adult cardiometabolic risks had a specific constellation of early-life growth (faster growth after infancy, lower body mass decline approaching age 5, absence of a definitive body mass nadir in early childhood, higher 5-year body mass) and a distinct midlife growth pattern (larger body mass increases from childhood to young adulthood and lower levels of expected growth deceleration approaching young adulthood).
- Larger and faster increases in BMI and a failure of BMI growth to decline or decelerate at specific developmental periods differentiated individuals who would and would not have adult cardiometabolic risks.

How might these results change the direction of research?

- These findings call for further understanding of discernible patterns of BMI growth across development, from birth to young adulthood, that precede cardiometabolic risks.
- Obesity interventions implemented from infancy to late adolescence may be effective for reducing cardiometabolic risks.

Introduction

Obesity during childhood is a known risk factor for poor adult cardiometabolic (CM) functioning (1,2). Recently, BMI growth trajectories have been examined in relation to cardiovascular health. These studies generally have linked specific BMI growth patterns to later CM risks (3-7) or evaluated how age-specific changes in BMI relate to cardiovascular disease (7-9). However, longitudinal studies in which both BMI growth patterns and adult CM disease are known can also be useful for understanding how growth patterns differ according to the presence or absence of CM risks. A few studies have used this approach. Giudici et al. (10) found that higher parent-reported child BMI from age 4 to 10 years distinguished those who had metabolic syndrome (MetS) at 20 to 60 years of age. Fall et al. (11) found that those with MetS at ages 26 to 32 years had greater BMI gain from infancy to adolescence than those not having MetS. Although such studies have adopted an interesting approach of contrasting growth patterns by known CM risk, neither study compared the rate of BMI change or possible BMI growth acceleration or deceleration by

[1] Department of Pediatrics, School of Medicine, University of California, San Diego, La Jolla, California, USA. Correspondence: Patricia East (peast@ucsd.edu)
[2] Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA [3] Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile.

 Received: 22 May 2019; **Accepted:** 5 January 2020; **Published online 28 February 2020. doi:10.1002/oby.22754**

subsequent CM risk. Yet larger and faster BMI increases have been associated with poorer CM outcomes (7,9,12). Thus, comparing BMI growth, as well as BMI at various ages, by subsequent CM risk allows one to not only determine whether distinct growth patterns precede CM risk, but also to quantify how such growth patterns might diverge.

This study investigated whether the level, rate, and acceleration of BMI growth from birth to age 23 years differ according to the presence or absence of CM risk factors in young adulthood. We also examined the age at which BMI first diverged by the presence or absence of CM risks and the age at which BMI ≥ 25 and BMI ≥ 30 for those with and without specific CM risks. CM risks studied were MetS and its components (hyperglycemia, hypertriglyceridemia [high triglycerides, TG], low high-density lipoprotein cholesterol [HDL-C], hypertension, abdominal obesity) and inflammation (elevated C-reactive protein [CRP]).

Methods

Sample and study design

Data are from 1,000 participants of the Santiago Longitudinal Study, which initially involved 1,790 Chilean infants in an iron-deficiency anemia preventive trial and neurological maturation study (13). Infants were recruited at 6 months (1991-1996) from community clinics serving low- to middle-income families. Eligible infants were healthy full-term singletons with birth weight ≥ 3,000 g. The preventive trial involved random assignment of 1,657 nonanemic infants to receive an iron-fortified formula (12 mg/L, comparable to the level of iron in infant formulas available in the United States), a low iron-fortified formula (2.3 mg/L), or a no–added iron formula (13). An additional 133 infants participated in a neurological maturation study, involving laboratory assessments in addition to core components of the Santiago Longitudinal Study. Weight and height (length) (converted to BMI in kilograms per meter squared) were measured at birth, 3 months, 6 months, 1 year, 5 years, 10 years, 21 years, and 23 years as well as up to three times in adolescence (between 11 and 18 years; mean = 15.3 years). For participants assessed more than once during adolescence, height and weight from the assessment closest to age 15 years were used, excluding those < 14 years (n = 52) or > 16 years (n = 123). CM risk biomarkers were measured in 1,040 participants at age 23 years. Analyses utilized data from the 1,000 participants who had risk biomarker data at young adulthood and BMI at six or more time points (i.e., missing no more than three BMI values) (14). This criterion was based on having adequate data coverage on all variables in tandem with randomly distributed missingness (14). Of the participants who had CM biomarker data at young adulthood, > 99% had BMI data at birth, 3 months, 6 months, 1 year, and 23 years. However, a substantial budget cut at the 5-year follow-up necessitated that the low-iron supplementation group (n = 405) as part of the infancy preventive trial was not studied. In order to maximize use of the available age 5 data, we employed the threshold requiring participants to have at least six complete BMI time points. This allowed us to utilize 69.1% of the data collected at age 5 and a minimum of 87.6% of data collected at the other time points (Table 1). These are deemed acceptable levels of missing data when data are assumed to be missing completely at random (14,15). The missing completely at random test provided evidence that data within the current analytic sample were missing completely at random (Little's χ^2 [df = 77] 90.33; P = 0.134) (15). Sample follow-up and loss at each study time point are shown in Supporting Information Figure S1).

Characteristics of the sample (duration of breastfeeding, mothers' age, socioeconomic status [SES], etc. (16)) were assessed when participants were age 1 year (Table 1). When children were 10 years, mothers self-reported their prepregnancy height and weight, from which maternal BMI was calculated. Participants included in the current analyses were similar in background characteristics, age, and BMI at all time points to those not included. However, those analyzed were more likely to be female, from families with higher SES, and less likely to have received iron supplementation as part of the preventive trial (Supporting Information Table S1). Approval for this study was obtained from the authors' institutional review boards in the United States and Chile. Informed written consent was obtained from children's parents at all time points prior to child age 21; participants gave written informed consent at ages 21 and 23 years. Participants received a stipend at the 23-year assessment. All study procedures were in accord with the Code of Ethics of the World Medical Association (17).

Measurements

Anthropometric assessment. Weight and length at birth and 3 months were abstracted from medical records. Infants' unclothed weight at 6 months and 1 year was measured using an electronic scale (to the nearest 0.01 kg), and length was measured using a recumbent length board (to the nearest 0.1 cm) by a trained research clinician at the Institute of Nutrition and Food Technology at the University of Chile. At all other time points, standardized procedures were used at the Institute of Nutrition and Food Technology to measure height (centimeters) to the nearest 0.1 cm (using a Holtain stadiometer; Holtain Ltd., Crosswell, Crymmich, UK) and weight (kilograms) to the nearest 0.1 kg (using a Seca 703 scale; Seca, Hamburg, Germany). Measurements at age 5 years and older were taken twice, with a third measurement if the difference between the first two exceeded 0.3 kg for weight or 0.5 cm for height. BMI was calculated from weight and height (kilograms per meter squared) (or weight and length). Raw BMI scores at all time points were used in analyses for consistency in estimating the trajectory. Studies support the use of raw BMI scores as an indicator of obesity in children (18,19) and as a useful measure of adiposity change in longitudinal research that involves children and adults (20). At the 23-year follow-up, waist circumference (WC) was measured with nonelastic flexible tape and recorded to 0.1 cm.

CM risk assessment. At the young adult assessment (mean age = 23.0 years), after 15 minutes of rest, systolic and diastolic blood pressures were measured three times on the nondominant arm using a standard mercury sphygmomanometer. The first measurement was discarded, and the second two were averaged for analysis (21). Fasting serum total glucose (milligrams per deciliter), total cholesterol (milligrams per deciliter), TG (milligrams per deciliter), HDL-C (milligrams per deciliter), and high-sensitivity CRP (milligrams per liter) were measured after a 12-hour overnight fast. Serum glucose concentrations were measured with an enzymatic colorimetric test (Quimica Clinica Aplicada, Amposta, Spain). Cholesterol profile was determined by dry analytical methodology (Vitros; Ortho Clinical Diagnostics, Johnson & Johnson Inc., Raritan, New Jersey). High-sensitivity CRP was measured with a sensitive latex-based immunoassay, with elevated inflammation defined as CRP ≥ 3.0 mg/L (22). MetS was based on the 2009 consensus definition (23), which involves having at least three of the following five risk factors: abdominal obesity (WC ≥ 94 cm males; ≥ 80 cm females), high arterial blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg), high TG (TG ≥ 150 mg/dL), low HDL-C (< 50 and < 40 mg/dL in females and males, respectively), and fasting hyperglycemia (glucose ≥ 100 mg/dL) (23). Additionally, we calculated a continuous score representing a composite CM risk profile as the sum of the five MetS risks (range: 0-5).

TABLE 1 Sample characteristics ($N = 1,000$)

	n	Mean or %	SD
Child sex (% female)	1,000	51%	
Maternal BMI (kg/m^2)[a]	855	28.9	5.1
Maternal age (y)[b]	993	26.3	6.0
Family SES[c]	995	27.3	6.3
Received iron supplementation[d]	925	63.2%	
Duration of breastfeeding (mo)[e]	979	3.6	3.1
Birth weight (g)	1,000	3545.34	365.76
BMI (kg/m^2)[f]			
Birth	1,000	13.8	1.1
3 mo	997	17.5	1.4
6 mo	1,000	18.0	1.5
1 y	1,000	17.8	1.4
5 y	691	17.0	2.2
10 y	876	19.4	3.3
15 y	962	23.1	4.4
21 y	916	26.4	5.3
23 y	1,000	26.7	5.6
Cardiometabolic risks at young adulthood			
Hyperglycemia, glucose ≥ 100 mg/dL	1,000	3.5%	
Hypertriglyceridemia, triglycerides ≥ 150 mg/dL	1,000	14.3%	
Low HDL-C, < 40 mg/dL male and < 50 mg/dL female	1,000	59.5%	
Hypertension, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg	1,000	9.3%	
Abdominal obesity, ≥ 94 cm male and ≥ 80 cm female	1,000	31.2%	
Metabolic syndrome[g]	1,000	12.2%	
Number of CM risks (%)	1,000		
0		30.2%	
1		37.7%	
2		19.9%	
3		8.8%	
4		3.1%	
5		0.3%	
Inflammation, CRP ≥ 3.0 mg/L	1,000	36.7%	

[a]Maternal prepregnancy BMI assessed retrospectively at child age 10.
[b]Maternal age at study intake.
[c]Higher scores reflect greater family socioeconomic disadvantage at child age 1 (range 11-47).
[d]Randomly assigned to receive iron-supplemented formula at 6 to 12 months as part of preventive trial.
[e]Duration exclusively breastfed (i.e., age at first bottle).
[f]We used calculated BMI scores at all time points for consistency in trajectory.
[g]Defined as at least three cardiometabolic risks.
SES, socioeconomic status; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CM, cardiometabolic; CRP, C-reactive proteins.

Covariate selection

We selected the following covariates that could potentially confound the BMI-CM relationship (24): participants' sex, maternal BMI, mothers' age at the participant's birth, duration of breastfeeding, iron supplementation as part of the preventive trial, and family SES. Covariates were included on the growth parameters.

Statistical analysis

Given the number and timing of BMI measurements available within the current study, and the expectation of a variety of nonlinear change patterns (25), we analyzed BMI growth within the following three developmental phases: birth to 6 months, 6 months to 5 years, and 5 to 23 years. These age phases were based on global BMI growth curves that show rapid BMI growth from birth to approximately 6 months, followed by decreases leading to a nadir at approximately 4 to 7 years and then by steady increasing growth to young adulthood (age 20) (26,27). Piecewise latent growth curve analysis was conducted in M*plus* 8.2 (Muthen & Muthen, Los Angeles, California) to estimate the BMI trajectories within each age period for those with and without each CM risk (28). We used BMI at birth as the intercept for the initial phase, 6-month BMI as the intercept for the second phase, and 5-year BMI as the intercept for the third phase. We defined the intercept for each model at these time points because we were interested in BMI at these ages as well as in the growth following these ages, that is, in the three distinct developmental phases we have outlined. Latent growth curve analysis quantifies slope (the degree of linear change in BMI) and nonlinear quadratic change (change in the rate of change), with the quadratic term indicating accelerated growth (a speeding up of BMI increase) or decelerated growth (a slowing down or flattening out of BMI growth) (25). The time scores for the quadratic slope factor are the squared values of the linear time scores, and these time scores are automatically computed by M*plus*. We used the Satorra and Bentler (29) scaled χ^2 difference test to determine whether a model that included a quadratic term provided a better fit with the data than a nested model that omitted the quadratic. χ^2 differences were calculated for each of the three age periods. The χ^2 difference test was significant for the last age period only (5-23 years). Thus, growth during the first two age periods was estimated by intercept and slope, and growth during the last phase (5-23 years) was estimated by intercept, slope, and quadratic. The growth terms were evaluated in independent regression models. Model fit was evaluated based on well-established recommendations (30,31), with comparative fit index (CFI) > 0.90, root mean square error of approximation (RMSEA) < 0.06, and standardized root mean square residual (SRMR) < 0.08. The CFI is the χ^2 comparison of the target model to the baseline model (the model in which all the regression paths are set to zero). The RMSEA is the average of the residuals between the observed sample covariance and the expected model estimated for the population. The SRMR is the standardized square root of the difference between the residuals of the observed and predicted covariance matrix. These indices comprise a combination of absolute fit indices (RMSEA, SRMR), an incremental fit index (CFI), and a parsimony-adjusted index (RMSEA) (30,31).

To test differences in growth according to the presence or absence of CM risks, we estimated the growth parameters (random effects derived from growth models) for each participant using the full sample. We report the means of each of these parameters stratified by CM risk (adjusted for covariates). Next, we assessed associations between the presence of each CM risk (1 = present, 0 = absent) and each growth factor. The growth factors were used as continuous latent variables and analyzed as dependent variables in multivariable linear regression models. In each model, the independent variable of interest was CM risk (presence vs. absence), adjusting for maternal BMI, breastfeeding duration, sex, SES, mothers' age, and iron supplementation. A statistically significant effect estimate indicates that the risk-present and risk-absent growth parameters are significantly different. Data were retained for all participants ($N = 1,000$) using the full information maximum likelihood specification, which fits the model being tested directly onto the nonmissing data for each participant and which has been shown to be superior to other

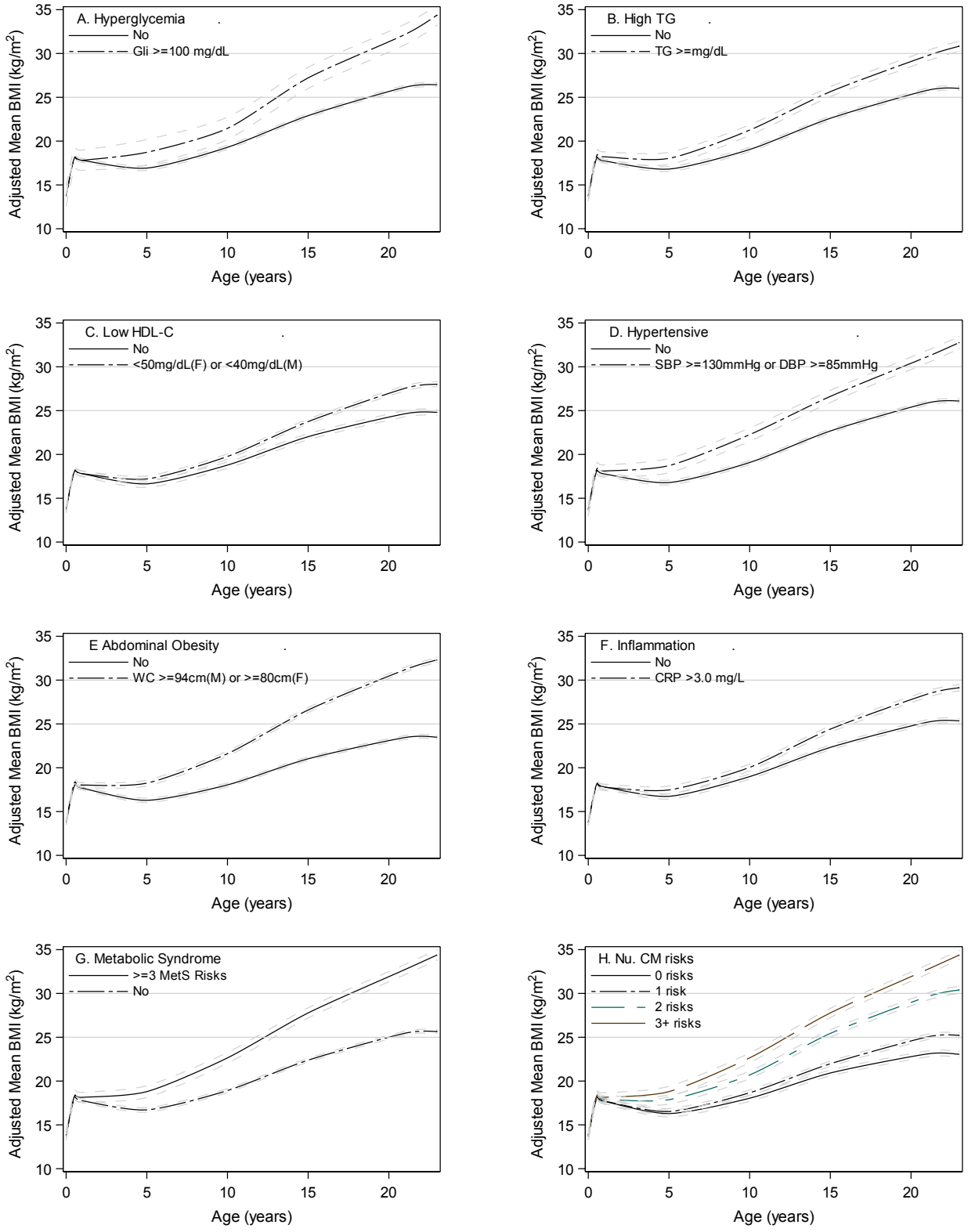

Figure 1 BMI trajectories from birth to age 23 years by cardiometabolic risk in young adulthood, adjusted for sex, maternal BMI, maternal age, family SES, iron supplementation from age 6 to 12 months, and duration of breastfeeding. Dashes surrounding trajectories represent 95% CI. TG, triglycerides; HDL-C, high-density lipoproteins cholesterol; MetS, metabolic syndrome; CM, cardiometabolic; Gli, glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; CRP, C-reactive protein. [Color figure can be viewed at wileyonlinelibrary.com]

missing data strategies (32). For descriptive purposes, we used SAS (version 9.4; SAS Institute Inc., Cary, North Carolina) mixed-effects modeling (with a quadratic term for age) to plot BMI trajectories per each CM risk (Figure 1). We performed a sensitivity analysis to assess bias introduced by the missing data by reestimating the growth analyses using data from participants who had BMI data at all nine time points ($n=549$). We also conducted analysis of covariance to determine the age at which BMI first significantly diverged ($P<0.05$) according to the presence or absence of each CM risk. We also extrapolated the ages at which BMI ≥ 25 and BMI ≥ 30 from known BMI values per each CM risk group to illustrate the disparity in age at which critical BMI milestones are attained for those with or without various CM risks (33).

Results

Sample characteristics

At the 23-year follow-up, 12.2% of the sample was classified as having MetS and approximately 70% had at least one CM risk (Table 1). The prevalences of low HDL-C, abdominal obesity, and inflammation were quite high (59.5%, 31.2%, and 36.7%, respectively), whereas the prevalence of high TG (14.3%), hypertension (9.3%), and hyperglycemia (3.5%) were moderate to low.

Growth parameters for the total sample

The fit indices indicated that the model for each developmental phase fit the data (CFI: 0.951-0.986; RMSEA: 0.080-0.159; SRMR: 0.017-0.042). The growth parameters for the total sample (Table 2) indicated an average BMI at birth of 13.75 and significant linear BMI increase from birth to 6 months (slope = 0.72). The parameters for the second phase (6 months-5 years) indicated an average 6-month BMI of 18.06, with significant linear decrease in BMI from 6 months to 5 years (slope = −0.11). The parameters for the third phase (5-23 years) indicated a mean 5-year BMI of 16.98, with significant linear upward growth (slope = 3.34), followed by significant deceleration (a slowing down) of growth when approaching young adulthood (quadratic = −0.10). (Supporting Information Figure S2 shows the growth trajectory for the total sample.)

Growth parameters by CM risk

The growth parameters for each developmental phase by the presence or absence of each risk factor are shown in Table 3. At level of significance $\alpha=0.05$, our data do not provide evidence to suggest that the intercepts at birth varied by subsequent CM risk. However, those with young adult abdominal obesity had greater linear growth (a faster rise in BMI) from birth to 6 months than those without abdominal obesity. Regarding growth from 6 months to 5 years, none of the CM risks differed by 6-month BMI. However, the slope of BMI growth during this phase was significantly different by presence versus absence of CM risk for all risks examined, with the risk-absent trajectories having a significant linear decrease in BMI growth, whereas the risk-present trajectories remained largely stable (flat). The parameters for the period from 5 to 23 years indicated that all CM risks were associated with a higher BMI at age 5. Five of the seven risks studied were also associated with greater linear growth from 5 to 23 years (high TG, low HDL-C, hypertension, abdominal obesity, MetS). Additionally, five of the risk-present trajectories had less decelerated growth than the risk-absent trajectories (i.e., differed in quadratic growth: hyperglycemia, low HDL-C, abdominal obesity, MetS, inflammation). Inspection of the quadratic parameters indicated that the risk-present trajectories showed nonsignificant growth deceleration, reflecting continued steady growth, or in the case of hyperglycemia, significant accelerated growth (s = 0.45; $P<0.001$). In contrast, all of the quadratic terms for the risk-absent models were significant and negative, indicating significant growth deceleration or a slowing down of growth when approaching young adulthood. Thus, failure of BMI growth to decelerate when approaching young adulthood distinguished those with versus without CM risks.

TABLE 2 Adjusted means of growth parameters for total sample at age 23 years ($N=1,000$)

Total sample	Adjusted mean
Intercept_{B}	13.75*
$\text{Slope}_{B\text{-}6\ mo}$	0.72*
$\text{Intercept}_{6\ mo}$	18.06*
$\text{Slope}_{6\ mo\text{-}5\ y}$	−0.11*
$\text{Intercept}_{5\ y}$	16.98*
$\text{Slope}_{5\text{-}23\ y}$	3.34*
$\text{Quadratic}_{5\text{-}23\ y}$	−0.10*

*$P<0.001$.
B, birth.

Growth parameters by number of CM risks

When examining the growth parameters by number of CM risks (Table 4), compared with participants with no adult CM risks, those with one risk factor had a higher BMI at birth. No differences were found for linear growth from birth to 6 months by number of CM risks. However, compared with those with zero adult risks, those with two or more risks had flatter (less declining) growth from 6 months to 5 years, a higher 5-year BMI, faster linear growth from 5 to 23 years, and less decelerated growth when approaching young adulthood.

Age at growth divergence by CM risk

When examining the age at which BMI first diverged by subsequent CM risk, those with at least one risk factor had a significantly higher BMI at birth than those with zero risk factors, and those with adult abdominal obesity and high TG had a higher BMI at 3 months (Table 5). BMI diverged significantly at 1 year for individuals with or without MetS, and BMI diverged at 5 years for those with or without adult hyperglycemia, low HDL-C, hypertension, or inflammation.

Age BMI ≥ 25 and BMI ≥ 30 by CM risk

Those with MetS in young adulthood attained BMI ≥ 25 at 12.3 years on average, whereas those absent MetS achieved BMI ≥ 25 approximately 8 years later or at age 20.1 (Table 6). BMI ≥ 30 could not be estimated for any of the risk-absent groups, for those with inflammation or low HDL-C, or for those with zero or one CM risk because these individuals avoided BMI ≥ 30 during the study period. Those with no CM risks avoided BMI ≥ 25.

Sensitivity analyses

The complete case analyses testing differences in growth parameter by the presence of CM risks using the 549 participants who had BMI at all nine

TABLE 3 Adjusted means of growth parameters by cardiometabolic risk at age 23 years (*N* = 1,000)

	Risk present, adjusted mean	Risk absent, adjusted mean	Unstd. effect estimate (SE)	*P*
Hyperglycemia	(*n* = 35)	(*n* = 965)		
$Intercept_{B}$	13.69*	13.76*	−0.09 (0.19)	0.619
$Slope_{B\text{-}6\ mo}$	1.31*	1.23*	0.004 (0.05)	0.934
$Intercept_{6\ mo}$	17.85*	18.07*	0.35 (0.22)	0.114
$Slope_{6\ mo\text{-}5\ y}$	0.05	−0.12*	0.20 (0.06)	0.003
$Intercept_{5\ y}$	18.05*	16.78*	1.47 (0.45)	0.001
$Slope_{5\text{-}23\ y}$	3.17*	2.93*	0.07 (0.57)	0.883
$Quadratic_{5\text{-}23\ y}$	0.45*	−0.13*	0.45 (0.13)	0.001
High TG	(*n* = 143)	(*n* = 857)		
$Intercept_{B}$	13.71*	13.76*	−0.07 (0.10)	0.461
$Slope_{B\text{-}6\ mo}$	1.34*	1.22*	0.05 (0.03)	0.072
$Intercept_{6\ mo}$	18.22*	18.03*	0.18 (0.13)	0.167
$Slope_{6\ mo\text{-}5\ y}$	−0.003	−0.13*	0.10 (0.03)	0.002
$Intercept_{5\ y}$	17.82*	16.69*	0.90 (0.25)	0.001
$Slope_{5\text{-}23\ y}$	3.76*	3.07*	0.74 (0.26)	0.004
$Quadratic_{5\text{-}23\ y}$	−0.02	−0.13*	0.05 (0.06)	0.441
Low HDL-C	(*n* = 595)	(*n* = 405)		
$Intercept_{B}$	13.81*	13.67*	0.12 (0.07)	0.077
$Slope_{B\text{-}6\ mo}$	1.23*	1.25*	−0.02 (0.02)	0.348
$Intercept_{6\ mo}$	18.04*	18.10*	−0.06 (0.09)	0.556
$Slope_{6\ mo\text{-}5\ y}$	−0.09	−0.14*	0.05 (0.02)	0.007
$Intercept_{5\ y}$	17.02*	16.56*	0.38 (0.15)	0.007
$Slope_{5\text{-}23\ y}$	3.29*	2.99*	0.31 (0.16)	0.047
$Quadratic_{5\text{-}23\ y}$	−0.05	−0.20*	0.11 (0.04)	0.007
Hypertension	(*n* = 93)	(*n* = 905)		
$Intercept_{B}$	13.77*	13.65*	0.16 (0.09)	0.092
$Slope_{B\text{-}6\ mo}$	1.36*	1.23*	0.04 (0.04)	0.205
$Intercept_{6\ mo}$	18.14*	18.06*	−0.18 (0.16)	0.267
$Slope_{6\ mo\text{-}5\ y}$	0.04	−0.13*	0.20 (0.04)	0.001
$Intercept_{5\ y}$	18.54*	16.66*	1.88 (0.34)	0.001
$Slope_{5\text{-}23\ y}$	4.00*	3.09*	0.93 (0.30)	0.002
$Quadratic_{5\text{-}23\ y}$	−0.02	−0.12*	0.10 (0.08)	0.207
Abdominal obesity	(*n* = 312)	(*n* = 688)		
$Intercept_{B}$	13.80*	13.73*	0.002 (0.07)	0.846
$Slope_{B\text{-}6\ mo}$	1.47*	1.23*	0.06 (0.02)	0.006
$Intercept_{6\ mo}$	18.07*	18.06*	0.05 (0.11)	0.672
$Slope_{6\ mo\text{-}5\ y}$	0.05	−0.17*	0.20 (0.02)	0.001
$Intercept_{5\ y}$	18.12*	16.25*	1.92 (0.19)	0.001
$Slope_{5\text{-}23\ y}$	4.20*	2.70*	1.49 (0.19)	0.001
$Quadratic_{5\text{-}23\ y}$	−0.03	−0.15*	0.13 (0.05)	0.009
Metabolic syndrome	(*n* = 122)	(*n* = 878)		
$Intercept_{B}$	13.79*	13.75*	0.02 (0.11)	0.831
$Slope_{B\text{-}6\ mo}$	1.32*	1.23*	0.03 (0.03)	0.312
$Intercept_{6\ mo}$	18.10*	18.06*	−0.06 (0.14)	0.644
$Slope_{6\ mo\text{-}5\ y}$	0.07	−0.13*	0.20 (0.04)	0.001
$Intercept_{5\ y}$	18.44*	16.59*	1.71 (0.26)	0.001
$Slope_{5\text{-}23\ y}$	4.22*	3.03*	1.24 (0.26)	0.001
$Quadratic_{5\text{-}23\ y}$	0.02	−0.14*	0.13 (0.07)	0.050

TABLE 3 (continued).

	Risk present, adjusted mean	Risk absent, adjusted mean	Unstd. effect estimate (SE)	*P*
Inflammation	(*n* = 365)	(*n* = 629)		
Intercept$_{B}$	13.77*	13.75*	0.01 (0.07)	0.898
Slope$_{B\text{-}6\ mo}$	1.21*	1.25*	−0.01 (0.02)	0.745
Intercept$_{6\ mo}$	17.93*	18.13*	−0.15 (0.10)	0.117
Slope$_{6\ mo\text{-}5\ y}$	−0.05	−0.14*	0.09 (0.02)	0.001
Intercept$_{5\ y}$	17.25*	16.61*	0.68 (0.16)	0.001
Slope$_{5\text{-}23\ y}$	3.34*	3.09*	0.20 (0.18)	0.253
Quadratic$_{5\text{-}23\ y}$	0.002	−0.18*	0.18 (0.04)	0.001

Models adjusted for sex, maternal BMI, maternal age, family socioeconomic status, iron supplementation from age 6 to 12 months, and duration of breastfeeding on intercept, slope, and quadratic.
*$P < 0.001$.
B, birth; unstd., unstandardized; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

TABLE 4 Adjusted mean growth parameters by number of cardiometabolic risks at age 23 years (*N* = 1,000)

Number of risks	0	1		2		≥3	
	(*n* = 302) Adj. mean	(*n* = 377) Adj. mean	*P*, 1 different from 0	(*n* = 199) Adj. mean	*P*, 2 different from 0	(*n* = 122) Adj. mean	*P*, ≥3 different from 0
Intercept$_{B}$	13.66**	13.85**	0.017	13.70**	0.419	13.80**	0.378
Slope$_{B\text{-}6\ mo}$	1.25*	1.18*	0.174	1.27*	0.404	1.23*	0.407
Intercept$_{6\ mo}$	18.08**	18.00**	0.673	18.16**	0.713	18.10**	0.980
Slope$_{6\ mo\text{-}5\ y}$	−0.18*	−0.15*	0.085	−0.01	0.001	0.07	0.001
Intercept$_{B}$	16.21**	16.40**	0.143	17.49**	0.001	18.44**	0.001
Slope$_{5\text{-}23\ y}$	2.65**	2.94**	0.142	3.81**	0.001	4.22**	0.001
Quadratic$_{5\text{-}23\ y}$	−0.21**	−0.13*	0.077	−0.07	0.016	0.02	0.001

Models adjusted for sex, maternal BMI, maternal age, family socioeconomic status, iron supplementation from age 6 to 12 months, and duration of breastfeeding.
*$P < 0.01$.
**$P < 0.001$.
B, birth.

TABLE 5 Age and BMI at significant growth curve divergence by presence or absence of cardiometabolic risk at age 23 years

	Age at significant growth curve divergence	Adjusted BMI at age of divergence (95% CI)		
		Risk present	Risk absent	*P*
0 vs. 1 CM risk[a]	Birth	13.89 (13.76, 14.01)	13.68 (13.55, 13.82)	0.030
Abdominal obesity	3 mo	17.61 (17.44, 17.77)	17.36 (17.24, 17.47)	0.020
Hypertriglyceridemia	3 mo	17.68 (17.43, 17.93)	17.40 (17.30, 17.50)	0.040
MetS	1 y	18.04 (17.77, 18.32)	17.75 (17.65, 17.85)	0.048
Hyperglycemia	5 y	18.42 (17.32, 19.53)	17.02 (16.82, 17.21)	0.014
Low HDL-C	5 y	17.28 (17.03, 17.52)	16.73 (16.42, 17.04)	0.008
Hypertension	5 y	18.57 (17.97, 19.17)	16.89 (16.69, 17.09)	0.001
Inflammation	5 y	17.63 (17.30, 17.96)	16.77 (16.53, 17.01)	0.001

Models adjusted for sex, maternal BMI, maternal age, family socioeconomic status, iron supplementation from age 6 to 12 months, and duration of breastfeeding. Slight differences in BMI shown here and those shown in Tables 2, 3 and 4 are due to the absence of full information maximum likelihood specification in these estimates.
[a]Presence of any of the following five risk factors: hyperglycemia, hypertriglyceridemia, low HDL-C, hypertension, abdominal obesity.
CM, cardiometabolic; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol.

time points retained all but one of the significant effects found using the full analytic sample (Supporting Information Table S2). Additionally, the growth parameters and magnitude of effect estimates were highly similar. When analyzing the growth parameter differences by number of CM risks, the complete case analyses retained seven of the nine significant effects found using the full analytic sample (Supporting Information Table S3).

TABLE 6 Mean age at BMI ≥ 25 and BMI ≥ 30 by cardiometabolic risk

	Risk present		Risk absent	
	BMI ≥ 25	BMI ≥ 30	BMI ≥ 25	BMI ≥ 30
MetS	12.3 y	17.7 y	20.1 y	–
Abdominal obesity	13.0 y	18.8 y	–	–
Hyperglycemia	13.1 y	18.4 y	18.9 y	–
Hypertension	13.2 y	19.5 y	19.4 y	–
High TG	14.3 y	21.5 y	19.5 y	–
Inflammation	15.9 y	–	20.6 y	–
Low HDL-C	16.9 y	–	–	–
Number of CM risks[a]				
0	–	–		
1	21.0 y	–		
2	14.6 y	22.0 y		
3	13.1 y	18.9 y		
4 or 5	10.6 y	14.7 y		

Ages extrapolated from known BMI values per each cardiometabolic risk group. Dash indicates that average BMI for individuals with that risk did not equal or exceed 25 or 30.
[a]Total number of cardiometabolic risks: hyperglycemia, hypertriglyceridemia, low HDL-C, hypertension, and abdominal obesity.
MetS, metabolic syndrome; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; CM, cardiometabolic risk.

Discussion

In this Chilean sample, individuals who had CM risk factors showed different patterns of BMI growth from birth to 23 years than those without CM risks. Individuals with adult CM risks had faster BMI growth from birth to 6 months, lower levels of expected BMI growth decline approaching age 5, a higher BMI at age 5, faster growth from 5 to 23 years, and lower levels of growth deceleration approaching young adulthood.

Unlike studies that have found differences in growth after only 4 years of age by subsequent CM risk (12), current findings show that poor adult CM health was preceded by specific growth patterns discernable from 6 months onward. Indeed, the growth pattern found in the current study reflecting faster growth from birth to 6 months and a smaller decline in BMI from 6 months to 5 years parallels the growth pattern believed to be responsible for an early age at adiposity rebound (34,35), which itself is a well-established risk factor for later obesity and obesity-related morbidity (34,36). The absence of a distinct BMI nadir can also be discerned in several of the risk-present trajectories (Figure 1). This constellation of early-life factors (faster growth after infancy, lower BMI decline approaching age 5, absence of a definitive BMI nadir in early childhood, higher 5-year BMI) consistently distinguished those who would develop CM morbidities from those who would not. It is widely held that rapid weight gain during infancy plays an etiological role in programming later-life obesity, which, in turn, is consequential for poor adult cardiovascular health (37,38). Current findings augment such work by indicating that a constellation of early-life growth factors is directly associated with subsequent CM morbidities.

Study findings also show that an absence of slowed growth when approaching young adulthood discriminated the presence of several adult CM risk factors. This is consistent with findings by Attard et al. (5), who found that a high and increasing BMI from 13 to 21 years was associated with elevated blood pressure and insulin resistance, whereas a declining adiposity trajectory was protective (5). Normally growing youth typically show decelerated growth during the transition to adulthood, as pubertal influences decline and skeletal growth subsides (27,39). Preventive measures would, thus, involve achieving graduated linear growth from early childhood onward and a slowing down of growth when approaching adulthood (i.e., successive reductions in BMI increases).

Findings also illustrate the disparity in age at which critical BMI milestones are attained for those with and without adult CM risks. Avoiding BMI ≥ 30 prior to age 23 served as a protective factor against all of the CM risks studied, and individuals with zero risk factors maintained BMI < 25 to age 23. Such findings, in alliance with other studies (1,2), may be of value to clinicians and public health surveillance programs for identifying individuals at risk of CM risk based on age-specific BMI.

Several factors should be considered when interpreting study findings. All participants were born at term and had birthweights ≥ 3.0 kg as eligibility criteria. Thus, premature and low–birth weight infants were not included, which likely affected this sample's BMI distribution and growth (40) and, perhaps, the likelihood of CM risks (37). However, this sample restriction allowed us, by design, to control for cardiovascular risks associated with preterm and low birth weight. The reduced data available at age 5 (because of a funding cut) limited selection of the analytic sample. However, the analytic strategy made use of all available data, and we did not find evidence that the assumption of missing completely at random was violated. Moreover, a sensitivity analysis involving participants who had BMI at all nine study time points showed highly similar findings as the analytic sample, increasing confidence in the relations found. The absence of BMI measurements at closer age intervals precluded more specific estimates of growth change and limited the estimation of age at BMI growth divergence. The follow-up intervals between later visits were relatively large (5 years), which may cause biased estimations in the BMI growth curves. This study also did not have baseline measures of CM biomarkers or CRP. Thus, whether the associations found are independent of baseline levels of CM risk factors is not clear. Additionally, the sample was somewhat atypical in that approximately 60% of participants had low HDL-C in young adulthood. High prevalence of low HDL-C has been found in Latino populations (41), with some finding a genetic predisposition to dyslipidemia (42). Thus, findings should be considered within the racial/ethnic and cultural (diet, lifestyle) background of study participants. Finally, the relatively low numbers of participants with hyperglycemia may have reduced statistical power to detect differences between the growth parameters of those with and without this risk.

Study strengths include the availability of growth data from a large cohort studied from birth to young adulthood. Data on weight and height were measured objectively by trained clinical staff from age 6 months to 23 years, giving greater validity to the results. This study also had multiple objectively measured biomarkers of CM health in early adulthood, when disease states often first appear (43). The piecewise growth curve approach allowed us to determine the unique contribution of various parameters of growth during separate developmental periods for subsequent CM health. Finally, several important confounders were controlled, reducing the possibility that study findings can be attributed to such factors.

In conclusion, how BMI changes across development is important for CM health. Individuals with CM risks in young adulthood had unique

early-life growth patterns, indicating that an early-life preventive approach may be useful (44). However, continued high and accelerated growth from early childhood to young adulthood also consistently related to many CM risks, suggesting additional points of intervention into one's early 20s.O

Funding agencies: This research was supported by the following grants from the National Institutes of Health: R01-HL-088530 (PI: SG), R01-HD-033487 (PI: SG and BL), T32-HL-079891 (PI: Matthew Allison), and R03-HD-097295 (PI: PE).

Disclosure: The authors declared no conflicts of interest.

Supporting information: Additional Supporting Information may be found in the online version of this article.

References

1. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ* 2012;345:e4759. doi:10.1136/bmj.e4759
2. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. *N Engl J Med* 2015;373:1307-1317.
3. Araujo J, Barros H, Ramos E, Li L. Trajectories of total and central adiposity throughout adolescence and cardiometabolic factors in early adulthood. *Int J Obes* (Lond) 2016;40:1899-1905.
4. Attard SM, Herring AH, Howard AG, Gordon-Larsen P. Longitudinal trajectories of BMI and cardiovascular disease risk: The National Longitudinal Study of Adolescent Health. *Obesity (Silver Spring)* 2013;21:2180-2188.
5. Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Body mass index trajectories in childhood is predictive of cardiovascular risk: results from the 23-year longitudinal Georgia Stress and Heart Study. *Int J Obes (Lond)* 2018;42:923-925.
6. Ziyab AH, Karmaus W, Kurukulaaratchy RJ, Zhang H, Arshad SH. Developmental trajectories of body mass index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health* 2014;68:934-941.
7. Xian H, Vasilopoulos T, Liu W, et al. Steeper change in body mass across four decades predicts poorer cardiometabolic outcomes at midlife. *Obesity (Silver Spring)* 2017;25:773-780.
8. Howe LD, Tilling K, Benfield L, et al. Changes in ponderal index and body mass index across childhood and their associations with fat mass and cardiovascular risk factors at age 15. *PLoS One* 2010;5:e15186. doi:10.1371/journal.pone.0015186
9. Sovio U, Kaakinen M, Tzoulaki I, et al. How do changes in body mass index in infancy and childhood associate with cardiometabolic profile in adulthood? Findings from the Northern Finland Birth Cohort 1966 Study. *Int J Obes* (Lond) 2014;38:53-59.
10. Giudici KV, Rolland-Cachera MF, Gusto G, et al. Body mass index growth trajectories associated with the different parameters of the metabolic syndrome at adulthood. *Int J Obes* (Lond) 2017;41:1518-1525.
11. Fall CH, Sachdev HS, Osmond C, et al. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of body mass index gain during infancy: data from the New Delhi birth cohort. *Diabetes Care* 2008;31:2349-2356.
12. Bornhorst C, Tilling K, Russo P, et al. Associations between early body mass index trajectories and later metabolic risk factors in European children: The IDEFICS Study. *Eur J Epidemiol* 2016;31:513-525.
13. Lozoff B, DeAndraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. *Pediatrics* 2003;112:846-854.
14. Enders CK. Applied Missing Data Analysis. New York: Guilford Press; 2010.
15. Little RA. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc* 1988;83:1198-1202.
16. Graffar M. A method of social classification of samples of population. *Courier* 1956;6:455-459.
17. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191-2194.
18. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? *Eur J Clin Nutr* 2005;59:419-425.
19. Roy SM, Spivack JG, Faith MS, et al. Infant BMI or weight-for-length and obesity risk in early childhood. *Pediatrics* 2016;137:e20153492. doi:10.1542/peds.2015-3492
20. Must A, Anderson SE. Body mass index in children and adolescents: considerations for population-based applications. *Int J Obes* (Lond) 2006;30:590-594.
21. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Laboratory Procedures Manual. https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/2011-12_laboratory_procedures_manual.pdf. Published March 2011.
22. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511.
23. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640-1645.
24. VanderWeele TJ. Principles of confounder selection. *Eur J Epidemiol* 2019;34:211-219.
25. Grimm KJ, Ram N, Hamagami F. Nonlinear growth curves in developmental research. *Child Dev* 2011;82:1357-1371.
26. World Health Organization. WHO child growth standards. BMI-for-age. https://www.who.int/childgrowth/standards/bmi_for_age/en/. Published November 1, 2009. Accessed April 15, 2019.
27. Centers for Disease Control and Prevention; National Center for Health Statistics. CDC growth charts: United States. Body mass index-for-age percentiles: boys, 2 to 20 years. Individual growth charts. https://www.cdc.gov/growthcharts/charts.htm. Published May 30, 2000. Accessed April 15, 2019.
28. Muthén LK, Muthén BO. Mplus User's Guide. 8th ed. Los Angeles: Muthen and Muthen; 2017.
29. Satorra A, Bentler PM. Ensuring positiveness of the scaled difference chi-square test statistic. *Psychometrika* 2010;75:243-248.
30. Kline RB. Principles and Practice of Structural Equation Modeling. New York: Guilford Press; 2015.
31. Wu W, West SG, Taylor AB. Evaluating model fit for growth curve models: Integration of fit indices from SEM and MLM frameworks. *Psychol Methods* 2009;14:183-201.
32. Raykov T. Analysis of longitudinal studies with missing data using covariance structure modeling with full-information maximum likelihood. *Struct Equ Modeling* 2005;12:493-505.
33. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: International survey. *BMJ* 2000;320:1240-1245.
34. Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: causes and consequences for obesity in children and adults. *Int J Obes* 2006;30(suppl 4):S11-S17.
35. Cole TJ. Children grow and horses race: is the adiposity rebound a critical period for later obesity? *BMC Pediatr* 2004;4:6. doi:10.1186/1471-2431-4-6
36. Koyama S, Ichikawa G, Kojima M, Shimura N, Sairenchi T, Arisaka O. Adiposity rebound and the development of metabolic syndrome. *Pediatrics* 2013;133:e114-e119.
37. Barker DJP, Osmond C, Forsen TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med* 2005;353:1802-1809.
38. Gillman MW. The first months of life: a critical period for development. *Am J Clin Nutr* 2008;87:1587-1589.
39. Lee H, Lee D, Guo G, Harris KM. Trends in body mass index in adolescence and young adulthood in the United States: 1959-2002. *J Adolesc Health* 2011;49:601-608.
40. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. *Pediatrics* 2003;112(1 Pt 1):e30-e38.
41. Aguilar-Salinas CA, Olaiz G, Valles V, et al. High prevalence of low HDL cholesterol concentrations and mixed hyperlipidemia in a Mexican nationwide survey. *J Lipid Res* 2001;42:1298-1307.
42. Pullinger CR, Goldfine ID, Tanyolaç S, et al. Evidence that an HMGA1 gene variant associates with type 2 diabetes, body mass index, and high-density lipoprotein cholesterol in a Hispanic-American population. *Metab Syndr Relat Disord* 2014;12:25-30.
43. Gungor N, Thompson T, Sutton-Tyrrell K, Janosky J, Arslanian S. Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. *Diabetes Care* 2005;28:1219-1221.
44. Gahagan S, Uauy R, Roseboom TJ. Developmental origins of pediatric obesity. *Int J Pediatr* 2012;2012:309863. doi:10.1155/2012/309863