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Body mass index trajectories in early childhood in relation to cardiometabolic risk profile and body composition at 5 years of age

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ABSTRACT

Background: Both impaired and accelerated postnatal growth have been associated with adult risks of obesity and cardiometabolic diseases, like type 2 diabetes and cardiovascular disease. However, the timing of the onset of cardiometabolic changes and the specific growth trajectories linking early growth with later disease risks are not well understood.

Objectives: The aim of this study was to identify distinct trajectories of BMI growth from 0 to 5 y and examine their associations with body composition and markers of cardiometabolic risk at age 5 y.

Methods: In a prospective birth cohort study of 453 healthy and term Ethiopian children with BMIs assessed a median of 9 times during follow-up, we identified subgroups of distinct BMI trajectories in early childhood using latent class trajectory modeling. Associations of the identified growth trajectories with cardiometabolic markers and body composition at 5 y were analyzed using multiple linear regression analyses in 4 adjustment models for each outcome.

Results: We identified 4 heterogeneous BMI growth trajectories: stable low BMI (19.2%), normal BMI (48.8%), rapid catch-up to high BMI (17.9%), and slow catch-up to high BMI (14.1%). Compared with the normal BMI trajectory, children in the rapid catch-up to high BMI trajectory had higher triglycerides (TGs) (range of β-coefficients in Models 1–4: 19–21%), C-peptides (23–25%), fat masses (0.48–0.60 kg), and fat-free masses (0.50–0.77 kg) across the 4 adjustment models. Children in the stable low BMI trajectory had lower LDL cholesterol concentrations (0.14–0.17 mmol/L), HDL cholesterol concentrations (0.05–0.09 mmol/L), fat masses (0.60–0.64 kg), and fat-free masses (0.35–0.49 kg), but higher TGs (11–13%).

Conclusions: The development of obesity and cardiometabolic risks may be established already in early childhood; thus, our data provide a further basis for timely interventions targeted at young children from low-income countries with unfavorable growth patterns. The birth cohort was registered at ISRCTN as ISRCTN46718296. *Am J Clin Nutr* 2019;110:1175–1185.

Keywords: body composition, cohort study, child, developmental origins of health and disease, growth, latent class trajectory modeling, noncommunicable diseases, sub-Saharan Africa

Introduction

The prevalence of childhood obesity is a major threat to public health worldwide (1, 2). While some progress has been seen in high-income countries, many low-income countries experience a dual burden of malnutrition and a rising prevalence of childhood overweight, coinciding with high pre- and postnatal undernutrition (3, 4). Both ends of this spectrum of malnutrition have been associated with adult risks of obesity, type 2 diabetes, and cardiovascular disease (4, 5), and studies have shown that growth patterns in early childhood are associated with these outcomes (6–8).

Most of these studies have examined associations of variability in early-life nutrition with adult risks of disease and were not, therefore, designed to address the timing of onset of the cardiometabolic adaptations that may already occur in

childhood (9–11). Another issue is that early-life growth is typically assessed at 1 or a few timepoints in childhood. However, as childhood growth is a dynamic process and diverging longitudinal growth patterns are likely to associate differently with later cardiometabolic outcomes, studies with detailed and repeated assessments of body sizes are needed. Additionally, very few of the studies that have explored longitudinal growth patterns and their associations with adiposity and cardiometabolic risk were conducted in low-income populations. These populations are, nonetheless, likely to be particularly affected in many countries as a result of the dual burden of malnutrition and rapid economic and nutritional transitions (12). The stratification of children into different trajectories of growth, associated with different levels of adiposity and cardiometabolic risk profiles, may therefore provide an opportunity to identify early and targeted interventions in children from low-income populations.

Thus, we aimed to identify distinct trajectories of BMI growth from birth to 5 y, and to estimate patterns of fat mass (FM) and fat-free mass (FFM) growth in infancy for each of the identified BMI trajectories. Furthermore, we examined the relationships of the identified BMI trajectories with cardiometabolic markers and body composition (BC) at 5 years of age in a low-income, urban population.

Methods

Study setting and participants

We used data from the Infant Anthropometry and Body Composition (iABC) birth cohort study, as described elsewhere (13, 14). Briefly, mother–child pairs were recruited within 48 hours after delivery at Jimma University Specialized Hospital, Jimma, Ethiopia, between December 2008 and October 2012. Eligible mothers were residing in Jimma town and had given birth to a term (gestational age at birth ≥37 completed weeks of pregnancy) and apparently healthy child above 1500 g without congenital malformations. From birth to 60 mo of age, we planned a total of 12 visits (0, 1.5, 2.5, 3.5, 4.5, 6, 12, 18, 24, 36, 48, and 60 mo). The modeling of BMI trajectories from 0 to 5 y included children with BMIs assessed at the birth visit and at least 1 time in each of the periods between the 1.5–6-mo and 12–60-mo visits. For the subsequent regression analysis with the 5-y outcomes, the analyses were restricted to children with a valid measurement of the specific outcome in question and full covariate information. As some participants refused blood sampling or were unable to deliver enough blood for analyses of all biomarkers, the number of children included in the regression analyses differed by specific outcomes.

Data collection

Anthropometry and body composition.

Length was measured to the nearest 0.1 cm in the recumbent position using a Seca 416 Infantometer for children below 2 y and in the standing position using a Seca 213 portable height measurer for children above 2 y (Seca, Hamburg, Germany). Waist circumference was measured to the nearest 0.1 cm in the standing position with the feet together midway between the iliac crest and lowest costal margin, using a nonstretchable measuring tape. Weight from birth to 6 mo was measured to the nearest 0.1 g using the built-in electronic scale of the infant air displacement plethysmography (ADP) instrumentation (PEA POD, COSMED, Rome, Italy); weight from 1 to 3 years was measured to the nearest 0.1 kg using an electronic UNICEF scale (Seca, Hamburg, Germany); and weight from 4 to 5 y was measured to the nearest 1 g using the attached electronic scale of the child/adult ADP instrumentation (BOD POD, COSMED, Rome, Italy). FM and FFM from birth to 6 mo and at 5 y were measured using ADP in the PEA POD and the BOD POD with a pediatric chair insert, respectively. Both ADP systems are accurate, precise, feasible, and safe methods for the assessment of BC in infants and children (15, 16) and, in the present cohort, the PEA POD was previously validated against a 3-component model with deuterium dilution (13). In brief, these BC systems estimate total body density from weight and volume measurements and, assuming known values of the density of FM and FFM, calculate the proportion of FM in body weight. The theory and methods behind the PEA POD and BOD POD are described in detail elsewhere (17, 18). A full BC assessment lasted 5–10 min and, during the volume measurements, the child was placed on a plastic bed (PEA POD) or in a pediatric chair insert (BOD POD) in an enclosed test chamber, not wearing any clothes besides a swim cap (PEA POD and BOD POD) or tight-fitted underpants (BOD POD). Calibration of the BC equipment was performed each morning. All calculations were performed by the built-in computer (PEA POD software version 3.3.0 and BOD POD software version 5.2.0). BMIs, FM indexes (FMIs), and FFM indexes (FFMIs) were calculated by dividing weight, FM, and FFM with the squared height in meters, respectively.

Blood pressure at 5 y.

After the child relaxed for 5 min, their systolic and diastolic blood pressure were measured in the sitting position using a blood pressure device with age-appropriate cuffs (Pressostabil model, Welch Allyn Inc.). Measurements were done in duplicate and averaged.

Cardiometabolic markers at 5 y.

A 2-mL venous blood sample was drawn from the antecubital fossa as the last element of assessment of the child, following

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Supplemental Methods, Supplemental Figures 1–5, and Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ADP, air displacement plethysmography; BC, body composition; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin; iABC, Infant Anthropometry and Body Composition; IWI, International Wealth Index; LCT, latent class trajectory; TG, triglyceride.

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a minimum of 3 h of fasting. Glucose concentrations were measured in whole blood using the HemoCue Glucose 201 RT System (HemoCue, Ängelholm, Sweden). Glycosylated hemoglobin (HbA1c, mmol/mol) was measured on whole blood using a DCCT-aligned Quo-Test A1c Analyzer (EKF Diagnostics, Cardiff, Wales). Subsequently, serum was obtained by centrifuging the whole blood sample, which was aliquoted in 3 × 0.4 mL and frozen at −80°C until analyzed. The serum samples were analyzed at the Ethiopian Public Health Institute, using module c501 of the Cobas 6000 analyzer (Roche Diagnostics International Ltd., Rotkreuz, Switzerland) for total, LDL, and HDL cholesterol, as well as for triglyceride (TG) concentrations (all lipids in mmol/L), and module e601 for insulin (μU/mL) and C-peptide (ng/mL). The HOMA-IR was calculated as insulin × glucose/22.5 (19).

Covariates.

Information on birth order, child's sex, gestational age at birth, maternal age, maternal educational level, and socioeconomic status of the family was obtained at the birth visit. Maternal postpartum height was measured to the nearest 0.1 cm using a Seca 214 Stadiometer (Seca, Hamburg, Germany). Birth order was self-reported as the number of previous pregnancies. The gestational age of the newborn was assessed by trained research nurses using the New Ballard Score test (20). The International Wealth Index (IWI) was used to assess the socioeconomic status of the family. The IWI assesses the material well-being of households in low- and middle-income countries (21), and includes information on 12 material well-being dimensions, including possession of 7 household assets, access to 2 public services, and 3 characteristics of the house. The IWI ranges from 0 to 100 (highest wealth). Information on breastfeeding status was assessed at 4–6 mo postpartum and divided into 4 categories: exclusive (no other foods given), almost exclusive (no other foods given except water), predominant (breast milk as primary food), and partial/no (breast milk not the primary food/not breastfeeding) (22).

Ethics

Ethical approval was granted by the Jimma University Ethical Review Committee (reference number RPGC/279/2013). Written informed consent was obtained from parents or caregivers of all eligible children. Children with any medical condition observed by the research nurses were referred in accordance with local clinical guidelines.

Statistical methods

All descriptive data are presented as means ± SDs or medians (IQRs) for continuous variables and percentages for categorical variables. P values < 0.05 were considered statistically significant. All analyses were carried out in R version 3.4.1 (R Foundation for Statistical Computing).

Identification of latent BMI trajectories in childhood.

Heterogeneity in repeated measures of BMI was analyzed using latent class trajectory (LCT) modeling to identify distinct subgroups of children with similar trajectories of BMI growth from 0 to 5 y (23, 24). We ran a series of LCT models with various specifications of BMI as a function of age and number of subgroups (classes). As described in detail in the **Supplemental Methods**, the best-fitting model according to our a priori criteria was obtained with a 4-class model specified with natural cubic splines with knot points at 0, 3, 6, 24, 48, and 60 mo. Using the class assignments from the LCT modeling, we re-estimated the BMI trajectories from 0 to 60 mo for girls and boys separately to assess whether there were any sex differences in BMI growth for each of the 4 assigned classes.

Fat mass index and fat-free mass index growth in infancy.

For each of the identified BMI trajectory classes, we applied mixed-effects modeling to estimate the corresponding mean growths in FMI and FFMI from 0 to 6 mo of age. We required children to have a minimum of 3 FMI and FFMI measurements during the first 0–6 mo to be included in the modeling. The FMI and FFMI as functions of age were modelled separately and fitted with natural cubic splines with knot points at ages 0, 3, and 6 mo.

Associations of BMI trajectories with body composition and cardiometabolic markers at 5 y.

We analyzed the relationships of the identified BMI trajectory classes with BC and cardiometabolic markers at 5 y using a multiple linear regression analysis. The normal BMI trajectory class was used as the reference. In all analyses, we log-transformed outcomes where the corresponding model residuals were not normally distributed, which resulted in normally distributed model residuals. The resulting estimates were back-transformed and presented on the relative scale as percentwise changes. We ran 4 separate models for each outcome. Model 1 was adjusted for child sex, birth order, and gestational age at birth. Model 2 was additionally adjusted for the child's exact age at the 5-y visit, maternal age at delivery, maternal postpartum height, maternal educational status, and family socioeconomic status (per IWI). Model 3 was additionally adjusted for child birth weight. Model 4 was additionally adjusted for child BMI at the 5-y visit. Because BMI comprises both FM and FFM, the analyses of the outcomes of FM and waist circumference were adjusted for the lean component of BMI (FFM and height at 5 y), instead of BMI, in Model 4. Similarly, the analysis of the outcome FFM was adjusted for FM and height at 5 y (the fat component of BMI). We compared the estimated associations across the 4 models for each given outcome and exposure using a complete case approach, limiting the analyses to data with complete information on all covariates in Model 4. In further analyses, we accounted for multiple testing using the Benjamini–Hochberg approach (25), where the number of tests was set to 45 (15 outcomes for 3 exposure groups; **Supplemental Figure 1**). To account for breastfeeding, we ran sensitivity analyses on a smaller sample with available information on breastfeeding status at 4–6 mo postpartum (**Supplemental Figure 2**).

Results

At birth, the mothers were, on average, 24.6 y old, and 49% were primiparous. Half of the mothers had completed primary school or higher and 94% were breastfeeding either exclusively,

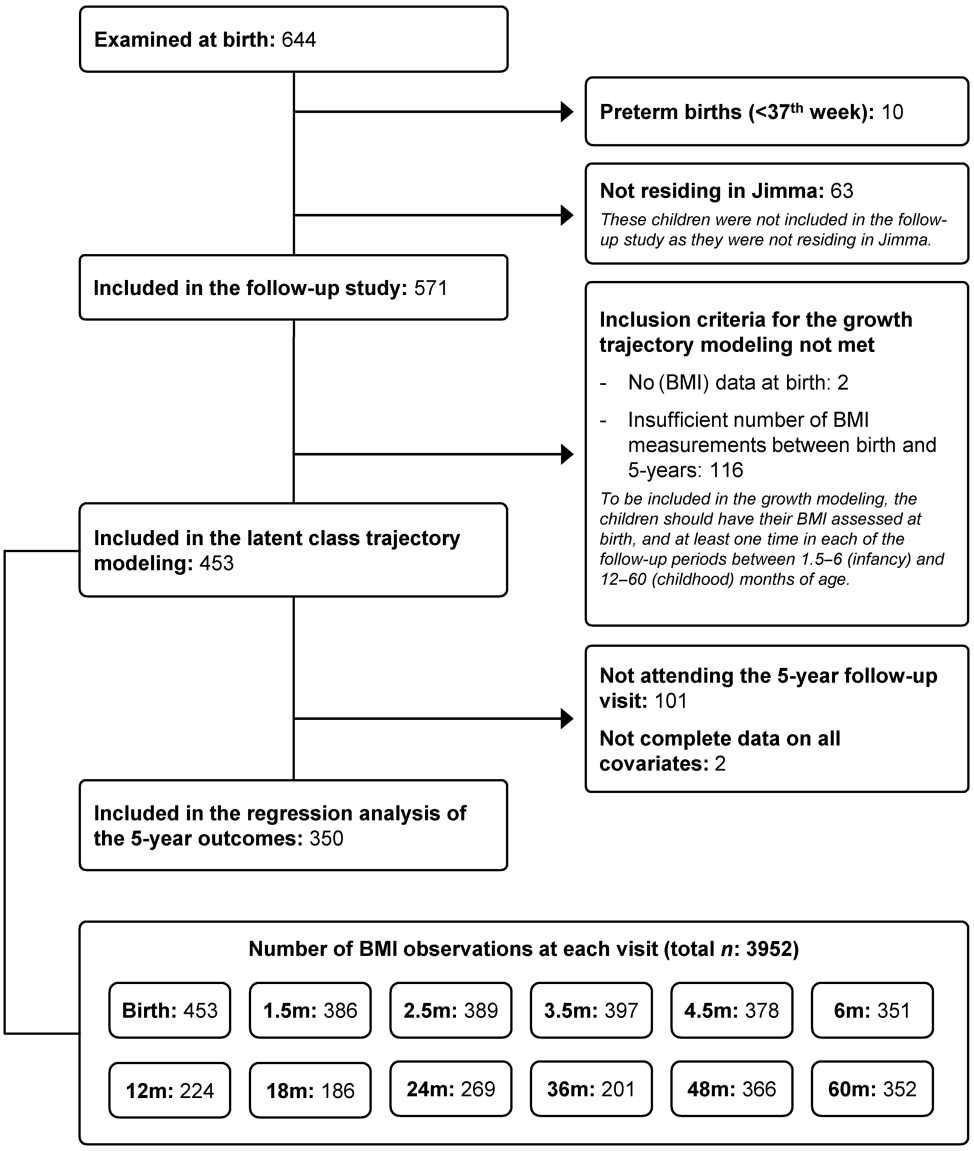

FIGURE 1 Flow diagram of the included children and number of BMI observations at each follow-up visit from birth to 60 mo.

almost exclusively, or predominantly during the first 4–6 mo after birth (**Supplemental Table 1**). Low birth weight was seen in 9.4% of the children. At 5 y, the children were, on average, more than 1.2 SDs below the WHO international growth standards for height, 15.3% were stunted, and 5.9% were overweight or obese. The average BMI of 15.0 kg/m^2 at 5 y was similar to the average of the WHO international growth standards (**Supplemental Table 2**) (26).

Latent BMI trajectories in early childhood

A total of 453 children were included in the modeling of the BMI trajectories (**Figure 1**). The children had their BMIs assessed a median of 9 (IQR 8–10) times during the follow-up period, contributing a total of 3952 observations to LCT modeling. We identified 4 distinct BMI trajectory classes from birth to 5 y (**Figure 2**; **Supplemental Figure 3**): *1*) stable low BMI (19.2%, $n = 87$), *2*) normal BMI (48.8%, $n = 221$), *3*) rapid catch-up to high BMI (17.9%, $n = 81$), and *4*) slow catch-up to high BMI (14.1%, $n = 64$). The ability of the LCT modeling to discriminate between the identified classes was acceptable, with high median posterior probabilities of assigned class membership above 85% for all 4 classes (**Supplemental Figure 4**) (27). Children in the stable low BMI trajectory class presented, on average, slow initial BMI gains, which plateaued after 4 mo and remained at a relatively low level in infancy, with a small catch-up from around 8 to 27 mo. The normal BMI trajectory was very similar to the WHO international growth standards, with the infancy peak at around 5 mo (26). The rapid catch-up to high BMI trajectory presented, on average, accelerated initial BMI gains, peaking at around 9 mo and steadily declining towards a normal BMI level at 60 mo. The slow catch-up to high BMI trajectory presented,

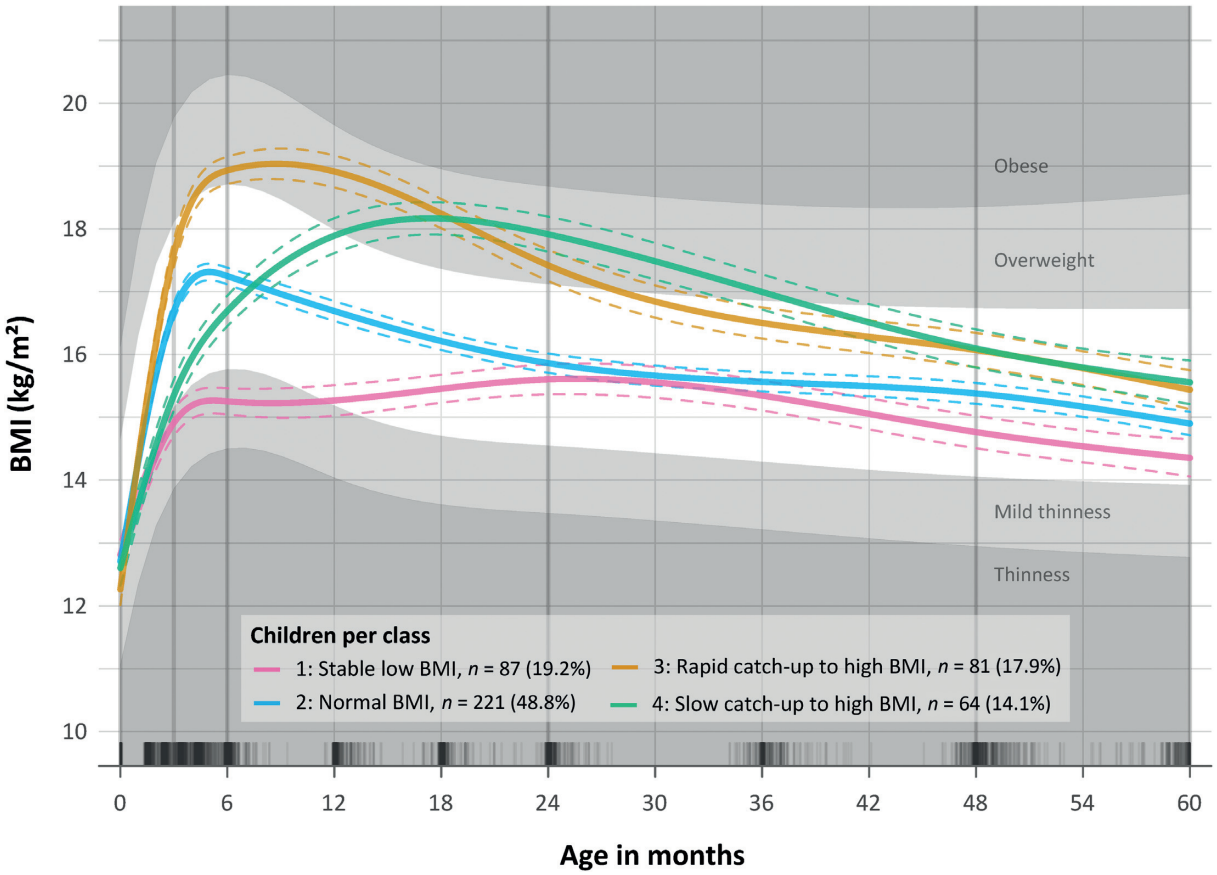

FIGURE 2 Distinct BMI trajectories from 0 to 5 y of children in the Infant Anthropometry and Body Composition (iABC) birth cohort, derived from a latent class trajectory modeling. Solid lines display the class-specific estimated average BMI as a function of age. The dashed lines show the estimated 95% CIs. The shaded areas indicate the reference in SDs from the median BMI for age, according to the international growth standards developed by the WHO. A normal BMI (white) is defined as a BMI-for-age SD from −1 to 1, mild thinness as ≥−2 to <−1 SDs (light gray), thinness as <−2 SDs (gray), overweight as >1 to ≤2 SDs (light gray), and obese as >2 SDs (gray). The density of BMI observations is shown as a rug plot along the *x*-axis.

on average, slow BMI gains from birth, peaking at around 17 mo.

Characteristics of the latent BMI trajectories

Background characteristics, BC measures, and cardiometabolic markers of the mother–child pairs according to the BMI trajectory class memberships are shown in **Tables 1** and **2**. At birth, we did not observe any statistically significant differences between the 4 trajectories, besides for gestational age. The highest proportions of low birth weight (13–18%) were seen in the 2 catch-up trajectory classes. At 5 y, children in all groups were, on average, lighter and shorter than the WHO international growth standards (26). At 5 y, children in the stable low BMI class presented the highest proportions of stunting and underweight and the lowest proportions of overweight, while children in the rapid catch-up to high BMI class presented the lowest proportions of stunting and underweight and had, on average, 1.2 kg more FM than the stable low BMI class.

Fat mass index and fat-free mass index growth in infancy

Each of the 4 BMI trajectory classes differed in terms of the average velocity of both FMI and FFMI growth from 0 to 6 mo (**Figure 3**). Children in the rapid catch-up to high BMI class had the lowest FMIs at birth, but their FMIs increased at accelerated rates through infancy, resulting in the highest average FMI at 6 mo. While growth in FMIs largely reflected the patterns of the BMI classes in the first 3–4 mo (Figure 3; Supplemental Figure 3), the accretion patterns of FFMIs were slightly concave, with much smaller variations between the classes. At 6 mo, the differences between the highest and lowest growth trajectory were 2.68 kg/m^2 for FMI and 1.32 kg/m^2 for FFMI.

Associations of BMI trajectories with body composition and cardiometabolic markers at 5 y

Compared with children classified in the normal BMI trajectory (reference group), children in the rapid catch-up to high BMI class had higher concentrations of TGs (range of β-coefficients in Models 1–4: 19–21%) and C-peptide (23–25%) across the 4 models (**Figure 4**; **Supplemental Table 4**). Tendencies of positive associations were also seen for insulin, HbA1c, and HOMA-IR, although the confidence bands were wide and included 0. Conversely, children classified in the stable low BMI class had lower concentrations of LDL cholesterol (0.14–0.17 mmol/L) and HDL cholesterol (0.05–0.09 mmol/L),

TABLE 1 Description of the mother–child pairs

	Trajectory group					
	1: Stable low BMI, $n = 69$	2: Normal BMI, $n = 173$	3: Rapid catch-up to high BMI, $n = 60$	4: Slow catch-up to high BMI, $n = 50$	P value[1]	Missing, n
Maternal characteristics						
Age at birth, y	24.8 (4.8)	24.7 (4.6)	24.1 (4.6)	24.4 (5.5)	0.825	0
Postpartum height, cm	156.6 (5.8)	157.5 (6.3)	157.7 (5.5)	155.6 (6.3)	0.187	2
Postpartum BMI, kg/m^2	21.91 (3.06)	22.09 (3.65)	22.33 (3.39)	23.02 (3.78)	0.352	6
Birth order of current child						
First	44.9	44.5	66.7	54.0	—	—
Second	27.5	29.5	16.7	26.0	—	—
Third or above	27.5	26.0	16.7	20.0	0.122	0
Breastfeeding status at 4–6 mo postpartum						
Exclusive	8.8	15.1	15.5	4.3	—	—
Almost exclusive, water given	20.6	20.1	24.1	23.4	—	—
Predominant	66.2	57.9	56.9	63.8	—	—
Partial or no	4.4	6.9	3.4	8.5	0.581	20
Maternal education						
No school	5.8	8.7	1.7	10.0	—	—
Some primary school	47.8	47.4	41.7	34.0	—	—
Completed primary school	11.6	14.5	20.0	20.0	—	—
Completed secondary school	18.8	17.9	20.0	26.0	—	—
Higher education	15.9	11.6	16.7	10.0	0.496	0
Socioeconomic status, International Wealth Index	45.9 (17.2)	44.6 (16.7)	48.2 (18.6)	45.4 (16.5)	0.565	0
Child characteristics at birth						
Sex, boys	47.8	50.3	51.7	52.0	0.965	0
Gestational age, wk	39.2 (0.9)	39.1 (1.0)	39.0 (1.0)	38.7 (0.8)	0.020	0
Weight, kg	3.10 (0.40)	3.07 (0.38)	2.95 (0.43)	2.98 (0.47)	0.076	0
Length, cm	49.2 (2.1)	49.3 (1.9)	49.0 (1.9)	48.7 (2.1)	0.291	0
Fat mass, kg	0.25 (0.20)	0.23 (0.15)	0.18 (0.15)	0.22 (0.16)	0.076	2
Fat-free mass, kg	2.85 (0.29)	2.85 (0.32)	2.78 (0.35)	2.78 (0.35)	0.322	2
Low birth weight, %[2]	5.8	6.9	13.3	18.0	0.061	0
Child characteristics at 5 y						
Age at 5-y visit, mo	59.8 (1.7)	60.0 (1.4)	60.1 (1.5)	59.8 (1.4)	0.702	0
Weight, kg	15.14 (1.72)	16.25 (1.88)	17.49 (2.32)	16.76 (2.05)	<0.001	0
Length, cm	102.8 (4.8)	104.2 (4.2)	106.0 (4.5)	103.8 (3.8)	<0.001	0
Weight for age z-score[3]	−1.40 (0.81)	−0.90 (0.80)	−0.39 (0.89)	−0.67 (0.87)	<0.001	0
Height for age z-score	−1.44 (0.98)	−1.15 (0.86)	−0.78 (0.95)	−1.25 (0.79)	<0.001	0
BMI for age z-score	−0.73 (0.91)	−0.27 (0.79)	0.14 (0.79)	0.15 (0.84)	<0.001	0
Underweight[4]	21.7	8.7	0.0	6.0	<0.001	0
Stunted[5]	26.1	12.1	11.7	16.0	0.043	0
Wasted by BMI, thinness[6]	7.2	2.3	0.0	2.0	0.090	0
Overweight[7]	1.4	1.7	10	14.0	0.001	0
Obese[8]	0.0	0.6	3.3	2.0	0.164	0

Data are for pairs attending the 5-y follow-up visit and included in the trajectory modeling according to the BMI trajectory class membership ($n = 352$). Data are presented as mean ±SD (for continuous, normally distributed variables) and percentages (for categorical variables).

[1]Differences between trajectory groups were calculated by 1-way ANOVA F-test (for continuous variables), Pearson's chi-square test of independence (for categorical variables with expected counts ≥5 in all cells), and Fisher's exact test of independence (for categorical variables with expected counts in any cell <5).

[2]Low birth weight is defined as a birth weight <2500 g.

[3]z-Scores are derived using the 2006 (aged <61 mo) and 2007 (aged ≥61 mo) WHO child growth standards.

[4]Weight for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards.

[5]Height for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards.

[6]BMI for age more than 2 SDs below the age- and sex-specific median of the WHO child growth standards.

[7]BMI for age from 1 to 2 SDs above the age- and sex-specific median of the WHO child growth standards.

[8]BMI for age more than 2 SDs above the age- and sex-specific median of the WHO child growth standards.

but higher concentrations of TGs (11–13%) across the 4 models. Tendencies of inverse associations were also seen for total cholesterol and systolic blood pressure, although confidence bands were wide and included 0.

In relation to the BC and anthropometry measures, children in the rapid catch-up to high BMI class were taller (1.3–1.8 cm) and had larger waist circumferences (0.9–1.6 cm), higher FMs (0.48–0.60 kg), and higher FFMs (0.50–0.77 kg), while children in the stable low BMI class were shorter (1.2–1.5 cm) and had smaller waist circumferences (1.0–1.3 cm), lower FMs (0.60–0.64 kg), and lower FFMs (0.35–0.49 kg) across the 4 models. Moreover, children in the slow catch-up to high BMI

TABLE 2 Cardiometabolic markers and body composition at 5 y of age

	Trajectory group					
	1: Stable low BMI, $n = 69$	2: Normal BMI, $n = 173$	3: Rapid catch-up to high BMI, $n = 60$	4: Slow catch-up to high BMI, $n = 50$	P value[1]	Missing, n
Glucose metabolism						
Glucose, mmol/L	5.84 (0.83)	5.90 (0.83)	5.98 (1.08)	5.89 (0.63)	0.844	26
HbA1c, mmol/mol	37 (5)	37 (4)	38 (4)	38 (5)	0.736	83
Insulin, μU/mL[2]	5.47 (2.62–11.58)	5.89 (3.15–11.08)	8.29 (4.12–11.61)	6.39 (3.04–9.43)	0.166	34
C-peptide, ng/mL[2]	0.99 (0.57–1.24)	1.05 (0.59–1.54)	1.31 (0.77–1.84)	1.01 (0.70–1.35)	0.094	39
HOMA-IR[2,3]	1.12 (0.55–2.53)	1.21 (0.63–2.33)	1.86 (0.86–2.58)	1.31 (0.65–2.07)	0.196	34
Lipids						
Total cholesterol, mmol/L	3.32 (0.63)	3.43 (0.58)	3.49 (0.71)	3.37 (0.55)	0.430	30
LDL, mmol/L	1.54 (0.52)	1.68 (0.55)	1.70 (0.68)	1.66 (0.49)	0.322	31
HDL, mmol/L	0.76 (0.23)	0.81 (0.26)	0.77 (0.27)	0.78 (0.24)	0.434	35
Triglycerides, mmol/L[2]	1.00 (0.79–1.29)	0.91 (0.68–1.27)	1.04 (0.83–1.53)	0.90 (0.72–1.15)	0.042	35
Blood pressure						
Systolic, mmHg	86.1 (6.7)	88.0 (7.2)	89.3 (8.0)	87.5 (7.5)	0.092	2
Diastolic, mmHg	53.6 (6.8)	54.2 (8.2)	55.4 (10.3)	54.3 (9.3)	0.673	2
Anthropometry and body composition						
BMI, kg/m^2	14.32 (1.16)	14.92 (1.10)	15.51 (1.21)	15.52 (1.20)	<0.001	0
Waist circumference, cm	50.09 (2.69)	51.38 (2.89)	52.77 (3.21)	51.99 (2.85)	<0.001	1
Fat mass, kg	3.50 (1.22)	4.13 (1.15)	4.68 (1.34)	4.64 (1.24)	<0.001	16
Fat-free mass, kg	11.64 (1.14)	12.14 (1.33)	12.86 (1.69)	12.10 (1.43)	<0.001	16
Fat mass index, kg/m^2	3.30 (1.10)	3.79 (0.99)	4.14 (1.05)	4.29 (1.03)	<0.001	16
Fat-free mass index, kg/m^2	11.02 (0.78)	11.17 (0.80)	11.41 (1.01)	11.26 (0.96)	0.079	16

Data are from the children attending the 5-y follow-up visit and included in the trajectory modeling according to the BMI trajectory class membership ($n = 352$). Data are shown as mean ± SD for continuous variables that are normally distributed and median (IQR) for continuous variables that are not following a normal distribution. HbA1C, glycated hemoglobin.

[1]Differences between trajectory groups were calculated by 1-way ANOVA F-test for continuous, normally distributed variables. Variables found not to follow a normal distribution were log-transformed prior to the tests of group differences.

[2]Nonnormally distributed.

[3]Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin (μU/mL) × glucose (mmol/l)/22.5.

class had higher FMs (0.46–0.58 kg), but not higher FFMs. When accounting for multiple testing in the results presented in the fully adjusted model (Model 4), the associations for the markers of lipid metabolism were no longer significant. However, the inverse associations of stable low BMI with waist circumference and FM remained significant, as did the positive associations of rapid catch-up to high BMI with height, FM, and FFM (Supplemental Figure 1). Adjusting all the models for breastfeeding status at 4–6 mo postpartum did not alter the associations markedly (Supplemental Figure 2).

Discussion

This is the first study from a sub-Saharan African population to examine how distinct trajectories of adiposity-related BMIs in the first years of life have different implications on markers of cardiometabolic risk and BC in early childhood. We found that accelerated BMI growth in infancy was associated with taller heights, higher concentrations of TGs and C-peptides, larger waist circumferences, and higher FMs and FFMs, while low BMI growth was associated with shorter heights, lower concentrations of LDLs and HDLs, smaller waist circumferences, and lower FMs and FFMs, but higher concentrations of TGs, at 5 y in Ethiopian children. The effect estimates for the cardiometabolic markers did not change markedly across the different adjustment models. Thus, the associations were independent of maternal characteristics, socioeconomic status, and birth weight and were not mediated through size at 5 y. As this investigation was exploratory rather than confirmatory, we did not account for multiple testing in the primary analysis.

Studies examining the health effects of variability in early-life growth have typically used predefined cutoffs to define low, normal, or accelerated growth between 2 or more timepoints (7, 28). This a priori classification forces observations into specific categories that may not fully reflect the complex and dynamic trajectories of child growth. Using an exploratory, data-driven approach, we were able to identify trajectories of low, normal, and accelerated growth associated with markers of adiposity, insulin, and lipid metabolism without a priori categorization of growth variability. The generalizability of these trajectories was supported by their similarity to BMI trajectories identified in studies from high-income countries, using similar data-driven modeling and overlapping age periods (29–32). In line with the present findings, these studies also reported associations of accelerated or stable high BMI trajectories in early childhood with the risk of obesity (29, 30, 32), elevated levels of markers of adiposity (11, 30), and changes in cardiometabolic status (11, 31) in childhood or early adolescence.

The present findings and existing evidence are consistent with the capacity-load model of cardiometabolic risk (33), with early low BMI growth constraining the metabolic capacity (e.g., lean mass deficits), while accelerated BMI growth increases the metabolic load (e.g., excess FM and waist circumference). Both a low metabolic capacity and high metabolic load challenge

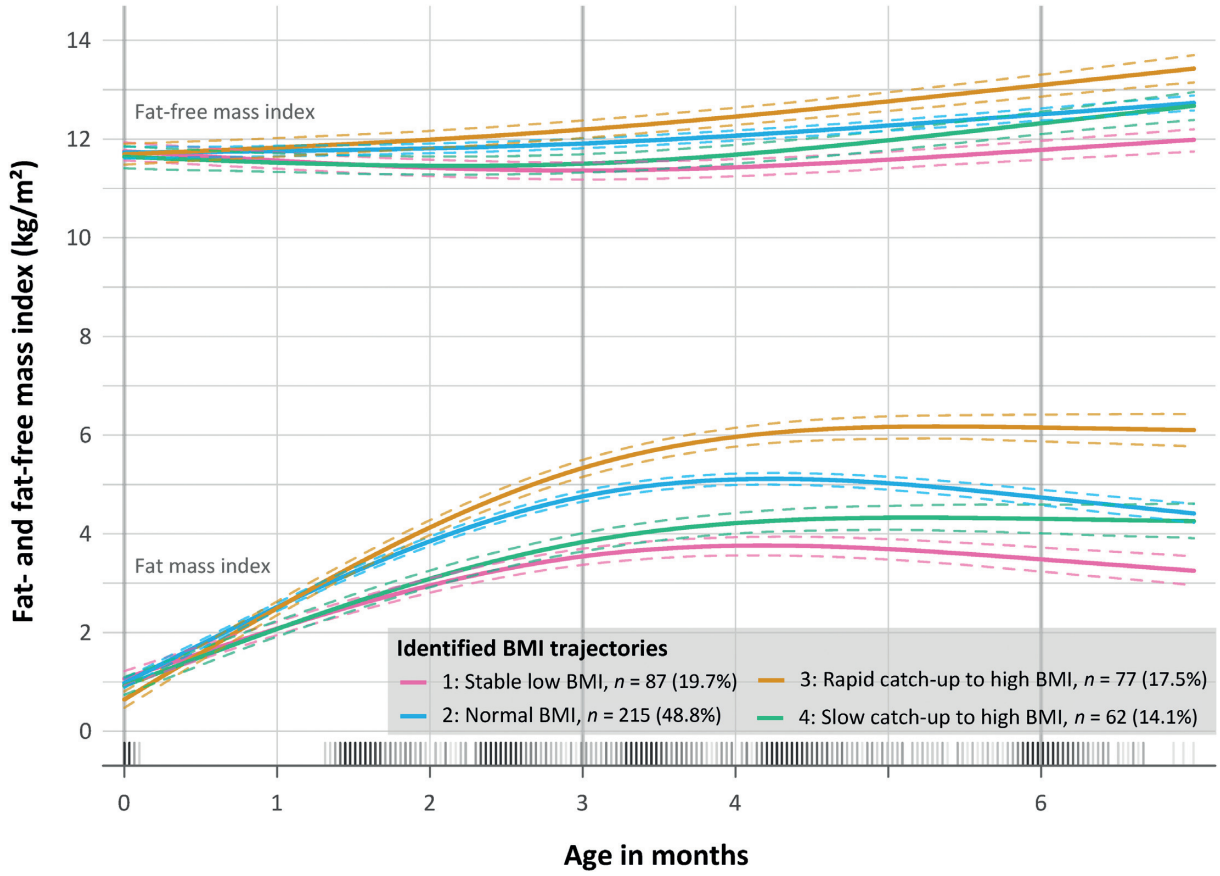

FIGURE 3 Estimated changes in fat mass index and fat-free mass index from 0 to 6 mo for each of the 4 identified BMI trajectory classes.

metabolic homeostasis. We found that FMI accretion from 0 to 6 mo largely reflected the patterns of BMI growth. Children with accelerated BMI growth, therefore, had the highest FM accretion and, on average, 0.5 kg and 1 kg more FM at 5 y than the children with normal and low BMI growth, respectively. Compared with UK children, the Ethiopian children also had higher average FMs (boys: 3.11 vs. 4.19 kg, respectively; girls: 3.97 vs. 4.14 kg, respectively) and markedly lower FFMs (boys: 16.35 vs. 12.27 kg, respectively; girls: 14.60 vs. 12.04 kg, respectively) at 5 y (34). As the children with accelerated BMI growth were larger overall, they also presented the highest FFMI accretions and FFMs at 5 y. However, the effect estimates for the associations with FM and FFM were of almost similar size, despite the average weight of FFM at 5 y being almost 3 times larger than the average weight of FM. Moreover, we recently showed that FM accretion during the first 4 mo of life was positively associated with the FMI at 4 y, but not the FFMI (35), and also that a lower birth weight associates with a FM, but not a FFM, catch-up growth pattern (36). Altogether, it is therefore possible that accelerated BMI growth during a critical window in the first 6 mo of life induces the disproportionally high accretion of FM in relation to FFM, which may already result in unfavorable cardiometabolic changes in childhood. Moreover, children with accelerated BMI growth may be particularly vulnerable to the effects of a high FM, as they had the lowest weight at birth, indicating the constrained development of metabolic capacity during fetal life, and had the highest waist circumference at 5 y, related to an increased metabolic load. Slow growth during infancy may continue to constrain the development of metabolic capacity, which is supported by a high proportion of stunting at 5 y in children with low BMI growth. However, these children did not appear to have particularly unfavorable cardiometabolic statuses, as they presented lower cholesterol concentrations and FMs compared with the children with normal BMI growth. These findings are similar to a study of survivors of severe–acute malnutrition in Malawi, where cardio-metabolic risk markers were not elevated despite several indices of low metabolic capacity (37). The likely explanation is that the accompanying lower FM is not sufficient to challenge the low metabolic capacity in these groups of children.

Continued follow-up of the present cohort will confirm whether these proposed relationships will persist in the longer term, but it is possible that children with either low or accelerated early growth are at the highest risk of developing obesity and cardiometabolic diseases later in life. These new insights may help identify potential early-life targets for interventions that promote FFM accretion, linear growth, and normal birth weight (i.e., metabolic capacity) without increasing excess BMI growth and FM accretion (i.e., metabolic load). This is particularly relevant for public health professionals working in low-income

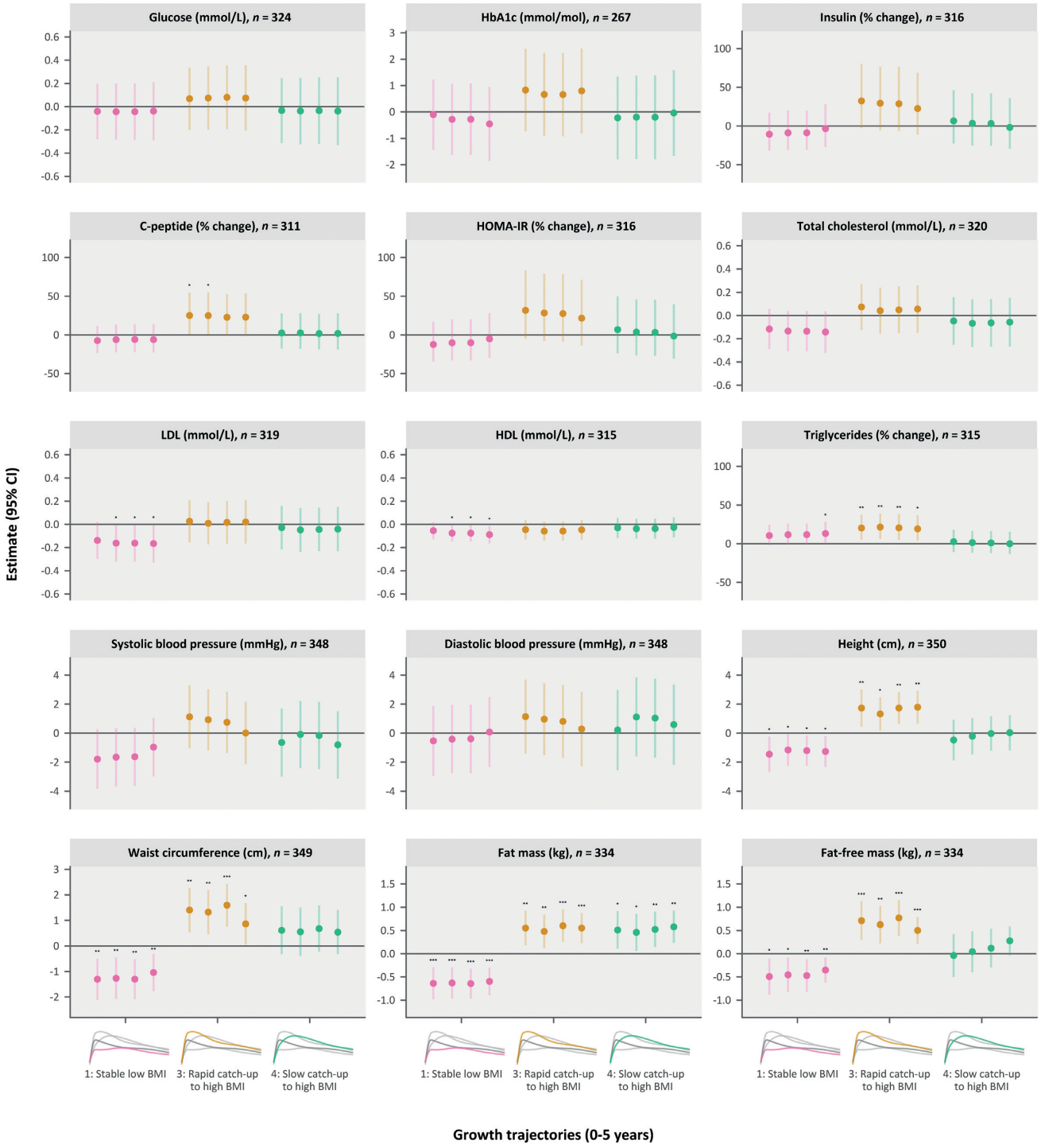

FIGURE 4 The coefficients (95% CIs) displayed in the forest plots were derived from multiple linear regression models and represent the mean difference in concentrations of cardiometabolic markers and body composition indices between the reference trajectory (2: normal BMI) and the 3 BMI trajectory categories (1: stable low BMI; 3: rapid catch-up to high BMI; and 4: slow catch-up to high BMI). The 4 distinct BMI trajectories (exposure variable) were derived from a latent class trajectory modeling. The outcome variables of insulin, C-peptide, HOMA-IR, and triglycerides were log-transformed prior to analyses. The resulting effect estimates were back-transformed and are presented as the percentwise change. Model 1 (the leftmost circle) was adjusted for child sex, birth order, and gestational age at birth. Model 2 was additionally adjusted for the child's exact age at the 5-y visit, maternal age at delivery, maternal postpartum height, maternal educational status, and family socioeconomic status (per the International Wealth Index). Model 3 was additionally adjusted for child birth weight. Model 4 (the rightmost circle) was additionally adjusted for child BMI at the 5-y visit. In Model 4, the analyses of FM and waist circumference were adjusted for FFM and height at 5 y instead of for BMI, and the analysis of FFM was adjusted for FM and height at 5 y instead of for BMI. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. FM, fat mass; FFM, fat-free mass; HbA1C, glycated hemoglobin.

countries where both undernutrition and excess fat accumulation in early life are pertinent and discernible issues associated with an ongoing nutritional transition (12).

The strengths of this study include the 5-y longitudinal design, with an average of 9 repeated BMI assessments per child; the detailed assessments of changes in BMIs and BCs in a critical window of development from birth to 6 mo; and the assessment of multiple cardiometabolic markers and BC indices at 5 y of age. Another strength is the ability of the LCT modeling to capture the complex and dynamic patterns of child growth and let the data speak for themselves by a posteriori identification of distinctive subgroups of BMI growth. Finally, over a 5-y period and 12 assessment waves, it was possible to retain 79% and 61% of the cohort of children included in the follow-up study for the growth modeling and regression analyses of the 5-y outcomes, respectively.

However, the study also had some limitations. First, longitudinal attrition inevitably makes the LCT modeling of BMI trajectories more uncertain. Second, we cannot excluded the possibility that children not able to participate in the 5-y follow-up visit caused some selection bias in the estimated associations, although these mother–child pairs were largely similar to those included in the analysis (**Supplemental Table 3**). Third, the data-driven nature of the LCT modeling may limit generalizability of the present findings, and future studies should assess whether the classifications of the distinct BMI trajectories commonly apply to BMI growth in this age range. Moreover, as the LCT modeling is not forcing children into groups using predefined cutoffs, the size of each identified class may vary substantially, which may limit the power in the subsequent regression analyses. Although we obtained relatively large class sizes, the effect estimates presented in the regression analyses had relatively large confidence bands, which may have resulted in type 2 errors. Fourth, we did not stratify the LCT modeling by sex, as this would have resulted in small class sizes and limited the power in the subsequent regression analyses. However, when re-estimating the BMI trajectories separately for boys and girls using the 4 identified classes from the whole study sample, we found no clinically meaningful sex differences in BMI growth for any of the 4 classes (**Supplemental Figure 5**). Fifth, as BMI comprises both weight and height, we were not able to assess how growth trajectories of these individual components were associated with later BC and cardiometabolic risk markers. Finally, the observational nature of this study does not allow us to imply any causal effects. We cannot rule out that important, unmeasured covariates, such as prepregnancy maternal nutritional status, gestational weight gain, paternal BMI, fetal growth trajectories, comprehensive dietary assessment in infancy and childhood, and duration of breastfeeding, confounded our results. However, in a sensitivity analysis, we adjusted our results for a crude measure of breastfeeding status at 4–6 mo postpartum, which did not affect our results noticeably.

In a birth cohort of Ethiopian children, we identified considerable heterogeneity in BMI growth in early childhood, which was associated with FM accretion in early infancy and markers of cardiometabolic status and indices of BC at 5 y. Collectively, our findings offer an important contribution to understanding the pathways from early growth to later cardiometabolic health, by suggesting that distinct trajectories of BMI growth in early life may be key in the complex etiology of obesity and cardiometabolic risk development. This is highly relevant for public health professionals in low-income countries, where the dual burden of malnutrition and rapid economic and nutritional transitions is a pertinent problem, as it offers potential early-life targets for interventions by identifying subgroups of children that may present unfavorable growth trajectories.

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The authors' responsibilities were as follows—TG, PK, JCKW, KFM, HF, GSA: designed the research; RW, BA, MA, PK, AA, GSA: conducted the research; RW, GSA, DV: performed the statistical analysis; RW: wrote the paper; RW, GSA: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

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