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Original Research Article

Associations of weight and body composition at birth with body composition and cardiometabolic markers in children aged 10 y: the Ethiopian infant anthropometry and body composition birth cohort study

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A B S T R A C T

Background: Although birth weight (BW) has been associated with later cardiovascular disease and type 2 diabetes, the role of birth fat mass (BFM) and birth fat-free mass (BFFM) on cardiometabolic health is unclear.
Objectives: To examine associations of BW, BFM, and BFFM with later anthropometry, body composition, abdominal fat, and cardiometabolic markers.
Methods: Birth cohort data on standardized exposure variables (BW, BFM, and BFFM) and follow-up information at age 10 y on anthropometry, body composition, abdominal fat, and cardiometabolic markers were included. A linear regression analysis was used to assess associations of exposures with outcome variables, adjusting for maternal and child characteristics at birth and current body size in separate models.
Results: Among 353 children, mean (SD) age was 9.8 (1.0) y, and 51.5% were boys. In the fully adjusted model, 1-SD higher BW and BFFM were associated with 0.81 cm (95% CI: 0.21, 1.41 cm) and 1.25 cm (95% CI: 0.64, 1.85 cm) greater height at 10 y, respectively. The 1-SD higher BW and BFM were associated with 0.32 kg/m^2 (95% CI: 0.14, 0.51 kg/m^2) and 0.42 kg/m^2 (95% CI: 0.25, 0.59 kg/m^2) greater fat mass index at 10 y, respectively. In addition, 1-SD higher BW and BFFM were associated with 0.22 kg/m^2 (95% CI: 0.09, 0.34 kg/m^2) greater FFM index, whereas a 1-SD greater BFM was associated with a 0.05 cm greater subcutaneous adipose tissue (95% CI: 0.01, 0.11 cm). Furthermore, 1-SD higher BW and BFFM were associated with 10.3% (95% CI: 1.4%, 20.0%) and 8.3% (95% CI: −0.5%, 17.9%) greater insulin, respectively. Similarly, 1-SD higher BW and BFFM were associated with 10.0% (95% CI: 0.9%, 20.0%) and 8.5% (95% CI: −0.6%, 18.5%) greater homeostasis model assessment of insulin resistance, respectively.
Conclusions: BW and BFFM rather than BFM are predictors of height and FFM index at 10 y. Children with higher BW and BFFM showed higher insulin concentrations and homeostasis model assessment of insulin resistance at 10 y of age.
This trial was registered at ISRCTN as ISRCTN46718296.

Keywords: birth weight, birth fat mass, birth fat-free mass, air displacement plethysmograph, abdominal fat, cardiometabolic markers, children, cohort study, Ethiopia

Abbreviations: ADP, air displacement plethysmograph; BFFM, birth fat-free mass; BFM, birth fat mass; BW, birth weight; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HOMA-IR, homeostasis model assessment of insulin resistance; iABC, infant anthropometry and body composition; JUSH, Jimma University Specialized Hospital; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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Introduction

The fetal environment plays a key role in the future health status, and birth weight is an important marker of the intrauterine environment [1]. Both low and high birth weight (BW) has been associated with risk of developing cardiovascular disease (CVD) and type 2 diabetes (T2D) [2,3]. Over the past 3 decades, the prevalence of childhood obesity has increased globally and is considered one of the most important predisposing factors for cardiometabolic diseases [4–7]. Children in many low-income and middle-income countries (LMICs) are experiencing a double burden of malnutrition with undernutrition alongside an increasing prevalence of overweight and obesity [8]. Several studies, primarily from high-income countries (HICs), have shown a positive association between BW and obesity later in life [9–11].

Studies have revealed inconsistent associations between BW and cardiometabolic disease risk later in life. Longitudinal studies conducted in HICs have reported an inverse association between BW and cardiometabolic disease risk in childhood [12,13], whereas other studies showed a U-shaped relation between BW and cardiometabolic risk in childhood and adolescence [14,15].

One reason for the conflicting findings on the association between BW and later cardiometabolic risk could be the substantial variation in birth fat mass (BFM) and birth fat-free mass (BFFM) for a given BW [16,17]. This highlights the importance of understanding the extent to which any observed association between BW and cardiometabolic markers is driven by the fat or fat-free component of BW.

Despite the potential relevance of birth body composition in predicting later body composition [18,19] and disease risk [20–22], few studies have investigated associations of BFM and BFFM with later body composition and cardiometabolic markers. From LMICs, evidence is particularly scarce; however, a study from India reported that proxy measurements of birth fat and lean mass were not associated with childhood body fat% and cardiometabolic markers but that fat tissue accretion after 5 y was positively associated with body fat% and homeostasis model assessment of insulin resistance (HOMA-IR) at 13.5 y [19]. In the current birth cohort study, higher BFFM and FFM accretion in infancy consistently predicted greater fat-free mass (FFM) at 5 y, but BFM was not associated with FM at 5 y. Higher BFM and higher fat mass (FM) accretion from 0 to 3 mo were associated with greater cholesterol concentrations at 5 y [23].

Because risk of noncommunicable diseases such as CVD and T2D is complex and varies by age-related physiologic changes [20,24], it is essential to track changes in body composition and cardiometabolic markers of the same children in different periods of the life course. Thus, this study aimed to examine associations of BW, BFM, and BFFM with anthropometry, body composition, abdominal fat, and cardiometabolic markers in Ethiopian children aged 10 y.

Methods

Study setting and participants

The Ethiopian infant anthropometry and body composition (iABC) birth cohort study was established in 2008 in Jimma, Ethiopia. We conducted convenience sampling to recruit healthy term infants and their mothers within 48 h of delivery at the Jimma University Specialized Hospital (JUSH) maternity ward between December 2008 and October 2012. Participants were recruited until the calculated sample size was reached [25]. Mothers living in Jimma town and giving birth to a term child without congenital malformation and serious medical conditions with a BW of ≥1500 g were eligible. Further details of the data collection procedure at birth are described elsewhere [25].

The follow-up visits were performed from June 2019 to December 2020, in children aged 7–12 y, hereafter referred to as the 10-y follow-up. In brief, at the 10-y follow-up, mother/guardian–child pairs participating in the follow-up study were invited based on the registered information during earlier visits such as telephone number and/or residence address. Information about the visit and data collection procedure such as child fasting before the data collection were clearly explained to the mother/guardian when scheduling the visit. Data collection was performed at the Jimma University Clinical and Nutrition Research Center by experienced research nurses and laboratory technicians involved in the iABC birth cohort study.

Anthropometry and body composition measurements at birth

BW was measured to the nearest 0.1 g using a PEA POD scale. BFM and BFFM were assessed using a PEA POD, an infant air displacement plethysmograph (ADP) (COSMED). PEA POD is designed for the assessment of body composition in infants from birth to 6 mo of age [26]. ADP is considered a simple, acceptable, reliable, and valid measure of body composition in both infants and children [27].

Anthropometry and body composition measurements at 10 y

Height was measured in duplicate in the standing position using a portable stadiometer (SECA) to the nearest 0.1 cm, and an average was used. Weight was measured to the nearest 1 g using the attached electronic scale of an adult ADP instrument in BOD POD (COSMED). BMI (in kg/m^2) was calculated as weight (kg) divided by height (m) squared. Height-for-age *z*-score and BMI-for-age *z*-score were calculated using the World Health Organization (WHO) 2007 AnthroPlus R package (version 0.9.0) [28]. Children were identified as stunted if height-for-age z-score <-2, wasted if BMI-for-age z-score <-2, normal BMI if BMI-for-age z-score between –2 and 1, and overweight/obese if BMI-for-age z-score >1. The research nurses calibrated the BOD POD every morning before body composition measurements began as has been described in detail elsewhere [29]. During the ADP measurement, the child wore only tightly fitted underwear pants and a swimming cap to displace accumulated air in the hair [30]. FM and FFM were measured to the nearest 1 g using ADP. For analysis, FM index (FMI) and FFM index (FFMI) were calculated as FM (kg) or FFM (kg) divided by height in meters (m) squared [31].

Abdominal fat measurements at 10 y

Abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were measured by a radiologist using ultrasound following a standard protocol [32–34]. The measurements were performed in supine position using linear array probe (GE Logic P6) (11 MHz for SAT) and convex array probe (GE Logic) (3.5 MHz for VAT). The probe was kept perpendicular to skin on the upper median abdomen, and an axial scan was performed in the midpoint between the xiphoid appendix and the navel along the linea alba. During the measurement of SAT and VAT, children were asked to take a deep breath in, followed by a deep breath out, and then hold their breath for a few seconds until the radiologist could fix the image for the measurements. SAT was measured as the depth (in centimeters) from the inner edge of the skin to outer edge of linea alba and VAT as the distance (in centimeters) from the peritoneum to the front of lumbar spine.

Cardiometabolic markers assessment at 10 y

A laboratory technician collected a 4-mL venous blood sample after an overnight fast. Immediately after giving the blood sample, the children were offered some food or drinks. Blood glucose concentration was measured on whole blood using the HemoCue Glucose 201 RT System. Subsequently, serum was obtained by centrifuging the whole blood sample at 1107 × *g* force (relative centrifugal force) for 10 min, divided to a minimum of 3 × 0.3 mL aliquots, frozen at −80°C, and kept for a maximum of 2 y and 3 mo until the serum samples were analyzed. The stored serum samples were analyzed at JUSH, Clinical Chemistry Unit using module e601 of the COBAS 6000 analyzer (Roche Diagnostics International) for insulin (in microunits per milliliter) and C-peptide (in nanograms per milliliter) concentrations, and module c501 for lipids [total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, and triglyceride (in millimoles per liter) concentrations]. The HOMA-IR was calculated as insulin (in microunits per milliliter) × glucose (in millimoles per liter)/22.5.

Covariates

A structured questionnaire was used to collect data on background sociodemographic characteristics of participants and potential confounding variables such as maternal age at delivery, type of delivery, child's sex, childbirth order, maternal educational status, and family economic status at delivery. Gestational age was assessed using The Ballard Score within 48 h of birth [35]. Family economic status was assessed using the International Wealth Index [36]. Maternal height was measured in duplicate to the nearest 0.1 cm using a SECA 214 stadiometer, and maternal weight was assessed within 48 h after delivery to the nearest 0.1 kg using the scale of the Tanita 418 Bioimpedance analyzer.

Statistical analyses

Data were double entered and cross-checked using EpiData version (4.42.0). Identified discrepancies in data entry were corrected referring to registries except for cardiometabolic makers that were corrected using COBAS 6000 analyzer printouts. Data were presented using mean [standard deviation (SD)], and median [interquartile range (IQR)] for continuous normally distributed and skew variables, respectively. Categorical variables were presented using frequencies (*n*) and percentages. Exposure variables (BW, BFM, and BFFM) were standardized before regression analyses to obtain comparable estimates across the exposure variables. Thus, the estimates indicate the change in outcome variables per 1 study population SD higher value of the exposure variables. Normal distribution of variables and model assumptions were checked visually by histograms and QQ plots (quantile-quantile plots). If skew, outcome variables were log-transformed before the regression analyses. The estimates for skew variables were back-transformed and reported as percentage change.

Associations between exposure and outcome variables were analyzed using multiple linear regression. We ran 3 separate models for each outcome variable. Model 1 was adjusted for the child's sex and exact age at the 10-y follow-up. Model 2 was additionally adjusted for childbirth order, gestational age at birth, maternal age at delivery, maternal height, maternal educational status, and family economic status [5,37]. Model 3 was further adjusted for current FM, except for FMI, which was adjusted for current FFMI, FFMI for current FMI, and both SAT and VAT were adjusted for current FFM. The adjustment of adiposity outcomes for FFMI controlled for the lean component of body size. However, BMI was not further adjusted for current body size because it correlated strongly with both FM and FFM. The correlation observed between FMI and FFMI was $r = 0.18$; SAT and FFM, $r = 0.32$; and VAT and FFM, $r = 0.24$. In the sensitivity analysis, differences between the girls and boys in associations of birth body size (BW, BFM, and BFFM) with 10-y outcomes were examined by including interaction terms (sex × birth body size) in the final regression models. We presented the associations of the exposure variables and 10-y outcomes for significant-interaction *P* values for boys and girls separately. Regression models were performed as complete case analyses. *P* values of <0.05 were considered significant. We performed sensitivity analyses considering multiple testing using Benjamini-Hochberg method [38] in the final regression models. Data were analyzed using R statistical software version 4.2.1 (R Foundation for Statistical Computing).

Ethical consideration

Ethical clearance was obtained from the research ethics review board (RERB) of the College of Public Health and Medical Sciences of Jimma University, Ethiopia (RERB reference number: IHRPHD/333/18) and the ethics committee of the London School of Hygiene and Tropical Medicine (reference number: 15976). Written informed consent of participation was obtained from the mother/caretaker of the child before participation. Children who were found with serious medical conditions were referred to the pediatric unit of JUSH for further investigation and treatment.

Results

Of the 571 children included in the cohort study, 355 (62.2%) children were followed up to 10 y of age, and 353 (99.4%) were included in the regression analyses (Figure 1). We compared mother–child characteristics at birth between those who attended the 10-y follow-up and those who did not; among mother–child pairs who attended, maternal age was higher (24.7 vs. 23.3 y; $P < 0.001$) and a lower proportion of children were first born (49.0 vs. 62.9%; $P = 0.006$) (Supplemental Table 1). The mean (SD) maternal age at delivery was 25.1 (4.9) y and gestational age was 39.0 (1.0) wk, and 183 (51.5%) were boys (Table 1).

Children's parameters at birth and 10 y

The mean (SD) BW was 3.1 (0.4) kg, and 31 children (8.7%) recorded low birth weight (<2500 g) (Table 2). The mean (SD) age, height, and BMI of children at the 10-y follow-up were 9.8 (1) y, 132.3 (7.7) cm, and 15.5 (2.2) kg/m^2, respectively. At 10 y, 34 (9.6%) of the children showed stunted growth, 283 (79.7%) recorded normal BMI *z*-score, and 43 (12.2%) were considered wasted, and 29 (8.2%) were overweight/obese. Overall, the children were shorter and thinner compared with the WHO child growth standards. The mean (SD) FMI, FFMI, and VAT at 10 y were 3.1 (1.8) kg/m^2, 12.4 (1.1) kg/m^2, and 3.9 (0.9) cm, respectively. The children showed a median (IQR) HOMA-IR of 0.89 (0.51–1.44) and a mean (SD) total cholesterol of 3.36 (0.77) mmol/L at the 10-y follow-up (Table 2).

Associations of BW, BFM, and BFFM with anthropometry, body composition, and abdominal fat at 10 y

BW and BFFM, but not BFM, were associated with height at 10 y: in model 3, a 1-SD higher BW (1-SD = 412 g) and BFFM (1-SD = 329 g) was associated with 0.81 cm (95% CI: 0.21, 1.41 cm) and 1.25 cm (95% CI: 0.64, 1.85 cm) increase in height, respectively (Figure 2 and Supplemental Table 2). In addition, BW, BFM, and BFFM were positively associated with BMI at 10 y: a 1-SD greater BW, BFM (1-

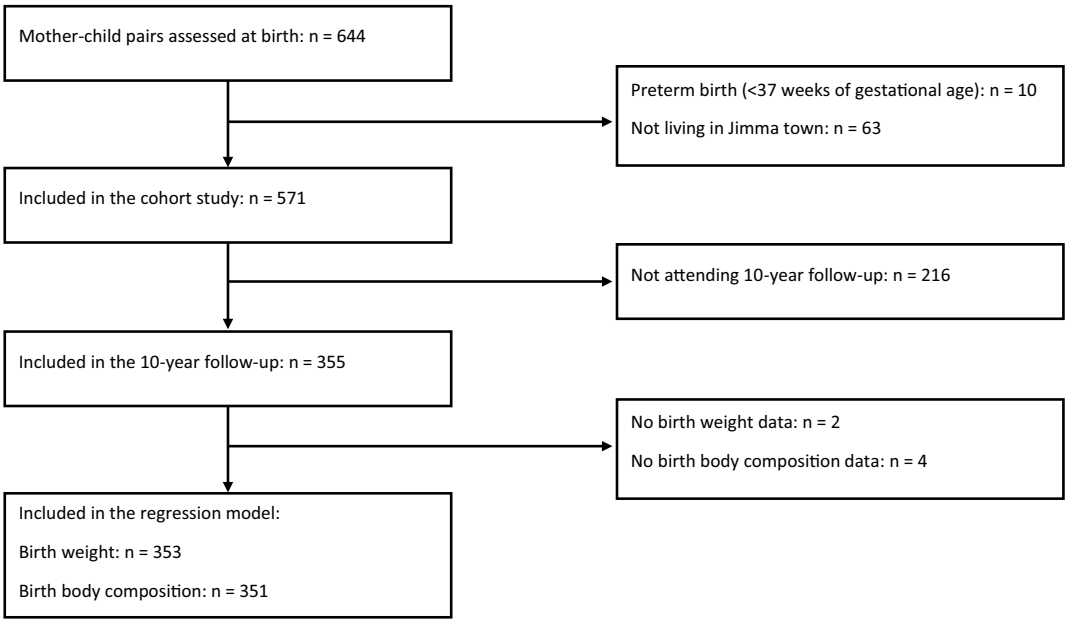

FIGURE 1. Flow diagram of the study participants.

TABLE 1
Characteristics of mother and child at birth

	N	Mean (SD) or *n* [%][1]
Maternal characteristics		
Age at delivery (y)	354	25.1 (4.9)
Height (cm)	345	157.0 (6.0)
Weight within 48 h of delivery (kg)	343	54.8 (10.2)
BMI within 48 h of delivery (kg/m^2)	342	22.2 (3.7)
Maternal educational status	355	
No school		19 [5.3]
Primary school		122 [34.4]
Secondary school		142 [40.0]
Higher education		72 [20.3]
Family economic status (IWI)	354	46.3 (17.1)
Child characteristics		
Mode of delivery	355	
Vaginal		330 [93.0]
Cesarean section		25 [7.0]
Gestational age (wk)	355	39.0 (1.0)
Birth order	353	
First		173 [49.0]
Second		94 [26.6]
Third and above		86 [24.4]
Sex, male	355	183 [51.5]

Abbreviations: BMI, body mass index; IWI, international wealth index.
[1] Data are mean (SD) for continuous and *n* [%] for categorical variables.

SD = 164 g), and BFFM was associated with an increase of 0.58 kg/m^2 (95% CI: 0.36, 0.81 kg/m^2), 0.55 kg/m^2 (95% CI: 0.33, 0.76 kg/m^2), and 0.45 kg/m^2 (95% CI: 0.21, 0.68 kg/m^2) in BMI, respectively (model 2).

BW and BFM, but not BFFM, were positively associated with FMI after adjusting for current FFMI. For example, a 1-SD greater BW and BFM was associated with 0.32 kg/m^2 (95% CI: 0.14, 0.51 kg/m^2) and 0.42 kg/m^2 (95% CI: 0.25, 0.59 kg/m^2) greater FMI, respectively (model 3). On the contrary, BW and BFFM, but not BFM, were associated with FFMI at 10 y, and the estimates were slightly decreased after adjusting for current FMI. However, the effect estimates and 95% CIs of both BW and BFFM with FFMI were similar in all models: in the final model, a 1-SD higher BW and BFFM were associated with a 0.22 kg/m^2 (95% CI: 0.09, 0.34 kg/m^2) higher FFMI (Figure 2 and Supplemental Table 2).

BW and BFM, but not BFFM, were associated with SAT, and after adjusting for current FFM, only BFM was associated with SAT. A 1-SD higher BFM was associated with 0.05 cm (95% CI: 0.01, 0.11 cm) higher SAT (model 3). None of the exposure variables was associated with VAT, but there was a tendency toward a positive association between BFM and VAT in model 2 (Figure 2 and Supplemental Table 2).

Associations of BW, BFM, and BFFM with cardiometabolic markers at 10 y

The associations of BW, BFM, and BFFM with cardiometabolic markers are presented in Figure 3 and Supplemental Table 2**.** BW and BFFM were associated with insulin, C-peptide, and HOMA-IR at 10 y. In the final model, a 1-SD greater BW was associated with 10.3% (95% CI: 1.4%, 20.0%) higher insulin, 11.4% (95% CI: −3.8%, 29.0%) higher C-peptide, and 10.0% (95% CI: 0.9%, 20.0%) higher HOMA-IR. A 1-SD higher BFFM was associated with 8.3% (95% CI: −0.5%, 17.9%) greater insulin, 18.1% (95% CI: 1.8%, 37.1%) greater C-peptide, and 8.5% (95% CI: −0.65, 18.5%) greater HOMA-IR.

BFM was associated with insulin and HOMA-IR in models 1 and 2, and the effect estimates were attenuated when further adjusted for current FM in model 3. BFM was positively associated with HDL cholesterol in model 2 although adjustment for current FM in the subsequent model attenuated the effect estimate. A 1-SD higher BFM (model 2) was associated with a 1.33-mmol/L (95% CI: 0.05, 2.60 mmol/L) higher HDL cholesterol (Figure 3). BW, BFM, and BFFM were not associated with other lipids and glucose at 10 y. In the sensitivity analyses of associations of BW, BFM, and BFFM with 10-y outcomes with a significant-interaction *P* value, BW in girls was inversely associated with total cholesterol (β = −5.59; 95% CI: −10.55, −0.63 mmol/L), and there was a tendency toward a positive association between BW of boys and total cholesterol at 10 y of age (Supplemental Table 3 and Supplemental Figure 1). Furthermore, after considering multiple testing using the Benjamin-Hochberg method in the sensitivity analysis, height, BMI, FMI, and FFMI were associated with exposure variables (Supplemental Figure 2).

TABLE 2
Child parameters at birth and 10 y by sex

	n	Girls[1]	*n*	Boys[1]
Child characteristics at birth				
Anthropometry				
Length (cm)	171	49.0 (1.9)	182	49.4 (2.0)
Weight (kg)	171	3.0 (0.4)	182	3.1 (0.4)
Ponderal index (kg/m^3)	171	2.55 (0.23)	182	2.56 (0.24)
Low birth weight[2]	172	19 [11.1]	183	12 [6.6]
Body composition				
FM (kg)	171	0.24 (0.16)	180	0.21 (0.17)
FFM (kg)	171	2.8 (0.3)	180	2.9 (0.3)
Child characteristics at 10 y				
Age (y)	172	9.8 (1.0)	183	9.8 (0.9)
Anthropometry				
Height (cm)	172	132.5 (7.7)	183	132.1 (7.7)
Weight (kg)	172	27.5 (6.0)	183	27.2 (6.0)
BMI (kg/m^2)	172	15.6 (2.4)	183	15.4 (2.1)
Height-for-age (*z*-score)	172	−0.76 (0.91)	183	−0.76 (0.96)
Stunted[3]	172	14 [8.1]	183	20 [10.9]
BMI-for-age (*z*-score)	172	−0.72 (1.14)	183	−0.81 (1.17)
Wasted[4]	172	17 [9.9]	183	26 [14.2]
Normal BMI[5]	172	143 [83.1]	183	140 [76.5]
Overweight/obese[6]	172	12 [7.0]	172	17 [9.3]
Body composition				
FM (kg)	171	6.0 (3.7)	182	5.3 (3.3)
FFM (kg)	171	21.5 (3.2)	182	22.0 (3.5)
FMI (kg/m^2)	171	3.3 (1.9)	182	2.9 (1.6)
FFMI (kg/m^2)	171	12.2 (1.1)	182	12.5 (1.1)
Abdominal fat				
Subcutaneous adipose tissue (cm)	170	0.74 (0.54)	180	0.61 (0.52)
Visceral adipose tissue (cm)	170	3.83 (0.93)	180	3.99 (0.89)
Glucose metabolism (fasting values)				
Glucose (mmol/L)	169	5.17 (0.65)	180	5.25 (0.65)
Insulin (μU/mL)	166	4.46 (3.01–6.58)	180	3.41 (1.87–5.70)
C-peptide (ng/mL)	166	0.32 (0.09–0.72)	180	0.31 (0.09–0.84)
HOMA-IR[7]	166	1.06 (0.66–1.56)	180	0.78 (0.45–1.30)
Lipids				
Total cholestrol (mmol/L)	167	3.40 (0.76)	180	3.33 (0.77)
HDL cholesterol (mmol/L)	167	0.98 (0.30)	180	0.99 (0.29)
LDL cholesterol (mmol/L)	167	1.76 (0.46)	180	1.70 (0.48)
Triglycerides (mmol/L)	166	0.86 (0.69–1.09)	180	0.79 (0.63–0.95)

Abbreviations: BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index.

[1] Data are mean (SD) for continuous normally distributed, median (IQR) for skew, and *n* [%] for categorical variables.

[2] Birth weight <2500 g.

[3] Height-for-age z-score <-2.

[4] BMI-for-age z-score <-2.

[5] BMI-for-age z-score between −2 and 1.

[6] BMI-for-age z-score >1.

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

Discussion

In this prospective birth cohort study, we investigated the associations of BW, BFM, and BFFM with anthropometric measurements, body composition, abdominal fat, and cardiometabolic markers at 10 y of age. Independent of potential confounding factors, such as maternal and child characteristics at birth and current body size, BW and BFFM were positively associated with height at 10 y. BW, BFM, and BFFM were positively associated with BMI, whereas BW and BFM rather than BFFM predicted FMI at 10 y. Moreover, BW and BFFM but not BFM were associated with FFMI. On the contrary, only BFM was associated with SAT. BW and BFFM were also positively associated with insulin and HOMA-IR, whereas only BFFM predicted C-peptide. At 10 y, only BFM was associated with HDL cholesterol, and BW, BFM, and BFFM were not associated with other lipids.

That it was the FFM rather than FM component of BW that contributed to the positive association of BW with height is consistent with a previous follow-up of this cohort, where we found positive associations of BW and BFFM with linear growth and height at 2 and 5 y [23,39–41]. Confirming these findings at 10 y of age highlights the importance of appropriate weight and FFM gain in fetal life for childhood linear growth.

Correspondingly, studies conducted in middle-income countries have shown a positive association between BW and height in childhood [42,43], with similar findings for adult height reported from 5 birth cohort studies in LMICs [44]. There are limited studies that investigated the association of BFM and BFFM with later anthropometric measurements such as height; however, an Indian birth cohort that assessed BFM using skinfolds found an inverse association between BFM and height at 13.5 y [19]. Similarly, after adjusting for current FM, we observed a tendency of an inverse relationship between BFM and height at 10 y. This indicates a trade-off between achieving a linear growth potential and fat accretion in early life.

In this study, BW, BFM, and BFFM were positively associated with BMI. These associations could be explained by strong relation of BMI with both lean mass and FM [45]. Correspondingly, several studies conducted in middle-income countries and HICs have found a positive association between BW and BMI in childhood [42,46–48]. However, BFM was not associated with BMI at 13.5 y in an Indian birth cohort [19]. These inconsistent findings could be attributed to a difference in body composition measurement techniques, age variabilities, and differences in the nutritional status of the population. In the Indian study, birth adiposity was assessed using skinfold measurements, whereas, in this study, BFM and BFFM were assessed using APD.

We found that children born with higher BW, BFM, and BFFM showed greater FMI and those with higher BW and BFFM showed greater FFMI at 10 y. However, the association between BFFM and FMI was attinuated after adjusting for current FFMI, suggesting that the association is mediated by childhood FFM. Previously, we have shown positive associations of BW and BFFM with FM and FFM. However, BFM was associated with FFM rather than with FM at 5 y [23,41]. This may highlight that children in this birth cohort who were born with higher BFM tend to use this energy for growth in the first 5 y of life and gradually reaccumulate FM.

Several longitudinal studies in middle-income countries and HICs have consistently reported positive association of BW with lean and FM in childhood [9,43,49–53]. By contrast, in a Brazilian study, Moura-Dos-Santos et al. [42] found a positive association between BW

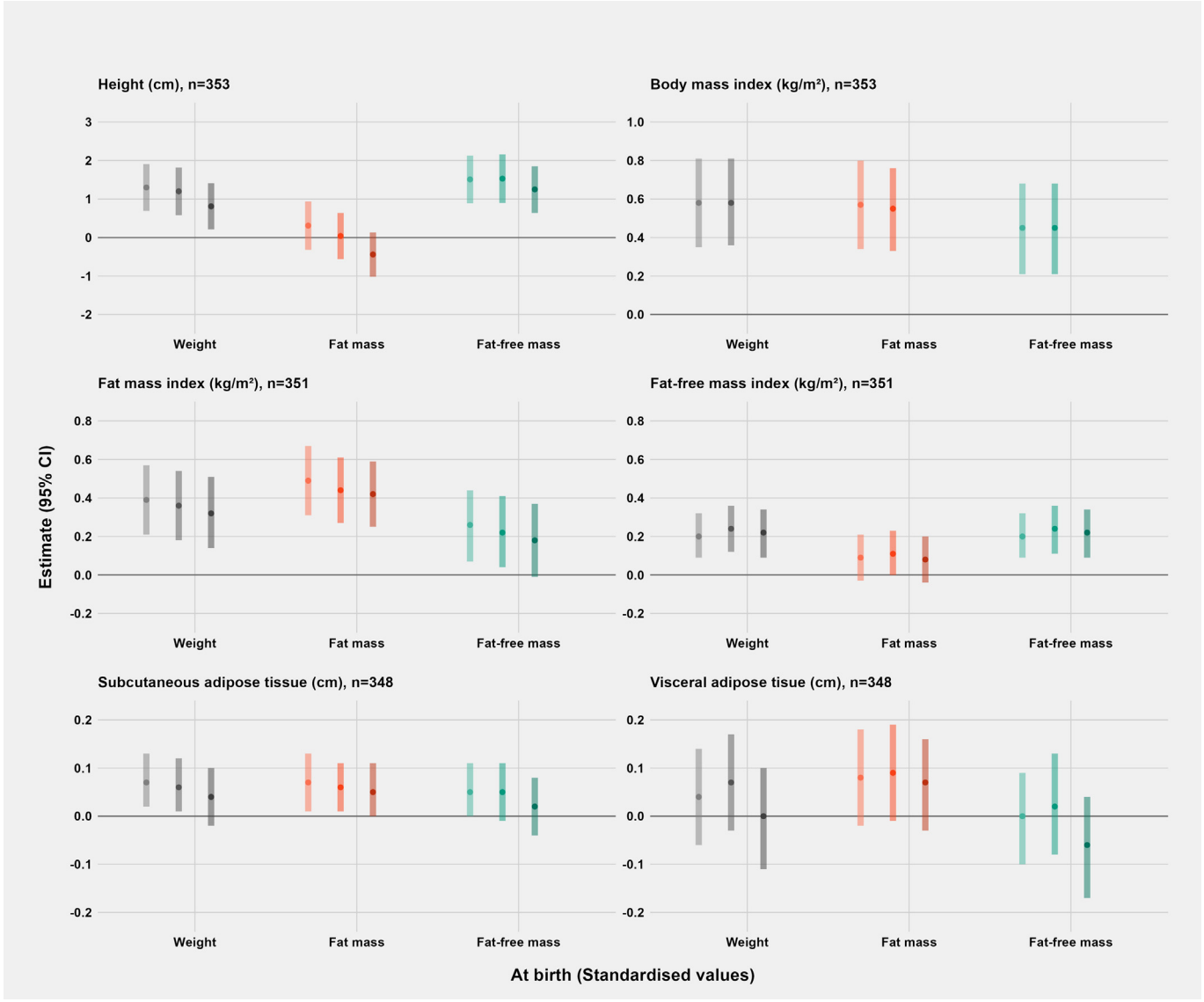

FIGURE 2. Associations of birth weight, birth fat mass, and birth fat-free mass with anthropometry, body composition, and abdominal fat at 10 y. The exposure variables (weight, fat mass, and fat-free mass) at birth were standardized before the regression analyses. The coefficients with 95% CI were derived from separate multiple linear regression analyses and represent the change in the outcome variables per 1-SD higher value of the exposure variables. We ran 3 separate models for each outcome, and the vertical bars from left to right represent models 1, 2, and 3, respectively. Model 1 was adjusted for child's sex and age at the 10-y follow-up. Model 2 was additionally adjusted for childbirth order, gestational age at birth, maternal age at delivery, maternal height, maternal educational status at delivery, and family economic status. In model 3, height was further adjusted for current fat mass. Fat mass index (FMI) and fat-free mass index (FFMI) were adjusted for current FFMI and FMI, respectively. Subcutaneous and visceral adipose tissues were adjusted for current fat-free mass. Body mass index was not further adjusted.

and childhood FFM but not with FM. The difference between this study findings and other studies could be attribed to difference in adjusting for later body size, body composition measurement techniques, age variabilities, and difference in nutritional status of the population.

In this study, BW and BFM were positively associated with SAT although adjustment for current FFM attenuated the estimate for BW, suggesting that direct tracking of adiposity is the primary pathway [54]. On the contrary, none of BW, BFM, and BFFM predicted VAT at 10 y. This could be explained by the relatively narrow range of peritoneal fat variation in children [55], possibly because the children in this cohort were thinner compared with the WHO growth standard population. Several longitudinal studies in both children and adults have shown positive associations between weight gain after birth and abdominal fat but not with BW [47,56,57]. VAT may also emerge primarily in postnatal life, and, hence, show little relationship to birth body composition.

Our results showed that higher BW and BFFM were associated with higher insulin, C-peptide, and HOMA-IR, but the effect estimate of BW with C-peptide was attenuated when further adjusted for current FM. Greater BFM was also associated with higher insulin and HOMA-IR, but only before, not after, adjustment for current FM. It has been suggested that adjusting for current size removes the association between early size and later outcome, and that is, the relationship is more explained by the change in later than early size [54]. Thus, the lack of association between BFM and glucose metabolism after adjusting for current FM could suggest that gaining FM after birth is more related to insulin and HOMA-IR than BFM.

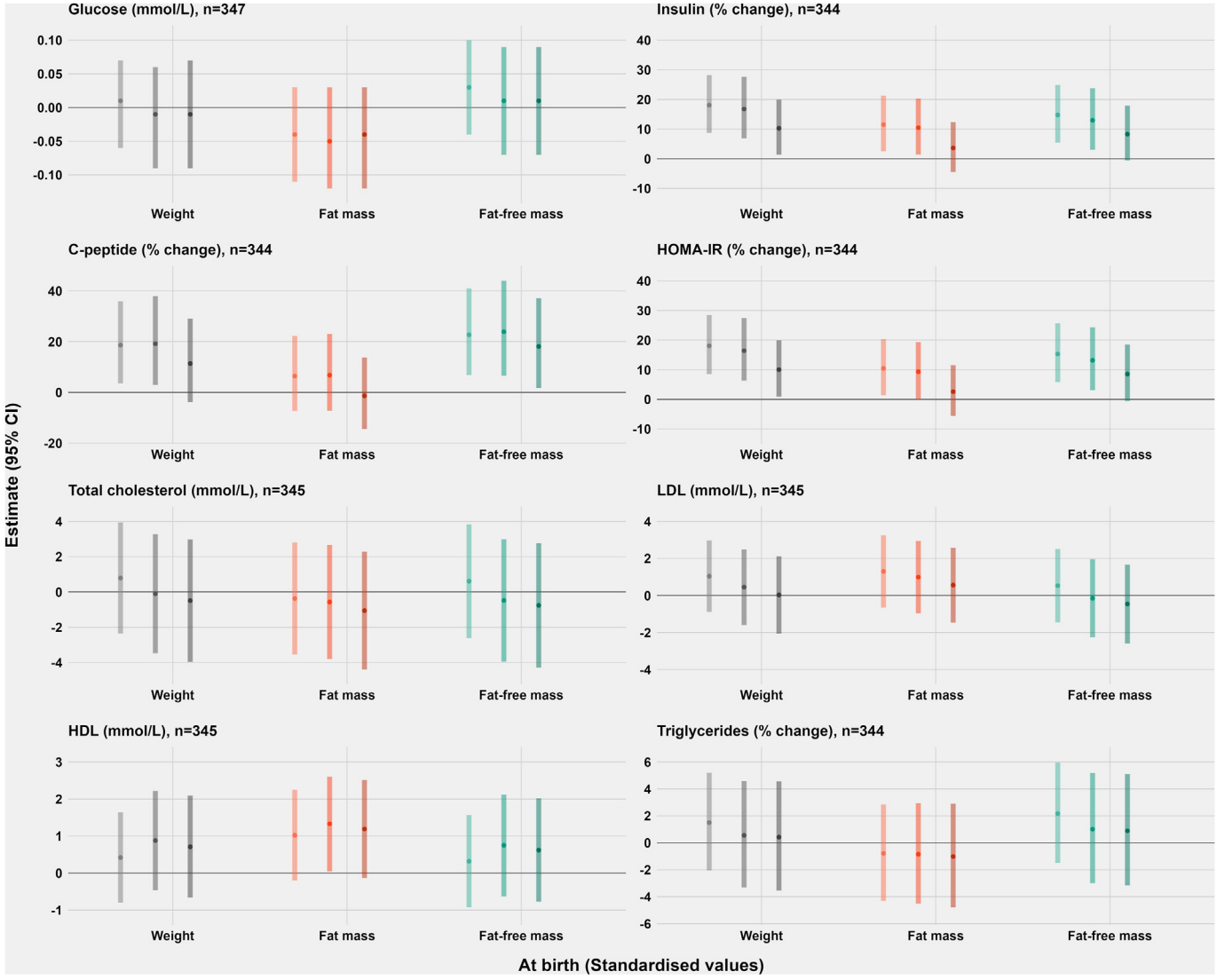

FIGURE 3. Associations of birth weight, birth fat mass, and birth fat-free mass with cardiometabolic markers at 10 y. The exposure variables (weight, fat mass, and fat-free mass) at birth were standardized before the regression analyses. The coefficients with 95% CI were derived from separate multiple linear regression analyses and represent the change in the outcome variables per 1-SD higher value of the exposure variables. The skew variables [insulin, C-peptide, homeostasis model assessment of insulin resistance (HOMA-IR), and triglycerides] were log-transformed before the regression analyses, and the estimates of these variables were back-transformed and presented as percentage changes. We ran 3 separate models for each outcome, and the vertical bars from left to right represent models 1, 2, and 3, respectively. Model 1 was adjusted for child's sex and age at 10-y follow-up. Model 2 was additionally adjusted for childbirth order, gestational age at birth, maternal age at delivery, maternal height, maternal educational status at delivery, and family economic status. Model 3 was further adjusted for current fat mass.

The mechanisms linking birth size with later glucose metabolism are poorly understood. Possible candidates include epigenetic and transcriptional mechanisms, cellular stresses, metabolic adaptations, alterations to the microbiome, and social determinants. Epigenetic mechanisms may commence through perinatal insults that may have long-lasting implications on gene expression in postnatal life, resulting in metabolic disease [58]. For example, epigenetic modifications have been found in target tissues of insulin such as skeletal muscle and adipose tissue of people with T2D [59]. These modifications include altered DNA methylation, which has been found in candidate genes of T2D and myoblasts and adipose tissue of people with obesity [59,60].

By contrast, the contribution of endoplasmic reticulum stress to metabolic disease may be greater during postnatal than prenatal life [58]. Our findings that higher BFFM was associated with insulin, C-peptide, and HOMA-IR independent of current FM were unexpected because FFM compartment is the primary source of energy expenditure and glucose uptake. The biological mechanism linking higher BFFM with greater insulin, C-peptide, and HOMA-IR is also unclear. It may indicate functional characteristics or intramyocellular accumulation of lipids [53] and/or an imbalance in the glycolytic to oxidative enzymatic capacities [61]. Other studies have also linked higher FFM with adverse cardiometabolic outcomes [21,62].

At 5-y follow-up of the iABC cohort, BW, BFM, and BFFM were not associated with insulin, C-peptide, and HOMA-IR. However, positive associations were observed between weight velocity after 4 y and insulin, C-peptide, and HOMA-IR [23,41]. Thus, the findings of this study indicate that the association of BW, BFM, and BFFM with glucose metabolism becomes noticeable after 5 y. In contrast to our findings, studies conducted in middle-income countries and HICs

found inverse associations of BW with insulin and HOMA-IR in childhood after adjusting for current body size [13,63].

We found a positive association between BFM and HDL cholesterol in model 2 after accounting for child and maternal characteristics at birth; however, when further adjusted for current FM, the effect estimate was attenuated. In the iABC birth cohort, we have previously shown positive associations of BFM and fat accretion from 0 to 3 mo with HDL cholesterol at 5 y [23], indicating that children born with higher BFM have greater HDL cholesterol in childhood, a more favorable lipid profile. Correspondingly, some birth cohort studies found no association between BW and HDL cholesterol [13,19], whereas others reported positive associations [12,64]. Difference in nutritional status of the population and age variabilities could be the reasons for the difference between our study findings and other studies.

In contrast to our follow-up of the iABC cohort at 5 y, in this study, BFM was not associated with total or LDL cholesterol, suggesting that those children with higher BFM are not at increased risk of dyslipidemia at 10 y of age. At 5 y, children in this cohort showed higher FM than those in the UK reference data [23], and higher FM accumulation has been associated with greater cholesterol concentrations in childhood [65]. By contrast, at 10-y follow-up, these children showed lower FM and FFM than those in the UK and United States reference data [66,67]. Compared with body composition reference data from the United Kingdom, the deficit in FFM for girls and boys were 4.39 and 3.98 kg, respectively, whereas the deficit in FM for girls and boys were 2.89 and 0.80 kg, respectively. Thus, the lower accumulation of FM between 5 and 10 y of age might explain the lack of association between BFM and LDL cholesterol in this follow-up.

One strength of this study is that we have detailed body composition measurements using ADP both at birth and at the 10-y follow-up. In addition, 62% of the children were kept in the cohort at 10 y after birth and could be identified for future follow-up studies. Supplemental Table 4 describes strategies we used to retain the participants in the follow-up study. However, this study has several limitations. First, owing to the observational nature of the study, it is not possible to ascertain cause-effect relationship, and therefore, the observed associations should be interpreted cautiously. Second, maternal characteristics before and during pregnancy, such as intrauterine factors, and child factors such as breastfeeding, dietary pattern in infancy and childhood, physical activity, potential diseases/alterations, and medications might have confounded the observed associations of BW, BFM, and BFFM with the outcome variables at 10 y. However, we have controlled for maternal and child characteristics at birth and family economic status. Another limitation of this study is that 9 children who provided nonfasting blood samples were included in the main analyses. However, we performed a sensitivity analysis without those children, and the results of sensitivity analyses showed similar associations with the main analyses (Supplemental Table 5). Finally, the inclusion criteria were restricted to mothers living in Jimma town with term healthy children. Therefore, the findings of this study may only be generalized to urban settings of Ethiopia and other sub-Saharan African urban settings with similar socioeconomic background.

Conclusions

The findings of this birth cohort study showed that the BW components, BFM and BFFM, play important and different roles in predicting anthropometric measurements, body composition, abdominal fat, and cardiometabolic markers. Greater BW and BFFM are associated with higher height, FFMI, fasting insulin, and HOMA-IR, whereas higher BFM is associated with greater FMI, SAT, and HDL cholesterol at 10 y. However, this study needs to be interpreted cautiously until further research confirm these findings. Further studies exploring the causal pathways leading to metabolic health at 10 y are also fundamental to understand better these associations and dismiss residual confounding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.06.010.

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