Journal of Developmental Origins of Health and Disease (2016), **7**(2), 132–143.

doi:10.1017/S2040174415007953
Themed Issue: Developmental Origins of Health and Disease: Importance of research for Africa

ORIGINAL ARTICLE

Relationship between early growth and CVD risk factors in adolescents

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Low birth weight and a rapid weight gain in early childhood may lead to an increased risk for developing cardiovascular disease later in life, such as hypertension and dyslipidaemia. In this study, we examined the associations between size at birth, relative weight gain in infancy and childhood with specific cardiovascular disease risk factors in early adulthood. Adolescents (n = 1935) from the Birth to Twenty plus (BT20+) cohort were included in the analysis. The following were treated as exposure variables: weight at birth, and relative conditional weight gain (CW), independent of height, between ages 0–24 months and 24–48 months. Outcomes were serum lipids and body composition variables at age 18 years. After adjusting for sex and other confounders, early life exposures were not associated with adolescent lipid profile. Following adjustment for sex and height (body size), birth weight [β = 0.704 (0.40, 1.01)], CW 0–24 [β = 1.918 (1.56, 2.28)] and CW24–48 [β = 1.485 (1.14, 1.82)] accounted for 48% of the variance in fat mass. However, birth weight [β = 0.773 (0.54, 1.01)], CW 0–24 [β = 1.523 (1.24, 1.80)] and CW24–48 [β = 1.226 (0.97, 1.49)] were also positively predicted and accounted for 71% of the variance in fat mass in adolescence ($P < 0.05$). Our data suggests that birth weight and weight gain during infancy and early childhood independent of linear growth are related to adolescent body composition but not blood lipid profiles in an urban African population.

Received 13 July 2015; Revised 15 October 2015; Accepted 12 November 2015; First published online 26 January 2016

Key words: birth weight, body composition, cardiovascular risk, developmental origins of adult disease, lipids

Introduction

Associations between growth patterns in early life and the development of non-communicable diseases (NCDs) such as hypertension, stroke, type 2 diabetes, obesity and cardiovascular disease have been reported by numerous studies, mainly from high-income countries.[1–5] The first series of epidemiological studies by Barker *et al.* suggested a strong link between fetal growth, birth weight and cardiovascular disease in adulthood.[6,7] One of such studies showed a strong inverse relationship between low birth weight and altered lipid metabolism, a risk marker for cardiovascular disease, in adulthood.[8] Adults who had a small body size (low birth weight and abdominal circumference) at birth presented raised serum concentrations of total and low-density lipoprotein (LDL) cholesterol in adulthood.[8] Serum cholesterol concentrations and LDL cholesterol increased by 0.25 mmol/l (95% confidence interval 0.09–0.42) and 0.26 mmol/l (0.11–0.42), respectively, with each 1-inch decrease in abdominal circumference at birth.[8] Similar results have been reported in other high-income settings,[9–12] however; only a few studies have examined these associations in African populations.[13–15]

Body composition (fat and fat-free mass) has been shown be an independent predictor of cardio-metabolic health in later adult life.[16,17] Evidence suggests adults who were low birth weight tend to have a disproportionately high ratio of fat to fat-free mass if they were overweight.[18] Comparable data from both low and high-income countries that examined the relationships between birth weight and adult body composition showed a positive association between birth weight and later fat-free mass but a weak or non-significant association with later fat mass.[19–22]

A number of studies showed positive associations between early postnatal growth patterns and later cardio-metabolic disease risk in pre-pubertal children. A study in a Dutch population showed that a rapid weight gain in the first year of life was negatively associated with risk factors such as insulin sensitivity, serum high-density lipoprotein (HDL) cholesterol and was positively associated with level of triglycerides in early adulthood. Furthermore, rapid weight gain during the first 3 months of life resulted in a higher percentage of body fat, more central adiposity and reduced insulin sensitivity in early adulthood (21 years) than when slower weight gain occurred during the entire first year.[23] Similarly, other studies have shown a positive association of infant weight gain with enlarged waist circumference and increased fat mass[24] and other risk factors like fasting insulin concentration, basal lipid levels and systolic blood pressure in individuals born small for gestational age.[25]

In South Africa, the rapid and complex health transition over the past 2 decades has been accompanied by the triple burden of disease (HIV and AIDS, malnutrition-related infectious and non-communicable diseases).[26] Owing to the adverse early life environment and subsequent nutritional excess in late childhood

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and adulthood, cardio-metabolic disease risk is high in both urban and rural parts of the country.[27–29] Age-standardized prevalence of NCDs such as hypertension and hypercholesterolemia (total cholesterol >5 mmol/l) have been reported to be 27.1 and 35.5%, respectively.[27,28] Furthermore, adult mortality rates from hypertensive heart disease (20%) and ill-defined heart diseases (23%) between 1999 and 2006 are high in South Africa.[30]

Studies in the Soweto region of Johannesburg, South Africa have reported on the associations between early growth and adult outcome variables such as blood pressure,[31] body composition[29,32] and glucose metabolism[33] but no data are available on associations between early life exposures to lipid concentrations. In studies where associations between birth weight and lipids have been shown, it remains unclear whether these might be a direct effect of under nutrition coupled with changes in body size during infancy and childhood.[34] Using data from the Birth to Twenty Plus (BT20+) cohort, we aimed to assess how birth weight and childhood weight gain are associated with adult cardio-metabolic disease risk factors including serum lipid profiles and body composition (fat mass, fat free mass and fat-to-fat free mass ratio) in an urban African adolescent population undergoing a health transition.

Research design and methods

Study population

The sample for this study was drawn from the BT20+ cohort study in Soweto area of Johannesburg, South Africa. The cohort comprises of children followed up since birth (23 April to 9 June 1990) from which information on birth, growth and a number of other characteristics have been recorded till date.[35–38] Follow-up was done telephonically or through field visits and contact with parents/caregivers and participants were maintained between data collection time points by newsletters and birthday cards. The original aim, design and recruitment of the BT20 cohort are explained in detail elsewhere.[36,37]

At age 18, male and female subjects ($n = 1935$) who were free of congenital skeletal deformations, Down's syndrome, chromosomal abnormalities, multiple congenital deformations, or inborn errors of metabolism were invited for a follow-up visit where anthropometric measures and venous serum samples were drawn. There were no significant differences between the study sample and the excluded participants with respect to key socio-demographic variables (See Table 1A).

Informed consent was obtained from the participants before the study and the Human Research Ethics Committee of University of the Witwatersrand, South Africa granted ethical clearance (M111182).

Exposures

Weight at birth, 12, 24 and 48 months

Birth weight was obtained from the participants' birth records measured by fully trained staff using hospital scales. Low birth weight was defined as a weight at birth of <2500 g, as set internationally by the World Health Organization (WHO). Research staff using standardized methods took weight measurements at infancy and childhood. Weight was measured to the nearest 0.1 kg using a digital scale (Dismed, USA) and height was measured to the nearest 1 mm using a wall-mounted stadiometer (Holtain, UK) in the Frankfort horizontal plane. These measurements were used to calculate the body mass index [BMI (weight (kg)/height (m^2)] of each individual.

Conditional weight independent of length/height

Examining the consequences of weight gain at different ages requires statistical methods to address the high correlation of weight with length, and of repeated measurements in the same individual over time.

Our conditional size measures are standardized residuals derived from regressing size at that age (represented as Fisher–Yates transformed weight or length/height Z-scores) on all prior size measures.[28,29] Relative conditional weight gain (CW) is current weight accounting for current height and all prior weight and height measures. For example, CW at age 2 years (48 months) derives from regressing age 2 weight on age 2 length, weight and length at age 1 year, and BW. Conditional variables represent children's deviation from expected size based on their own prior measures and on the growth of the other children in each cohort, and can be interpreted as representing faster or slower relative weight gain. For example, a child with a positive value for mid-childhood CW is weighs more than expected given his or her prior weight and size and thus had a faster rate of relative weight gain from age 2 to mid-childhood.

Outcome variables

Dual-energy X-ray absorptiometer (DXA)-derived body composition

Total body fat (FM) and fat-free mass (FFM) were measured by DXA scans performed according to standard procedures using a Hologic QDR 4500A dual-energy X-ray absorptiometry (Hologic Inc., Bedford, USA).

Lipid profiles

Serum from fasting blood samples were centrifuged at 200 ***g*** for 20 min at 4°C and aliquots were stored at −70°C until assayed. Total cholesterol (TC), HDL cholesterol, LDL cholesterol and triglyceride (TG) concentrations were measured by an auto-analyzer (Randox Daytona Clinical Analyzer Randox Laboratories, UK) using enzymatic methods. Coefficients of variance for all analyses were <8%.

Statistical analysis

All analyses were conducted using the STATA 12 statistical software. All data are presented as mean (S.D.) and percentages for continuous and categorical variables, respectively.

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press

t-Independent tests were used to compare early life characteristics (birth weight, weight at 12, 24 and 48 months) and adult cardiovascular disease risk factors ((i) body composition variables: fat mass, fat free mass and fat to fat-free ratio (ii) lipid profile: HDL, LDL, TC, TG (iii) blood pressure) between groups (sex and birth weight categories). Bivariate and multiple linear regression models were computed and fitted for early life anthropometric characteristics and childhood weight gain using conditionals (independent variables) on the following adolescent cardiovascular disease risk factors (dependent variables): (i) body composition variables: fat mass, fat-free mass and fat to fat free mass ratio (ii) lipid profile: HDL, LDL, TC, TG. Regression data are presented as β (95%CI) and R^2 values. All statistical significant results were defined using a two-tailed $P < 0.05$. Multiple linear regressions were adjusted for several confounders including wealth quantile index, breastfeeding duration, sex and height at 18. The wealth quantile index was derived from the total household assets score which was grouped into quantiles from the poorest (1) to the wealthiest (5) and breastfeeding duration.

Results

Table 1 presents early life and adolescent variables including cardiovascular disease risk factors (body composition, serum lipid concentrations, blood pressure) by sex as means (S.D.). The following early life variables were significantly higher in the boys as compared to the girls ($P < 0.05$): birth weight [3.1 (0.5) *v.* 3.0 (0.5)], weight at 12 months [9.7 (1.4) *v.* 9.2 (1.4)], weight at 24 months [11.5 (1.4) *v.* 11.2 (1.4)] and weight at 48 months [15.7 (1.9) *v.* 15.3 (2)]. Weight, height, systolic blood pressure and fat free mass at 18 years were significantly higher in the boys while BMI, waist circumference, HDL, LDL, TC, FM and FM/FFM ratio were significantly higher in the girls ($P < 0.05$). Low birth weight males and females accounted for 9.3 and 12.4% of the sample, respectively. In addition, the prevalence of risk, as per the National Cholesterol Education Program (NCEP), for each lipid profile indicator was: TC (4.8%), HDL (8.1%); LDL (2.2%) and TG (1.3%).

Table 2 compares early life and adult characteristics including cardio-metabolic disease risk factors by birth weight categories. As expected, all early life variables including birth weight, weights at 12, 24 and 48 months were significantly higher in the NBW group as compared to the LBW group ($P < 0.05$). The following anthropometric variables at age 18: weights, adult height, BMI, adult waist circumference were significantly higher in the NBW group as compared with the LBW group ($P < 0.05$). The lipid profiles (HDL, LDL, total cholesterol, triglycerides) were not statistically different between the two birth weight categories. For all body composition variables at age 18, only FFM was significantly higher in the NBW group as compared to the LBW group [41.5 (7.3) *v.* 45.2 (8.6) $P < 0.05$].

Table 1. *Baseline early life characteristics and adult cardiovascular disease risk factors by gender*

Early life variables	Males (n = 1591)	Females (n = 1682)	P-value
Birth weight (kg)	3.1 (0.5)	3.0 (0.5)	0.0000
Weight at 12 months (kg)	9.7 (1.4)	9.2 (1.4)	0.0000
Weight at 24 months (kg)	11.5 (1.4)	11.2 (1.4)	0.0000
Weight at 48 months (kg)	15.7 (1.9)	15.3 (2)	0.0000
	%	%	
Low birth weight	9.3	12.4	
Adult life variables	Males (n = 933)	Females (n = 1002)	
Age (years)	18.1 (0.54)	18.1 (0.52)	0.27
Weight (kg)	60 (11.1)	58.4 (12.1)	0.002
Height (cm)	170.9 (7.5)	159.7 (6.3)	0.000
BMI (kg/m^2)	20.5 (3.5)	22.9 (4.5)	0.000
Waist circumference (cm)	72.7 (7.7)	75.4 (10.5)	0.0000
Fat mass (kg)	8.7 (5)	19.4 (7.7)	0.000
Fat-free mass (kg)	51 (6.7)	39.0 (5.4)	0.000
Fat mass/fat-free mass ratio	0.2 (0.1)	0.5 (0.2)	0.000
High-density lipoprotein (mmol/l)	1.1 (0.3)	1.1 (0.3)	0.003
Low-density lipoprotein (mmol/l)	1.6 (0.7)	1.8 (0.8)	0.000
Total cholesterol (mmol/l)	3.5 (0.9)	3.8 (0.9)	0.000
Triglycerides (mmol/l)	0.8 (3.5)	0.7 (0.3)	0.3

N, number; BMI, body mass index.
All values except birth weight are mean (S.D.) (P values based on independent t-test).
Significant difference based at level $P < 0.05$.

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press

Table 2. *Baseline early life characteristics and adult cardiovascular disease risk factors by birth weight category*

	LBW (<2.5 kg) (n = 352)	NBW (⩾2.5 kg) (n = 2915)	P-value
Early life variables			
Birth weight (kg)	2.1 (0.4)	3.2 (4.9)	0.0000
Weight at 12 months (kg)	8.7 (1.3)	9.7 (1.4)	0.0000
Weight at 24 months (kg)	10.7 (1.3)	11.4 (1.4)	0.0000
Weight at 48 months (kg)	14.3 (1.8)	15.6 (2.0)	0.0000
Adult life variables			
Weight (kg)	55.1 (10.3)	59.7 (11.7)	0.0000
Height (cm)	161.5 (8.5)	165.6 (8.8)	0.0000
BMI (kg/m^2)	21.2 (4.1)	21.8 (4.2)	0.04
Waist circumference (cm)	72.3 (8.9)	74.3 (9.4)	0.0000
Fat mass (kg)	13.4 (7.4)	14.3 (8.5)	0.15
Fat-free mass (kg)	41.5 (7.3)	45.2 (8.6)	0.0000
Fat mass/fat-free mass ratio	0.34 (0.2)	0.33 (0.2)	0.65
High-density lipoprotein (mmol/l)	1.1 (0.3)	1.1 (0.3)	0.297
Low-density lipoprotein (mmol/l)	1.7 (0.7)	1.7 (0.7)	0.86
Total cholesterol (mmol/l)	3.7 (1.0)	3.6 (0.9)	0.44
Triglycerides (mmol/l)	0.7 (0.3)	0.73 (2.6)	0.74

N, number; BMI, body mass index; LBW, low birth weight; NBW, normal birth weight.
All values except birth weight are mean (S.D.) (P values based on independent t-test).
Significant difference based at level $P < 0.05$.

Table 3 presents bivariate linear regression coefficients β (95% CI) and r^2 values by sex for each of the early life variables (birth weight, weight at 12, 24 and 48 months) for FM, FFM, FM/FFM ratio at age 18. CWs (conditional weight gain z-scores independent of height) were positively associated with body composition ($P < 0.05$) in both sexes, except that birth weight in the females did not significantly predict adult FM/FFM ratio.

Table 4 shows multivariate linear regression coefficients β (95% CI) and r^2 values for CW during childhood adjusted for sex, socioeconomic class and breastfeeding duration (6 months). All early life variables were significantly and positively predictive of FM, FFM and FM/FFM ratio, respectively ($P < 0.05$). After adjusting for adolescent height (body size), socioeconomic class and breastfeeding duration (Table 4), the associations with early life variable and fat mass and fat free mass ($P < 0.05$) strengthened.

Table 5 shows bivariate linear regression coefficients β (95% CI) and r^2 values by sex for each of the early life variables (birth weight, weight at 12, 24 and 48 months) for serum lipids (HDL, LDL, TC and TG) at age 18. In males, the only associations between early life variables and serum lipids at age 18 were found between birth weight and HDL and weight at 48 months and HDL. For every 1 kg increase in birth weight, HDL concentration decreased by 0.06 mmol/l ($P < 0.05$). Similarly, for each 1kg increase in weight at 48 months was associated with a decrease in HDL levels by 0.01 mmol/l ($P < 0.05$). There were no associations between early life variables and serum LDL, TC, TG concentrations at age 18. In females, early life variables were not associated with serum lipid levels at age 18.

Table 6 presents multivariate regression coefficients β (95% CI) and r^2 values for CW during childhood and for serum lipids at age 18. Data were adjusted for sex, socioeconomic class and breastfeeding duration. CW 0–12 months, CW 12–24 months, CW 24–48 months were not associated with any of the lipid outcomes. Sex was the only factor significantly predicting LDL [β = 0.203, (0.098, 0.307)] and TC [β = 0.285, (0.156, 0.413)] in that being female had higher concentrations. After adding adolescent height to the model, being female was still the only factor significantly predicting lipid profiles but only for LDL and TC (Supplementary Table S1). When fat mass was added to the model, only sex was positively associated with HDL [β = 0.06, (0.001, 0.119)] and TC [β = 0.215, (0.037, 0.393)] (Supplementary Table S2).

Discussion

We investigated the association between birth weight, weight in infancy and mid-childhood and body composition and lipid profiles in black South African adolescents. The positive association between birth weight and childhood rapid relative weight gain and later metabolic disease risk, such as impaired fasting glucose,[33] and blood pressure[31] have been previously demonstrated in the BT20+ cohort. However, early life factors and its relationship with lipid profiles have not been previously studied. Our data indicated that by age 18 years there was a low but emerging prevalence of dyslipidaemia risk, but unlike in other population studies, birth weight, childhood weight and relative weight gain had little to no association with lipid outcomes in late adolescence. However, early life factors were associated with body composition indices.

Early life factors and adult body composition

Although early life factors strongly predicted both adult FM and FFM after adjusting for height at age 18, the fact that a larger percentage of the variance in FFM was explained by these exposures suggests that birth weight, a proxy for poor fetal growth, might programme FFM in later life. Additionally, the findings that lower birth weight individuals had lower FFM in comparison to normal birth weight individuals might explain the significant weight differences seen at age 18. But, despite differences in total weight and size, FM/FFM ratio as not different between low and normal birth weight groups. Earlier studies have shown conflicting associations between birth weight and adult body composition. Although a high birth weight is usually linked to a greater BMI in later life, it has also been linked to a reduced adiposity.[39] Data from a study in

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press

Table 3. *Bivariate regression coefficients for early life variables and body composition at age 18 years*

		Fat mass (kg)			Fat-free mass (kg)			Fat mass:fat-free mass		
Gender	Variables	β (95% CI)	*P* value	r^2	β (95% CI)	*P*-value	r^2	β (95% CI)	*P*-value	r^2
Males	Birth weight (kg)	1.499 (0.864–2.135)	0.000	0.02	3.764 (2.944–4.585)	0.000	0.08	0.015 (0.004–0.026)	0.008	0.01
	Weight at 12 months (kg)	1.054 (0.731–1.377)	0.000	0.09	1.952 (1.541–2.364)	0.000	0.17	0.136 (0.008–0.019)	0.000	0.05
	Weight at 24 months (kg)	1.031 (0.780–1.282)	0.000	0.08	1.976 (1.673–2.278)	0.000	0.19	0.012 (0.008–0.017)	0.000	0.04
	Weight at 48 months (kg)	1.048 (0.872–1.224)	0.000	0.16	1.864 (1.657–2.072)	0.000	0.30	0.013 (0.010–0.016)	0.000	0.08
	CWG 0–24 months	0.869 (0.452–1.285)	0.000	0.03	1.468 (0.950–1.986)	0.000	0.05	0.113 (0.004–0.019)	0.000	0.02
	CWG 24–48 months	1.113 (0.692–1.534)	0.000	0.05	0.775 (0.247–1.302)	0.004	0.01	0.019 (0.011–0.026)	0.000	0.04
Females	Birth weight (kg)	1.976 (0.989–2.963)	0.000	0.02	2.512 (1.838–3.186)	0.000	0.05	0.017 (−0.002 to 0.037)	0.086	0.00
	Weight at 12 months (kg)	1.978 (1.509–2.451)	0.000	0.13	1.737 (1.410–2.067)	0.000	0.18	0.024 (0.015–0.035)	0.000	0.05
	Weight at 24 months (kg)	2.188 (1.814–2.562)	0.000	0.15	1.990 (1.737–2.242)	0.000	0.24	0.027 (0.019–0.035)	0.000	0.06
	Weight at 48 months (kg)	1.613 (1.374–1.853)	0.000	0.18	1.567 (1.411–1.723)	0.000	0.33	0.019 (0.014–0.024)	0.000	0.06
	CWG 0–24 months	2.485 (1.924–3.045)	0.000	0.10	1.548 (1.141–1.955)	0.000	0.08	0.040 (0.029–0.052)	0.000	0.07
	CWG 24–48 months	1.540 (0.972–2.117)	0.000	0.04	0.998 (0.578–1.418)	0.000	0.03	0.025 (0.014 -0.036)	0.000	0.03

β, beta coefficient; r^2, square of the Pearson correlation coefficient; CI, confidence interval; CWG, conditional weight gain.
Significant difference based at level $P < 0.05$.

Table 4. *Multivariate regression coefficients for relative weight gain in early life and body composition at age 18 years adjusted for sex, socioeconomic class, adult height and breastfeeding duration*

	Fat mass (kg)		Fat free mass (kg)		Fat mass:fat free mass	
Variables	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
(A) Adjusted for sex, socioeconomic class and breastfeeding duration						
Birth weight (z-score)	0.751 (0.445–1.057)	0.000	1.530 (1.221–1.838)	0.000	0.006 (−0.001 to 0.012)	0.098
CWG 12–24 months	1.936 (1.571–2.316)	0.000	1.732 (1.385–2.080)	0.000	0.029 (0.022–0.037)	0.000
CWG 24–48 months	1.480 (1.113–1.826)	0.000	1.157 (0.825–1.489)	0.000	0.025 (0.018–0.032)	0.000
Sex	10.51 (9.799–11.222)	0.000	−12.04 (−12.73 to 11.35)	0.000	0.322 (0.307–0.337)	0.000
r^2	0.49		0.59		0.67	
(B) Adjusted for sex, adult height, socioeconomic class and breastfeeding duration						
Birth weight (z-score)	0.660 (0.310–1.010)	0.000	0.973 (0.704–1.007)	0.000		
CWG 12–24 months	1.866 (1.480–2.252)	0.000	1.503 (1.207–1.799)	0.000		
CWG 24–48 months	1.633 (1.265–2.002)	0.000	1.304 (1.021–1.586)	0.000		
Sex	10.75 (10.76–12.73)	0.000	−7.425 (−818 to 6.668)	0.000		
Adult height	0.10 (0.047–0.159)	0.007	0.413 (0.370–0.456)	0.000		
r^2	0.50		0.71			

β, beta coefficient; r^2, square of the Pearson correlation coefficient; CI, confidence interval; CWG, conditional weight gain.
Significant difference based at level $P < 0.05$.

Table 5. *Bivariate regression coefficients (95% CI) for early life variables for serum lipids at age 18 years*

		High-density lipoprotein (mmol/l)			Low-density lipoprotein (mmol/l)		
Gender	Variables	β (95% CI)	*P*-value	r^2	β (95% CI)	*P*-value	r^2
Males	Birth weight (kg)	−0.055 (−0.097 to 0.012)	0.011	0.009	0.010 (−0.089 to 0.108)	0.846	0.000
	Weight at 12 months (kg)	−0.002 (−0.023 to 0.019)	0.880	0.000	−0.008 (−0.056 to 0.039)	0.728	0.000
	Weight at 24 months (kg)	−0.012 (−0.028 to 0.003)	0.127	0.004	−0.011 (−0.049 to 0.027)	0.569	0.001
	Weight at 48 months (kg)	−0.013 (−0.024 to 0.001)	0.030	0.008	0.008 (−0.019 to 0.036)	0.547	0.001
	CWG 0–24 months	−0.012 (−0.038 to 0.013)	0.338	0.002	−0.03 (−0.09 to 0.032)	0.342	0.002
	CWG 24–48 months	−0.003 (−0.029 to 0.023)	0.837	0.000	0.017 (−0.045 to 0.08)	0.588	0.001
Females	Birth weight (kg)	−0.002 (−0.045 to 0.041)	0.918	0.000	0.012 (−0.09 to 0.119)	0.819	0.000
	Weight at 12 months (kg)	0.021 (−0.001 to 0.044)	0.059	0.009	0.021 (−0.032 to 0.073)	0.443	0.002
	Weight at 24 months (kg)	0.004 (−0.013 to 0.022)	0.627	0.000	0.017 (−0.028 to 0.062)	0.452	0.001
	Weight at 48 months (kg)	0.005 (−0.006 to 0.017)	0.346	0.001	0.005 (−0.024 to 0.034)	0.737	0.000
	CWG 0–24 months	0.004 (−0.022 to 0.031)	0.736	0.000	0.044 (−0.022 to 0.110)	0.188	0.003
	CWG 24–48 months	−0.003 (−0.029 to 0.023)	0.831	0.000	−0.042 (−0.107 to 0.023)	0.207	0.003
		Total cholesterol (mmol/l)			Triglycerides (mmol/l)		
Gender	Variables	β (95% CI)	*P*-value	r^2	β (95% CI)	*P*-value	r^2
Males	Birth weight (kg)	−0.084 (−0.209 to 0.042)	0.193	0.0023	0.064 (−0.45 to 0.576)	0.807	0.0001
	Weight at 12 months (kg)	0.033 (−0.032 to 0.097)	0.317	0.003	0.035 (−0.333 to 0.403)	0.850	0.0001
	Weight at 24 months (kg)	0.007 (−0.041 to 0.055)	0.779	0.0001	0.104 (−0.117 to 0.325)	0.356	0.0015
	Weight at 48 months (kg)	0.006 (−0.029 to 0.041)	0.732	0.0002	0.077 (−0.08 to 0.238)	0.349	0.0015
	CWG 0–24 months	−0.003 (−0.08 to 0.077)	0.947	0.000	0.19 (−0.200 to 0.581)	0.339	0.0019
	CWG 24–48 months	0.014 (−0.067 to 0.09)	0.734	0.0003	0.271 (−0.138 to 0.680)	0.194	0.0039
Females	Birth weight (kg)	0.007 (−0.122 to 0.136)	0.913	0.000	−0.026 (−0.074 to 0.022)	0.289	0.0014
	Weight at 12 months (kg)	0.059 (−0.008 to 0.126)	0.082	0.008	−0.003 (−0.027 to 0.021)	0.793	0.0002
	Weight at 24 months (kg)	0.032 (−0.214 to 0.085)	0.241	0.0022	0.003 (−0.017 to 0.023)	0.761	0.0001
	Weight at 48 months (kg)	0.020 (−0.015 to 0.054)	0.261	0.0019	0.004 (−0.009 to 0.017)	0.550	0.0005
	CWG 0–24 months	0.061 (−0.017 to 0.139)	0.128	0.0043	0.022 (−0.005 to 0.049)	0.115	0.0046
	CWG 24–48 months	−0.026 (−0.104 to 0.051)	0.504	0.0009	−0.005 (−0.032 to 0.022)	0.715	0.0003

β, beta coefficient; r^2, square of the Pearson correlation coefficient; CI, confidence interval; CWG, conditional weight gain.
Significant difference based at level $P < 0.05$.

twins also contradicts the notion that fetal growth might influence on later adiposity by showing that difference in birth weight was related to differences in later height but not BMI.[31] These inconsistent findings could be explained in part by the use of surrogate measures of obesity (BMI) rather than DXA-derived whole body composition. Alternatively, birth weight in other populations has been shown to be positively associated with adult FFM, and indicate that lower birth weight individuals are at a higher predisposition for cardiovascular disease.[22,40] Rapid changes in childhood weight also predict body composition in adulthood and represent an important pathway by which early life might influence adult chronic disease risk.[1,41–44] Previously published data from LMIC cohort studies have similar findings with those reported here, however none of studies relied on the use of CWs and simultaneous modelling of FM and FFM in their analyses. Data from the Cebu Philippines cohort showed that weight gain between 0 and 6 months was a strong predictor of FFM and muscle strength in males but not females.[45] In India, rapid increases in BMI during infancy and early childhood were more related to adult FFM than with adiposity or central adiposity, whereas rapid increases in BMI during late childhood or adolescence were associated more with increased adult adiposity and central adiposity.[21] In a Guatemalan cohort, BMI in infancy and later childhood was positively associated with adult BMI, percentage body fat, abdominal circumference, and FFM; from mid-childhood these associations were stronger with BMI, percentage body fat, and abdominal circumference than with FFM.[46] Studies from high-income populations such as the UK[47,48] and Sweden[24] have also report similar findings showing that rapid weight gain during infancy predicts an adverse metabolic risk profile and body composition in adulthood. In summary, our findings initially seems to suggest that low birth weight might result in the programming of a lower fat free mass later in life which could have implications for adult disease as skeletal muscle is important for glucose uptake in response to insulin and less lean tissue mass might compromise insulin sensitivity. But examining the FM/FFM ratio it would appear that birth weight is more of an indicator of size with minimal impact on FM and FFM. However, rapid relative weight gain in infancy

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press

Table 6. *Multivariate regression coefficients for weight gain in early life and serum lipids at age 18 years, adjusted for sex, socioeconomic class and breastfeeding duration*

	High-density lipoprotein (mmol/l)		Low-density lipoprotein (mmol/l)		Total cholesterol (mmol/l)		Triglycerides (mmol/l)	
Variables	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Birth weight (z-score)	−0.008 (−0.028 to 0.008)	0.394	0.011 (−0.036 to 0.056)	0.639	0.018 (−0.04 to 0.076)	0.548	0.007 (−0.012 to 0.272)	0.488
CWG 0–24 months	−0.006 (−0.027 to 0.015)	0.563	−0.004 (−0.056 to 0.048)	0.888	0.006 (−0.058 to 0.071)	0.842	0.010 (−0.012 to 0.032)	0.365
CWG 24–48 months	−0.005 (−0.026 to 0.015)	0.613	−0.011 (−0.061 to 0.039)	0.662	−0.016 (−0.078 to 0.046)	0.605	0.003 (−0.018 to 0.025)	0.767
Sex	0.029 (−0.014 to 0.071)	0.186	0.203 (0.098–0.307)	0.000	0.285 (0.156–0.413)	0.000	−0.011 (−0.056 to 0.033)	0.614
Adjusted r^2	0.007		0.018		0.026		0.000	

β, beta coefficient; r^2, square of the Pearson correlation coefficient; CI, confidence interval; CWG, conditional weight gain.
Significant difference based at level $P < 0.05$.

and childhood results in a great FM/FFM ratio. Sex was negatively correlated with FFM in our sample, and is in agreement with other studies,[45] being female was significantly correlated with a lower FFM and higher FM compared to males by age 18 years.

Relationship between body composition and lipids

The amount of body fat an individual accumulates in his/her life course is an important determinant of adult lipid and lipoprotein profiles.[49–52] BMI, as a proxy measure of adiposity, has mostly been used in adult studies and in adults, there is a strong positive association between BMI and TG, LDL and TC and a negative association with HDL cholesterol.[53] Such data must however be interpreted with caution as BMI does not distinguish between fat and fat-free tissues, both of which have distinct effects on lipid and lipoprotein levels. Data from a study conducted on healthy Caucasian men and women, participating in the Fels Longitudinal Study showed that increased FM contributed to elevated TG, LDL and TC concentrations and decreased HDL cholesterol levels. FFM on the other hand, was significantly associated with low HDL and high TG levels in both sexes.[54] In contrast to these studies, our study in adolescent urban African population showed that FM was only related to HDL concentrations. When adjusted for sex, our data showed that lower HDL and higher TC levels were related to females. Other studies in the Africans have also shown that lipids, with the exception of TG, were higher in adolescent females.[55–61]

Birth weight and differences in lipid profile

Associations between birth weight and other cardiovascular disease risk factors such as blood pressure and insulin resistance for example have been shown to increase with age,[62] although similar associations between lipid levels have not been suggested. From our data, birth weight was not associated with lipid outcomes after adjusting for current body size (height and fat mass) and does not support the fetal origins hypothesis in this population group. Studies investigating the relationship between birth weight and lipid concentrations in adolescents have demonstrated conflicting results with some studies.[63,64] A few studies from high-income settings have shown an association between low birth weight and high levels of total cholesterol[65] LDL cholesterol,[66] and lower levels of HDL cholesterol.[67] Data from some low-income settings have also shown similar trends.[68–70] In contrast, numerous studies show no association between low birth weight and lipid concentrations in young adults in both high and low income settings even after adjusting for confounders such as sex and current body size (waist circumference, weight, height and BMI).[59,61,71,72] The disparities between data in these studies may be due to various factors such as differences in study populations in terms of age, sex and ethnic or genetic background. In addition, although serum lipid concentrations are known to track from early childhood, it may be that the effects

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press

of an adverse prenatal influence emerge in later life. In a commentary to a review on the birth weight-adult lipid relationship,[73] Barker postulated that the effects of birth weight were being masked by the subsequent effects of infant feeding which have been shown to influence levels of total and LDL cholesterol in adult life.[74,75] Another suggestion was that intrauterine nutrition was probably a better indicator of future lipid profiles than birth weight. Irrespective of birth size, adults exposed to the Dutch famine *in utero* had higher levels of serum lipids in comparison to people not exposed to the same environment.[76] Similarly, a study involving Chinese men showed that elevated total and LDL cholesterol concentrations were related to low maternal body mass index in early pregnancy and not related to low birth weight.[77] Adult studies serum lipid concentrations have demonstrated strong inverse associations with abdominal circumference at birth and not birth weight.[8] A small abdominal circumference at birth also predicted death from congenital heart disease among men.[8] Few studies, including ours, incorporate this birth measurement in analyses. Measures of maternal nutrition could introduce valuable variables required for a better understanding of the developmental origins of elevated serum lipid concentrations.[75]

Early weight gain and adult lipids

Our data showed that birth weight, rapid relative weight gain in infancy, and between infancy and mid-childhood were not associated with lipid profiles outcomes in late adolescence. These findings differ from other studies, particular in high-income settings and of other population groups, which suggest that excessive weight gain during childhood may be determinant of adult cardiovascular risk, such as lipid concentrations.[58,74,76] In contrast to other ethnicities, Africans consistently appear to display an athero-protective lipid profiles even after adjusting for age, gender and BMI[78,79] and differences in the genetic basis of lipid metabolism between ethnic groups may explain these disparities.

Limitations

As this research in is not in an older population and does not include confounders such as alcohol consumption and smoking may be limitations of the current analyses. We aim to repeat the analyses with additional confounders (socioeconomic class, maternal pre-pregnancy weight, breastfeeding duration) when the cohort is in their later adulthood. We could not include maternal pregnancy weight as a confounder as this data was not collected in the cohort.

In conclusion, our observations suggest that although birth weight and weight gain during infancy and early childhood did not correlate with adolescent lipid profile in this population, they were related to adolescent body composition. The implication is that developmental origins of cardiometabolic disease in Africans may be differential to other population groups potentially due to genetic variation and susceptibility.

Acknowledgements

The authors would like to thank the Birth to Twenty plus staff, and the adolescents and parents of the BT20+ study for their participation.

Financial Support

The Wellcome Trust (UK) [grant number 092097/Z/10/Z], Human Sciences Research Council, National Research Foundation and the South African Medical Research Council and the University of the Witwatersrand, Johannesburg, supported this work. M.M., J.K. and S.N. were supported by the UK MRC/DfID African Research Leader Scheme.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the University of the Witwatersrand on Human Research Ethics Committee.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S2040174415007953

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Appendix

Table A1. *Differences between included and excluded study participants from BT20 cohort sample*

	n	Included	*n*	Excluded	*P*-value
Maternal height (cm)	855	158.8 (6.0)	57	158.3 (4.8)	0.549
Maternal age (years)	1015	25.59 (6.1)	172	26.52 (6.0)	0.060
Fat:lean mass ratio	1016	0.34 (0.2	61	0.37 (0.2)	0.205
Cholesterol (mmol/l)	1016	3.60 (0.9)	53	3.56 (1.0)	0.749
Participant age (years)	1016	18.0 (6.1)	71	18.1 (6.7)	0.072
Participant height (cm)	1016	165.03 (8.8)	69	163.53 (8.7)	0.174
Gender					
Male	488	48.03%	79	45.93%	0.610
Female	528	51.97%	93	54.07%	
Birth weight					
Low birth weight	102	10.04%	22	13.02%	0.241
Normal birth weight	914	89.96%	147	86.98%	

All values are expressed as mean (S.D.) (*P* values based on independent t-test) or n (%) from a χ^2 test. Significant difference based at level $P < 0.05$.

https://doi.org/10.1017/S2040174415007953 Published online by Cambridge University Press