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Body size and composition of Samoan toddlers aged 18–25 months in 2019

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ABSTRACT
Background: The "*Foafoaga O le Ola* (Beginning of Life)" study is a prospective birth cohort of $n = 160$ Samoan mother-infant dyads established in 2017–2018. A primary study aim is to explore how a missense variant at *CREBRF* rs373863828 impacts growth in early life, given its association with increased body size but lower risk of diabetes in adult Samoans. Here, we examine body size and composition by genotype among toddlers aged 18.7–24.5 months.
Methods: Height, weight, head circumference, mid-upper-arm circumference, and abdominal circumference, as well as subscapular, triceps, iliac crest and thigh skinfold thickness were measured among 107 toddlers with known rs373863828 genotype; 42 of these toddlers completed dual-energy X-ray absorptiometry (DXA) scans from which body composition (total body less head fat mass, lean mass, bone mass, % fat mass and % fat-free mass) was estimated.
Results: After controlling for sex and age, toddlers with at least one copy of the *CREBRF* minor allele (AA/AG) were 1.31 cm taller (SE = 0.64, $p = 0.045$) than toddlers with the GG genotype.
Conclusion: Whether greater linear growth in early childhood could contribute to the metabolically protective effects associated with the *CREBRF* variant in adulthood should be explored in future studies.

Background

Across the Pacific Islands, obesity prevalence has increased dramatically over the past several decades (Hawley and McGarvey 2015). A genome-wide association study in Samoan adults identified a missense variant in CREB3 regulatory factor (*CREBRF*) rs373863828, associated with increased BMI but decreased odds of type 2 diabetes mellitus (T2DM). Little is known about how the variant influences body composition and growth during critical periods of early development. Recently, Arslanian et al. (2021) reported no association between *CREBRF* genotype and birthweight among Samoan infants. However, the variant was associated with greater lean and bone mass at age 4 months. Here, we examine body size and composition by rs373863828 genotype among Samoan toddlers at age 18.7–24.5 months.

Sample

Participants belong to a prospective birth cohort of $n = 160$ Samoan mother-infant dyads (Arslanian et al. 2021). Mothers were recruited at 35–40 weeks gestation, and dyads participated in assessments at four time points: immediately after

birth (0–41 days) and at approximately 2 (1.8–3.4), 4 (3.6–6.5) and 21 (18.7–24.5) months. *CREBRF* genotyped toddlers ($n = 107$) who participated in the 21-month assessment are included in this analysis. Mothers gave written informed consent for participation. Protocols were approved by the Yale University Institutional Review Board (HIC #2000021076) and the Health Research Committee of the Samoa Ministry of Health.

Data collection

Toddler height was measured to the nearest 0.1 cm using a portable GPM anthropometer (Pfister Imports, USA) and weight to the nearest 0.1 kg using a digital weight scale (HD351, Tanita Corporation of America, USA). Left subscapular, triceps, iliac crest, and thigh skinfold thickness were measured using a Harpenden calliper (FG1056, UK). The sum of skinfolds was calculated as a proxy for subcutaneous fat. Head, left mid-upper-arm (MUAC), and abdominal circumference were measured using a standard tape measure (201, SECA, Germany). Abdominal circumference-to-height ratio was calculated as a proxy for abdominal visceral fat. All

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measurements were collected in duplicate and averaged for analyses.

Dual x-ray absorptiometry (DXA) scans were performed on toddlers wearing clean diapers and standardised clothing (Lunar iDXA, version enCORE 17, GE Healthcare Medicine, USA). Scans were aborted if movement artefacts interfered with scan readability. While obtaining DXA images of neonates is relatively straightforward, as they develop motor skills, avoiding movement artefacts becomes difficult until old enough to reliably follow directions. Thus, only 42 of 107 toddlers completed successful DXA scans. DXA-derived body composition outcomes were absolute total body less head (TBLH) fat, lean and bone mass, as well as percent (%) fat and fat-free (lean + bone) mass.

Data management and statistical analysis

Age- and sex- standardised z-scores were calculated using World Health Organisation Child Growth Standards (WHO Multicentre Growth Reference Study Group 2006). Depending on normality, independent two-sample t-tests or Mann-Whitney U tests were used to examine differences in anthropometric characteristics by DXA completion status. Multivariable linear regression was used to test whether CREBRF genotype was associated with body size and composition, controlling for age and sex. Non-parametric measures were normalised using box-cox transformations. Given the expected small sample size of toddlers with AA genotype, and because both AG and AA genotypes are associated with increased body size in Samoan adults (Minster et al. 2016; Carlson et al. 2020), AG and AA genotypes were pooled for all analyses, providing a comparison of toddlers with no copies of the variant (GG) versus those with at least one copy (AA or AG) (Arslanian et al. 2021). All analyses were conducted in RStudio version 1.2.1335 (www.rstudio.com). Reported probabilities are two-sided and the threshold for statistical significance was set at $\alpha = 0.05$.

Results

On average, Samoan toddlers were 0.82 standard deviations shorter and 0.56 standard deviations heavier than WHO standards (Table 1). After adjustment for sex and age, multivariable linear regression revealed the CREBRF variant was associated with 1.31 cm greater height (SE = 0.64, $p = 0.045$)

and 1.23 mm lower thigh skinfold thickness (SE = 0.49, $p = 0.014$). Other anthropometric measures did not vary significantly by genotype (Table 2).

DXA-scanned toddlers were 0.83 months younger (95%CI [0.26–1.45], $p = 0.006$), and were consequently 1.85 cm shorter (95%CI [0.62–3.09], $p = 0.004$), and 0.60 kg lighter (95%CI [0.05–1.20], $p = 0.04$) than unscanned toddlers. Scanned toddlers also had 0.90 mm thinner triceps skinfolds (95%CI [0.20–1.55], $p = 0.007$), 0.95 mm thinner iliac crest skinfolds (95%CI[0.25–1.70], $p = 0.005$), 1.20 mm thinner thigh skinfolds (95%CI [0.19–2.21], $p = 0.02$), and thereby exhibited 3.65 mm less subcutaneous fat (95%CI [1.35–5.70], $p = 0.002$) compared to unscanned toddlers. Differences in skinfold thickness between scanned and unscanned toddlers remained significant after controlling for age and sex. DXA-estimated body composition measures did not vary significantly by genotype (Table 2).

Comments

Among Samoan toddlers aged 18.7–24.5 months, having at least one copy of the CREBRF rs373863828 variant was associated with greater height. Similar findings have been documented in both Samoan (Carlson et al. 2020) and other Polynesian adults (Metcalfe et al. 2020), and Samoan children aged 5–18 years (Carlson et al. 2020). Among children in New Zealand, the CREBRF variant was associated with increased height at 4 years, but not at 2 years (Berry et al. 2018). However, Major et al. (2018) previously called in to question the validity of their findings, given the unexpectedly high rs37386328 A allele frequencies reported among the European (1.5%) and Asian (1.1%) samples. Further, the European rs37386328 genotype frequencies reported by Berry et al. deviate from Hardy-Weinberg equilibrium, suggesting genotyping errors or population groupings which do not accurately reflect genetic ancestry (Major et al. 2018). The pooling of all ethnicities prior to testing for association with body size further compounds these issues. If their study results are indeed valid, our results suggest that height differences by rs373863828 genotype may emerge earlier among Samoans living in Samoa, potentially due to gene-environment interactions. The association between rs37386328 variant and taller stature may appear at different ages according to the nutritional context encountered during development. The CREBRF variant was also associated with

Table 1. Toddler age and z-scores by sex at 18–25 months.

	Girls		Boys		All	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
Age (months)	21.35 (1.43)	49	21.27 (1.58)	58	21.31 (1.51)	107
Height-for-age z-score	−0.64 (1.08)	48	−0.97 (1.11)	58	−0.82 (1.11)	106
Weight-for-age z-score	0.70 (1.02)	48	0.44 (1.00)	58	0.56 (1.02)	106
Weight-for-height z-score	1.34 (1.02)	48	1.23 (0.92)	58	1.28 (0.96)	106
BMI-for-age z-score	1.51 (1.04)	48	1.45 (0.92)	58	1.48 (0.97)	106
Head circumference-for-age z-score	0.80 (1.18)	49	0.38 (1.29)	58	0.57 (1.25)	107
MUAC-for-age z-score	1.14 (1.00)	49	1.20 (1.20)	58	1.17 (1.11)	107
Subscapular skinfold-for-age z-score	1.29 (0.93)	47	1.09 (0.98)	58	1.18 (0.96)	105
Triceps skinfold-for-age z-score	0.67 (1.05)	48	0.38 (0.95)	58	0.51 (1.00)	106

Table 2. Toddler body size and composition by sex and genotype at 18–25 months.

	Girls						Boys									
	All girls		GG		AG/AA		All boys		GG		AG/AA		All GG		All AG/AA	
	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)	n
Height (cm)	82.0 (3.4)	48	81.8 (3.3)	31	82.4 (3.7)	17	82.5 (3.5)	58	81.9 (3.6)	33	83.3 (3.2)	25	81.9 (3.4)	64	82.9 (3.4)	42
Weight (kg)	12.0 (1.6)	48	11.9 (1.2)	31	12.3 (2.2)	17	12.3 (1.4)	58	12.2 (1.2)	33	12.4 (1.6)	25	12.1 (1.2)	64	12.3 (1.8)	42
BMI (kg/m²)	17.9 (1.6)	48	17.8 (1.4)	31	18.0 (2.0)	17	18.0 (1.4)	58	18.1 (1.1)	33	17.8 (1.7)	25	18.0 (1.3)	64	17.9 (1.8)	42
Head circumference (cm)	47.9 (1.7)	49	47.9 (1.7)	31	48.0 (1.6)	18	48.4 (1.8)	58	48.5 (1.8)	33	48.3 (1.8)	25	48.2 (1.8)	64	48.2 (1.7)	43
MUAC (cm)	16.2 (1.4)	49	16.0 (1.3)	31	16.5 (1.5)	18	16.5 (1.6)	58	16.7 (1.6)	33	16.3 (1.2)	25	16.4 (1.5)	64	16.4 (1.6)	43
Abdominal circumference (cm)	49.9 (3.8)	49	49.4 (3.3)	31	50.8 (4.5)	18	49.1 (3.3)	58	49.0 (2.9)	33	49.2 (3.9)	25	49.2 (3.0)	64	49.9 (4.2)	43
Abdominal circumference-to-height ratio	.61 (.05)	48	.61 (.05)	31	.61 (.05)	17	.60 (.04)	58	.60 (.04)	33	.59 (.05)	25	.60 (.04)	64	.60 (.05)	42
Subscapular skinfold thickness (mm)	8.3 (2.0)	47	8.0 (1.6)	29	8.7 (2.6)	18	7.6 (1.5)	58	7.7 (1.4)	33	7.5 (1.6)	25	7.8 (1.5)	62	8.0 (2.1)	43
Triceps skinfold thickness (mm)	9.2 (2.1)	48	8.9 (1.7)	30	9.6 (2.7)	18	8.8 (6.0)	58	8.6 (1.5)	33	8.2 (1.6)	25	8.8 (1.6)	63	8.8 (2.2)	43
Iliac crest skinfold thickness (mm)	6.8 (2.5)	47	6.5 (2.1)	29	7.5 (3.0)	18	6.2 (1.9)	58	6.4 (2.1)	33	6.0 (1.5)	25	6.4 (2.1)	62	6.6 (2.3)	43
Thigh skinfold thickness (mm)	13.8 (2.8)	47	14.4 (2.8)	29	12.8 (2.7)	18	13.4 (2.3)	58	13.8 (2.0)	33	12.8 (2.6)	25	14.0 (2.4)	62	12.8 (2.6)	43
Subcutaneous fat (mm)	38.0 (7.1)	47	37.7 (6.4)	29	38.5 (8.3)	18	35.7 (4.9)	58	36.5 (4.8)	33	34.6 (4.9)	25	37.1 (5.6)	62	36.2 (6.7)	43
TBLH fat mass (g)	2788.16 (529.09)	19	2793.42 (484.53)	12	2779.14 (639.72)	7	2717.13 (455.59)	23	2757.07 (354.99)	15	2645.12 (625.27)	8	2773.22 (409.29)	27	2707.67 (612.91)	15
TBLH lean mass (g)	6342.16 (734.96)	19	6341.92 (596.49)	12	6342.57 (1004.06)	7	6800.17 (622.59)	23	6904.13 (558.27)	15	6605.25 (726.85)	8	6654.26 (631.98)	27	6482.67 (845.35)	15
TBLH bone mass (g)	170.32 (24.35)	19	170.58 (14.49)	12	169.86 (37.33)	7	176.57 (24.75)	23	182 (24.05)	15	166.38 (22.81)	8	176.93 (20.83)	27	168.00 (29.89)	15
Percent fat mass	29.80 (3.13)	19	29.84 (2.96)	12	29.73 (3.64)	7	27.92 (2.96)	23	27.97 (2.58)	15	27.81 (3.76)	8	28.80 (2.86)	27	28.71 (3.70)	15
Percent fat-free mass	70.20 (3.13)	19	70.16 (2.96)	12	70.27 (3.64)	7	72.08 (2.96)	23	72.03 (2.58)	15	72.19 (3.76)	8	71.20 (2.86)	27	71.29 (3.70)	15

decreased thigh skinfold thickness in our sample. However, the biological significance of genotype differences in skinfold thickness at one site alone is unclear.

While toddlers with the minor allele were taller, the *CREBRF* variant was not significantly associated with greater bone mass. In contrast, the minor allele was associated with greater lean and bone mass in this cohort at age 4 months (Arslanian et al. 2021). It is possible that genotype differences in body composition are transient in infancy. However, this discrepancy is most likely due to the small sample size of DXA-scanned toddlers ($n = 42$ versus $n = 110$ at 4 months), the primary limitation of this study. Further, successful DXA scan completion was associated with lower age, weight, height and skinfold thicknesses. This is likely because younger and smaller toddlers were more likely to remain still during the DXA scan. Elucidating the relationship between rs373863828 genotype and body composition in toddlers and young children will require studies with larger sample sizes. Further, longitudinal study designs are required to determine whether the *CREBRF* variant promotes accelerated growth throughout childhood or only during specific developmental windows, and whether greater linear growth helps mediate the metabolically protective effects associated with the variant in adulthood. Future studies should also aim to refine our understanding of how variation in nutritional conditions and infectious disease loads interact with the rs373863828 genotype.

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