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SHORT REPORT

Is early postnatal growth velocity, a proxy of minipubertal androgen action, related to adult second-to-fourth digit (2D:4D) ratios in men? A test in Cebu, Philippines

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Abstract

Objectives: The ratio of the length of the second to the fourth digit (2D:4D) of the hand is often used as an index of prenatal androgen exposure but it might also be affected by androgens during "minipuberty", a period of temporarily high testosterone (T) production in the first few months of life. To examine this, we tested the prediction that men with lower 2D:4D ratios had greater weight growth velocities during the first months of life - a metric recently shown to correlate with concurrent T levels.

Methods: We related early growth data to 2D:4D ratios of both hands measured in 756 men (25-26 years) from Cebu, The Philippines.

Results: Birth-to-fourth-month (B4M) weight gain velocity (a proxy of early postnatal androgen action) was not associated with adult 2D:4D ratios of either hand, when the latter was measured continuously. When comparing men with more male-typical digit ratios (<1.0) to those with more female-typical ratios (≥ 1.0), the group of men with more male-typical ratios had greater B4M weight velocity, but this was only the case for the left hand.

Conclusions: We found modest evidence that adult digit ratios relate to an anthropometric correlate androgen exposure during minipuberty. Definitive assessment of the role of postnatal T in shaping digit ratios will require direct measures of perinatal T related to longitudinally assessed digit ratios.

Prenatal androgens affect embryonic digit development (Zheng and Cohn, 2011), leading to the ratio of the second-to-fourth digit length (2D:4D) being frequently used as a noninvasive proxy of intrauterine hormonal profiles with a lower ratio corresponding to higher androgen exposure (Manning, 2011). Questions remain, however, about whether 2D:4D ratio is solely determined in utero, as widely assumed, or whether it is also affected by the temporarily high testosterone (T) production during "minipuberty" in the first months of postnatal life (Galis et al., 2009; Knickmeyer et al., 2011; Ventura et al., 2013).

Testosterone production during minipuberty has important effects on sex-typical patterns of development both in terms of somatic growth and neurobehavioral differentiation. In a sample of infants from Finland, boys showed greater linear growth velocities through their first 6 months of life than girls with the greatest difference observed at 1 month of age – the time of peak testosterone production (Kiviranta et al., 2016). Specifically, urinary testosterone levels were positively and significantly associated with linear growth velocities in both sexes through their first five months of life, with the strongest association observed in the second month (Kiviranta et al., 2016). In a separate sample of boys in the Philippines, greater weight velocity from birth to six months of age, but not at later ages, predicted earlier age at puberty, higher adult testosterone levels, stature, muscularity, and grip strength (Kuzawa et al., 2010). Men who had greater birth-to-six-month weight velocity also reported having had an earlier age of sexual debut and a greater number of lifetime sexual partners (Kuzawa et al., 2010). Apart from somatic development, T exposure during the critical period of minipuberty has also been shown to affect gendered neurobehavioural development (Hines et al., 2016).

Despite direct and indirect evidence that minipubertal exposure to T can have important consequences for adult male reproductive strategies and their subsequent fitness outcomes, little is presently known about the potential role of minipubertal T production on digit ratio, and thus, the extent to which 2D:4D might partly reflect organizational effects of postnatal T production. In the only study of its kind that we are aware of, digit ratios measured sequentially at 2 weeks, 12 months and 24 months revealed instability and variability in 2D:4D ratio during this time (Knickmeyer et al., 2011). While no direct relationship was found between infant T levels measured at 3-months and digit ratios in that study, T levels did interact significantly with CAG repeat polymorphism in the androgen receptor gene (which influences target tissue sensitivity to T) to predict 2D:4D in infants at 12 and 24 months of age (Knickmeyer et al., 2011).

To examine the possible relationship between postnatal androgen action and adult 2D:4D ratios, here we relate 2D:4D ratios measured in young (25-26 years old) adult males from Cebu, The Philippines, to weight growth velocities measured during the first year of postnatal life, a proxy of androgen action during this period. Because recent work shows that postnatal T peaks between 1 and 4 months (Kiviranta et al., 2016), we predicted that a higher weight velocity from birth to 4 months of age would predict a more masculine digit ratio, while weight velocities after this period —when T is already low or absent—would be unrelated to adult 2D:4D. This hypothesis builds on our previous report from this population that weight velocity at the age of the minipuberty predicts a wide range of adult testosterone-dependent somatic, hormonal and behavioral traits, consistent with organizational effects of T production at this age (Kuzawa et al 2010).

METHODS

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a population-based birth cohort study of mothers and their infants born in 1983-84 in Metropolitan Cebu, Philippines (Adair et al., 2011). This research was conducted with human subject clearance from the Institutional Review Boards of the University of North Carolina, Chapel Hill and Northwestern University and under conditions of informed consent. Infant weight was obtained at birth and then at 2-month intervals (Adair, 1989). Birthweight was adjusted for gestational age. Digit lengths were measured in triplicate with calipers in 2009 by five different observers. For each digit, we calculated the mean of three repeat measures of the 2D:4D ratio for each hand. Intraclass correlation coefficients for the repeated digit measures were high (all >0.99) but given that these measures were undertaken in close succession by the same observer they cannot be considered statistically independent. To rule out observer effects, we calculated residual 2D:4D by regressing 2D:4D on observer identity which are then used in subsequent analyses (Georgiev et al., 2017). We excluded 6 outliers each from the measures of L and R-hand 2D:4D ratios (values > 3SD from the mean). A total of 756 men had all variables available (Table 1). Previous studies have examined digit ratio for the left and the right hand, and using a continuous ratio or a binary metric (masculine being < 1.0; feminine ≥1.0; e.g., Klimek et al., 2014). To allow comparisons with published studies, we applied the same approach and constructed 4 separate models. We used linear and logistic regression, respectively, to model continuous and high/low 2D:4D. All variables (birthweight adjusted for gestational age, and weight velocities for the three 4-month intervals of the first year of life) were converted to SD-scores and entered simultaneously into multiple regression models in Stata v.13.1 (Stata Corporation, State College, Texas).

RESULTS

In multiple regression models adjusting for birth weight, there were no significant relationships between early-life weight velocities (birth-to-4mo, 4-to-8-mo, or 8-to12-mo) and adult 2D:4D ratios (L2D:4D: $F_{4,751} = 1.49$, Adj. $R^2 = 0.003$, $P = 0.203$; R2D:4D: $F_{4,751} = 0.62$, Adj. $R^2 = -0.002$, $P = 0.648$).

We next used logistic regression to model digit ratios as a categorical variable with low/masculinized being those <1.0 and high/feminized ≥ 1.0. In these models, men with low/masculinized digit ratios (<1.0) on the left hand had greater weight growth velocity during their first four months of life (P = 0.013; Table 2). There was no similar relationship for the digit ratio of the right hand (logistic regression: $\chi^2 = 1.99$; N = 756; P = 0.737; pseudo $R^2 = 0.004$). Greater weight velocities past the 4th month of life were not predictive of lower digit ratios (Table 2). The p-value linking early growth with a masculine digit ratio (P = 0.013) was on the cusp of the significance threshold after adjusting for multiple comparisons (P < 0.0125).

DISCUSSION

Using prospectively collected data from a large cohort of men from the Philippines we showed that men who grew more rapidly during the age of the early postnatal minipubertal spike in testosterone production were more likely to have masculinized left-hand digit ratios (<1.0) in adulthood. Importantly, weight velocities during the subsequent 8 months of infancy, wherein T levels are no longer elevated, were not related to digit ratios. Given previous evidence for a relationship between early postnatal growth and T levels (both peaking in the first few months of life; Kiviranta et al., 2016; Kuzawa et al., 2010), this suggests, at least in this sample, that left-hand 2D:4D ratios might serve as a proxy for minipubertal androgen action.

At Cebu, we previously reported that faster weight velocity during the first 6 months of life, but not in subsequent intervals, predicted higher adult T, lean mass, muscle, stature and several measures of sexual activity, which we interpreted as evidence for an organizational role of early postnatal T on these sexually dimorphic traits (Kuzawa et al., 2010). The present finding that faster early postnatal growth predicts a more masculine digit ratio bolsters this interpretation, and supports the hypothesis that adult digit ratios might not only index the organizational effects of prenatal T, as widely assumed in the literature, but also of early postnatal T (McIntyre et al., 2006; Galis et al., 2009; Knickmeyer et al., 2011; Ventura et al., 2013).

Why early postnatal weight velocity only predicted digit ratio in the left hand among Cebu males is unclear. However, it is notable that, unlike in most populations studied to date, the left hand exhibited a lower (more masculine) ratio in these men than the right hand (Georgiev et al., 2017). If left hand digit ratio is more sensitive to postnatal T at Cebu, we speculate that this could help explain the stronger relationships between early postnatal weight velocity and left-hand digit ratio, a finding that should be testable in other populations. Collectively, our studies at Cebu add to growing evidence for an organizational effect of minipubertal T production on later T-dependent phenotypes, findings extended here to include adult digit ratio. However, the inconsistencies that we report point to the need for validation of these findings using direct, longitudinal measures of T and digit ratio, and suggests that caution is warranted when using digit ratios as retrospective indices of early life androgen exposure.

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Table 1. Descriptive statistics of the sample of men from Cebu (N = 756)

Variable	Mean	SD	Min	Max
Age at time of digit measurement (years)	26.0	0.3	25.3	26.6
Unadjusted birth weight (g)	3015.7	430.0	907.2	4195.7
Birth-to-four-months (B4M) weight velocity (g/week)	189.9	42.8	-7.4	370.4
Four-to-eight-months weight velocity (g/week)	69.0	31.8	-60.9	373.0
Eight-to-twelve-months weight velocity (g/week)	37.7	26.7	-121.3	152.9
L2D:4D	0.961	0.029	0.883	1.062
R2D:4D	0.965	0.028	0.892	1.068
% With low/masculine (<1.00) L2D:4D	90.87%			
% With low/masculine (<1.00) R2D:4D	89.68%			

Table 2. Logistic regression model* predicting high L2D:4D ratio (≥1.0) among young men from Cebu, The Philippines.

Independent variables	Odds Ratio	95% CI	P-value
Adjusted birth weight	1.124	(0.874; 1.444)	0.362
Birth-to-four-months (B4M) weight velocity (g/week)	**0.721**	**(0.557; 0.935)**	**0.013**
Four-to-eight-months weight velocity (g/week)	0.902	(0.695; 1.171)	0.440
Eight-to-twelve-months weight velocity (g/week)	1.269	(0.983; 1.638)	0.067
Constant	0.093	(0.071; 0.121)	<0.0001

**Full model:* $\chi^2 = 11.91$*, N = 756 men, P = 0.018, pseudo* $R^2 = 0.026$