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Low Digit Ratio Predicts Early Age at Menarche in Colombian Schoolgirls

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Abstract

Background: The ratio between the lengths of the second and fourth fingers (digit ratio: 2D : 4D), a purported negative correlate of prenatal androgen exposure, has been inversely related to age at menarche. However, a recent study found high digit ratios in carriers of a single variant in the *LIN28B* gene, which has been linked to delayed menarche.

Methods: We investigated the association of digit ratio and age at menarche in 299 pre-menarcheal girls aged 5–12 years who participated in a longitudinal cohort study in Bogotá, Colombia. Finger lengths were measured at baseline and the occurrence of menarche was periodically ascertained over a median 32 months of follow-up. We used time-to-event analysis to estimate median ages at menarche as well as hazard ratios for menarche according to tertiles of the digit ratio for each hand.

Results: Estimated median age at menarche was lower for girls in the lowest digit ratio tertile of the right hand compared with those in the highest (12.0 vs. 12.3 years; P-value = 0.04). After adjustment for baseline age, height- and body mass index-for-age z-scores, the hazard of menarche was 86% higher in girls of the lowest digit ratio tertile (hazard ratio 1.9 [95% confidence interval 1.2, 2.9]) compared with those in the highest digit ratio tertile of the right hand. No significant associations were found with the left hand.

Conclusions: Digit ratio was positively associated with age at menarche in this longitudinal investigation, consistent with results from a recent gene-linkage study.

Keywords: *Anthropometry*, *Digit ratio*, *Menarche*, *Cohort studies*.

Sexual dimorphism in the ratio between the index and ring finger lengths (2D : 4D; usually higher in males than females) manifests already *in utero*.[1] It has been proposed that lower digit ratios indicate greater androgen exposure *in utero*,[2] and studies have linked the digit ratio with a variety of reproductive, behavioural and health outcomes including fertility,[2] sexual orientation,[3,4] physical performance,[5,6] spatial ability[7] and autism.[8] The direction and magnitude of these associations, however, has not been consistent across studies.

Because the hormonal intrauterine environment might influence the timing of pubertal development,[9] recent investigations have addressed the association between the digit ratio and age at menarche. In students from the US[10] and among British women,[11] low digit ratio in the right hand was related to delayed age at menarche. In contrast, no association was reported between digit ratio in either hand and age at menarche in a retrospective study of post-menopausal Finnish women.[12] In a recent study of Australian and British girls, the digit ratio was strongly associated with a single variant in the *LIN28B* gene; each copy of the minor allele was associated with a 0.006 increase in mean 2D : 4D.[13] As this variant has been linked to height[14] and delayed age at menarche,[15,16] the finding would suggest a positive association between digit ratio and age at menarche.[13]

Previous studies examining the relation of digit ratio and age at menarche have been cross-sectional or retrospective in nature; that is, the age at menarche has been self-reported at the time when the digit ratio was ascertained. In these studies it is not possible to determine the temporal relation between the exposure (digit ratio) and the outcome (age at menarche). We conducted a prospective study of pre-menarcheal

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schoolgirls from Bogotá, Colombia to investigate the potential association between the digit ratio and menarche.

Methods

Study population

The Bogotá School Children Cohort is an ongoing longitudinal study to investigate the nutrition and health status of school-age children. Details of the study design have been reported previously.[17] In brief, 3202 children aged 5–12 years who were enrolled in the public primary school system of Bogotá, Colombia, were recruited into the study in February 2006. The public school system enrols a majority of children from low- and middle-income families in the city and the use of a cluster sampling technique ensured that the cohort was representative of this population. Information on sociodemographic characteristics and health habits of the children and their families was collected through a self-administered questionnaire that was sent to the parents at enrolment (response rate 82%). In the following weeks, research assistants made school visits to obtain anthropometric measurements in all participating children, including height and weight, according to standardised procedures.[18] In addition, we measured finger lengths in a random sample of 652 children with the use of digital calipers (Digimatic Caliper CD-6″ CX, 500-171 series, Mitutoyo Corporation, Aurora, IL, USA) with 0.01-mm precision. Each finger of both hands was measured twice by the same observer. The fixed jaw of the caliper was placed midline of the basal crease of each finger and the sliding jaw was extended to the fingertip without exerting pressure. Additional follow-up visits occurred in June and November 2006, and once annually thereafter. If children were absent from school on the day of the assessment, they were visited at home. At each of these assessments, girls were asked whether or not they had started menstruating; among those who provided an affirmative response we recorded the date of the first menstrual period.

The parents or primary care providers provided written informed consent before enrolment. The study protocol was approved by the Ethics Committee of the National University of Colombia Medical School; the Institutional Review Board at the Harvard School of Public Health approved the use of data from the study.

Statistical analyses

There were 321 girls in the subsample with finger length measurements. Seven of them had already experienced menarche at the time of enrolment and 15 were lost to follow-up; thus the final sample size for analysis was 299. The primary exposure of interest was the digit ratio, estimated as the ratio of the index (second) and ring (fourth) fingers of each hand. The primary end-point was whether menarche occurred during follow-up and at what age.

We first examined the reliability of the finger ratio measurements by calculating intraclass correlations (ICCs) between the two assessments of each finger, separately for each hand (Table 1). Because reliability was high, we estimated digit ratios using the mean values from the two measurements of each finger.

Potential confounders were investigated by comparing the distribution of digit ratios according to

Table 1. Finger measurements (mm) in 299 girls of the Bogotá School Children Cohort

	Mean (SD)		Variance		
	Measure 1	Measure 2	Between	Within	ICC
Right hand					
2: index finger	54.2 (5.6)	54.2 (5.6)			
4: ring finger	56.9 (5.5)	56.9 (5.4)			
2 : 4 digit ratio	0.952 (0.034)	0.953 (0.033)	0.0010	0.00013	0.88
Left hand					
2: index finger	54.0 (5.5)	54.0 (5.5)			
4: ring finger	56.7 (5.4)	56.7 (5.3)			
2 : 4 digit ratio	0.953 (0.037)	0.953 (0.035)	0.0012	0.00015	0.88

ICC, intraclass correlation coefficient.

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baseline characteristics of the girls and their mothers. These included the girl's age, handedness, anthropometric status and birthweight; the mother's age, height and body mass index (BMI); and the household's socio-economic status (SES). SES was determined according to the local government's classification of households that determines public service fees. We calculated height- and BMI-for-age standardised *z*-scores according to the World Health Organization reference.[19] Height-for-age *z*-score was classified as <–1, –1 to <0 and ≥0 as the prevalence of stunting (*z*-score <2) in this population is <10%.[20] Weight status was categorised as thin, normal or overweight according to BMI-for-age, based on the recommendations of the International Obesity Task Force.[21] We first compared the distributions of digit ratios by categories of these potential confounders with the use of ANOVA *F*-tests.

Next, we conducted time-to-event analyses with the use of Kaplan–Meier curves. In these analyses, the time to event was age at menarche in decimal years, estimated from the date of menarche and the date of birth. Girls who did not have menarche during follow-up were censored at the last time they reported that menarche had not occurred. Median age at menarche was estimated from the Kaplan–Meier curves for each tertile of the digit ratio, and these were compared with the log-rank test. Next, we estimated adjusted hazard ratios (HR) with the use of Cox proportional hazards models. In these, the occurrence of menarche was modelled with age in decimal years as the underlying timescale, and tertiles of the digit ratio as predictors. Adjustment covariates included known correlates of menarche or baseline characteristics that were associated with the digit ratio at $P < 0.10$ in univariate analyses. The girl's age at baseline and predictors that remained significantly associated with menarche ($P < 0.05$) after multiple adjustment were retained in the final models. Because the associations of weight and height with age at menarche are fairly linear,[22] these covariates were also considered as continuous. The proportional hazards assumption was evaluated by introducing terms for interaction between age and the covariates in the model. All analyses were carried out for the digit ratio of each hand separately. Analyses were performed in SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). Kaplan–Meier plots were produced in R statistical software version 2.12.0 (The R project for statistical computing - www.r-project.org).

Results

Mean age of participating girls at baseline was 8.8 ± 1.7 years. ICCs were high for the digit ratios of both hands, indicating that measurement error was not substantial (Table 1).

We next examined the distributions of digit ratios according to baseline characteristics separately for each hand. Digit ratios were higher in older compared with younger girls, and also in thin and overweight girls compared with those with normal weight (Table 2). Left-handedness, weight at birth and height-for-age *z*-score at the time of recruitment, or the family's SES were not associated with digit ratio. Maternal BMI was positively associated with the girl's left hand digit ratio (Table 2).

The median length of follow-up was 32 months (interquartile range: 20–44); it was not related to the digit ratio. During this time, 141 girls (47%) experienced menarche. Estimated median [95% confidence interval, CI] age at menarche was 12.2 [12.0, 12.3] years overall. The cumulative probability curve of menarche for girls in the lowest tertile of digit ratio in the right hand was consistently above those for the higher tertiles (Figure 1). Estimated median age at menarche was the lowest for girls in the lowest right hand digit ratio tertile (12.0 years) compared with those in the mid- (12.2 years) or highest tertiles (12.3 years) respectively (log-rank test P-value = 0.04; Figure 1). There was no significant association between digit ratio of the left hand and age at menarche; estimated median age at menarche in the lowest, mid- and highest tertiles were, respectively, 12.0, 12.3 and 12.2 years (log-rank test P-value = 0.17; Figure 2).

We next modelled the occurrence of menarche according to digit ratio tertiles for each hand with the use of Cox regression models (Table 3). The hazard rate of menarche was the highest among girls in the lowest right hand digit ratio tertile (HR = 1.7 [95% CI 1.1, 2.5] compared with girls in the highest tertile). Adjustment for age and anthropometric indicators at baseline (height- and BMI-for-age *z*-score) increased the magnitude of the association slightly (HR = 1.9 [95% CI 1.2, 2.9]), whereas adjustment for maternal BMI or family SES had no influence on the estimates (results not shown). The associations were not statistically significant for the left-hand digit ratio. Tests of potential violations to the proportional hazard assumption were negative for the digit ratio and all covariates considered.

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Table 2. Digit ratio and estimated age at menarche according to baseline characteristics in 299 girls from the Bogotá School Children Cohort

		Digit ratio				Menarche		
		Right hand		Left hand				
Characteristic	n[a]	Mean	P[b]	Mean	P[b]	Menarche during follow-up (n)	Median estimated age at menarche[c]	P[d]
Age, years			0.005		0.08			0.06
5–6	61	0.944		0.947		3	–	
7–8	101	0.950		0.950		25	12.3	
9–10	113	0.954		0.956		91	12.1	
11–12	24	0.972		0.966		22	12.5	
Left-handedness			0.93		0.11			0.51
No	213	0.953		0.952		111	12.2	
Yes	26	0.952		0.964		15	12.0	
Height-for-age z[e]			0.14		0.17			<0.0001
<–1	110	0.950		0.951		43	12.5	
–1 to <0	108	0.950		0.950		55	12.1	
≥0	75	0.959		0.960		39	11.8	
Weight status[f]			0.16		0.04			0.10
Thin	37	0.960		0.962		22	12.2	
Normal	218	0.950		0.950		93	12.2	
Overweight	38	0.956		0.961		22	12.0	
Birthweight < 2500 g			0.40		0.72			0.15
No	210	0.952		0.952		96	12.2	
Yes	22	0.946		0.954		13	12.0	
Mother's age, years			0.03		0.41			0.59
20–29	60	0.942		0.946		24	11.8	
30–34	81	0.954		0.955		38	12.2	
35–39	64	0.959		0.954		26	12.3	
≥40	74	0.953		0.955		42	12.1	
Mothers height, cm			0.18		0.76			0.36
<154	54	0.949		0.953		26	12.0	
154 to <158	72	0.959		0.953		33	12.3	
158 to <162	62	0.954		0.956		28	12.3	
≥162	77	0.948		0.950		34	12.2	
Mother's BMI, kg/m^2			0.28		0.02			0.81
<18.5	9	0.939		0.930		5	12.0	
18.5–24.9	163	0.952		0.951		72	12.1	
25–29.9	64	0.956		0.959		27	12.2	
≥30	24	0.961		0.965		14	12.2	
Household SES[g]			0.91		0.07			0.30
1 + 2 (lowest)	62	0.954		0.955		23	12.4	
3	199	0.952		0.955		103	12.0	
4	38	0.952		0.941		15	12.3	

[a] Totals may be <299 because of missing values.
[b] ANOVA *F*-test.
[c] Estimated from Kaplan–Meier survival curves.
[d] Log-rank test.
[e] Age-standardised according to the World Health Organization's reference.[19]
[f] According to body mass index (BMI)-for-age criteria by the International Obesity Task Force.[21]
[g] Socio-economic status according to the local government's classification.

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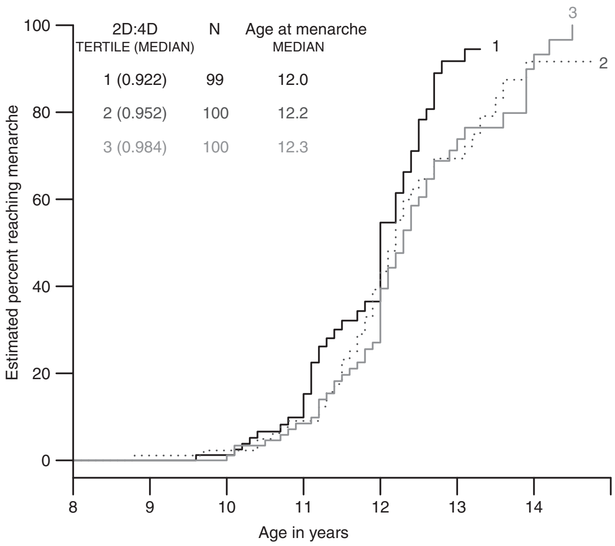

Figure 1. Menarche according to tertiles of 2D : 4D (right hand).

Comments

Digit ratio was positively associated with age at menarche in this prospective study of schoolgirls from Bogotá, Colombia. The finding is in contrast with previously reported associations of low digit ratio with delayed age at menarche.[10,11] The inconsistency of the findings could partly be a result of methodological differences between the studies. In one of the studies finger length measurements were obtained by the participants themselves, according to instructions

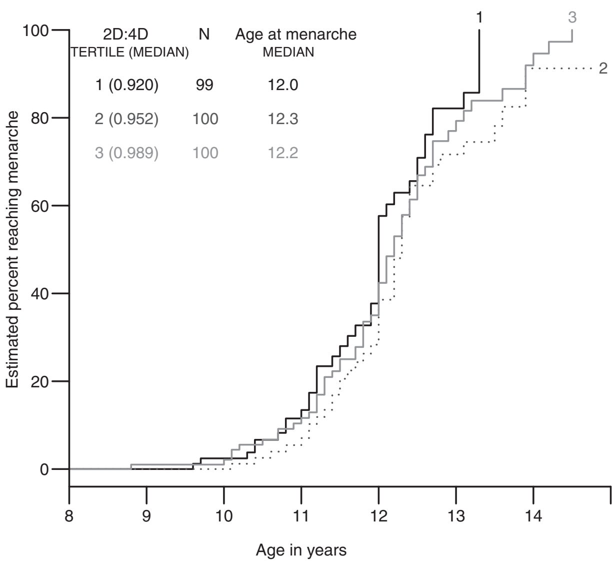

Figure 2. Menarche according to tertiles of 2D : 4D (left hand).

Table 3. Hazard ratios (HR) and confidence intervals (CI) for menarche according to digit ratio in 299 girls from the Bogotá School Children Cohort

		Right hand			Left hand		
	N	Menarche during follow-up, *n* (%)	Crude[a] HR [95% CI]	Adjusted[b] HR [95% CI]	Menarche during follow-up, *n* (%)	Crude[a] HR [95% CI]	Adjusted[b] HR [95% CI]
Digit ratio tertile (right/left medians)							
1 (0.922/0.920)	99	45 (45.5)	1.66 [1.09, 2.52]	1.86 [1.19, 2.91]	39 (39.4)	1.35 [0.91, 2.00]	1.48 [0.94, 2.33]
2 (0.952/0.952)	100	42 (42.0)	1.04 [0.69, 1.59]	1.20 [0.77, 1.85]	41 (41.0)	0.86 [0.59, 1.25]	0.87 [0.56, 1.34]
3 (0.984/0.989)	100	54 (54.0)	Reference	Reference	61 (61.0)	Reference	Reference
P, linear trend[c]			0.03	0.009		0.52	0.15
Age, years	299	141 (47.2)		0.90 [0.76, 1.05]	141 (47.2)		0.88 [0.75, 1.04]
Height-for-age z^d	293	137 (46.8)		1.57 [1.28, 1.92]	137 (46.8)		1.55 [1.27, 1.90]
BMI-for-age z^e	293	137 (46.8)		1.26 [1.05, 1.51]	137 (46.8)		1.22 [1.02, 1.46]

[a] From Cox proportional hazard models.
[b] In addition to indicator variables for digit ratio tertiles, predictors included the girl's baseline age, height-for-age *z* and body mass index (BMI)-for-age *z* as continuous variables.
[c] For a categorical variable representing digit ratio tertiles that was introduced into the model as continuous.
[d] Age-standardised according to the World Health Organization's reference.[19]
[e] According to BMI-for-age criteria by the International Obesity Task Force.[21]

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provided in a questionnaire.[11] Because determinations of finger length are subject to substantial measurement error, the validity of self-measurements is questionable. In contrast, our study used finger length measurements made in duplicate by trained research personnel, and high ICCs between measurements indicated that intra-rater reliability was adequate. None of the previous investigations had a longitudinal design; digit ratios were measured after menarche had occurred, and age at menarche was ascertained by recall.[10,11] We used a longitudinal design in which finger ratios were measured before the occurrence of menarche, largely precluding potential reverse causation bias. Ascertaining the occurrence of menarche in a prospective manner should also serve to minimise recall bias.

Albeit opposite to the results of initial studies, our findings are consistent with those of a recent report showing that minor allele carriers of a single variant in a gene (*LIN28B*) related to delayed menarche[15] had high digit ratios.[13] Also, the direction of the association in our study is consistent with that reported in an investigation of 282 Finnish women, in whom a standard deviation increase of the digit ratio was related to a non-statistically significant 14% lower hazard of menarche.[12]

The digit ratio was first proposed as a proxy for prenatal androgen exposure from the observation that sexual dimorphism in this trait appears early in life.[2] Genetic conditions that increase or decrease early exposure to androgens have also been related to lower or higher digit ratios respectively.[23,24] Thus, previous findings of an inverse association between digit ratio and age at menarche were interpreted as suggesting that prenatal androgen exposure may delay sexual maturation in females.[10] Some evidence from animal experiments lent support to this view, as exposure of rhesus monkeys or sheep to prenatal testosterone have induced delayed age at menarche[25] and ovulatory failure[26] respectively. Nevertheless, information from epidemiological studies to support a direct link between prenatal exposure to sex hormones and the timing of puberty is limited. Also sparse is the evidence of a direct effect of the prenatal hormonal environment on the digit ratio. In a study of 30 mother–infant pairs, there were no correlations between testosterone or oestrogen levels in amniotic fluid and the children's digit ratio at 2 years of age; however, an inverse correlation was noted with the testosterone/oestrogen ratio.[27]

Although digit ratios have been related to postnatal conditions that purportedly represent the effect of early differential exposures to sex hormones including sperm count,[2] sexual orientation,[3,4] physical performance,[5,6] spatial ability[7] and aggressive behaviour,[28] the associations reported do not consistently follow the direction expected if a low digit ratio were to represent high exposure to androgens in early life. For example, homosexuality has been linked to both high and low digit ratio in different populations.[4] Also, a recent meta-analysis of studies of the digit ratio and spatial ability found that their correlation was negligible.[7]

While androgens play an indisputable role in the regulation of sexual differentiation and maturation, their action likely depends on the timing of exposure as well as their interactions with other sex hormones. Using the digit ratio as a proxy for prenatal hormone exposure may be limited by its inability to differentiate the potential effect of exposure *in utero* from that occurring postnatally.[29] There are reports indicating a correlation between the digit ratio and testosterone or oestradiol serum levels in adults,[2,30] but these have also been contradicted by a meta-analysis showing no such associations.[29] Lastly, the digit ratio does not appear to be constant throughout life. In line with findings from previous longitudinal assessments,[31,32] we noted a positive association of the digit ratio with baseline age in cross-sectional analyses. Whether age-related differences are a result of postnatal hormonal effects has not been established.

We observed stronger associations in the right than in the left hand. This finding is consistent with many of the previous reports that examined the digit ratio in relation to traits and health outcomes.[2,5,10,11,30] While potential mechanisms are poorly understood, the male form of sexually dimorphic traits appears to be most strongly expressed on the right side of the body.[33,34] It has also been proposed that the right hand may be more sensitive to the effect of testosterone *in utero*.[35]

There are some limitations to our study. Follow-up was not sufficiently long as to allow us to observe the occurrence of menarche in all participants; this could have decreased statistical power. Also, we relied on the ascertainment of the exposure at a single time point (at start of follow-up), and serial measurements in children suggest that the digit ratio increases with age.[31,32] However, other studies indicate that sex differences in the digit ratio remain stable over time, and

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Spearman correlation coefficients for repeated measures of digit ratios are high.[32] It is thus possible that these changes occur systematically, without altering the ranking of girls according to their digit ratio over time. Finally, although ICCs were high, there was no formal evaluation of inter-observer variation in the measurement of finger lengths.

In summary, a low digit ratio was associated with earlier menarche in this longitudinal study. Whether the digit ratio is a valid proxy of prenatal hormone exposure in the prediction of postnatal health outcomes requires further evaluation in longitudinal investigations.

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