

*Short Report***Does Second-to-Fourth Digit Length Ratio (2D:4D) Predict Age at Menarche in Women?**

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ABSTRACT Prenatal steroid levels, estimated as the ratio of second-to-fourth digit length (2D:4D), have been related to reproductive success in women, but direct associations between 2D:4D and physiological measures of fertility remain rare. A recent study reported that lower, masculinized right hand 2D:4D was correlated with delayed age at menarche in women. We addressed this question by investigating whether 2D:4D was associated with recalled age at menarche in 282 post-reproductive Finnish women, using Cox regression model that controlled for a woman's sibling composition, urban or rural residence and temporal trend in menarcheal age. We found no evidence that neither the 2D:4D of the right nor the left hand were related to a woman's age at menarche among these Finnish women. *Am. J. Hum. Biol.* 22:418–420, 2010. © 2009 Wiley-Liss, Inc.

Recent decades have witnessed a growing understanding of the importance of prenatal programming on individual's reproductive success during adulthood (Gluckman and Hanson, 2005; Lummaa and Clutton-Brock, 2002). Prenatal steroid levels (mainly androgens) have also been related to reproductive competence, as suggested by the associations found between second-to-fourth digit length ratio (2D:4D) and offspring count in humans (Manning, 2002; Manning and Fink, 2008). During the last 10 years, 2D:4D has thus been strongly highlighted as a potentially useful retrospective marker of steroid exposure in utero (Manning, 2002; McIntyre, 2006). This theory holds that the lower the 2D:4D, the higher testosterone but the lower estrogen levels during the fetal life of an individual.

Studies investigating directly whether the 2D:4D of women relates to the physiological measures of fertility are much fewer than those investigating the measures of mating and reproductive success. It has recently been suggested that 2D:4D could predict age at menarche in women (Matchock, 2008)—an important life-history trait that has a genetic basis (Rowe, 2000) and might be under natural selection even in modern day populations (Kirk et al., 2000). This study reported using Pearson correlations that among 206 college students, the 2D:4D of the right hand but not the left hand negatively correlated with the age at menarche of these women. To our knowledge, this finding has not yet been replicated in any other populations.

Here, we investigated whether 2D:4D was related to age at menarche in 282 contemporary Finnish women. Our current analysis advances this question by using Cox regression model to simultaneously examine the relative effects of both the right and the left hand 2D:4D and by controlling for several factors that have been suggested to affect women's age at menarche.

METHODS*Participants*

In 2006, data on age at menarche (in years) and the right and the left hand 2D:4D was collected from 282 women who were born during the years 1946–1958 in Finland (Helle, 2008; Helle and Lilley, 2008). The data on

women's age at menarche (mean \pm SD = 13.2 \pm 1.5) and all the covariates included in the analysis (see below) were collected by questionnaires and their both hands were scanned (Canon Canoscan D660U) for 2D:4D measurements. These women consist of a random, racially homogeneous and geographically diverse sample of 50 to 60-year-old women who participated voluntarily in a Finnish national screening program for cervical cancer. The digits were measured from the tip of the finger to the crease proximal to the palm with program Image-J (<http://rsb.info.nih.gov/ij/>) by one person. Sixty randomly selected hands were measured twice by the same person in order to estimate the repeatability (i.e. intraclass correlation coefficient) of 2D:4D measurements using one-way ANOVA (Lessells and Boag, 1987). The 2D:4D measurements showed a repeatability of 0.79 ($F_{1,59} = 8.44, P = 0.0052$).

Statistical analysis

The simultaneous effects of both the right and the left hand 2D:4D on women's age at menarche was examined using Cox proportional hazards regression model (Allison, 1995), as the response variable was years to menarche. This model controlled for the potential confounding effects of the number of brothers and sisters a woman had (Matchock and Susman, 2006; Roberts et al., 1975) and temporal variation with birth cohort (1946–47, 1951–52, or 1956–58) (Okasha et al., 2001) on age at menarche. Because urban residence has been suggested to be associated with an earlier age at menarche (Marrodan et al., 2000; Padez, 2003), women were categorized having either a rural or urban growth environment based on their birth town (born in major cities or habitation centers vs. rural areas). The resulting variable was included in the model

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as well. In order to obtain more biologically interpretable parameter estimates, both the right (SD = 0.031) and the left hand 2D:4D (SD = 0.033) were standardized to zero mean and 1 standard deviation. Therefore, the parameter estimates represent how the change of 1 SD in the 2D:4D measures affected women's age at menarche. The assumption of proportional hazards was examined by including time-dependent effects of predictor variables in the model. No evidence for nonproportionality was found ($P > 0.15$ in all cases). No stepwise model reduction was applied, because such methods dramatically increase the rate of Type I errors (Mundry and Nunn, 2009) and because our aim here was to obtain accurate point estimates and their confidence intervals (CI) (Harrell, 2001). The model fit to individual observations was checked using martingale and deviance residuals and deemed appropriate. Multicollinearity among continuous independent variables was assessed with variance inflation factors and tolerance values. The largest variance inflation factor was 1.51 and the lowest tolerance value 0.66, suggesting no severe bias in the CIs of hazard ratios. All analyses were conducted with SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Neither the right nor the left hand 2D:4D was significantly associated with a woman's age at menarche (Table 1). Age at menarche seemed to be related to the number of sisters and brothers a woman had, as one additional sister reduced a woman's hazard of menarche, on average, by 10% while having one additional brother increased it, on average, by 12% (Table 1). This effect of the number of brothers and sister on women's menarcheal age differed statistically from each other ($\chi^2_1 = 4.51, P = 0.034$). Birth cohort and whether women were born in rural or urban area were not related to age at menarche in these women (Table 1).

DISCUSSION

These data on Finnish women provide no evidence to suggest that 2D:4D could be used to predict age at menarche. There are at least three potential explanations for our failure to establish a proposed association between 2D:4D and women's age at menarche. First, 2D:4D may not be a precise enough measure of intrauterine exposure to testosterone in women. At present, there is more convincing evidence from "natural experiments" that women diagnosed for polycystic ovarian syndrome (PCOS) and congenital adrenal hyperplasia (CAH), which are associated with increased exposure to prenatal testosterone, experience delayed menarche (New, 2004; Sadrzadeh et al., 2003) than there is for the causal link between prenatal testosterone and 2D:4D. In other words, prenatal testosterone may well affect menarcheal age, but not 2D:4D to such an extent to produce a detectable association between 2D:4D and menarcheal age. In addition, although some studies have also demonstrated that women with PCOS and CAH have lower 2D:4D (Brown et al., 2002; Cattrall et al., 2005), a correlation between a woman's 2D:4D and her age at menarche does not directly mean a link between prenatal testosterone and menarcheal age (Hönekopp et al., 2007).

TABLE 1. The effects of the right and the left hand 2D:4D and the confounding factors considered on women's age at menarche

Predictor	Hazard ratio (95% CIs)	df	χ^2	P
Right hand 2D:4D	0.86 (0.72, 1.04)	1	2.49	0.12
Left hand 2D:4D	1.09 (0.91, 1.31)	1	0.95	0.33
Number of sisters	0.90 (0.81, 1.01)	1	2.95	0.086
Number of brothers	1.12 (0.98, 1.28)	1	2.91	0.088
Birth cohort	–	2	3.99	0.14
Urban vs. rural residence	0.84 (0.61, 1.16)	1	1.11	0.29

Parameter estimates of categorical variables having more than two categories are omitted for simplicity. CI = confidence interval.

Second, it is likely that there might have been some errors in women's self-reported age at menarche, as the women were in their 50s and 60s when they completed the questionnaire for their age at menarche. Large-scale studies have suggested that recalled age at menarche even decades later seems to correspond rather well with the true age at menarche, irrespective of actual age at menarche (Cooper et al., 2006; Must et al., 2002). Furthermore, in this study the age at menarche was recorded in years, which, although reducing the variation of recorded menarcheal age, likely also reduced the consequences of slight inaccuracies of recalled age at menarche.

Third, the reason for our failure to repeat the findings of Matchock (2008) might be due to the different statistical models applied. Matchock (2008) used Pearson correlation coefficients, whereas our approach was based on a Cox proportional hazards regression, designed for time-to-an-event data, such as women's age at menarche (Allison, 1995). Moreover, our Cox model controlled for several factors suggested to be related to menarcheal age in women, such as the number of sister and brothers, urban or rural residence, and temporal variation in age at menarche. However, even Pearson correlation coefficients neither in the right ($r = 0.06, P = 0.30$) nor in the left hand 2D:4D ($r = -0.02, P = 0.75$) showed a statistically significant correlation with age at menarche in this Finnish sample. This indicates that our failure to replicate previous findings was not due to differences in the statistical approach used.

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