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Regular Article

Associations of the digit ratio with adolescent behavior problems are inconsistent with an intrauterine androgenic origin

Allison L. Seeley[1], Mercedes Mora-Plazas[2], Henry Oliveros[3], Constanza Marín[3] and Eduardo Villamor[1]

[1]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, USA, [2]Foundation for Research on Nutrition and Health, Bogotá, Colombia and [3]Facultad de Medicina, Universidad de La Sabana, Chía, Colombia

Abstract

A low second-to-fourth digit ratio (2D:4D) is a purported biomarker of increased intrauterine androgenic exposure, presumably linked to postnatal behavior. We aimed to examine the associations between 2D:4D and adolescence behavior problems expected from high (externalizing and attention problems) or low (internalizing problems) prenatal androgen exposure. We conducted a cross-sectional study of 1042 Colombian schoolchildren aged 11–18 y. We examined whether caliper-assessed 2D:4D was associated with behavior problems per the Youth Self-Report questionnaire. Mean problem standardized score point differences were estimated between hand- and sex-specific quintiles of 2D:4D with use of multivariable linear regression. Lower right-hand 2D:4D was associated with decreased externalizing and internalizing behavior problem scores. Corresponding lowest-to-median quintile adjusted mean differences (95% CI) were −4.6 (−7.5, −1.7) and −3.5 (−6.4, −0.6) points in boys; and −3.4 (−5.9, −0.9) and −3.5 (−6.2, −0.8) points in girls. Lower right-hand 2D:4D was also related to less attention and thought problems in boys, and to less social problems among girls. Associations were nonlinear, apparent only below 2D:4D medians, and stronger with the right than the left hand. In conclusion, right-hand 2D:4D is related to behavior problems in adolescence in directions that are not fully consistent with an androgenic exposure origin.

Keywords: Digit ratio; 2D:4D; Externalizing behavior; Internalizing behavior; Prenatal androgen exposure; Adolescence

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Introduction

Mental health problems affect 10–20% of children and adolescents worldwide (Kieling et al., 2011) and are particularly concerning in low- and middle-income countries, including in Latin America, where there are considerable mental health workforce shortages and wide disparities in treatment access (Kohn et al., 2018). Externalizing and internalizing behavior disorders, including conduct, attention deficit/hyperactivity, depressive, and anxiety disorders, greatly contribute to the global burden of mental health problems (Whiteford et al., 2013). These disorders are at the extreme of a spectrum of more subtle, yet also highly relevant behavior problems that can affect mental and physical health in the long term (Prince et al., 2007). Risk factors for the development of behavior problems include characteristics of the social environment (Hann, 2001), poor nutritional status (Doom et al., 2018; Robinson, Marín, et al., 2020; Robinson et al., 2018, 2021; Robinson, Oliveros, et al., 2020), childhood infections and inflammation (Beer et al., 2021), and sleep problems (Zhu et al., 2022); but much is still unknown about the etiology of these conditions.

Emerging evidence suggests that alterations of the prenatal environment, including imbalanced exposure to sex hormones, may be involved in the development of behavior problems and disorders in the offspring (Auyeung et al., 2013; Hines, 2006). Differential exposure to prenatal testosterone affects gray matter development (Auyeung et al., 2013) in ways that may influence the establishment of behavior patterns postnatally. Available measures of intrauterine hormone exposure include quantification in amniotic fluid, cord blood, or maternal blood. These methods are all limited in their ability to capture a representative measurement of the early prenatal hormone environment (Auyeung et al., 2013; Hines, 2006), and their implementation may be invasive or logistically unfeasible in large population studies. Given the potential importance of *in utero* sex hormone levels in child neurobehavioral development, an accurate, safe, and efficient measure of exposure is needed.

The digit ratio (2D:4D), the ratio between the length of the 2nd (index) to 4th (ring) fingers, has been proposed as an inversely proportional biomarker of prenatal androgen exposure that is established early *in utero* and that remains invariant postnatally (Manning et al., 1998). In support of this hypothesis, investigators have reported inverse associations between 2D:4D and phenotypically androgenic health outcomes including male fertility

Corresponding author: Eduardo Villamor; Email: villamor@umich.edu.

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(Manning et al., 2009), physical performance (Hönekopp & Schuster, 2010), and prostate cancer (Bunevicius, 2018). Nevertheless, whether 2D:4D represents intrauterine androgen exposure remains a matter of debate (Leslie, 2019) because amniotic testosterone and estrogen concentrations have been unrelated to 2D:4D in infancy (Lutchmaya et al., 2004), and 2D:4D changes postnatally (Knickmeyer et al., 2011; Kralik et al., 2014; McIntyre et al., 2005; Trivers et al., 2006; Wong & Hines, 2016).

Emerging literature has focused on the relation between 2D:4D and the development of behaviors conventionally associated with androgenic exposure. Externalizing problems, including aggressive and rule-breaking behaviors, as well as attention problems, are associated with higher prenatal androgen exposure, whereas internalizing problems, such as anxiety, depression, and somatization, are generally related to lower levels of testosterone during gestation (Martel, 2013). Previous studies in adults (Hönekopp & Watson, 2011; Hampson et al., 2008) and children (Liu et al., 2012) found inverse associations between 2D:4D and externalizing behaviors. However, in many studies, the associations between 2D:4D and behaviors expected from increased androgen exposure are often absent or in the opposite direction as expected (Austin et al., 2002; Barrett et al., 2021; Hönekopp & Watson, 2011; Liu et al., 2012; Portnoy et al., 2015; Wong & Hines, 2016). Our understanding of the link between 2D:4D and behaviors related to androgenic exposure is undermined by methodological differences between studies. Few studies implemented valid finger length measurement procedures or focused on behaviors that can be measured using standardized and validated assessment tools. Studies during adolescence, the period when behavior problems typically arise, are also lacking. Additionally, very few studies have been conducted in Latin American populations, which are typically more heterogeneous with respect to exposure and outcome distributions than the populations where previous studies have been done (Rishishwar et al., 2015). Consistency of findings between this and more homogenous populations would enhance their external validity.

We conducted a cross-sectional study of adolescents from Bogotá, Colombia to examine the relation of 2D:4D with externalizing and internalizing behaviors and with attention, thought, and social problems. We hypothesized that a lower 2D:4D, as a surrogate for high intrauterine androgen exposure, would be associated with increased externalizing behavior and attention problems. By contrast, a higher 2D:4D indicating low prenatal exposure to androgens, should be related to increased internalizing behavior problems.

Methods

Study design, population, and data collection

We conducted a cross-sectional study in the context of the Bogotá School Children Cohort (BoSCCo). Details of the study design have been previously published (Arsenault et al., 2009; Robinson et al., 2018). In summary, we recruited 3202 randomly selected children aged 5–12 y in February 2006 from primary public schools in Bogotá, Colombia, which predominantly enroll children from low- and middle-income backgrounds. At baseline, we collected sociodemographic information from the parents through a self-administered questionnaire and conducted anthropometry on the children using standardized methods.

Between 2011 and 2015, an in-person follow-up assessment was conducted in a random sample of approximately one-third of the cohort ($n = 1139$) at schools or at home if the participant was absent from school. This cross-sectional study pertains to data collected at this follow-up assessment. Parents completed a self-administered survey that updated information on child habits, including the daily time spent watching television or playing videogames; maternal characteristics such as parity, anthropometry, and education; and socioeconomic factors involving the presence of food insecurity in the household per a validated Spanish version of the USDA Household Food Security Survey module (Harrison et al., 2003) and socioeconomic status (SES) according to the local government classification for public services fees and taxes. Children's height was measured without shoes to the nearest 1 mm using portable wall-mounted Seca 202 stadiometers (Seca Hanover, MD) and weight was measured in light clothing to the nearest 0.1 kg using Tanita H5301 electronic scales (Tanita, Arlington Heights, IL). Finger lengths were measured using digital calipers (Digimatic Caliper CD-6" CX, 500-171 series, Mitutoyo Corporation, Aurora, IL, USA) with 0.01 mm precision, on the palmar side with the hand extended on a flat hard surface. The fixed jaw of the caliper was placed midline of the basal crease of the finger and the sliding jaw was extended to the fingertip without exerting pressure. Each finger of both hands was measured twice.

Adolescent behavior problems were assessed using the Spanish language version of the Youth Self-Report (YSR), completed by the child. This instrument consists of 112 statements about behaviors or feelings to which the children report their level of agreement by classifying the statements as either not true, somewhat/sometimes true, or very/often true. Using these responses, software provided by the test developers computes continuous scores in eight behavior problem subscales (Achenbach, 2000), standardized by age and sex from a reference US population. The subscales include aggressive, rule-breaking, anxious/depressed, and withdrawn/depressed behaviors, somatic complaints, and attention, thought, and social problems. The software also provides composite scores that represent total externalizing and internalizing problems. Total externalizing problems comprise the aggressive and rule-breaking behavior subscales while total internalizing problems consist of the anxious/depressed, withdrawn/depressed, and somatic complaints subscales. The YSR has been validated for use in adolescents aged 11–18 y (Achenbach & Rescorla, 2001) and has been widely administered in Latin American populations (Rescorla et al., 2012).

Informed consent was obtained from the primary care providers prior to enrollment. The children provided assent to participate. The study protocol was approved by the Ethics Committee of the National University of Colombia Medical School. The University of Michigan Institutional Review Board approved the use of data from the study.

Data analyses

Outcomes

The primary outcomes of interest were total externalizing and internalizing behavior scores and scores from the attention, thought, and social behavior problem subscales. Secondary outcomes were scores from subscales of the externalizing (aggressive behavior, rule-breaking behavior) and internalizing (anxious/depressed, withdrawn/depressed, somatic complaints) behavior problems.

Exposures

The primary exposure was 2D:4D, computed as the ratio of the second-to-fourth digit lengths, separately for each hand. Reliability

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Table 1. 2D:4D and total externalizing and internalizing behavior problems in adolescent boys from Bogotá, Colombia

	2D:4D quintile (median right hand/left hand)					
Behavior problems	1 $n = 91$ (0.91/0.92)	2 $n = 92$ (0.94/0.94)	3 $n = 92$ (0.95/0.96)	4 $n = 92$ (0.97/0.98)	5 $n = 91$ (0.99/1.00)	P trend[1]
Total externalizing problems						
Right hand						
Mean ± SD	48.7 ± 8.5	53.2 ± 8.1	53.9 ± 10.8	50.7 ± 9.4	53.0 ± 10.2	0.02
Adjusted difference (95% CI)[2]	−4.6 (−7.5, −1.7)	−0.5 (−3.2, 2.1)	Reference	−2.9 (−5.8, 0.1)	−1.0 (−4.0, 2.1)	0.07
Left hand						
Mean ± SD	51.3 ± 8.4	51.9 ± 10.3	51.8 ± 9.7	52.2 ± 9.4	52.3 ± 10.2	0.47
Adjusted difference (95% CI)	−0.4 (−3.2, 2.5)	0.2 (−2.9, 3.2)	Reference	0.6 (−2.4, 3.6)	0.8 (−2.4, 3.9)	0.41
Total internalizing problems						
Right hand						
Mean ± SD	51.6 ± 9.1	53.8 ± 9.1	55.2 ± 10.4	52.4 ± 9.8	54.0 ± 9.7	0.21
Adjusted difference (95% CI)	−3.5 (−6.4, −0.6)	−0.7 (−3.6, 2.2)	Reference	−2.4 (−5.2, 0.5)	−1.2 (−4.1, 1.7)	0.27
Left hand						
Mean ± SD	52.4 ± 10.5	52.6 ± 10.0	54.5 ± 9.9	53.4 ± 8.5	54.1 ± 9.3	0.19
Adjusted difference (95% CI)	−2.1 (−5.1, 0.9)	−2.0 (−4.9, 0.8)	Reference	−0.7 (−3.4, 2.0)	−0.1 (−3.0, 2.7)	0.12

[1]Wald test for an ordinal variable representing quintile medians, introduced into a linear regression model as a continuous predictor.
[2]From multiple linear regression adjusted for child's age and handedness, maternal height, socioeconomic status, and presence of household food insecurity with hunger. Robust estimates of variance were specified in all models. Complete case analysis ($n = 448$).

of 2D:4D from the two replicate finger measurements was high; intraclass correlations (ICCs) ranged from 0.89 to 0.92 (Supplemental Table 1). Hence, we used the mean of the ratios from the two replicates for analysis. 2D:4D was categorized into sex-specific quintiles for the right and left hands; it was also considered as a continuous variable in analyses of nonlinear associations.

Covariates

We considered sociodemographic, anthropometric, and health characteristics as covariates. These included child's age at the time of outcome assessment, handedness (self-reported as the hand most frequently used for writing), and body mass index (BMI, kg/m^2)-for-age Z score calculated according to the World Health Organization growth reference for children and adolescents (de Onis et al., 2007). Screen time was the weekly number of hours spent watching television or playing video games. Maternal height was objectively measured in 27% and self-reported in the rest. The presence of severe food insecurity (household food insecurity with hunger) was defined as a sum of affirmative responses ≥13 to the survey's 16 questions on adverse food security experiences.

Statistical analysis

Valid YSR assessments were available from 1042 of the 1139 participants at the follow-up assessment; they constituted the analytic sample. All analyses were conducted separately for boys ($n = 458$) and girls ($n = 584$) and for right and left hands. We first examined correlates of digit ratio by comparing the distributions of sociodemographic and anthropometric characteristics across quintiles of 2D:4D. Next, we compared the continuous distributions of each behavior problem score between 2D:4D quintiles using means ± SD. We conducted tests for linear trend by introducing a variable representing the median value of each 2D:4D quintile as a continuous predictor into a linear regression model. We estimated mean adjusted differences and 95% confidence intervals (CI) for behavior problem scores between quintiles of 2D:4D using multivariable linear regression, with the middle quintile as reference. Adjustment variables included characteristics that were known independent predictors of behavior problems in this population (Robinson et al., 2018), which could also be related to the exposure without being its consequence. Because the 2D:4D is purportedly set *in utero* and constant postnatally (Manning et al., 1998), the primary adjustment strategy included only the independent predictors of outcome that could also reasonably represent the environment during the prenatal period and not be a consequence of 2D:4D. These were maternal height, SES, and food insecurity with hunger. We also adjusted for child's age and handedness as potential sources of extraneous variation. In supplemental analyses, we additionally adjusted for postnatal predictors of outcome such as child's BMI-for-age Z scores and screen time since it is not possible to rule out that the 2D:4D may change postnatally in relation to these factors. Because the categorical analyses suggested that the associations were nonlinear, we conducted additional analyses to illustrate the shape of the associations introducing the 2D:4D as a continuous predictor with nonlinear terms from restricted cubic splines (Durrleman & Simon, 1989) into linear regression models. Robust estimates of the variance were specified in all models.

All analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC).

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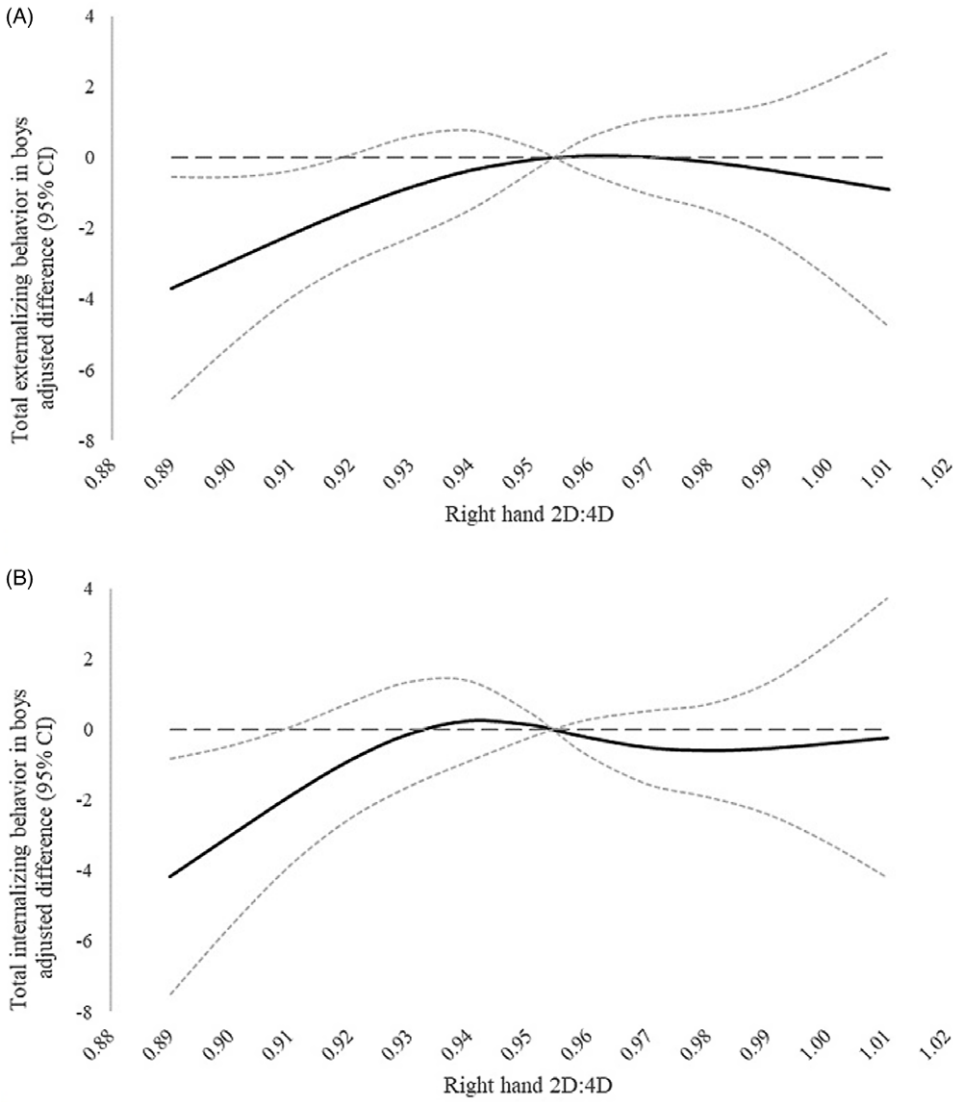

Figure 1. Adjusted differences in total externalizing (A) and internalizing (B) behavior scores according to right-hand 2D:4D in boys from Bogotá, Colombia. The solid line represents adjusted differences between behavior problem scores at each 2D:4D value and the problem score at the median value of the 2D:4D distribution. Dotted lines represent 95% confidence intervals. Estimates are from multivariable linear regression models with restricted cubic splines. Behavior score is the continuous outcome and predictors include linear and two spline terms for 2D:4D, child's age and handedness, socioeconomic status, presence of food insecurity with hunger in the household, and maternal height. Robust estimates of variance were specified in all models. Complete case analysis ($n = 448$).

Results

Mean ± SD age at assessment was 14.7 ± 1.7 years; 44% of children were boys. Right-hand 2D:4D was 0.953 ± 0.031 in boys and 0.957 ± 0.032 in girls (mean difference = −0.004; 95% CI: −0.008, −0.0006; $P = 0.02$). Corresponding left-hand values were 0.962 ± 0.032 and 0.969 ± 0.036 (mean difference = −0.006; 95% CI: −0.01, −0.002; $P = 0.003$). Mean total externalizing behavior problem scores were 51.9 ± 9.6 for boys and 53.1 ± 9.6 for girls. Mean total internalizing behavior problem scores were 53.4 ± 9.7 for boys and 54.1 ± 10.1 for girls. Attention, thought, and social problem scores were 51.9 ± 3.6, 54.7 ± 6.1, and 56.1 ± 6.6, respectively, for boys and 52.6 ± 3.7, 54.6 ± 5.8, and 56.8 ± 7.4, respectively, for girls.

Boys

Right-hand 2D:4D was positively associated with child's age (Supplemental Table 2). Both right and left-hand 2D:4D were positively related to BMI-for-age Z score and screen time, and inversely to food insecurity with hunger (Supplemental Table 2).

Externalizing behavior

Right-hand 2D:4D was positively related to total externalizing behavior in a nonlinear manner (Table 1, Figure 1A). Compared with the middle 2D:4D quintile, mean externalizing behavior for adolescents at the lowest quintile was an adjusted 4.6 (95% CI: −7.5, −1.7) units lower. The association was not significant for 2D:4D values above the median. This association was driven by both aggressive and rule-breaking behaviors (Supplemental Table 3). Left-hand 2D:4D was not significantly associated with total externalizing behavior (Table 1) or its subscales (Supplemental Table 3).

Internalizing behavior

Lower right-hand 2D:4D was related to decreased total internalizing behavior (Table 1, Figure 1B). The adjusted behavior score difference between first and third 2D:4D quintiles was −3.5 (95% CI: −6.4, −0.6). This association was driven by all 3 internalizing behavior subscales (Supplemental Table 4). Left-hand 2D:4D was not significantly related to internalizing behavior (Table 1, Supplemental Table 4).

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Table 2. 2D:4D and attention, thought, and social problems in adolescent boys from Bogotá, Colombia

	2D:4D quintile (median right hand/left hand)					
Behavior problems	1 $n = 91$ (0.91/0.92)	2 $n = 92$ (0.94/0.94)	3 $n = 92$ (0.95/0.96)	4 $n = 92$ (0.97/0.98)	5 $n = 91$ (0.99/1.00)	*P* trend[1]
Attention problems						
Right hand						
Mean ± SD	51.2 ± 2.6	51.8 ± 3.8	52.7 ± 4.7	52.1 ± 3.5	51.6 ± 2.9	0.27
Adjusted difference (95% CI)[2]	−1.4 (−2.5, −0.3)	−0.9 (−2.1, 0.3)	Reference	−0.4 (−1.6, 0.7)	−1.2 (−2.3, −0.1)	0.41
Left hand						
Mean ± SD	51.5 ± 3.4	52.1 ± 4.5	52.6 ± 3.8	51.7 ± 3.1	51.7 ± 2.9	0.99
Adjusted difference (95% CI)	−1.2 (−2.2, −0.2)	−0.4 (−1.6, 0.8)	Reference	−0.8 (−1.7, 0.2)	−0.8 (−1.8, 0.2)	0.70
Thought problems						
Right hand						
Mean ± SD	53.3 ± 4.5	54.6 ± 6.0	55.3 ± 6.4	54.9 ± 6.4	55.3 ± 6.7	0.02
Adjusted difference (95% CI)	−2.1 (−3.8, −0.5)	−0.7 (−2.5, 1.0)	Reference	−0.4 (−2.2, 1.5)	0.0 (−1.9, 1.8)	0.02
Left hand						
Mean ± SD	53.7 ± 5.2	54.9 ± 6.6	55.8 ± 6.6	55.0 ± 6.3	54.1 ± 5.4	0.67
Adjusted difference (95% CI)	−2.3 (−4.1, −0.6)	−0.8 (−2.7, 1.1)	Reference	−0.6 (−2.5, 1.3)	−1.6 (−3.4, 0.2)	0.43
Social problems						
Right hand						
Mean ± SD	55.0 ± 5.5	56.5 ± 6.6	56.7 ± 7.2	56.1 ± 6.6	56.3 ± 7.1	0.21
Adjusted difference (95% CI)	−1.9 (−3.9, 0.0)	0.1 (−1.9, 2.1)	Reference	−0.6 (−2.6, 1.4)	−0.3 (−2.3, 1.7)	0.20
Left hand						
Mean ± SD	56.2 ± 6.5	56.5 ± 7.4	56.3 ± 7.1	55.7 ± 5.8	55.9 ± 6.2	0.54
Adjusted difference (95% CI)	−0.1 (−2.2, 1.9)	0.3 (−1.8, 2.4)	Reference	−0.4 (−2.3, 1.5)	−0.3 (−2.3, 1.6)	0.65

[1]Wald test for an ordinal variable representing quintile medians, introduced into a linear regression model as a continuous predictor.
[2]From multiple linear regression adjusted for child's age and handedness, socioeconomic status, presence of household food insecurity with hunger, and maternal height. Robust estimates of variance were specified in all models. Complete case analysis ($n = 448$).

Attention, thought, and social problems

Both right- and left-hand lower 2D:4D were significantly related to decreased attention and thought problems (Table 2, Supplemental Figures 1A and 1B). Right-hand 2D:4D was related to social problems (quintiles 1–3 adjusted mean difference = −1.9; 95% CI: −3.9, 0.0) (Table 2, Supplemental Figure 1C).

Girls

Right-hand 2D:4D was positively associated with age and BMI-for-age Z score (Supplemental Table 5). Left-hand 2D:4D was positively related to BMI-for-age Z score, left-handedness, and maternal height; and inversely associated with food insecurity with hunger (Supplemental Table 5).

Externalizing behavior

Lower right-hand 2D:4D was related to less total externalizing behavior (Table 3, Figure 2A). The adjusted mean difference in externalizing behavior between quantiles 1 and 3 was −3.4 (95% CI: −5.9, −0.9). This difference was driven by the aggressive behavior subscale (Supplemental Table 6). Left-hand 2D:4D was positively related to rule-breaking behavior (Supplemental Table 6).

Internalizing behavior

Girls at the lowest right-hand 2D:4D quintile had an adjusted 3.5 units lower (95% CI: −6.2, −0.8) total internalizing behavior score than did girls at the third quintile (Table 3, Figure 2B). This association was primarily driven by the anxious/depressed behavior subscale (Supplemental Table 7).

Attention, thought, and social problems

Low right-hand 2D:4D was marginally related to decreased attention problems (Supplemental Figure 2A) but not to thought problems (Table 4, Supplemental Figure 2B). Social problems were an adjusted −2.5 units lower (95% CI: −4.5, −0.6) in girls at the lowest right-hand 2D:4D quintile than in those at the third quintile (Table 4, Supplemental Figure 2C).

Further adjustment for child's BMI-for-age and screen time did not change the associations in boys (Supplemental Table 8) or girls (Supplemental Table 9).

Discussion

In this cross-sectional study, a lower 2D:4D was associated with decreased total externalizing and internalizing behavior problem scores in boys and girls. In addition, low 2D:4D was related to decreased attention and thought problems in boys, and to less

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Table 3. 2D:4D and total externalizing and internalizing behavior problems in adolescent girls from Bogotá, Colombia

	2D:4D quintile (median right hand/left hand)					
Behavior problems	1 *n* = 116 (0.92/0.93)	2 *n* = 117 (0.94/0.95)	3 *n* = 117 (0.96/0.97)	4 *n* = 117 (0.97/0.99)	5 *n* = 117 (1.00/1.01)	*P* trend[1]
Total externalizing problems						
Right hand						
Mean ± SD	51.6 ± 9.7	52.3 ± 8.8	55.0 ± 10.2	52.9 ± 9.6	53.6 ± 9.4	0.08
Adjusted difference (95% CI)[2]	−3.4 (−5.9, −0.9)	−2.4 (−4.8, 0.0)	Reference	−2.3 (−4.8, 0.2)	−1.7 (−4.1, 0.7)	0.17
Left hand						
Mean ± SD	52.0 ± 9.5	53.9 ± 9.4	53.9 ± 10.3	53.3 ± 9.3	52.2 ± 9.4	0.91
Adjusted difference (95% CI)	−2.3 (−4.9, 0.3)	−0.3 (−2.8, 2.2)	Reference	−0.7 (−3.1, 1.7)	−1.8 (−4.2, 0.5)	0.91
Total internalizing problems						
Right hand						
Mean ± SD	52.1 ± 10.9	53.1 ± 9.2	55.6 ± 10.3	55.3 ± 10.3	54.6 ± 9.3	0.02
Adjusted difference (95% CI)	−3.5 (−6.2, −0.8)	−2.4 (−4.8, 0.0)	Reference	−0.4 (−2.9, 2.2)	−1.5 (−4.0, 1.0)	0.05
Left hand						
Mean ± SD	53.5 ± 10.6	55.0 ± 9.7	54.4 ± 10.4	54.4 ± 9.6	53.4 ± 10.2	0.82
Adjusted difference (95% CI)	−1.1 (−3.8, 1.6)	0.5 (−2.0, 3.0)	Reference	0.1 (−2.3, 2.6)	−1.3 (−3.8, 1.2)	0.77

[1]Wald test for an ordinal variable representing quintile medians, introduced into a linear regression model as a continuous predictor.
[2]From multiple linear regression adjusted for child's age and handedness, maternal height, socioeconomic status, and presence of household food insecurity with hunger. Robust estimates of variance were specified in all models. Complete case analysis ($n = 569$).

social problems among girls. The associations between 2D:4D and behavior problem scores were nonlinear and apparent only below the sex-specific 2D:4D medians. Associations were generally stronger with the right-hand 2D:4D than with the left.

The positive association between 2D:4D and externalizing behavior problems is contrary to our study hypothesis and to results from some previous studies (Hönekopp & Watson, 2011; Hampson et al., 2008; Liu et al., 2012). For example, in a study of 239 Chinese adolescents, there was an inverse association between left-hand 2D:4D and YSR externalizing behavior among boys (Liu et al., 2012). Also, in a meta-analysis of studies in adults there was a weak inverse association between 2D:4D and aggression in males (Hönekopp & Watson, 2011); whereas among 164 Canadian undergraduate students, a lower 2D:4D was associated with higher levels of aggressiveness in both sexes (Hampson et al., 2008). Also contrary to previous findings was the positive association between 2D:4D and attention problems in boys. In the study of Chinese adolescents, there was an inverse association between 2D:4D and attention problems among boys (Liu et al., 2012). In addition, while we found no association between 2D:4D and attention problems in girls, among 187 college students from the United States, lower left-hand 2D:4D was related to a greater number of attention deficit/hyperactivity disorder symptoms among females (Stevenson et al., 2007).

Different reasons could explain the discrepancies between studies. First, there are differences between study populations with respect to age and ethnicity. Most studies examined young children or adults, whereas our study focused on adolescents. It is possible that the direction of an association between 2D:4D and externalizing behavior changes with age. This may imply, however, that 2D:4D changes postnatally, contrary to the initial assumption that it is set *in utero* and does not vary thereafter. Some longitudinal investigations have demonstrated changes in 2D:4D throughout childhood (Knickmeyer et al., 2011; Kralik et al., 2014; McIntyre et al., 2005; Trivers et al., 2006; Wong & Hines, 2016). Thus, 2D:4D assessed in adolescence may not necessarily reflect an intrauterine androgenic effect. Another relevant difference is that our study population has substantial genetic admixture (Rishishwar et al., 2015) whereas some of the previous investigations have been conducted in relatively more homogeneous groups. Differences in 2D:4D may be more substantial across ethnic groups than between sexes (Manning et al., 2009), and few previous studies have assessed 2D:4D in Latin American populations. Variability in behavior problem scores may also differ between populations. Second, there are differences in the methods used to assess digit length across studies. We measured digit lengths directly using calipers; but many studies have used indirect measures such as digit length from photocopies of the hand. Hand photocopies can involve exerting excessive pressure on the soft tissue of the digits, which results in less accurate 2D:4D estimates than the direct measurements yield. For example, sex differences in 2D:4D tend to be larger from hand photocopy assessments than they are from direct caliper measurements (Hönekopp & Watson, 2010). The magnitude of 2D:4D sex differences in our study is comparable to that in other studies that used direct caliper measurements (Austin et al., 2002; Barrett et al., 2021; Liu et al., 2012; Manning et al., 2009; Portnoy et al., 2015; Yuan et al., 2021) but smaller than that from studies that used hand photocopies (Berenbaum et al., 2009; Fink et al., 2004; Knickmeyer et al., 2011; Lutchmaya et al., 2004; Manning et al., 2000, 2004; Millet & Dewitte, 2006; Putz et al., 2004; Wong & Hines, 2016). Few studies of 2D:4D and behavior have used direct caliper measurements, and among those that did, associations were not consistently found in both sexes, both hands, or in the expected directions, similar to our results (Austin et al., 2002; Barrett et al., 2021; Liu et al., 2012; Portnoy et al., 2015; Stevenson et al., 2007).

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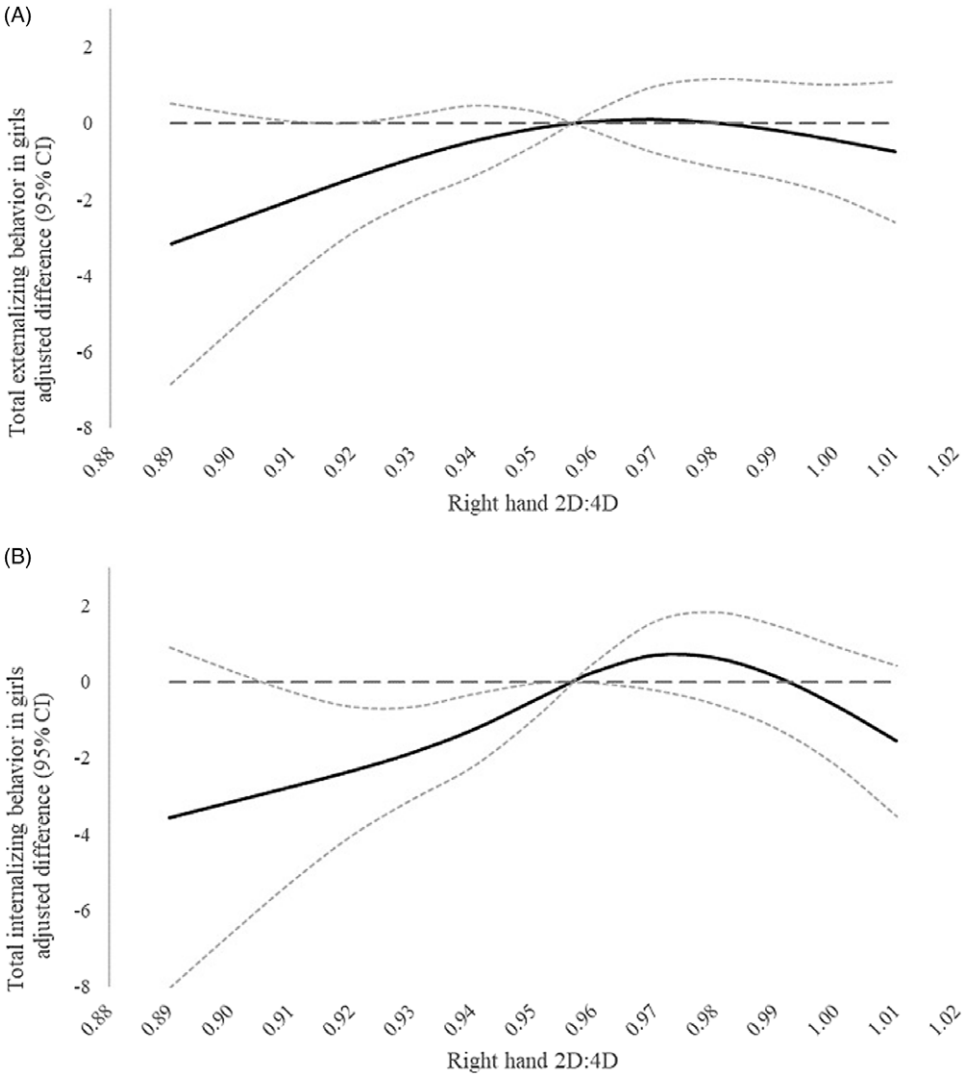

Figure 2. Adjusted differences in total externalizing (A) and total internalizing (B) behavior problem scores according to right-hand 2D:4D in girls from Bogotá, Colombia. The solid line represents adjusted differences between behavior problem scores at each 2D:4D value and the problem score at the median value of the 2D:4D distribution. Dotted lines represent 95% confidence intervals. Estimates are from multivariable linear regression models with restricted cubic splines. Behavior score is the continuous outcome and predictors include linear and two spline terms for 2D:4D, child's age and handedness, socioeconomic status, presence of food insecurity with hunger in the household, and maternal height. Robust estimates of variance were specified in all models. Complete case analysis ($n = 569$).

Although a majority of studies found inverse relations between 2D:4D and externalizing behavior, a positive association has been reported previously. In a study of 353 adolescents from the United States, right-hand 2D:4D was positively associated with YSR total externalizing behavior scores among boys (Portnoy et al., 2015), consistent with our findings. Of note, 80% of participants in the study were African American, which highlights a potential role of ethnicity on the direction of this association. In addition, there was an interaction between 2D:4D and cortisol reactivity on the prediction of externalizing problems, which led authors to suggest that prenatal androgen exposure may moderate the relation between postnatal sex hormones and externalizing behavior, potentially explaining the heterogeneity of this finding across studies (Portnoy et al., 2015).

Internalizing problems may arise from decreased testosterone antagonism at serotonin receptors, which would increase serotonin reuptake in low testosterone conditions (Ebinger et al., 2009). By contrast, the etiology of externalizing problems may involve decreased expression of genes encoding dopamine receptors as a result of increased androgen exposure (Weeland et al., 2015). If low postnatal 2D:4D represents high prenatal testosterone exposure and increased exposure to prenatal testosterone causes phenotypically androgenic outcomes, a low 2D:4D should be associated with increased externalizing behaviors. Notwithstanding, in our study this association was in the opposite direction. This lack of consistency may call into question the usefulness of postnatal 2D:4D in predicting sex hormone-dependent health outcomes.

One explanation for this lack of consistency could be that postnatal 2D:4D may not represent intrauterine androgenic exposure. First, the differential effect of intrauterine androgens on finger growth may be weaker than initially hypothesized. While one animal experiment showed that intrauterine androgens decreased the 2D:4D (Zheng & Cohn, 2011), another found the opposite (Huber et al., 2017). Also, testosterone concentrations in amniotic fluid were unrelated to the 2D:4D in children aged 2 years (Lutchmaya et al., 2004). Second, many longitudinal studies have found that 2D:4D changes postnatally (Knickmeyer et al., 2011; Kralik et al., 2014; McIntyre et al., 2005; Trivers et al., 2006; Wong & Hines, 2016); our own finding of a cross-sectional positive association between age and 2D:4D in boys and girls is consistent with this notion. Hence, the correlation of postnatal 2D:4D values with those purportedly set *in utero* may vary with age. Third, if the 2D:4D were an immutable trait determined *in utero*, it should be uncorrelated with postnatal characteristics that are unaffected by intrauterine sex hormones; yet, we found significant associations between 2D:4D and some of such variables, including screentime

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Table 4. 2D:4D and attention, thought, and social problems in adolescent girls from Bogotá, Colombia

	2D:4D quintile (median right hand/left hand)					
Behavior problems	1 $n = 116$ (0.92/0.93)	2 $n = 117$ (0.94/0.95)	3 $n = 117$ (0.96/0.97)	4 $n = 117$ (0.97/0.99)	5 $n = 117$ (1.00/1.01)	*P* trend[1]
Attention problems						
Right hand						
Mean ± SD	52.1 ± 3.4	52.4 ± 4.0	53.0 ± 4.1	52.1 ± 2.7	53.2 ± 4.0	0.07
Adjusted difference (95% CI)[2]	−0.9 (−1.9, 0.1)	−0.5 (−1.5, 0.5)	Reference	−0.8 (−1.7, 0.0)	0.1 (−0.9, 1.1)	0.09
Left hand						
Mean ± SD	52.6 ± 3.8	52.8 ± 4.0	52.4 ± 4.0	52.6 ± 3.7	52.4 ± 3.1	0.56
Adjusted difference (95% CI)	0.0 (−1.0, 1.0)	0.2 (−0.8, 1.2)	Reference	0.2 (−0.8, 1.2)	0.0 (−0.9, 0.9)	0.99
Thought problems						
Right hand						
Mean ± SD	54.1 ± 5.8	53.8 ± 5.0	55.1 ± 6.4	55.1 ± 5.8	54.9 ± 5.7	0.08
Adjusted difference (95% CI)	−1.0 (−2.6, 0.5)	−1.1 (−2.6, 0.3)	Reference	−0.1 (−1.6, 1.5)	−0.4 (−1.9, 1.2)	0.18
Left hand						
Mean ± SD	53.8 ± 5.5	55.4 ± 6.1	55.2 ± 6.6	54.2 ± 5.3	54.4 ± 5.2	0.99
Adjusted difference (95% CI)	−1.4 (−3.0, 0.1)	0.2 (−1.4, 1.7)	Reference	−1.0 (−2.5, 0.5)	−0.9 (−2.3, 0.6)	0.99
Social problems						
Right hand						
Mean ± SD	55.6 ± 6.6	56.1 ± 6.7	58.1 ± 8.4	56.8 ± 7.0	57.5 ± 7.9	0.03
Adjusted difference (95% CI)	−2.5 (−4.5, −0.6)	−1.8 (−3.8, 0.1)	Reference	−1.0 (−3.0, 0.9)	−0.7 (−2.8, 1.4)	0.04
Left hand						
Mean ± SD	56.0 ± 6.7	57.6 ± 8.4	57.3 ± 7.0	56.8 ± 7.9	56.4 ± 6.8	0.99
Adjusted difference (95% CI)	−1.7 (−3.5, 0.1)	0.1 (−1.8, 2.1)	Reference	−0.4 (−2.3, 1.5)	−1.2 (−2.9, 0.6)	0.84

[1]Wald test for an ordinal variable representing quintile medians, introduced into a linear regression model as a continuous predictor.
[2]From multiple linear regression adjusted for child's age and handedness, socioeconomic status, presence of household food insecurity with hunger, and maternal height. Robust estimates of variance were specified in all models. Complete case analysis ($n = 569$).

and food insecurity, within each sex. Another explanation to the unexpected findings is that, contrary to convention, externalizing behaviors may not preponderantly result from androgenic exposure in all populations. For example, we found that girls had higher externalizing behavior scores than boys, on average. This highlights the importance of considering that estimates of association may not be transportable between population groups, and examining the reasons for these differences.

In our study, the associations between behavior problems and 2D:4D were stronger for the right hand than they were for the left hand. This is consistent with many previous investigations of the digit ratio in relation to personality traits and health outcomes (Fink et al., 2004; Hampson et al., 2008; Manning et al., 1998). It has been proposed that the right hand may be more sensitive to the effect of testosterone *in utero* than the left hand (Hönekopp & Watson, 2010); however, because the role of intrauterine androgens on finger growth has not been settled, the reason for the differences in the associations by laterality is still uncertain.

The inverse association of a low SES indicator, namely food insecurity, with 2D:4D in boys, deserves consideration. We are unaware of studies examining social disadvantage with respect to the 2D:4D, an important follow-up question. Because 2D:4D reflects the physical growth of the extremities, it might be influenced by environmental factors that affect postnatal growth generally, including poor diet and infectious morbidity, which result from socioeconomic disadvantage. Future studies on this area are warranted.

Our study has several strengths. First, it was conducted in a large and representative sample of adolescents from an understudied population. Second, 2D:4D was computed from direct caliper measurements, which may be more valid than those obtained using hand photocopies. The measurements had high ICCs, indicating adequate reliability. Additionally, there was indirect evidence of internal validity, since the 2D:4D sex differences were similar to those in previous studies that also utilized caliper measurements (Austin et al., 2002; Liu et al., 2012; Manning et al., 2009; Yuan et al., 2021). Third, we employed an outcome assessment instrument, the YSR questionnaire, that has been validated in populations similar to ours (Ivanova et al., 2007). Finally, we had an opportunity to control for relevant potential confounders of the association between digit ratio and behavior problems.

One important limitation of the study is its cross-sectional design, which precludes us from establishing the temporal sequence of the associations. However, under the original assumption that 2D:4D is determined *in utero* and does not change thereafter (Lutchmaya et al., 2004; Malas et al., 2006; Manning et al., 1998), the temporality of the exposure-outcome

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association can be reasonably inferred and reverse causation bias should not affect the results.

In conclusion, right-hand low digit ratio in adolescence is related to decreased behavior problem scores in both males and females. 2D:4D does not consistently predict behavior outcomes in the directions expected from an intrauterine androgenic exposure origin only. Because virtually all investigations of the 2D:4D in relation to behavior problems have been cross-sectional, their results are heterogeneous, and the 2D:4D may change postnatally, longitudinal studies of the associations between 2D:4D change and the development of behavior problems are warranted to elucidate the nature of these relations.

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