RESEARCH ARTICLE

• Article No: 9

Turkish Journal of Psychiatry (2026) **37**:67–76
https://doi.org/10.5080/u27834

Prenatal Hormonal Markers in Neurodevelopment: The 2D:4D Digit Ratio in Children with Tic Disorders

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ABSTRACT

Objective: This study investigates the association between tic disorders in children and adolescents and the 2D:4D digit ratio (the ratio of index to ring finger lengths), a widely recognized indirect marker of prenatal hormonal exposure. Given the higher prevalence of tic disorders among males, we assessed whether 2D:4D ratios are related to both the presence and severity of tic disorders.

Methods: This observational, cross-sectional study included 57 children and adolescents diagnosed with tic disorders according to DSM-5 criteria and 52 age and sex-matched healthy controls. The lengths of the second (2D) and fourth (4D) digits on both hands were measured using digital calipers, and 2D:4D ratios were calculated accordingly. Tic severity was evaluated using the Yale Global Tic Severity Scale (YGTSS). Statistical analyses included group comparisons, correlation analyses, and logistic regression models.

Results: The tic disorder group exhibited significantly shorter absolute 2D and 4D finger lengths bilaterally compared to healthy controls. With respect to digit ratios, the right-hand 2D:4D ratio was significantly higher in the tic disorder group compared to controls ($p < 0.01$), while no significant difference was observed for the left-hand 2D:4D ratio. No significant correlations were identified between right- or left-hand 2D:4D ratios and total or subscale scores of the YGTSS. Logistic regression analysis demonstrated that an increase in the right-hand 2D:4D ratio was inversely associated with the likelihood of a tic disorder diagnosis, whereas age and sex were not significant contributors to the model.

Conclusions: These findings reveal pronounced group differences in absolute finger lengths between children and adolescents with tic disorders and healthy controls; however, 2D:4D ratios were not directly associated with tic severity. The results suggest that the 2D:4D ratio may be more appropriately considered a supportive biological marker reflecting neurodevelopmental vulnerability, rather than a robust or specific clinical indicator for tic disorders.

Keywords: 2D:4D digit ratio, Neurodevelopment, Prenatal hormonal exposure, Tic disorders, Yale Global Tic Severity Scale

INTRODUCTION

Tic disorders are neurodevelopmental conditions characterized by involuntary, sudden, rapid, non-rhythmic, and repetitive motor movements or vocalizations. Clinical presentations may include motor tics, vocal tics, or a combination of both symptom domains. Tic disorders typically arise in childhood, exhibit a fluctuating clinical course, and display considerable variability in symptom severity over time. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), tic disorders are classified into three main categories: Tourette Disorder, Persistent (Motor or Vocal) Tic Disorder, and Provisional Tic Disorder ((American Psychiatric Association [APA], 2013), Ünal et al. 2019a).

Population-based epidemiological studies indicate that the lifetime prevalence of tic disorders in childhood ranges from 4% to 12%, with approximately 5% reported for provisional tic disorder, 0.5–3% for persistent motor or vocal tic disorder, and around 1% for Tourette disorder (Khalifa and von Knorring 2005, Robertson 2008). Tic disorders are observed significantly more frequently in boys

How to cite: Karaca BŞ, Özyurt G. (2026) Prenatal Hormonal Markers in Neurodevelopment: The 2D:4D Digit Ratio in Children with Tic Disorders. *Turk Psikiyatri Derg* **37**:67–76.. https://doi.org/10.5080/u27834

Received: 22.10.2025, **Accepted:** 12.02.2026, **Publication Date:** 31.03.2026

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than in girls, with reported male-to-female ratios ranging from 2:1 to 4:1 (Leckman et al. 2014). This pronounced sex difference is evident not only in prevalence rates but also in clinical presentation, patterns of psychiatric comorbidity—particularly attention-deficit/hyperactivity disorder and obsessive-compulsive disorder—and several clinical characteristics (Garcia-Delgar et al; EMTICS Collaborative Group 2022, Szejko et al. 2022).

Although the etiopathogenesis of tic disorders has not been fully elucidated, current evidence indicates that their development is multifactorial, involving genetic susceptibility, functional alterations in dopaminergic neurotransmission, structural and functional abnormalities within basal ganglia–cortical circuits, and both environmental and prenatal–perinatal risk factors (Albin and Mink 2006). Within this context, increasing attention has been directed towards the potential influence of prenatal biological factors, particularly in neurodevelopmental disorders that display pronounced sex differences.

One biological marker posited to indirectly reflect the effects of prenatal androgen exposure on neurodevelopment is the second-to-fourth digit ratio (2D:4D), defined as the ratio of the lengths of the index (second) and ring (fourth) fingers. This ratio is believed to be determined by the balance of prenatal testosterone and estrogen during early gestation and is considered to remain relatively stable after birth (Manning 2002, Zheng and Cohn 2011). Lower 2D:4D ratios have been hypothesized to reflect higher prenatal androgen exposure. Additionally, the 2D:4D ratio has been shown to be associated not only with biological processes but also with individuals' behavioral and psychosocial characteristics (Csathó et al., 2003).

The 2D:4D ratio has been explored as an indirect biomarker of fetal hormonal exposure across a range of neurodevelopmental and psychiatric conditions, particularly those involving dopaminergic and frontostriatal circuitry (Noipayak, 2009, Kornhuber et al. 2011). Low 2D:4D ratios have also been shown to be associated with behavioral traits such as aggression, attention-deficit/hyperactivity disorder, and risk-taking (Kornhuber et al. 2011). However, findings in the literature remain heterogeneous, with several studies failing to identify significant associations between 2D:4D ratios and clinical features or symptom severity (Wernicke et al. 2020). These inconsistencies suggest that the 2D:4D ratio may be more accurately conceptualized as a developmental indicator with low-to-moderate sensitivity, rather than a direct and highly specific biomarker of prenatal hormonal exposure (Richards 2017, Wernicke et al. 2020).

The lateralization of the 2D:4D ratio remains a subject of ongoing debate in the literature. While some studies suggest that right-hand 2D:4D ratios more distinctly reflect biological sex differences, others argue that the left hand may be more sensitive to prenatal hormonal influences (Manning et al. 1998, Hönekopp and Watson 2010, Kornhuber et al., 2011). Accordingly, separately evaluating right and left-hand 2D:4D ratios is important for discerning potential asymmetrical patterns related to prenatal biological factors.

The elevated prevalence of tic disorders in males, coupled with their neurodevelopmental features involving dopaminergic frontostriatal circuitry, underscores the relevance of exploring biologically informed markers of prenatal androgen exposure. Nevertheless, the literature on the 2D:4D ratio in tic disorders is limited, with findings remaining inconsistent. Some recent studies have identified lower left-hand 2D:4D ratios in children with tic disorders compared to healthy controls, yet the generalizability of these results remains to be established (Şahin et al. 2024).

The present study sought to compare right and left-hand 2D:4D ratios between children diagnosed with tic disorders and healthy controls, and to assess the relationship between digit ratios and tic severity. The primary hypothesis posited that children with tic disorders would show significant differences in right and/or left-hand 2D:4D ratios compared to healthy controls. As a secondary aim, the association between 2D:4D ratios and Yale Global Tic Severity Scale (YGTSS) scores was investigated. This approach is grounded in the assumption that prenatal biological influences may confer neurodevelopmental vulnerability, although they may not directly determine the current severity of clinical symptoms.

METHODS

Study Design and Procedure

This study utilized an observational, cross-sectional design. Data collection was conducted between February 2024 and March 2025 at a tertiary care center providing services in child and adolescent psychiatry. During this period, participants were systematically assessed using semi-structured clinical interviews (K-SADS-PL) that incorporated both parent and child evaluations.

The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (Date/Approval No: 18.01.2024/0016). Written informed consent was obtained from parents, and verbal consent was secured from participating children. All data

were anonymized using unique identification codes and stored in a secure digital environment accessible exclusively to the research team.

Participants

A total of 109 children and adolescents were included in this study, comprising 57 participants diagnosed with tic disorders according to DSM-5 criteria and 52 healthy controls. All participants were between 8 and 18 years of age, and the tic disorder and control groups were comparable in terms of age and sex distribution.

The tic disorder group consisted of consecutive cases presenting to the child and adolescent psychiatry outpatient clinic who met DSM-5 diagnostic criteria for Tourette Disorder, Persistent (Motor or Vocal) Tic Disorder, or Provisional Tic Disorder (APA 2013). Initially, 65 patients were assessed; eight were excluded due to not meeting diagnostic criteria or declining participation, resulting in a final sample of 57 participants.

The control group was recruited from children and adolescents attending the pediatric outpatient clinic at the same hospital who volunteered to participate. Of 60 potential controls screened, eight were excluded following comprehensive psychiatric evaluation due to a current or lifetime psychiatric diagnosis, yielding a final sample of 52 healthy participants. Psychiatric assessments in the control group were conducted using the K-SADS-PL, ensuring the absence of any psychiatric disorders.

Inclusion criteria were: age between 8 and 18 years, right-hand dominance (to ensure measurement standardization), and provision of informed consent by parents and participants.

Exclusion criteria included: history of finger trauma, deformity, fracture, or surgery; neurological disorders such as epilepsy, cerebral palsy, or traumatic brain injury; intellectual disability; autism spectrum disorder; psychotic disorders; and any endocrine or systemic medical conditions.

All participants were enrolled following evaluation according to the predefined inclusion and exclusion criteria. Before digit ratio measurements, all individuals underwent a comprehensive psychiatric assessment involving semi-structured interviews and detailed clinical evaluation.

Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)

All participants were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL), a semi-structured diagnostic interview designed to assess major psychiatric disorders in children and adolescents based on DSM criteria (APA 2013). The K-SADS-PL facilitates systematic assessment of both current symptomatology and lifetime psychiatric history.

The interview was conducted separately with parents and children and encompasses a broad spectrum of diagnostic domains, including mood disorders, anxiety disorders, tic disorders, attention-deficit/hyperactivity disorder, and other neurodevelopmental conditions. This comprehensive approach enabled a thorough evaluation of psychopathology across multiple clinical domains.

The Turkish adaptation of the K-SADS-PL, validated by Ünal et al. (2019b), has demonstrated satisfactory reliability and validity. In this study, K-SADS-PL interviews were administered by experienced child and adolescent psychiatrists, and diagnostic decisions were established through clinical consensus based on information obtained from both parent and child interviews.

Yale Global Tic Severity Scale (YGTSS)

Tic severity was assessed using the clinician-administered Yale Global Tic Severity Scale (YGTSS), a semi-structured instrument that provides a multidimensional evaluation of motor and vocal tic severity in tic disorders. The YGTSS is widely utilized in both research and clinical settings (Leckman et al. 1989).

The scale assesses five core dimensions—number, frequency, intensity, complexity, and interference—separately for motor and vocal tics, with each dimension rated from 0 to 5. Subscores for motor and vocal tics range from 0 to 25 each, and their sum constitutes the Total Tic Severity Score (0–50).

Additionally, the YGTSS includes a Functional Impairment subscale (0–50) evaluating the impact of tics on academic, social, and daily functioning, enabling a comprehensive measure of tic-related impairment. The overall YGTSS total score incorporates both tic severity and functional impairment (Leckman et al. 1989).

The Turkish version of the YGTSS, validated by Zaimoğlu et al. (1995), has demonstrated high inter-rater reliability and internal consistency. In this study, YGTSS assessments were performed by an experienced child and adolescent psychiatrist using standardized administration procedures for all participants.

2D:4D Digit Ratio Measurement

The lengths of the second (2D) and fourth (4D) digits were measured on both hands of all participants using a digital

caliper (Torq®, accuracy: 0.01 mm). Finger length was defined as the distance from the metacarpophalangeal crease to the fingertip, with participants seated and the dorsal surface of the hand facing upward.

For each digit, two measurements were taken; if the difference exceeded ±0.5 mm, a third measurement was obtained and the mean value was used for analysis.

Digit measurements were performed by two independent raters. Prior to data collection, both raters received standardized training on a uniform 2D:4D measurement protocol, which was consistently applied throughout the study. Although raters were not blinded to group allocation, potential measurement bias was minimized by having both raters independently assess all participants, and the arithmetic mean of their measurements was used for statistical analysis. Inter-rater reliability, assessed using the intraclass correlation coefficient (ICC), indicated a high level of agreement (ICC=0.91). Although direct measurements using digital calipers are commonly employed, computer-assisted measurement methods have been reported to provide higher intra- and interobserver reliability (Allaway et al. 2009).

Sociodemographic Data Form

A sociodemographic data form was administered to collect information on participant characteristics, including age, sex, parental age, education level, occupational status, family structure, and medical history. Developed by the research team based on a literature review, the form was completed by parents.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) program version 29.0 (IBM Corp., Armonk, NY, USA). The distributional properties of continuous variables were evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics are presented as mean ± standard deviation or median (minimum-maximum) for continuous variables, and as frequencies and percentages for categorical variables.

Group comparisons were performed using independent-samples t-tests or Mann-Whitney U tests, as appropriate for data distribution. Categorical variables were analyzed using the chi-square test or Fisher's exact test when applicable.

Associations between 2D:4D ratios and tic severity were assessed with Spearman correlation analyses. Analysis of covariance (ANCOVA) was employed to control for potential effects of age and sex, with all underlying assumptions evaluated prior to analysis. Linear relationships between covariates (age and sex) and dependent variables were checked, and homogeneity of regression slopes was tested via interaction terms. Normality of residuals was assessed using Q–Q plots and normality tests. All ANCOVA assumptions were met.

Additionally, binary logistic regression analysis was performed to identify predictors of tic disorder diagnosis, including age, sex, and right- and left-hand 2D:4D ratios as independent variables. All statistical tests were two-tailed, with a significance threshold set at $p < 0.05$.

RESULTS

A total of 109 children participated in the study, consisting of 57 with tic disorders and 52 healthy controls. The mean age was 11.6±3.1 years for the tic disorder group and 11.7±2.3 years for the control group, with no significant difference between groups ($t(107)=0.09$, $p=0.93$). Sex distribution was 93.1% male (n=54) and 6.9% female (n=3) in the tic disorder group, and 82.7% male (n=43) and 12.2% female (n=9) in the control group; this difference was not statistically significant ($\chi^2=0.84$, $p=0.36$).

Comparisons of parental age, parental educational level, occupational status, family structure, parental marital status, household income, and the presence of medical illnesses revealed no statistically significant differences between the tic disorder and control groups (all $p > 0.05$) (Table 1).

According to K-SADS-PL assessments, 29.8% of children in the tic disorder group had a comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD), and 12.3% had obsessive-compulsive disorder (OCD). No mood or psychotic disorders were identified in either group.

When finger lengths and 2D:4D ratios were compared between children with tic disorders and healthy controls, both the second (2D) and fourth (4D) digit lengths on the right and left hands were significantly shorter in the tic disorder group.

Specifically, right-hand second digit (2D) length was significantly lower in the tic disorder group compared to controls ($p=0.017$). Similarly, right-hand fourth digit (4D) length was significantly shorter in the tic disorder group ($p=0.001$). Analysis of left-hand digit lengths yielded comparable results, with both 2D and 4D lengths significantly reduced in the tic disorder group relative to controls ($p=0.005$ and $p=0.009$, respectively) (Table 2).

With respect to digit ratios, the right-hand 2D:4D ratio was significantly higher in the tic disorder group than in controls ($p=0.002$), with a moderate effect size. In contrast, no statistically significant difference was observed between

Table 1. Detailed sociodemographic and clinical characteristics of the sample

Variable	Tic Disorder (n=57)	Control (n=52)	p
Age (years), Mean ± SD	11.6±3.1	11.7±2.3	0.93
Sex, n (%)			0.36
Male	54 (93.1)	43 (82.7)	
Female	3 (6.9)	9 (17.3)	
Maternal age (years), Mean ± SD	40.8±4.9	40.5±4.6	0.74
Paternal age (years), Mean ± SD	44.6±4.2	43.2±4.8	0.18
Maternal education level, n (%)			0.81
Primary school	8 (14.0)	6 (11.5)	
Middle school	10 (17.5)	9 (17.3)	
High school	17 (29.8)	16 (30.8)	
University or higher	22 (38.6)	21 (40.4)	
Paternal education level, n (%)			0.67
Primary school	6 (10.5)	5 (9.6)	
Middle school	12 (21.1)	10 (19.2)	
High school	15 (26.3)	15 (28.8)	
University or higher	24 (42.1)	22 (42.3)	
Maternal occupation, n (%)			0.59
Homemaker/Unemployed	36 (63.2)	31 (59.6)	
Civil servant	8 (14.0)	9 (17.3)	
Self-employed	13 (22.8)	12 (23.1)	
Paternal occupation, n (%)			0.72
Civil servant	16 (28.1)	15 (28.8)	
Self-employed	41 (71.9)	37 (71.2)	
Family structure, n (%)			0.64
Nuclear family	49 (86.0)	46 (88.5)	
Extended family	5 (8.8)	4 (7.7)	
Living with mother	2 (3.5)	1 (1.9)	
Living with father	1 (1.7)	1 (1.9)	
Parental marital status, n (%)			0.61
Together	48 (84.2)	45 (86.5)	
Separated/Divorced	8 (14.0)	6 (11.5)	
Parental loss	1 (1.8)	1 (1.9)	
Household income level, n (%)			0.78
Low	9 (15.8)	7 (13.5)	
Middle	24 (42.1)	23 (44.2)	
Upper-middle	17 (29.8)	16 (30.8)	
High	7 (12.3)	6 (11.5)	
Medical illness, n (%)			0.88
Absent	53 (93.0)	49 (94.2)	
Present	4 (7.0)	3 (5.8)	
ADHD comorbidity, n (%)	17 (29.8)	0	—
OCD comorbidity, n (%)	7 (12.3)	0	—

Values are presented as mean ± standard deviation (SD) or number (percentage). n denotes sample size and % denotes percentage. ADHD: Attention-Deficit/Hyperactivity Disorder; OCD: Obsessive-Compulsive Disorder. p values refer to comparisons between Tic Disorder and Control groups.

Table 2. Group Comparisons of Finger Lengths and 2D:4D Ratios

Variable	Tic Disorder (n = 57) Mean ± SD	Control (n = 52) Mean ± SD	t (df)	p	Cohen's d
Right hand measurements					
2nd digit (2D) length (mm)	67.20 ± 8.76	71.55 ± 9.95	−2.43 (107)	0.017	−0.47
4th digit (4D) length (mm)	66.96 ± 8.09	73.53 ± 12.58	−3.27 (107)	0.001*	−0.63
2D:4D ratio	0.997 ± 0.051	0.971 ± 0.035	3.12 (107)	0.002*	0.60
Left hand measurements					
2nd digit (2D) length (mm)	67.12 ± 8.26	72.17 ± 10.26	−2.84 (107)	0.005	−0.54
4th digit (4D) length (mm)	68.47 ± 8.13	73.84 ± 12.60	−2.67 (107)	0.009	−0.51
2D:4D ratio	0.976 ± 0.051	0.975 ± 0.029	0.10 (107)	0.922	0.02

Note. Group comparisons were conducted using independent-samples t-tests.
For the left-hand 2D:4D ratio, an ANCOVA was additionally performed including age and sex as covariates; the adjusted group effect remained non-significant ($F(1,105) = 0.018$, $p = .895$, partial $\eta^2 = .000$). SD: standard deviation

groups for the left-hand 2D:4D ratio in independent-samples comparisons (p=0.922). Analysis of covariance (ANCOVA), conducted to control for potential effects of age and sex on the left-hand 2D:4D ratio, also showed no significant group effect ($F(1,105)=0.018$, p=0.895, partial $\eta^2=0.000$) (Table 2).

Spearman correlation analyses were conducted to examine associations between 2D:4D ratios and tic severity within the tic disorder group. No statistically significant relationships were found between left-hand 2D:4D ratios and total Yale Global Tic Severity Scale (YGTSS) scores ($r_s=-0.05$, p=0.71), nor between right-hand 2D:4D ratios and total YGTSS scores ($r_s=-0.08$, p=0.58).

Furthermore, none of the correlations between right- or left-hand 2D:4D ratios and YGTSS motor and vocal subscale components (number, frequency, intensity, complexity, and suppressibility of tics) reached statistical significance (all p values >0.05) (Table 3).

A binary logistic regression analysis was performed to identify variables predicting tic disorder diagnosis. The overall model was statistically significant (Omnibus $\chi^2(4)=21.99$, p <0.001), accounting for 18–24% of the variance (Cox and Snell $R^2=0.18$; Nagelkerke $R^2=0.24$). The Hosmer-Lemeshow goodness-of-fit test indicated adequate model fit ($\chi^2(8)=6.08$, p=0.638). Predictors included age, sex, and right- and left-hand 2D:4D ratios.

Both right- and left-hand 2D:4D ratios significantly predicted tic disorder diagnosis. An increase in the right-hand 2D:4D ratio was associated with a lower likelihood of being in the tic disorder group (B=−35.66, Wald=10.86, p=0.001), while higher left-hand 2D:4D ratios were associated with increased likelihood of belonging to the control group (B=25.82, Wald=6.08, p=0.014). Age (p=0.073) and sex (p=0.289) were not significant contributors to the model. The model's overall classification accuracy was 64.2% (Table 4).

Table 3. Correlations Between 2D:4D Ratios and YGTSS Subscale Scores

YGTSS Subscales	Right Hand 2D:4D, r (p)	Left Hand 2D:4D, r (p)
Motor Tic Domains		
Motor Tic Number	−0.02 (.91)	0.03 (.80)
Motor Tic Frequency	0.22 (.09)	0.19 (.16)
Motor Tic Intensity	0.16 (.23)	0.16 (.25)
Motor Tic Complexity	−0.04 (.79)	−0.06 (.69)
Motor Tic Suppressibility	−0.10 (.47)	−0.03 (.85)
Vocal Tic Domains		
Vocal Tic Number	−0.18 (.18)	−0.16 (.22)
Vocal Tic Frequency	−0.17 (.21)	−0.11 (.40)
Vocal Tic Intensity	−0.18 (.19)	−0.09 (.49)
Vocal Tic Complexity	−0.14 (.30)	−0.10 (.46)
Vocal Tic Suppressibility	−0.13 (.35)	−0.10 (.46)
Global Severity Measures		
Functional Impairment	−0.10 (.47)	−0.02 (.86)
YGTSS Motor Total Score	0.06 (.66)	0.07 (.59)
YGTSS Vocal Total Score	−0.15 (.26)	−0.12 (.37)
YGTSS Total Score	−0.08 (.58)	−0.05 (.71)

Note. Values represent Pearson correlation coefficients (r) with two-tailed p values shown in parentheses. None of the correlations reached statistical significance (all $p > .05$). YGTSS: Yale Global Tic Severity Scale

Exploratory subgroup analyses within the tic disorder group compared children with tic disorder only to those with comorbid attention-deficit/hyperactivity disorder (ADHD) or obsessive-compulsive disorder (OCD). No significant differences in mean 2D:4D ratios were observed between the tic-only group and subgroups with comorbid ADHD (p=0.21) or OCD (p=0.34).

Table 4. Binary Logistic Regression Model Predicting Tic Disorder Diagnosis

Predictor	B	SE	Wald χ^2	p	OR (Exp(B))	95% CI Lower	95% CI Upper
Age	0.17	0.10	3.22	.073	1.19	0.98	1.43
Sex (Male)	–0.55	0.52	1.12	.289	0.58	0.21	1.59
Right hand 2D:4D ratio	–35.66	10.82	10.86	.001	<0.001	<0.001	<0.001
Left hand 2D:4D ratio	25.82	10.47	6.08	.014	1.63×10^{11}	198.33	1.34×10^{20}
Constant	7.88	6.38	1.52	.217	2642.50	—	—

Note. Model fit indices: Omnibus $\chi^2(4) = 21.99$, $p < .001$; –2 Log Likelihood = 128.88; Cox & Snell $R^2 = 0.18$; Nagelkerke $R^2 = 0.24$; Hosmer–Lemeshow $\chi^2(8) = 6.08$, $p = .638$; overall classification accuracy = 64.2%.

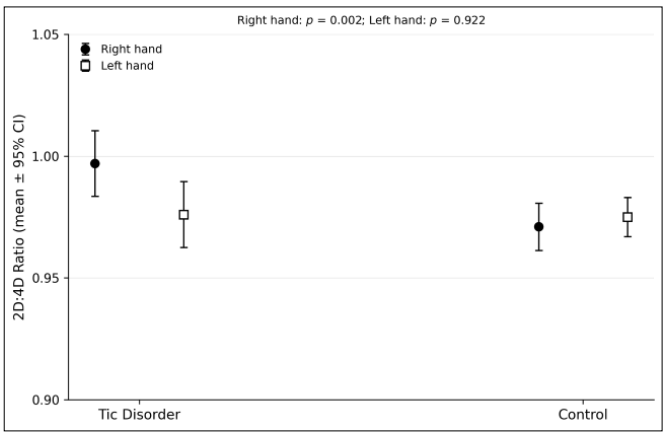

Figure 1. Comparison of right- and left-hand 2D:4D digit ratios between children with tic disorder and healthy controls [Mean 2D:4D digit ratios (±95% CI) for the right and left hands in tic disorder and control groups. A significant group difference was observed for the right hand (p=0.002), whereas the left hand was not significant (p=0.922)].

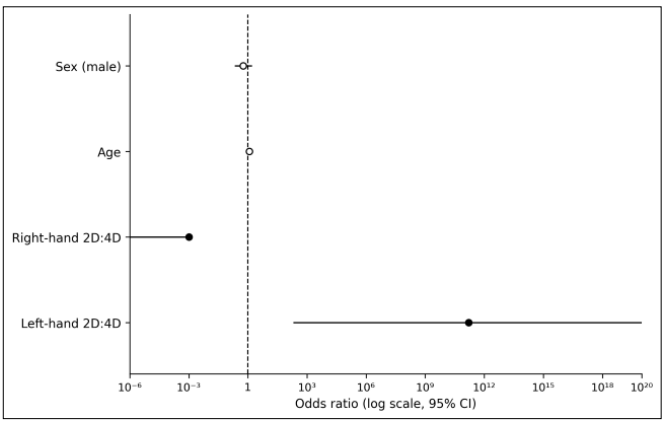

Figure 3. Predictors of tic disorder in logistic regression analysis. [Forest plot showing odds ratios (ORs) and 95% confidence intervals for predictors of tic disorder from the logistic regression model. The vertical dashed line indicates OR=1 (no effect). Right- and left-hand 2D:4D ratios were significant predictors, whereas sex and age were not].

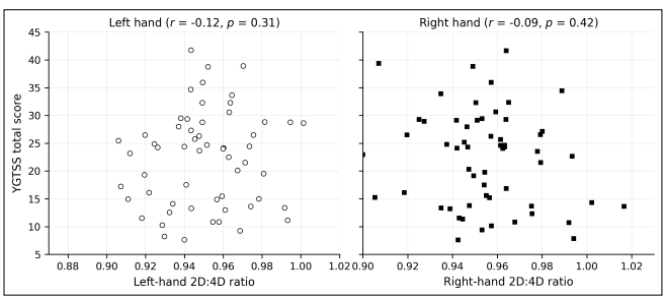

Figure 2. Correlations between 2D:4D digit ratios and tic severity. [Scatter plots showing the associations between left- and right-hand 2D:4D digit ratios and YGTSS total scores in the tic disorder group. No significant correlations were observed for either hand (left: r=–0.12, p=0.31; right: r=–0.09, p=0.42)].

DISCUSSION

This study evaluated 2D:4D digit ratios in a clinical sample of children and adolescents with tic disorders, comparing absolute finger lengths and digit ratios between those with tic disorders and healthy controls. The results revealed that absolute finger lengths were significantly shorter in the tic disorder group for both hands, while group differences in 2D:4D ratios were restricted to the right hand. Importantly, no significant associations were detected between 2D:4D ratios and measures of tic severity, including total and subscale scores on the Yale Global Tic Severity Scale (YGTSS). The lack of group differences in age, sex, and core sociodemographic variables enhances the validity of these findings by minimizing potential confounding effects.

The observation that the right-hand 2D:4D ratio was significantly higher in the tic disorder group compared to healthy controls may indicate lateralized developmental differences potentially related to prenatal hormonal influences. This finding is consistent with previous literature suggesting that right-hand 2D:4D ratios more prominently reflect sex-related differences and prenatal androgen sensitivity (Manning et al. 1998, Hönekopp and Watson 2010). The lateralization observed here aligns with prior research indicating that the right-hand 2D:4D ratio may be more sensitive to prenatal hormonal exposure. Within this framework, the present findings suggest that prenatal hormonal signaling influencing digit development could be indirectly associated with neurodevelopmental mechanisms underlying tic disorders. However, this association should be interpreted as indicative of developmental susceptibility rather than a direct causal relationship (McIntyre 2006; Noipayak, 2009).

Moreover, the observed effect sizes ranged from small-to-moderate to moderate, reinforcing the interpretation that

2D:4D ratios serve as supportive biological indicators rather than robust or specific clinical biomarkers. Indeed, it has been suggested that the 2D:4D ratio may serve not as a direct diagnostic marker for certain psychiatric conditions, but rather as an indicator of developmental vulnerability (Kornhuber et al. 2011).

Although the number of studies investigating 2D:4D ratios in tic disorders and related neurodevelopmental conditions remains limited, the literature reports inconsistent findings. Some studies, particularly those with predominantly male samples, have identified significant associations between 2D:4D ratios and the presence of tic disorders (Myers et al. 2018, Suchonova et al. 2019). Conversely, other investigations have not found significant relationships between 2D:4D ratios and tic severity or clinical subtypes, suggesting limited sensitivity of the 2D:4D ratio as a clinical marker (Jiang et al. 2024). Within this context, the current study's findings align more closely with reports indicating that while 2D:4D ratios may be associated with the presence of tic disorders, they do not appear to reflect symptom severity.

The inconsistencies in the literature may be attributable to differences in sample characteristics and methodological approaches. Factors such as age range, sex distribution, the use of clinical versus community samples, and variability in measurement techniques may all influence results related to 2D:4D ratios. Furthermore, while some studies have focused exclusively on the right hand, others have evaluated both hands, potentially masking lateralization effects (Manning et al. 1998, McIntyre 2006, Hönekopp and Watson 2010). The group difference limited to the right hand observed in this study supports the notion that methodological variation may substantially contribute to inconsistencies across studies.

Taking these methodological and sample-related differences into account, the absence of a significant correlation between 2D:4D ratios and tic severity in the present study suggests that prenatal biological influences may confer vulnerability to tic disorders rather than directly determining current symptom severity. This finding is consistent with theoretical models proposing that the 2D:4D ratio reflects early neurodevelopmental organization, whereas the clinical phenotype is shaped over the lifespan through learning, environmental reinforcement, and cognitive control mechanisms (Albin and Mink 2006, Leckman et al.,2014, Wernicke et al. 2020). The lack of association between tic severity and 2D:4D ratios is also in line with previous reports emphasizing the significant influence of environmental, learning-based, and contextual factors on tic severity (Leckman et al. 2014). Collectively, these findings support conceptual models that distinguish prenatal biological vulnerability markers from the severity of clinical symptom expression.

Contemporary neurobiological models of tic disorders highlight developmental differences within cortico-striato-thalamo-cortical (CSTC) circuits and their relevance to habit learning, motor inhibition, and reward sensitivity (Albin and Mink 2006). It is posited that prenatal androgen–estrogen balance may affect the organizational development of striatal and frontostriatal networks, while tic severity and symptom fluctuations are more strongly shaped by learning-based and environmental mechanisms (Leckman et al. 2014). Within this framework, the current findings may be interpreted as reflecting a developmental vulnerability indicator, particularly within the Cognitive Control and Habit domains of the Research Domain Criteria (RDoC) framework (Zheng and Cohn 2011). This is consistent with findings suggesting that prenatal hormones may play a role not only in morphological development but also in the shaping of behavioral and psychological characteristics (Csathó et al. 2003).

The frequent co-occurrence of tic disorders with attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) in clinical practice suggests the possibility of shared neurodevelopmental and neurobiological substrates (Leckman et al. 2014, Wernicke et al., 2020). Rather than representing independent external confounders, such comorbidities may reflect overlapping developmental mechanisms and shared clinical features.

One methodological strength of the present study is the use of a standardized measurement protocol for digit length assessment, utilizing a high-precision digital caliper. Measurement error and related bias are important concerns in 2D:4D research, and repeated measurements based on clear anatomical reference points are considered essential for minimizing such risks (Manning 2002, McIntyre 2006). The procedure used in this study aligns with methodological recommendations in the 2D:4D literature and supports the reliability of the measurements obtained (Manning et al. 1998, Allaway et al. 2009, Beaton et al. 2011).

Nevertheless, whether the 2D:4D ratio serves as a direct and highly sensitive biomarker of prenatal hormonal exposure remains debated. Previous research has reported weak or inconsistent associations between sex hormone levels measured during early gestation and 2D:4D ratios assessed postnatally or during childhood (Richards 2017). Thus, the 2D:4D ratio should be interpreted as a developmental biological indicator associated with low-to-moderate effect sizes, rather than a causal determinant (Manning and Fink 2008, Crewther et al. 2015).

In conclusion, the present study suggests that finger lengths and 2D:4D ratios may differ in certain respects among children with tic disorders. Specifically, the right-hand 2D:4D ratio may reflect a developmental pattern potentially linked to prenatal biological influences. However, 2D:4D

ratios were not associated with current tic severity, reinforcing a distinction between prenatal biological vulnerability and the dynamic determinants of clinical phenotype. Future research involving larger and more balanced samples, direct hormonal measurements, and longitudinal designs will be necessary to further elucidate the potential role of 2D:4D ratios in tic disorders.

Limitations

Several methodological limitations should be considered when interpreting the findings of this study. First, the cross-sectional design precludes causal inferences regarding the observed associations. Additionally, the relatively modest sample size and marked sex imbalance within the tic disorder group may limit the interpretation of sex-related differences in 2D:4D ratios, which are known to exhibit sexual dimorphism.

Comorbid attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) identified in the tic disorder group were not included as covariates in the primary analyses. This decision was made to avoid loss of statistical power and potential overadjustment, given the small sizes of these subgroups. Nonetheless, this limitation should be considered when evaluating the findings.

In the logistic regression analysis, the relatively large regression coefficient observed for the left-hand 2D:4D ratio may reflect model sensitivity related to sample size and group distribution. Consequently, regression results were interpreted cautiously and reported primarily using odds ratios and 95% confidence intervals rather than raw β coefficients. Moreover, subgroup analyses lacked sufficient statistical power due to small subgroup sizes and were considered exploratory rather than conclusive.

The absence of direct prenatal or postnatal hormonal measurements limited the evaluation of biological variables such as pubertal status and body mass index. Although a standardized measurement protocol was used, measurement bias specific to 2D:4D assessment cannot be entirely excluded. Direct measurements using digital calipers are widely used; however, computer-assisted techniques may offer superior intra- and interobserver reliability (Allaway et al., 2009). Tic severity was evaluated by a single clinician using the Yale Global Tic Severity Scale (YGTSS), which may introduce potential rater bias. Finally, the influence of unmeasured confounding factors, including environmental and genetic variables, cannot be ruled out.

In light of these limitations, the findings of this study should be interpreted as supportive rather than definitive. Future research with larger and more sex-balanced samples, direct hormonal assessments, pubertal measures, and longitudinal designs is required to clarify the relationship between 2D:4D ratios and tic phenotypes (Manning 2002, Hönekopp and Watson 2010).

Ethics Committe Approval: The study protocol was approved by the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee on January 18, 2024, with decision number 0016.

Conflict of Interest: The authors declare no conflicts of interest.

Funding: This research received no external funding.

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