Review
https://doi.org/10.9758/cpn.2021.19.1.26 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2021;19(1):26-45

Second-to-Fourth Digit Ratio (2D:4D) in Psychiatric Disorders: A Systematic Review of Case-control Studies

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The second-to-fourth digit ratio (2D:4D) is an indirect, retrospective, non-invasive measure that correlates negatively with intrauterine exposure to testosterone. The present meta-analysis aimed to evaluate if 2D:4D differs between patients with psychiatric disorders and controls. In September 2019, we searched in Web of Knowledge, PsycINFO, Embase, and CINHAL, and retrieved 619 papers. We finally included 43 case-control studies which compared the 2D:4D ratio of patients with autism spectrum disorder (ASD) (n = 16), schizophrenia (n = 8), gender non-conformity (n = 7), addictions (n = 5), attention deficit-hyperactivity disorder (ADHD) (n = 4), mood disorders (n = 2), and intellectual disability (n = 1) to non-clinical controls. Meta-analyses showed that, overall, psychiatric patients had lower 2D:4D than healthy controls (n = 43, overall sample = 9,484, mean difference = −0.0056, 95% confidence interval from −0.0093 to −0.002, I^2 = 74%), with more pronounced differences in the right hand, males, and children. Considering psychiatric disorders individually, significant differences were found in the ASD, ADHD, and addictions groups, in which 2D:4D was significantly lower than healthy controls. Conversely, the right hand of males with schizophrenia showed higher 2D:4D than healthy controls. No other significant differences were detected. Although our results need to be cautiously interpreted and find limited applications in clinical practice, they may suggest that 2D:4D is altered in some psychopathological conditions, underlining the role of prenatal exposure to sex steroids in the etiology of psychiatric disorders.

KEY WORDS: Meta-analysis; Mental disorders; Testosterone; Autism spectrum disorder; Attention deficit disorder with hyperactivity; Substance addiction.

INTRODUCTION

The second-to-fourth digit ratio (2D:4D) is a biological marker, defined as the ratio of the length of the index (second digit) to the length of the ring finger (fourth digit) of the same hand. 2D:4D is constant throughout life [1,2] and represents an indirect, retrospective, and non-invasive measure that correlates negatively with intrauterine exposure to testosterone, i.e., a lower 2D:4D is the result of increased levels of fetal testosterone [3,4]. Many debates exist around the reasons why 2D:4D could be considered an indirect marker of the prenatal, but not the present, testosterone level [5] and even more strongly, a marker of the ratio between prenatal testosterone and estradiol levels. More evidence is provided by molecular genetic association studies, relating a polymorphism of the androgen receptor gene to individual differences in the 2D:4D ratio [6].

In humans, the 2D:4D ratio has been assumed to reflect the exposure to testosterone during the second trimester of gestation, because of the sex difference detectable in childhood, and because of postulated mechanisms regarding digit development [2]. Prenatal hormone exposure is critical for sexual differentiation and masculinization. In fact, males are exposed to higher levels of testosterone than females, particularly from about week 8 to 24 of gestation and week 2 to 26 of postnatal life [7]. This is con-

Received: May 7, 2020 / **Revised:** July 24, 2020
Accepted: July 26, 2020
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firmed by the observation that the 2D:4D ratio is sexually dimorphic: generally, females have a higher 2D:4D than males and this effect is more pronounced in the right hands, although the reasons still need to be clarified [8].

Digit ratio has been reported to correlate with a wide number of traits and conditions, ranging in almost every field of medicine, with particular regard to sex hormones-dependent conditions, i.e., breast cancer [9], prostate cancer [10,11], obesity [12], and osteoarthritis [13]. It has also been associated with physical characteristics, such as facial shape [14], sperm count [15], age of menarche [16], and penis size [17]. Of interest, scholars have also investigated the association between the 2D:4D ratio and behavioral features, such as aggression [18], stuttering [19], visuo-spatial ability [20], handedness [21], schizotypal personality [22], sporting ability [23], successful financial risk-taking [24], and sexual orientation [25].

Given the findings obtained in the field of behavioral sciences, over the last years, many researchers have sought to examine potential links between the 2D:4D ratio and psychiatric disorders, aiming to find a significant correlation between intrauterine exposure to testosterone and those conditions. Since the amount of available literature has been constantly growing, we aimed to perform a systematic review and meta-analysis to examine if the 2D:4D ratio consistently differed between people with psychiatric disorders and non-clinical controls. Second, we aimed to investigate potential mediators of 2D:4D differences, such as gender, age, and hand.

METHODS

Search Strategy

We followed the PRISMA Statement guidelines to perform a systematic search [26]. The protocol was registered on PROSPERO, an international database of prospectively registered systematic reviews in health and social care managed by the Centre for Reviews and Dissemination, University of York (Registration number: CRD42019124184).

In September 2019, we searched the following databases: Web of Knowledge℠ (including Web of Science, MEDLINE®, KCI—Korean Journal Database, Russian Science Citation Index, and SciELO Citation Index), PsycINFO, Embase, and CINAHL. The complete search string can be found in the Supplementary Materials, Appendix 1 (available online) [27]. The search was not restricted to any language, reference type, or year of publication. The electronic search was supplemented by hand-searching of reference lists of the included review articles to identify any additional sources.

Study Selection

We selected all the studies published in English on peer-reviewed journals, which fulfilled the following inclusion criteria:

(1) Participants: Individuals of any age and gender, diagnosed with any psychiatric disorder according to valid international diagnostic criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders; International Classification of Diseases), or with validated scales (e.g., Hamilton Rating Scale for depression and Positive and Negative Syndrome Scale for schizophrenia), or followed by clinics or mental health services. Studies with patients recruited through web-surveys or subjects divided into groups according to scores obtained at self-reported questionnaires were excluded.

(2) Controls: Individuals with no psychiatric disorders.

(3) Outcome: Measurement of 2D:4D ratio through direct or indirect tools, and availability of data.

(4) Study design: Case-control studies.

Data Extraction

Couples of researchers (SS, BC, AN, DA) independently reviewed and extracted the information from the included articles. Discrepancies were solved after consultation with a third reviewer (LF). We extracted data using a format which included:

(1) Study characteristics: author, year, country.

(2) Participants' characteristics: type of diagnosis, diagnostic tool (only for psychiatric patients), sample size, mean age, age range, proportion of males.

(3) 2D:4D measurement tool.

(4) Mean and standard deviation (SD) of the 2D:4D ratio. If reported in the studies, data were extracted separately for left and right hand, and for males and females.

We contacted study authors via e-mail to request missing data or for clarification, providing an individualized data table for reporting the requested information.

Appraisal of Quality

Quality of the included studies was assessed by two review authors (AR, DA) using the Newcastle-Ottawa qual-

ity assessment scale for case-control studies [28]. Any discrepancy was solved after consultation with a third reviewer (LF). The Newcastle-Ottawa comprises eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded such that the highest quality studies are awarded up to nine stars [28].

Statistical Analyses

Meta-analysis calculations

The primary aim of this study was to compare the 2D:4D digit ratio in all psychiatric conditions, regardless of the hand measured and the gender of the included subjects. Most of the studies reported the means of 2D:4D divided by hand and gender. Some studies reported results only for the left or the right hand, while other studies reported aggregated data for left and right hands. Thus, we decided to combine the data to have a common estimate of the digit ratio, regardless of gender and hand. First, in order to combine the measure of right and left hand, we calculated the averaged means for left and right hands digit ratio. To avoid an underestimation of the SD, that might be the case in within-subjects data combination, we used the formula suggested by Borenstein *et al.* [29], setting as a correlation coefficient 0.8, as proposed in previous literature. Then, we computed a weighted mean for each study, in order to combine males and females digit ratios, while we calculated SD according to the Cochrane Handbook formula for grouping independent samples [30]. In case SD was missing [31], we replaced it with the mean of the SD among the same diagnostic category (i.e., autism spectrum disorder, ASD).

Effect size and heterogeneity

We used mean differences (MD) as effect size, being the 2D:4D always measured in the same unit. Studies were pooled using a random-effects model since a consistent heterogeneity among observational studies was expected. Between-study heterogeneity was assessed using the I^2 statistic. According to the Cochrane handbook, an I^2 of 0−40% represents a low heterogeneity, I^2 of 30−60% is moderate heterogeneity, I^2 of 50−90% indicates substantial heterogeneity [30]. Small study effects as a proxy of publication bias were explored with contour-enhanced funnel plots for the visual detection of asymmetries. Egger's regression test was used to detect asymmetry in the funnel plots.

Subgroup analyses

For each psychiatric disorder, we conducted subgroup meta-analyses on males and females and left and right hands, separately. In the main analysis of the overall sample, we conducted a subgroup analysis also on children and adults. Chi-squared (χ^2) was used to test differences between subgroups.

Analyses were conducted using meta package (v.4.9-9) within the open-source software environment R (v3.6). α was set at 0.05.

RESULTS

Characteristics of the Included Studies

Our search yielded a total of 619 articles, while four additional papers were retreived from other sources. After duplicates removal, we screened the titles and abstracts of 399 papers and read the full texts of 96 papers. We finally included 43 articles, evaluating the 2D:4D ratio in patients with the following psychiatric diagnoses:

(1) Neurodevelopmental disorders, specifically attention deficit-hyperactivity disorder (ADHD; n = 4), ASD (n = 16), and intellectual disability (ID; n =1)

(2) Schizophrenia (n = 8)

(3) Addictions, specifically alcohol dependence (n = 3) and heroin dependence (n = 2)

(4) Gender nonconformity, such as gender dysphoria, gender identity disorder, transsexualism, or transgenderism (n = 7)

(5) Mood disorders, specifically bipolar disorder (n = 1) and depression (n = 1).

The study selection process and the reasons for exclusion are reported in the PRISMA Flow Diagram (Fig. 1).

Neurodevelopmental disorders

Twenty-one studies evaluated the 2D:4D ratio in neurodevelopmental disorders, such as ADHD, ASD, and ID. Thirteen studies were conducted in Europe, specifically in the United Kingdom, The Netherlands, Belgium, Germany, Greece, Slovak Republic, Sweden, and Turkey. Six stud-

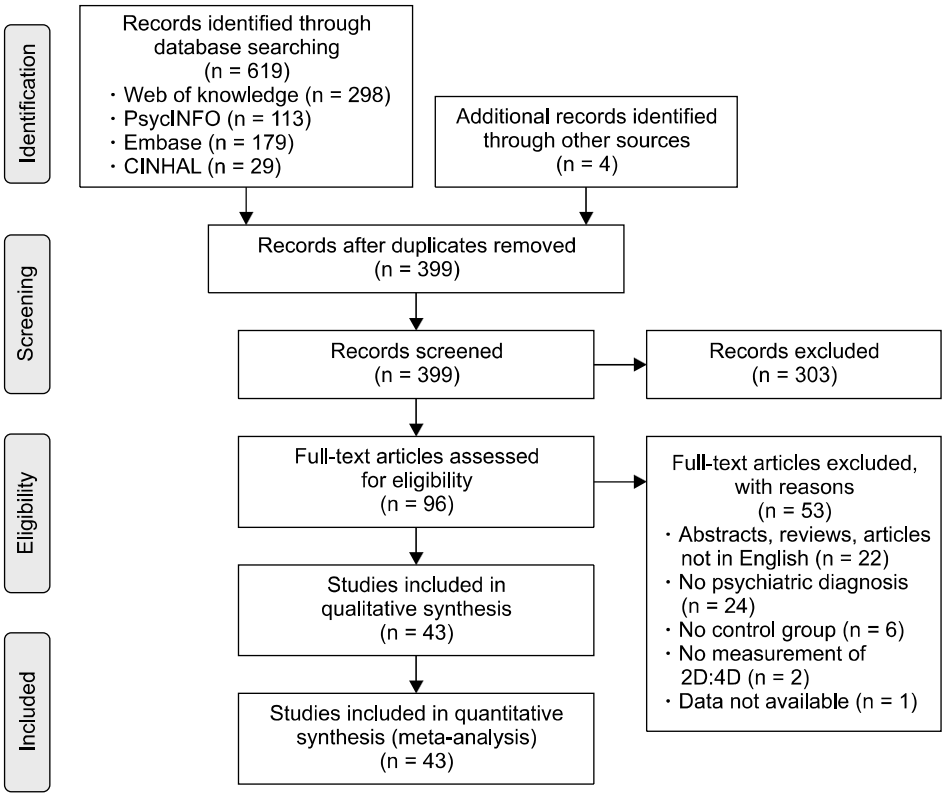


Fig. 1. PRISMA Flow Chart of the study selection process.
2D:4D, Second-to-fourth Digit Ratio.

ies were conducted in Asia, specifically in Japan, Iran, Saudi Arabia, and Thailand. Finally, three studies were conducted in the United States. Participants were children in all the studies involving patients with ADHD and ID. Moreover, five studies evaluated 2D:4D in adults with ASD [32-36], and two studies included mixed samples of children and adults with ASD [37,38]. Four papers included only males [36,39-41], and in two articles [31,42], the proportion of males represented almost the entirety of the sample. Five studies evaluated the 2D:4D only in the right hand, twelve studies in both hands (left and right). In one paper the mean between the 2D:4D of left and right hands was calculated, and in two studies it was unclear which hand was measured. Measurement of 2D:4D was mostly direct (14 studies).

Characteristics of the included studies about 2D:4D ratio in patients with neurodevelopmental disorders are reported in Table 1 [31-51].

Schizophrenia

Eight studies measured 2D:4D in patients with schizophrenia and controls. Half of the studies were conducted in Asia, and particularly two in India [52,53], one in China [54], and one in Singapore [55]. Moreover, two studies were conducted in Turkey [56,57], one in Spain [58], and one in Germany [22]. All participants were adults with mean ages ranging from 22 [57] to 47 [58]. Samples generally included both males and females, apart from Bolu *et al.* [57] that recruited only males. All papers have evaluated 2D:4D in both hands, apart from Collinson *et al.* [55] that has measured the ratio solely of the right hand. Measurements were always direct, except in two cases [22,54]. Characteristics of the included studies about 2D:4D ratio in patients with schizophrenia are reported in Table 2.

Addictions

Two papers recruited individuals with alcohol dependence and were conducted in South Korea [59] and Germany [60]. Moreover, we included three studies involving participants with heroin dependence, which were conducted in Turkey [61,62] and Germany [63]. Participants were all adults, with mean ages ranging from 22.8 [61] to 51.2 [59]. Three studies included only men [59,61,62], while in the remaining two articles samples were mixed. Three papers measured 2D:4D ratio in both hands; one paper

Table 1. Characteristics of studies evaluating 2D:4D in neurodevelopmental disorders, i.e., attention deficit-hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and intellectual disability (ID)

Diagnosis (tool)	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
ADHD (DSM-IV)	Buru	2017	Turkey	104	/ (7−17)	77 (74.03)	436	/ (7−17)	240 (55.04)	L, R	Digital compass (direct)
ADHD (DSM-IV-TR)	Lemiere	2010	Belgium	64	/ (7−12)	47 (73.44)	46	/ (7−12)	25 (54.35)	/	Scanned photocopies (indirect)
ADHD (Clinical)	Martel	2009	USA	168	12.71 (8−17)	106 (63.10)	144	14.01 (8−17)	72 (50)	R	Ruler (direct)
ADHD (DSM-IV-TR)	McFadden	2005	USA	46	9.83 (7−15)	34 (73.91)	33	10.6 (7−15)	17 (51.51)	L, R	Photocopy or digital scanner (indirect)
ASD (DSM-IV)	Al-Zaid	2015	Saudi Arabia	31	5.59 (3−8)	31 (100)	29	5.59 (3−8)	29 (100)	R	Digital Caliper (direct)
ASD (DSM-IV-TR, ADOS)	Baharara	2014	Iran	48	7.38 (7−8)	38 (79.17)	41	7.46 (7−8)	31 (75.61)	L, R	Ruler (direct)
ASD (Clinical, ADOS)	Bejerot	2012	Sweden	50	30 (20−47)	26 (52)	53	30.3 (20−47)	28 (52.83)	L, R	Digital Caliper (direct)
ASD (DSM-IV)	De Bruin	2006	The Netherlands	24	9 (6−14)	24 (100)	96	9 (6−13)	96 (100)	L, R	Digital Caliper (direct)
ASD (DSM-IV-TR)	Falter	2008	UK	28	12.7 (/)	27 (96.43)	28	12.7 (/)	27 (96.43)	L, R	Digital Caliper (direct)
ASD (ADI-R)	Hauth	2014	The Netherlands	216	11.6 (4−21)	178 (82.40)	174	11 (4−21)	79 (45.40)	L, R	Tape (indirect)
ASD (DSM-IV)	Krajmer	2011	Slovak Republic	56	11.2 (/)	56 (100)	32	12.1 (/)	32 (100)	R	Scanner (indirect)
ASD (DSM-IV-TR, ICD-10)	Lai	2013	UK	60	27.5 (18−49)	0	60	27.8 (18−49)	0	L, R	Digital Caliper (direct)
ASD (DSM-5, DISCO)	Masuya	2015	Japan	52	28.5 (/)	35 (67.31)	116	27.74 (/)	59 (42.45)	L, R	Digital Caliper (direct)
ASD (DSM-IV)	Milne	2006	UK	23	10.8 (/)	22 (95.65)	23	10.8 (/)	10 (43.48)	/	Digital Caliper (direct)
ASD (ASQ)	Manning	2001	UK	72	/ (2−15)	62 (86.11)	72	/ (2−15)	62 (86.11)	Mean L, R	Digital Caliper (direct)
ASD (DSM-IV)	Noipayak	2009	Thailand	46	5.25 (1.5−15)	39 (84.78)	46	5.25 (1.5−15)	39 (84.78)	L, R	Digital Caliper (direct)
ASD (Clinical)	Rohde	2018	Germany	26	42.86 (20−55)	14 (53.84)	26	41.44 (20−55)	14 (53.85)	R	Ruler (direct)
ASD (ADOS, ADI-R)	Schieve	2018	USA	599	/ (2−5)	487 (81.30)	811	/ (2−5)	431 (53.14)	L, R	Scanner (indirect)
ASD (DSM-IV)	Sugie	2010	Japan	98	12.7 (5−31)	82 (85.71)	89	/	/	R	Digital Camera (indirect)
ASD (DSM-IV-TR)	Togo	2019	Japan	20	26.75 (/)	20 (100)	14	26 (/)	14 (100)	L, R	Digital Photos (indirect)
Intellectual disability (WISC-III)	Ypsilanti	2008	Greece	100	17.4 (14−18)	47 (47)	85	19.24 (18−23)	37 (43.53)	R	Digital Caliper (direct)

2D:4D, Second-to-fourth Digit Ratio ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASQ, Autism Screening Questionnaire; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; R, right; WISC-III, Wechsler Intelligence Scale for Children-Third Edition; ICD, International Classification of Diseases; DISCO, Diagnostic Interview for Social and Communication Disorders; /, not available.

Table 2. Characteristics of studies evaluating 2D:4D in schizophrenia

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Schizophrenia (DSM-IV)	Akgül	2017	Turkey	48	39.85 (18－55)	25 (52.08)	48	39.73 (18－55)	25 (52.08)	L, R	Digital Caliper (direct)
Schizophrenia (SCID-I)	Bolu	2015	Turkey	103	22.73 (/)	103 (100)	100	21.98 (/)	100 (100)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Collinson	2010	Singapore	64	30.5 (/)	33 (51.56)	64	27.4 (/)	33 (51.56)	R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Divakaran	2012	India	200	31.61 (/)	106 (53)	177	33.82 (/)	92 (51.97)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV)	Paipa	2018	Spain	51	47 (18－65)	33 (64.71)	50	45.5 (18－65)	31 (62)	L, R	Digital Caliper (direct)
Schizophrenia (DSM-IV-TR)	Qian	2016	China	178	33.8 (15－62)	76 (42.70)	365	33.16 (17－63)	218 (59.73)	L, R	Photography (indirect)
Schizophrenia (DSM-IV)	Venkatasubramanian	2011	India	79	24.4 (/)	41 (51.90)	75	31.1 (/)	37 (49.33)	L, R	Digital Caliper (direct)
Schizophrenia (SCID-I)	Zhu	2014	Germany	51	26.49 (18－45)	24 (47.06)	51	24.98 (18－45)	23 (45.10)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; R, right; SCID-I: Structured Clinical Interview for DSM IV Axis I Disorders; /, not available.

Table 3. Characteristics of studies evaluating 2D:4D in addictions

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Alcohol dependence (DSM-IV)	Han	2016	South Korea	87	51.2 (/)	87 (100)	52	48.32 (/)	52 (100)	L, R	Scanner (indirect)
Alcohol dependence (DSM-5, ICD-10)	Lenz	2017	Germany	200	48 (42－54)	113 (56.50)	240	48 (39－56)	133 (55.42)	Mean L, R	Scanner (indirect)
Alcohol dependence (ICD-10)	Kornhuber	2011	Germany	131	/ (24－77)	87 (66.41)	185	/ (24－77)	83 (44.86)	L, R	Scanner (indirect)
Heroin dependence (DSM-5)	Canan	2018	Turkey	150	22.8 (/)	150 (100)	266	23 (/)	266 (100)	L, R	Digital Caliper (direct)
Heroin dependence (DSM-IV)	Cicek	2017	Turkey	62	24.09 (18－45)	62 (100)	50	24.42 (18－45)	50 (100)	R	Digital Caliper (direct)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; L, left; R, right; /, not available.

Table 4. Characteristics of studies evaluating 2D:4D in individuals with gender non-conforming identities

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	M-to-F, n (%)	Number	Mean age (range)	M-to-F, n (%)		
Gender identity disorder (DSM-IV)	Hisasue	2012	Japan	37	27 (19−45)	0	20	35 (23−60)	0	L, R	Photocopies (indirect)
Gender identity disorder (DSM-IV)	Kraemer	2009	Switzerland	56	37.1 (18−65)	39 (69.64)	366	37.1 (18−65)	176 (48.08)	L, R	Digital Caliper (direct)
Transgender (Clinical)	Leinung	2017	USA	118	Not reported	68 (57.62)	37	Not reported	19 (51.35)	Dominant	Digital Caliper (direct)
Transsexualism (Clinical)	Schneider	2006	Germany	106	37.24 (/)	63 (59.53)	123	39 (/)	58 (47.15)	L, R	Photocopies (indirect)
Gender identity disorder (DSM-IV)	Vujović	2014	Republic of Serbia	80	31.25 (/)	42 (52.50)	93	29 (/)	45 (48.39)	L, R	Digital Caliper (direct)
Gender identity disorder (DSM-IV)	Wallien (study 1)	2008	The Netherlands	147	40.53 (/)	96 (65.30)	202	41.25 (/)	90 (44.55)	L, R	Scanner (indirect)
	Wallien (study 2)	2008	The Netherlands	101	8.29 (/)	67 (66.33)	146	7.8 (/)	74 (50.68)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; L, left; M-to-F, male-to-female; R, right; /, not available.

Table 5. Characteristics of studies evaluating 2D:4D in mood disorders

Diagnosis	First author	Year	Country	Patients			Controls			Hand	2D:4D measurement tool
				Number	Mean age (range)	Male, n (%)	Number	Mean age (range)	Male, n (%)		
Bipolar Disorder (MINI)	Tegin	2019	USA	50	52.9 (/)	21 (42)	50	48.6 (/)	21 (42)	L, R	Scanner (indirect)
Depression (DSM-IV)	Sanwald	2019	Germany	139	39.4 (18−65)	49 (35.3)	137	28.74 (18−63)	49 (35.8)	L, R	Scanner (indirect)

2D:4D, Second-to-fourth Digit Ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; MINI, Mini-International Neuropsychiatric Interview; L, left; R, right; /, not available.

considered the average between the left and right hand [60] and one measured only right hand [62]. Measurements were indirect in three papers [59,60,63], and direct in two articles [61,62]. See Table 3 for details regarding studies evaluating 2D:4D in addictions.

Gender non-conforming identity

Six papers (including seven studies) measured 2D:4D in people with gender nonconforming identity who had a psychiatric diagnosis or were followed by specialized clinics. Particularly, in four studies participants had a diagnosis of gender identity disorder, in one study a diagnosis of transsexualism, whereas they were defined as transgender in one paper. Studies were conducted mainly in Europe, specifically one in The Netherlands (including two studies) [64], one in Germany [65], one in the Republic of Serbia [66], and one in Switzerland [67]. Moreover, one study was conducted in Japan [68] and one in the United States [69]. One study involved children [64]; all the other studies recruited adults, with the exception of Leinung and Wu [69], where the age of participants was not reported. All studies evaluated 2D:4D in both hands; Leinung and Wu [69] have measured the ratio only in the dominant hand. Measurements were conducted directly in half of the studies, and indirectly in the remaining articles. Study characteristics are reported in Table 4 [66].

Mood disorders

One paper [70] recruited patients with major depression in Germany, and another study recruited individuals affected by bipolar disorder [71] in the United States. All participants were adults and mainly women. In the two studies regarding mood disorders, 2D:4D was measured in both hands and using indirect measurement tools. Details regarding the study characteristics are reported in Table 5.

Meta-analyses of the Included Studies

2D:4D ratio in all psychiatric disorders

To evaluate the global differences of 2D:4D in psychiatric disorders, we conducted four main meta-analyses. In the first one, we pooled the data of all 43 studies, finding that psychiatric patients had significantly lower 2D:4D than healthy controls (n = 43, overall sample = 9,484, MD = −0.0056, 95% confidence interval [CI] from −0.0093 to −0.002, I^2 = 74%). The forest plot is presented in Figure 2 and the funnel plot in Figure 3.

Then, data extracted from included studies were pooled by hand, gender, and age. No differences were found between left and right hand in any psychiatric disorder (χ^2 = 0.85, df = 1, p = 0.36). However, considering each subgroup independently, it could be observed that the 2D:4D in the right hand showed significant lower 2D:4D in psychiatric patients than controls; conversely, no differences between psychiatric patients and controls were detected in the left hand. Moreover, no significant differences were detected between males and females (χ^2 = 0.44, df = 1, p = 0.51), even if both groups showed significantly lower 2D:4D in psychiatric patients than controls. Finally, dividing the studies by age, it could be observed that both adults and children showed significantly lower 2D:4D ratio in psychiatric patients than controls, with no significant differences between the two groups (χ^2 = 0.77, df = 1, p = 0.38). The forest plots are presented in the Supplementary Materials, Appendix 2 (available online) [27].

2D:4D ratio in autism spectrum disorder

The analyses of the 2D:4D ratio in ASD, with data pooled by hand and gender, showed a statistically significant difference between patients and controls (n = 16, overall sample = 2,981, MD = −0.006, 95% CI from −0.0119 to −0.0001). Heterogeneity was moderate (I^2 = 53%). The results of the meta-analysis are presented in Figure 4A.

Subgroup analyses with studies divided by hand and gender did not detect any significant difference between ASD patients and controls. The forest plots of subgroup analyses are presented in the Supplementary Materials, Appendix 3 (available online) [27].

2D:4D ratio in attention deficit-hyperactivity disorder

The meta-analysis of 2D:4D ratio in ADHD showed a statistically significant difference between patients and controls (n = 4, overall sample = 1,128, MD = −0.0124, 95% CI from −0.0188 to −0.0059). Heterogeneity was low (I^2 = 0%). The results of the meta-analysis are presented in Figure 4B.

Subgroup analyses revealed significant differences in the right hand of both males (n = 3, overall sample = 526, MD = −0.0198, 95% CI from −0.036 to −0.0036, I^2 = 65%) and females (n = 3, overall sample = 382, MD = −0.0245,

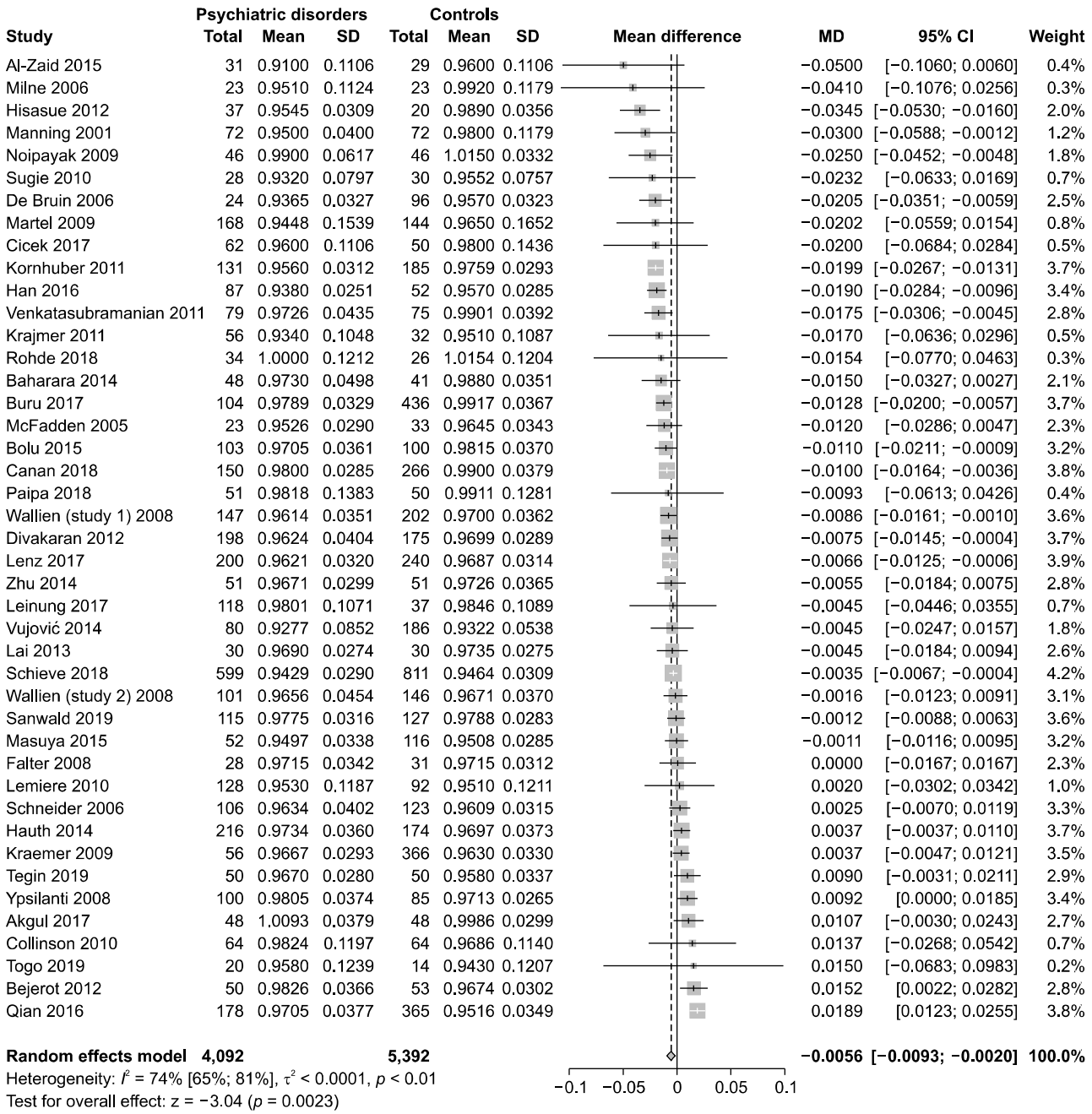


Fig. 2. Meta-analysis of the 2D:4D ratio pooling all psychiatric disorders (n = 43).
2D:4D, Second-to-fourth Digit Ratio; SD, standard deviation; MD, mean difference; CI, confidence interval.

95% CI from −0.0451 to −0.0039, I^2 = 66%). No significant differences were found in the left hand, neither in males nor in females. The forest plots of the subgroup analyses plot are presented in the Supplementary Materials, Appendix 4 (available online) [27].

2D:4D ratio in intellectual disability

Only one study [48] evaluated 2D:4D ratio in ID, without detecting any significant difference. Forest plot is presented in Figure 4C [27].

2D:4D ratio in schizophrenia

The meta-analysis of pooled data did not show any sig-

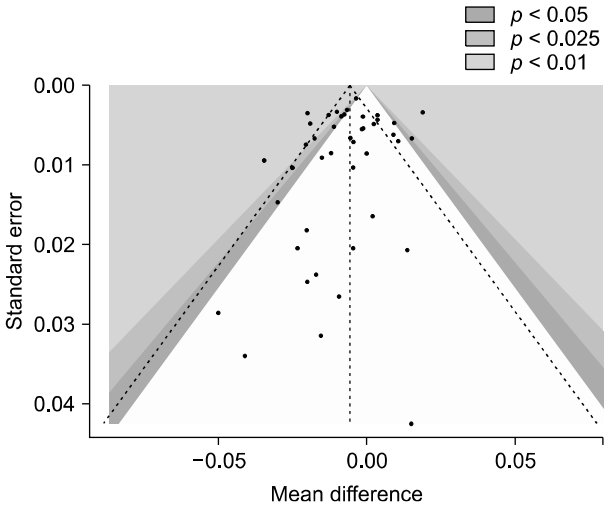


Fig. 3. Funnel plot of the included studies (n = 43).

nificant difference between patients with schizophrenia and other psychotic disorders and non-clinical controls (n = 8, overall sample = 1,700, MD = −0.0012, 95% CI from −0.0129 to 0.0105). Heterogeneity was high (I^2 = 86%). The forest plot is presented in Figure 4D.

Subgroup analyses with data divided by gender and hand did not reveal any significant difference except for the right hand in males: in this group, the 2D:4D ratio was significantly higher in patients than controls (n = 6, overall sample = 882, MD = 0.009, 95% CI from 0.0004 to 0.0177, I^2 = 64%). The subgroup analyses are presented in the Supplementary Materials, Appendix 5 (available online) [27].

2D:4D ratio in addictions

Pooling data of patients affected by addictions, we did find a significant difference, as patients had a significantly lower 2D:4D than controls (n = 5, overall sample = 1,423, MD = −0.014, 95% CI from −0.0199 to −0.0081). Heterogeneity was moderate (I^2 = 50%). The forest plot is presented in Figure 4E.

The subgroup analyses revealed statistically significant differences in both the males right and left hands, while for females the difference between the patients and the control group was limited to the right hand. In all cases, the patients suffering from addictions had a smaller 2D:4D ratio than controls. The analyses are presented in the Supplementary Materials, Appendix 6 (available online) [27].

2D:4D ratio in gender non-conforming people

No significant differences were found between individuals with gender non-conforming identities (n = 7, overall sample = 1,725, MD = −0.0051, 95% CI from −0.0131 to 0.0028). Heterogeneity was substantial (I^2 = 65%). Forest plot is presented in Figure 4F.

Subgroup analyses did not detect any significant differences according to hand or biological sex (see Supplementary Materials, Appendix 7 [available online] [27]).

2D:4D ratio in mood disorders

We found no significant differences between patients with depression or bipolar disorder and healthy controls (n = 2, overall sample = 342, MD = 0.0027, 95% CI from −0.0071 to 0.0125). Heterogeneity was moderate (I^2 = 49%). Forest plot is presented in Figure 4G.

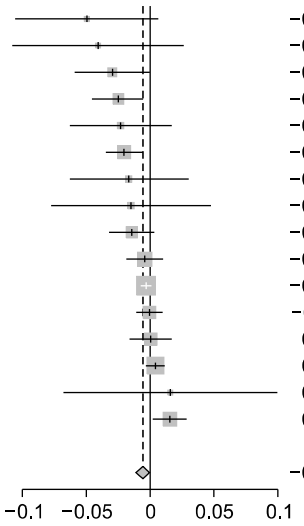
Quality of the Included Studies

The quality of the studies included in the systematic review and meta-analysis has been reported in Table 6. Two studies were judged with a score of 4 out of 9 points [41,42], four studies with 5 out of 9 [49,55,65,66], ten studies with 6 out of 9, four studies with 7 out of 9 and the the remaining papers with 8 or 9 stars. As concerns the study selection, we have found a relatively low risk of bias in diagnostic criteria: in fact, we included only studies in which participants had received a psychiatric diagnosis by a clinician. Only two studies were judged as having high risk: first, participants recruited by Manning *et al.* [50] were members of an autistic society and the diagnoses were confirmed only using the Autism Screening Questionnaire (ASQ), which is not intended as a diagnostic tool [72]; second, in Schneider *et al.* [65], transgenders were followed by a specific clinic for transition, thus we assumed that a clinical diagnosis had been performed, even if not explicitly reported in the paper. As for the remaining items of study selection, the most problematic criterion was the representativeness of cases, as in most studies the authors did not report consecutive recruitment of patients, thus raising concerns regarding potential selection biases. Ten studies did not match patients to controls according to socio-demographic variables, while in seven study only one variable was considered (age or gender). Regarding exposure, we did not find major biases, since the 2D:4D ratio was measured in cases and controls using the same methodology with direct or indirect measures.

A Autism spectrum disorder (ASD)

Study	ASD Total	ASD Mean	ASD SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Al-Zaid 2015	31	0.9100	0.1106	29	0.9600	0.1106	−0.0500	[−0.1060; 0.0060]	1.0%
Milne 2006	23	0.9510	0.1124	23	0.9920	0.1179	−0.0410	[−0.1076; 0.0256]	0.8%
Manning 2001	72	0.9500	0.0400	72	0.9800	0.1179	−0.0300	[−0.0588; −0.0012]	3.4%
Noipayak 2009	46	0.9900	0.0617	46	1.0150	0.0332	−0.0250	[−0.0452; −0.0048]	5.8%
Sugie 2010	28	0.9320	0.0797	30	0.9552	0.0757	−0.0232	[−0.0633; 0.0169]	1.9%
De Bruin 2006	24	0.9365	0.0327	96	0.9570	0.0323	−0.0205	[−0.0351; −0.0059]	8.6%
Krajmer 2011	56	0.9340	0.1048	32	0.9510	0.1087	−0.0170	[−0.0636; 0.0296]	1.5%
Rohde 2018	34	1.0000	0.1217	26	1.0154	0.1215	−0.0154	[−0.0775; 0.0467]	0.9%
Baharara 2014	48	0.9730	0.0498	41	0.9880	0.0351	−0.0150	[−0.0327; 0.0027]	6.9%
Lai 2013	30	0.9690	0.0274	30	0.9735	0.0275	−0.0045	[−0.0184; 0.0094]	9.0%
Schieve 2018	599	0.9429	0.0291	811	0.9464	0.0310	−0.0035	[−0.0067; −0.0004]	17.2%
Masuya 2015	52	0.9497	0.0338	116	0.9508	0.0285	−0.0011	[−0.0116; 0.0095]	11.5%
Falter 2008	28	0.9715	0.0342	31	0.9715	0.0312	0.0000	[−0.0167; 0.0167]	7.4%
Hauth 2014	216	0.9734	0.0360	174	0.9697	0.0374	0.0037	[−0.0037; 0.0110]	14.2%
Togo 2019	20	0.9580	0.1239	14	0.9430	0.1207	0.0150	[−0.0683; 0.0983]	0.5%
Bejerot 2012	50	0.9826	0.0367	53	0.9674	0.0303	0.0152	[0.0022; 0.0283]	9.6%
Random effects model	**1,357**			**1,624**			**−0.0060**	**[−0.0119; −0.0001]**	**100.0%**

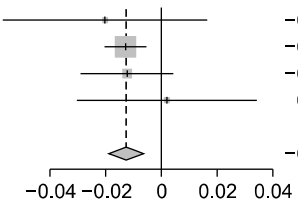
Heterogeneity: I^2 = 53% [17%; 73%], τ^2 < 0.0001, p < 0.01
Test for overall effect: z = −1.99 (p = 0.0461)



B Attention deficit-hyperactivity disorder (ADHD)

Study	ADHD Total	ADHD Mean	ADHD SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Martel 2009	168	0.9448	0.1574	144	0.9650	0.1670	−0.0202	[−0.0564; 0.0160]	3.2%
Buru 2017	104	0.9789	0.0333	436	0.9917	0.0367	−0.0128	[−0.0201; −0.0056]	78.0%
McFadden 2005	23	0.9526	0.0291	33	0.9645	0.0342	−0.0120	[−0.0286; 0.0047]	14.9%
Lemiere 2010	128	0.9530	0.1187	92	0.9510	0.1211	0.0020	[−0.0302; 0.0342]	4.0%
Random effects model	**423**			**705**			**−0.0124**	**[−0.0188; −0.0059]**	**100.0%**

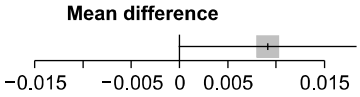
Heterogeneity: I^2 = 0% [0%; 52%], τ^2 = 0, p = 0.81
Test for overall effect: z = −3.77 (p = 0.0002)



C Intellectual disability (ID)

Study	Intellectual disability Total	Intellectual disability Mean	Intellectual disability SD	Controls Total	Controls Mean	Controls SD	MD	95% CI
Ypsilanti 2008	100	0.9805	0.0376	85	0.9713	0.0267	0.0092	[−0.0001; 0.0185]

Heterogeneity: I^2 = NA%



D Schizophrenia

Study	Schizophrenia Total	Schizophrenia Mean	Schizophrenia SD	Controls Total	Controls Mean	Controls SD	MD	95% CI	Weight
Venkatasubramanian 2011	79	0.9726	0.0436	75	0.9901	0.0394	−0.0175	[−0.0306; −0.0044]	14.2%
Bolu 2015	103	0.9705	0.0361	100	0.9815	0.0370	−0.0110	[−0.0211; −0.0009]	15.4%
Paipa 2018	51	0.9818	0.1388	50	0.9911	0.1282	−0.0093	[−0.0614; 0.0428]	3.9%
Divakaran 2012	198	0.9624	0.0405	175	0.9699	0.0292	−0.0075	[−0.0146; −0.0004]	16.3%
Zhu 2014	51	0.9671	0.0299	51	0.9726	0.0365	−0.0055	[−0.0184; 0.0075]	14.3%
Akgül 2017	48	1.0093	0.0379	48	0.9986	0.0299	0.0107	[−0.0030; 0.0243]	14.0%
Collinson 2010	64	0.9824	0.1202	64	0.9686	0.1174	0.0137	[−0.0274; 0.0549]	5.5%
Qian 2016	178	0.9705	0.0378	365	0.9516	0.0349	0.0189	[0.0123; 0.0255]	16.4%
Random effects model	**772**			**928**			**−0.0012**	**[−0.0129; 0.0105]**	**100.0%**

Heterogeneity: I^2 = 86% [75%; 92%], τ^2 = 0.0002, p < 0.01
Test for overall effect: z = −0.20 (p = 0.8407)

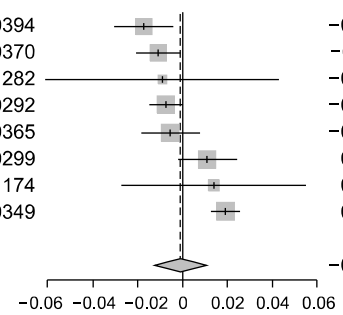


Fig. 4. Meta-analyses of the 2D:4D ratio in individual psychiatric disorders.
2D:4D, Second-to-fourth Digit Ratio; SD, standard deviation; MD, mean difference; CI, confidence interval.

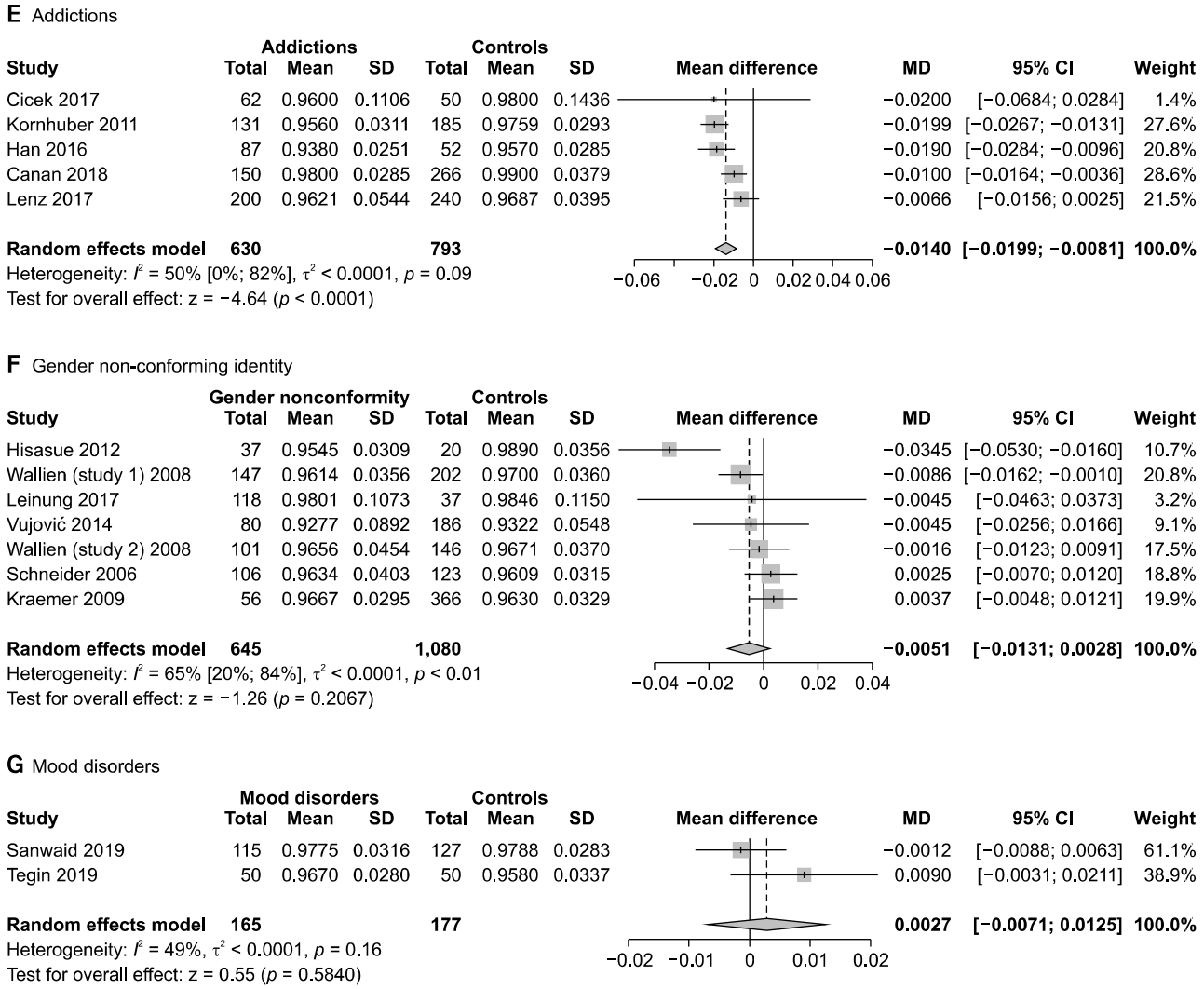


Fig. 4. Continued.

However, in five studies [35,41,42,51,65] concerns were raised because of missing data.

DISCUSSION

The present meta-analysis aimed to evaluate the differences in 2D:4D ratio between psychiatric patients and controls, and thus to explore its potential usefulness as a clinical biomarker for psychiatric disorders. The first and main finding of our meta-analysis is that the 2D:4D ratio is significantly lower in patients than controls, indicating exposure to higher levels of prenatal testosterone in individuals with psychiatric disorder. The effect seemed more pronounced in males than females, in the right than the left hand, and in children than adults, even if between-groups differences were not statistically significant. Our finding is important because, on one hand, it may propose 2D:4D as a potential biomarker for psychiatric disorders in general; on the other hand, it highlights the role of prenatal exposure to hormones, specifically testosterone, in the etiopathogenesis of psychiatric disorders. Interestingly, prenatal exposure to androgens may explain the different sex ratios encountered in several conditions (e.g., schizophrenia, ASD, addictions).

As shown by the number of studies included in our meta-analysis, the literature has extensively evaluated the 2D:4D in ASD for which we have included 16 case-control studies. Nevertheless, the effective measurement of sex steroid levels in the amniotic fluid with a prospective follow-up has been performed by a few researchers.

Table 6. Quality assessment of the included studies using the Newcastle-Ottawa Scale

Diagnosis	Study characteristics			Selection					Comparability		Exposure				Total (n)
	First author	Year	Country	Diagnostic adequacy	Representativeness of the cases	Selection of controls	Definition of controls	Total (n)	Comparability	Total (n)	Ascertainment of 2D:4D	Same method of ascertainment for cases and controls	Missing data rate	Total (n)	
Attention deficit-hyperactivity disorder															
	Buru	2017	Turkey	*	*	/	/	2	/	0	*	*	*	3	5
	Lemiere	2010	Belgium	*	/	*	*	3	/	0	*	*	*	3	6
	Martel	2009	USA	*	*	*	*	4	* (age)	1	*	*	*	3	8
	McFadden	2005	USA	*	*	*	*	4	** (age, gender, CEOAEs)	2	*	*	*	3	9
Autism spectrum disorder															
	Al-Zaid	2015	Saudi Arabia	*	/	/	*	2	** (age, gender)	2	*	*	*	3	7
	Baharara	2014	Iran	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Bejerot	2012	Sweden	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	De Bruin	2006	The Netherlands	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Falter	2008	UK	*	/	*	*	3	** (age, sex, non-verbal reasoning ability)	2	*	*	*	3	8
	Hauth	2014	The Netherlands	*	*	/	*	3	/	0	*	*	*	3	6
	Krajmer	2011	Slovak Republic	*	/	/	*	2	/	0	*	*	/	2	4
	Lai	2013	UK	*	/	/	*	2	** (age, gender)	2	*	*	*	3	7
	Masuya	2015	Japan	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Milne	2006	UK	*	/	/	/	1	* (age)	1	*	*	/	2	4
	Manning	2001	UK	/	/	*	*	2	* (age)	1	*	*	*	3	6
	Nojpayak	2009	Thailand	*	/	/	/	1	** (age, gender)	2	*	*	*	3	6
	Rohde	2018	Germany	*	*	/	*	3	** (age, gender)	2	*	*	/	2	7
	Schieve	2018	USA	*	*	*	/	3	* (age)	1	*	*	/	2	6
	Sugie	2010	Japan	*	/	/	/	1	** (age, gender, IQ)	2	*	*	*	3	6
	Togo	2019	Japan	*	*	*	/	3	** (age, handedness, full scale IQ)	2	*	*	*	3	8
Intellectual disability															
	Ypsilanti	2008	Greece	*	*	*	*	4	/	0	*	*	*	3	7

Table 6. Continued

Diagnosis	Study characteristics			Selection					Comparability		Exposure				Total (n)
	First author	Year	Country	Diagnostic adequacy	Representativeness of the cases	Selection of controls	Definition of controls	Total (n)	Comparability	Total (n)	Ascertainment of 2D:4D	Same method of ascertainment for cases and controls	Missing data rate	Total (n)	
Schizophrenia															
	Akgul	2017	Turkey	*	/	*	*	3	** (age, gender, education)	2	*	*	*	3	8
	Bolu	2015	Turkey	*	/	*	*	3	* (age)	1	*	*	*	3	7
	Collinson	2010	Singapore	*	/	*	/	2	/	0	*	*	*	3	5
	Divakaran	2012	India	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Paipa	2018	Spain	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Qian	2016	China	*	/	*	*	3	** (age, gender)	2	*	*	*	3	8
	Venkatasubramanian	2011	India	*	*	/	*	3	** (age, sex)	2	*	*	*	3	8
	Zhu	2014	China	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
Alcohol dependence															
	Han	2016	South Korea	*	/	*	*	3	/	0	*	*	*	3	6
	Lenz	2017	Germany	*	*	*	*	4	** (age, gender)	2	*	*	*	3	9
	Kornhuber	2011	Germany	*	*	*	/	3	/	0	*	*	*	3	6
Heroin dependence															
	Canan	2018	Turkey	*	*	*	*	4	* (age)	1	*	*	*	3	8
	Cicek	2017	Turkey	*	*	/	/	2	* (age, education)	1	*	*	*	3	6
Gender nonconformity															
	Hisasue	2012	Japan	*	/	/	/	1	** (age, gender)	2	*	*	*	3	6
	Kraemer	2009	Switzerland	*	*	*	*	4	** (age, gender, sexual orientation)	2	*	*	*	3	9
	Leinung	2017	USA	*	/	*	*	3	/	0	*	*	*	3	6
	Schneider	2006	Germany	/	*	/	/	1	** (age, gender)	2	*	*	/	2	5
	Vujović	2014	Serbia	*	*	/	/	2	/	0	*	*	*	3	5
	Wallien (study 1, 2)	2008	The Netherlands	*	*	*	*		** (age, gender, sexual orientation)		*	*	*	3	9
Mood disorders															
	Sanwald	2019	Germany	*	/	*	*	3	** (age, gender, handedness)	2	*	*	*	3	8
	Tegin	2019	USA	*	*	*	*	4	** (age, gender, race, dominant hand)	2	*	*	*	3	9

One star (*) indicates that the item is satisfied, while a slash (/) is assigned when the item is not fulfilled by the study. Comparability can be judged with up to two stars according to the number of control parameters reported by the researchers. One star (*) indicates that the control group has been matched with the patients' group according to one parameter; two stars (**) indicate two or more control parameters. The total score for each study is given by the sum of the stars.
2D:4D, Second-to-fourth Digit Ratio; CEOAEs, click-evoked otoacoustic emissions; IQ, intelligence quotient.

Auyeung *et al.* [73] positively correlated fetal testosterone levels with autism-related behaviors at 18−24 months and at 6−9 years [74]. Elevated fetal steroidogenic activity during the prenatal masculinization window in the amniotic fluid of autistic boys was confirmed by subsequent research [75]. On the contrary, Kung *et al.* [76] recently found no relationship between prenatal androgen exposure and autistic traits in typically developed children nor in young children with congenital adrenal hyperplasia. Of note, 2D:4D has been negatively associated with empathy [77], which is typically lower in people with ASD [78]; conversely, it seems positively correlated with systemizing traits [79], which are more pronounced in autistic individuals [80]. In 2002, Baron-Cohen developed the so-called theory of the "extreme male brain". This theory assumes that women tend to have more social intelligence (i.e., empathizing ability), whereas men tend to excel at following rules and recognizing patterns (i.e., systemizing ability). The "male brain" is typical of individuals in whom systemizing is significantly better than empathizing, while the "female brain" defines the opposite cognitive profile. Using these definitions, ASD could be considered as an expression of the "extreme male brain" [81]. The potential role of fetal testosterone in the onset of ASD is further supported by the link found between autism and maternal polycystic ovarian syndrome, a condition associated with androgenic excess [82]. Moreover, both autistic women and their mothers have elevated rates of steroid-related cancers, such as breast and ovarian cancer [83]. In summary, our findings reflect previous literature: subjects with ASD have significantly lower 2D:4D than controls, suggesting higher levels of fetal testosterone exposure.

Contrary to previous studies [84], our results did not support the notion that patients with schizophrenia would be exposed to lower levels of prenatal testosterone. In fact, it has been hypothesized that schizophrenia, in opposition with ASD, could reflect the "extreme female brain", with higher empathizing and lower systemizing abilities [81]. However, as underlined by other researchers, this theory might be erroneously based on the presumption that "*hyperdeveloped theory-of-mind skills*" in psychotic patients "*would be accurate and adaptive, rather than pathological*" [85]. Indeed, our findings did not confirm the theory of the "extreme female brain", as 2D:4D did not significantly differ between patients with schizophrenia and controls, thus suggesting no differences in empathizing and/or systemizing traits, neither in prenatal exposure to sex hormones. In fact, a significant difference was found only in the right hand of males with schizophrenia (MD = 0.009).

The evidence on addictions was quite robust, as 2D:4D resulted significantly lower in patients than healthy controls (MD = −0.014), indicating exposure to higher levels of prenatal testosterone. Even if no specific studies have evaluated the levels of sex steroids in the amniotic fluid in people with addictions—due to the obvious difficulties in following up the subjects for many years—some studies have linked several typical features of individuals with substance misuse to the digit ratio. For instance, it has been shown that 2D:4D is negatively correlated with risk-taking [18,86] and sensation-seeking [87,88]. Such features have been in turn linked to a higher vulnerability to addictions [89]. 2D:4D appears also negatively correlated with aggression [90] and impulsivity [91], which are in turn connected to the use of illicit substances, particularly alcohol and heroin [92], such as those used by the groups of patients included in our meta-analysis. Other authors [93] have argued an association between 2D:4D and externalizing behavioral symptoms in young boys: it is well-known that conduct disturbances confer an increased risk for substance abuse later in life [94]. Notably, this negative association between 2D:4D and externalizing behaviors may partially explain also the significant difference found between children with ADHD and non-clinical controls (MD = −0.0124).

Our meta-analyses did not retrieve any significant differences between people with non-conforming gender identities, mood disorders and ID, and non-clinical controls. The case of gender identity might seem surprising since in the imagination sex hormones are strictly connected to gender expression. However, it has been reported that gender identity is not exclusively related to prenatal exposure of androgens [95,96], but appears to be strongly influenced by genetic and social factors, with adolescence being a key period for the development of non-conforming identities [97,98]. As far as concern ID and mood disorders, it is worth noting that we have retrieved only one and two studies, respectively, and thus it is too premature to drive to any conclusion.

To our knowledge, this is the most up-to-date and comprehensive meta-analysis examining the 2D:4D ratio in

psychiatry. However, some limitations should be discussed. First, we have included only papers in which psychiatric diagnoses were confirmed by clinicians or valid international diagnostic criteria. Therefore, we have excluded papers reporting analyses about 2D:4D in self-diagnosed individuals, or individuals which were classified as having a disorder only according to self-reported questionnaires [99,100]. Also, we excluded papers about new addictions, such as videogames or computer addiction, which have been instead considered in a previous meta-analysis [101]. A second major limitation is related to the different types of measurement used by the authors included in the studies. In fact, some authors have suggested that indirect 2D:4D measurements (such as in many of the studies included in the present review) may overestimate the length of the ring finger thereby distorting the 2D:4D ratio [16]. Another limitation, directly related to the meta-analytic approach, is the presence of clinical heterogeneity which could not be controlled as for statistical heterogeneity. Even if we tried to reduce clinical heterogeneity by selecting patients with standardized diagnoses, we could not account for the presence of individual or genetic differences, as well as for the influence of environmental factors. Finally, the number of studies included in the meta-analyses were generally small.

In conclusion, our results are promising and highlight the importance of prenatal hormonal factors in the etiopathogenesis of some psychiatric disorders. However, they need to be cautiously interpreted as the measurement of 2D:4D ratio cannot prescind from a complex and exhaustive assessment process. It is important to consider, in fact, that a number of other physiological and pathological conditions linked to the prenatal exposure to sex hormones may influence the length of digit ratio, thus representing potential confounders. The absence of a definite cut-off also represents a limitation for the clinical application of 2D:4D. Future research should investigate more in-depth the relationships between 2D:4D and psychiatric disorders, focusing on other conditions characterized by traits that seem to be linked to lower or higher digit ratio, such as borderline and antisocial personality disorders, eating disorders, or disruptive mood dysregulation disorder.

SUPPLEMENTARY MATERIALS

Supplementary data is available online (https://doi.org/10.6084/m9.figshare.12220493.v1).

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Laura Fusar-Poli conceptualized the study, supervised data extraction, and wrote the original draft of the manuscript. Alessandro Rodolico performed statistical analyses and participated to write the first draft of the manuscript. Serena Sturiale, Bianca Carotenuto, Antimo Natale, and Davide Arillotta performed data extraction and edited the manuscript. Spyridon Siafis helped in statistical analyses and contributed to write the manuscript. Maria Salvina Signorelli and Eugenio Aguglia supervised the project and edited the draft of the manuscript. All authors have read and approved the final version of the manuscript.

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