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Digit Ratio (2D:4D) as a potential biomarker of sexual dimorphism, reproductive characteristics and behavioural traits: A Review

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ABSTRACT

The second-to-fourth digit (2D:4D) ratio is a sexually dimorphic trait, with men having lower ratios than women, indicating relatively higher prenatal testosterone exposure compared to oestrogen. The 2D:4D ratio is fixed in intrauterine conditions that are affected by foetal sex steroids (testosterone and oestrogen) and an indirect method to determine intrauterine sex hormone levels that significantly correlate with somatic features, behavioural traits, fertility measures, reproductive characteristics, and predisposition to certain chronic diseases. Researchers discovered that a more masculine (low 2D<4D) digit ratio and a more feminine (high; 2D>4D) digit ratio are manifestations of increased prenatal testosterone and oestrogen exposure, respectively. Furthermore, digit ratio (2D:4D) values are widely used to predict reproductive capacity and success, fertility measures, natural menopause, and age at menarche, which varies between populations. The current review paper attempted to discuss sexual dimorphism in 2D:4D ratios, as well as its potential association and utility in evaluating certain reproductive characteristics and behavioural traits in populations. Methodological comparisons, benefits and drawbacks of determining the 2D:4D for studying the effect of prenatal sex steroids are also highlighted.

Keywords: 2D:4D ratio, Fertility, Menarche, Menopause, Sexual dimorphism

INTRODUCTION

Digit ratio (2D:4D) refers to the ratio of the second (2D) to the fourth (4D) digit lengths and is thought to be indirect, though potentially significant, biomarker reflecting the exposure to prenatal- testosterone (PT) and oestrogen (PE), more particularly, their relative concentrations (Manning, 2002; Fink et al., 2003; McIntyre, 2006). This relative intrauterine ratio of these two hormones may have a lifelong impact on physiology, behaviour, physiological behaviour of fertility and fecundity, illness, disease risks and pubertal development (Manning et al., 2000; Manning, 2002; Fink et al., 2003; McIntyre, 2006; Matchock, 2008; Manning and Fink, 2011; Kalichman et al., 2013; Manning et al., 2014; Klimek et al., 2016; Vélez et al., 2016; Kirchengast et al., 2020; Tabachnik et al., 2020; Fischer Pedersen et al., 2021), several aspects of a woman's lifespan are thought to be strongly influenced by it (e.g., Vélez et al., 2016; Klimek et al., 2017; Tabachnik et al., 2020). A lower 2D:4D, i.e, longer fourth- relative to the second digit, indicates a higher exposure to PT relative to PE during prenatal growth and development (Manning et al., 1998, 2000, 2014). The 2D:4D ratio is sexually dimorphic, with men showing its lower values than women, at the population level, indicating a relatively greater exposure to testosterone compared to oestrogen, in a male foetus, during a narrow developmental window around the 8th week of gestation (Manning et al., 2000; Manning, 2002; Fink et al., 2003; Lutchmaya et al., 2004; McIntyre, 2006; Manning et al., 2007). This sex difference emerges after the second trimester and exhibits lifelong. The action of the Homeobox (HOX) genes, which may affect the production of prenatal androgens during development and controls the differentiation of digits and toes and implicated in sex determination, morphogenesis of the urogenital system, appendicular skeleton, and fertility, has been described as a potential underlying mechanism for the correlation between 2D:4D and prenatal balance of sex steroid hormones (Manning et al., 1998, 2003; Manning, 2002; Kyriakidis and Papaioannidou, 2008; Zhang et al., 2014; Tabachnik et al., 2020). The assessment of the prenatal hormonal environment at the embryonic stage is difficult, having serious ethical implications given the safety of the pregnant women and foetus (Manning, 2002; Tabachnik et al., 2020).

Numerous studies (e.g., Manning et al., 1998; Fink et al., 2003; Klimek et al., 2016; Kirchengast et al., 2020) provided evidence that a more masculine (low 2D<4D) and more feminine (high; 2D>4D) digit ratio might indicate a person's susceptibility to particular chronic illnesses and hormonal disorders (Hong et al., 2014; Luijken et al., 2017; Tabachnik et al., 2020). The 2D:4D has also been associated with increased levels of putatively androgenic outcomes, such as left-handedness and pubertal development, as well as improved athletic ability and higher autism risk (Manning et al., 2000; Fink et al., 2003; Manning, 2002; Li et al., 2019; Manning and Taylor, 2001; Mackus et al., 2017). Additionally, 2D:4D was shown to significantly correlate with several somatic and behavioural traits, fertility measures, reproductive outcomes, and predisposition to specific diseases (Manning et al., 1998; Manning 2002; Fink et al., 2004; Klimek et al., 2016; Kirchengast et al., 2020). The 2D:4D has also been linked to age at menarche (Matchock, 2008; Manning and Fink, 2011; Eresheim et al., 2020), age at menopause (Kirchengast et al., 2020), facial asymmetry (Fink et al., 2004), reproductive success (Klimek et al., 2016), breast cancer (Muller et al., 2012; Hong et al., 2014), reproductive and general health (Tabachnik et al., 2020), and cardiovascular disease risks (Luijken et al., 2017; Bagepally et al., 2020; Fischer Pedersen et al., 2021), The 2D:4D ratio was often shown to be able to predict the age of menarche (Matchock, 2008; Manning and Fink, 2011). Additionally, according to a number of studies, relatively masculinized hands (low 2D:4D) in females were substantially connected with delayed menarche age (e.g., Matchock, 2008; Manning and Fink, 2011; Kalichman et al., 2013), polycystic ovarian disease (Cattrall et al., 2005; Deepika and Preethy, 2021), systemic lupus erythematosus (Doe et al., 2015) and certain cancers (Muller et al., 2012; Hong et al., 2014; Bunevicius, 2018; Wang et al., 2018).

BACKGROUND AND OBJECTIVES

In addition to the above information, numerous research studies over the past few decades have focused strongly on understanding and identifying potential relationships between prenatal sex steroids (such as testosterone and oestrogen) activities that are determined in terms of indirect putative markers (such as the 2D:4D ratio) in intrauterine phase and sex differences, reproductive characteristics, sexual behaviour, and disease prevalence in various ethnic populations. The objectives of the present review study were to explore sexual dimorphism in 2D:4D ratio, evaluate the available evidence of probable associations, and assess the possibility of identifying specific reproductive and behavioural traits in populations. Besides, the comparisons of methodological aspects, benefits, and drawbacks to establishing the 2D:4D for examining the impact of prenatal sex steroids were also highlighted.

METHODOLOGY

The literature review for the present article was conducted using a variety of electronic databases, including "PubMed", "Google Scholar," "Scopus," and "Research Gate." The terms, ‘digit lengths’, ‘digit ratios’, ‘menarche’, ‘menopause’, ‘reproductive success’, ‘fertility’, ‘sexual dimorphism’, ‘sex-steroid’, ‘pubertal development’, ‘prenatal development’, ‘anthropometric measurements’, and ‘illness risk’ and their several possible combinations were the main search words utilised to identify the pertinent literature. All manuscripts for publications relevant to the objectives of the study were identified and screened after the necessary search. According to a set of criteria, the search research papers were evaluated to determine whether they should be included in the order to explore the relationship. These criteria included descriptive studies, review articles, cross-sectional studies, original survey studies, experimental studies, systematic review and meta-analysis, etc. For this comprehensive article, the literature published between 1998 and 2022 was surveyed. The research studies written in English were only included. New papers were incorporated into this study throughout preparation and until the last editing of the manuscript, although there was no requirement for a definite publishing date. A thorough analysis of the published literature revealed 80 suitable research papers to be taken into consideration. For the purpose of understanding, revising, and completing this manuscript, the finalized papers (both abstracts and full-length manuscripts) were downloaded.

DIGIT LENGTHS MEASUREMENTS AND DIGIT RATIO (2D:4D)

Direct anthropometric measurement procedures are very widely used, easy-to-use, and convenient method used by researchers to measure digit lengths in humans, and digit ratio is the ratio of the length of different digits or fingers typically measured from the mid-point of the bottom crease where the fingers join the hands to the tip of the fingers (Fink et al., 2003; Kyriakidis and Papaioannidou, 2008; Sen et al., 2014; Agnihotri et al., 2015; Sen et al., 2015; Jeevanandam and Muthu, 2016; Dey and Kapoor, 2016; Eresheim et al., 2020; Deepika and Preethy, 2021). The length of the digits was measured from the proximal crease at the base of the finger to the tip of the finger in the midline on the palmar aspect of the hand using a digital Vernier calliper closest to 0.01 mm without exerting pressure by a single experienced observer, and protruding fingernails were excluded (Manning et al., 1998; Manning, 2002). These digit ratios are the most frequently measured (Figure I). When measuring the participant's hand's digit lengths—its right finger (4D) and index finger (2D)—the participant's hand was positioned on a plastic board with the palm facing up. According to reports, this measurement is highly repeatable (Manning et al., 1998; Manning, 2002). To ensure the accuracy of the measurements, at least two replicated measurements were taken, and the means of the measurements were calculated separately and recorded (Bailey and Hurd, 2005). The 2D:4D ratio, which is the product of the lengths of the 2D and 4D, is used to determine the digit ratio. In both hands, the individuals' calculated 2D:4D ratio was divided into two groups based on the 2D:4D value: more feminine (2D:4D, ≥1), the index finger longer than the ring finger implies greater androgenic exposure) and more masculine (2D:4D, <1), the ring finger longer than the index finger implies greater androgenic exposure) (e.g., Klimek et al., 2016; Vélez et al., 2016).

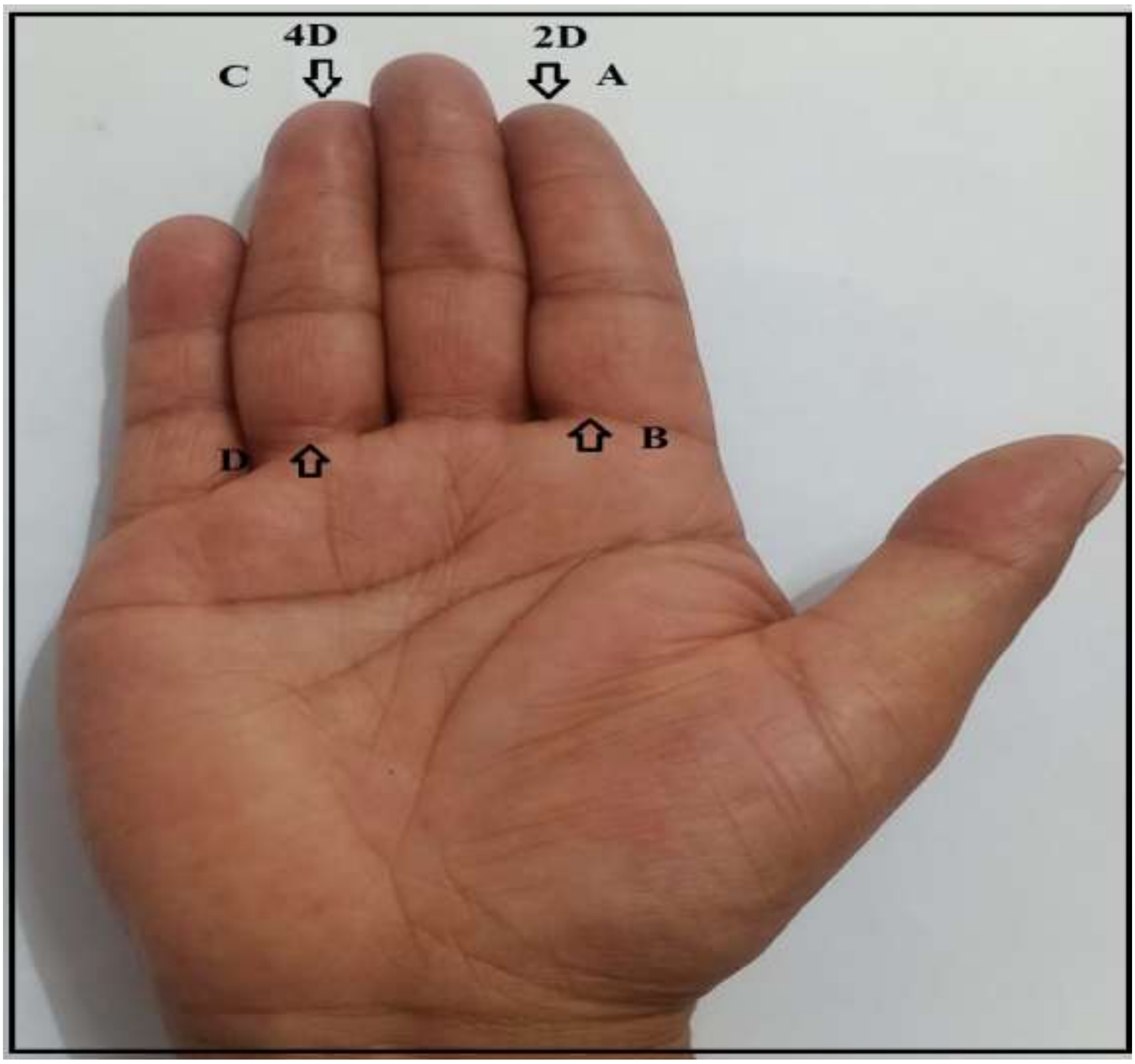

Figure 1: Figure showing the landmarks involved to direct measure of index finger (2D, A-B) and ring finger lengths (4D, C-D)

The X-ray method is frequently used to determine digit lengths and ratios (Kalichman et al., 2013). Furthermore, self-reported or measured digit lengths methods using rulers were used to report ethnic variations in digit ratio (Manning et al., 2007; Richards and James, 2019; Eresheim et al., 2020), and it was found that self-reported digit ratio yielded higher digit ratio values and a lower pattern of effect size (Manning et al., 2007; Richards and James, 2019), and it was also suggested that direct comparisons could be problematic or unreliable than researcher measured (Caswell and Manning, 2009; Richards and James, 2019; Eresheim et al., 2020). Digit ratios were calculated using various types of X-ray measurements of the second and fourth finger lengths. The soft tissue thickness of 2D and 4D fingertips was also measured using X-ray methods (Xi et al., 2014). Several studies have reported the digit ratio by measuring lengths on the ventral surface of hands with photocopies (Fink et al., 2003; Matchock 2008; Caswell and Manning, 2009), and the results were significantly lower (2D:4D) than direct measurements (Manning et al., 2005; Caswell and Manning, 2009). Furthermore, a few research studies have reported digit lengths and ratios using scanning techniques (Bailey and Hurd, 2005), image editing software (Mathangi et al., 2012), and X-ray method due to their precision, practicability, and cost involvement, but direct digit measurements are required to compare with other indirect obtainable digit length measurements methods (Bailey and Hurd, 2005; Manning et al., 2005; Xi et al., 2014).

SEXUAL DIMORPHISM AND DIGIT RATIO (2D:4D)

The digit ratio (2D:4D) is thought to be a putative proxy biomarker for prenatal androgen exposures, and it has been shown to demonstrate sexual dimorphism in humans to a considerable extent (Manning et al., 1998; Fink et al., 2003; Bailey and Hurd, 2005; Bull and Benson, 2006; Kyriakidis and Papaioannidou, 2008; Zheng and Cohn, 2011). Being a sexually dimorphic trait (the mean 2D:4D is lower in males than females), 2D:4D can be used as an indirect retrospective method of estimating the relative intrauterine androgenic exposure, particularly PT and/or PE (Fink et al., 2003; Lutchmaya et al., 2004; Bailey and Hurd, 2005; Kyriakidis and Papaioannidou, 2008; Zheng and Cohn, 2011; Manning et al., 2014; de Sanctis et al., 2017). According to research, the digit ratio is negatively correlated with prenatal testosterone and positively correlated with oestrogen exposures (Manning et al., 1998, 2005; Fink et al., 2003; Lutchmaya et al., 2004; Bull and Benson, 2006; Manning and Fink, 2008). The relative concentrations of PT and PE, reflected by the 2D:4D ratio, influence sexual differences, sexually differentiated behaviours, and sexual orientation in humans, plausibly, through its impact on the brain "reorganisation" during the narrow developmental period

(Manning, 2002; Manning et al., 2007; Wallien et al., 2008; Breedlove, 2010; de Sanctis et al., 2017).

Due to a well-established sexually dimorphic population marker, recent studies have reported that digit lengths (such as 2D and 4D) and 2D:4D ratios have been used to predict sex for an individual or population (Fink et al., 2003; Bailey and Hurd, 2005; Voracek et al., 2006; Kyriakidis and Papaioannidou, 2008; Manning and Fink 2008; Sen et al., 2014, 2015; Agnihotri et al., 2015; Dey and Kapoor, 2016; Khan et al., 2017). Besides, a number of studies have documented sexual dimorphism in populations based on their 2D:4D ratio or relative finger lengths (e.g., 2D and 4D) (McIntyre et al., 2005; Trivers et al., 2006; Kyriakidis and Papaioannidou, 2008; Zheng and Cohn, 2011; Xi et al., 2014; Agnihotri et al., 2015; Sen et al., 2015; Dey and Kapoor, 2016). Results showed that males tend to have shorter 2D, relative to the 4D lengths than females, and those males had considerably lower digit ratios than females (Fink et al., 2003; Bailey and Hurd, 2005; Kyriakidis and Papaioannidou, 2008; Agnihotri et al., 2015; Sen et al., 2015; Xu and Zheng, 2015; Dey and Kapoor, 2016; de Sanctis et al., 2017; Khan et al., 2017).

Moreover, the in-utero balance of androgens-to-oestrogen is thought to be the fundamental cause of the considerable and constant sex differences across distinct ethnic populations as measured by the digit ratio (2D: 4D) (Viveka et al., 2014; de Sanctis et al., 2017). Additionally, studies have shown that there are considerable bilateral variances, sex differences, and ratios of digit lengths (2D:4D) among individuals and ethnic groups (Voracek et al., 2006; Kyriakidis and Papaioannidou, 2008; Manning and Fink 2008, Sen et al., 2014; Sen et al., 2015; Agnihotri et al., 2015; Khan et al., 2017). Additionally, several longitudinal and cross-sectional studies have suggested that sex differences in the 2D:4D ratio did emerge at a very early developmental stage (i.e., the 14th week of foetal life), remained unaffected by puberty, stable through physical growth and sexual maturity and during menstrual cycles (Barrett et al., 2015; Klimek et al., 2017; Richards et al., 2018), and may potentially be connected to circulating adult sex steroids (Hönekopp et al., 2007). Additionally, it was stressed that adult people could have prenatally acquired phalangeal ratios that were substantially linked with sex-specific finger lengths and looked stable from early infancy into adulthood (Manning et al., 2001; Manning, 2002) and strongly correlated with digit lengths (Manning 2002; McIntyre et al., 2005).

REPRODUCTIVE CHARACTERISTICS, AGE AT MENARCHE, FERTILITY, MENOPAUSE AND DIGIT RATIO (2D:4D)

The 2D:4D digit ratio has been significantly portrayed as a retrospective biomarker of PT and PE during intrauterine development in the past two decades (Manning et al., 1998, 2000; Manning, 2002; McIntyre, 2006). Additionally, digit ratio (2D:4D) values are widely employed as a crucial indirect marker to predict connections with higher reproductive capacity and success, longer reproductive lifespan, fertility indicators, natural menopause, age of menarche, and adverse reproductive outcomes which considerably differ among populations (Manning, 2002; Matchock, 2008; Helle, 2010; Manning and Fink, 2011; Kalichman et al., 2013; Klimek et al., 2016; Eresheim et al., 2020; Kirchengast et al., 2020; Tabachnik et al., 2020). Additionally, a number of cultural factors, such as age at marriage, number of years of education, breastfeeding, nutrition status, and postpartum ovarian function, disease prevalence do affect population reproduction (Matchock, 2008; Klimek et al., 2016; Vélez et al., 2016; Tabachnik et al., 2020).

Interestingly, several researchers have reported that women with more feminine digit ratio (2D:4D) tend to marry at an earlier age, prefer marriage at an earlier age, have higher reproductive success, longer reproductive lifespan, and number of children (Manning and Fink, 2008; Sorokowski et al., 2012; Klimek et al., 2016; Kirchengast et al., 2020), have experienced early onset of reproductive period and meiosis, and have experienced early menopause age (Manning and Fink, 2008; Matchock, 2008; Manning and Fink, 2011; Li et al., 2019; Eresheim et al., 2020; Tabachnik et al., 2020), pubertal development (Gooding and Chambers, 2018; Li et al., 2019), severity of premenstrual symptoms (Kaneoke et al., 2017), and also heavier menstrual bleeding as well as dysmenorrhea (Tabachnik et al., 2020), than the masculine digit ratio (2D:4D). However, Kirchengast et al. (2020) reported that a higher age at menopause and higher number of children were both strongly associated with a more feminine digit ratio, which indicates higher oestrogen level during intrauterine period. Similar studies have found that women are more likely than men to reach puberty early, with a higher digit ratio in comparison to a low digit ratio (e.g., Matchock, 2008; Manning and Fink, 2011; Li et al., 2020; Tabachnik et al., 2020).

Studies indicated that the 2D:4D ratio was negatively correlated with foetal testosterone levels (Manning et al., 1998, 2000, 2003, 2005). Possible explanations were drawn from the condition of congenital adrenal hyperplasia, on one hand, is very often associated with a lower 2D:4D, and on the other, the complete androgen insensitivity syndrome, exhibiting a higher 2D:4D. The plausible link may be sought through a connection shown between 2D:4D and androgen receptor polymorphisms (Breedlove, 2010; Zhang et al., 2013; de Sanctis et al., 2017). Additionally, a low 2D:4D ratio was also shown to be correlated with high sperm counts, testosterone levels, and reproductive success (Okten et al., 2002). Additionally, multiple studies have shown that lower digit ratios (2D:4D<1) greatly raise the risk of the polycystic ovarian syndrome (PCOS) and a number of malignancies, including prostate, stomach, and brain tumours (Bunevicius, 2018) and PCOS (Cattrall et al., 2005; Deepika and Preethy, 2021).

Furthermore, a number of additional studies found that the 2D:4D ratio was strongly inversely related to menarcheal age (Matchock 2008; Kalichman et al., 2013; Eresheim et al., 2020). An association between 2D:4D and age at menarche was explained as the positive relationship between delayed menarche and increased intrauterine androgen exposure (Manning et al., 2003; Matchock, 2008). Additionally, 2D:4D ratios were linked to less-than-ideal reproductive circumstances, such as late menarche, greater menstrual bleeding, and dysmenorrhea (Tabachnik et al., 2020). In addition, it is believed that adult fertility may have been decreased in women exposed in the uterine to imbalanced sex steroids (Vélez et al., 2016). According to several studies, young age of menarche is strongly linked to an increased risk of developing diseases such as type II diabetes, hypertension, cardiovascular disease, metabolic disorders, and malignancies in menopausal women (Muller et al., 2012; Luijken et al., 2017; Wang et al., 2018; Fischer Pedersen et al., 2021).

Additionally, female-typical variables, pubertal characteristics or early pubertal onset and development, and certain disease prevalence are suggested to be strongly expressed on the left side of the body. Researchers have also suggested that left 2D:4D is a more accurate marker of prenatal hormone exposure (Manning 2002; Lu et al., 2012; Klimek et al., 2016; Gooding and Chambers, 2018; Wang et al., 2018; Li et al., 2019; Tabachnik et al., 2020). Numerous studies have demonstrated relationships between left-hand 2D:4D and biological factors, habits, and disease prevalence in women (e.g., Mackus et al., 2017; Wang et al., 2018), and early diagnosis of infertility (Lu et al., 2012). Therefore, it is believed that the left-hand 2D:4D is a useful predictor of a variety of reproductive features (such as age of menarche and reproductive success), and that it is biologically appropriate for reproductive women to examine the 2D:4D in both hands (Manning and Fink, 2008; Klimek et al., 2016; Li et al., 2019; Tabachnik et al., 2020).

BEHAVIOUR TRAITS AND DIGIT RATIO (2D:4D)

Numerous studies have identified a connection between digit ratio and adult population behavioural qualities including assertiveness, dominance and aggression, increased risk-taking propensity and occupational preferences (Benderlioglu and Nelson, 2004; Lippa, 2006; Martel et al., 2009; Zheng and Cohn et al., 2011; Hampson and Sankar, 2012; Lyons and Helle, 2013; Trabert et al., 2013; Butovskaya et al., 2015; Kainz et al., 2017). Numerous psychological and sexually dimorphic behaviours, including sex-related psychopathology and physiology, have been connected to the digit ratio (Manning et al., 1998; Evardone and Alexander, 2009; Schwerdtfeger et al., 2010). Male-related disorders like autism have been connected to lower digit ratios (Mackus et al., 2017; Lee et al., 2021), which indicate higher perinatal androgen activity, while female-linked disorders have been linked to greater digit ratios, which indicate weaker perinatal androgen action (e.g., depression and eating disorders) (Evardone and Alexander, 2009). Martel et al. (2009) reported that females' vulnerability to mental illnesses in adolescence and males vulnerable to behavioural disorders in childhood. Certain characteristics, such as aggression, and assertiveness or dominance, are associated with a low digit ratio (Benderlioglu and Nelson, 2004; Bailey and Hurd, 2005; Hampson et al., 2008; Hampson and Sankar, 2012; Butovskaya et al., 2015). A similar correlation was found between greater digit ratios and eating disorders, anxiety, and depression in both boys and girls with feminine digit ratios (Evardone and Alexander, 2009; Manning et al., 2013). Furthermore, men who had more characteristics and behaviours associated with sex, such as higher digit ratios, expressed higher anxiety (Evardone and Alexander, 2009). Adult aggression is more likely to appear in people who were exposed to high levels of androgens. Similarly, the propensity for aggressive behaviour may be predicted by lower digit ratio with boxers fractures that general population (Joyce et al., 2013; Joyce et al., 2017) and traffic rule violation for car drivers (Schwerdtfeger et al., 2010).

CONCLUSION

The present review article has demonstrated that a low 2D:4D digit ratio can be used as a proxy for prenatal hormone exposure and may be linked to delayed menarche, longer gestation periods, successful pregnancy, menopause naturally and behavioural traits. Additionally, this very attempt has focused on the growing body of data that highlights that prenatal hormone exposure (i.e., as represented in the 2D:4D ratio) has a substantial impact on a woman's ability to reproduce successfully, when she reaches menarche, and when menopause begins. Women who have high levels of prenatal testosterone and low levels of prenatal oestrogen typically experience delayed menarche and menopause as a result. It has previously been established in the population that there is sexual dimorphism in the 2D:4D ratio, which is used to assess the links between prenatal androgen exposures. More research is needed to determine the potential impact and correlation between the 2D:4D ratio and age at menarche, reproductive success, age at menopause and behavioural aspects in different ethnic populations.

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AUTHORS CONTRIBUTION

NM: Conceived the idea, carried out the literature search and downloaded the published articles, and wrote the manuscript. RC: Carefully revised the draft manuscript, and contributed important intellectual content to the final manuscript. All the listed authors have contributed substantially towards finalisation of the manuscript.

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