Digit ratio (2D:4D): a biomarker for prenatal sex steroids and adult sex steroids in challenge situations

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Digit ratio (2D:4D) denotes the relative length of the second and fourth digits. This ratio is considered to be a biomarker of the balance between fetal testosterone (T) and estrogen (E) in a narrow window of early ontogeny. Evidence for this assertion is derived from direct and indirect measures of prenatal hormonal exposure (in experimental animals, via amniotic fluid samples and in the study of sex-typical traits) in relation to 2D:4D. In contrast, the relationships between 2D:4D and levels of sex steroids in adults are less clear, as many correlational studies of 2D:4D and adult sex steroids have concluded that this association is statistically non-significant. Here, we suggest that in order to understand the link between 2D:4D and sex hormones, one must consider both fetal organizing and adult activating effects of T and E. In particular, we hypothesize that 2D:4D correlates with organizing effects on the endocrine system that moderate activating effects in adulthood. We argue that this is particularly evident in “challenging” conditions such as aggressive and sexual encounters, in which individuals show increased levels of T. We discuss this refinement of the 2D:4D paradigm in relation to the links between 2D:4D and sports performance, and aggression.

Keywords: digit ratio, testosterone, estrogen, performance, aggression, organizing effects, activating effects

INTRODUCTION

Digit ratio (or 2D:4D) is the relative lengths of the second and fourth digit. This ratio is considered to be a biomarker of the balance between fetal testosterone (T) and estrogen (E) in a narrow window of early ontogeny. Evidence for this assertion is derived from direct and indirect measures of prenatal hormonal exposure (in experimental animals, via amniotic fluid samples and in the study of sex-typical traits) in relation to 2D:4D. In contrast, the relationships between 2D:4D and levels of sex steroids in adults are less clear, as many correlational studies of 2D:4D and adult sex steroids have concluded that this association is statistically non-significant. Here, we suggest that in order to understand the link between 2D:4D and sex hormones, one must consider both fetal organizing and adult activating effects of T and E. In particular, we hypothesize that 2D:4D correlates with organizing effects on the endocrine system that moderate activating effects in adulthood. We argue that this is particularly evident in “challenging” conditions such as aggressive and sexual encounters, in which individuals show increased levels of T. We discuss this refinement of the 2D:4D paradigm in relation to the links between 2D:4D and sports performance, and aggression.

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HYPOTHESIS AND THEORETICAL ARTICLE

The sex difference in 2D:4D is now well understood [see Ref. (5) for a meta-analysis]. It is found in fetuses as early as the end of the first trimester (6,7) and although it may change postnatally as the fingers grow, this change is in the form of a gentle increase in 2D:4D (8,9). Fetal levels of T are sexually dimorphic with male fetuses having higher T than female fetuses. Therefore, this pattern of prenatal determination of the sexual dimorphism in 2D:4D is consistent with – but does not prove that – the sex difference in 2D:4D reflects fetal levels of sex steroids.

It is difficult to measure the effect of FT and FE on 2D:4D in humans directly because of ethical constraints. This is why a readily measured indirect correlate of the balance between FT and FE (such as 2D:4D) is valuable in investigating organizing effects on sex-typical traits. However, the difficulties associated with measuring fetal hormones and fetal 2D:4D means that the link between FT/FE and 2D:4D is considered to be a biomarker of the balance between fetal testosterone (T) and estrogen (E) in a narrow window of early ontogeny. Evidence for this assertion is derived from direct and indirect measures of prenatal hormonal exposure (in experimental animals, via amniotic fluid samples and in the study of sex-typical traits) in relation to 2D:4D. In contrast, the relationships between 2D:4D and levels of sex steroids in adults are less clear, as many correlational studies of 2D:4D and adult sex steroids have concluded that this association is statistically non-significant. Here, we suggest that in order to understand the link between 2D:4D and sex hormones, one must consider both fetal organizing and adult activating effects of T and E. In particular, we hypothesize that 2D:4D correlates with organizing effects on the endocrine system that moderate activating effects in adulthood. We argue that this is particularly evident in “challenging” conditions such as aggressive and sexual encounters, in which individuals show increased levels of T. We discuss this refinement of the 2D:4D paradigm in relation to the links between 2D:4D and sports performance, and aggression.

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to investigate this relationship may be considered as of two kinds, i.e., correlational studies and experimental studies.

Correlational studies have considered relationships between 2D:4D and sexually dimorphic physical and behavioral traits that are thought to be linked to FT and FE. There are many of these; here we focus on some of the more important ones, i.e., those that are very likely to be affected by FT and/or FE. Congenital adrenal hyperplasia (CAH) is a trait associated with an increase in the size of the fetal adrenal glands and an elevated level of fetal androgens. To date, there have been four studies of CAH and 2D:4D. All have shown a tendency for low 2D:4D (i.e., “masculinized” 2D:4D) to be linked to CAH and in three such studies, the effects were significant [see Ref. (5) for a meta-analysis of these studies]. In contrast to CAH patients, individuals with Klinefelter’s syndrome (males with 47 chromosomes, including XXY) have low fetal androgen levels. In Klinefelter patients, 2D:4D is significantly higher (i.e., “feminized” 2D:4D) than that of the population norm (10). This pattern of “feminized” 2D:4D has also been found in individuals who suffer from androgen insensitivity (11), i.e., a clinical condition that results in a partial or complete inability of cells in their response to androgens. All these studies have focused on FT. However, Lutchmaya et al. (12) obtained both FT and FE concentrations from amniotic fluid samples in order to investigate relationships with 2D:4D. It was found that 2D:4D of neonates was related to a balance of FT and FE, such that high FT and low FE were linked to “masculinized” 2D:4D.

The link of digit ratio to CAH, Klinefelter’s syndrome, and androgen insensitivity is strong evidence for a link between 2D:4D and prenatal sex steroids. However, one trait, the anogenital distance (AGD), may well be influenced by prenatal T, but shows little or no correlation with 2D:4D in rodents [for mice, see Ref. (13, 14); for rats, see Ref. (15)]. Why is this so? In humans the sex difference in 2D:4D is of medium effect size (5). It is determined toward the end of the first trimester of pregnancy, in a narrow time window [for mice see Ref. (14)] and its magnitude changes little with subsequent growth (8, 9). In contrast, AGD shows a large sex difference, which varies from 1.4-fold-longer in males at 11–13 weeks to 2.0-fold-longer at 17–20 week gestation and a smaller difference is found in adults (16). This variability suggests that – unlike 2D:4D – the sex difference in AGD is not fixed early in utero but is influenced by fluctuations in second–trimester and post-natal androgens. Indeed, there has been one study in mice that experimentally confirmed these suggested effects [see Ref. (4, 14) for discussion]. There have been reports that both AGD and 2D:4D change when fetuses are exposed to endocrine disruptors [AGD, see Ref. (16); 2D:4D, see Ref. (15)]. The study by Auger et al. is of particular relevance here, as these authors compared the effect of estrogenic and anti-androgenic compounds on 2D:4D and AGD in rats. The authors reported a feminization effect for 2D:4D, but not so for AGD, which again suggests different times of developmental fixation of the sexual dimorphism in 2D:4D and AGD.

Correlational studies have also focused on the relationship between 2D:4D and the structure of the androgen receptor gene (AR), with emphasis on the number of CAG repeats in the AR.

Sensitivity to T is negatively associated to CAGn, such that in general population samples the highest sensitivity is found for CAGn of about 10 and lowest sensitivity for CAGn of about 30. Therefore, we might expect that 2D:4D is positively correlated with CAGn. There is mixed evidence from studies that have investigated this relationship and a recent meta-analysis including 14 samples and 1904 participants found no association between 2D:4D and CAGn (17). However, a closer inspection of the link between CAGn and T-dependent phenotypic traits suggests that normal variability of CAGn has mostly no, very small, or inconsistent effects [for example see Ref. AGD; (18)]. Thus, Hönekopp (17) concluded that “the lack of a clear correlation between CAGn and 2D:4D has no negative implications for the latter’s validity as a marker of prenatal testosterone effects.”

Experimental studies of the effects of FT and FE on 2D:4D are based on the assumption that the effects of prenatal hormones on human 2D:4D are essentially similar to those observed in other mammals. Consistent with this assumption, the 2D:4D of mammals, such as chimpanzees and bonobos (19), mice (20, 21), and rats (15) have been reported to show a sexual dimorphism, which is similar to that observed in humans (i.e., lower 2D:4D in males compared to females). In addition, comparative studies of primates showed that selection for high FT, resulting from a polygamous mating system, leads to the evolution of low 2D:4D (22). Moreover, the manipulation of FT and FE in animal models provides persuasive evidence for the developmental origins of 2D:4D. In rodents, there have been three such studies. Talarivcova et al. (23) reported that maternal enhancement of PT during pregnancy increased 4D length and reduced 2D:4D in both male and female rats. Zheng and Cohn (14) found that in mice a balance of FT to FE controlled 2D:4D, such that high FT increased 4D (leading to a reduction in 2D:4D) and high FE reduced 4D (leading to an increase in 2D:4D). The ratio of FT/FE had a marked effect on 4D because this fetal digit was richly supplied with receptors for FT and FE. Hence, Zheng and Cohn concluded that “digit ratio is a lifelong signal of prenatal hormonal exposure.” This model was developed further by Auger et al. (15) who exposed rat fetuses to environmental levels of estrogenic and anti-androgenic disruptors. They found that, in comparison to controls, such disruptors feminized digit ratios in male rats and concluded 2D:4D was a biomarker of prenatal exposure to low-dose environmental levels of endocrine disruptors.

RIGHT–LEFT DIFFERENCES IN 2D:4D

Zheng and Cohn’s (14) study has been influential in clarifying the relationship between 2D:4D and T/E ratios in the fetus. It has also shed some light on right–left differences (Dr–l) and associated effects on sex differences in 2D:4D. In their initial study, Manning et al. (2) reported that in humans right 2D:4D showed stronger relationships with target traits (such as T, E, and sperm numbers) than did left 2D:4D, suggesting that right 2D:4D is more sensitive to prenatal sex steroids than left 2D:4D (2); see also Ref. (3), p.211. More recently, Hönekopp and Watson (5) reported that the sex difference in right 2D:4D was greater than that of left 2D:4D. In order to determine whether 2D and 4D length is specified differently in males and females, Zheng and Cohn (14) used expression of Sox9, the earliest molecular marker of cartilage differentiation, to label the primordium of each digit in a sample of mice. They then measured the length of the Sox9 domain in the second and fourth
A few studies have reported a negative correlation between 2D:4D and adult testosterone (24). (ii) With regard to the latter study, 45 participants were exposed to an aggressive video (rugby tackles and a "haka") and a control video (a blank screen). Testosterone was assayed before and after each video and an aggression questionnaire completed after each video. The aggressive video was associated with a marginally significant increase in T, but the control video was not. Low 2D:4D (this time left 2D:4D) predicted high aggression scores after the aggressive video, and the association was particularly strong in participants showing the highest increase in T. However, there were no associations between 2D:4D and aggression after the control video (25).

If low 2D:4D predicts high T spikes in response to competitive sports, we should not be surprised that low 2D:4D is associated with performance in many competitive sports.

2D:4D AND THE "CHALLENGE" LINK WITH SPORTS

Digit ratio shows relationships with many traits, but the effect sizes of reported associations are often small. For example, in sports there are considerable relationships with negative correlations of about 0.4–0.6 reported in some sports such as distance running, rowing, rugby, and surfing, but also weak associations in sprinting and strength events [see Ref. (40) for a meta-analysis].

We suggest that many of these associations are driven by the link between low 2D:4D and pronounced spikes of T after challenge. For example, it is known that low Dr–l is predictive of high performance in elite rugby union players, with low Dr–l associated with high representation at international level (number of "caps") and high number of tries scored (41). Low Dr–l is also a predictor of high T spikes, and this correlation may underlie the link between 2D:4D and sports. There are also behavioral traits, which are associated with 2D:4D, but in general the effect sizes of such relationships are much weaker than the link with sports. An appropriate and related example is aggression. Aggression is important in many sports, and low 2D:4D has been reported to be correlated with high physical aggression. However, in a non-sporting context the association is generally considered to be weak and requires large sample sizes to be demonstrated convincingly (5, 42). Given this dichotomy of results, we suggest that low 2D:4D is robustly linked to high aggression, but it is the context in which aggression is measured that is important here. The work of Millet (43) illustrates this inter-actionist perspective, suggesting that low 2D:4D does predict high aggression if the participants are subject to provocation or are placed in a threatening context (43, 44). In such situations, we expect marked spikes in T and robust correlations between 2D:4D and aggression. However, if participants are tested in neutral conditions then links between 2D:4D and aggression should be tenuous. Another example of such context-dependent findings is the intensely competitive environment of short-term financial trading. We should not be surprised that in this setting a strong negative correlation between 2D:4D and financial success was reported (45). On the contrary, in neutral...
laboratory conditions the links between 2D:4D and aggression are typically much weaker and should be seen with caution (46).

Studies on the associations between 2D:4D and sport are often focused on male participants. However, there is some evidence that low 2D:4D is linked to high levels of performance in females also (40), yet the overall picture with regard to 2D:4D in female athletes remains obscure [e.g., for handgrip strength, see Ref. (47)]. Little is known with regard to “challenge-related” spikes of T in females, although there is some support for a link between 2D:4D and sensitivity to administered T in women. In three studies, Van Honk and colleagues have shown that administered T modulates empathy (48), cooperation (49), and moral judgments (50) in women, and that 2D:4D strongly moderates the effects. The sample sizes in these studies are small, but the effect sizes are very large with 2D:4D explaining 25–44% of the variance of the effects of T. It is yet unclear why 2D:4D predicts response to administered spikes in T in such studies, but similar relationships between 2D:4D and response to T may also be found in men.

CONCLUSION
We conclude that 2D:4D is a biomarker for the balance between FT and FE, such that high FT and low FE is linked to low 2D:4D. There is evidence that 2D:4D is fixed in a relatively narrow developmental window at the end of the first trimester of pregnancy and that it does not change substantially with age. Considering 15 years of work on this topic, we feel that there is quite strong evidence for this link. However, more constantly, we hypothesize that the relative levels of FT and FE have organizing effects on the adult endocrine system, which are particularly evident in “challenging” situations, such as aggressive or sexual encounters. This means that 2D:4D should correlate with T spikes produced under challenge and it may also be linked to response to such spikes. In consequence, low 2D:4D may be a predictor of high performance in sports and high aggression when provoked. We suggest that future studies regarding the links between 2D:4D and such traits as cooperation and aggression and testosterone in men exposed to an aggressive video stimulus. Proc Biol Sci (2013) 280:20131532, doi:10.1098/rspb.2013.1532.

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