The 2D:4D ratio, a proxy for prenatal androgen levels, differs in men with and without MS

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ABSTRACT

Objective: To determine whether the 2D:4D ratio (ratio of the second and fourth digit lengths), a proxy for lower prenatal androgen to estrogen ratio, differs in men with and without multiple sclerosis (MS) using a case-control study design.

Methods: We obtained 2 digital scans of the right hand for men with MS presenting to a scheduled clinic visit at a large MS referral center, and for men without autoimmune or endocrine diseases. All individuals were aged 18 to 65 years, right-handed, and reported no prior digit trauma. We calculated a mean 2D:4D ratio using digital calipers. In participants with MS, we assessed age at first MS symptoms, MS type, and the MS Severity Score; 51 had provided a testosterone level within 10 years of symptom onset. Our primary analysis was a cross-sectional comparison of the 2D:4D ratio between men with and without MS, using a 2-sample *t* test for independent samples assuming unequal variance.

Results: In total, we scanned 137 men with MS and 145 men without MS. A statistically significant association between 2D:4D ratio and MS status was observed in the univariate logistic regression model ($p < 0.05$). These differences were not associated with age or race, which differed between the 2 groups. In participants with MS, the 2D:4D ratio was not correlated with MS type, age at first symptoms, or MS Severity Score ($p > 0.15$ for each), and it was not correlated with adult testosterone levels ($r = 0.06$, $p = 0.68$, n = 51).

Conclusions: During the prenatal period, low androgens could represent a risk factor for MS.
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GLOSSARY

MS = multiple sclerosis; **MSSS** = Multiple Sclerosis Severity Score.

Men are less likely to develop multiple sclerosis (MS) than women, but they are more likely to display progressive forms of the disease and to develop more rapid brain atrophy.[1] In addition to chromosomal and epigenetic factors, gonadal hormones may contribute to sex-related differences in inflammation and neurodegeneration in MS. In fact, some studies have found decreased levels of testosterone in men with MS relative to healthy controls (reviewed in reference 1), as well as an association between hypogonadism and subsequent MS diagnosis.[2]

The prenatal period is increasingly understood as a period of vulnerability to subsequent inflammatory and neurologic diseases including MS.[3] The ratio of an individual's second and fourth digit lengths (2D:4D ratio) reflects digit growth, which is highly influenced by the ratio of prenatal androgen to estrogen levels.[4] This sexually dimorphic ratio can be considered as a lifelong signature of prenatal hormonal levels: a higher ratio has been shown to be associated with a lower in utero balance of androgens to estrogen. On the balance, this association is more clearly manifest in men.[4] We are not aware of published data for its association with autoimmune diseases.

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In this study, we hypothesized that the 2D:4D ratio may be increased in men with MS relative to men without MS. Secondarily, in recognition that some MS risk factors may influence not only MS risk but also disease course (e.g., smoking[5,6] and vitamin D levels[7]), we explored a possible association between the 2D:4D ratio and clinical features of a more aggressive MS course.

METHODS

Participants. ***Men with MS.*** We recruited male patients of the Partners MS Center, including those enrolled in the CLIMB study (www.climbstudy.org). Patients met the diagnostic criteria of MS by the 2005 McDonald criteria; 51 had provided blood samples for a testosterone level within 10 years of their first MS symptom onset, as previously described.[8]

Men without MS. Concurrently with our recruitment of patients with MS, we recruited men from a large medical office building, which houses the MS Center. Participants included individuals presenting to a number of medical offices or the phlebotomy laboratory in the building, postal and construction workers, janitorial and medical staff, as well as individuals (spouses, partners, friends) accompanying MS Center patients to their visits. Of all participants without MS, >95% were known to be unrelated to MS Center patients. Screening procedures excluded men with MS or other autoimmune (e.g., asthma) or endocrine (e.g., Addison disease) diseases.

Table 1 Demographic characteristics of study participants

	Men with MS (n = 137)	Men without MS (n = 145)
Age,[a] y, mean (SD)	45.7 (11.4)	41.4 (11.7)
Race,[b] n (%)		
White	127 (92.7)	111 (76.6)
Black/African American	5 (3.7)	8 (5.5)
American Indian	0 (0.0)	2 (1.4)
Asian	1 (0.7)	13 (9.0)
More than one race	1 (0.7)	7 (4.8)
Unknown	3 (2.2)	4 (2.7)
Age at first symptom, y, mean (SD)	33.3 (10.4)	
Disease duration, y, mean (SD)	12.4 (8.2)	
Disease category, n (%)		
RRMS	102 (74.5)	
PPMS	12 (8.7)	
SPMS	21 (15.3)	
PRMS	2 (1.5)	
EDSS, median (IQR)	1.5 (0.0–3.5)	
MSSS, mean (SD)	2.6 (2.5)	

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score; PPMS = primary progressive multiple sclerosis; PRMS = progressive relapsing multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.
[a] $p < 0.05$.
[b] $p < 0.0001$.

Inclusion criteria for all men were ages 18 to 65 years, right-handedness (to reduce potential variability in the 2D:4D ratio introduced by handedness[4]), and no history of trauma to the right hand.

Among 171 patients with MS approached, 9 refused, 3 were ineligible, and 159 were enrolled. Among 209 individuals without MS approached, 26 refused, 22 were ineligible based on general screening criteria (age, handedness, or prior hand trauma), and 161 were enrolled. Based on their medical history obtained after enrollment, a further 8 were excluded because of diagnoses of autoimmune or endocrine diseases. The differences in the number of individuals with MS vs those without MS agreeing to participate likely reflected differences in the groups' schedules (participants with MS were awaiting medical appointments, while participants without MS were often just passing by the clinic).

2D:4D ratio. Each participant underwent 2 digital scans of their right hand, using a digital scanner. The second and fourth digits were measured on each digital image using digital calipers by 2 investigators blinded to disease status. Digit length was measured on the ventral surface of the hand from the basal crease of the digit to the tip, as detailed.[9] Specifically, the basal crease of the digit was assessed at the midline. The caliper was then placed on the tip of the finger producing the longest length measurement. The 2D:4D ratio was calculated for each scan; the average of the 2 scans was used for analyses. At the measurement stage, 27 (20 MS, 7 non-MS) scans were excluded because of poor image quality, mostly reflecting difficulties among patients with MS to achieve a relaxed, resting hand position on the scanner.

MS clinical outcomes. For patients with MS, age at first symptoms and MS type at closest clinic visit within 12 months of their digital scan were obtained from the CLIMB database. The MS Severity Score (MSSS) was calculated for each patient, adjusting clinical severity (Expanded Disability Status Scale) for time since first symptoms.[10]

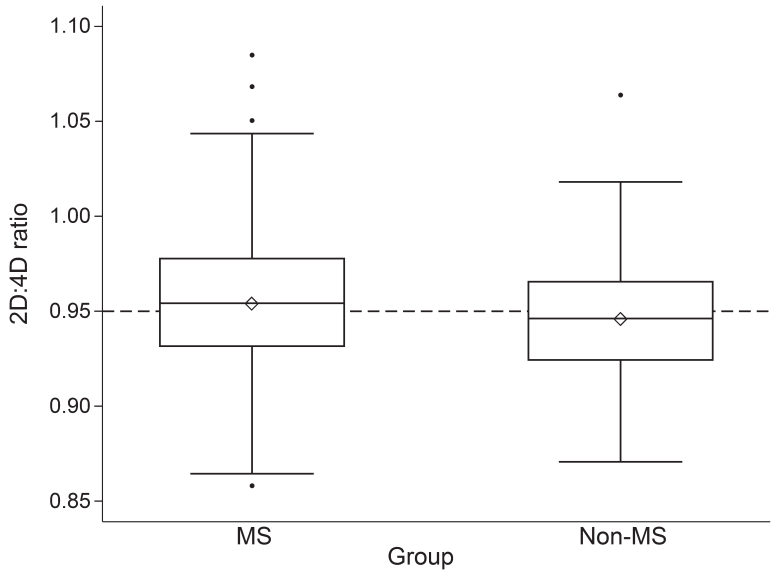
Standard protocol approvals, registrations, and participant consents. Institutional review board approval was granted by the Partners Human Research Committee and all participants provided written informed consent.

Statistical analyses. Our primary statistical analysis assessed the association between 2D:4D ratio and MS status using logistic regression. We first compared the mean ratio in the 2 groups using a 2-sample t test for independent samples assuming unequal variance. This test was selected after we had ensured that the 2D:4D ratios were normally distributed in each group using the Shapiro-Wilk test for normality for the mean 2D:4D ratios in both groups. The results showed that normality was achieved for the mean ratio in both the participants without MS ($W = 0.99$; $p = 0.30$) and those with MS ($W = 0.98$; $p = 0.26$). Then, in our main analysis, we assessed the association between 2D:4D ratio and MS status using logistic regression. Since significant discordances were observed between groups for age and race, we further used a multiple logistic regression model adjusting for age at visit and race. We then repeated these analyses in white participants only, given that most participants with MS were white.

To assess the reproducibility of digit lengths between the 2 scans, we performed a Bland-Altman plot for the lengths of both the second and fourth digits and identified one outlier. Excluding this individual from analyses did not alter the significance of any of our findings.

In participants with MS, we then assessed the association between 2D:4D ratio and age at first symptoms, measured MSSS,

Figure Higher mean and median 2D:4D ratio in men with MS than in men without MS



Boxplot comparing 2D:4D ratios in adult men with MS (n = 137) and without MS (n = 145). The diamond symbol represents the mean, and the horizontal bar in the center of the box represents the median. MS = multiple sclerosis.

and adult testosterone levels using the Pearson correlation coefficient. Further, we assessed the association between 2D:4D ratio and MS type using logistic regression, with MS type (progressive forms [secondary progressive, primary progressive, progressive remitting] vs relapsing-remitting) as the outcome and 2D:4D as the predictor.

RESULTS A total of 137 participants with MS and 145 without MS contributed scans to the analysis. Participants with MS were older (*t* test, $p = 0.0015$) and more likely to be white than were those without MS (χ^2 test for equality of proportions test, $p < 0.0001$) (table 1).

Comparison of 2D:4D ratio in participants with and without MS. In our sample, men with MS had a higher mean (median, SD) 2D:4D ratio (0.955 [0.954, 0.040]) than men without MS (0.946 [0.946, 0.032]; $p = 0.03$) (figure). A statistically significant association between 2D:4D ratio and MS status was observed in the univariate logistic regression model (table 2). After adjusting for age and race, the results remained suggestive of an effect of 2D:4D ratio on MS status (table 2).

Given the very small number of nonwhite participants with MS, we further restricted the analysis to white participants only in both groups. Using a 2-sample *t* test for independent samples assuming unequal variance, again the mean 2D:4D ratio in the participants with MS (n = 127) was significantly higher than in those without MS (n = 111; M = −0.012; 95% confidence interval: −0.022 to −0.003; $p = 0.01$). When a multivariate logistic regression model adjusting for age at scan was fit, a significant estimated change in the odds of an MS diagnosis was observed (table 2).

Association between 2D:4D ratio and MS disease course. In participants with MS, we found no support for our hypothesis that a higher 2D:4D ratio is associated with worse MS course (table 3), including earlier age at first MS symptom ($r = -0.03$, $p = 0.71$) or measured MSSS ($r = -0.12$, $p = 0.16$). The estimated change in the odds of developing a relapsing form of MS for a 0.01-unit increase in 2D:4D ratio was not significant (odds ratio = 1.05; 95% confidence interval: 0.98–1.12; $p = 0.18$). Finally, in the 51 patients with MS who had morning testosterone levels available for analysis, we found no correlation between adult testosterone levels and the 2D:4D ratio ($r = 0.06$, $p = 0.68$).

DISCUSSION In this study, we found that the 2D:4D ratio is elevated in men with MS relative to men without MS or other autoimmune diseases. This ratio was not correlated with age, adult testosterone levels, or MS clinical characteristics.

The main implication of this study is that prenatal androgens may affect MS risk in men. The prenatal period has come recently into view as a period of key regulation for MS susceptibility, with prenatal vitamin D levels, maternal energetic status, and maternal smoking identified as possible risk factors.[3,11,12]

Over the past few years, a body of work has arisen supporting a correlation between higher 2D:4D ratios and higher ratios of androgens to estrogens in the prenatal, and immediately postnatal, period (including in samples obtained from amniocenteses),[4,13,14] and specifically with prenatal Leydig cell function.[15] Beyond this period of susceptibility, while bone growth continues to be regulated by many factors including nutrition and hormonal influences, the 2D:4D ratio has been found to change only minimally,[16] appears stable with age,[17] and does not seem to be influenced with later regulatory periods such as puberty[18,19] or by adult testosterone levels.[20–22] Mechanistically, given reported anti-inflammatory and neuroprotective effects in animal models,[23,24] a higher androgen to

Table 2 Logistic regression analysis for the effect of 2D:4D on MS status

Model	Risk factors	OR (95% CI)	*p* Value
All participants			
Univariate	2D:4D[a]	1.07 (1.004–1.146)	0.04
Multivariate[b]	2D:4D	1.07 (1.000–1.146)	0.05
White participants only			
Univariate	2D:4D	1.10 (1.021–1.181)	0.01
Multivariate[c]	2D:4D	1.10 (1.023–1.185)	0.01

Abbreviations: CI = confidence interval; MS = multiple sclerosis; OR = odds ratio.
[a] The estimated change in odds corresponds to a 0.01 unit increase in 2D:4D ratio.
[b] Multivariate model adjusting for age at scan and race (white/nonwhite).
[c] Multivariate model adjusting for age at scan.

Table 3 Pearson correlation coefficients between 2D:4D ratio in patients with MS and both clinical characteristics (MSSS, age at first MS symptom) and adult testosterone levels

	MSSS	Age at first symptom (y)	Testosterone level (ng/dL)
No.	136	137	51
r	−0.12	−0.03	0.06
p Value	0.16	0.71	0.68

Abbreviations: MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Score.

estrogen ratio might have an organizing role in modulating downstream inflammatory responses.

The association between 2D:4D ratio and a variety of adult phenotypes has been explored. The most robust have included a lower 2D:4D ratio associated with athletic ability[25–27] and with autism spectrum disorders.[28,29] Regarding neurologic diseases, in men a higher 2D:4D ratio has been linked with higher risk of Alzheimer disease, while a lower 2D:4D ratio was associated with risk in women.[30] In contrast, a lower 2D:4D ratio has been associated with a higher risk of amyotrophic lateral sclerosis; however, this study did not stratify by sex.[31] While we are not aware of published data for its association with autoimmune diseases, a higher 2D:4D ratio was recently linked to higher levels of the inflammatory marker interleukin 6 in girls aged 9 to 13 years.[32] Here in this first assessment in MS, we examined only men, given marked sexual dimorphism in the ratio and as the association between 2D:4D ratio and prenatal androgens is overall more clearly manifest in men[4]; however, women may be included in future studies. The results of the current study, if replicated, indicate the need to further explore the association between 2D:4D ratios and inflammatory markers.

It is well recognized that some factors influence both MS risk and course (such as smoking[5,6]), while others appear mainly associated with susceptibility (such as genetics[33]). We have previously reported associations between lower adult endogenous testosterone levels and higher EDSS.[8] Thus, we also asked whether a higher 2D:4D ratio, possibly through downstream effects on immune regulation or neuroprotection, might also be associated with a more aggressive MS course. We found no association between 2D:4D ratio and MS severity. Here, consistent with results reported by other groups,[20–22] there was no association between 2D:4D ratio and adult testosterone levels in men with MS. Thus, we hypothesize that at different times, exposure to androgen levels could influence MS risk and MS progression.

Strengths of this study included the use of a well-phenotyped MS cohort and adequate statistical power. It should be noted that the 2D:4D ratio is only a marker, not a measure, of hormonal levels in utero. The selection of individuals without MS, while providing a large group of individuals without autoimmune or endocrine diseases, did pose limitations. First, a few of the men without MS were first-degree relatives of patients with MS, and therefore at greater risk of developing MS themselves; however, the majority of our participants without MS were unrelated individuals. Second, the 2 groups differed in age and race. Of note, neither age nor race showed associations with the 2D:4D ratio. When we looked at white participants only, which composed the majority of our participants with MS, differences in 2D:4D ratio between participants with and without MS remained significant. In addition, more scans from participants with MS than those without MS were excluded because of poor quality; as we found no association between 2D:4D and MS clinical features, it is unlikely that the exclusion of more MS than non-MS scans significantly altered the main findings. Finally, while restriction of the analyses to right-handed individuals could introduce confounding, as handedness may also be influenced by prenatal hormones,[34] 13.6% of CLIMB males report being left-handed, in line with the 11.1% general population prevalence.[35]

The prenatal period is emerging as a period during which endocrine (e.g., vitamin D), environmental (e.g., UV light), and behavioral (e.g., maternal obesity) aspects may all contribute to an increased risk of MS.[3] Our study results, if independently replicated, suggest that prenatal androgens may also have a role in subsequent susceptibility to MS.

AUTHOR CONTRIBUTIONS

R.B., T.C.: study concept and design. A.C., B.C.H.: statistical analysis and interpretation of data. M.T.M., C.D.-C., T.J.S., E.G., D.B., B.I.G.: acquisition of data and interpretation of results. R.B., T.C., M.T.M., C.D.-C., T.J.S., E.G., D.B., B.I.G., B.C.H.: manuscript drafting and revising.

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DISCLOSURE

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