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Understanding COVID-19: Digit ratio (2D:4D) and sex differences in national case fatality rates

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ABSTRACT

Background: The reported national case fatality rates (CFRs) for coronavirus disease 2019 (COVID-19) shows a sex bias with males > females. The relative lengths of the index (2D) and ring (4D) fingers (digit ratio; 2D:4D) is a sexually dimorphic (males < females) proxy of fetal sex steroids (low 2D:4D indicates high prenatal testosterone/low prenatal estrogen).
Aim: To examine sex-specific relationships of 2D:4D per nation with national values of COVID-19 CFRs. Study design: COVID-19 CFRs and the percent of male deaths were related to mean national (self-reported) 2D:4D by sex and hand from a large online survey (the BBC Internet Study).
Subjects: 103,482 men and 83,366 women.
Outcome measures: Relationships of mean national 2D:4D with CFRs from 41 countries and with national male death rates from 16 countries.
Results: Male right and left hand 2D:4D showed positive relationships with CFR. These relationships remained significant after removing the influence of female 2D:4D. A positive association of male right and left 2D:4D was detected with the percentage of male deaths.
Conclusions: At the national level, high mean 2D:4D (indicating low prenatal testosterone/high prenatal estrogen) is associated with high CFRs and percent male mortality. At the individual level, high 2D:4D may be a risk factor for severity of COVID-19 in males. We speculate that male 2D:4D is a negative correlate for expression of the SARS-CoV2 receptor (ACE2).

1. Introduction

Research has documented an excess of male relative to female deaths in the SARS-CoV2 (COVID-19) pandemic [1,2]. This sex-dependent pattern has been observed also for other pathogenic coronaviruses (CoVs), including the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV [3]. The excess of severe male cases may provide clues as to the pathogenic effects of COVID-19 and the immunological responses to these effects. Males tend to generate less robust immune responses than females and are more susceptible to a variety of infectious agents including RNA viruses [4–6]. This has led to the suggestion that testosterone (among other sex-steroids) may have a negative effect on the human immune system [7].

Here we consider the relationship between COVID-19 case fatality rates (CFR; a measure of the national severity of the disease) and digit ratio (2D:4D), a proxy for prenatal sex-steroid levels that correlates negatively with prenatal testosterone and positively with prenatal estrogen [8,9]. National CFRs from COVID-19 vary considerably as do the percent male deaths per country [10,11]. We examined the relationship between CFRs and percent male deaths from cases of COVID-19 and mean national values of 2D:4D in males and females.

A straightforward hypothesis would be that high prenatal testosterone (low 2D:4D) is linked to immune suppression and high CFRs. However, strong immune responses in females may also lead to immunopathology, resulting in fatal outcomes [4]. Another possibility is that testosterone facilitates cell entry by SARS-CoV2 and is one of the driving factors of the epidemic ("androgen-driven COVID-19 pandemic theory") [12,13]. Infectivity of COVID-19 depends on priming of the spike proteins by transmembrane protease, serine 2 (TMPRSS2) [14,15], and TMPRSS2 may cleave angiotensin converting enzyme 2 (ACE2) for augmented viral entry [16]. Importantly, androgen receptor activity is a requirement for the transcription of the TMPRSS2 gene, suggesting that testosterone facilitates SARS-CoV2 cell entry [12,13].

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The androgen-driven COVID-19 pandemic theory concerns circulating levels of testosterone and has some support from the relationship between age-related COVID-19 mortality rates. For example, it may explain why children are more resistant to infections before adrenarche and puberty [12,13]. Thus, high mortality from SARS-CoV2 in men should be related to hypergonadism and to low (masculinized) 2D:4D.

The androgen-driven theory would predict that low 2D:4D (high prenatal testosterone) correlates with high severity of COVID-19 cases. However, there are some theory-inconsistent anomalies with the relationship between age, testosterone, and COVID-19 in males. If high testosterone is associated with mortality, one should expect a mini-peak during the activation of the hypothalamic-pituitary-gonadal axis in the 6-8th week after delivery of male neonates. In this period, the levels of sex steroids are similar to early-middle pubertal levels [17]. There is no support for elevated frequencies of COVID-19 at this age. Moreover, in men COVID-19 mortality rates increase with age [1] but testosterone levels decrease [18]. The expression of ACE2 is sex-dependent with a higher expression in females compared to males, and in the latter, levels of ACE2 decline with age [19]. Paradoxically, ACE2 is necessary for SARS-CoV2 cell entry, but its expression correlates negatively with mortality from the virus. Thus, there is the possibility that the severity of COVID-19 relates to male *hypo*gonadism and not *hyper*gonadism and that high (feminized) 2D:4D in men relates to increased severity of cases.

We examined the association between mean national values of 2D:4D and the CFRs, and percent of male mortality across 41 nations, thus assessing the two competing views of the relationship between testosterone and prognosis in cases of COVID-19. A negative association would support the androgen-driven COVID-19 pandemic theory, whereas a positive association would indicate that male hypogonadism relates to high severity of COVID-19 cases.

2. Material and methods

The BBC Internet Study was a multi-national and multiethnic online survey that included around 200 questions concerning sex-dependent aspects of demographics and behavior, along with self-measurement of the lengths of index finger (2D) and the ring finger (4D). Reimers [19] reports the details of recruitment and ethical issues in the Study. A sample of 255,116 participants from > 100 countries completed all sections of the Study. The most commonly represented nationalities were the United Kingdom (46.9%), United States (27.7%), Canada (5.2%), and Australia (3.6%) with 11 other nations represented by > 1000 participants. The predominant ethnicity was "White", which was reported by 84.1% of participants. However, there were substantial numbers of other groups. Participants self-measured 2D and 4D of right and left hands. A diagram of the hand illustrated the measurements, taken from on the ventral side of the digit with a conventional ruler and reported to the nearest millimeter. The right and left hand 2D:4D's were calculated by dividing the 2D by 4D digit lengths, respectively. Manning et al. [20] have examined the effects of sex and ethnicity on 2D:4D in the Study. Means of 2D:4D from the Study showed the expected sex difference (males < females) and this extended across all ethnic groups. Previous research including the Study data (e.g., [20,21]) restricted the age of participants to ≥18 years and the 2D:4D range of 0.80 to 1.20. This had the effect of reducing *SD*'s to about 0.05. In the present study, we adopted these restrictions, thus leaving for analysis 2D:4D of 103,482 men and 83,366 women.

The COVID-19 CFR statistics were obtained on April 21st from the World Health Organization (WHO) reports [10] and gender-segregated data from Global Health 50/50 [11]. The WHO reports CFRs by country but without ethnic details. Therefore, we included all ethnic groups in the national means for 2D:4D.

Table 1
COVID 19 number of cases, numbers of deaths, and case fatality rate in 41 nations.

Nation	Number cases	Number deaths	Case fatality rate	Log case fatality rate	Percent male cases	Percent male deaths
Argentina	1628	53	3.256	0.513		.
Australia	5956	45	0.756	−0.121	48	60
Austria	12,640	243	1.922	0.284	50	.
Belgium	22,194	2035	9.169	0.962	45	50
Brazil	12,056	553	4.587	0.662		.
Bulgaria	577	23	3.986	0.601		.
Canada	17,049	349	2.047	0.311	48	56
China	83,157	3342	4.019	0.604	51	64
Croatia	1282	18	1.404	0.147		.
Czech	5017	88	1.754	0.244	49	.
Denmark	5071	203	4.003	0.602	46	64
Finland	2308	34	1.473	0.168	50	.
France	77,226	10,313	13.354	1.126		61
Germany	103,228	1861	1.803	0.256	50	63
Greece	1832	81	4.421	0.646	55	72
Hungary	895	58	6.480	0.812		.
Iceland	1586	6	0.378	−0.423		.
India	5194	149	2.869	0.458		.
Ireland	5709	210	3.678	0.566	45	63
Israel	9404	71	0.755	−0.122		.
Italy	135,586	17,129	12.633	1.102	53	68
Japan	4257	81	1.903	0.279	60	.
Malaysia	3963	63	1.590	0.201		.
Mexico	2439	125	5.125	0.710		.
N Zealand	969	1	0.103	−0.987		.
Netherlands	19,580	2101	10.730	1.031	47	61
Norway	5863	69	1.177	0.071	50	54
Pakistan	4072	58	1.424	0.154	72	.
Philippines	3764	177	4.702	0.672	60	.
Poland	4848	129	2.661	0.425		.
Portugal	12,442	345	2.773	0.443	43	54
Romania	4417	182	4.120	0.615	41	.
Russia	7497	58	0.774	−0.111		.
Singapore	1481	6	0.405	−0.393		.
Spain	140,510	13,798	9.820	0.992	49	63
Sweden	7693	591	7.682	0.885	50	60
Switzerland	22,164	641	2.892	0.461	47	62
Turkey	34,109	725	2.126	0.328		.
UK	55,246	6159	11.148	1.047		.
UAE	2359	12	0.509	−0.293		.
USA	363,321	10,845	2.985	0.475		.

3. Results

3.1. Descriptive statistics

There were 41 nations in the sample (Table 1). Mean and standard deviation ($M \pm SD$) of CFR was 3.89 ± 3.51 and the distribution showed a rightward skew (skew = 1.371, kurtosis = 1.043; Shapiro-Wilk $W = 0.833$, $p < .0001$). We log-transformed CFR (log CFR), which resulted in a mean of 0.400 (0.457) (skew = −0.724, kurtosis = 0.898, Shapiro-Wilk $W = 0.959$, $p = .151$). The percent of male deaths per nation was available from 16 countries ($M = 60.94 \pm 5.46\%$).

3.2. Statistical analyses

There were significant sex differences in right and left hand 2D:4D, with males < females (males: right hand $M = 0.983 \pm 0.003$, left hand $M = 0.940 \pm 0.003$; females: right hand $M = 0.993 \pm 0.004$, left hand $M = 0.992 \pm 0.005$; right hand $t = 14.88$, $p < .0001$, left hand $t = 11.22$, $p < .0001$) (Tables 2 and 3). Male (but not female) 2D:4D correlated positively with log CFR (males: right hand $r = 0.34$, $p < .05$ [Fig. 1], left hand $r = 0.29$, $p = .07$; females: right hand $r = 0.03$, $p = .83$, left hand $r = 0.03$, $p = .83$). Male 2D:4D correlated positively with female 2D:4D (right hand $r = 0.37$, $p < .05$; left hand

Table 2
Means, SD and SEMs for right and left hand male 2D:4D in 41 nations.

	n	Males right hand			Males left hand		
		Mean 2D:4D	SD	SE	Mean 2D:4D	SD	SE
Argentina	125	0.990	0.048	0.004	0.988	0.041	0.004
Australia	4103	0.981	0.046	0.001	0.982	0.046	0.001
Austria	213	0.980	0.042	0.003	0.986	0.043	0.003
Belgium	764	0.981	0.045	0.002	0.984	0.043	0.002
Brazil	170	0.979	0.047	0.004	0.980	0.044	0.003
Bulgaria	172	0.990	0.047	0.004	0.989	0.046	0.004
Canada	5723	0.981	0.048	0.001	0.981	0.047	0.001
China	169	0.985	0.043	0.003	0.985	0.039	0.003
Croatia	95	0.981	0.038	0.004	0.984	0.038	0.004
Czech	146	0.984	0.04	0.003	0.986	0.042	0.003
Denmark	380	0.982	0.044	0.002	0.988	0.046	0.002
Finland	875	0.984	0.046	0.002	0.985	0.045	0.002
France	535	0.983	0.044	0.002	0.987	0.044	0.002
Germany	866	0.983	0.044	0.001	0.985	0.042	0.001
Greece	420	0.986	0.049	0.002	0.987	0.045	0.002
Hungary	97	0.986	0.04	0.004	0.988	0.039	0.004
Iceland	85	0.980	0.053	0.006	0.984	0.047	0.005
India	2274	0.986	0.056	0.001	0.986	0.056	0.001
Ireland	2307	0.983	0.049	0.001	0.983	0.047	0.001
Israel	195	0.987	0.044	0.003	0.987	0.042	0.003
Italy	248	0.984	0.041	0.003	0.986	0.044	0.003
Japan	289	0.984	0.044	0.003	0.982	0.043	0.003
Malaysia	418	0.976	0.044	0.002	0.976	0.041	0.002
Mexico	208	0.976	0.051	0.004	0.977	0.047	0.003
N Zealand	970	0.980	0.046	0.001	0.982	0.045	0.001
Netherland	1172	0.981	0.047	0.001	0.985	0.046	0.001
Norway	305	0.982	0.042	0.002	0.984	0.042	0.002
Pakistan	245	0.983	0.05	0.003	0.984	0.051	0.003
Philippines	190	0.983	0.054	0.004	0.980	0.051	0.004
Poland	197	0.984	0.05	0.004	0.989	0.046	0.003
Portugal	187	0.983	0.051	0.004	0.983	0.049	0.004
Romania	166	0.986	0.05	0.004	0.985	0.046	0.004
Russia	88	0.976	0.047	0.005	0.986	0.043	0.005
Singapore	817	0.977	0.043	0.002	0.974	0.042	0.001
Spain	468	0.987	0.052	0.002	0.988	0.045	0.002
Sweden	760	0.982	0.049	0.002	0.981	0.046	0.002
Switzerland	323	0.984	0.041	0.002	0.983	0.041	0.002
Turkey	653	0.987	0.048	0.002	0.987	0.048	0.002
UK	51,324	0.985	0.048	2.000E−4	0.986	0.046	2.000E−4
UAE	169	0.981	0.044	0.003	0.983	0.048	0.001
USA	24,571	0.984	0.053	3.000E−4	0.984	0.051	3.000E−4

Table 3
Means, SD and SEMs for right and left hand female 2D:4D in 41 nations.

	n	Females right hand			Females left hand		
		Mean 2D:4D	SD	SE	Mean 2D:4D	SD	SE
Argentina	78	0.992	0.050	0.006	0.992	0.057	0.006
Australia	3690	0.990	0.046	0.001	0.988	0.044	0.001
Austria	170	0.990	0.046	0.004	0.994	0.042	0.003
Belgium	499	0.989	0.047	0.002	0.989	0.044	0.002
Brazil	109	0.994	0.054	0.005	0.991	0.051	0.005
Bulgaria	186	0.997	0.049	0.004	0.998	0.048	0.004
Canada	5279	0.994	0.051	0.001	0.992	0.050	0.001
China	124	0.989	0.044	0.004	0.985	0.050	0.004
Croatia	102	0.998	0.038	0.004	0.996	0.037	0.004
Czech	94	1.000	0.047	0.005	0.999	0.043	0.004
Denmark	347	0.987	0.046	0.002	0.990	0.048	0.003
Finland	675	0.991	0.044	0.002	0.990	0.042	0.002
France	376	0.990	0.045	0.002	0.986	0.043	0.002
Germany	546	0.993	0.046	0.002	0.991	0.044	0.002
Greece	392	0.997	0.054	0.003	0.998	0.050	0.003
Hungary	103	0.999	0.050	0.005	0.995	0.047	0.005
Iceland	88	0.986	0.051	0.005	0.987	0.050	0.005
India	577	0.997	0.057	0.002	0.992	0.059	0.002
Ireland	2177	0.991	0.050	0.001	0.991	0.049	0.001
Israel	131	1.001	0.052	0.005	0.996	0.050	0.004
Italy	166	0.994	0.048	0.004	0.989	0.047	0.004
Japan	163	0.985	0.046	0.004	0.982	0.043	0.003
Malaysia	350	0.992	0.049	0.003	0.991	0.049	0.003
Mexico	131	0.989	0.050	0.004	0.984	0.049	0.004
N Zealand	954	0.990	0.047	0.002	0.987	0.044	0.001
Netherlands	798	0.990	0.049	0.002	0.992	0.047	0.002
Norway	213	0.990	0.050	0.003	0.989	0.048	0.003
Pakistan	72	0.988	0.049	0.006	0.990	0.050	0.006
Philippines	201	0.992	0.057	0.004	0.991	0.057	0.004
Poland	225	0.999	0.046	0.003	0.997	0.044	0.003
Portugal	139	0.988	0.049	0.004	0.986	0.038	0.003
Romania	173	0.998	0.048	0.004	1.001	0.048	0.004
Russia	96	0.996	0.050	0.005	1.002	0.045	0.005
Singapore	944	0.989	0.046	0.002	0.986	0.043	0.001
Spain	289	0.995	0.044	0.003	0.992	0.049	0.003
Sweden	386	0.994	0.051	0.003	0.992	0.048	0.002
Switzerland	206	0.991	0.046	0.003	0.987	0.040	0.003
Turkey	595	0.999	0.050	0.002	1.000	0.048	0.002
UK	40,207	0.993	0.050	3.000E−4	0.992	0.047	3.000E−4
UAE	117	1.001	0.062	0.006	0.993	0.048	0.004
USA	21,198	0.996	0.055	4.000E−4	0.993	0.052	4.000E−4

$r = 0.49$, $p < .001$). We performing multiple regressions with the dependent variable log CFR and the independent variables male and female right 2D:4D or male and female left 2D:4D. Male right hand 2D:4D remained positively related to log CFR and female 2D:4D showed no relationship (males: right hand 2D:4D $B = 51.84$, $SE\ B = 22.25$, $beta = 0.38$, $p < .05$; females: right 2D:4D $B = -11.26$, $SE\ B = 17.32$, $beta = -0.11$, $p = .52$). Male left hand 2D:4D also remained positively related to log CFR and female 2D:4D showed no relationship (males: left 2D:4D $B = 48.53$, $SE\ B = 23.81$, $beta = 0.36$, $p < .05$; females: left: 2D:4D $B = -13.63$, $SE\ B = 17.09$, $beta = -0.14$, $p = .43$).

The sample size for examining 2D:4D relationships with percent of male deaths ($n = 16$) was small. Nevertheless, there were positive correlations for males with both right ($r = 0.63$, $p < .01$, Fig. 2) and left 2D:4D ($r = 0.52$, $p < .05$), and a weak association for female right hands ($r = 0.50$, $p = .049$) but no correlation for female left hands ($r = 0.41$, $p = .12$). Multiple regression analysis showed male right hand 2D:4D ($B = 1513.03$, $SE\ B = 705.07$, $beta = 0.51$, $p = .050$) remained significantly related to percent of male deaths independent of female right 2D:4D ($B = 495.91$, $SE\ B = 459.45$, $beta = 0.26$, $p = .30$). For male left hand 2D:4D there was a marginally significant relationship with percent of male deaths ($B = 1122.12$, $SE\ B = 527.77$, $beta = 0.47$, $p = .053$) and no relationship for female left hand 2D:4D ($B = 579.00$, $SE\ B = 375.07$, $beta = 0.34$, $p = .15$).

4. Discussion

We detected a positive association between mean male right hand 2D:4D per nation and log CFR ($n = 41$ nations), and a positive (but non-significant) association for mean male left hand 2D:4D. There were no correlations between mean female 2D:4D per nation and log CFRs. Male and female 2D:4Ds correlated positively. Male right and left hand 2D:4D correlated positively with log CFR when the influence of female 2D:4D was removed. Similar patterns of positive relationships pertained between male mean 2D:4D and percent of male deaths per nation. Here the sample size was lower ($n = 16$ nations), but the focus on male deaths rather than overall mortality would be expected to increase the effect size. This is what we found as the effect size for the correlation between nations increased from an r^2 value of about 10% to > 30%.

Our findings support a link between high 2D:4D (low prenatal testosterone) and high severity of COVID-19 in men. However, we are considering comparative data across nations and this introduces some limitations to our analysis. Testing regimes vary across nations with some testing widely in the population and others focusing mainly on hospital admissions for COVID-19. This affects comparative values of CFRs. Therefore, we strongly advise that future investigations of associations of 2D:4D and COVID-19 severity consider patients. If there is a strong positive correlation with disease severity in men, the measurement of 2D:4D (particularly right hand 2D:4D) may be of prognostic use

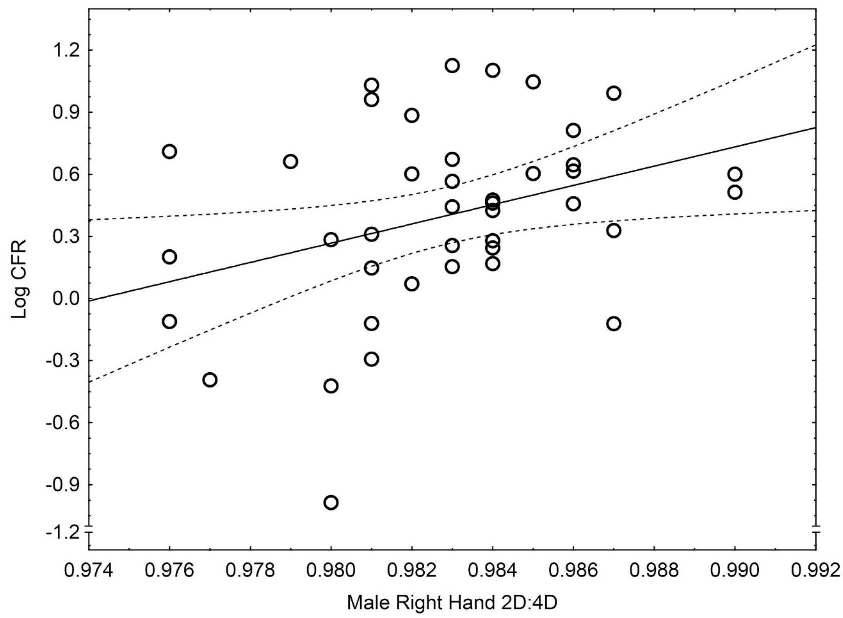

Fig. 1. The relationship between male mean right digit ratio per nation and log-transformed national case fatality rate (log CFR) in 41 nations. Note: $y = -45.33 + 46.53 * x$; $r^2 = 0.12$.

for the severity of COVID-19.

Advocates of the androgen-driven theory have suggested treatment with androgen blockers such as spironolactone [12,13]. This seems reasonable given the substantial excess in male mortality associated with the disease [22]. However, there is support for the counter-theory that treatment of COVID-19 should involve an increase the amount of ACE2 in the lungs [23]. ACE2 protects from lung injury, but ACE2 is also the critical SARS-CoV receptor. The severity of COVID-19 could be explained by SARS-CoV spike protein binding to ACE2, which leads to endocytosis of the virus but the loss of ACE2 from the surface of the cell. This establishes a circle of viral infection and local loss of lung protection. In support of this model, Monteil et al. [24] showed that soluble human ACE2 molecule could significantly inhibit SARS-CoV-2 infections and reduce viral load by a factor of 1000–5000.

Our findings support an association between low prenatal testosterone (high 2D:4D) and high severity of COVID-19, and high mortality in males. They are in accord with the knowledge of the variation in expression and regulation of the SARS-CoV2 receptor ACE2 gene. The ACE2 gene is more strongly expressed in females compared to males, in young males compared to old males and in healthy men compared to those with several co-morbidities including type 2 diabetes [23]. These associations suggest a negative correlation between ACE2 expression and CovID19 fatality at both population and molecular levels, which will be instrumental when designing potential prevention and treatment strategies for ACE2 binding coronaviruses in general [23]. The down-regulation of ACE2 may therefore be associated with poor prognosis from COVID-19. The finding that soluble ACE2 reduces viral load substantially supports this position [24]. Hence, ACE2 [24] and

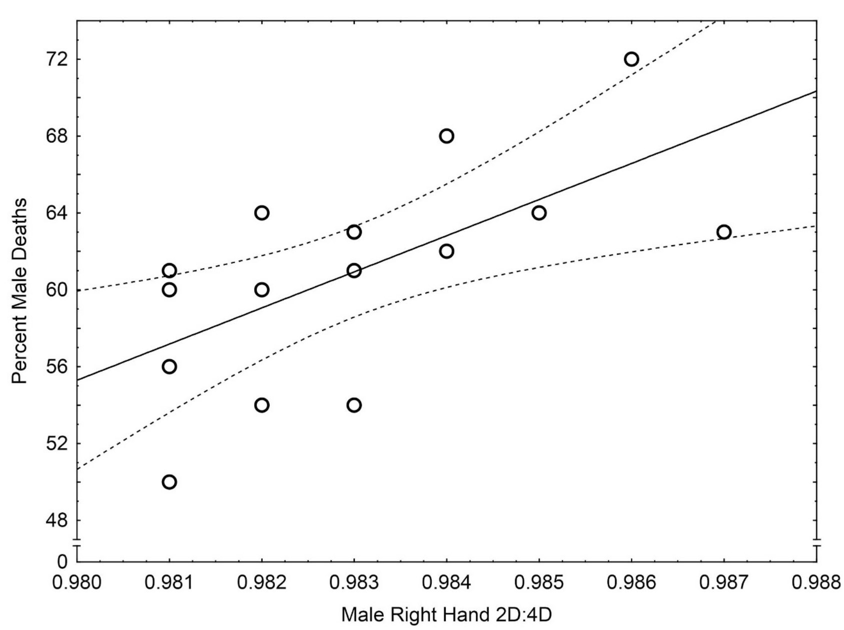

Fig. 2. The relationship between mean male right 2D:4D per nation and the national percentage of male deaths in 16 countries. Note: $y = -1787.10 + 1880 * x$; $r^2 = 0.40$.

alternatives to ACE2 such as spironolactone [22] may constitute treatments for COVID-19.

ACE2 is also expressed in the Leydig cells of the testes, which indicates a regulatory function in spermatogenesis [25–27]. Research suggests that testosterone in men and estrogen in women up-regulates ACE2 [23]. A comparison of testicular function in COVID-19 patients and healthy controls showed similar testosterone levels in both groups but higher LH in the former, suggesting that the patients' pituitary has to work harder than that of the controls to maintain testosterone levels. This may be evidence that COVID-19 damages testicular function, however the same results would be obtained if the patients had compromised gonadal function before infection [28]. It may be relevant that men who have few or no sperm and low testosterone have high 2D:4D [29,30]. Moreover, the severity of COVID-19 is associated with cardiovascular disease and high 2D:4D correlates with early heart attacks in men [31]. Such correlations support an association between high 2D:4D and high CFRs.

In conclusion, we have found that mean male 2D:4D per nation correlates positively with CFR and percent of male deaths due to COVID-19. The effect was independent of mean female 2D:4D. Thus, high prenatal testosterone (low 2D:4D) in men may be protective of the serious effects of COVID-19. Our findings suggest that an excess of male deaths resulting from COVID-19 is not the product of high prenatal testosterone but rather a marker for prenatal hypogonadism. SARS-CoV2 enters cells via the receptor molecule ACE2. Paradoxically, the up-regulation of ACE2 relates to protective effects from COVID-19 infection, possibly because it opposes the loss of ACE2 from cell surfaces. We speculate that in men the up-regulation of ACE2 relates to high testosterone and low 2D:4D. A strong positive association between male 2D:4D and mortality may provide a biomarker for male COVID-19 susceptibility and identify those for whom it would be advisable to exercise social distancing.

CRediT authorship contribution statement

John T. Manning: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft; Writing - review & editing. **Bernhard Fink:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft; Writing - review & editing

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