Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Understanding COVID-19: A hypothesis regarding digit ratio (2D:4D), ACE I/D polymorphism, oxygen metabolism and national case fatality rates

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ABSTRACT

Objective: Male digit ratio (2D:4D) correlates positively with the national case fatality rate (CFR) for COVID-19. The severity of COVID-19 may be influenced by a counterbalance between the angiotensin-converting enzyme (ACE) and angiotensin-converting enzyme 2 (ACE2). SARS-CoV2 cleaves with ACE2 and enters cells leaving an unopposed effect of ACE in the lungs. Both 2D:4D and the ACE I/D polymorphism are covariates of oxygen metabolism. COVID-19 leads to lung damage and a reduction in oxygen saturation of the blood. Here, we examine the interrelationships between 2D:4D, ACE polymorphism, and COVID-19 CFR.

Methods: National frequencies/rates were obtained for 2D:4D from the BBC Internet study (n = 41), published values of ACE I/II (n = 39), and COVID-19 CFR from three World Health Organization situation reports (n = 41).

Results: 2D:4D was negatively associated with national ACE I/II frequencies. However, there was a positive relationship between male 2D:4D and CFR (right and left 2D:4D, two, and three situation reports respectively). The relationships between ACE I/II and CFR were non-significant. Relationships between male 2D:4D and CFR's were independent of female 2D:4D and ACE I/II.

Conclusions: The ACE I/D polymorphism may influence 2D:4D such that ACE II individuals have lower 2D:4D than ACE DD individuals. Low 2D:4D and ACE II individuals show efficient oxygen metabolism. Therefore, low 2D:4D and ACE II together may protect against COVID-19 severity. The sex-dependent positive correlation between male 2D:4D and CFR is independent of ACE I/II, suggesting that the sex-dependent variation in the ACE2 gene may also influence the 2D:4D phenotype.

1. Introduction

The severity of COVID-19 is sex-dependent (males > females) [1,2]. Case fatality rates (CFR) vary across nations and correlate positively with national male (but not female) digit ratio (2D:4D) - a proxy for prenatal sex-steroids [3–5]. This relationship suggests that high prenatal testosterone to oestrogen ratios are protective against COVID-19 severity. Testosterone and oestrogen are important modulators of blood pressure through their regulatory effect on the renin-angiotensin system (RAS) [6]. In particular, angiotensin-converting enzyme (ACE) and its antagonist angiotensin-converting enzyme 2 (ACE2) play a key role in the RAS. Blood pressure is sex-dependent (males > females) and is determined by a balance of vasoconstriction (by ACE) and vasodilation (by ACE2) [6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) enters cells by cleaving with membrane-bound ACE2, thus removing ACE2 from cell surfaces and leaving an unopposed effect of ACE on the lungs and other organs. The result is an increase of vasoconstriction, thrombosis, and inflammation of the lungs [7]. One important feature of the ACE gene is that it is highly polymorphic [8]. In the present study, we examine the relationship between 2D:4D, ACE polymorphism, and COVID-19 CFR across nations.

Digit ratio is a normally distributed sexually dimorphic trait (male 2D:4D < female 2D:4D) that is thought to be a negative correlate of prenatal testosterone and a positive correlate of prenatal oestrogen [9]. National values of male (but not female) 2D:4D correlate positively with national COVID-19 CFR's [3], i.e. nations with high COVID-19 mortality have male populations that have experienced low prenatal testosterone relative to oestrogen. The link between high male 2D:4D and COVID-19 severity may lie in the association between 2D:4D and oxygen metabolism. COVID-19 leads to lung damage and a reduction in

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Table 1
The frequencies of the I allele and the II genotype (I/II) in the gene for angiotensinogen converting enzyme (ACE), mean male 2D:4D (right and left), mean female 2D:4D (right and left) and log case fatality rates (log CFR for WHO Situation Report 165, 3rd July 2020) for 41 nations.

Source/n of studies	Nation	Freq. ACE I/II	Male R2D:4D	Male L2D:4D	Female R2D:4D	Female L2D:4D	log CFR
Li et al., 2011/1 [21]	Argentina	0.490/0.213	0.990	0.988	0.992	0.992	0.307
Li et al., 2011/3 [21]	Australia	0.460/0.209	0.981	0.982	0.990	0.988	0.114
Li et al., 2011/4 [21]	Austria	0.485/0.201	0.980	0.986	0.990	0.994	0.594
Gu et al., 1994/1 [22] Li et al., 2007/1 [23]	Belgium	–/0.238	0.981	0.984	0.989	0.989	1.199
Li et al., 2011/3 [21]	Brazil	0.373/0.136	0.979	0.980	0.994	0.991	0.622
Stambolova et al., 2017/1 [24]	Bulgaria	0.390/0.150	0.990	0.989	0.997	0.998	0.640
Li et al., 2011/3 [21]	Canada	0.422/0.194	0.981	0.981	0.994	0.992	0.916
Li et al., 2011/88 [21]	China	0.610/0.396	0.985	0.985	0.989	0.985	0.736
Li et al., 2011/1 [21]	Croatia	0.470/0.220	0.981	0.984	0.998	0.996	0.577
Li et al., 2011/5 [21]	Czech	0.467/0.224	0.984	0.986	1.000	0.999	0.460
Li et al., 2011/2 [21]	Denmark	0.495/0.241	0.982	0.988	0.987	0.990	0.675
Li et al., 2011/3 [21]	Finland	0.457/0.224	0.984	0.985	0.991	0.990	0.656
Li et al., 2011/4 [21]	France	0.430/0.201	0.983	0.987	0.990	0.986	1.275
Li et al., 2011/5 [21]	Germany	0.457/0.218	0.983	0.985	0.993	0.991	0.663
Li et al., 2011/1 [21]	Greece	0.380/0.173	0.986	0.987	0.997	0.998	0.744
Li et al., 2011/1 [21]	Hungary	0.513/0.254	0.986	0.988	0.999	0.995	1.149
	Iceland		0.980	0.984	0.986	0.987	−0.267
Li et al., 2011/6 [21]	India	0.540/0.299	0.986	0.986	0.997	0.992	0.464
	Ireland		0.983	0.983	0.991	0.991	0.834
Li et al., 2011/6 [21]	Israel	0.397/0.153	0.987	0.987	1.001	0.996	0.084
Li et al., 2011/10 [21]	Italy	0.394/0.168	0.984	0.986	0.994	0.989	1.160
Li et al., 2011/13 [21]	Japan	0.651/0.422	0.984	0.982	0.985	0.982	0.709
Ali et al., 2015/1 [25]	Malaysia	0.689/0.452	0.976	0.976	0.992	0.991	0.146
Li et al., 2011/7 [21]	Mexico	0.599/0.318	0.976	0.977	0.989	0.984	1.090
Li et al., 2011/1 [21]	N Zealand	0.460/0.225	0.980	0.982	0.990	0.987	0.270
Li et al., 2011/10 [21]	Netherlands	0.482/0.226	0.981	0.985	0.990	0.992	1.084
Goleva-Fjellet et al., 2020/1 [26]	Norway	0.492/0.229	0.982	0.984	0.990	0.989	0.450
Shaheen et al., 2019/1 [27]	Pakistan	0.268/0.05	0.983	0.984	0.988	0.990	0.312
Li et al., 2011/1 [21]	Philippines	0.550/0.295	0.983	0.980	0.992	0.991	0.516
Li et al., 2011/3 [21]	Poland	0.570/0.256	0.984	0.989	0.999	0.997	0.628
Li et al., 2011/1 [21]	Portugal	0.440/0.170	0.983	0.983	0.988	0.986	0.569
Marginean et al., 2015/1 [28]	Romania	0.301/0.151	0.986	0.985	0.998	1.001	0.784
Li et al., 2011/2 [21]	Russia	0.480/0.233	0.976	0.986	0.996	1.002	0.169
Li et al., 2011/4 [21]	Singapore	0.692/0.475	0.977	0.974	0.989	0.986	−1.229
Li et al., 2011/9 [21]	Spain	0.413/0.170	0.987	0.988	0.995	0.992	1.055
Li et al., 2011/5 [21]	Sweden	0.492/0.242	0.982	0.981	0.994	0.992	0.884
Lovati et al., 2001/1 [29]	Switzerland	0.509/0.211	0.984	0.983	0.991	0.987	0.723
Li et al., 2011/21 [21]	Turkey	0.418/0.181	0.987	0.987	0.999	1.000	0.407
Li et al., 2011/14 [21]	UK	0.476/0.231	0.985	0.986	0.993	0.992	1.190
Saeed et al., 2005/1 [30]	United Arab Emirates	–/0.06	0.981	0.983	1.001	0.993	−0.193
Li et al., 2011/5 [21]	USA	0.440/0.196	0.984	0.984	0.996	0.993	0.680

oxygen saturation (SpO_2) of the blood. Low presenting SpO_2 in COVID-19 patients is predictive of high severity of outcomes such as pneumonia, acute respiratory distress syndrome, and admission to intensive care [10,11]. Low 2D:4D individuals may be resistant to oxygen depletion. Thus, high performances in endurance running and rowing are related to low 2D:4D, and this is particularly so for males [12,13]. Moreover, in high 2D:4D individuals (as compared to low 2D:4D individuals), low right-hand relative to left-hand 2D:4D is related to higher VO_2max (maximum rate of oxygen consumption measured during the exercise of increasing intensity [14]), VO_2peak (highest value of VO_2 attained in an incremental exercise test [15]), and ventilatory threshold (the point at which ventilation increases at a faster rate than VO_2 [16]).

In contrast to the continuous variation in 2D:4D, the genes of the RAS system have several discontinuous forms. We focus on one such, the insertion/deletion (I/D) polymorphism at intron 16 of the ACE gene. There have been > 250 polymorphisms reported in the ACE gene, with the I/D polymorphism attracting the most attention [17]. This involves either the presence (I) or the absence (D) of a 287 bp fragment. The presence of the extra fragment is associated with lower circulating and tissue ACE activity, while its absence is associated with relatively higher ACE activity [18]. In common with low 2D:4D, the I allele is associated with endurance performance in sports such as distance running and rowing and fatigue resistance in skeletal muscle. However, these correlations are probably not as markedly sexually dimorphic as those related to 2D:4D [18,19].

Both 2D:4D and ACE I/D show geographic and ethnic variation. Mean 2D:4D is low in South-East Asian nations and the frequency of ACE I is high. In contrast, European nations have high mean 2D:4D and low frequencies of ACE I. Comparative analyses of mean national 2D:4D show that high national male 2D:4D is associated with high CFR from COVID-19. It is possible, therefore, that high national frequencies of ACE I are related to low CFR. However, Delanghe et al. [20] have reported a negative correlation between ACE DD frequency and national prevalence of COVID-19 (n/million). That is, countries with high frequencies of ACE II have a high prevalence of the virus. Prevalence is not the same as CFR, which is partly determined by the number of deaths (i.e. the severity of COVID-19 after infection). It is mortality that we focus on here.

We hypothesise that there are links between 2D:4D/ACE I, oxygen metabolism, and geographical variation that suggest that ACE polymorphism may influence both the 2D:4D phenotype and CFR from COVID-19. Thus, in the present study, we examined the relationships between (i) national values of male and female 2D:4D and ACE I/D, and (ii) national values of male and female 2D:4D, ACE I/D, and CFR's for COVID-19. Our prediction for (i) was that 2D:4D would be negatively related to the frequency of the ACE I allele and the ACE II genotype. Concerning (ii), we predicted the following relationships: a positive

association between male 2D:4D and CFR, a null-relationship between female 2D:4D and CFR, and a negative relationship between ACE I or II and CFR. To address the issue of the temporal stability of our results we considered associations at three time points: WHO situation reports 113, 127 (which have been reported on earlier), and the more recent situation report 165.

2. Methods

National means for 2D:4D by sex and hand were obtained from a large online survey (the BBC Internet study). The data comprised means from 41 nations calculated from self-reported lengths of the 2nd (index finger) and 4th digits (ring finger) of 103,482 men and 83,366 women.

Mean national values of the allele ACE I and the genotype ACE II for the 41 BBC study nations were obtained principally from reviews of the worldwide genetic structure of the ACE gene [17,21]. Where nations in the BBC study were not represented in these reviews of ACE I/D we searched Pubmed (https://pubmed.ncbi.nlm.nih.gov), using keywords 'angiotensin-converting enzyme', 'ACE' 'polymorphism' and country names (e.g., 'Belgium'). The search revealed publications for the following nations: Belgium [22,23], Bulgaria [24], Malaysia [25], Norway [26], Pakistan [27], Romania [28], Switzerland [29], United Arab Emirates [30].

National CFR's were calculated ([number of deaths / number of cases] * 100) from three WHO situation reports 113 (May 12th 2020), 127 (May 26th 2020; see [4]), and 165 (July 3rd 2020). To ensure normality the CFR's were log-transformed.

3. Results

3.1. Descriptive statistics

The frequency of the ACE I allele was available for 38 nations (Table 1). Mean (SD) frequency of I was 0.474 (0.093) with a range of 0.268 to 0.692. For the ACE II genotype, there were values for 39 nations and the mean frequency was 0.228 (0.089) with a range of 0.05 to 0.475. The correlation between the ACE I and ACE II frequencies was high ($r = 0.949$, $p < .0001$).

Table 1 presents mean national 2D:4D values for 41 nations. Mean male right hand 2D:4D was 0.983 (0.003) with a range from 0.976 to 0.990, and mean left hand 2D:4D was 0.984 (0.003), ranging from 0.974 to 0.989. Right and left male 2D:4D correlated positively ($r = 0.731$, $p < .0001$, $n = 41$). Mean female right 2D:4D was 0.993 (0.004) with a range from 0.985 to 1.001, and mean left hand 2D:4D was 0.992 (0.005), ranging from 0.982 to 1.002. As for males, right and left female 2D:4D correlated positively ($r = 0.809$, $p < .0001$). Male national 2D:4D was lower than female national 2D:4D (right hand, $\Delta = -0.010$, $t = 14.88$, $p < .0001$; left hand, $\Delta = -0.007$, $t = 11.22$, $p < .0001$).

The CFR's reported in WHO 113 correlated positively with those of WHO 127 ($r = 0.996$, $p < .0001$), and WHO 127 CFR's correlated positively with those of WHO 165 ($r = 0.985$, $p < .0001$).

3.2. 2D:4D, ACE I, and ACE II

There were significant negative associations between male and female national 2D:4D and the national frequency of the I allele of ACE ($n = 38$, males: right 2D:4D, $r = -0.367$, $p = .02$, left 2D:4D, $r = -0.458$, $p = .004$; females: right 2D:4D, $r = -0.362$, $p = .03$, left 2D:4D, $r = -0.429$, $p = .007$). A similar pattern of associations was also found between male and female national 2D:4D and the national frequency of the II genotype of ACE ($n = 39$, males: right 2D:4D, $r = -0.335$, $p = .04$, left 2D:4D, $r = -0.492$, $p = .002$; females: right 2D:4D, $r = -0.381$, $p = .02$, left 2D:4D, $r = -0.404$, $p = .01$) (Fig. 1).

3.3. 2D:4D, ACE I, ACE II and log CFR

The correlations between male national 2D:4D and log CFR for WHO 113, 127, 165 were all positive and varied from right 2D:4D = 0.293 (WHO 165) to left 2D:4D = 0.387 (WHO 165). Five were significant with p values ranging from 0.01 to 0.03 and one was non-significant with $p = .06$. National female 2D:4D did not correlate with log CFR, with values of r ranging from 0.006 ($p = .97$, WHO 165) to 0.054 ($p = .74$, WHO 113) (Table 2).

The correlations of ACE I and ACE II with log CFR were both negative. They ranged from $r = -0.211$ ($p = .20$, ACE II, WHO 165) to $r = -0.242$ ($p = .14$, ACE II, WHO 113). None were significant with p values ranging from 0.14 to 0.18 (Table 2).

We performed four multiple regressions with independent variables male 2D:4D (right or left), female 2D:4D (right or left), and ACE (I or II) for each of the dependent variables log CFR 113, 127 and 165 (i.e. 12 associations in all). Male national 2D:4D was positively associated with log CFR independent of female 2D:4D and ACE in nine relationships across the three WHO Situation reports (three for right 2D:4D and six for left 2D:4D). There were no significant associations between female 2D:4D and log CFR or ACE (I or II) and log CFR (Table 3).

4. Discussion

We have found that national means for 2D:4D are negatively related to national values of the frequency of the ACE I alleles and the ACE II genotype. Nations with high frequencies of I also have populations with low right- and left-hand 2D:4D in both males and females. The frequency of the I allele explained 13% to 21% of the variance in 2D:4D and the frequency of the II genotype 11% to 24% of 2D:4D. We acknowledge the important limitation that this relationship is that between populations (i.e. nations) and not individuals. However, it does suggest that at the individual level the genotype of ACE (II, ID, DD) influences 2D:4D such that II genotypes have lower 2D:4D than ID or DD genotypes. This relationship is significant for both males and females.

Despite the negative association between ACE I or II and 2D:4D, the former did not correlate with CFR but the latter did. CFR's are sex-dependent (males > females) as are 2D:4D's (males < females). Thus, the variation in 2D:4D that is not dependent on ACE I/D may be influenced by a sex-dependent trait. This possibility is supported by a positive correlation between national 2D:4D and CFR, independent of ACE I/D and female national 2D:4D.

Our findings may help in part in understanding the between-individual pattern of COVID-19 severity. In this regard, we focus on the links between ACE II, 2D:4D, and oxygen metabolism. ACE II and low 2D:4D are associated with high performance in endurance sports such as distance running and rowing [12,13,18,19]. For example, 2D:4D correlated positively with finishing times in a half marathon for both men and women, i.e. those with low 2D:4D ran faster than those with high 2D:4D. However, the relationship was significantly stronger for men (right hand: $r = 0.45$, $p < .001$; left hand: $r = 0.42$, $p < .001$) than for women (right hand: $r = 0.26$, $p < .01$; left hand: $r = 0.23$, $p = .02$) [13]. The explanation may lie in higher prenatal androgenisation in the former compared to the latter. Between-individual differences in oxygen metabolism may account for much of the variance in endurance running times. Low cardiorespiratory fitness (quantifiable as VO_2max) is associated with a high risk of cardiovascular disease [31]. Thus, between-individual variation in cardio-vascular fitness may contribute to between-individual variation in COVID-19 severity. At first sight, this may seem unlikely because COVID-19 mortality is higher in males than females and VO_2max is higher in males than females [32]. However, we suggest that males who have experienced low prenatal testosterone and high prenatal oestrogen (high 2D:4D) have low cardiovascular fitness and high COVID-19 mortality. This group is driving high sex-dependent CFR's. Cardiovascular disease is associated with

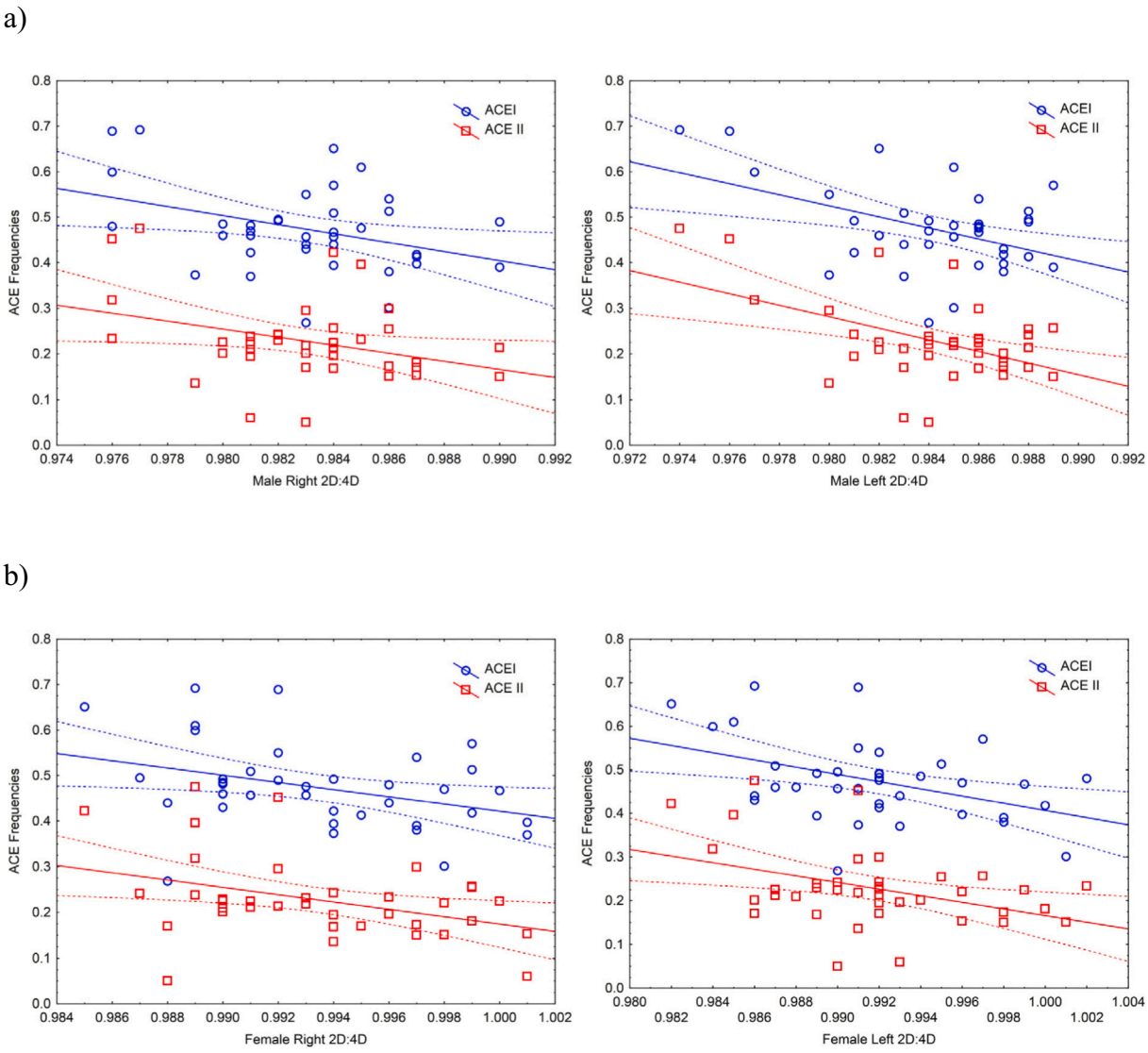

Fig. 1. The relationship between the national frequencies of the ACE I and ACE II alleles and national mean male (a) and female (b) right and left 2D:4D in 38 nations. ACE I: males, right hand $r^2 = 0.13$, left hand $r^2 = 0.21$; females right hand $r^2 = 0.13$, left hand $r^2 = 0.18$. ACE II: males, right hand $r^2 = 0.11$, left hand $r^2 = 0.24$; females right hand $r^2 = 0.15$, left hand $r^2 = 0.16$.

Table 2
Relationships between national frequencies of the ACE I allele, ACE II genotype and 2D:4D (male right and left; female right and left) and log CFR's from WHO Situation Reports 113, 127 and 165.

	Log CFR's situation report 113		Log CFR's situation report 127		Log CFR's situation report 165	
	r	p	r	p	r	p
ACE I allele $n = 38$	−0.240	0.15	−0.240	0.15	−0.225	0.18
ACE II genotype $n = 39$	−0.242	0.14	−0.233	0.15	−0.211	0.20
Male R2D:4D $n = 41$	0.358	0.02	0.349	0.03	0.293	0.06
Male L2D:4D $n = 41$	0.373	0.02	0.376	0.02	0.387	**0.01**
Female R2D:4D $n = 41$	0.054	0.74	0.045	0.78	0.014	0.93
Female L2D:4D $n = 41$	0.010	0.95	0.016	0.92	0.006	0.97

high 2D:4D [33] and the ACE DD genotype [8], and the severity of COVID-19 increases in individuals with hypertension and other cardiovascular problems [1,2].

Polymorphism at the ACE locus may influence the 2D:4D phenotype but variation in the former is discontinuous and in the latter it is continuous. Therefore, other loci may be involved. These could include genes in the classical RAS axis (ACE→angiotensin II → AT1/AT2 receptor) in which ACE is a key component of the vasoconstrictor angiotensin II production. The ACE2 → angiotensin$_{1-7}$ → Mas receptor axis accomplishes the conversion of angiotensin II to the vasodilator angiotensin$_{1-7}$ [7]. COVID-19 severity is sex-dependent and 2D:4D is sexually dimorphic and established in utero. Therefore, it is of interest if the genes in these two axes are polymorphic, X-linked, and involved in embryogenesis, steroidogenesis, or gametogenesis [34–36]. Three such genes are AT2 receptor, ACE2, and the Mas receptor. The AT2 gene is X-linked and the receptors are highly expressed in foetal tissues, although their expression dramatically decreases after birth, being restricted to a few organs, including the cardiovascular system. This suggests the gene might play a role in foetal cardiovascular development [34]. The ACE2 gene is also X-linked and has at least 32 variants. It is expressed in tissues other than the lungs and is abundant in the

Table 3
Multiple regressions with independent variables (i) male right 2D:4D, female right 2D:4D, ACE I, (ii) male left 2D:4D, female left 2D:4D, ACEI, (iii) male right 2D:4D, female right 2D:4D, ACE II, (iv) male left 2D:4D, female left 2D:4D, ACE II. Dependent variables log CFR 113, log CFR 127 and log CFR 165.

	Log CFR situation report 113			Log CFR situation report 127			Log CFR situation report 165		
	r	*t*	*p*	*r*	*t*	*p*	*r*	*t*	*p*
Male R2D:4D	0.363	2.104	0.04	0.353	2.037	0.0495	0.294	1.663	0.11
Female R2D:4D	−0.176	1.019	0.32	−0.182	1.051	0.30	−0.193	1.096	0.28
ACE I allele	−0.170	0.976	0.34	−0.176	1.010	0.32	−0.187	1.048	0.30
Male L2D:4D	0.50	2.780	0.009	0.499	2.768	0.009	0.526	2.939	0.006
Female L2D:4D	−0.333	1.882	0.07	−0.323	1.820	0.08	−0.333	1.891	0.07
ACE I allele	−0.153	0.884	0.38	−0.150	0.862	0.40	−0.126	0.732	0.47
Male R2D:4D	0.344	2.039	0.049	0.337	1.991	0.054	0.282	1.634	0.11
Female R2D:4D	−0.228	1.326	0.19	−0.230	1.330	0.19	−0.238	1.350	0.19
ACE II genotype	−0.214	1.249	0.22	−0.208	1.210	0.23	−0.207	1.181	0.25
Male L2D:4D	0.495	2.724	0.01	0.499	2.739	0.01	0.531	2.934	0.006
Female L2D:4D	−0.338	1.958	0.06	−0.326	1.878	0.07	−0.334	1.942	0.06
ACE II genotype	−0.135	0.782	0.44	−0.119	0.687	0.50	−0.085	0.491	0.63

testes including the Leydig and Sertoli cells, suggesting its involvement in steroidogenesis in the former and spermatogenesis in the latter [35]. The Mas receptor is also expressed in the testes and deletion mutations in Mas perturb spermatogenesis reducing ejaculate size [36]. Thus, variation in the phenotype of 2D:4D may be dependent on polymorphisms in AT2, ACE2, and Mas receptor genes. If so this may explain the links between 2D:4D, prenatal androgen:oestrogen ratios, spermatogenesis, and performance in endurance sports.

We have thus far focussed on a hypothesized relationship between 2D:4D and a reduction in cardio-respiratory reserve when ACE2 is removed from the cell surfaces of the lungs. However, the eventual outcomes of COVID-19 depend in large part on complement and coagulation dysfunction (e.g., increases in fibrinogen and D-dimers) with hyper-inflammation leading to increases in severity and fatality rates [37–39]. Such associations depend on sex (males > females) and age, which may explain the positive relationship between male (but not female) 2D:4D and CFR's. There is accumulating evidence that fibrinogen independently predicts diseases associated with coagulation dysfunction such as myocardial infarction (MI). Fibrinogen levels are higher in males than females, increase with age and correlate positively with 2D:4D in men (i.e. men who experienced low prenatal testosterone and high oestrogen have high fibrinogen), and research suggest that high 2D:4D in men is associated with MI (for review see [33]). Cardiovascular problems are one of the comorbidities of high COVID-19 severity. High 2D:4D in men together with coagulation dysfunction may characterize several comorbidities associated with COVID-19 severity. Thus, prenatal sex steroids (as measured by 2D:4D) may relate to a complex pattern of COVID-19 severity through relationships with ACE and ACE2 function, leading to age- and sex-dependent hyper-inflammation.

In conclusion, national means for 2D:4D correlate negatively with the national frequencies of ACE I and ACE II. The relationships were significant for mean 2D:4D of men and women. The association between low 2D:4D and high ACE I/II is expected because both are linked to high performance in endurance sports and high capacity in oxygen metabolism. ACE acts as a vasoconstrictor and its action is counterbalanced by the vasodilatory effect of ACE2. COVID-19 severity is thought to initially arise because SARS-CoV2 removes ACE2 from cell surfaces thus nullifying its counterbalancing effect on ACE. There is a positive correlation between male (but not female) national 2D:4D and CFR for COVID-19 and no correlation between ACE I/II and CFR. We hypothesise that the polymorphisms in the genes of the ACE→angiotensin II → AT1/AT2 receptor and the ACE2 → angiotensin$_{1-7}$ → Mas receptor axes may explain variation in the 2D:4D phenotype and in CFR for COVID-19. Further work should clarify the relationship of sex-and age-dependent relationships of 2D:4D and the severity of COVID-19 at the individual level.

CRediT authorship contribution statement

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

Declaration of competing interest

None.

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