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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Sex differences in the relationship between digit ratio (2D:4D) and national case fatality rates for COVID-19: A reply to Sahin (2020)

Sahin [1] re-examined our finding of a positive association between national male (but not female) digit ratios (2D:4D; the relative lengths of the index and ring fingers) and case fatality rates (CFR's) for COVID-19 [2]. The re-analysis confirms the positive relationship in a more recent data set provided by the World Health Organization, suggesting that the relationship of national male 2D:4D and CFR's is temporally stable [3]. In addition, Sahin added a regional variable (EURO/Non-EURO) and a "country size" variable (number of cases) to the regression equation, and detected a negative association between female 2D:4D and CFR's. Thus, the re-analysis extends previous findings of sex differences in mortality (males > females) in the relationship between 2D:4D and national CFR's for COVID-19 [2]. It also replicates the null finding of Jones et al. [4] for an association between 2D:4D and the percent male deaths in a smaller and less reliable sample. Jones et al.'s [4] focus on this without considering the main finding of 2D:4D and national CFR's for COVID-19 had the effect of obfuscating the latter [3].

Digit ratio is sexually dimorphic (males < females) [5]. The dimorphism arises early in foetal development and does not change substantially during development [6]. Digit ratio is presumably influenced by the ratio of foetal testosterone (T) to oestrogen (E) (high T/E = low 2D:4D) [5]. A positive association between national male 2D:4D and CFR's suggest that populations of males who have experienced low prenatal T/E are prone to high COVID-19 mortality. Conversely, a negative association between national female 2D:4D and CFR's suggest that populations of females who have experienced high prenatal T/E are prone to high COVID-19 mortality. Thus, low prenatal T males and/or high prenatal T in females may account for a substantial proportion of the national differences in COVID-19 mortality.

Cardiovascular problems are co-morbidities that increase COVID-19 mortality [7]. Endogenous T in men correlates negatively with blood pressure and deaths from cardiovascular disease [8]. However, in women, endogenous T shows positive relationships with obesity and the metabolic syndrome [9]. Important in this is the control of blood pressure by angiotensin-converting enzyme (ACE) and ACE2 enzymes; the action of the former leads to vasoconstriction and the latter to vasodilation. ACE2 is the entry point into cells for SARS-CoV-2 [10]. Testosterone is necessary for this as activity of the androgen receptor and transcription of the transmembrane protease serine 2 (TMPRSS2) gene is required for SARS-CoV2 cell entry [10]. This reduces the numbers of ACE2 molecules on the cell's surface, causing an imbalance in ACE/ACE2 interaction, which in turn causes lung damage.

At the national level, the re-analysis [1] confirms a positive relationship between 2D:4D and CFR for COVID-19 in males [2] and reports a new negative relationship in females. This supports a sex difference in the relationship between 2D:4D and COVID-19 severity. At the individual level, it is important to determine whether severity of COVID-19 correlates positively with 2D:4D in men and negatively with 2D:4D in women.

Declaration of competing interest

None declared.

References

[1] H. Sahin, A further analysis of Manning and Fink, Early Hum. Dev. (2020) 105121, , https://doi.org/10.1016/j.earlhumdev.2020.105121 In press.
[2] J.T. Manning, B. Fink, Understanding COVID-19: digit ratio (2D:4D) and sex differences in national case fatality rates, Early Hum. Dev. 146 (2020) 105074, , https://doi.org/10.1016/j.earlhumdev.2020.105074.
[3] J.T. Manning, B. Fink, Evidence for (mis-)understanding or obfuscation in the COVID-19 and digit ratio relationship? A reply to Jones et al. (2020), Early Hum. Dev. (2020) 105100, , https://doi.org/10.1016/j.earlhumdev.2020.105100 In press.
[4] A.P. Jones, L.P. Satchell, B. Jaeger, C. Schild, (Mis-)understanding COVID-19 and digit ratio: methodological and statistical issues in Manning and Fink (2020), Early Hum. Dev. (2020) 105095, , https://doi.org/10.1016/j.earlhumdev.2020.105095 In press.
[5] J.T. Manning, D. Scutt, J. Wilson, D.I. Lewis-Jones, The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen, Hum. Reprod. 13 (1998) 3000–3004, https://doi.org/10.1093/humrep/13.11.3000.
[6] J.T. Manning, B. Fink, Sexual dimorphism in the ontogeny of second (2D) and fourth (4D) digit lengths, and digit ratio (2D:4D), Am. J. Hum. Biol. 30 (2018) e23138, , https://doi.org/10.1002/ajhb.23138.
[7] A.B. Docherty, E.M. Harrison, C.A. Green, H.E. Hardwick, R. Pius, L. Norman, K.A. Holden, J. et al. on behalf of the ISARIC4C investigators, Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study, BMJ 369 (2020) m1985, , https://doi.org/10.1136/bmj.m1985.
[8] K.-T. Khaw, M. Dowsett, E. Folkerd, S. Bingham, N. Wareham, R. Luben, A. Welch, N. Day, Endogenous testosterone and mortality due to all causes, cardiovascular

https://doi.org/10.1016/j.earlhumdev.2020.105120
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disease, and cancer in men, Circulation 116 (2007) 2694–2701, https://doi.org/10.1161/circulationaha.107.719005.
[9] T.G. Valderhaug, J.K. Hertel, N. Nordstrand, P.O. Dale, D. Hofsø, J. Hjelmesæth, The association between hyperandrogenemia and the metabolic syndrome in morbidly obesewomen, Diabetol. Metab. Syndr. 7 (2015) 46, , https://doi.org/10.1186/s13098-015-0040-5.
[10] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2020) 271–280, https://doi.org/10.1016/j.cell.2020.02.052.

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