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## Commentary

## Sex-biased clinical presentation and outcomes from COVID-19

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Around the world, while males and females are equally likely to test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), males are significantly more likely to be hospitalized, to be admitted into intensive care units, and to die from coronavirus disease 2019 (COVID-19) [1,2]. Although globally the proportions of males and females testing positive for SARS-CoV-2 are similar, a number of gender-associated differences—including behaviour (e.g. acceptance of public health measures that limit virus spread) [3], occupation [4], and access to healthcare for testing [5]—contribute to notable regional differences in SARS-CoV-2 exposure between the sexes [6].

Gender differences (i.e. a social construct that defines norms for men and women) are separate from but complementary to biological sex differences that are mediated by sex chromosome complement, differential reproductive tissues, and differential concentrations of sex steroid hormones. The enrichment of the X chromosome for immune response genes [7], combined with the presence of sex steroid hormone receptors on diverse innate and

adaptive immune cells, and the presence of hormone response elements in the promoters of numerous immune response genes, can give rise to sex differences in immunity to viruses [8]. Consequently, there are sex differences in immunity to SARS-CoV-2, control of virus replication, development of immunopathologies, and long-term protection [9]. For example, deleterious mutations in X-linked genes (e.g. *TLR7*) have been linked to worse COVID-19 outcomes in males [10]. Males consistently have greater proinflammatory cytokine production (e.g. IL-6) than females in the context of COVID-19, although it is unclear whether this difference is a marker of sex differences in disease severity [11,12]. Older males with COVID-19 have lower CD8+ T-cell activity (e.g. IFN- $\gamma$  production and proliferation) [13], but have greater antibody responses [14] than females. The durability of neutralizing antibodies, however, is lower for males than females over time [15].

Consistent with observations of sex differences in inflammation, the paper by Mussini et al. [16] reported that baseline as well as follow-up concentrations of C-reactive protein (CRP) and ferritin were greater in males than in females. This was despite the fact that females were significantly more likely to be obese, a condition which is generally associated with increased inflammation. These male COVID-19 patients also had more respiratory impairment at presentation (i.e. baseline PaO<sub>2</sub>/FiO<sub>2</sub>) and were more likely than females to require mechanical ventilation and to die from COVID-19. In linear mixed models, it was CRP that was the greatest mediator of the risk of invasive mechanical ventilation and death from COVID-19 pneumonia.

The population under study in the paper by Mussini et al. [16] included only those patients already meeting a definition of severe disease on presentation; the persistence of sex differences even in this group points to biological mechanisms that underlie differential outcomes in males and females. These data highlight the need to disaggregate and analyse data for sex differences to better understand the pathogenesis of COVID-19 disease. It remains unknown what role CRP has in prospectively predicting sex-specific risk, or whether it should be analysed using different sex-specific cut-offs. Larger datasets are needed to help answer these questions. It will be necessary for future studies to evaluate whether sex differences in inflammatory mediators exist in patients with less-severe COVID-19 from other centres. It will also be equally important for studies of the COVID-19 vaccine to disaggregate data by sex. While vaccine efficacy appears to be similar between the sexes [17],

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adverse reactions are more frequently reported by female than male vaccinees, which could provide insight into sex-specific dosing and monitoring of vaccinees.

In summary, the study by Mussini et al. [16] provides evidence that respiratory failure caused by COVID-19 is worse for males than for females, and that inflammatory proteins, including CRP, may serve as biomarkers for severe disease in males.

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### References

- [1] GlobalHealth5050. The sex, gender and COVID-19 project. <https://globalhealth5050.org/the-sex-gender-and-covid-19-project/>. [Accessed 28 December 2020].
- [2] Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ICU admission. *Nat Commun* 2020;11:6317.
- [3] Galasso V, Pons V, Profeta P, Becher M, Brouard S, Foucault M. Gender differences in COVID-19 attitudes and behavior: panel evidence from eight countries. *Proc Natl Acad Sci USA* 2020;117:27285–91.
- [4] Wenham C, Smith J, Morgan R, on behalf of the Gender and COVID-19 Working Group. COVID-19: the gendered impacts of the outbreak. *Lancet* 2020;395:846–8.
- [5] Ryan NE, El Ayadi AM. A call for a gender-responsive, intersectional approach to address COVID-19. *Glob Publ Health* 2020;15:1404–12.
- [6] Bischof E, Wolfe J, Klein SL. Clinical trials for COVID-19 should include sex as a variable. *J Clin Invest* 2020;130:3350–2.
- [7] Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* 2008;8:737–44.
- [8] Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016;16:626–38.
- [9] Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* 2020;20:442–7.
- [10] van der Made CI, Simons A, Schuurs-Hoeijmakers J, van den Heuvel G, Mantere T, Kersten S, et al. Presence of genetic variants among young men with severe COVID-19. *JAMA* 2020;324:1–11.
- [11] Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636–43.
- [12] Meng Y, Wu P, Lu W, Liu K, Ma K, Huang L, et al. Sex-specific clinical characteristics and prognosis of coronavirus disease-19 infection in Wuhan, China: a retrospective study of 168 severe patients. *PLoS Pathog* 2020;16:e1008520.
- [13] Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature* 2020;588:315–20.
- [14] Klein SL, Pekosz A, Park HS, Ursin RL, Shapiro JR, Benner SE, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest* 2020;130:6141–50.
- [15] Grzelak L, Velay A, Madec Y, Gallais F, Staropoli I, Schmidt-Mutter C, et al. Sex differences in the decline of neutralizing antibodies to SARS-CoV-2. *medRxiv* 2020. 11.12.20230466.
- [16] Mussini C, Cozzi-Lepri A, Menozzi M, Meschiari M, Franceschini E, Rogati C, et al., Modena Covid-19 Working Group (MoCo19), Office of information and communication technologies of Policlinico di Modena. Better prognosis in females with severe COVID-19 pneumonia: possible role of inflammation as potential mediator. *Clin Microbiol Infect* 2021;27(8):1137–44. <https://doi.org/10.1016/j.cmi.2020.12.010>.
- [17] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99–111.