

Invited Editorial

COVID-19: Is there a weaker sex?



Sex is one of the most relevant factors often associated with health, disease severity, mortality, and life expectancy [1]. From neonatal diseases to non-communicable disorders, men often have higher risks and poorer prognosis; however, the causes of these disparities are still subject to debate [2–7]. In this context, the new coronavirus disease of 2019 (COVID-19) has again called attention to these differences, mainly due to the observations of a higher level of complications and fatality rates among men [8]. According to data from the Global Health 50/50 initiative, which collects sex-disaggregated information from COVID-19 cases worldwide, from the 75 countries reporting case and death data by sex, 63 revealed a male:female ratio of mortality over 1, three countries having a value of 1 and only nine a ratio below this mark (Fig. 1). Furthermore, a recent study observed that although the male: female ratio of deaths per 100,000 individuals varied by age, the probability of death remained higher in males across all age categories [9]. In addition, a recently published study from India revealed that the magnitude of the differential risk by sex was higher as age increased, suggesting a role of age in this association [10]. Beyond these population observations, several studies have concluded that male sex is a risk factor for COVID-19 adverse outcomes, even in multivariate analyses after adjusting for potential confounders [11–14]. The association between male gender and adverse outcomes, such as mortality, seems consistent across all geographical areas, as revealed by several meta-analyses [15–18].

The reasons for this trend are likely to be multifactorial, including physiological factors, lifestyle, and socio-cultural behaviors [19] (Fig. 2). The physiological differences between the sexes may initially be directly involved in this differential risk of COVID-19 adverse outcomes [20]. For example, recent evidence has suggested that SARS-CoV-2 expression may induce angiotensin-converting enzyme-2 (ACE-2) downregulation due to the binding of the viral spike protein to its receptor, then promoting a decrease in the angiotensin- [1–7] production [21]. In this context, there is evidence suggesting an important role of sex hormones in the regulation of ACE-2 in a tissue-specific manner [20]. For example, female mice were observed to have a higher expression of ACE-2 in adipose tissue compared with male mice, leading to higher levels of Ang- [1–7], which in turn were associated with lower levels of hypertension, another risk factor for COVID-19 negative outcomes [22,23]. Similarly, higher testosterone levels in males may be related to a higher risk of coagulation disorders, resulting in complications such as venous thromboembolism and systemic embolisms, which are frequently observed in severe COVID-19 patients [24,25].

Furthermore, differences in the immune responses against SARS-CoV-2 between sexes may also play an important role. Takahashi et al. observed that men had higher plasma levels of IL-8 and IL-18, along with a more potent induction of non-classical monocytes among

patients with moderate COVID-19 who had not received immunomodulatory medications [26]. On the other hand, women had a more robust CD8 T cell activation. In this study, poor T cell responses were associated with disease progression in males, while higher cytokine levels were predictors of worsening of clinical status in females [26]. In addition, females may produce larger amounts of neutralizing antibodies, as evidenced by the study of Zeng et al., in which the concentration of IgG antibodies against SARS-CoV-2 was higher in women, especially during the early phase of the disease [27]. Finally, several studies have supported the direct role of sex hormones in immune responses. For example, the phytoestrogen silibinin was shown to reduce the expression of the pro-inflammatory cytokines IL-17 and TNF- α , potentially reducing the risk of complications such as the cytokine storm observed in cases of severe SARS-CoV-2 infection [28].

On the other hand, lifestyle differences between the two sexes need consideration. Women tend to have a healthier lifestyle than men, with lower frequencies of smoking and heavy drinking [29]. This is reflected in a lower prevalence of classic cardiovascular (CV) risk factors, mostly before the menopausal transition [30]. Furthermore, adipose tissue distribution differences may also impact the outcome of COVID-19, as abdominal adiposity has been identified as an independent predictor of pulmonary function in several studies [31–33]. Nevertheless, recent studies have concluded that CV risk factors may have a stronger association with CV disease in women, highlighting the need for sex-specific analyses to clarify the reason for this trend [34,35].

Finally, socio-cultural variables are paramount to explain these differences. At first, the estimated global ratio of female to male labor force participation for 2020 was around 0.6, positioning work-related transmission as a relevant factor supporting male higher risk in several occupational groups [36]. Similarly, school closures have forced -more often- women to provide care for their children and immediate families, potentially inducing them to stay at home [37]. Furthermore, religious restrictions for women could play a role in the spread of the virus. For example, in certain cultures, facial covering is relatively common; therefore, women are likely to be less exposed to air-borne pathogen transmission, also being less prone to touching their faces [38]. In addition to this, men with voluminous facial hair might have limitations with mask fit, causing increased exposure to the virus and air leakage during non-invasive positive pressure ventilation [39].

From a behavioral perspective, men are usually more likely to engage in health-related risk activities, increasing their exposure to the virus [29]. On the other hand, women tend to be more cautious and tend to have better hygiene knowledge and practice [40]. In addition, women may have a lesser risk of contagion through distancing from men or separation from the broader workforce and community in some cultures. Moreover, women are less inclined to seek medical

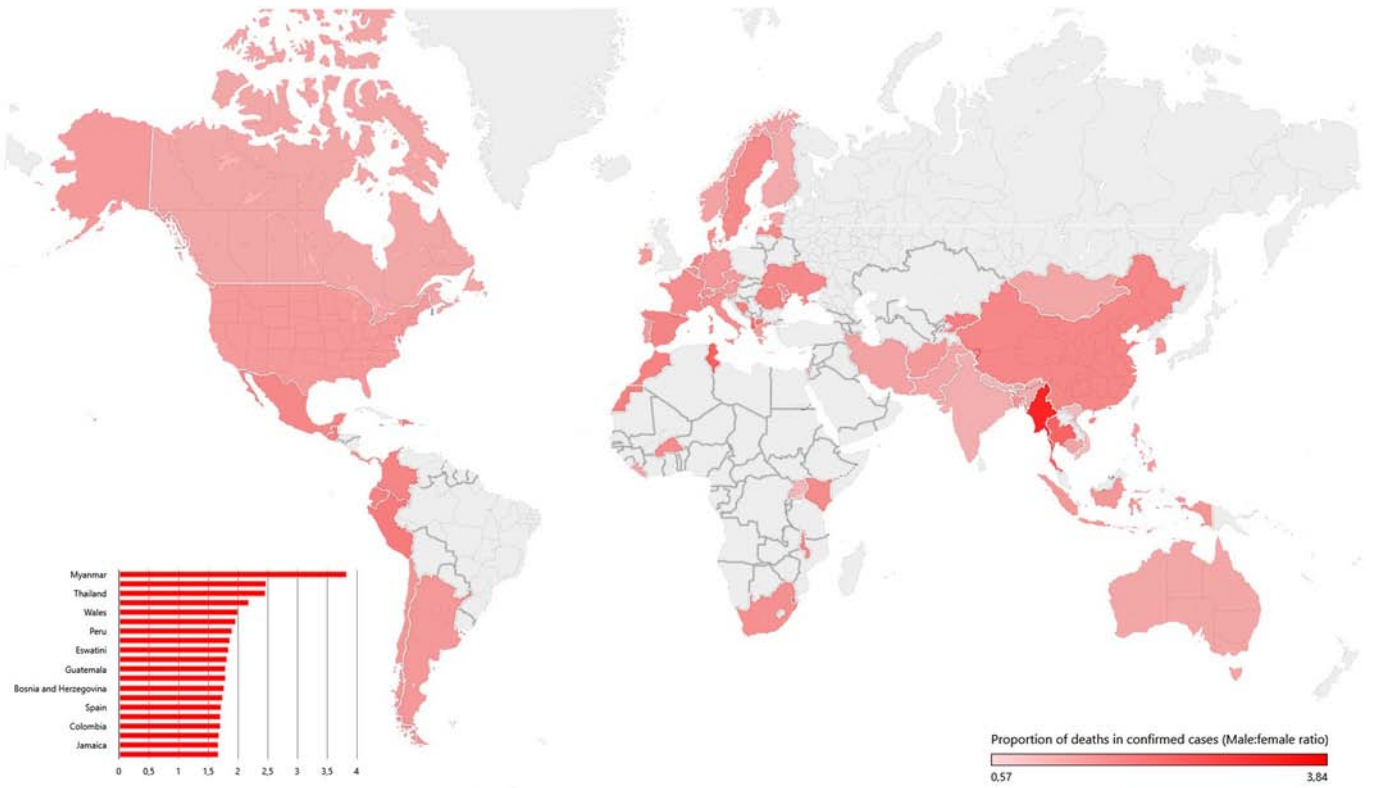


Fig. 1. Male to female ratio of deaths in COVID-19 confirmed cases. Source: [44].

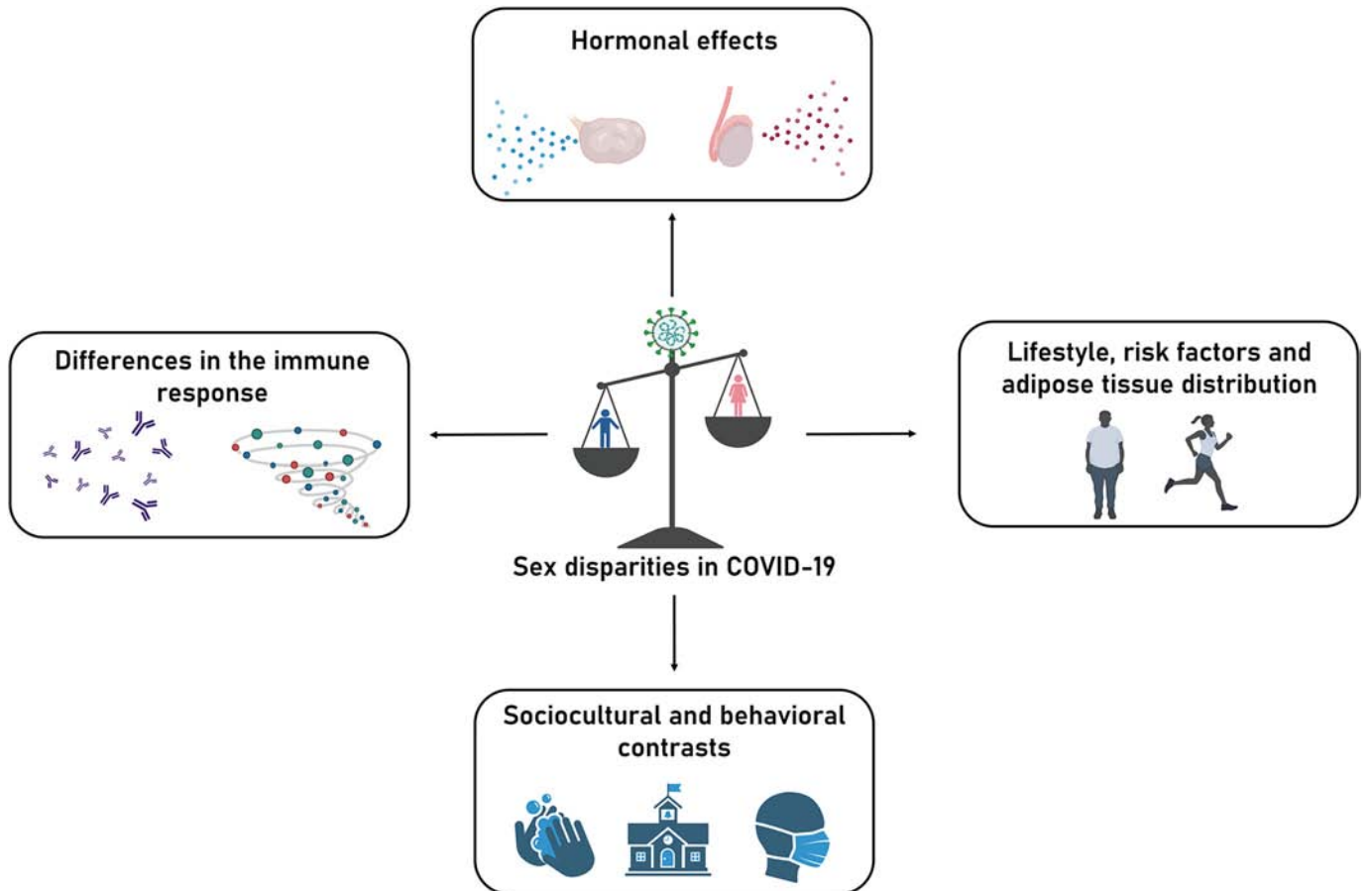


Fig. 2. Summary of the potential mechanisms and variables involved in the sex differential between men and women regarding COVID-19 adverse outcomes. Source: Authors. Created with BioRender.com

attention in some settings, which may favor a potential underrepresentation in data collected regarding infection incidence in selected regions [41,42]. Finally, education has been identified as a factor influencing health outcomes in several clinical conditions; however, gender studies have revealed a larger effect on men's mortality than women's [43]. Therefore, more research is needed to assess the role of education in COVID-19.

Considering all these differences, it is essential to take a sex- and gender-based approach to the identification, diagnosis, treatment, and overall management in the COVID-19 pandemic to elucidate further additional pathophysiological mechanisms and socio-cultural variables that may play a role in the differential expression of SARS-CoV-2 infection by sex, ultimately leading to an optimal prevention and care.

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References

- [1] V. Regitz-Zagrosek, Sex and gender differences in health, *EMBO Rep.* 13 (7) (2012) 596–603.
- [2] J. Ding, W. Wu, J. Fang, J. Zhao, L. Jiang, Male sex is associated with aggressive behaviour and poor prognosis in Chinese papillary thyroid carcinoma, *Sci. Rep.* 10 (2020).
- [3] M.A. El Sharouni, A.J. Witkamp, V. Sigurdsson, P.J. van Diest, M.W.J. Louwman, N.A. Kukutsch, Sex matters: Men with melanoma have a worse prognosis than women, *J. Eur. Acad. Dermatol. Venereol. JEADV.* 33 (11) (2019) 2062–2067.
- [4] K.A. Ribbons, P. McElduff, C. Boz, M. Trojano, G. Izquierdo, P. Duquette, et al., Male sex is independently associated with faster disability accumulation in relapse-onset MS but not in primary progressive MS, *PLoS ONE* 10 (6) (2015).
- [5] S. Kraemer, The fragile male, *BMJ.* 321 (7276) (2000) 1609–1612.
- [6] S.-Y. Shim, S.J. Cho, K.A. Kong, E.A. Park, Gestational age-specific sex difference in mortality and morbidities of preterm infants: A nationwide study, *Sci. Rep.* 7 (2017).
- [7] G.L. Drevstedt, E.M. Crimmins, S. Vasunilashorn, C.E. Finch, The rise and fall of excess male infant mortality, *Proc. Natl. Acad. Sci. U. S. A.* 105 (13) (2008) 5016–5021.
- [8] L.H. Gargaglioni, D.A. Marques, Let's talk about sex in the context of COVID-19, *J. Appl. Physiol.* 128 (6) (2020) 1533–1538.
- [9] S.S. Bhopal, R. Bhopal, Sex differential in COVID-19 mortality varies markedly by age, *Lancet* 396 (10250) (2020) 532–533.
- [10] R. Laxminarayan, B. Wahl, S.R. Dudala, K. Gopal, C. Mohan, S. Neelima, et al., Epidemiology and transmission dynamics of COVID-19 in two Indian states, *Science* (2020), eabd7672[still ahead of printing].
- [11] T. Mikami, H. Miyashita, T. Yamada, M. Harrington, D. Steinberg, A. Dunn, et al., Risk factors for mortality in patients with COVID-19 in New York City, *J. Gen. Intern. Med.* (2020) 1–10.
- [12] O. Albitar, R. Ballouze, J.P. Ooi, S.M. Sheikh Ghadzi, Risk factors for mortality among COVID-19 patients, *Diabetes Res. Clin. Pract.* 166 (2020) 108293.
- [13] L. Palaiodimos, D.G. Kokkinidis, W. Li, D. Karamanis, J. Ognibene, S. Arora, et al., Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York, *Metabolism.* 108 (2020) 154262.
- [14] G.N. Ioannou, E. Locke, P. Green, K. Berry, A.M. O'Hare, J.A. Shah, et al., Risk factors for hospitalization, mechanical ventilation, or death among 10 131 US veterans with SARS-CoV-2 infection, *JAMA Netw. Open* 3 (9) (2020) e2022310.
- [15] P. Qiu, Y. Zhou, F. Wang, H. Wang, M. Zhang, X. Pan, et al., Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: A systematic review and meta-analysis, *Aging Clin. Exp. Res.* (2020) 1–10.
- [16] Z. Zheng, F. Peng, B. Xu, J. Zhao, H. Liu, J. Peng, et al., Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis, *J. Inf. Secur.* 81 (2) (2020) e16–e25.
- [17] M. Parohan, S. Yaghoubi, A. Seraji, M.H. Javanbakht, P. Sarraf, M. Djalali, Risk factors for mortality in patients with coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of observational studies, *Aging Male.* (2020) 1–9.
- [18] M.J. Nasiri, S. Haddadi, A. Tahvildari, Y. Farsi, M. Arbabi, S. Hasanzadeh, et al., COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic review and meta-analysis, *Front. Med.* 7 (2020) 459.
- [19] S. Falahi, A. Kenarkoobi, Sex and gender differences in the outcome of patients with COVID-19, *J. Med. Virol.* (2020) <https://doi.org/10.1002/jmv.26243>.
- [20] S. La Vignera, R. Cannarella, R.A. Condorelli, F. Torre, A. Aversa, A.E. Calogero, Sex-specific SARS-CoV-2 mortality: Among hormone-modulated ACE2 expression, risk of venous thromboembolism and hypovitaminosis D, *Int. J. Mol. Sci.* 21 (8) (2020).
- [21] D. Gurwitz, Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics, *Drug Dev. Res.* 81 (5) (2020) 537–540.
- [22] P.L.M. Dalpiaz, A.Z. Lamas, I.F. Caliman, R.F. Ribeiro, G.R. Abreu, M.R. Moyses, et al., Sex hormones promote opposite effects on ACE and ACE2 activity, hypertrophy and cardiac contractility in spontaneously hypertensive rats, *PLoS One* 10 (5) (2015), e0127515.
- [23] K. Honorato-Sampaio, V.M. Pereira, R.A.S. Santos, A.M. Reis, Evidence that angiotensin-(1-7) is an intermediate of gonadotrophin-induced oocyte maturation in the rat preovulatory follicle, *Exp. Physiol.* 97 (5) (2012) 642–650.
- [24] S. Cui, S. Chen, X. Li, S. Liu, F. Wang, Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia, *J. Thromb. Haemost. JTH.* 18 (6) (2020) 1421–1424.
- [25] S. Luo, S.L. Au Yeung, J.V. Zhao, S. Burgess, C.M. Schooling, Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction: Mendelian randomisation study in UK Biobank, *BMJ.* 364 (2019) 1476.
- [26] T. Takahashi, M.K. Ellingson, P. Wong, B. Israelow, C. Lucas, J. Klein, et al., Sex differences in immune responses that underlie COVID-19 disease outcomes, *Nature.* (2020) 1–9.
- [27] F. Zeng, C. Dai, P. Cai, J. Wang, L. Xu, J. Li, et al., A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: A possible reason underlying different outcome between sex, *J. Med. Virol.* (2020) <https://doi.org/10.1002/jmv.25989>.
- [28] M.L. Dupuis, F. Conti, A. Maselli, M.T. Pagano, A. Ruggieri, S. Anticoli, et al., The natural agonist of estrogen receptor β silibinin plays an immunosuppressive role representing a potential therapeutic tool in rheumatoid arthritis, *Front. Immunol.* 9 (2018).
- [29] L.A. Walter, A.J. McGregor, Sex- and gender-specific observations and implications for COVID-19, *West. J. Emerg. Med.* 21 (3) (2020) 507–509.
- [30] A.E. Peters Sanne, M. Paul, W. Mark, Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016, *Circulation.* 139 (8) (2019) 1025–1035.
- [31] H.M. Ochs-Balcom, B.J.B. Grant, P. Muti, C.T. Sempos, J.L. Freudenheim, M. Trevisan, et al., Pulmonary function and abdominal adiposity in the general population, *Chest.* 129 (4) (2006) 853–862.
- [32] Y. Saxena, G. Sidhwani, R. Upmanyu, Abdominal obesity and pulmonary functions in young Indian adults: A prospective study, *Indian J. Physiol. Pharmacol.* 53 (4) (2009) 318–326.
- [33] J. Pan, L. Xu, T.H. Lam, C.Q. Jiang, W.S. Zhang, Y.L. Jin, et al., Association of adiposity with pulmonary function in older Chinese: Guangzhou Biobank Cohort Study, *Respir. Med.* 132 (2017) 102–108.
- [34] M. Woodward, Cardiovascular disease and the female disadvantage, *Int. J. Environ. Res. Public Health* 16 (7) (2019).
- [35] K. Humphries, M. Izadnegadar, T. Sedlak, J. Saw, N. Johnston, K. Schenck-Gustafsson, et al., Sex differences in cardiovascular disease – impact on care and outcomes, *Front. Neuroendocrinol.* 46 (2017) 46–70.
- [36] The World Bank, International Labour Organization, ILOSTAT database, <https://data.worldbank.org/indicator/SL.TLF.CACT.FM.ZS?view=map> June 2020.
- [37] J. Kopel, A. Perisetti, A. Roghani, M. Aziz, M. Gajendran, H. Goyal, Racial and gender-based differences in COVID-19, *Front. Public Health* 8 (2020) 418.
- [38] S. Rengasamy, B. Eimer, R.E. Shaffer, Simple respiratory protection—evaluation of the filtration performance of cloth masks and common fabric materials against 20–1000 nm size particles, *Ann. Occup. Hyg.* 54 (7) (2010) 789–798.
- [39] I. Sandaradura, E. Goeman, G. Pontivivo, E. Fine, H. Gray, S. Kerr, et al., A close shave? Performance of P2/N95 respirators in healthcare workers with facial hair: Results of the BEARDS (BEncrmarking Adequate Respiratory DefenceS) study, *J. Hosp. Infect.* 104 (4) (2020) 529–533.
- [40] L.K.P. Suen, Z.Y.Y. So, S.K.W. Yeung, K.Y.K. Lo, S.C. Lam, Epidemiological investigation on hand hygiene knowledge and behaviour: A cross-sectional study on gender disparity, *BMC Public Health* 19 (1) (2019) 401.
- [41] O.T. Muurlink, A.W. Taylor-Robinson, COVID-19: Cultural predictors of gender differences in global prevalence patterns, *Front. Public Health* 8 (2020) 174.
- [42] J. Wainer, L. Bryant, R. Strasser, Sustainable rural practice for female general practitioners, *Aust. J. Rural Health.* 9 (Suppl. 1) (2001) S43–S48.
- [43] C.E. Ross, R.K. Masters, R.A. Hummer, Education and the gender gaps in health and mortality, *Demography.* 49 (4) (2012) 1157–1183.
- [44] Global Health 50/50 COVID-19: data disaggregated by age and sex. <https://globalhealth5050.org/covid19/age-and-sex-data/> Date accessed: September 30, 2020.

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