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.

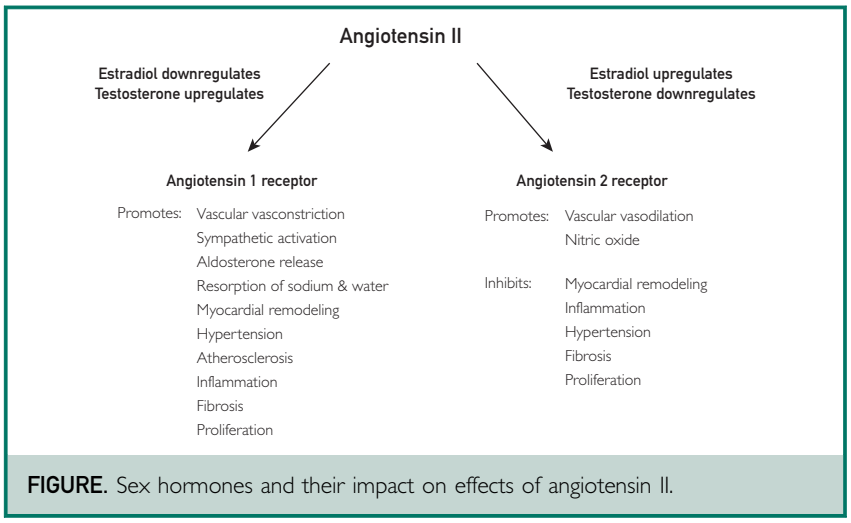

FIGURE. Sex hormones and their impact on effects of angiotensin II.

binding to the angiotensin 2 receptor, rather than the angiotensin 1 receptor. This alternative binding promotes vascular vasodilation and inhibits cardiac remodeling, in contrast to angiotensin 1 receptor binding that facilitates vasoconstriction and additional pro-inflammatory actions (Figure).

In addition to advantageous hormonal differences, females possess 2 X chromosomes, further contributing to the "female immune advantage." Although the "extra" X chromosome is deactivated, more than 10% of the second X chromosome genetic material, most related to immune function, stays active throughout a woman's life.[5] For example, the TLR7 gene is found on the X chromosome and escapes X inactivation, resulting in higher expression levels in females. Additionally, during embryonic times in females, both X chromosomes remain active for a short while, resulting in epigenetic modifications, further enabling females to better survive infections. Females likely evolved to better withstand viral infections, and understanding all contributing factors is essential to optimizing care.

We greatly appreciate this article's focus on the sex differences involved in immune responses and subsequent CV risk related to the current COVID-19 pandemic. Heightened awareness that such differences exist will hopefully foster expanded research into the significant inherent immune variances between males and females, and between reproductive and postmenopausal women, with the goal of pragmatically and successfully improving medical care.

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1. Ritter O, Kararigas G. Sex-Biased Vulnerability of the Heart to COVID-19. *Mayo Clin Proc*. 2020;95(11):2332-2335.
2. Vikse J, Lippi G, Henry BM. Do sex-specific immunobiological factors and differences in angiotensin converting enzyme 2 (ACE2) expression explain increased severity and mortality of COVID-19 in males? *Diagnosis(Berl)*. 2020;7(4):385-386.
3. Mauvais-Jarvis F, Klein SL, Levin ER. Estradiol, progesterone, immunomodulation, and COVID-19 outcomes. *Endocrinology*. 2020;161(9):bqaa127.
4. White MC, Fleeman R, Arnold AC. Sex differences in the metabolic effects of the renin-angiotensin system. *Biol Sex Differ*. 2019;10(1):31.
5. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Moller M. The X chromosome and sex-specific effects in infectious disease susceptibility. *Hum Genomics*. 2019;13(1):2.

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In Reply — COVID-19, the Female Immune Advantage, and Cardiovascular Impact

To The Editor: We thank Gersh and colleagues[1] for their letter in response to our article "Sex-Biased Vulnerability of the Heart to COVID-19."[2] In fact, we are pleased to see that our article is fulfilling its purpose of drawing attention to a topic little explored, putting forward notions and hypotheses for the field to contemplate.

We agree with Gersh and colleagues regarding the importance and relevance of the role of sex hormones beyond the reproductive system, particularly in the cardiovascular system as we have shown previously.[3,4] Given the importance of angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus 2 host cell entry, Gersh and colleagues accurately point out the influence of estradiol on the renin-angiotensin-aldosterone system (RAAS). In this context, we have recently discussed the modulatory actions of estradiol on RAAS in detail, thereby impacting several components of the cardiovascular system.[5,6]

The purpose of our article was to postulate on the role of biological sex and the potential mechanisms that could increase risk of cardiac complications more in male than female coronavirus disease 2019 (COVID-19) patients, thereby providing a hypothesis on the molecular factors related to the cardiovascular system that may contribute to the observed sex-biased crude fatality rates. At the same time, the importance of the potential impact of sex hormones on COVID-19—induced cardiovascular complications has been recently discussed in *Mayo Clinic Proceedings*.[7]

Therefore, we concur with Gersh and colleagues, and we consider their comments insightful, contributing to awareness of the role of biological sex and the regulatory effects of sex hormones on (patho)physiological mechanisms.

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1. Gersh FL, O'Keefe JH, Henry BM, et al. COVID-19, the female immune advantage, and cardiovascular impact. *Mayo Clin Proc*.. 2021;96(3):818-819.
2. Ritter O, Kararigas G. Sex-biased vulnerability of the heart to COVID-19. *Mayo Clin Proc*. 2020;95(11):2332-2335.
3. Kararigas G, Bito V, Tinel H, et al. Transcriptome characterization of estrogen-treated human myocardium identifies Myosin regulatory light chain interacting protein as a sex-specific element influencing contractile function. *J Am Coll Cardiol*. 2012;59(4):410-417.
4. Kararigas G, Nguyen BT, Zelarayan LC, et al. Genetic background defines the regulation of postnatal cardiac growth by 17beta-estradiol through a beta-catenin mechanism. *Endocrinology*. 2014;155(7):2667-2676.
5. Sabbatini AR, Kararigas G. Estrogen-related mechanisms in sex differences of hypertension and target organ damage. *Biol Sex Differ*. 2020;11(1):31.
6. Sabbatini AR, Kararigas G. Menopause-related estrogen decrease and the pathogenesis of HFpEF: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(9):1074-1082.
7. Al-Lami RA, Urban RJ, Volpi E, Algburi AMA, Baillargeon J. Sex hormones and novel corona virus infectious disease (COVID-19). *Mayo Clin Proc*. 2020;95(8):1710-1714.

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Cardiorespiratory Fitness Attenuates the Impact of Risk Factors Associated With COVID-19 Hospitalization

To the Editor: As highlighted in the editorial "Fit Is It in COVID-19, Future Pandemics, and Overall Healthy Living," published in the January 2021 issue of the *Mayo Clinic Proceedings,* it is important to bring more awareness to cardiorespiratory fitness (CRF) as an independent predictor of morbidity and mortality.[1] To that end, we present additional data regarding the interaction of CRF with the traditional risk factors often associated with increased illness severity from coronavirus disease 2019 (COVID-19). Details regarding the methods and data extraction can be found in Brawner et al.[2] Briefly, 246 patients who tested positive for severe acute respiratory syndrome coronavirus 2 and completed a clinically indicated stress test between January 2016 and February 2020 were retrospectively identified. Hospitalization for COVID-19 was identified through July 2020.

Using logistic regression, in univariate analyses we found that 8 of 13 previously identified risk factors were associated with an increased likelihood of hospitalization due to COVID-19 (Table). However, when adjusted for CRF (ie, peak metabolic equivalents of task) in a multivariable analysis, only age (≥65 years), male sex, and chronic kidney disease remained as significant predictors (Table).

These results show how CRF improves the risk profile of higher-risk individuals and builds upon other studies that have reported similar findings.[3-5] Although our limited sample size may have contributed to the large confidence intervals in the adjusted analysis, it is important to note that fitness attenuated the point estimate for all of the comorbidities that were significant in univariate analyses.

Surprisingly, in the univariate analysis, obesity was not associated with increased hospital risk and when CRF was introduced as a covariate it showed a paradoxical protective effect. This finding may simply be due to the nature of the cohort in this study, which consisted of individuals who were able to perform an exercise stress test on a treadmill. With respect to obesity showing a paradoxical protective effect, this has been reported previously[6] and may again speak to the interaction between CRF and body mass index,[7] with more fit individuals potentially having greater muscle mass, which body mass index does not differentiate.

In conclusion, our study shows the value of including CRF as an additional health indicator and adds to the importance of the public health message of the benefits of fitness and exercise, particularly for attenuating the risk associated with other health disorders. When performing risk stratification for research or clinical purposes, efforts should be made to include a measure of CRF.