3-1-2021

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

Dennis J. Kerrigan
Henry Ford Health, dkerrig1@hfhs.org

Clinton A. Brawner
Henry Ford Health, cbrawne1@hfhs.org

Jonathan K. Ehrman
Henry Ford Health, jehrman1@hfhs.org

Steven J. Keteyian
Henry Ford Health, SKeteyi1@hfhs.org

Recommended Citation

Kerrigan DJ, Brawner CA, Ehrman JK, and Keteyian S. Cardiorespiratory Fitness Attenuates the Impact of Risk Factors Associated With COVID-19 Hospitalization. Mayo Clin Proc 2021; 96(3):822-823.

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.

Oliver Ritter, MD
Department of Cardiology, Nephrology and Pulmonology
Campus Clinic Brandenburg
Faculty of Health Sciences Brandenburg
Brandenburg Medical School Theodor Fontane
Brandenburg an der Havel, Germany

Georgios Kararigas, PhD
Department of Physiology
Faculty of Medicine
University of Iceland
Reykjavik

Potential Competing Interests: The authors report no potential competing interests.

ORCID
Georgios Kararigas: https://orcid.org/0000-0002-8187-0176

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.

https://doi.org/10.1016/j.mayocp.2020.12.020

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.

TABLE. Effect of Fitness on the Relationship Between Select Variables and Likelihood of Complications Due to COVID-19[a]

Variable	Univariate analyses			Adjusted for peak METs		
	Wald X^2	*P*	OR (95% CI)	Wald X^2	*P*	OR (95% CI)
Age ≥65 years	18.3	<.001	3.31 (1.91 to 5.73)	10.8	.001	2.65 (1.48 to 4.74)
Male	3.9	.048	1.70 (1.00 to 2.88)	8.1	.004	2.29 (1.30 to 4.05)
Asthma	0.5	.49	1.28 (0.64 to 2.57)	0.6	.43	1.34 (0.74 to 0.92)
Obesity[b]	2.2	.13	0.67 (0.39 to 1.13)	3.9	.048	0.57 (0.33 to 0.995)
CKD	7.9	.005	5.39 (1.66 to 17.5)	4.6	.03	3.76 (1.12 to 12.7)
DM	4.8	.03	1.83 (1.06 to 3.13)	2.6	.11	1.57 (0.90 to 2.75)
COPD	1.4	.23	2.28 (0.60 to 8.71)	0.7	.41	1.78 (0.46 to 6.95)
CHD	4.5	.03	2.48 (1.07 to 5.72)	3.6	.06	2.31 (0.98 to 5.47)
Cancer	3.8	.05	2.26 (0.99 to 5.12)	2.6	.11	2.00 (0.87 to 4.62)
HTN	5.0	.03	1.95 (1.09 to 3.50)	1.9	.16	1.55 (0.84 to 2.85)
Stroke	0.04	.83	0.88 (0.26 to 3.00)	0.3	.59	0.70 (0.20 to 2.49)
Smoking	0.15	.70	0.86 (0.41 to 1.82)	0.1	.79	0.90 (0.42 to 1.94)
HF	4.6	.03	3.42 (1.11 to 10.55)	1.9	.16	2.29 (0.71 to 7.35)

[a]CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MET, metabolic equivalents of task; OR, odds ratio.
[b]BMI≥30 kg/m^2.

Dennis J. Kerrigan, PhD
Preventive Cardiology
Henry Ford Hospital
Detroit, MI

Clinton A. Brawner, PhD
Preventive Cardiology
Henry Ford Hospital
Detroit, MI

Jonathan K. Ehrman, PhD
Preventive Cardiology
Henry Ford Hospital
Detroit, MI

Steven Keteyian
Preventive Cardiology Cardiovascular Medicine
Henry Ford Hospital
Detroit, MI

Potential Competing Interests: The authors report no potential competing interests.

ORCID
Dennis J. Kerrigan: https://orcid.org/0000-0002-5372-1544; Clinton A. Brawner: https://orcid.org/0000-0002-1705-6620

1. Lavie CJ, Sanchis-Gomar F, Arena R. Fit is it in covid-19, future pandemics, and overall healthy living. *Mayo Clin Proc.* 2021;96(1):7-9.
2. Brawner CA, Ehrman JK, Bole S, et al. Maximal exercise capacity is inversely related to hospitalization secondary to coronavirus disease 2019. *Mayo Clin Proc.* 2021;96(1):36-39.
3. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: A case for fitness as a clinical vital sign: A scientific statement from the american heart association. *Circulation.* 2016;134(24):e653-e699.
4. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis.* 2015;57(4):306-314.
5. Barry VW, Baruth M, Beets MW, Durstine JL, Liu J, Blair SN. Fitness vs. fatness on all-cause mortality: a meta-analysis. *Prog Cardiovasc Dis.* 2014;56(4):382-390.
6. Oktay AA, Lavie CJ, Kokkinos PF, Parto P, Pandey A, Ventura HO. The interaction of cardiorespiratory fitness with obesity and the obesity paradox in cardiovascular disease. *Prog Cardiovasc Dis.* 2017;60(1):30-44.
7. Sanchez-Lastra MA, Ding D, Dalene K-E, Ekelund U, Tarp J. Physical activity and mortality across levels of adiposity: a prospective cohort study from the uk biobank. *Mayo Clin Proc.* 2021;96(1):105-119.

https://doi.org/10.1016/j.mayocp.2021.01.003

In Reply — Cardio respiratory Fitness Attenuates the Impact of Risk Factors Associated With COVID-19 Hospitalization

To the Editor: We appreciate the interest by Kerrigan et al[1] regarding the cardiorespiratory fitness (CRF) editorial that we wrote about their Henry Ford Hospital CRF and coronavirus disease 2019 (COVID -19) study.[2] This small study of only 246 patients did not show increased risk of obesity for hospitalizations in their univariate analysis, and in the multivariate analysis, there was an obesity paradox, with the obese having a 43% lower risk of requiring hospitalizations.

However, many other reports on much larger series containing many thousands of patients[3-5] including papers in the *Mayo Clinic Proceedings*,[6,7] point out the high risk of obesity in COVID -19. These other papers all focus on much "harder" clinical outcomes, including intensive care unit admissions, intubation and mechanical ventilation, and mortality, not just hospitalizations. Nevertheless, these other studies also did not account for physical activity, much less CRF. As Kerrigan et al[1] mention, an obesity paradox has been found in many cardiovascular conditions, especially among