BRIEF RESEARCH REPORT

The Multifaceted Benefits of Exercise in Prevention of COVID-19

Jeff A. Schlicht, PhD[1], Kate M. Edwards, PhD[2]

Keywords: Sars-CoV-2, coronavirus, exercise immunology, vaccine

EXERCISE AND COVID-19

As the global death toll from the novel coronavirus disease 2019 (COVID-19) rises above 1.5 million, with more than 300,000 deaths in the US compared to 1,000 in Australia (1), health professionals must consider all interventions that have potential to reduce infection rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and morbidity and mortality associated with COVID-19. Exercise is a potent immune system stimulus (2) that mitigates many health risk factors associated with COVID-19 hospitalization. In this article we review how exercise enhances immune system function, discuss conditions and diseases associated with COVID-19 mitigated by exercise, and provide exercise prescription information for primary and secondary prevention of SARS-CoV-2 infection.

EXERCISE ENHANCES THE IMMUNE SYSTEM

The immune system includes many types of cells that work together to locate and destroy viruses, as illustrated in Figure 1. These include lymphocytes, neutrophils, and macrophages. Lymphocytes and neutrophils increase in number and function during exercise, enhancing the immune system response. It is commonly well-accepted that moderate intensity cardiorespiratory exercise benefits immune system function by increasing white cell counts and activity (4), but there is debate about the risks and benefits associated with vigorous intensity exercise.

A long-standing tenet of exercise immunology, called the open window theory, suggests that after very intense and prolonged exercise the body enters a period of immunosuppression (5). Recently, some researchers have begun questioning this principle, arguing that the science which supports the open window theory lacks necessary rigor to reveal the true relationship between exercise intensity and immune system function (6). They suggest many variables, such as increased exposure to pathogens at large events and circadian rhythm disturbances caused by travel, contribute to increased upper respiratory tract infection rates in athletes. This increased upper respiratory tract infection incidence is a commonly cited justification for the open window theory. Some scientists advocate that common-sense examination of the relationship between exercise and disease risk, which demonstrates that exercise benefits health, is reason enough to suspect that intense and prolonged exercise does not, in fact, suppress the immune system. Indeed, this theory is at best limited to endurance athletes performing these types of exercise bouts; no evidence has been found during moderate intensity or shorter (<2 hours) exercise bouts. Readers interested in further discussion are encouraged to read a recently published debate on the topic (7).

Another way exercise, particularly resistance training, may help support a robust immune system is by promoting gains in muscle mass. Muscle, relative to other body compartments, is a low-inflammatory environment during periods of infection. A recent study in mice demonstrated that lymphocyte CD8+ T cells, which kill virus-infected cells, were protected from cellular exhaustion during viral infection when they resided in muscle tissue versus the circulation. These intramuscular CD8+ cells produce more progeny,

[1]Western Connecticut State University, Danbury CT 06810 USA
[2]University of Sydney, Sydney, NSW 2006 Australia
Address for correspondence: Jeff Schlicht, Western Connecticut State University, 181 White Street, Danbury, CT 06810 USA; (203) 837 8687; e-mail: schlichtj@wcsu.edu.

Conflicts of Interest and Source of Funding: Neither author received funding for this paper. We have no conflicts of interest.

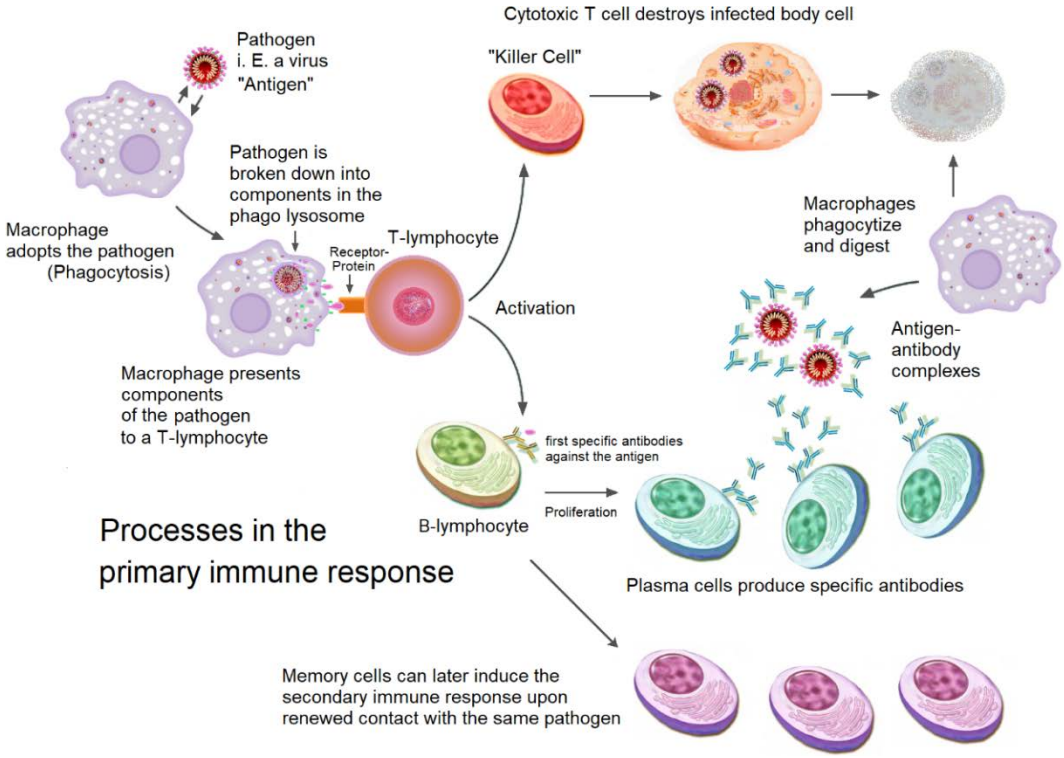

FIGURE 1. Primary immune system function (3).

allowing for greater CD8+ cell proliferation, and more virus-infected cell death (8). Thus, in theory people with greater muscle mass should be able to produce a more robust immune response during times of infection.

Interesting work in astronauts suggests individuals with higher cardiorespiratory fitness who already have a viral infection are less likely to experience virus reactivation. If reactivation does occur it produces lower viral loads (9). This may have implications for SARS-CoV-2 as there is some indication that people can become reinfected. Because research in this area is new, it is unclear whether reinfection is occurring from latent virus in the body or by new viral exposure.

EXERCISE REDUCES RISK OF SERIOUS INFECTION AND ASSOCIATED CHRONIC DISEASE

A recent analysis of comorbidities associated with hospitalization due to SARS-CoV-2 infection in the US suggests the 3 comorbid conditions most strongly linked to hospitalization are obesity, hypertension, and diabetes (Figure 2) (10). Decades of research have proven the strong link between exercise and reduction in all 3 of these conditions (11).

Obesity

A recent network analysis of the effect of exercise on obesity concluded the most effective intervention is a combination prescription that includes both high-intensity interval training and high-intensity strength training (12). The authors conclude that weight loss in these exercise interventions is modest, but significant reductions in body mass index and improved body composition can occur, emphasizing the idea that weight loss exercise program goals should focus on changes in composition, not weight.

Hypertension

Another recent review of randomized controlled trials involving exercise and hypertension demonstrated that aerobic exercise decreases ambulatory systolic and diastolic blood pressures (13). These benefits extended to both daytime and nighttime readings. Most studies find that exercise decreases ambulatory blood pressures during the day, but there is conflicting evidence regarding the effect of exercise on nighttime blood pressure.

Diabetes

A metaanalysis from 2018 concluded that combined aerobic plus resistance exercise is the most effective intervention for controlling blood glucose as determined by hemoglobin A1c (HbA1c), a marker of control over several months (14). This review also compared supervised versus unsupervised exercise and illustrated that supervised exercise is more effective for blood glucose control.

The common theme for exercise prescription among these 3 comorbidities associated with COVID-19 hospitalization is that greatest efficiency will be found with combined aerobic and strength training prescription performed under supervision.

Anxiety and Depression

Exercise is also a potent mediator of anxiety and depression, 2 common conditions resulting from social isolation and COVID-19 stress. Research suggests more than 20% of

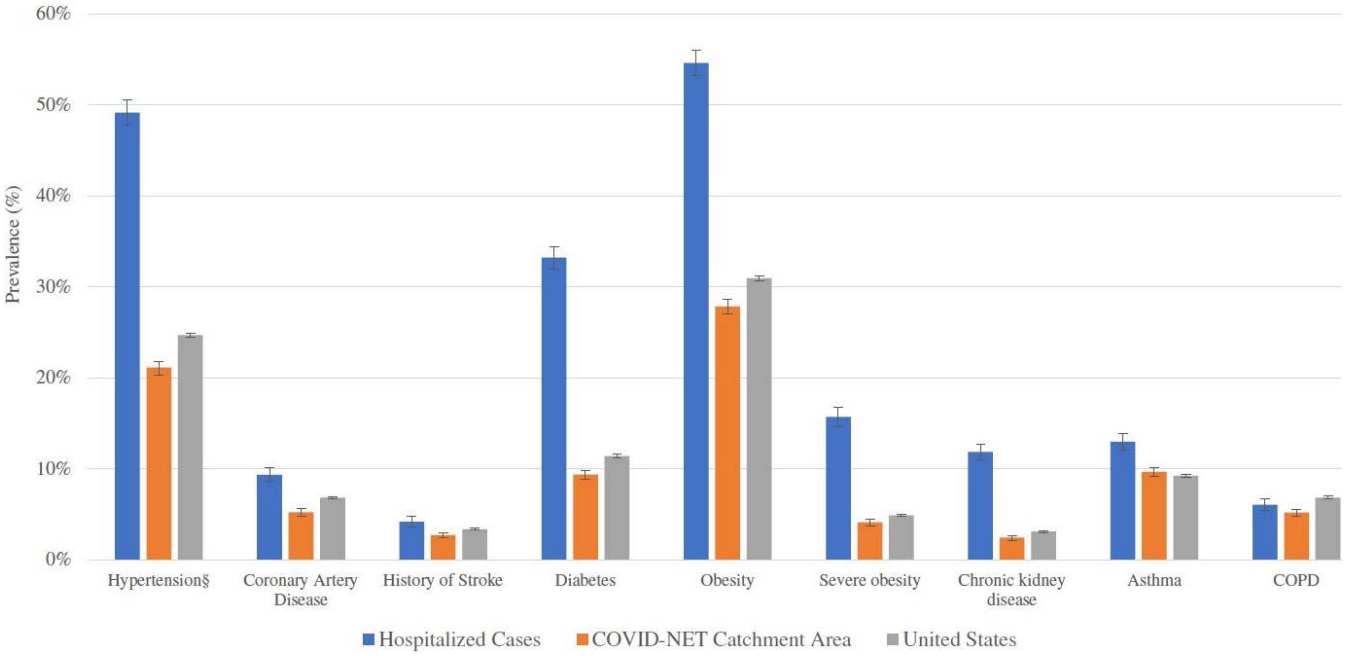

FIGURE 2. Prevalence of underlying medical conditions: community dwelling adults with COVID-19-associated hospitalizations. Original published by Oxford University Press for the Infectious Diseases Society of America 2020. This work is written by (a) US Government employee(s) and is in the public domain in the US (10).

health care workers suffer from these conditions, with higher rates seen in general populations (15). A current review of the literature that provides potential mechanisms of action summarizes that aerobic exercise has been strongly linked to improved depression and anxiety outcomes, while noting the body of evidence supporting resistance training as an efficacious intervention continues to grow, and that exercise effects are similar to those provided by pharmacotheraputics (16).

EXERCISE PROMOTES A ROBUST RESPONSE TO VACCINATION IN OLDER ADULTS AND PERHAPS YOUNGER PEOPLE

It is now apparent that vaccines against SARS-CoV-2 will become widely available in 2021. How effective these vaccines will be (i.e., how much of, and importantly, how enduring the immune response elicited will be) remains to be understood. There is robust research evidence that cardiorespiratory exercise promotes a stronger vaccine response in older adults (17), resulting in more efficacious vaccination, with at least 8 studies in adults aged over 60 years (18). In younger persons the effect of exercise is less pronounced, possibly because their immune systems are more robust. However, it is possible that this exercise benefit to vaccination extends to all age groups who are immunocompromised. In general it appears that exercise improves vaccine effectiveness in older adults, and may improve effectiveness in other adults and children.

In addition to the effects of frequent exercise (or cardiovascular fitness), there is evidence that a single acute bout of exercise may boost vaccine response. One interesting study with younger people assessed how a 15-minute bout of upper body resistance training performed immediately before vaccination affected subjects who received a half pneumococcal intramuscular vaccine dose vs full dose (19). The results suggest that arm exercise prior to injection may provide benefit to younger people if a vaccine is not sufficiently effective, with significantly stronger antibody responses in the exercise group compared to control when a half dose vaccine was used. There was no difference between groups using a full dose. It is also worth considering the additional benefits of exercise immediately prior to vaccination; exercise is a known analgesic, and recent evidence suggests that pain at the site of a vaccination and subsequent vaccine reactions (tenderness, swelling, reduced appetite, and feeling unwell) are decreased by exercise (20).

It is possible that some COVID-19 vaccines will induce a response that is not completely protective in all populations. If this is the case, exercise may have an important role to play for not only older adults, but for all age groups, particularly people with comorbidities. There is emerging evidence that vaccine response is blunted in those who are obese (21) and have hypertension (22); diabetes does not appear to reduce effectiveness (23).

Initial research findings on the effects of acute and chronic exercise on vaccination responses suggest that as we learn more about this topic we may discover that exercise benefits younger as well as older individuals.

EXERCISE PRESCRIPTION FOR COVID-19 PREVENTION AND TREATMENT OF COMORBIDITIES

Cardiorespiratory Exercise

It is clear that moderate intensity cardiorespiratory exercise enhances the immune system. Current guidelines recommend 150 to 300 minutes of moderate intensity

cardiorespiratory exercise per week (24–26). Vigorous intensity cardiorespiratory exercise for a relatively short period of time (for example, a 30-minute high-intensity interval training workout) will probably not increase risk for infection, and 75 to 150 minutes a week of vigorous cardiorespiratory exercise is a public health target (24–26). The effect of extended bouts of vigorous exercise lasting more than 2 hours per session are controversial (7). Given the severe consequences of COVID-19 infection, it may be prudent to avoid engaging in exercise at this level. High-intensity interval training may be used with older adults and people with chronic conditions (27).

Muscle Strengthening Exercise

Research into the acute effect of resistance training on the immune system is lacking. Two or more days per week of weight training are recommended by American, Australian, and Canadian guidelines (24–26). Given that greater muscle mass may provide a haven for immune system cells during infection, engaging in muscle quality improvement activities should be recommended and follow national and professional organization guidelines.

Additional Precautions

Because initial infection is a major concern, people should continue to follow general disease prevention principles during exercise: remain 6 feet apart, though 12 feet may be desirable with forced expiration during exercise which can be aerosol generating; wear a face mask (face masks do not interfere with breathing in exercise, even to exhaustion) (28); wash hands frequently; don't touch your face; spend less than 15 minutes in an environment with people you don't live with; and exercise outdoors whenever possible.

If someone is ill, general prescription advice is to refrain from exercise in the presence of fever or respiratory complications. If these symptoms are not present, reducing usual exercise intensity is suggested. People infected with SARS-CoV-2 but asymptomatic for COVID-19 may follow the above guidelines with the exception that they remain in quarantine for ~14 days and do not exercise outside where they may emit aerosolized virus that may infect others. Return to exercise recommendations in previously infected individuals, especially those hospitalized, are not yet published. It may be prudent to be conservative when returning to resistance and aerobic exercise.

CONCLUSION

Both acute and chronic exercise have a robust effect on the immune system. Exercise and high fitness can protect people against initial and worsening infection, may protect against reinfection, and may reduce community spread by lowering viral loads in people who are infected and increasing the effectiveness of vaccines. Exercise should be recommended as a primary prevention strategy and a secondary COVID-19 recovery treatment modality.

Acknowledgments: Many thanks to Kimberly Yousey-Hindes from the Yale School of Public Health for her presentation at Western Connecticut State University of COVID-19 hospitalization prepublication data used to develop a section of this article.

REFERENCES

1. Johns Hopkins University & Medicine. Coronavirus resource center. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. Updated 2021. Accessed February 11, 2021. https://coronavirus.jhu.edu/map.html
2. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019 May;8(3):201–17.
3. Sciencia58, Domdomegg, Fæ, Petr94, Manu5. Immune System. Updated 2020. Accessed February 11, 2021. https://commons.wikimedia.org/w/index.php?curid=90421209. This file is licensed under the Creative commons Attribution-Share Alike 4.0 International license.
4. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. Prog Mol Biol Transl Sci. 2015;135:355–80.
5. Peake JM, Neubauer O, Walsh NP, Simpson RJ. Recovery of the immune system after exercise. J Appl Physiol (1985). 2017;122(5):1077–87.
6. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Front Immunol. 2018;9:648. doi:10.3389/fimmu.2018.00648
7. Simpson RJ, Campbell JP, Gleeson M, Krüger K, Nieman DC, Pyne DB, Turner JE, Walsh NP. Can exercise affect immune function to increase susceptibility to infection? Exerc Immunol Rev. 2020;26:8–22.
8. Wu J, Weisshaar N, Hotz-Wagenblatt A, Madi A, Ma S, Mieg A, Hering M, Mohr K, Schlimbach T, Borgers H, Cui G. Skeletal muscle antagonizes antiviral $CD8^+$ T cell exhaustion. Sci Adv. 2020;6(24):eaba3458. doi:10.1126/sciadv.aba3458
9. Agha NH, Mehta SK, Rooney BV, Laughlin MS, Markofski MM, Pierson DL, Katsanis E, Crucian BE, Simpson RJ. Exercise as a countermeasure for latent viral reactivation during long duration space flight. FASEB J. 2020;34(2):2869–81.
10. Ko JY, Danielson ML, Town M, Derado G, Geenlunch KJ, Kirley PD, Alden NB, Yousey-Hindes K, Anderson EJ, Ryan PA, Kim S, Lynfield R, Torres SM, Barney GR, Bennett NM, Sutton M, Talbot HK, Hill M, Hall AJ, Fry AM, Garg S, Kim L, COVID-NET Surveillance Team. Risk factors for COVID-19-associated hospitalization: COVID-19-associated hospitalization surveillance network and behavioral risk factor surveillance system. Clin Infect Dis. 2020;ciaa1419. doi:10.1093/cid/ciaa1419
11. Physical Activity Guidelines Advisory Committee. 2018 Physical activity guidelines advisory committee scientific report. Washington: US Department of Health and Human Services; 2018.
12. O'Donoghue G, Blake C, Cunningham C, Lennon O, Perrotta C. What exercise prescription is optimal to improve body composition and cardiorespiratory fitness in adults living with obesity? A network meta-analysis. Obes Rev. 2020;22(2):e13137. doi:10.1111/obr.13137

13. Saco-Ledo G, Valenzuela PL, Ruiz-Hurtado G, Ruilope LM, Lucia A. Exercise reduces ambulatory blood pressure in patients with hypertension: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2020;9(24):e018487. doi:10.1161/JAHA.120.018487
14. Pan B, Ge L, Xun YQ, Chen YJ, Gao CY, Han X, Zuo LQ, Shan HQ, Yang KH, Ding GW, Tian JH. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Act. 2018;15(1):72. doi:10.1186/s12966-018-0703-3
15. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsi E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: a systematic review and meta-analysis. Brain Behav Immun. 2020;88:901–7.
16. Smith PJ, Merwin RM. The role of exercise in management of mental health disorders: an integrative review. Annu Rev Med. 2021;72(1):45–62.
17. de Araújo AL, Silva LC, Fernandes JR, Matias Mde S, Boas LS, Machado CM, Garcez-Leme LE, Benard G. Elderly men with moderate and intense training lifestyle present sustained higher antibody responses to influenza vaccine. Age (Dordr). 2015;37(6):105. doi:10.1007/s11357-015-9843-4
18. Pascoe AR, Fiatarone Singh MA, Edwards KM. The effects of exercise on vaccination responses: a review of chronic and acute exercise interventions in humans. Brain Behav Immun. 2014;39:33–41. doi:10.1016/j.bbi.2013.10.003
19. Edwards KM, Pung MA, Tomfohr LM, Ziegler MG, Campbell JP, Drayson MT, Mills PJ. Acute exercise enhancement of pneumococcal vaccination response: a randomised controlled trial of weaker and stronger immune response. Vaccine. 2012;30(45):6389–95.
20. Lee VY, Booy R, Skinner SR, Fong J, Edwards KM. The effect of exercise on local and systemic adverse reactions after vaccinations - Outcomes of two randomized controlled trials. Vaccine. 2018 Nov 12;36(46):6995–7002.
21. Park HL, Shim SH, Lee EY, Cho W, Park S, Jeon HJ, Ahn SY, Kim H, Nam JH. Obesity-induced chronic inflammation is associated with the reduced efficacy of influenza vaccine [published online ahead of print March 10, 2014]. Hum Vaccin Immunother. 2014;10(5):1181–6. doi:10.4161/hv.28332
22. Kwetkat A, Heppner HJ. Comorbidities in the elderly and their possible influence on vaccine response. Interdiscip Top Gerontol Geriatr. 2020;43:73–85. doi:10.1159/000504491
23. Dos Santos G, Tahrat H, Bekkat-Berkani R. Immunogenicity, safety, and effectiveness of seasonal influenza vaccination in patients with diabetes mellitus: a systematic review. Hum Vaccin Immunother. 2018;14(8):1853–66.
24. US Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd ed. Washington: US Department of Health and Human Services; 2018.
25. The Australian Government Department of Health. Australia's physical activity and sedentary behaviour guidelines and the Australian 24-hour movement guidelines. Updated 2019. Accessed February 11, 2021. https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines
26. Canadian Society for Exercise Physiology. Canadian 24-hour movement guidelines for adults ages 18-64 years: an integration of physical activity, sedentary behaviour, and sleep. Updated 2021. Accessed February 11, 2021. https://csepguidelines.ca/adults-18-64/
27. Ross LM, Porter RR, Durstine JL. High-intensity interval training (HIIT) for patients with chronic diseases. J Sport Health Sci. 2016;5(2):139–44.
28. Shaw K, Butcher S, Ko J, Zello GA, Chilibeck PD. Wearing of cloth or disposable surgical face masks has no effect on vigorous exercise performance in healthy individuals. Int J Environ Res Public Health. 2020;17(21):8110. doi:10.3390/ijerph17218110