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.

Brain, Behavior, and Immunity 87 (2020) 6–7

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Viewpoint

The immunological case for staying active during the COVID-19 pandemic

Richard J. Simpson[a,b,c,*], Emmanuel Katsanis[b,c]

[a] Department of Nutritional Sciences, University of Arizona, Tucson, AZ, USA
[b] Department of Pediatrics, University of Arizona, Tucson, AZ, USA
[c] Department of Immunobiology, University of Arizona, Tucson, AZ, USA

1. Viewpoint

On April 17th 2020, the number of people diagnosed with COVID-19 worldwide was over 2.2-million with more than 154,000 deaths. Government shelter-in-place orders have restricted the movement of ~3 billion people around the globe in an attempt to minimize the spread and devastation of this novel virus. While these countermeasures are necessary, spending prolonged periods of time in isolation and confinement, coupled with the stress and anxiety people are experiencing, are likely to lead to many other stress-related health problems. A particular concern are the restrictions these orders have placed on our daily activity and exercise routines. Regular physical activity exerts a multitude of beneficial health effects but, perhaps more importantly during this pandemic, is its ability to both enhance immune defense and mitigate the deleterious effects of stress on immunity (Duggal et al., 2019; Simpson et al., 2015). Implementations of social distancing has resulted in the mass closure of gyms and parks where exercise and training regimens would normally be undertaken, but it is essential that physical activity be encouraged during this viral outbreak.

The COVID-19 pandemic has raised many questions regarding how we can boost immunity through exercise. There is no scientific data on how physical activity may enhance immune responses against coronaviruses, but we do know that having elevated levels of cardiorespiratory fitness and exercising at moderate to vigorous intensity can improve immune responses to vaccination, reduce chronic low-grade inflammation and improve various immune markers in several disease states including cancer, HIV, cardiovascular disease, diabetes, cognitive impairment and obesity (Duggal et al., 2019; Walsh et al., 2011). Epidemiological data also indicate that physically active people are less likely to report symptoms of upper respiratory illness and there is evidence that exercise can protect the host from many types viral infection including influenza, rhinovirus (another cause of the common cold) and the reactivation of latent herpesviruses such as Epstein-Barr (EBV), varicella-zoster (VZV) and herpes-simplex-virus-1 (HSV-1) (Duggal et al., 2019; Martin et al., 2009). Moderate intensity exercise training during an active influenza infection has been shown to protect mice from death and promote favorable immune cell composition and cytokine shifts in the lungs associated with improved survival (Martin et al., 2009). Physically active individuals also exert better control over their latent viral infections, even during periods of isolation and confinement. For instance, recent work from our laboratory demonstrated that astronauts with increased levels of cardiorespiratory fitness and skeletal muscle endurance were ~40% less likely to reactivate a latent herpesvirus during a 6-month mission to the International Space Station (ISS), particularly if they were able to maintain their fitness levels on the ISS (Agha et al., 2020). Even in astronauts who did reactivate a virus, copies of viral DNA were fewer in the fitter astronauts indicating that they were less contagious than their less-fit counterparts. Latent viral reactivation is a hallmark of compromised immunity, which, in this context, we deem to be due to the stressors associated with isolation and inactivity as a result of confinement on the ISS. Indeed, periods of isolation and confinement elevate glucocorticoids (e.g. cortisol) that can inhibit many critical functions of our immune system. These include the ability of our lymphocytes to multiply in response infectious agents and the effector functions of NK-cells and CD8+ T-cells, all of which are essential in the recognition and elimination of cancerous or virally infected cells (Duggal et al., 2019).

How exercise augments host immune defenses is multi-faceted, but a key mechanism is the frequent mobilization and redistribution of effector lymphocytes. Literally billions of lymphocytes are mobilized in response to just a single bout of exercise, particularly if the exercise is dynamic and taxes the cardiorespiratory system (e.g. running, cycling or rowing). Importantly, there is a catecholamine-mediated preferential mobilization of those lymphocyte subtypes that are capable of tissue migration, and their phenotypic signatures indicate they are primed and 'looking for a fight' (e.g. to recognize and kill virus-infected cells). Virus-specific memory T-cells mobilized with exercise exhibit enhanced proliferation responses to viral antigens such as those derived from CMV, EBV and HSV-1, and non-latent viruses such as adenovirus (Duggal et al., 2019). These mobilized cells firstly enter the blood compartment from marginated vascular pools, the spleen and the bone marrow before immediately trafficking to secondary lymphoid organs and tissues, particular to the lungs and the gut where increased immune defense may be required. This facilitates immune surveillance by

* Corresponding author at: Department of Nutritional Sciences, Department of Pediatrics, Department of Immunobiology, The University of Arizona, 1625 N Campbell Ave, Tucson, AZ 85719, USA.
E-mail address: rjsimpson@email.arizona.edu (R.J. Simpson).

https://doi.org/10.1016/j.bbi.2020.04.041
Received 14 April 2020; Accepted 15 April 2020
Available online 18 April 2020
0889-1591/

increasing immune cell 'patrolling' in these vulnerable areas (e.g. the upper respiratory tract and the lungs) to prevent viruses and other pathogens from gaining a foothold. This process is also vital to minimize the impact of the virus and to expedite viral resolution should our immune barriers be breached and we become infected. Exercise also releases various cytokines from the skeletal muscle (i.e. myokines) that can help maintain immune competency. Muscle-derived IL-6 has been shown to direct immune cell trafficking towards areas of infection, while IL-7 can stimulate T-cell production from the thymus and IL-15 helps maintain T-cell and NK-cell homeostasis in the periphery, all of which work in concert to increase host immune defense (Duggal et al., 2019).

To help boost immunity and mitigate the deleterious effects of inactivity and social isolation stress on our immune system, it is imperative that we strive to maintain recommended exercise levels during this COVID-19 pandemic. The Physical Activity Guidelines for Americans recommend 150–300 min of moderate to vigorous intensity cardiorespiratory physical activity per week and two sessions per week of muscle strength training (Piercy et al., 2018). While this can be challenging without access to gyms and parks and following social distancing and hygienic guidelines, there are many creative ways to stay active at home. The recent surge in home-based exercise platforms, such as online instructor-led classes and 'exergaming', will be particularly useful for some people during this time. However, specialized technology and equipment is not required; keeping active indoors or outdoors through brisk walking, stair climbing, yard/house work and/or playing active games with the family can be just as effective. What is important is that we avoid prolonged periods (> 60-min) of time sitting and try to implement even a few minutes of activity at regular intervals throughout the day, all of which count toward achieving these weekly goals. Exceeding recommended physical activity levels during this time is not recommended as there is some evidence that excessive exercise (e.g. those activities performed by highly athletic individuals) might impair immunity and increase infection risk (Simpson et al., 2020).

Exercise might not prevent us from developing COVID-19, but it is our perspective that physical activity will help maintain and counteract the negative effects of isolation and confinement stress on immune competency and should, therefore, be strongly promoted during this worldwide mitigation strategy. The available scientific evidence from other viral infections would indicate that physically active people will have less severe symptoms, shorter recovery times, and may be less likely to infect others they come into contact with. Exercise is also likely to be most beneficial for those who are asymptomatic or experiencing only mild symptoms. Exercise training has been shown to improve immune responses to both the influenza and pneumococcal vaccines in older adults (Duggal et al., 2019), a particularly vulnerable population during this COVID-19 outbreak. This could be important to help our seniors develop better immunity to an anticipated COVID-19 vaccine and minimize future complications should a second wave of the virus occur. It is our expectation that a large body of research will follow this pandemic so that we may provide more specific exercise recommendations as they pertain to infection risk and control.

Acknowledgement

This work was supported by NASA grant 80NSSC19K105.

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