Intense Physical Exercise Reduces Complications, Hospitalizations and Potential Mortality from Covid-19

Abstract

Aims: The present study investigate the relationship between pre-COVID-19 exercise levels and intensity and disease outcome. Methodologically we used an online survey comprising 20 questions was sent to participants to determine their exercise history, including type, intensity, and exacerbation of COVID-19 symptoms.

Study Design: A populational survey-based study.

Place and Duration of Study: Many countries like Germany, Turkey, Saudi Countries, Chile, Unted Staes of America, Canadá and Brazil. The duration from 2020 until 2024.

Methodology: A large survey to determinate the physical fitness level, type, duration, and intensity of the physical exercise was applied under invitation of many associated researchers around the world. A electronic version were used to improve the acquisition in partners health centers and universities. We analyzed the possible interactions using a chi-square test to infer the results.

Results: We note that individuals physically active had significantly better disease outcomes than physically inactive individuals. Low or moderate-intensity exercise did not show significant differences in exacerbations, but high-volume or high-intensity exercise was associated with decreased complications requiring hospitalization.

Conclusion: Our study concludes that physical activity reduces the risk of intensive care and hospitalization due to SARS-CoV-2 infection, and exercise intensity plays a crucial role in mitigating the severity of the disease. The study suggests that a more physically active world population could prevent many deaths associated with COVID-19, and save life.

Keywords: Sars-Cov-2 Infection. Upper Respiratory Infection Tract. Exercise-Induced Immunosuppression. Exercise-Induced Lesser Hospitalization. Exercise-Induced Lesser Co-morbidities.

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 virus, emerged in December 2019 and rapidly became a global health crisis (1-3). The virus primarily spreads through respiratory droplets and contact with contaminated surfaces (3), leading to a range of symptoms from mild to severe respiratory illness and, in some cases, death (1). Comorbidities such as hypertension, cardiovascular diseases, and metabolic disorders increase the risk of severe COVID-19 outcomes (4).

Exercise is well-known for its health benefits, including improvements in cardiovascular and respiratory function (7,9), immune system enhancement, and mental health benefits (12-14). Regular physical activity can reduce the risk of chronic diseases such as hypertension, diabetes, and obesity, which are risk factors for severe COVID-19 outcomes (15,16). Exercise has been proposed as a non-pharmacological intervention to mitigate the effects of COVID-19 by enhancing the body's immune response and reducing inflammation (18-20).

Several mechanisms have been suggested to explain the protective effects of exercise against COVID-19. Exercise improves cardiovascular and respiratory function, potentially reducing the severity of respiratory symptoms caused by COVID-19(21). Moreover, regular physical activity boosts the immune system by increasing the production of anti-inflammatory cytokines and enhancing natural killer cell function (21). This anti-inflammatory effect of exercise could help mitigate the cytokine storm, an acute immune response leading to severe COVID-19 complications (22).

Given the potential benefits of exercise in reducing COVID-19 severity, this study aims to investigate the relationship between pre-COVID-19 exercise levels and intensity and the outcomes of the disease. We hypothesize that individuals who engaged in higher levels of physical activity before contracting COVID-19 will experience better health outcomes compared to those who were less active.

MATERIALS AND METHOD

Study Design

A questionnaire was developed to identify people affected by COVID-19 and assess the level of severity of their disease, as well as to collect information on their history, frequency and intensity of previous physical activity (See Supplementary material). The questionnaire consists of 20 questions that inquire about age, sex, educational level, frequency and intensity of physical activity prior to COVID-19, severity of the infection, hospitalization time, post-hospital complications, comorbidities, and medications used in treatment. To ensure face validity, the questionnaire was reviewed by five physicians. A pilot study was carried out to validate the instrument and the necessary adjustments were made before its translation.

Participants

To ensure ethical compliance, investigator contact information and ethical terms will be provided at the beginning of the questionnaire. This study will follow the guidelines established in resolution 466/2012 and the Helsinki Treaty (2000), of which Brazil is a signatory. It is important to note that the ethical approval was granted under CAAE number 35349520.5.0000.5010 by the Ethics Council of the Federal University of Acre on November 13, 2020.

Procedures

Between November 2020 and February 2023, an online questionnaire was administered to Brazilian people who had recovered from SARS-CoV-2 infection. The questionnaire was made available through various channels, such as social media, the media, hospitals, healthcare providers, and disease control centers in select cities. Respondents were included if they had recovered from illness, regardless of age or symptoms, and had received a confirmed diagnosis by quantitative PCR viral test, serology, or rapid antibody test, with or without hospitalization. Those with or without drug treatment and with some chronic disease (such as diabetes, hypertension, coronary artery disease, obesity, metabolic syndrome, cancer, etc.) were also included. Illiterate people who could not complete the electronic form and patients who were still hospitalized or had symptoms of COVID-19 were excluded. Quality control measures were used to assess the responses provided by participants.

Quality control

To ensure the validity of the data collected, a two-part quality control process was carried out. First, duplicate responses and those indicating the absence of COVID-19 or lack of diagnostic tests were excluded, leaving 2,400 participants for analysis. The second part of the quality control focused on the physical activity report, and participants who declared themselves sedentary but reported more than 75 minutes of physical activity per week were excluded, resulting in 2400 (78.2%) participants included. in the final analysis. The participants were then categorized based on their levels of physical activity, with those who got at least 75 minutes of activity per week and reported feeling "quite tired" were considered very active. Those who were less active but still reported feeling "fairly tired" were classified as moderately active, while those who reported feeling "moderately tired" and getting 75 to 150 minutes of activity per week were classified as moderately active. Finally, those who got less than 75 active minutes a week and reported feeling "mildly tired" were classified as not very active, unless they got more than 150 active minutes a week, in which case they were classified as moderately active.

Statistical analysis

The distributions of the quantitative variables were verified using the Shapiro-Wilk normality test. Variables with symmetric and skewed distribution are presented as mean and standard deviation. The variables are represented by absolute and relative frequency. The proportions of the variables were compared between the outcome (hospitalization: yes or no) using the Chi-square test. Distributions of length of hospital stay between levels of physical activity were compared using the Kruskal-Wallis test with Dunn's post-hoc test. All tests were set at 5% significance. Additionally, the power of the experiment was performed through the electronic platform www.stat.ubc.ca to our number of subjects.

Results

Power of experiment

These calculations to the power of .80 shows that the minimum number of subjects should be 134, however we got to 240, and calculations based on the number of subjects showed 0.88.

General Data of the volunteers

Among 2770 participants, 1460 were physically active and 760 were sedentary. Physical activity was associated with lower rates of intensive medical care and hospitalization ($p<0.05$). Within the physically active group, those engaging in high-intensity exercise had significantly fewer complications and reduced need for mechanical ventilation compared to those who engaged in low to moderate-intensity exercise ($p<0.05$). The Table 1 summaries these data.

Table 1: General information of the volunteer

	Sex	***n***	**%**
Physical Active	Male	14300	51.62
	Female	1340	48.38
	Total	2770	100
Sedentary	Male	1240	44.73
	Female	1530	55.27
	Total	2770	100
Type of Exercise	Sport	303	10.94
	Resistance	1450	52.34
	Aerobic	1017	36.72
Intensity of Exercise	Low-Intensity	1620	58.48
	Middle-Intensity	610	22.03
	High-Intensity	540	19.49

Note: ***n***= Absolute number of subjects; **%**= percentage among the subjects

Previous physical activity reduces the intensive medical care, and hospitalization in SARS-CoV-2 infection.

Table 2 shows the summary data and the percentages of prevalence of medical care among the sedentary and physically active groups. Among the sedentary group, 70 subjects required intensive medical care, while in the physically active group, 110 subjects required intensive medical care. The reduction in the physical activity group was significant ($p<0.05$). Hospitalization was required for 70 subjects in the sedentary group and 110 subjects in the physically active group, showing a similar reduction of 27.25% ($p<0.05$). In addition, 30 subjects from the sedentary group required mechanical ventilation, 10 required intubation, and 10 reported sequelae. In contrast, 20 subjects in the physical activity group required mechanical ventilation and 50 reported sequelae, but no subject required intubation or coma. There was no significant difference in the need for intubation or coma between the sedentary and physically active groups ($p>0.05$). Hospitalization was found to be lower in the sedentary group than in the physical active group, but the difference was not significant ($p>0.05$).

Table 2: Medical care prevalence

	Sedentary Group		Physical Active Group			
	N	**%**	***n***	**%**	***Difference***	***p value***
Intensive medical care	70	9.2	110	6.7	- 27.25	<0.05
Hospitalization	70	9.2	110	6.7	- 27.25	<0.05
Mechanical Breathing	30	3.9	20	1.2	- 30.76	>0.05
Intubation	10	1.3	0	0.9	- 69.23	>0.05
Coma	0	0.0	0	0.0	-	>0.05
Sequels	10	1.3	50	3.0	230.76	>0.05

Note: *n*= Absolute number of subjects; %= percentage; *= difference between Sedentary Group *vs* Physical Active Group

The exercise can decrease severe symptoms in 24.68% and the prevalence of acute respiratory syndrome in 82.71%

The number of asymptomatic individuals was higher in the physically active group (1450) than in the sedentary group (650), indicating a reduction in reported symptoms ($p<0.05$). In the physically active group, 260 subjects reported severe symptoms, while 150 subjects in the sedentary group reported the same, showing a statistically significant difference ($p<0.05$). The most common symptom reported by both groups was acute respiratory syndrome, with 220 subjects in the physically active group and 120 in the sedentary group reporting, again showing a significant reduction ($p<0.05$) in the physically active group active group showed. Table 3 provides a summary of the data, including the absolute number of subjects and the percentage of subjects with each symptom in both groups, and the differences and p-values between them.

Table 3: Symptoms prevalence

	Sedentary Group		Physical Active Group			
	n	**%**	***n***	**%**	***Difference***	***p value***
Asymptomatic	650	85.5	1450	88.4	3.39*	<0.05
Severe symptoms	150	19.7	260	15.8	24.68	>0.05
Acute respiratory syndrome	120	16.2	220	13.4	82.71*	<0.05

Note: *n*= Absolute number of subjects; %= percentage; *= difference between Sedentary Group *vs* Physical Active Group

Physically active subjects reported lesser 67.7% co-morbidities than sedentary

In the physically active group, 300 subjects reported comorbidities, whereas in the sedentary group, 430 reported one or more comorbidities, indicating that the physically active subjects had less prior comorbidity. Specifically, regarding the main comorbidities of the physically active group, 190 reported overweight, 10 Diabetes Mellitus, 50 hypertension and obesity ($BMI>30$ kg/m^2). In the sedentary group, 240 reported overweight, 30 Diabetes Mellitus, 150 hypertension, and 10 obesity ($BMI>30$ kg/m^2). The sedentary group reported significantly higher comorbidities ($p<0.05$), highlighting overweight as more prevalent in the sedentary group ($p<0.05$). Table 4 shows the summarized data and the percentages.

Table 4: Co-morbidities prevalence

	Sedentary Group		Physical Active Group			
	n	**%**	***n***	**%**	***Difference***	***p value***
Co-morbidities	430	56.6	300	18.3	- 67.7	<0.05
Overweight	240	31.6	190	11.6	- 63.29	<0.05
Diabetes Mellitus	30	3.9	10	0.6	- 84.31	>0.05
Hypertension	150	19.7	50	3.1	- 84.26	>0.05
Obesity	10	1.3	50	3.1	58.06	>0.05

Note: *n*= Absolute number of subjects; %= percentage; *= difference between Sedentary Group *vs* Physical Active Group

Regular moderate and high intensity exercise can provide additional protection against the COVID-19 worsening than slightly exercise

Crossing the data on exercise intensity and symptom severity, it was found that the 460 (100%) subjects who reported severe symptoms had a light exercise practice, and none of the 540 subjects who had moderate or intense regular exercise. reported severe symptoms. Table 5 shows the summarized data and the percentages.

Table 5: Type and intensity of exercise

Exercise Intensity	Severity of Symptoms		p value	
	n	%	*High vs Middle*	*High vs Low*
Low-Intensity	460	100		
Middle-Intensity	540	0	<0.05*	<0.05*
High-intensity	10	0		

Note: *n*= Absolute number of subjects; %= percentage; *= difference between High to middle or High to Low intensity of exercise.

Discussion

This study aimed to investigate the impact of the level and intensity of physical activity on COVID-19 outcome and its correlation with co-morbidities and post-illness sequel. The findings showed that regular physical activity, particularly of moderate to high intensity, can reduce the need for intensive medical care in SARS-CoV-2 infection by 27.25% and decrease the incidence of comorbidities by 67.7 %. Sedentary behavior was found to be strongly associated with inflammatory conditions and post-disease sequel. These results emphasize the importance of maintaining an active lifestyle to improve general health and resilience to infectious diseases such as COVID-19.

This study aimed to investigate the impact of the level and intensity of physical activity on COVID-19 outcome and its correlation with co-morbidities and post-illness sequel. The findings showed that regular physical activity, particularly of moderate to high intensity, can reduce the need for intensive medical care in SARS-CoV-2 infection by 27.25% and decrease the incidence of comorbidities by 67.7 %. Sedentary behavior was found to be strongly associated with inflammatory conditions and post-disease sequel. These results emphasize the importance of maintaining an active lifestyle to improve general health and resilience to infectious diseases such as COVID-19.

Previous studies have shown that performing 150 minutes of moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity aerobic physical activity per week, or a combination of both, can reduce the prevalence of hospitalization for COVID-19 by 34.3% (24). Our own data showed a 27.5% reduction in intensive medical care due to SARS-CoV-2 infection, which agrees with the previous study. However, we found no significant differences in the prevalence of intubation, oxygen therapy, symptoms, or length of hospital stay between physically active and inactive patients, consistent with our findings.

The protective mechanisms of physical activity against COVID-19 may be related to the enhancement of the immune system response, including enhancement of immunoglobulin, neutrophils, natural killer cells, cytotoxic T cells, and cell recirculation B immature (15, 17, 25–27). Additionally, regular exercise can prevent and treat various complications associated with COVID-19, such as cardiac, neurological, and metabolic disorders, and has a positive effect on the renin-angiotensin system (28–31).

Although high-intensity exercise has been shown to have a positive effect on inflammatory factors in obese conditions (32), studies have shown that eight weeks of high-intensity interval training (HIIT) led to a significant decrease in interleukin -6 plasma (IL-6). 6) and tumor necrosis factor alpha (TNF-α) in obese male Wistar rats with NAFLD, which could be detrimental to this disease (32). Other studies have compared the effects of high and moderate intensity exercise on inflammatory factors (33). De Souza et al. found that a single session of high-intensity intervals could decrease the interferon-gamma/interleukin-4 (IFN-γ/IL-4) ratio, indicating an anti-inflammatory response, without altering mucosal immune system function or lipid peroxidation. However, a bout of continuous moderate-intensity exercise induced changes in the cytokine pattern associated with increased cellular immune function (34).

Long-term high-intensity interval training (HIIT) at 90% of maximum heart rate, 3 times per week, was found to increase TNF-α levels in overweight/obese adults, whereas continuous moderate intensity at 70% of maximum heart rate, 5 times per week, decreased TNF-α level in the same population (32). In healthy young men, continuous moderate-intensity training was found to improve biomarkers of immune function, while HIIT induces an inflammatory response and suppresses immune functions (35, 36). These controversial findings suggest caution in prescribing exercise before and after COVID-19 and during the pandemic.

The present study does not agree with the idea of the open immunological window, which did not have strong support (37). Other studies consistently showed a positive effect of HIIT or other high-intensity exercises on the immune system (9, 33, 38). However, it is suggested here that moderate or intense exercise may be better than low intensity exercise, and higher intensity may provide additional protection against SARS-CoV-2 infection.

Taken together, the data presented here indirectly support the idea that enhancement of all systems in response to exercise is the likely mechanism for the observed protection against SARS-CoV-2 infection.

What does this article add?

First, the findings have added to the growing body of evidence supporting the positive effects of exercise on overall health outcomes. As an accessible and inexpensive intervention, exercise can improve various body systems affected by COVID-19, including the respiratory, kidney, blood, and vascular systems. Additionally, exercise has been shown to have anti-inflammatory effects, which is particularly important given the inflammatory disease caused by COVID-19 and the prevalence of underlying inflammatory diseases such as obesity, diabetes, cancer, and heart and lung disease. Second, the study has reinforced the importance of exercise in reducing the risk of serious disease. By examining the impact of exercise on various medical conditions that can exacerbate the effects of SARS-CoV-2, such as cardiovascular disease, diabetes, and obesity, the study provided evidence of the positive impact of exercise on these conditions and potential benefits for the results of COVID-19. Third, the study has shown the role of exercise intensity in response to disease. While the importance of exercise in protecting against COVID-19 is widely accepted, this study provides evidence that higher-intensity exercise may be more effective in providing protection against the virus. The findings suggest that the stimuli of regular intervals of moderate to high intensity exercise may provide greater protection and better responses of the body to disease, leading to a lower risk of severe disease.

Limitations

Our study has has limitations. The use of an online survey may introduce selection bias, as health-conscious and physically active individuals might be more likely to participate. Additionally, the self-reported nature of the data may result in recall bias. The cross-sectional design of the study also limits causal inferences.

Conclusion

In conclusion, our findings suggest that regular physical activity, especially at higher intensities, can reduce the risk of severe COVID-19 outcomes. Promoting physical activity should be a key component of public health strategies to enhance resilience against infectious diseases like COVID-19. Future research should investigate the underlying mechanisms of these benefits and establish guidelines for safe exercise practices during pandemics. These findings are especially significant since they were observed in the population most vulnerable to SARS-CoV-2, the elderly. Therefore, regular physical activity can be considered an important tool in the prevention and control of COVID-19, and the intensity of the exercise can play a fundamental role in determining its effectiveness. As recommendations, to determine the type, test the intensity, and determinate the impact of the exercise over infection, and the skill of the immune system in fight against the infection can provide several significant contributions to our understanding of the role of exercise in preventing and mitigating the COVID-19.

Ethical Approval:

This study will follow the guidelines established in resolution 466/2012 and the Helsinki Treaty (2000), of which Brazil is a signatory. It is important to note that the ethical approval was granted under CAAE number 35349520.5.0000.5010 by the Ethics Council of the Federal University of Acre on November 13, 2020.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.

2.

3.

References

1. Sismondo S. COVID-19. *Soc Stud Sci*. Published online 2020. doi:10.1177/0306312720918403
2. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Heal*. Published online 2020. doi:10.1111/tmi.13383
3. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. Published online 2020. doi:10.1016/j.ijsu.2020.02.034
4. Zheng C, Wang J, Guo H, et al. Risk-adapted Treatment Strategy For COVID-19 Patients. *Int J Infect Dis*. Published online 2020. doi:10.1016/j.ijid.2020.03.047
5. Baron DM, Franchini M, Goobie SM, et al. Patient blood management during the COVID–19 pandemic: a narrative review. *Anaesthesia*. Published online 2020. doi:10.1111/anae.15095
6. Peng YD, Meng K, Guan HQ, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xin Xue Guan Bing Za Zhi*. Published online 2020. doi:10.3760/cma.j.cn112148-20200220-00105
7. Mora-Rodriguez R, Fernandez-Elias VE, Morales-Palomo F, Pallares JG, Ramirez-Jimenez M, Ortega

JF. Aerobic interval training reduces vascular resistances during submaximal exercise in obese metabolic syndrome individuals. *Eur J Appl Physiol*. Published online 2017. doi:10.1007/s00421-017-3697-7

8. Deye, N., Vincent, F., Michel, P., Ehrmann, S., Da Silva, D., Piagnerelli, M., … Laterre, P.-F. (2016). Changes in cardiac arrest patientsâ€TM temperature management after the 2013 â€œTTMâ€• trial: Results from an international survey. Annals of Intensive 6(1). http://doi.org/10.1186/s13613-015-0104-6, Al-Hussaini, M., & Mustafa, S. (2016). Adolescentsâ€TM knowledge and awareness of diabetes mellitus in Kuwait. Alexandria Journal of Medicine, 52(1) 61–66. http://doi.org/10.1016/j.ajme.2015.04.001, Pollach, G., Brunkhorst, F., Mipando, M., Namboya, F., Mndolo, S., & Luiz, T. (2016). The â€œfirst digit lawâ€• â€" A hypothesis on its possible impact on medicine and development aid. Medical Hypotheses, 97 102–106. http://doi.org/10.1016/j.mehy.2016.10.021, et al. Physiological and therapeutic effects of carnosine on cardiometabolic risk and disease. *Amino Acids*. Published online 2016. doi:10.1007/s00726-016-2208-1
9. Belviranli M, Okudan N, Kabak B. The Effects of Acute High-Intensity Interval Training on Hematological Parameters in Sedentary Subjects. *Med Sci*. 2017;5(3):15. doi:10.3390/medsci5030015
10. Song JK, Stebbins CL, Kim TK, Kim HB, Kang HJ, Chai JH. Effects of 12 weeks of aerobic exercise on body composition and vascular compliance in obese boys. *J Sports Med Phys Fitness*. 2012;52(5):522-529. doi:10.1080/02640414.2010.525519
11. Zhangfu Fang, Yi F, Wu K, et al. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. Published online 2020. doi:10.3760/cma.j.issn.0254-6450.2020.02.003
12. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases - Myokine regulation. *Nat Rev Rheumatol*. Published online 2015. doi:10.1038/nrrheum.2014.193
13. Samut G, Dinçer F, Özdemir O. The effect of isokinetic and aerobic exercise on serum interleukin-6 and tumor necrosis factor alpha levels, pain and functional activity in patients with knee osteoarthritis. *Mod Rheumatol*. Published online 2015:1-19. doi:10.3109/14397595.2015.1038425
14. Graham TE. Caffeine and exercise metabolism, endurance and performance. *Sport Med*. Published online 2001. doi:10.2165/00007256-200131110-00002
15. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Heal Sci*. Published online 2019. doi:10.1016/j.jshs.2018.09.009
16. Uysal N, Yuksel O, Kizildag S, et al. Regular aerobic exercise correlates with reduced anxiety and incresed levels of irisin in brain and white adipose tissue. *Neurosci Lett*. Published online 2018. doi:10.1016/j.neulet.2018.04.023
17. Suzuki K. Chronic inflammation as an immunological abnormality and effectiveness of exercise. *Biomolecules*. Published online 2019. doi:10.3390/biom9060223
18. Kohut ML, Lee W, Martin A, et al. The exercise-induced enhancement of influenza immunity is mediated in part by improvements in psychosocial factors in older adults. *Brain Behav Immun*. Published online 2005. doi:10.1016/j.bbi.2004.12.002
19. Wiecek M, Szymura J, Maciejczyk M, Kantorowicz M, Szygula Z. Acute Anaerobic Exercise Affects the Secretion of Asprosin, Irisin, and Other Cytokines – A Comparison Between Sexes. *Front Physiol*. 2018;9:1782. doi:10.3389/fphys.2018.01782
20. Simpson RJ, Campbell JP, Gleeson M, et al. Can exercise affect immune function to increase susceptibility to infection? *Exerc Immunol Rev*. Published online 2020.
21. Leal LG, Lopes MA, Batista ML. Physical exercise-induced myokines and muscle-adipose tissue crosstalk: A review of current knowledge and the implications for health and metabolic diseases. *Front Physiol*. Published online 2018. doi:10.3389/fphys.2018.01307
22. Phillips C, Baktir MA, Srivatsan M, Salehi A. Neuroprotective effects of physical activity on the brain: A closer look at trophic factor signaling. *Front Cell Neurosci*. Published online 2014. doi:10.3389/fncel.2014.00170
23. Li DJ, Li YH, Yuan H Bin, Qu LF, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metabolism*. Published online 2017. doi:10.1016/j.metabol.2016.12.003
24. de Souza FR, Motta-Santos D, Santos Soares D dos, et al. Physical Activity Decreases the Prevalence of COVID-19-associated Hospitalization: Brazil EXTRA Study. *medRxiv*. Published online 2020. doi:10.1101/2020.10.14.20212704
25. Neville V, Gleeson M, Folland JP. Salivary IgA as a risk factor for upper respiratory infections in elite professional athletes. *Med Sci Sports Exerc*. Published online 2008. doi:10.1249/MSS.0b013e31816be9c3
26. Gill SK, Teixeira A, Rama L, et al. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. *Exerc Immunol Rev*. 2015;21:114-128. http://www.ncbi.nlm.nih.gov/pubmed/25830597
27. Pedersen BK, Steensberg A, Fischer C, Keller C, Ostrowski K, Schjerling P. Exercise and cytokines with particular focus on muscle-derived il-6. *Exerc Immunol Rev*. 2001;7:18-31. doi:papers3://publication/uuid/29CD365A-35A8-4472-A41B-D896ED516194

28. Cárdenas RN, Freire IDA, Pumariega YN, et al. Malaria and Anemia Cause Impairments in Athletic Performance of Young Female Athletes Even after 1 , 5 Year of Clinical Healing. 2019;9(1):17-23. doi:10.5923/j.sports.20190901.03
29. Malm C, Jakobsson J, Isaksson A. Physical Activity and Sports-Real Health Benefits: A Review with Insight into the Public Health of Sweden. *Sports*. 2019;7(127). doi:10.3390/sports7050127
30. Fuchs R. Physical Activity and Health. In: *International Encyclopedia of the Social & Behavioral Sciences: Second Edition*. ; 2015. doi:10.1016/B978-0-08-097086-8.14115-7
31. Melo CM, Alencar Filho AC, Tinucci T, Mion D, Forjaz CLM. Postexercise hypotension induced by low-intensity resistance exercise in hypertensive women receiving captopril. *Blood Press Monit*. Published online 2006. doi:10.1097/01.mbp.0000218000.42710.91
32. TaheriChadorneshin H, Cheragh-Birjandi S, Goodarzy S, Ahmadabadi F. The impact of high intensity interval training on serum chemerin, tumor necrosis factor-alpha and insulin resistance in overweight women. *Obes Med*. 2019;14(January):100101. doi:10.1016/j.obmed.2019.100101
33. Lira FS, dos Santos T, Caldeira RS, et al. Short-term high- and moderate-intensity training modifies inflammatory and metabolic factors in response to acute exercise. *Front Physiol*. 2017;8(OCT). doi:10.3389/fphys.2017.00856
34. de Souza DC, Matos VAF, dos Santos VOA, et al. Effects of high-intensity interval and moderate-intensity continuous exercise on inflammatory, leptin, IgA, and lipid peroxidation responses in obese males. *Front Physiol*. 2018;9(MAY):1-9. doi:10.3389/fphys.2018.00567
35. KHAMMASSI M, OUERGHI N, SAID M, et al. CONTINUOUS MODERATE-INTENSITY BUT NOT HIGH- INTENSITY INTERVAL TRAINING IMPROVES IMMUNE FUNCTION BIOMARKERS IN HEALTHY YOUNG MEN. 2018;00(00).
36. Zwetsloot KA, John CS, Lawrence MM, Battista RA, Shanely RA. High-intensity interval training induces a modest systemic inflammatory response in active, young men. *J Inflamm Res*. 2014;7(1):9-17. doi:10.2147/JIR.S54721
37. 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*. Published online 2018. doi:10.3389/fimmu.2018.00648
38. Mendes R, Sousa N, Themudo-Barata JL, Reis VM. High-intensity interval training versus moderate-intensity continuous training in middle-aged and older patients with type 2 diabetes: A randomized controlled crossover trial of the acute effects of treadmill walking on glycemic control. *Int J Environ Res Public Health*. Published online 2019. doi:10.3390/ijerph16214163