European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2024 vol. 13, ISSUE N. 2, May-August

PHYSICAL ACTIVITY AND BRAIN HEALTH: "MENS SANA IN CORPORE SANO"

F. Pandolfi[1*] and R. Padula[2]

[1] Allergy and Clinical Immunology, Fondazione Policlinico Universitario A, Gemelli IRCCS, Catholic University, Rome, Italy;
[2] Clinical and experimental biology, University of Foggia, Italy.

Correspondence to:
Franco Pandolfi,
Allergy and Clinical Immunology,
Fondazione Policlinico Universitario A. Gemelli IRCCS,
Catholic University,
00168 Rome, Italy.
e-mail: franco.pandolfi@unicatt.it

ABSTRACT

Physical activity has beneficial effects for the health of the entire body, including the central nervous system (CNS). Periodic physical exercises and consistent physical activity leads to increased cardiovascular endurance and capacity, enhanced muscular tone, increased muscular strength, improved metabolism, decreased adiposity, and additionally, strengthens the immune system, making the body less vulnerable to certain diseases. Recently, it was noticed that in physically trained subjects, the number of leukocytes was increased; this contributed to greater resistance to infections by microorganisms. An important immune protein that increases in individuals who are physically active is interleukin-1 (IL-1), which is responsible for the feverish effect, and is primarily produced by monocytic cells and lymphocytes.

KEYWORDS: *physical activity, sport, immunity, IL-1, neurodegenerative, health, CNS*

INTRODUCTION

It is well known that physical activity is good for the health of the entire body (1). Periodic physical exercises and consistent physical activity has benefits for our health by positively affecting cardiovascular and muscular strength and metabolism, by decreasing adiposity, and additionally, by strengthening the immune system, making the body less vulnerable to certain diseases (2).

During physical activity, fatigue can occur with activation of the sympathetic system and the hypothalamus, resulting in the release of catabolic products and inflammatory molecules, including cytokines (3). Athletes who engage in intense and prolonged physical exercise have altered neuropsychological conditions and experience the loss of bodily fluids with sweating. Intense exercise can cause the release of cortisol which is an immunosuppressive molecule, and this effect can be damaging. On the other hand, it is known that physical activity improves cognitive and brain functions and moderate exercise can strengthen the immune system (4).

The impacts of physical activity and exercise on the immune system

Starting from the general concept that white blood cells defend the body and immunize it from infectious diseases, it is easy to understand that a physiological increase of these cells can strengthen the immune system (5). It has been seen that the number of leukocytes was increased in physically trained subjects; this contributes to a greater resistance to infections by microorganisms (6). The reason for the increase in leukocytes is not clear, but there are some possible

Received: 28 March, 2024
Accepted: 20 May, 2024

2974-6345 (2024)

hypotheses: a) physical exercise causes a loss of extracellular fluids, resulting in a greater concentration of blood cells, and therefore, a greater number of both leukocytes and red blood cells; b) after physical exercise, there is an increase in the levels of catecholamines and adrenaline, which regulate the number of leukocytes in the blood circulation; c) the production of some hormones during physical activity can affect the pool of leukocytes in circulation (7).

The increase in white blood cells plays an important role in the body's defense against infections, although apparently the leukocytes of athletes do not appear functionally indistinguishable from those of sedentary individuals (8). The increase in leukocytes seems to affect T lymphocytes (anti-viral and anti-tumor) more than B lymphocytes, which protect from bacterial infections (9). Another important immune element that increases in individuals who are physically active is interleukin-1 (IL-1), a protein produced by some leukocytes that is responsible for mediating fever and the inflammatory response (10).

IL-1 causes fever in humans and is responsible for producing heat in cold-blooded animals (11). Human fever is an immune reaction that serves to protect the body from insults, such as bacterial and viral infections. During the inflammatory reaction, IL-1 is produced by macrophagic cells and increases inflammation, which is detrimental to the body (12). Elevated levels of IL-1 produce fever, and a subsequent drop in blood iron levels, a reaction that protects the body from microbial invasion (13). IL-1 activates leukocytes such as lymphocytes and macrophages, which are responsible for the immune reaction.

The increase in temperature due to exercise stimulates the production of IL-1 which mediates the immune response (14). Hyperthermia after exercise depends on both the metabolic activity of the muscles and the production of IL-1 (15). In general, when the leukocytes of athletes are stimulated *in vitro*, they produce more IL-1 than those who do not participate in sports, and athletes are less likely to experience states of depression (16). Again, in the laboratory, by bringing the peripheral blood leukocytes of sedentary individuals into contact with the serum of athletes, cellular stimulation and greater reactivity against microorganisms were obtained (17).

IL-1 is an endogenous mediator of fever and belongs to the cytokine family composed of pleiotropic molecules that are involved in many pathological processes (18). Animals treated with IL-1 were seen to develop hypotension caused by the induction of nitric oxide (NO) and decreased systolic blood pressure (19). The cytokine IL-2 (or T cell growth factor) also causes fever with an indirect mechanism on the hypothalamus, unlike IL-1 (20). IL-2 induces IL-1, tumor necrosis factor (TNF), and interferon gamma (IFN-γ), but not the marker C-reactive protein which is induced by IL-1 (21).

Physical training with an immune stimulus can be part of anti-tumor therapy without harmful effects on the body compared to conventional anti-tumor therapies which cause inflammation and immunodepression. Physical exercises reduce pro-inflammatory markers such as C-reactive protein and TNF, a potent inducer of inflammation and mediator of neuroinflammation, without inhibiting natural killer (NK) cells and cytotoxic T lymphocytes (22). However, this data still needs to be confirmed by future studies.

Different studies highlight the stimulus, albeit mild, of physical activity on NK cells, which are important for the immune response against malignant tumor diseases (23). NK cells are circulating lymphocytes that increase after physical exercise and are involved in the anti-tumor immune response with a cytotoxic effect (24). In addition, it was noted that individuals (not professional athletes) who practiced periodic exercises had a longer life expectancy than those who did not partake in physical activity (25).

The cytokines and chemokines that are involved in inflammation and could be regulated by physical activity are shown below (26) (Table I).

Table I. *Cytokines and chemokines mediating inflammation that could be regulated by physical activity.*

Cytokines:	Interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor (TNF), interferon gamma (IFN-γ)
Chemokines:	monocyte chemoattractant protein (MCP)-1 and MCP-3

The belief that exposing the body to cold can lower its resistance to infections finds a scientific explanation in the fact that certain viruses and bacteria that habitually and harmlessly live in the organism become pathogenic when body temperature is lowered (27). Experiments and studies have clearly demonstrated that recurring physical exercises reduce the risk of cardiovascular disease and contribute to longevity. But not only that, exercise helps to keep body weight under control, increase energy, and reduce stress (28).

If adrenaline is injected into a resting individual in quantities equal to those produced by an athlete after effective physical exercise, the increase in the number of leukocytes will be the same as that of the athlete (29). This means that adrenaline, which is also one of the compounds responsible for growth (GH), is stimulated by physical activity (30). This,

as is known, is co-responsible, together with other compounds, for the production of antibodies, rejection reactions, and the increase in neutrophils (31).

To date, there is no clinical evidence to demonstrate that physical exercise has anti-tumor effects, but what is certain is that physical activity increases NK cells which are capable of killing tumor cells. When the NK cells of an athlete are collected after intense physical exercise and put into contact with tumor cells *in vitro*, there is a greater degree of killing by the leukocytes compared to NK cells derived from individuals who do not practice sport (32). Several expert scientists, specializing in sport and immunity, have stated that vigorous and periodic physical activity provides the body with a natural defense, protecting individuals against ageing and cardiac ischemia and its consequences (33).

The impacts of physical activity and exercise on brain health

Physical activity has beneficial effects for the brain and the central nervous system (CNS) (34). Research has shown that exercise positively affects cognition, and that lack of physical activity is a risk factor for many diseases, including cardiovascular pathologies and neurodegenerative disorders (35). The immune-modifying properties of physical activity and exercise have anti-inflammatory effects throughout the entire body, including the CNS (36).

Reactive oxygen species (ROS) are produced by muscles during physical exercise and stimulate the transport of glucose necessary for an increase in metabolism (37). In the brain, there is an increase in metabolic activity as blood flow increases and ROS are produced by neuronal cells (38). The production of ROS occurs mainly in the mitochondria, and their increase could contribute to ageing (39).

A sedentary lifestyle is damaging for bodily health and cognitive and brain functions. Studies on physical activity in the elderly have shown that neurocognitive activity is enhanced by daily exercise (40). The benefits of physical activity are undeniable and clear, however, the exact mechanisms by which it benefits brain health are not completely understood.

The neurological effects of physical activity have been evaluated with magnetic resonance imaging (MRI) and neurocognitive measures (41). It seems that physical activity leads to an increase in neurotrophic factor, which helps to maintain brain volume and provide protection for neurons, and affects lipid transport and amyloid load, which can lower the risk of dementia and prevent the development of neurodegenerative diseases (42). However, it is still unclear if physical activity affects amyloid and tau protein metabolism that occurs in Alzheimer's disease.

The benefits of exercise were also found to be relevant in children, where physical activity has been correlated with improvements in attention and cognition (43). Regular physical activity in children has positive effects on brain structure and function, enhancing attention, learning, and memory.

Furthermore, physical activity is important to prevent obesity, which is associated with an increased risk of chronic diseases, including neurological disorders, such as dementia (44). Evidence shows that obesity is associated with cognitive deficits and functional and structural changes in the brain, as well as being a risk factor for the development of Alzheimer's disease (45).

CONCLUSIONS

When practiced regularly, moderate physical activity has many beneficial effects for the body and can help prevent the onset of vascular, inflammatory and autoimmune, and neurological diseases. In modern times, life is often sedentary which can be harmful to health, and exercise should be stressed as an important habit to maintain health of the entire body, including the brain. Further studies should continue to clarify the mechanisms by which physical activity affects the immune and neurological systems.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Waddington GS. Covid-19, mental health and physical activity. *Journal of Science and Medicine in Sport*. 2021;24(4):319. doi:https://doi.org/10.1016/j.jsams.2021.02.009
2. Garber CE, Blissmer B, Deschenes MR, et al. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults. *Medicine & Science in Sports & Exercise*. 2011;43(7):1334-1359. doi:https://doi.org/10.1249/mss.0b013e318213fefb

3. Exercise and the stress system. Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP. *Hormones (Athens)*. 2005;4(2):73-89.
4. Jopowicz A, Wiśniowska J, Tarnacka B. Cognitive and Physical Intervention in Metals' Dysfunction and Neurodegeneration. *Brain Sciences*. 2022;12(3):345. doi:https://doi.org/10.3390/brainsci12030345
5. Kumar S, Gupta E, Kaushik S, Jyoti A. Neutrophil Extracellular Traps: Formation and Involvement in Disease Progression. *Iranian journal of allergy, asthma, and immunology*. 2018;17(3):208-220.
6. Benoni G, Bellavite P, Adami A, et al. Changes in Several Neutrophil Functions in Basketball Players Before, During and After the Sports Season. *International Journal of Sports Medicine*. 1995;16(01):34-37. doi:https://doi.org/10.1055/s-2007-972960
7. Zouhal H, Jacob C, Delamarche P, Gratas-Delamarche A. Catecholamines and the effects of exercise, training and gender. *Sports medicine (Auckland, NZ)*. 2008;38(5):401-423. doi:https://doi.org/10.2165/00007256-200838050-00004
8. Quero CD, Manonelles P, Fernández M, et al. Differential Health Effects on Inflammatory, Immunological and Stress Parameters in Professional Soccer Players and Sedentary Individuals after Consuming a Synbiotic. A Triple-Blinded, Randomized, Placebo-Controlled Pilot Study. *Nutrients*. 2021;13(4):1321. doi:https://doi.org/10.3390/nu13041321
9. Deng Z, Zhang Q, Zhao Z, et al. Crosstalk between immune cells and bone cells or chondrocytes. *International Immunopharmacology*. 2021;101(Pt A):108179. doi:https://doi.org/10.1016/j.intimp.2021.108179
10. Meier TB, Guedes VA, Smith EG, et al. Extracellular vesicle-associated cytokines in sport-related concussion. *Brain, Behavior, and Immunity*. 2022;100:83-87. doi:https://doi.org/10.1016/j.bbi.2021.11.015
11. Mantovani A, Dinarello CA, Molgora M, Garlanda C. IL-1 and related cytokines in innate and adaptive immunity in health and disease. *Immunity*. 2019;50(4):778-795. doi:https://doi.org/10.1016/j.immuni.2019.03.012
12. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720-3732. doi:https://doi.org/10.1182/blood-2010-07-273417
13. Dinarello CA, Bunn PA Jr. Fever. *Seminars in oncology*. 1997;24(3):288-298.
14. Pedersen B, Bruunsgaard H, Klokker M, et al. Exercise-Induced Immunomodulation - Possible Roles of Neuroendocrine and Metabolic Factors. *International Journal of Sports Medicine*. 1997;18(S 1):S2-S7. doi:https://doi.org/10.1055/s-2007-972695
15. Rhind SG, Gannon GA, Shephard RJ, Buguet A, Shek PN, Radomski MW. Cytokine induction during exertional hyperthermia is abolished by core temperature clamping: neuroendocrine regulatory mechanisms. *International Journal of Hyperthermia*. 2004;20(5):503-516. doi:https://doi.org/10.1080/02656730410001670651
16. Kurosawa N, Shimizu K, Seki K. The development of depression-like behavior is consolidated by IL-6-induced activation of locus coeruleus neurons and IL-1β-induced elevated leptin levels in mice. *Psychopharmacology*. 2015;233(9):1725-1737. doi:https://doi.org/10.1007/s00213-015-4084-x
17. Butcher LR, Thomas A, Backx K, Roberts A, Webb R, Morris K. Low-Intensity Exercise Exerts Beneficial Effects on Plasma Lipids via PPARgamma. *Medicine & Science in Sports & Exercise*. 2008;40(7):1263-1270. doi:https://doi.org/10.1249/mss.0b013e31816c091d
18. Dinarello CA. Interleukin-1. *Clinical Infectious Diseases*. 1984;6(1):51-95. doi:https://doi.org/10.1093/clinids/6.1.51
19. Blanco FJ, Lotz M. IL-1-Induced Nitric Oxide Inhibits Chondrocyte Proliferation via PGE2. *Experimental Cell Research*. 1995;218(1):319-325. doi:https://doi.org/10.1006/excr.1995.1161
20. Anisman H, Kokkinidis L, Borowski T, Merali Z. Differential effects of interleukin (IL)-1β, IL-2 and IL-6 on responding for rewarding lateral hypothalamic stimulation. *Brain Research*. 1998;779(1-2):177-187. doi:https://doi.org/10.1016/s0006-8993(97)01114-1
21. Heaton KM, Ju G, Grimm EA. Induction of lymphokine-activated killing with reduced secretion of interleukin-1β, tumor necrosis factor-α, and interferon-γ by interleukin-2 analogs. *Annals of surgical oncology*. 1994;1(3):198-203. doi:https://doi.org/10.1007/bf02303524
22. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *Journal of Applied Physiology*. 2005;98(4):1154-1162. doi:https://doi.org/10.1152/japplphysiol.00164.2004
23. Dayanc BE, Beachy SH, Ostberg JR, Repasky EA. Dissecting the role of hyperthermia in natural killer cell mediated anti-tumor responses. *International Journal of Hyperthermia*. 2008;24(1):41-56. doi:https://doi.org/10.1080/02656730701858297

24. Nieman DC, Henson DA, Gusewitch G, et al. Physical activity and immune function in elderly women. *Medicine & Science in Sports & Exercise*. 1993;25(7):823-831. doi:https://doi.org/10.1249/00005768-199307000-00011
25. Zheng X, Chen S. [Life expectancy of people with physical disabilities in China]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2011;32(7):693-696.
26. Santos TPS, Pereira MM, Schinoni MI, et al. Atherogenic cytokines and chemokines in chronic hepatitis C are not associated with the presence of cardiovascular diseases. *Cytokine*. 2019;115:24-31. doi:https://doi.org/10.1016/j.cyto.2018.12.005
27. Boonarkart C, Suptawiwat O, Sakorn K, Puthavathana P, Auewarakul P. Exposure to cold impairs interferon-induced antiviral defense. *Archives of Virology*. 2017;162(8):2231-2237. doi:https://doi.org/10.1007/s00705-017-3334-0
28. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nature Reviews Cardiology*. 2018;15(12):731-743. doi:https://doi.org/10.1038/s41569-018-0065-1
29. Landmann R. Beta-adrenergic receptors in human leukocyte subpopulations. *European Journal of Clinical Investigation*. 1992;22 Suppl 1:30-36.
30. Kon M, Ikeda T, Homma T, Akimoto T, Suzuki Y, Kawahara T. Effects of Acute Hypoxia on Metabolic and Hormonal Responses to Resistance Exercise. *Medicine & Science in Sports & Exercise*. 2010;42(7):1279-1285. doi:https://doi.org/10.1249/mss.0b013e3181ce61a5
31. Schneider BS, Tiidus PM. Neutrophil Infiltration in Exercise-Injured Skeletal Muscle. *Sports Medicine*. 2007;37(10):837-856. doi:https://doi.org/10.2165/00007256-200737100-00002
32. Cho E, Stampley J, Wall R, et al. Acute Exercise Increases NK Cell Mitochondrial Respiration and Cytotoxicity against Triple Negative Breast Cancer Cells under Hypoxic Conditions. *Medicine and Science in Sports and Exercise*. 2023;55(12):2132-2142. doi:https://doi.org/10.1249/mss.0000000000003250
33. Booth FW, Roberts CK, Laye MJ. Lack of Exercise Is a Major Cause of Chronic Diseases. *Comprehensive Physiology*. 2012;2(2). doi:https://doi.org/10.1002/cphy.c110025
34. Yan L, Wei J, Yang F, et al. Physical Exercise Prevented Stress-Induced Anxiety via Improving Brain RNA Methylation. *Advanced Science*. 2022;9(24):2105731. doi:https://doi.org/10.1002/advs.202105731
35. Cunningham C, O' Sullivan R, Caserotti P, Tully MA. Consequences of physical inactivity in older adults: A systematic review of reviews and meta-analyses. *Scandinavian Journal of Medicine & Science in Sports*. 2020;30(5):816-827. doi:https://doi.org/10.1111/sms.13616
36. de Almeida EJR, Ibrahim HJ, Chitolina Schetinger MR, de Andrade CM, Cardoso AM. Modulation of Inflammatory Mediators and Microglial Activation Through Physical Exercise in Alzheimer's and Parkinson's Diseases. *Neurochemical Research*. 2022;47(11). doi:https://doi.org/10.1007/s11064-022-03713-x
37. Merry TL, McConell GK. Do Reactive Oxygen Species Regulate Skeletal Muscle Glucose Uptake During Contraction? *Exercise and Sport Sciences Reviews*. 2012;40(2):102-105. doi:https://doi.org/10.1097/jes.0b013e318245837b
38. Mattos JD, Campos MO, Fábio M, et al. Human brain blood flow and metabolism during isocapnic hyperoxia: the role of reactive oxygen species. *The Journal of physiology*. 2019;597(3):741-755. doi:https://doi.org/10.1113/jp277122
39. Qaisar R, Bhaskaran S, Van Remmen H. Muscle fiber type diversification during exercise and regeneration. *Free Radical Biology and Medicine*. 2016;98:56-67. doi:https://doi.org/10.1016/j.freeradbiomed.2016.03.025
40. Nooijen CFJ, Blom V, Ekblom Ö, Ekblom MM, Kallings LV. Improving office workers' mental health and cognition: a 3-arm cluster randomized controlled trial targeting physical activity and sedentary behavior in multi-component interventions. *BMC Public Health*. 2019;19(1). doi:https://doi.org/10.1186/s12889-019-6589-4
41. Johansson ME, Cameron IGM, van der Kolk NM, et al. Aerobic exercise alters brain function and structure in Parkinson's disease a randomized controlled trial. *Annals of Neurology*. 2021;91(2). doi:https://doi.org/10.1002/ana.26291
42. Wang R, Holsinger RMD. Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer's dementia. *Ageing Research Reviews*. 2018;48:109-121. doi:https://doi.org/10.1016/j.arr.2018.10.002
43. Bidzan-Bluma I, Lipowska M. Physical Activity and Cognitive Functioning of Children: A Systematic Review. *International Journal of Environmental Research and Public Health*. 2018;15(4). doi:https://doi.org/10.3390/ijerph15040800

44. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *The Lancet*. 2020;396(10248):413-446. doi:https://doi.org/10.1016/S0140-6736(20)30367-6

45. Sui SX, Pasco JA. Obesity and Brain Function: The Brain–Body Crosstalk. *Medicina*. 2020;56(10):499. doi:https://doi.org/10.3390/medicina56100499