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Exploring the Potential of Non-Pharmacological Therapeutic Interventions to Promote Resilience of the Human Immune System. Part I: Biological Foundations and Structured Exercise

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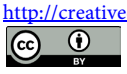

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Abstract

The human immune system relies on the dynamic, complex integration of various cells, proteins, tissues, and organs which work together in concert with the nervous system to recognize, adapt to, and neutralize pathogens. In parallel, there is a neurobiological network of systems which function to react and adapt to changes in the environment to restore and maintain homeostasis in the service of survival. Our dependency on the stability and resilience of this collective ecosystem of responses is amplified during times of heightened risk for illness and when healthcare systems are in fluctuating states of excessive strain, such as in the time of the COVID-19 pandemic of 2020. The nature of the adaptability of these systems is called into question when confronted with novel viruses that humans have no natural immunity against, and likewise when interfacing with future variants in transition through and into the endemic phase of such outbreaks. Nuanced multidisciplinary investigations of the pathways in which positive changes can be affected and subsequent advantages conferred are warranted for consideration in virtually all domains of healthcare, especially at times when a viral outbreak is uncontained. The following is a series of biological considerations with implications that warrant further discussion and potential extrapolation for individualized employment by healthcare and public health professionals in efforts to combat both current and future crises as they may arise.

Subject Areas

Biophysics, Immunology

Keywords

Immunity, Pandemic, Neuroimmunology, Non-Pharmacological Interventions, Structured Exercise, Immune Function, Neurobiology, COVID-19

1. Introduction

Since the beginning of recorded history, humankind has faced transformative adversity in the form of widespread viral contagions, leading to well-documented global pandemics and even civilizational catastrophe, with unique features and characteristics relative to their respective pathoetiology and course of action. These events have amounted to enormous physical, psychological, economic, organizational, and societal influences distinct in their time, summating as tremendous adversity. Such crises have had an incalculable impact on the course of history, with some of the most alarming statistics arising in the form of mortality rates, disability, and gross economic disturbances which disrupt food security, financial stability, and psychological equilibrium for innumerable individuals and families. Such events have coalesced into monumental burdens on human civilizations across our known history. So too, now humanity has encountered the novel coronavirus SARS-COVID-19 (abbreviated as COVID-19) as a viral contagion against which no prior natural immunity has existed, erupting in Wuhan, China in late 2019. The virus was recognized thereafter by the World Health Organization (WHO) as a Public Health Emergency of International Concern on January 30th, 2020, and was formally declared a global pandemic as of March 11, 2020 [1] [2]. This development constitutes a threat civilization faces indefinitely, with heightened precautionary measures warranted until a time when the spread of the virus is sufficiently controlled. The successful development and deployment of preventative and interventional measures for widespread utilization to combat the pathogen worldwide is essential for mitigating adverse outcomes while transitioning into the endemic phase of the current pandemic and beyond.

Over time, we have learned invaluable lessons from previous such emergencies in the form of prevention strategies for inhibiting viral spread, the necessity of effective educational public outreach, risk mitigation practices, managing the condition of positive diagnoses as they have arisen, and preserving life where possible. This notwithstanding, never in recorded history has a crisis the magnitude of the COVID-19 pandemic occurred in a time when the world is so inextricably interconnected, and wherein beliefs about which pathways of action to pursue are so intensely divided. To date, the scale and magnitude of the current crisis have been well documented on various platforms, with a staggering impact observed in many cities, states, and countries—perhaps most alarmingly in the United States [3]. However, we still are only glimpsing at the long-term toll and consequences that this pandemic will ultimately take on the world, and there is a

tremendous amount of work that needs to be done to effectively respond to adverse realities arising in every conceivable manner as they relate to the challenges we continue to confront.

As of April 2, 2022, the COVID-19 pandemic has resulted in 79,342,899 confirmed cases and 972,830 deaths in the United States alone [4]. As of the same date, 486,761,597 confirmed cases of COVID-19 have been reported globally to the WHO, including 6,142,735 deaths [4]. Compounding the complexity and gravity of the situation, the peak of the first wave occurring in the summer of 2020 in the United States specifically coincided with record unemployment rates, civil protests, widely distributed misinformation, and political posturing that have collectively imposed substantive stress on human physiology both physically and psychologically, and to society more broadly.

The COVID-19 pathophysiology has been recognized to be highly variable, with some individuals contracting the virus without expressing symptoms of any kind, and others presenting on a continuum of mild to severe symptom development with inconsistent speeds in the length of recovery which appear to be correlated with severity and comorbidities. One study of 142 patients who had recovered from COVID-19 found that only 12.6% were completely free of any COVID-19-related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more, with fatigue and dyspnea most commonly reported [5]. Similarly, a medRxiv preprint analyzing a group of hospitalized COVID-19 patients with no prior history of neurologic disease identified 37.4% of those patients with abnormalities on neurologic exam six months later [6]. In addition to the respiratory symptoms most often highlighted in various analyses, it is now recognized that a significant proportion of COVID-19 patients experience neurological symptoms and syndromes on various time scales following diagnosis [7]. While ultimate projections vary widely, this outbreak has been already understood to result in the loss of millions of lives globally, adversely affecting many sectors of business and commerce, and directly or indirectly contributing to incalculable levels of psychological duress and suffering. These events have amounted to arguably the greatest public health crisis in a century, resulting in the deepest economic crash since World War II and the greatest health insurance losses in American history [8].

1.1. Pathogenesis

COVID-19 is caused by the pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel RNA betacoronavirus that acts as an infecting agent by the binding of a spike protein on the viral surface to an ACE2 receptor, where the virus is then internalized and propagated with viral replication [9] [10] [11]. Although the ACE2 receptor can be found in high levels in various tissues throughout the human body including in the heart, kidneys, arteries, intestines, and on type 2 pneumocytes in the lungs, the anatomical orientation of the lungs as they interface with the external environment leaves them disproportionately vulnerable; the lungs therefore have subsequently been recognized as

the primary route of infection [12]. When bound to ACE2, SARS-CoV-2 leads to a host of deleterious physiological responses including increased pulmonary vascular permeability, together which often progresses to the clinical state of acute respiratory distress syndrome (ARDS) [13]. ARDS with a history of exposure to COVID-19 is routinely reclassified as SARS. These developments resulting in respiratory compromise, as seen with high frequency in COVID-19 patients requiring hospitalization, have created enormous demand for ventilators as in the late stages of ARDS/SARS, life often cannot be sustained without one.

A salient point of consideration here forward must be the fact that the overwhelming majority of SARS-CoV-2 infected patients requiring intensive care support (and as of May 1, 2020, ≥99% of patients who have subsequently lost their lives) have presented with one or more comorbidities including cardiovascular, cerebrovascular, endocrine, digestive, and respiratory disease [1]. Among 1590 laboratory-confirmed cases of COVID-19 in China, patients with any comorbidity were found to yield poorer clinical outcomes than those without, and a greater number of comorbidities also correlated with poorer clinical outcomes [14]. A recent meta-analysis of 30 studies including 53,000 patients with COVID-19 found hypertension (HTN), diabetes mellitus (DM), and cardiovascular disease (CVD) as the most common comorbidities respectively, and that each of these conditions were significantly more common in severe cases as compared with nonsevere cases [15]. Furthermore, HTN, DM, and CVD were each found to be independent prognostic factors for COVID-19-related death [15], and CVD specifically is hypothesized to leave humans more vulnerable to infection or disease progression [12]. Furthermore, COVID-19 infection causes a myriad of acute cardiac complications, with myocardial injury recognized as a key prognostic factor which is significantly associated with mortality in patients with COVID-19. A recent study of 400 patients hospitalized with COVID-19 in Wuhan, China, found that 20% of patients had cardiac injury, and that these patients were more likely than those without cardiac injury to require noninvasive ventilation (46% vs. 4%), more likely to require invasive ventilation (22% vs. 4%) and had a higher mortality rate (51% vs. 5%) [16]. In this same investigation, those with cardiac injury were more likely to experience ARDS (59% vs. 15%). While there are a number of tissues that may become involved or compromised following infection with COVID-19, the pulmonary and cardiovascular systems subsequently remain areas of exceptional concern for these reasons.

Acknowledging in full these realities that confront us, the author of this manuscript submits the notion that there is a great deal of productive work and therapeutic potential to be reached collectively as all disciplines in the medical establishment adapt their practices to best support the world at large in various capacities. The consequences of poor preparation and insufficient preventative action have become all too clear in light of the reality that many hospitals and inpatient facilities were operating at or beyond their full capacity for extended periods of time, on many occasions without sufficient personal protective equipment available to medical personnel to ensure the implementation of adequate

preventative measures while interacting with each patient in need. Worse still, because of the well-documented inadequate supply of life-supporting ventilators in high-volume facilities to combat the respiratory compromise occurring with the onset of ARDS and/or bilateral interstitial pneumonia as seen with high incidence for many in late stages of the novel coronavirus infection, many doctors with insufficient resources have been forced to make extraordinarily difficult ethical decisions in determining who will live and who will die. It has become abundantly clear that amongst the most critical things to be achieved amidst such crises is to limit the number of people ultimately requiring hospitalization to the greatest degree possible.

Perhaps the most pressing discussion point to preface any investigation of the therapeutic potential of interventions to influence the human immune system within light of the COVID-19 pandemic is the reality that, prior to exposure, human beings have no natural immunity to the virus. This fact of the matter is not to be lost, and clear language must be used in context to communicate that there are no scientifically supported interventional strategies to guarantee immunity when initially exposed. This reality then begs the question, why ought one make any effort at all to build the efficiency and resilience of their immune system function in any capacity? Anticipating such healthy skepticism, the following hypotheses are submitted to weigh independently and collectively with respect to individual health practices as well as inflection points to consider when making formal medical recommendations to those in need at various stages of care and consultation, each of which warranting further research:

1) All measures taken that may minimize the incidence of sickness or disease of any kind will help alleviate the burden on the global healthcare system, and therefore represent a benefit to all.

2) As an extension, all measures taken which effectively enhance health in manners which confer resilience in individuals who acquire the virus represent a similar attenuation of the burden to the healthcare system as well and decrease the likelihood of developing severe complications.

3) Reducing the number and/or minimizing the severity of co-morbidities presenting with COVID-19 contraction may help to minimize the loss of life in those diagnosed and accelerate the recovery in those who survive.

4) Building cardiovascular and respiratory capacity prior to infection of COVID-19 may help reduce the mortality rate especially of those who develop ARDS or acute interstitial pneumonia, when the respiratory system may otherwise become fatally compromised.

5) Developing and supporting multiple dimensions of health in a holistic sense may confer additional prognostic advantages including a more rapid return to premorbid level of function and diminished psychological adversity.

6) Enhancing various aspects of immune and nervous system function may improve viral exposure tolerance thresholds as determinants of a pathological state developing, in relation to a given volume of particles interfacing with human biology over a period of time.

7) There is plausibility that enhancing certain aspects of innate or adaptive immunity may help facilitate a more efficient, effective response in recovery from infection given the high correlation between pre-existing comorbidities and severe adverse outcomes as well as the disorganized immune response often characterized in the recovery from COVID-19.

8) Non-pharmacological interventions known previously to enhance vaccine response efficacy may similarly be implemented advantageously as adjuvants in concert with administration of novel COVID-19 vaccines as they become available.

The possibilities implied by these considerations should not be understated, as the duration of antibodies produced following infection which confer protection (natural immunity) against COVID-19 and its variants appears highly variable, dropping precipitously over the course of months in some studies, and in just weeks according to others. An early study by Ibarrondo and colleagues presented data conveying that these antibody levels may decrease by approximately half every 73 days in mild cases of COVID-19, which represented the majority of cases documented up until its publication [17]. Intriguingly, some authors have argued that natural immunity is superior to vaccination while antibodies are still produced, but it appears that natural immunity may fade more quickly than vaccine-induced immunity. A 2021 systematic review and pooled analysis investigating the equivalency of protection from naturally acquired immunity versus fully vaccinated persons found that all of the 9 clinical studies included yielded at least statistical equivalence between the protection of full vaccination and natural immunity, and three studies found superiority of natural immunity [18]. In any event, protection afforded by vaccination also has a finite duration, and there is uncertainty as to the degree to which antibodies generated from encountering one strain of COVID-19 or administering any individual vaccine protect against variant strains as they continue to evolve. Further still, a significant number of COVID-19 naive persons exist who for various reasons elect not to vaccinate. With such wide-ranging potential vulnerability, it is essential to maximize effectiveness of all complementary strategies to support immune function for all individuals in the current climate as this virus continues to circulate and evolve into the future.

1.2. Moving Forward

While the scale and complexity of the challenges we are confronted with is staggering, there too exists enormous potential for meaningful work in multiple dimensions to contribute to the betterment of health around the world and more broadly to society on the whole. There is real responsibility for healthcare practitioners of every discipline to broaden their knowledge, seek innovative solutions, and otherwise endeavor to facilitate the transformation of an informed medical system that will take the lessons of the present to meet the evolving demands in the future for each domain of healthcare. A fundamentally sound, enhanced collaborative approach to research and translation of scientific findings efficiently

into a means of effective action is needed. This review is a call to action for all sectors of the medical field to rise to the occasion in this pursuit.

The encouragement to adopt widespread practices of standard precautionary measures including hand sanitation, droplet precautions, wearing effectively preventative masks where possible, and behavioral strategies of social isolation when necessary to minimize the spread of COVID-19 have already been widely discussed and disseminated since the earliest months of the pandemic [19] [20]. For a period, additional behavioral considerations including avoidance of travel to high-risk geographical areas and the consumption of meat from regions with a known COVID-19 outbreak were also recommended [1] [19] [20]. The validity and effectiveness of each of these strategies is beyond the scope of this review, but it remains important to acknowledge these practices for a time were collectively agreed upon widely, with social isolation protocols and masking precautions maintaining the highest degree of durability in circulation by public health and medical professionals around the world through the first two years of the pandemic.

A key consideration amidst all of this is the surprising absence of narrative surrounding the tremendous degree to which the immune system can be influenced and enhanced with non-pharmacological measures, a phenomenon with profound implications even in the face of novel viruses. While establishing realistic expectations as to the extent of possible outcomes anticipated in this context is warranted, the lack of emphasis on these measures in public health messaging is disconcerting. The remainder of this manuscript, therefore, will focus on the non-pharmacological means by which healthcare professionals across multiple disciplines may be able to generate positive influences in supporting the functional resilience of the immune system and the nervous system more broadly in their patients in light of these conditions. Likewise, patients can advocate for themselves and others by introducing questions to their providers inquiring as to whether they stand to benefit from any given intervention. These efforts may be best employed in parallel with other measures promoting compliance and adherence to effective safety precautions where they do indeed exist to the full extent possible during times of such uncertainty, forced constraints, and continuously evolving challenges in the world at large.

The organizational structure of this series contains multiple cornerstones which arguably constitute distinctly different yet complementary pathways through which such positive influences may be possible. This first installment portrays the foundational biological architecture and landscape upon which these pathways may be leveraged and highlights the key dimension of structured exercise as a critical point of leverage in this domain. Subsequent installments thereafter will build upon this initial entry point, expanding with parallel practices of stress mitigation, pain management, sleep hygiene, nutritional intake, social connection, emotional regulation, and remaining alternative pathways which together orchestrate an interdependent ecosystem of strategies which may be employed

and adopted in an individualized manner in efforts to optimize the biology of those choosing to engage with this pursuit.

An important assumption herein is that individuals vary in their affinity, relative expertise, and skill level in actively supporting each dimension, both as patients and practitioners. A unifying aim of this review is to expand the reader's awareness of the breadth, depth, and interconnectedness of these pathways, and to shed light on any blind spots that may exist in this context in ways that may advantageously be recognized and acted upon. Certain diagnoses and co-morbidities may temporarily or indefinitely contraindicate the employment of some techniques and strategies, and precautionary measures may be necessary in those where no clear contraindication exists. In all such cases, a great deal of discretion is warranted in implementing clinical assessments and interpreting findings when discerning which approach is most appropriate for any given individual. Therefore, the present author asserts the essential importance of broadening one's range and depth of understanding and proficiency in assessing and appropriately intervening within the respective boundaries of practice for all relevant disciplines in healthcare.

2. Biological Foundations

To preface the remainder of this manuscript, it is instructive to account for several key fundamental biological constructs which give rise to function in the immune and nervous systems collectively, and to consider their interdependent relationships in the service of adaptation and survival. What follows is intended to highlight the biological architecture upon which advantageous processes emerge and unfold under certain conditions, and to offer direction in each area of research for future consideration.

2.1. Human Immunity

Two principal systems classically described within the immune system are responsible for protecting vertebrate species against viral contagions: the innate and adaptive immune systems. All effector responses generated by these systems can be considered on a spectrum defined by the costs associated with their maximal deployment, wherein excessive cost accumulation (uncontrolled summation) represents immunopathology [21]. The innate immune system is the body's immediate, nonspecific response to combat foreign invaders, acting as a first line of defense to rapidly impede pathogens, preventing their spread and movement throughout the body. This system consists of physical, chemical, and cellular defenses against pathogens including skin, mucous membranes, phagocytes, granulocytes, macrophages, neutrophils, dendritic cells, mast cells, basophils, and eosinophils. The adaptive (acquired) immune response is conversely much more complex by comparison and is effective towards neutralizing specific pathogens as they are encountered. This system is considered the second line of defense however, because it is slower in nature to be deployed into action upon

interfacing with a perceived threat. This notwithstanding, the effect of the adaptive response is long-lasting, highly specific, and is sustained long-term by lymphocytes integrally for future utilization. Lymphocytes are a type of white blood cell (WBC) that can be subclassified into T and B cells based on their distinctive features and adaptive function. Both cell types originate from stem cells in the bone marrow and can be found in the circulating blood and lymph tissue throughout the body in quantities that dynamically adjust and vary dramatically in certain conditions. B cells produce protein antibodies which are highly specific to individual antigens, whereas T cells destroy foreign substances and cells in the body which have already been taken over by viruses or have become cancerous. Another class of WBCs known as natural killer (NK) cells have been traditionally grouped with innate immunity that express cytolytic function against stressed cells such as virus-infected and tumor cells, exhibiting a broad array of tissue distribution and phenotypic variability [22]. However, some researchers have come to categorize at least some subsets of NK cells as part of adaptive immunity due to the high degree of antigen specificity exhibited and their capacity to be retained in long-term memory [23]. Similarly, astrocytes have been recognized for their role in some aspects of both innate and adaptive immune modulation [24]. The distinction between classes of lymphocytes has been elevated as a matter of increasing importance as some scientists orient their focus towards how T cells combat COVID-19 in the absence of matched specific antibodies, provided the variable rates of antibody production following infection and the widely variable limits in duration of their lifespan known to date. Given the pathogenesis and highly contagious nature of SARS-COVID-19 in its evolving array of variants, identifying and supporting the pathways through which an effective defense can be mounted may be of paramount importance for the mitigation and/or avoidance of adverse outcomes in this pandemic and through beyond into its endemic phase hereforward. Arguably, the adaptive immune system offers the greatest potential to provide an effective defense in the current conditions, at very least in mounting a response following infection, if not offering initial protection of any kind upon viral exposure. Intriguingly, there are data suggesting that some patients who had recovered from COVID-19 infection and tested negative for coronavirus antibodies did develop T cells in their response. While such studies are small, the findings have led some to speculate that individuals who experience little to no symptoms following COVID-19 infection may be eliminating the infection through this T cell response. Therefore, it is important to recognize the plausibility that aspects of innate immunity may still have a role to play, at least indirectly, in contributing to human defense against COVID-19, as the innate control of adaptive immunity is now a well-established paradigm [21].

2.2. The Interrelations of Stress, Immunity, and the Nervous System

Stress in principle is advantageously studied from both a biological perspective

as well as a psychological construct [25] [26], and foreign invaders such as a viral contagion may be considered as a stressor in this context. The physiological response of the human body under stressful conditions is mediated by way of multiple systems of various complexity harmoniously functioning as an integrated ecosystem, including the autocrine, paracrine, and immunomodulatory signaling capacities of chemokines (chemotactic cytokines) as well as a vast range of neural and autonomic mechanisms in the nervous system [27]. Chemokine-mediated innate immune cell trafficking, including the direction of effector cells to sites of tissue injury, forms an essential role in linking together the innate and adaptive immune responses [27]. Cytokines regulate the maturation, growth, and responsiveness of specific cell populations, serve to modulate the balance between cell-based and humoral immune responses, and help to mediate the inflammatory response [27] [28]. While there exists overlapping terminology, chemokines and cytokines are understood to be structurally and functionally distinct from hormones and growth factors as they coordinate different immune cells and the regulation of their activity to support the mounting of an effective immune defense [27]. However, cytokines have been functionally described by some as the "hormones of the immune system" due to their behavioral properties specific to immunity. A remarkable event observed is that a minority of SARS-CoV-2 patients have presented in severe conditions with a form of immunopathology called a cytokine storm, defined broadly as an excessive immune response to external stimuli, and the rapid deterioration of some patients has been closely related to this maladaptive phenomenon arising [29]. The cytokine storm is acknowledged as one of the major causes of ARDS and multiple-organ failure which have each been associated with mortality in these patients [29] [30].

A myriad of advances over the last century in neuroscience, genetics, cellular, and molecular biology have illuminated the elaborate interdependence of the immune and nervous systems, which were once thought to be functionally disparate with independent operations. These breakthroughs have given rise to new fields such as psychoneuroimmunology, built upon large bodies of evidence substantiating the bidirectional communications between the neural, neuroendocrine, and immune systems, and shedding light on many aspects of the human's adaptive responses to adversity [28]. Amongst the extensive communications existing therein include the following: 1) a structural 'hardwiring' of sympathetic and parasympathetic nerves to lymphoid organs; 2) the modulation of immune activity by neurotransmitters such as acetylcholine, norepinephrine, vasoactive intestinal peptide, substance P, and histamine; 3) the regulation of cytokine balance by neuroendocrine hormones such as corticotropin-releasing factor, leptin, and α-melanocyte stimulating hormone; 4) the modulation of brain activity resulting from stimulation of the immune system, including body temperature, sleep, and aspects of behavioral drive; 5) the direction of T cells to immunogenic molecules held in its cleft; and 6) the modulation of development of neuronal connections by the major histocompatibility complex and similar

molecules [31]. In a 2012 paper, Chiu *et al.* presented a comprehensive argument outlining how the peripheral nervous system plays a direct and active role in modulating innate and adaptive immunity, postulating that these immune and nervous system interactions create a common integrated protective function in host defense and the response to tissue injury [32]. Host defense herein entails the detection of noxious stimuli and initiation of avoidance behavior, with the response to tissue injury thereafter comprising the modulation to and combat against the harmful stimuli [32]. Congruently, the expression of chemokines, cytokines and their receptors have been demonstrated on both peripheral and central nerves [33]. Thus, traditional views of immunity and nervous system behavior must be reconciled with current evidence, enabling further inquiry into the nature of how and why these interactions exist and potential implications for therapeutic utility. Inferentially, these developments create a scaffolding which supports the notion that immune health is intimately dependent on nervous system function. A brief summary of the classical features of the nervous system function is offered here as a basis for building upon in subsequent discussion.

One of the principal divisions of the central nervous system (CNS) distinguishes the somatic motor division from the autonomic division, the latter of which holding the focus of this review. The autonomic regulatory pathways of the nervous system are classically described and understood through the sympathetic ("fight or flight") and parasympathetic ("rest and digest") branches as their functions manifest in oppositional nature, while simultaneously serving a larger purpose of achieving safety and homeostasis in the whole organism. The sympathetic adrenomedullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis are the primary neural and neuroendocrine components of the stress response [26] [28]. The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) are recognized as the two primary divisions within the autonomic nervous system (ANS), with antagonistic, yet complementary functions arising respectively in response to variations in stimuli from the internal and external environments. In circumstances of heightened danger, whether real or perceived, the SNS mobilizes to meet the demands of accumulating stressors which can be either or both physical and/or psychological in constitution. Stress by its fundamental nature is essential for life to exist, and therefore it is prudent to qualify operationally the term as it is used in this manuscript as the excess accumulation of stress that exceeds for any period of time normal homeostatic thresholds in otherwise healthy, resting conditions. Stress interacting with living tissues in this respect manifests in a variety of physiological ways, including biometric measures of heart rate (HR), respiratory rate (RR), blood pressure (BP), heart rate variability (HRV), galvanic skin response, neuroendocrine measures of hormonal action, as well as selective allocation and distribution of blood flow at local and systemic levels. Further, such outcomes can also be quantified in part by various psychological scales and questionnaires which are primarily subjective in nature. Wherein suprathreshold stressors naturally dissipate over a reasonable time course (with differing duration and magnitude

of regulatory responses depending on numerous variables), a healthy ANS is said to exist. This typically manifests by at least one cycle of elevated sympathetic system cascading effects arising rapidly to meet emerging circumstances, followed by a gradual shift towards increased PNS activity to counterbalance the resources exhausted during the initial response process. The PNS functions to promote the recovery and restoration of strained tissues and depleted resources accumulating to meet the demands of the SNS as it is employed. This subsequent window of parasympathetic expression is characterized by decreases in HR, RR, BP, blood concentrations of epinephrine and norepinephrine (adrenaline), redirection of blood flow away from large skeletal muscles towards the internal organs and viscera, and influences various measures of subjective experience related to arousal and vigilance. Over this recovery period, a broad suite of neurological activity can be recognized in transitional manners that reflect these very characteristics and subsequent subjective states of mind, including amongst the most distinguishable of these a diminishment of neuronal activity in the arousal circuitry and limbic system in parallel with anterior and posterior pituitary neurohormonal regulatory responses cascades to appropriately support various tissues in need. The collective result of these phenomena arising in concert allows for the recovery and replenishment of resources that were utilized or even exhausted during the sympathetic state of action, and supports further sympathetic drive when recruitment becomes once again necessary. Thus, an adaptive cycle of stress and recovery is established.

2.3. Models of Homeostasis, Allostasis, and Hormesis

The continuous unfolding of multi-system processes subserving the preservation of life has been recognized since the early 20th century by a simplistic model of homeostasis—which remains the central organizing principle of physiology. This collective process, however, has come to be appreciated in much greater depths of nuance, and the term allostasis was proposed by Sterling and Eyer in 1988 to depict and describe the subtleties not accounted for in the traditional model of homeostasis. Allostasis is characterized by the process of achieving stability through change, a phenomenon recognized as essential for the survival of any organism amidst changing environmental conditions [34] [35]. The goal in the allostasis model of regulation is to achieve fitness under natural selection (as opposed to restoring constancy alone). This is accomplished by using prior information to predict demands imposed and adjust all relevant parameters to meet it, preventing errors and minimizing costs over time. In this way, physiological adjustments can be produced in advance of need through anticipatory arousal. Contained within this model are adaptive signaling, physiological, and/or behavioral changes occurring in response to integration centers sensing fluctuations of stimuli beyond a given set point sufficient to disturb the stability of a system. This ability to adjust to perturbations through adaptive changes is a universal mechanism through which organisms interface with their environment, but there is a cost associated with these fluctuating adjustments [26]. The

term allostatic load may subsequently be used to refer to the physiological wear and tear on tissues which accumulate as an individual is exposed to stressors over time, and as a regulatory model is characterized by a bell-shaped curve when plotting performance against stress level [36].

A related model for understanding these concepts unified in response to noxious stimuli is referred to as hormesis, a dose-response phenomenon relative to the introduction of stressors characterized by low-dose stimulation and high-dose inhibition. The hormetic model of loading produces a non-linear response in the tissues stimulated wherein low input yields little to no response and high input yields damage. Critically however, imposing a stimulus in the non-provocative territory between these two opposing ends of the loading continuum results in enough stimulus to either maintain a baseline level of fitness at minimum, or optimally force further advantageous adaptation(s) in the system without causing harm at maximum. Intelligently leveraging this phenomenon has resulted in some of the most important interventional breakthroughs known to medicine, such as vaccine development and so-called adversity-mimetics as they are employed in anti-aging research. Benefits from hormesis can be widely found in more routine behaviors such as progressively exercising musculoskeletal tissues in the service of developing tissue capacities of strength, endurance, and power. Further still, hormetic effects are recognized as the basis of adaptation from which exposure to small amounts of bacteria, fungi, and even viral particles educate and ultimately shape the immune system to be versatile and resilient over time. Such phenomena are at the heart of parenting recommendations for nurturing a safe, exploratory manner through which children encounter and interact with the world around them, affording a rich diversity of exposure and subsequent adaptation.

2.4. Immune Senescence

Finally, it is helpful to consider how immunity changes over the lifespan, with two major windows of vulnerability identified; first in the early months of life while the immune system develops naturally in a relatively rapid manner, and again later as the human ages in the later years of life. The latter of these is a much slower process of decline by comparison, and the term immune senescence is used to denote the gradual deterioration of the immune system due to natural aging. To a large extent, this is a natural process that increasingly suppresses the immune system's functional integrity and leaves elderly populations more susceptible to acute and chronic infections, autoimmune diseases, and inflammatory diseases relative to their younger counterparts. This illuminates in part why the present COVID-19 virus has been so threatening to geriatric population especially, as they are unable to generate the necessary responses to combat the contagion on a systemic level than otherwise young, healthy individuals may be able to. T cells are of special recognition here as they are subject to change over time; some T cells undergo modification in which they lose their

advantageous qualities over time, as seen in CD4 and CD8 T cells, contributing to an overall diminishment in the function of both the innate and adaptive immune systems as well as the general effectiveness of the adaptive response [37].

These foundations shed light upon the biological architecture and organizational design amidst a vast array of pathways through which neuroimmunological change can be affected in the human being. While the role of pharmacology is a well-established paradigm and remains an indispensable means by which disease and pathology can be treated, there has been a sea change over recent decades in recognizing and appreciating the extraordinary degree to which health can be enhanced and disease can be both prevented and treated through non-pharmacological interventions of various nature. The first division of the latter of these interventions we will explore further here through the lens of exercise as medicine.

3. Exercise Immunology

Epidemiological evidence indicates that regular physical activity and/or frequent exercise participation reduces the incidence of many chronic diseases, especially in elderly individuals, including communicable diseases such as viral and bacterial infections as well as non-communicable diseases such as chronic inflammatory disorders [38]. In most populations, regular structured exercise has been established as a major protective factor for its role in supporting immune function, whereas a sedentary lifestyle by contrast is known to depress immunity [39] [40]. There is now a broad consensus overall that exercise is a physiological stimulus that beneficially enhances a wide range of qualities in the immune system when it is not otherwise contraindicated [37] [39].

Research has classically been distinguished on time scales by acute (single) bouts of exercise in contrast to chronic exercise (repeated bouts over longer intervals characterized by periods of rest in between), with acute exercise investigations representing the largest evidence base accumulated in this domain to date [39]. Acute bouts of exercise have dominated in this respect for many methodological and logistical reasons, perhaps most notably because confounding variables can be most readily controlled for. Acute bouts of exercise are known to modulate both the innate and adaptive immune responses by positively influencing immune cell numbers and their functional capacity [41] [42]. One of the most reproduced findings in exercise physiology is observed in the peripheral bloodstream, wherein a profound and transient time-dependent change is observed in the functional capacity and phenotypic composition of lymphocytes in response to a single bout of exercise [42]. When spaced by adequate rest and nutritional intake, consecutive bouts of exercise routinely maintained over a regular period confer additional advantages as discussed below.

There are many ways to classify and quantify exercise in terms of intensity of the workload, mode of implementation, and overall volume, dimensions of which are discussed in later sections of this review. Additionally, clear differenc-

es exist between anaerobic (resistance) training and aerobic (endurance) training, including the effects they elicit as well as their ability to be safely tolerated across different populations. Further, there is debate in the literature with respect to what is more beneficial between differing exercise intensity thresholds, and which populations stand to benefit most from specific training approaches when comparing pre-exercise vs. during exercise vs. post-exercise states based on the expression of relevant physiological biomarkers and related health outcomes. For example, recent studies reveal that the behavior of the exercise-induced mobilization of differentiated T cells is highly dependent on exercise intensity, training status, and individual characteristics such as age and the presence of comorbidities [37]. However, in both moderate and vigorous acute exercise where the participant is exposed to moderate and intense cardiovascular training respectively, there is a trend that the immune system is mobilized to respond advantageously as evidenced by increases in the lymphocyte pool and lymphocyte production as they are delivered to peripheral tissues [38]. Similarly, the behavior of almost all immune cell populations in the bloodstream is altered in some way during and after exercise [42] [43], as such serving as a systemic stimulus to the immune system [38].

While examining bouts of acute exercise in isolation produces important insight, it is essential to account for the cumulative advantageous effects that can be conferred when exercise programming is safely implemented with a degree of consistency and chronicity. Chronic exercise is defined broadly as repeated bouts of exercise completed over a certain period of time, which can be subclassified into short-term or long-term cycles based on strategical approach. Multiple studies have demonstrated that chronic exercise modulates the number and functional capacity of immune cells [37] [38] [43]. Higher physically fit subjects that participate in regular bouts of exercise have shown increases in memory regulatory T cell quantities and increased mobilization of naïve T cells, which may be especially beneficial for those who are at increased risk of reactivating latent viruses and developing new infections [37]. This is congruent with findings illustrating that the immune system of regularly active individuals is generally recognized as more prepared to protect against invading pathogens in comparison to sedentary individuals [37]. Further, if the T cell defense hypothesis holds for combating COVID-19 in the absence of antibodies, the elevated T cell quantity and enhanced subsequent capacity demonstrated in conjunction with optimal exercise exposure may be mechanisms through which immunoprotective advantages are conferred (or mediated) in the general population. It should be recognized however that moderate intensity exercise is most consistently identified in the literature as a reliable means to promote immunocompetency when compared with other exercise intensities; while vigorous intensity bouts are also associated with immune-enhancing effects, programming strategies become more complex as the risk for injury and overtraining increases over time on a continuum, factoring into risk-benefit analyses.

In experimental trials focusing on upper respiratory tract infections (URTI), incidence rates of URTI were consistently higher in subjects participating in non-exercise or low-intensity exercise groups as compared to those in moderate-intensity exercise groups. Moderate intensity exercise has been supported for implementation across many populations for numerous reasons including the adaptive regulatory responses observed such as increased production of immunoglobulins, neutrophils, and NK cells [43], as well as for the capacity of these exercise doses to be routinely well tolerated. Although initially the immune system returns to pre-exercise levels within a few hours of completing an acute bout of exercise, the summative effect of consecutive exercise sessions spaced by adequate recovery periods is recognized to elicit sufficient levels of adaptive responses to constitute an improvement in immune surveillance and overall enhancement of immune system function that reduces the risk of infection over the long-term [43]. These findings stand upon the more traditionally recognized benefits of physical activity including enhancements in strength, endurance, mobility, and aspects of cognitive function, which clearly still serve their purpose in the current climate.

These phenomena are observed in contrast to the open-window hypothesis, which historically has controversially suggested that there is a transient window immediately following exercise in which there is a relative drop in immune system capacity and subsequently an increased chance of infection during this time where the system is said to be suppressed. This notion has been near comprehensively overturned however, in part to begin with because very limited reliable evidence exists to support the claim that vigorous exercise heightens risk of opportunistic infections [38] [42]. Conversely, the observed reductions in lymphocyte quantity and function 1 - 2 hours after exercise reflects a redistribution of immune cells to peripheral tissues that is transient and time-dependent, resulting in an elevated state of immune surveillance and immune regulation, as opposed to immune suppression [38]. The activation of the HPA axis also changes dynamically in accordance with the mode, intensity, and duration of physical exercise that is performed [44]. A cascade of events occur when stimulated, beginning with the hypothalamic release of corticotropin-releasing hormone (CRH) which stimulates the pituitary gland to release adrenocorticotropic hormone, subsequently interacting with the adrenal gland to prompt secretion of the hormone cortisol in humans [45]. Cortisol is a principal component of the stress response, serving as a crucial systemic mobilizing force in meeting environmental challenges, yet is also associated with impairment, dysfunction, and disease when chronically elevated. Physical exercise is an acute stressor which elicits cortisol release through the HPA pathway, yet paradoxically confers stabilizing and neuroprotective effects when completed routinely (chronically) and supported by sufficient rest and recovery between each bout. One aspect of this phenomenon can be observed in cortisol regulation itself, as illustrated by the finding that well physically conditioned subjects have lower levels of cortisol

both at rest and in response to a stressor compared to sedentary subjects [46]. Other research has demonstrated that exercise, particularly when performed at moderate intensities, reduces the harmful effects of other stressors upon subsequent exposure [47]. In addition, exercise is known to engender a broad array of health benefits and to decrease peripheral risk factors which converge to cause brain dysfunction and neurodegeneration as well as hypertension, diabetes mellitus, and cardiovascular disease [48] [49].

With all in consideration, there is very limited evidence of any substantive suppression of the immune system eliciting higher risk of infection post-acute exercise, and there is an emerging consensus that the net benefits of exercise in terms of enhancing immunity and brain health overall strongly outweigh the potential for any harm or adverse incident to arise. Remaining concerns of potential deleterious nature, therefore, are more productively directed towards individuals who are combating an active infection, injury, or illness contraindicating exercise, have a medical condition precluding the possibility of exercise to be safely administered or otherwise warranting precautions, or to those who have overtrained over many extended workouts across longer time periods with insufficient rest and/or nutrition appropriated and consumed in context. Additionally, participants in competitive athletic events and/or extreme environmental conditions are uniquely exposed to the psychological stressors which may amount to chronic exposure to stress hormones, increase susceptibility to the deleterious effects of chronic stress, and/or contribute to temporary or chronic immune system impairment in concert with the stress mechanisms explored further in the sequel to this review. Such conditions are much more readily controlled for in non-competitive exercise environments.

3.1. Brain-Derived Neurotrophic Factor and the Neuroimmune Axis

Of considerable significance, high-intensity interval training and moderate to vigorous aerobic exercise have been demonstrated to be especially potent stimuli for the production of brain-derived neurotrophic factor (BDNF), a critical neurological growth factor that is a protein synthesized in the brain and widely distributed throughout the central and peripheral nervous systems respectively [50] [51]. BDNF was originally celebrated for its role in enhancing neuronal health and synaptic connectivity by promoting the survival, growth, differentiation, development, and proliferation of dendritic branches of neurons. BDNF is part of a family of trophic factors functioning as neuromodulators that appear to increase in conjunction with exercise interventions, including vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), nerve growth factor (NGF), neurotrophin-3 (NT3), glial cell line-derived neurotrophic factor (GDNF), fibroblast growth factor (FGF-2), and epidermal growth factor (EGF), each of which are capable of acting as CNS modulators and may also be modulated by neurotransmitters in turn [44] [52]. These effects are explanatory in the findings

that exercise promotes the delayed onset of multiple neurodegenerative processes [47] and that BDNF functions in part to facilitate fundamental aspects of the learning process at the cellular and structural levels.

The role of BDNF specifically has since been even more expansively illuminated however, and more recently has been identified as a key regulator in the neuroimmune axis [53]. This conjunctional term arises from the anatomical proximity of nerves and immune cells in both the central and peripheral nervous systems, and their subsequent interrelated functions responding to threats. Their association helps to determine whether there is a local threat that requires an immune response, a form of employment termed the neurogenic inflammatory response [33]. This relationship is highly advantageous as nerves are able to propagate signals to affect outcomes on a time scale orders of magnitude more quickly than immune cells would be able to independently. The neuroimmune axis is characterized by the bidirectional pathways between the nervous system and immune system, through which disturbances have been implicated in various brain-related pathologies including depressive and neurodevelopmental disorders [33].

Dopamine (DA), noradrenaline (norepinephrine), and serotonin are the three major monoamine neurotransmitters that are known to be modulated by exercise [54], and BDNF is understood to express a strong affinity as a neurotrophic factor for dopaminergic neurons [55]. Further, recent evidence has confirmed that DA plays a key role as an immune transmitter, and a large body of evidence exists which indicates DA has a functional role in regulating inflammation [56]. In addition to the well-established roles of controlling movement and influencing reward-related behaviors, DA is also understood to be involved in modulating the expression of several plasticity-associated molecular substrates [56]. In parallel, a substantial body of evidence indicates a critical role for norepinephrine in the regulation of innate immunity, in the CNS as well as in peripheral tissues [57]. Such features may hold explanatory power for the learning and memory-sustaining capacities of the immune system as it responds to threats over time in dynamic conjunction with the nervous system.

There is overwhelming evidence present to date indicating that exercise supports successful brain functioning, a paradigm which may be implicated in a broad array of pathologies and arguably is now integral in promoting immune health specifically [47]. In addition to previously outlined benefits, regular physical exercise is also known to augment vital aspects of nervous system function including inducement of increased cerebral blood flow, neurogenesis, and angiogenesis [44] [47]. Due to the aforementioned relationships and the intimate role of neurotrophic factors such as BDNF evident in supporting the balance and regulation of neuroimmune phenomena, structured exercise prescription has become an area of heightened focus for interventional purposes in a wide array of both nervous and immune related pathologies. Unfortunately, exercise is still infrequently recognized by mainstream health services as an effective interven-

tion in the care and treatment of brain and immune-related disease and illness [58].

3.1.1. Exercise and Immune Senescence

Relative to the long-term longevity of the immune system, one study conducted on adults 65 years and older assessing the relationship of exercise and immune function concluded that exercise promotes a reversal of immune senescence, as evidenced by the subsequent behavior of immune related biomarkers. Endurance exercises such as walking and running specifically have been shown to benefit both young and older adults (65 years and older) by increasing T cell proliferation, NK cell cytotoxicity, and neutrophil phagocytic activity [37]. While immune senescence is a natural occurrence that is to some degree unavoidable, such investigations offer evidence that sufficient doses of routine physical activity can limit the amount of degradation that occurs in the immune system with aging and elicit significant prophylactic effects across the lifespan.

An important consideration in the larger inquiry into the advantageous qualities exercise confers on immune function is its effectiveness demonstrated in combating some forms of cancer, as exercise oncology has emerged as a highly productive field in recent years. In one investigation of tumor onset in rodents, an increase in NK cell quantity was observed at the tumor sites initiating change and tumor elimination following exercise, an effect that was not observed in sedentary controls [38]. Naturally, implicit in animal study outcomes is the recognition of the relatively limited generalizability of such findings to humans. Human trials however have since supported the efficacy of exercise in various classes of oncology patients when appropriate precautions are adhered to, such as recently described in vitro observations in which NK cells with a highly mature effector phenotype were shown to exhibit a capacity to exert augmented cytotoxicity against lymphoma and myeloma cells, and to be preferentially redistributed after exercise [38] [59] [60]. It must be acknowledged however that programming strategies specifically designed for purposes in exercise oncology can vary greatly with respect to diagnosis and course of development, and that indications and contraindications can vary likewise in this population as a high degree of individualization is most often required.

3.1.2. Structured Exercise as a Clinical Adjuvant

Finally, results from various research trials have also indicated that risk of infection decreases while response to vaccines improves in parallel following an exercise intervention [37] [61]. A 2013 systematic review of randomized control trials, cross-sectional, and observational studies investigating the vaccine response of subjects following exposure to acute or chronic exercise indicated that the vast majority of trials identified significant augmentations in the immune response to vaccination, supporting the immunogenic action of exercise as an adjuvant [62]. An important consideration from the aforementioned review is the range in mode, intensity, and across age groups in which these effects emerged, and the

qualifier that not all studies produced significant outcomes. Campbell *et al.* provide additional depth and perspective to this subject in their impressive review of the exercise immunology field more broadly [38]. Overall, the findings illuminated by this body of work are congruent with others described in which enhanced immune responses to a vaccine administration when delivered in conjunction with a non-exercise stressor have been observed [61]. This has led to the theoretical speculation from an evolutionary perspective that exercise and short-term psychological stress exposure share similar physiological pathways which contribute to immunocompetence as a means of promoting survival of the species.

4. Conclusions

There is now a strong body of evidence suggesting that regular activation of the short-term stress response itself (irrespective of the mode of exposure), when in a magnitude and frequency that does not induce chronic stress, is one mechanism mediating the advantageous outcomes described across the fields of exercise immunology and exercise oncology research. Exercise itself serves in concert to ameliorate the deleterious effects of increased allostatic load. Structured exercise is now widely proposed to redeploy immune cells to peripheral tissues such as mucosal surfaces to conduct immune surveillance in a highly specialized and systematic response, wherein cells infected with pathogens (or those that have otherwise become damaged or malignant) are able to be identified and eradicated [38]. This cumulative response has been termed the *acute stress/exercise immune-enhancement hypothesis*, extrapolated from an exceptional review by Dhabhar on the allostatic, adaptive nature of the stress response more broadly from a multi-system perspective [61]. In context, various elements of this overarching construct in direct and indirect relation are explored with increasing nuance over the remaining sections.

Ultimately, interventional strategies must be sensitive to individual differences such as age, activity level, genetics, and the presence of complicating pathology. Current evidence suggests that supporting immunity should be considered amongst the range of indications in which therapeutic exercise can be most influential when not otherwise contraindicated. Here forward, it is essential to integrate foundational principles of stress physiology in understanding its interactions with all biological human systems. Structured exercise, while offering unique properties and advantageous qualities, is but one potential stressor of many that may be leveraged therapeutically with the aim of developing immunocompetency amongst other interrelated health goals. Like all stressors, exercise may produce advantageous or deleterious physiological outcomes depending on the dose of exposure and a vast myriad of individual factors including presenting conditions. Regardless of the specificity of the therapeutic aim, great care should be taken in prescribing exercise to patients with complicating pathologies of any kind. It is incumbent upon the clinician therefore to identify the

optimal training pathways which can be safely initiated in the service of these aims, and to develop adequate recovery strategies in the context of an overarching program design that can be adhered to and sustained in the long-term.

All in consideration, given the cost-effectiveness, relative access, therapeutic utility, and general practicality of implementation for structured exercise interventions, there is a strong body of evidence supporting its integration for general health support and prophylactic purposes at minimum in nearly all populations across the lifespan, and increasingly as individualized interventions for clinical populations with specific therapeutic aims when not otherwise contraindicated. Further, exercise is well established as an adjuvant for boosting the efficacy of vaccine implementation historically, providing theoretical plausibility for possible employment with the current COVID-19 vaccines and subsequent alternatives as they may arise; more research in this area is warranted before any formal recommendations can be made, however, in particular in light of the structural novelty of the mRNA constitution of several major current vaccines such as those from Pfizer and Moderna.

Structured exercise, however impressive, is but one pathway through which immune function can be non-pharmacologically enhanced, either in parallel with or independent of traditional pharmacological measures already known to confer benefits towards immune and nervous system function. The sequel of this review will build upon the base of knowledge articulated in this opening manuscript and explore further non-pharmacological avenues with similar therapeutic utility and potential in this context. The interdependent roles of therapeutic exercise, psychological stress attenuation, pain management, nutrition, sleep, alternative pathways, and community-oriented biopsychosocial dynamics in relation to supporting the functional capacity of the immune and nervous systems will be discussed. Many of these approaches offer low-risk, low-cost means to elicit substantive clinical responses relating to nervous system versatility, cardiorespiratory function, psychological health, and various levels of immunity which hold profound relevance in preventing and combating disease. Such pursuits hold potential universal value geographically, especially in those areas with limited access to resources such as developing nations or otherwise impoverished communities, and virtually all human beings stand to benefit from safely engaging with effective configurations of such measures.

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Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Sohrabi, C., Alsafi, Z., O'Neill, N., *et al.* (2020) World Health Organization Declares Global Emergency: A Review of the 2019 Novel Coronavirus (COVID-19). *International Journal of Surgery*, **76**, 71-76. https://doi.org/10.1016/j.ijsu.2020.02.034

[2] World Health Organization. Rolling Updates on Coronavirus Disease (COVID-19). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen

[3] Nicola, M., Alsafi, Z., Sohrabi, C., *et al.* (2020) The Socio-Economic Implications of the Coronavirus and COVID-19 Pandemic: A Review. *International Journal of Surgery*, **78**, 185-193. https://doi.org/10.1016/j.ijsu.2020.04.018

[4] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/

[5] Carfì, A., Bernabei, R., Landi, F., for the Gemelli Against COVID-19 Post-Acute Care Study Group (2020) Persistent Symptoms in Patients after Acute COVID-19. *JAMA*, **324**, 603-605. https://doi.org/10.1001/jama.2020.12603

[6] Pilotto, A., *et al.* (2021) COVID-19 Severity Impacts on Long-Term Neurological Manifestation after Hospitalisation. MedRxiv. https://www.medrxiv.org

[7] Vakili, K., Fathi, M., Hajiesmaeili, M., Salari, M., Saluja, D., Tafakhori, A., Sayehmiri, F. and Rezaei-Tavirani, M. (2021) Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies. *European Neurology*, **84**, 307-324. https://doi.org/10.1159/000516258

[8] Families USA (2020) The COVID-19 Pandemic and Resulting Economic Crash Have Caused the Greatest Health Insurance Losses in American History. https://www.familiesusa.org/resources/the-covid-19-pandemic-and-resulting-economic-crash-have-caused-the-greatest-health-insurance-losses-in-american-history/

[9] Zhou, P., Yang, X.L., Wang, X.G., *et al.* (2020) A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature*, **579**, 270-273. https://doi.org/10.1038/s41586-020-2012-7

[10] Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T. and Veesler, D. (2020) Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell*, **181**, 281-292.e6. https://doi.org/10.1016/j.cell.2020.02.058

[11] Duffy, E., Ayers, A., Caínzos-Achirica, M. and Blumenthal, R. (2020) Clinical Review of COVID-19 and CVD: What the Cardiovascular Practitioner Needs to Know. *Cardiology Today.* https://www.healio.com/cardiology/chd-prevention/news/print/cardiology-today/%7Bc7417d27-5908-4c8a-892b-317ee67cdb19%7D/clinical-review-of-covid-19-and-cvd-what-the-cardiovascular-practitioner-needs-to-know?utm_source=selligent&utm_medium=email&utm_campaign=cardiology%20news&m_bt=742684922117

[12] Hamming, T.W., Timens, W., Bulthuis, M.L.C., Lely, A.T., Navis, G.J. and van Goor, H. (2014) Tissue Distribution of ACE2 Protein, the Functional Receptor for SARS Coronavirus. A First Step in Understanding SARS Pathogenesis. *The Journal of Pathology*, **203**, 631-637. https://doi.org/10.1002/path.1570

[13] Zhang, H., Penninger, J.M., Li, Y., *et al.* (2020) Angiotensin-Converting Enzyme 2 (ACE2) as a SARS-CoV-2 Receptor: Molecular Mechanisms and Potential Therapeutic Target. *Intensive Care Medicine*, **46**, 586-590. https://doi.org/10.1007/s00134-020-05985-9

[14] Guan, W.-J., *et al.* (2020) Comorbidity and Its Impact on 1590 Patients with Covid-19 in China: A Nationwide Analysis. *European Respiratory Journal*, **55**, Article

ID: 2000547.

[15] Zhao, X., Zhang, B., *et al.* (2020) Incidence, Clinical Characteristics and Prognostic Factor of Patients with COVID-19: A Systematic Review and Meta-Analysis. MedRxIV.

[16] Shi, S., Qin, M., Shen, B., *et al.* (2020) Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiology*, **5**, 802-810. https://doi.org/10.1001/jamacardio.2020.0950

[17] Ibarrondo, F.J., Fulcher, J.A., Goodman-Meza, D., *et al.* (2020) Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. *New England Journal of Medicine*, **383**, 1085-1087. https://doi.org/10.1056/NEJMc2025179

[18] Shenai, M.B., Rahme, R. and Noorchashm, H. (2021) Equivalency of Protection from Natural Immunity in COVID-19 Recovered versus Fully Vaccinated Persons: A Systematic Review and Pooled Analysis. *Cureus*, **13**, e19102. https://doi.org/10.7759/cureus.19102

[19] Centers for Disease Control and Prevention (2020) 2019 Novel Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html

[20] World Health Organization. Novel Coronavirus (2019-nCoV) Advice for the Public. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public

[21] Iwasaki, A. and Medzhitov, R. (2015) Control of Adaptive Immunity by the Innate Immune System. *Nature Immunology*, **16**, 343-353. https://doi.org/10.1038/ni.3123

[22] Sourav, P. and Girdhari, L. (2017) The Molecular Mechanism of Natural Killer Cells Function and Its Importance in Cancer Immunotherapy. *Frontiers in Immunology*, **8**, Article 1124. https://www.frontiersin.org/article/10.3389/fimmu.2017.01124 https://doi.org/10.3389/fimmu.2017.01124

[23] Paust, S., Senman, B. and von Andrian, U.H. (2010) Adaptive Immune Responses Mediated by Natural Killer Cells. *Immunological Reviews*, **235**, 286-296. https://doi.org/10.1111/j.0105-2896.2010.00906.x

[24] Neibla, P. and Manuel, V. (2019) The Potential of Astrocytes as Immune Modulators in Brain Tumors. *Frontiers in Immunology*, **10**, Article 1314. https://doi.org/10.3389/fimmu.2019.01314

[25] Dantzer, R. (1991) Stress and Disease: A Psychobiological Perspective. *Annals of Behavioral Medicine*, **13**, 205-210.

[26] Gunnar, M. and Quevedo, K. (2007) The Neurobiology of Stress. *Annual Review of Psychology*, **58**, 145-173. https://www.annualreviews.org https://doi.org/10.1146/annurev.psych.58.110405.085605

[27] Sokol, C.L. and Luster, A.D. (2015) The Chemokine System in Innate Immunity. *Cold Spring Harbor Perspectives in Biology*, **7**, a016303. https://doi.org/10.1101/cshperspect.a016303

[28] Marques-Deak, A. and Sternberg, E. (2004) Psiconeuroimunologia: A relação entre o sistema nervoso central e o sistema imunológico. *Brazilian Journal of Psychiatry*, **26**, 143-144. https://doi.org/10.1590/S1516-44462004000300002

[29] Ye, Q., Wang, B. and Mao, J. (2020) The Pathogenesis and Treatment of the "Cytokine Storm" in COVID-19. *Journal of Infection*, **80**, 607-613. https://doi.org/10.1016/j.jinf.2020.03.037

[30] Chousterman, B.G., Swirski, F.K. and Weber, G.F. (2017) Cytokine Storm and Sepsis Disease Pathogenesis. *Seminars in Immunopathology*, **39**, 517-528.

https://doi.org/10.1007/s00281-017-0639-8

[31] Steinman, L. (2004) Elaborate Interactions between the Immune and Nervous Systems. *Nature Immunology*, **5**, 575-581. https://doi.org/10.1038/ni1078

[32] Chiu, I.M., von Hehn, C.A. and Woolf, C.J. (2012) Neurogenic Inflammation and the Peripheral Nervous System in Host Defense and Immunopathology. *Nature Neuroscience*, **15**, 1063-1067. https://doi.org/10.1038/nn.3144

[33] Kraneveld, A.D., de Theije, C.G., van Heesch, F., *et al.* (2014) The Neuro-Immune Axis: Prospect for Novel Treatments for Mental Disorders. *Basic & Clinical Pharmacology & Toxicology*, **114**, 128-136. https://doi.org/10.1111/bcpt.12154

[34] Schulkin, J. (2003) Rethinking Homeostasis: Allostatic Regulation in Physiology and Pathophysiology. MIT Press, Cambridge, MA. https://doi.org/10.7551/mitpress/5928.001.0001

[35] Copstead, L.-E. and Banasik, J. (2013) Pathophysiology. 5th Edition, Elsevier Saunders, St Louis, Missouri.

[36] Ogden, J. (2004) Health Psychology: A Textbook, 3rd Edition, Open University Press, McGraw-Hill Education, 259.

[37] Alack, K., Pilat, C. and Krüger, K. (2019) Current Knowledge and New Challenges in Exercise Immunology. *Deutsche Zeitschrift für Sportmedizin*, **70**, 250-260. https://doi.org/10.5960/dzsm.2019.391

[38] Campbell, J.P. and Turner, J.E. (2018) Debunking the Myth of Exercise-Induced Immune Suppression: Redefining the Impact of Exercise on Immunological Health across the Lifespan. *Frontiers in Immunology*, **9**, Article 648. https://doi.org/10.3389/fimmu.2018.00648

[39] Nieman, D. (1998) Exercise Immunology: Practical Applications. *Rehabilitation Oncology*, **16**, 31. https://doi.org/10.1097/01893697-199816030-00025

[40] Lancaster, G.I. and Febbraio, M.A. (2014) The Immunomodulating Role of Exercise in Metabolic Disease. *Trends in Immunology*, **35**, 262-269. https://doi.org/10.1016/j.it.2014.02.008

[41] Krüger, K., Mooren, F.C. and Pilat, C. (2016) The Immunomodulatory Effects of Physical Activity. *Current Pharmaceutical Design*, **22**, 3730-3748. https://doi.org/10.2174/1381612822666160322145107

[42] Walsh, N.P., Gleeson, M., Shephard, R.J., Gleeson, M., Woods, J.A., Bishop, N.C., Fleshner, M., Green, C., Pedersen, B.K., Hoffman-Goetz, L., Rogers, C.J., Northoff, H., Abbasi, A. and Simon, P. (2011) Position Statement. Part One: Immune Function and Exercise. *Exercise Immunology Review*, **17**, 6-63.

[43] Walsh, N.P., Gleeson, M., Pyne, D.B., Nieman, D.C., Dhabhar, F.S., Shephard, R.J., *et al.* (2011) Position Statement. Part Two: Maintaining Immune Health. *Exercise Immunology Review*, **17**, 64-103.

[44] Matta Mello Portugal, E., Cevada, T., Sobral Monteiro-Junior, R., Teixeira Guimarães, T., da Cruz Rubini, E., Lattari, E., Blois, C. and Deslandes, C. (2013) Neuroscience of Exercise: From Neurobiology Mechanisms to Mental Health. *Neuropsychobiology*, **68**, 1-14. https://doi.org/10.1159/000350946

[45] Stranahan, A.M., Lee, K. and Mattson, M.P. (2008) Central Mechanisms of HPA Axis Regulation by Voluntary Exercise. *NeuroMolecular Medicine*, **10**, 118-127. https://doi.org/10.1007/s12017-008-8027-0

[46] Papacosta, E. and Nassis, G.P. (2011) Saliva as a Tool for Monitoring Steroid, Peptide and Immune Markers in Sport and Exercise Science. *Journal of Science and Medicine in Sport*, **14**, 424-434. https://doi.org/10.1016/j.jsams.2011.03.004

[47] Deslandes, A., Moraes, H., Ferreira, C., Veiga, H., Silveira, H., Mouta, R., Pompeu, F.A.M.S., Coutinho, E.S.F. and Laks, J. (2009) Exercise and Mental Health: Many Reasons to Move. *Neuropsychobiology*, **59**, 191-198. https://doi.org/10.1159/000223730

[48] Cotman, C.W., Berchtold, N.C. and Christie, L.A. (2007) Exercise Builds Brain Health: Key Roles of Growth Factor Cascades and Inflammation. *Trends in Neurosciences*, **30**, 464-472. https://doi.org/10.1016/j.tins.2007.06.011

[49] Bassuk, S.S. and Manson, J.E. (2005) Epidemiological Evidence for the Role of Physical Activity in Reducing Risk of Type 2 Diabetes and Cardiovascular Disease. *Journal of Applied Physiology*, **99**, 1193-1204. https://doi.org/10.1152/japplphysiol.00160.2005

[50] Cotman, C. (2002) Exercise: A Behavioral Intervention to Enhance Brain Health and Plasticity. *Trends in Neurosciences*, **25**, 295-301. https://doi.org/10.1016/S0166-2236(02)02143-4

[51] Hu, J., *et al.* (2021) Elevated Lactate by High-Intensity Interval Training Regulates the Hippocampal BDNF Expression and the Mitochondrial Quality Control System. *Frontiers in Physiology*, **12**, Article 629914. https://www.frontiersin.org/article/10.3389/fphys.2021.629914 https://doi.org/10.3389/fphys.2021.629914

[52] Duman, R.S. (2005) Neurotrophic Factors and Regulation of Mood: Role of Exercise, Diet and Metabolism. *Neurobiology of Aging*, **26**, 88-93. https://doi.org/10.1016/j.neurobiolaging.2005.08.018

[53] Jin, Y., Sun, L.H., Yang, W., Cui, R.J. and Xu, S.B. (2019) The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disorders. *Frontiers in Neurology*, **4**, Article 515. https://doi.org/10.3389/fneur.2019.00515

[54] Lin, T.W. and Kuo, Y.M. (2013) Exercise Benefits Brain Function: The Monoamine Connection. *Brain Sciences*, **3**, 39-53. https://doi.org/10.3390/brainsci3010039

[55] Hyman, C., Hofer, M., Barde, Y.A., *et al.* (1991) BDNF Is a Neurotrophic Factor for Dopaminergic Neurons of the Substantia Nigra. *Nature*, **350**, 230-232. https://doi.org/10.1038/350230a0

[56] Thomas Broome, S., Louangaphay, K., Keay, K.A., Leggio, G.M., Musumeci, G. and Castorina, A. (2020) Dopamine: An Immune Transmitter. *Neural Regeneration Research*, **15**, 2173-2185. https://doi.org/10.4103/1673-5374.284976

[57] Scanzano, A. and Cosentino, M. (2015) Adrenergic Regulation of Innate Immunity: A Review. *Frontiers in Pharmacology*, **6**, Article 171. https://www.frontiersin.org/article/10.3389/fphar.2015.00171 https://doi.org/10.3389/fphar.2015.00171

[58] Callaghan, P. (2004) Exercise: A Neglected Intervention in Mental Health Care? *Journal of Psychiatric and Mental Health Nursing*, **11**, 476-483. https://doi.org/10.1111/j.1365-2850.2004.00751.x

[59] Bigley, A.B., Rezvani, K., Chew, C., Sekine, T., Pistillo, M., Crucian, B., *et al.* (2014) Acute Exercise Preferentially Redeploys NK-Cells with a Highly-Differentiated Phenotype and Augments Cytotoxicity against Lymphoma and Multiple Myeloma Target Cells. *Brain, Behavior, and Immunity*, **39**, 160-171. https://doi.org/10.1016/j.bbi.2013.10.030

[60] Bigley, A.B., Rezvani, K., Pistillo, M., Reed, J., Agha, N., Kunz, H., *et al.* (2015) Acute Exercise Preferentially Redeploys NK-Cells with a Highly-Differentiated Phenotype and Augments Cytotoxicity against Lymphoma and Multiple Myeloma Target Cells. Part II: Impact of Latent Cytomegalovirus Infection and Catechola-

mine Sensitivity. *Brain*, *Behavior*, *and Immunity*, **49**, 59-65.
https://doi.org/10.1016/j.bbi.2014.12.027

[61] Dhabhar, F.S. (2014) Effects of Stress on Immune Function: The Good, the Bad, and the beautiful. *Immunologic Research*, **58**, 193-210.
https://doi.org/10.1007/s12026-014-8517-0

[62] Pascoe, A.R., Singh, M.A.F. and Edwards, K.M. (2013) The Effects of Exercise on Vaccination Responses: A Review of Chronic and Acute Exercise Interventions in Humans. *Brain*, *Behavior*, *and Immunity*, **39**, 33-41.
https://doi.org/10.1016/j.bbi.2013.10.003