Molecular mechanisms involved in the positive effects of physical activity on coping with COVID-19

Ersilia Nigro[1,2], Rita Polito[1,2], Andreina Alfieri[2,3], Annamaria Mancini[2,3], Esther Imperlini[4], Ausilia Elce[5], Peter Krustrup[6,7,8], Stefania Orrù[2,3], Pasqualina Buono[2,3*], Aurora Daniele[1,2*]

[1] Dipartimento di Scienze e Tecnologie Ambientali, Biologiche, Farmaceutiche, Università della Campania "Luigi Vanvitelli", Via A. Vivaldi, 81100 Caserta, Italy; [2] CEINGE Biotecnologie Avanzate Scarl, Via G. Salvatore, 486 Naples, Italy; [3]Dipartimento di Scienze Motorie e del Benessere, Università "Parthenope", Naples, Italy; [4]IRCCS SDN, Via E. Gianturco, 80143 Naples, Italy; [5]Università Telematica Pegaso, Dipartimento di Scienze Umanistiche, Naples, Italy; [6] Department of Sports Science and Clinical Biomechanics, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark; [7] Shanghai University of Sport (SUS), Shanghai, China; [8] Sport and Health Sciences, University of Exeter, Exeter, United Kingdom.

** Corresponding Authors*

Aurora Daniele
* Professor of Human Nutrition
Dipartimento di Scienze e Tecnologie Ambientali Biologiche Farmaceutiche,
Università degli Studi della Campania, "Luigi Vanvitelli", Via G. Vivaldi 42, 81100 Caserta, Italy
* CEINGE-Biotecnologie Avanzate, Via Gaetano Salvatore, 486, 80145 Napoli, Italy
tel.: +39 081 3737856
fax: +39 081 3737808
email: aurora.daniele@unicampania.it

Pasqualina Buono
Dipartimento di Scienze Motorie e del Benessere, Università "Parthenope", Naples, Italy

Abstract

Purpose At a time of a pandemic SARS-CoV2 infection, and in the context of the multiorgan crosstalk widely accepted as a mechanism participating in the pathophysiology of all organs and systems, a correlation between adipose tissue, muscle and the immune system has been investigated. Physical Activity (PA) represents the first line of defence against metabolic diseases and infections, like SARS-CoV2, modulating several crucial functions such as inflammation and immune response. Conversely, obesity, type 2 diabetes and cardiovascular disorders – all correlated with PA - negatively impact on general health status, including susceptibility to infections. Here we review the complex interplay between type 2 diabetes, obesity, immune response, inflammation and viral infections, such as the current SARS-CoV2, focusing on the molecular mechanisms modulated by exercise.

Methods A comprehensive literature search was completed to identify joint biomarkers previously used to investigate acute and chronic exercise training.

Results we show that PA may counteract/mitigate viral adverse effects. We also describe data suggesting that vitamin D supplementation, frequently observed in practitioners of sport and regular exercise, could represent an additional positive factor in supporting COVID-19 with fighting against the virus.

Conclusion Altogether this evidence confirms that an active lifestyle and PA not only counteract dysmetabolic diseases but could also be effective for counteracting SARS-CoV2 infection. It is therefore essential to persuade people to keep active.

Keywords: Physical Activity, COVID-19, healthy lifestyle, metabolic disorders, immune system

List of abbreviations in alphabetical order

ACE2 Angiotensin-Converting Enzyme 2

AMPK 5' adenosine monophosphate-activated protein kinase

ARDS acute respiratory distress syndrome

Coronaviruses (CoVs)

COVID-19 corona virus disease 2019

CRP C-reactive protein

CVD cardiovascular disease

DPP4 dipeptidyl peptidase 4

FoxO Forkhead box O

hsCRP high-sensitive C-reactive Protein

IL interleukin

IL-1ra IL-1 receptor antagonist

IL-6R receptor

LPS lipopolysaccharide

M1 macrophages of subtype 1

M2 macrophages of subtype 2

MERS-CoV Middle East Respiratory Syndrome Coronavirus

NFAT activated nuclear T cell factor

NF-κB nuclear factor-kappa B

NLRs nucleotide-binding oligomerisation domain (NOD)-like receptors

PGC-1α peroxisome proliferator-activated receptor-gamma coactivator

PPRs pattern recognition receptors

SARS-CoV2 Severe Acute Respiratory Syndrome Coronavirus 2

SIRT1 sirtuin 1

SNS sympathetic nervous system

TLRs Toll-like receptors

TNF-α tumor necrosis factor-alpha

Introduction

Regular exercise positively contributes to general health status in all age groups, from children to elderly people (Fossati et al., 2020) (Wolfenden et al., 2020).Regular physical activity (PA) improves the health and metabolic status of various organs , mental wellness and the immune system in all ages (Whooten et al., 2019) (Rizzo et al., 2020). OMS recently defined the minimum level of PA (150 min of moderate/intense exercise; 10.000 steps) required to avoid a number of metabolic disorders, including obesity, type 2 diabetes, cardiovascular disease (CVD) and cancer (Warburton et al., 2006). The molecular mechanisms through which PA reduces the risk and severity of the above-mentioned disorders are multiple and complex, and are part of the context of chronic adaptations (Warburton et al., 2006). Regular PA also exerts protective effects against inflammatory processes through the regulation of immune responses and inflammatory processes (Nieman & Wentz, 2019). In addition, people performing regular PA are protected against infections (Romeo et al., 2010).

In December 2019, several cases of pneumonia of unknown origin occurred in Wuhan, China (Rothan & Byrareddy, 2020) and a new coronavirus, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), resembling the previous SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), was identified as the cause (Ahn et al., 2020). Coronaviruses are enveloped positive-sense RNA viruses that cause respiratory diseases; viral genome analysis has revealed that SARS-CoV2 is around 80% similar to SARS-CoV, but only 50% similar to MERS-CoV (*Https://Nextstrain. Org/Groups/Blab/Sars-like-Cov*, n.d.). Since December 2019, the SARS-CoV2 virus has spread from China to more than 200 countries worldwide (Rothan & Byrareddy, 2020). The World Health Organization update of 14 May on SARS-CoV2 contagion numbers reported 4,248,389 cases and 294,046 deaths globally (*Https://Www.Who.Int/Docs/Default-Source/Coronaviruse/Situation-Reports/20200414-Sitrep-85-SARS-CoV2-19.Pdf?Sfvrsn=7b8629bb_4).*, n.d.).

Subjects of all ages are susceptible, even though children often have a milder form of the disease than adults and child deaths have been extremely rare (Ludvigsson, 2020). Infection is transmitted through microdroplets generated when positive patients cough or sneeze, irrespective of the presence of symptoms (Singhal, 2020). The main symptoms, which generally manifest after 5 to 14 days of incubation, are fever, cough and fatigue, while other symptoms include sputum production, headache, haemoptysis and dyspnoea (Rothan & Byrareddy, 2020) (Lake, 2020). The manifestations are highly heterogeneous, with individuals being asymptomatic or displaying mild symptoms or a severe respiratory syndrome until death (Lai et al., 2020). The reasons determining the diversity of clinical manifestations of the disease

are largely unknown, though several comorbidities have been associated with an increased rate of contagiousness as well as a worse prognosis for the disease (Rodriguez-Morales et al., 2020). It is noteworthy that many of the comorbidities are metabolic-related disorders and/or immune dysregulations, both positively influenced by healthy lifestyle and PA. On the other hand, a sedentary lifestyle represents a clear risk factor for many diseases and for infections (Knight, 2012) (Nigro et al., 2017).

Here we review the current knowledge on the complex interplay between type 2 diabetes, obesity, immune response, inflammation and viral infections, such as the current SARS-CoV2, focusing on the molecular mechanisms positively influenced by PA that are likely to counteract/mitigate viral adverse effects.

SARS-CoV2 infection

Coronaviruses (CoVs) belong to the subfamily of Coronavirinae, classified into four genera namely, α–coronavirus, β–coronavirus, γ–coronavirus and δ-coronavirus, (de Groot et al., 2013) (W. Li et al., 2005). Of these four subfamilies, only α and β CoVs are able to infect humans, causing respiratory disease with a wide range of clinical phenotypes, from a mild influenza to a severe respiratory disease and, in the worst case, death (Hashem et al., 2020). CoVs are large enveloped viruses with a positive large single-stranded RNA, ranging from 26 to 32 kb (Perlman & Netland, 2009). As previously reported, two βCoVs, namely SARS-CoV and MERS-CoV, caused a severe epidemic respiratory syndrome, in 2002 and 2012, respectively (Ahn et al., 2020) while SARS-CoV2 emerged in 2019, reaching pandemic proportion within a few months of its appearance. The reservoirs of CoVs are bats and the intermediate host has been identified for SARS and MERS in masked palm civet cats and camels, respectively; the intermediate host of SARS-CoV2 has not yet been identified, although pangolins and mink represent a possible candidates (J. Xu et al., 2020).

The incubation time for SARS-CoV2 is between 4 to 14 days, and the clinical manifestations covers a wide spectrum, ranging from asymptomatic or slight forms to severe pneumonia, which can lead to acute respiratory distress syndrome (ARDS) and death (Jia et al., 2005).

SARS-CoV2 infects human epithelial cells through its surface glycoprotein, named Spike, which binds the Angiotensin-Converting Enzyme 2 (ACE2) transmembrane protein (Spinelli et al., 2020); ACE2 mediates the virus's entry into the cells. Although ACE2 is expressed in vascular endothelia, renal and cardiovascular tissues, and epithelia of the small intestine and testes, the high expression in alveolar epithelial cells accounts for the specificity of the lung infection

and the respiratory symptoms (Jia et al., 2005). Recently, the modelling structure of SARS-CoV-2 Spike predicts that this glycoprotein can also interact also with human dipeptidyl peptidase 4 (DPP4) (Bassendine et al., 2020). Spike proteins form homotrimers protruding from the viral surface, thus contacting host cells. Spike monomer comprises two domains, S1 and S2: the first mediates receptor association and stabilisation, while the latter promotes membrane fusion (Perrotta et al., 2020).

Physiologically, ACE2 provides a natural protection against acute lung injury exerting vasodilatory, anti-inflammatory and anti-fibrotic effects (Gaddam et al., 2014). During SARS-CoV2 infection, the virus induces a down-expression of the ACE2 proteins as a consequence of the entry into the cells contributing to the onset of the respiratory syndrome (Cheng et al., 2020). Virus replication itself causes an acute inflammatory response due to the activation of the innate immune system and the induction of cytokine expression by virus components such as the single-strand RNA. Accordingly, COVID-19 patients have high levels of circulating cytokines (tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-1Ra, sIL-2Rα, IL-6, IL-10, IL-17, IL-18, IFN-γ, MCP-3, M-CSF, MIP-1a, G-CSF, IP-10 and MCP-1), termed "hypercytokinemia", which is directly correlated to disease severity (Wu et al., 2020); in the very severe cases such high levels of circulating cytokines are referred to as a "cytokine storm" (Jamilloux et al., 2020). Interestingly, also a clinical deterioration of the infection is also associated with a pronounced increase in the inflammatory state, possibly diagnosed through the detection of the "cytokine storm" (Jamilloux et al., 2020).

Comorbidities in SARS-CoV2 infection

Although highly infectious, SARS-CoV2 has a higher incidence among people of older age and/or with comorbidities. Literature data have shown that hypertension, type 2 diabetes, coronary heart disease, cerebrovascular disease and severe obesity increase morbidity and mortality in patients with COVID-19, though the prevalence rate varied in different studies as well as in country-specific data (Guan et al., 2020) (Wang et al., 2020) (Pecoraro et al., 2017) (B. Li et al., 2020). Singh (2020) reported a prevalence of hypertension, type 2 diabetes and cardiovascular disorders in 21%, 11% and 7% of patients, respectively (Singhal, 2020). Similarly, in a study involving 46,248 patients, Yang et al. described a prevalence of hypertension, type 2 diabetes and CVD in 17%, 8% and 5% of patients, respectively (J. Yang et al., 2020). The Epidemiology Working Group of the Chinese Center for Disease Control and Prevention investigated 20,982 patients affected by SARS-CoV2 and found that hypertension, type 2 diabetes and CVD were associated in 13%, 5% and 4% of patients, respectively ("[The

epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China].," 2020). An Italian study by Onder et al. found type 2 diabetes in 36% and CVD in 43% of 355 Italian patients with SARS-CoV2 (Onder et al., 2020). Similar evidence of risk among persons with type 2 diabetes has been reported for the two earlier CoV infections, SARS in 2002 and MERS in 2012 (J. K. Yang et al., 2006) (Yu et al., 2006). In addition, plasma glucose levels and type 2 diabetes are independent predictors for mortality and morbidity in patients with SARS. Even for H1N1, metabolic disorders have been associated with symptom severity and mortality (Papp et al., 2002) (Sun et al., 2016).

Obesity has been added to the comorbidities able to exacerbate risk factors for poor outcome in corona virus disease 2019 (COVID-19) (Vaduganathan et al., 2020). As a matter of fact, the ACE2/RAS axis, activated in SARS-CoV2 lung infection, is also implicated in the pathophysiology of obesity; furthermore, ACE2 is not only highly expressed in adipocytes but its expression increases in adipocytes of obese and/or type 2 diabetic subjects (Kruglikov & Scherer, 2020). Such features could be the reason why seriously ill COVID-19 patients are often overweight or obese. Ryan and Caplice proposed a mechanism explaining how adipose tissue could act as a viral reservoir (Ryan & Caplice, 2020), able to support a sustained viral infection, as already proven for H5N1 virus infection: such a condition would occur in an already chronic low grade inflamed state, such as obesity, leading to a worse metabolic perturbation (Nishimura et al., 2000). Although it has not been described a direct SARS-CoV2 infection of adipose tissue has not been described, ACE2-expressing adipocyte cells are reported to be the entry point for other viruses, such as H1N1, type A influenza, and SARS-CoV, (Gu & Korteweg, 2007) (Maier et al., 2018), thus hypothetically allowing the spread of the viral infection to adjacent fat deposits in the heart, kidneys and intestines (Ryan & Caplice, 2020).

Several factors might link the presence of the above-mentioned metabolic diseases and worse SARS-CoV2 outcome; people suffering from metabolic disorders show a wide range of negative hallmarks, such as dysregulation of the glucose metabolism and immune system and increased inflammatory response that may contribute to worsening of the infection. The "cytokine storm" that mediates inflammatory and immune responses in SARS-CoV2 (Grant et al., 2020), appears to be exacerbated in metabolic disorders, thus interfering with infection resolution and management.

Immune and inflammatory response in COVID-19 infections

Innate immunity, the first-line host defence system, is able to recognise general patterns associated with viral, bacterial and fungal infections, thus eliminating pathogen-damaged cells (Amano et al., 2014). Specifically, after exposure to a pathogen, the cells that present antigens block its replication *via* the phagocytosis of infected host cells; in particular, the defence system acts through pattern recognition receptors (PPRs), such as Toll-like receptors (TLRs) and nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs), which bind the pathogen's components (Amano et al., 2014). Moreover, the rapid activation of PPR signalling cascades leads to the release of different cytokines and chemokines, which initiate an inflammatory response. The innate immune system-driven inflammatory responses are associated with the signalling of TLR2 and TLR4, which are highly expressed in pancreatic cells: notably, these responses are able to exacerbate insulin resistance in type 2 diabetes (Chan et al., 2019). In pancreatic islets, in fact, the overproduction of inflammatory cytokines, such as IL-1β and TNF-α, and chemokines, such as CCL2, induces the cell dysfunctions underlying type 2 diabetes (G. Chen et al., 2020) (N. Chen et al., 2020).

In addition to their function in counteracting infections, components of innate immunity also play a key role in maintaining metabolic homeostasis, thus properly regulating the so-called immune metabolic interactions (N. Chen et al., 2020) (Chan et al., 2019). As a consequence, macrophages, the major innate immune cells, increase in type 2 diabetes and accumulate in adipose tissue during obesity (X. Chen et al., 2020) (Donath, Dinarello, et al., 2019) (Drucker, 2020) (Dunachie & Chamnan, 2019). As mentioned above, type 2 diabetic subjects are at high risk for the COVID-19 infection, potentially complicated even more by a secondary bacterial infection. In general, diabetic subjects have a high susceptibility to human pathogen infections due to an impaired innate immune system, including neutrophil and monocyte dysfunctions (Guan & Zhong, 2020). The underlying mechanisms probably involve protein kinase C activation and TLR overexpression, with a consequent inhibition of the neutrophil function and decreased phagocytosis (S. Gupta et al., 2007). In addition, hyperglycaemia, which causes direct glycosylation of proteins, can alter the tertiary structure of complement inhibiting immunoglobulin-mediated opsonisation of bacteria and complement fixation to bacteria and decreasing phagocytosis (Murai et al., 2019).

Nevertheless, type 2 diabetic subjects have a dysregulated inflammatory response characterised by infiltration and accumulation of neutrophils and monocytes in metabolic tissues. The diabetes-related inflammatory state reduces the innate immune response by blunting pro-inflammatory cytokine production upon macrophage activation (R. Gupta et al., 2020) (Hill et al., 2018). Thus, type 2 diabetic subjects are more prone to bacterial infections

and other complications of COVID-19, including death (R. Gupta et al., 2020) (Lackey & Olefsky, 2016) (Luzi & Radaelli, 2020) (Magee & Narayan, 2013) (Morgan et al., 2010) (Moser et al., 2019).

The chronic and low-grade inflammation determined by metabolic disorders causes an increase in levels of the same pro-inflammatory cytokines, such as IL-6, that are hallmarks of the cytokine storm in viral infections, such as SARS-CoV2 (Ruiz et al., 2018) (Taguchi & Mukai, 2019) (Donath, Meier, et al., 2019). Haematological biomarkers related to the inflammatory state of COVID-19, such as IL-6, C-reactive protein (CRP), D-dimer and ferritin, are the main cytokines to be used as predictors of poor prognosis for SARS-CoV2. On top of that, during disease worsening, a further gradual increase of IL-6 has been observed, reaching extremely high levels in dead patients (Wu et al., 2020) (Ye et al., 2020) (Zheng et al., 2015).

Based on these biochemical findings, COVID-19 patients with type 2 diabetes are more likely, as a result of immune dysfunction and altered inflammatory response, to have adverse clinical outcomes, including admission to an intensive care unit, need for mechanical ventilation and death. Strict glycaemic control is therefore crucial for limiting any risk of favouring viral infections, including SARS-CoV2 (Honce & Schultz-Cherry, 2019) (Jafar et al., 2016). With this aim in mind, regular PA is a strategy that is adaptable to anyone's needs and capable of improving insulin sensibilisation as well as immune response in terms of macrophage activation (Rada et al., 2018).

Immune and inflammatory response regulation through PA: possible links with COVID infection

PA includes all activities performed daily, including work, transportation and structured exercise-training, such as playing ball-games, cycling, walking and other activities and, in association with equilibrated diet, represents the main component of a healthy lifestyle. To date, the effectiveness of performing a regular PA, including structured exercises and personalised training protocols, for all people is undisputed. Regular PA increases cardiorespiratory fitness, reduces the risk of cardiovascular mortality and improves psychosocial well-being (Sigal et al., 2006). Several studies, dealing with the association between exercise and inflammation, affirm that regular moderate PA (65-85%HRmax) (Hammami A, Harrabi B, Mohr M, 2020) has an anti-inflammatory effect counteracting metabolic disease, obesity increased inflammatory status as in ageing, CVD, etc. (Nicklas et al., 2008) (Park et al., 2014) (Lancaster & Febbraio, 2014) (Allen et al., 2015) (Bente Klarlund Pedersen, 2017). In addition, there is growing evidence to suggest that the immune system responds to PA and that the corresponding adaptations depend on the intensity and duration

of the effort and the type of exercise (Nieman & Wentz, 2019) (Bermon et al., 2017). PA, performed regularly and at moderate intensity (60 % VO2max/up to 60 minutes), stimulates the immune system by improving the function and antimicrobial action of tissue macrophages and promoting the activation and recirculation of key immune system factors, such as immunoglobulins, anti-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells and immature B cells. Over time, these favourable changes can improve immunosurveillance against infectious pathogens and protect or mitigate the symptoms of infectious diseases (Nieman & Wentz, 2019) (Davison et al., 2016) (Zheng et al., 2015); conversely, high-intensity training (>70-75% VO2max), competitive sport and related physiological, metabolic and psychological stress are strongly associated with temporary negative changes in the immune response, inflammation, oxidative stress and increased risk of disease (Laddu et al., 2020).

The anti-inflammatory response induced by regular PA is mediated by the muscle endocrine function; indeed, during contraction, muscle-derived cytokines, named myokines, are released to regulate not just both muscle metabolism but also the functioning of distant organs and tissues (bones, adipose tissue, brain and liver) in a paracrine/endocrine fashion. In this scenario, patients with type 2 diabetes, who are often overweight/obese, benefit from PA through a rapid improvement in the immune response, and concurrently reduced morbidity and mortality, even without substantial weight loss. On the other hand, stressful exercise also stimulates the release of cortisol and catecholamines (epinephrine and noradrenaline) due to activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (SNS). Both hormones act by reducing inflammatory cytokines (Prigent et al., 2004) (Kitamura et al., 2007), and, in particular, catecholamines (Uchida et al., 2014).

PA elicits potent effects on the immune system by reducing the risk, duration and severity of different viral infections, presumably including COVID-19 (Zbinden-Foncea et al., 2020). In a recent study conducted in obese mice with H1N1 viral infection, the authors demonstrated that PA reversed the immune system alterations associated with obesity in the host's immune defence (Warren et al., 2015). These results suggested that exercise stimulates the impaired immune system response in obese mice, thus promoting better recovery from viral infection (Luzi & Radaelli, 2020). The pattern of cytokines induced by moderate PA is typically anti-inflammatory, with a marked increase in serum levels of several anti-inflammatory cytokines, such as IL-10, IL-1 receptor antagonist (IL-1ra), IL-37, a natural inhibitor of innate and acquired immunity, and IL-6 (Bente K Pedersen & Febbraio, 2008) (P. Fernandes et al., 2019) (Abbasi et al., 2014) (Nold et al., 2010). In particular, the production and release of significant amounts of IL-6 helps to suppress the secretion of pro-inflammatory cytokines in several tissues, thus

creating an anti-inflammatory environment for several hours after exercise. It is well known that IL-6 has both pro and anti-inflammatory actions. In the "classic" signalling, IL-6 stimulates target cells by the binding its receptor (IL-6R) and the gp130 protein, inducing anti-inflammatory effects. However, very few cells express the membrane-bound IL-6R, whereas the majority of the cells presents only gp130, which is insensitive to IL-6 alone, but can interact with the soluble complex IL-6/IL-6R. This process, named “trans-signalling”, is responsible for the IL-6 pro-inflammatory response, observed in COVID-19 patients (Scheller et al., 2011). This process could explain, at least in part, the clinical efficacy of tocilizumab, the humanised monoclonal antibody that binds and neutralises both the soluble and the membrane-bound IL-6 receptor, in the treatment of several inflammatory diseases, including SARS-CoV2 (Radbel et al., 2020) (Hashizume et al., 2015). Hence, the anti-inflammatory effects of IL-6 induced by PA might interfere with the pro-inflammatory effects elicited by the virus.

Another mechanism supporting the anti-inflammatory effects of PA could be the modulation of TLR expression on monocytes and macrophages (Rada et al., 2018) (Flynn & McFarlin, 2006). In the past decade, the association between increased expression of TLRs, sedentary lifestyle, inflammation and disease has been consolidated. In vitro studies have shown that blood monocytes from physically active individuals exhibit a reduced inflammatory response after endotoxin stimulation, and reduced TLR4 expression both at mRNA and protein level, associated with a reduction in the production of inflammatory cytokines compared to inactive subjects (Lancaster et al., 2005) (Gleeson et al., 2011). Suppression or inactivation of TRL2 and TRL4 has been shown to reduce chronic inflammation in obese mice. The reduced expression of TLRs in adipose tissue, skeletal muscle and monocytes represents a molecular mechanism able to explain the anti-inflammatory response to both aerobic exercise and resistance training, especially in patients with low-grade chronic inflammation, such as obese and type 2 diabetic subjects. (Nold et al., 2010) (Collao et al., 2020) (Rada et al., 2018). Similarly, high TLR activity in obese subjects and smokers has been linked to insulin resistance (Könner & Brüning, 2011). McFarlin and colleagues also demonstrated, in physically active young and elderly subjects, a significant reduction in lipopolysaccharide-IL1β-stimulated IL6, TNF-α production, TLR4 expression and high-sensitive C-reactive Protein (hsCRP) compared to inactive participants (McFarlin et al., 2006). In addition, in obesity, PA is involved in the inhibition of inflammation through the reduction of immune cells infiltration into the adipose tissue. This mechanism involves the reduction of pro-inflammatory cytokines, as well as the reduction of plasma FFA levels, which suppresses TLR activation (Flynn & McFarlin, 2006) (Gleeson et al., 2011) (Ringseis et al., 2015) (Rada et al., 2018). Conversely, lipopolysaccharide (LPS), the major

pathogenic components of the cell wall of Gram-negative bacteria, and probably of SARS-CoV2, could bind to the TLR, triggering inflammation. This TLR-mediated intracellular pro-inflammatory signalling involves several proteins able to stimulate caspase 1 and induce the activation of the inflammasomes and the transcription of pro-inflammatory genes through the nuclear factor-kappa B (NF-κB) (Zbinden-Foncea et al., 2020).

Other mechanisms that could account for the positive PA effect against inflammation linked to COVID-19 infection are mediated by activated mitogen protein kinase (AMPK). This fuel-sensing enzyme, activated in contracting skeletal muscles, stimulates energy-generating pathways such as glucose uptake and fatty acid oxidation, and decreases energy-consuming processes such as protein and lipid synthesis (Richter & Ruderman, 2009). PA-mediated AMPK signalling accomplishes a dual purpose: it induces energy metabolism and can indirectly inhibit the inflammatory response induced by the NF-κB by means of several downstream targets of 5' adenosine monophosphate-activated protein kinase (AMPK), including sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), p53 and Forkhead box O (FoxO). This mechanism is linked to chronic stress, likewise occurring in metabolic syndrome as well as in type 2 diabetes and obesity (H.-W. Liu & Chang, 2018).

Other studies have recently demonstrated that the phosphorylation of ACE2, the main receptor for many coronaviruses, (Yan et al., 2020) improves Ang1-7, via AMPK, in pulmonary endothelial cells, thus reducing pulmonary hypertension (Zhang et al., 2018); Prata and colleagues demonstrated that moderate PA, performed by mice with bleomycin-induced pulmonary fibrosis, increased Ang1-7 via ACE2 in lung lesions, making these mice less susceptible to the disease (Prata et al., 2017). Figure 1 summarises the above-mentioned PA-mediated molecular mechanisms, which could help active subjects to counteract the current SARS-CoV2 infection.

The anti-inflammatory effects of regular PA on adipose tissue can be summarised in some fundamental mechanisms (Bente K Pedersen & Febbraio, 2008)(Mathur & Pedersen, 2008)(Flynn & McFarlin, 2006). The first mechanism can be ascribed to the reduction of visceral fat mass. Improvement in body composition results in decreased circulating levels of pro-inflammatory adipokines, such as TNFα, retinol binding protein 4 and leptin, and in increased anti-inflammatory cytokines, such as adiponectin (Mujumdar et al., 2011) (Ben Ounis et al., 2009) (Lim et al., 2008) (Metsios et al., 2020) (Nigro et al., 2014) (Orrù et al., 2017). Furthermore, reduction in adipose tissue is considered one of the main factors that can attenuate inflammation following regular exercise over the time. In fact, the adipose tissue acts as an endocrine organ, secreting many adipokines that coordinate/regulate multiple

physiological functions in a variety of tissues (Nigro et al., 2014) (Desruisseaux et al., 2007). The cellular composition of adipose tissue is heterogeneous and also includes also perycytes, monocytes and macrophages, thus highlighting an involvement of adipose tissue in the host immune response in an endocrine and/or paracrine fashion. In obese subjects, adipose tissue is responsible for the increase in pro-inflammatory factors; in particular, IL-6 and TNFα, deriving from macrophages present in adipose tissue, are higher in overweight/obese subjects compared to normal-weight subjects, and the activation of inflammatory processes occurs when the expansion of adipose tissue begins (Saltiel & Olefsky, 2017). In line with this, PA has been shown to significantly reduce fatty tissue compared to a low-calorie diet alone (Verheggen et al., 2016). Besides IL-6 and TNFα secretion, it should be noted that the obese state is characterised by an increase in macrophages in adipose tissue and of production of their corresponding cytokines and chemokines (IL-1b, IL-8, MCP-1 and IL-18) (Weisberg et al., 2003)(H. Xu et al., 2003), as well as by a rise in leptin and a reduction in adiponectin (Corbi et al., 2019). Moreover, several TLRs are expressed in adipocytes, and their response to eso/endotoxins induces high levels of pro-inflammatory cytokines, sometimes displaying a higher sensitivity than what observed in macrophages (Desruisseaux et al., 2007). The strong interplay between adipose tissue, immune system and inflammatory cytokines profoundly affects not only adipose tissue metabolism and endocrine function, but also non-adipose tissues. The power of this network also indicates that adipose tissue-derived cytokines could be instrumental in defending the host when facing an immune challenge, such as SARS-CoV2 (Al., 2020). An example is offered by PPARγ agonists, which are promising candidates for improving the clinical outcome of several viral diseases (Ciavarella et al., 2020).

In support of the anti-inflammatory effects of PA in the general population, exercise-induced IL-6 production has been shown to be regulated by an interaction between two pathways: that of activated nuclear T cell factor (NFAT) and that of mitogenic protein kinase activated by glycogen-p38 (MAPK) (Muñoz-Cánoves et al., 2013), without an increase in TNFα or NF-kB, usually elevated during prolonged inflammatory responses (Bente K Pedersen & Febbraio, 2008) (Bente Klarlund Pedersen, 2017). Similarly, in healthy exercising individuals there is a decrease in the pro-inflammatory macrophages of subtype 1 (M1) present in the muscles and an increase in the anti-inflammatory macrophages of subtype 2 (M2). PGC1α, which increases rapidly after one bout of exercise, has also been shown to generate polarisation of macrophages from M1 pro-inflammatory to M2 anti-inflammatory (Dinulovic et al., 2016). Moreover, it is also able to suppress the expression of inflammatory cytokines and increase the expression of anti-inflammatory cytokines (Eisele et al., 2015). Figure 2 shows the

inflammatory and immune events regulated by PA, with the release of cytokines and activation of elements of innate and adaptive immunity in muscle and adipose tissue.

Although further studies are needed, we can assume that good cardiorespiratory fitness, together with ameliorated exercise-induced immunosurveillance, counteracts, through the described molecular mechanisms, the amplified adverse effects observed in patients with COVID-19 infection.

Vitamin D supplementation and the risk of COVID-19

The role and metabolism of Vitamin D role in humans is well established (Holick, 2007). Known as the "sunshine vitamin", vitamin D is activated in the skin through the action of UVB radiation, then it is converted to 25(OH)D(calcidiol), in the liver, while the biologically active metabolite, 1,25(OH)2D (calcitriol), is produced principally in the kidneys and, to a lesser extent, in other organs. Calcitriol is able to enter the cell nucleus by activating its receptor, a DNA binding protein responsible for chromatin remodeling, modulating its target genes expression (Pike & Christakos, 2017).

Researchers' interest in vitamin D has been enhanced by recent advances related to its biology, as it plays an important role, far beyond calcium metabolism, as a key regulator of the immune system, able to reduce the risk of microbial infections (Hewison, 2012). In a recent review, the mechanisms of vitamin D on immune system were classified into three main categories: i) action on physical barriers (vitamin D helps maintain tight junctions, gap junctions, and adherent junctions, by cadherin expression induction), ii) regulation of cellular natural immunity (vitamin D induces antimicrobial peptides and modulates cytokines activity and production), and iii) adaptive immunity enhancement (vitamin D suppresses responses mediated by the T helper type 1 cell, induces differentiation of macrophages and modulates inflammation promoting cytokine production by the T helper type 2 cells) (Rondanelli et al., 2018).

The hypothesis for supplementing Vitamin D to enhance immunity, was proposed in relationship to COVID-19 disease (Misra et al., 2020) (J. Liu et al., 2020), because the severity of the infection is associated to aged patients and serum 25(OH)D concentrations tend to decrease with age (Vásárhelyi et al., 2011). Serum vitamin D levels may be important for evaluating COVID-19 case-fatality rates (CFRs) which result to be increased with age ("[The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China].," 2020). Vitamin D deficiency is therefore a risk factor for and/or a driver of the exaggerated and persistent inflammation that is a hallmark of ARDS (Dancer et al., 2015) and

its deficiency increases the risk for respiratory infections in both children and adults. Consistent with these findings, several recent meta-analyses assert that vitamin D supplementation may reduce the risk of respiratory tract infections. Accordingly, people at risk of influenza and/or COVID-19 might consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d, with the goal of raising 25(OH)D concentrations above 40 ng/mL (100-150 nmol/L); higher vitamin D3 doses might be useful for already infected subjects (Grant et al., 2020).

Indeed, there are certain factors possibly determining a vitamin D deficiency that, in turn, may increase susceptibility to SARS-CoV2 infection and poor prognosis: age, low exposure to sun, and physical inactivity. In the elderly, the progressive decrease of serum vitamin D levels may be a result of lower exposure time to the sun. In addition, several studies have highlighted that, during the winter months, at latitudes of >40°, little or no effective UVB radiation reaches the surface of the earth to activate vitamin D production. Living at high latitude therefore increases the risk of vitamin D deficiency during the winter (Leary et al., 2017). Factors like age and skin pigmentation features may partly explain the spread and severity of COVID-19 disease in northern countries (Garg et al., 2020) and in the Chinese population (Herold et al., 2020).

PA is also related to vitamin D status. Outdoor activities allow the synthesis of the vitamin D, thanks to the exposure to solar light (M. R. Fernandes & Barreto, 2017). However, recent studies have demonstrated that PA and exercise directly correlate with vitamin D levels regardless of outdoor practice, suggesting that the concentration of vitamin D is not only attributed to high sun exposure (van den Heuvel et al., 2013). On the other hand, poor levels of PA and fitness and obesity, two strictly interconnected conditions, are negatively correlated to plasma vitamin D levels (Brock et al., 2010). Table 1 reports the main literature data of the last seven years concerning the correlation between PA, fitness and serum vitamin D (Wanner et al., 2015) (Touvier et al., 2015) (Scott et al., 2015) (Pagels et al., 2016)(Valtueña et al., 2014) (Orces, 2019) (van den Heuvel et al., 2013) (Hossain et al., 2018).

Up to now, studies on serum level of vitamin D serum levels in severe COVID-19 patients are lacking. A simple comparison of vitamin D levels between survivors and confirmed fatalities, taking into account other factors such as age, pre-existing morbidities and cigarette smoking history, should be performed in a retrospective manner, in order to clarify the link between vitamin D serum levels and severity of COVID-19 disease. Randomised controlled trials in a large population should be conducted to evaluate the efficacy of a supplementation. Finally, lifestyle behaviour including outdoor physical activities should be promoted to achieve

adequate levels of vitamin D activation, sufficient protection against infections such as COVID-19 and a healthy status in all ages.

Authors	Year	Main findings
Valtueña et al.	2014	Outdoor physical training is associated with increased plasma concentration of vitamin D in athletes
Pagels et al.	2016	Exposure to the sun contributes to the synthesis of vitamin D
Orces et al.	2019	Physical activity is effective for modulating vitamin D only in the elderly
Hossai et al.	2018	Physical activity is effective for modulating vitamin D in children and adolescents
Scott et al.	2015	Indoors exercise results in increased levels of vitamin D
Touvier et al.	2015	Exercise results in increased levels of vitamin D, regardless of whether it is performed outdoors or indoors
Warnet et al.		
Van den Heuvel et al.	2013	Exercise results in increased levels of vitamin D, with the highest effects mediated by high-intensity training

Table 1. Summary of studies related to outdoor and indoor physical activity and vitamin D synthesis

Conclusions

Metabolic disorders such as obesity, and type 2 diabetes negatively impact on susceptibility to infections. Active lifestyle represents the first line of defense against metabolic disorders and positively modulates the inflammation status. As we wait for an anti-COVID-19 vaccine or the most promising treatment for the new CoV, experimental evidence suggests that mild-to-moderate PA could be a preventive strategy for positively modulating immune response, thus reducing comorbidities in COVID-19 infection. At a time of pandemic infection due to SARS-CoV2 infection, it is essential to persuade people to keep active in line with national recommendations in order to counteract metabolic-related disorders and reduce the impact on inflammatory status.

Conflicts of interest

The authors have no conflicts of interest that are directly relevant to the content of this research.

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Figure legends

Fig. 1: Physical activity and anti-inflammatory response in COVID infection. Regular physical activity may reduce the acute inflammatory response through at least three mechanisms: 1. by reducing the inflammatory signalling pathway mediated by TLRs; 2. by increasing the anti-inflammatory cytokines such as IL-10 and IL-37, which could inhibit the TLR-inflammatory signalling cascade and mitigate the inflammatory action produced by the inflammasome; 3. by reducing the lung inflammation through the activation of AMPK and promoting the conversion from Ang II to Ang 1-7.

Fig.2: Physical activity and anti-inflammatory response in muscle and adipose tissue. Physical activity induces an anti-inflammatory response in muscle and adipose tissue through the involvement of cells (e.g. macrophages), cytokines (e.g. interleukins (ILs)) and adipokines (e.g. adiponectin).

Bibliography

[The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. (2020). *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi*, *41*(2), 145–151. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003

Abbasi, A., Hauth, M., Walter, M., Hudemann, J., Wank, V., Niess, A. M., & Northoff, H. (2014). Exhaustive exercise modifies different gene expression profiles and pathways in LPS-stimulated and un-stimulated whole blood cultures. *Brain, Behavior, and Immunity*, *39*, 130–141. https://doi.org/10.1016/j.bbi.2013.10.023

Ahn, D.-G., Shin, H.-J., Kim, M.-H., Lee, S., Kim, H.-S., Myoung, J., Kim, B.-T., & Kim, S.-J. (2020). Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *Journal of Microbiology and Biotechnology*, *30*(3), 313–324. https://doi.org/10.4014/jmb.2003.03011

Al., P. R. et. (2020). The important role of adiponectin and orexin-A: two key proteins to improve health status. *Frontiers in Physiology Physiol*.

Allen, J., Sun, Y., & Woods, J. A. (2015). Exercise and the Regulation of Inflammatory Responses. *Progress in Molecular Biology and Translational Science*, *135*, 337–354. https://doi.org/10.1016/bs.pmbts.2015.07.003

Amano, S. U., Cohen, J. L., Vangala, P., Tencerova, M., Nicoloro, S. M., Yawe, J. C., Shen, Y., Czech, M. P., & Aouadi, M. (2014). Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. *Cell Metabolism*, *19*(1), 162–171. https://doi.org/10.1016/j.cmet.2013.11.017

Bassendine, M. F., Bridge, S. H., McCaughan, G. W., & Gorrell, M. D. (2020). Covid-19 and co-morbidities: a role for Dipeptidyl Peptidase 4 (DPP4) in disease severity? *Journal of Diabetes*. https://doi.org/10.1111/1753-0407.13052

Ben Ounis, O., Elloumi, M., Lac, G., Makni, E., Van Praagh, E., Zouhal, H., Tabka, Z., & Amri, M. (2009). Two-month effects of individualized exercise training with or without caloric restriction on plasma adipocytokine levels in obese female adolescents. *Annales d'endocrinologie*, *70*(4), 235–241. https://doi.org/10.1016/j.ando.2009.03.003

Bermon, S., Castell, L. M., Calder, P. C., Bishop, N. C., Blomstrand, E., Mooren, F. C., Krüger, K., Kavazis, A. N., Quindry, J. C., Senchina, D. S., Nieman, D. C., Gleeson, M., Pyne, D. B., Kitic, C. M., Close, G. L., Larson-Meyer, D. E., Marcos, A., Meydani, S. N., Wu, D., … Nagatomi, R. (2017). Consensus Statement Immunonutrition and Exercise. *Exercise Immunology Review*, *23*, 8–50.

Brock, K., Huang, W.-Y., Fraser, D. R., Ke, L., Tseng, M., Stolzenberg-Solomon, R., Peters, U., Ahn, J.,

Purdue, M., Mason, R. S., McCarty, C., Ziegler, R. G., & Graubard, B. (2010). Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. *The Journal of Steroid Biochemistry and Molecular Biology*, *121*(1–2), 462–466. https://doi.org/10.1016/j.jsbmb.2010.03.091

Chan, J. Y., Lee, K., Maxwell, E. L., Liang, C., & Laybutt, D. R. (2019). Macrophage alterations in islets of obese mice linked to beta cell disruption in diabetes. *Diabetologia*, *62*(6), 993–999. https://doi.org/10.1007/s00125-019-4844-y

Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., Wang, T., Zhang, X., Chen, H., Yu, H., Zhang, X., Zhang, M., Wu, S., Song, J., Chen, T., Han, M., Li, S., Luo, X., Zhao, J., & Ning, Q. (2020). Clinical and immunological features of severe and moderate coronavirus disease 2019. *The Journal of Clinical Investigation*, *130*(5), 2620–2629. https://doi.org/10.1172/JCI137244

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*, *395*(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y., Men, D., Huang, Q., Liu, Y., Yang, B., Ding, J., & Li, F. (2020). Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*. https://doi.org/10.1093/cid/ciaa449

Cheng, H., Wang, Y., & Wang, G.-Q. (2020). Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *Journal of Medical Virology*. https://doi.org/10.1002/jmv.25785

Ciavarella, C., Motta, I., Valente, S., & Pasquinelli, G. (2020). Pharmacological (or Synthetic) and Nutritional Agonists of PPAR-γ as Candidates for Cytokine Storm Modulation in COVID-19 Disease. *Molecules (Basel, Switzerland)*, *25*(9). https://doi.org/10.3390/molecules25092076

Collao, N., Rada, I., Francaux, M., Deldicque, L., & Zbinden-Foncea, H. (2020). Anti-Inflammatory Effect of Exercise Mediated by Toll-Like Receptor Regulation in Innate Immune Cells - A Review. *International Reviews of Immunology*, *39*(2), 39–52. https://doi.org/10.1080/08830185.2019.1682569

Corbi, G., Polito, R., Monaco, M. L., Cacciatore, F., Scioli, M., Ferrara, N., Daniele, A., & Nigro, E. (2019). Adiponectin Expression and Genotypes in Italian People with Severe Obesity Undergone a Hypocaloric Diet and Physical Exercise Program. *Nutrients*, *11*(9). https://doi.org/10.3390/nu11092195

Dancer, R. C. A., Parekh, D., Lax, S., D'Souza, V., Zheng, S., Bassford, C. R., Park, D., Bartis, D. G., Mahida, R., Turner, A. M., Sapey, E., Wei, W., Naidu, B., Stewart, P. M., Fraser, W. D., Christopher, K. B., Cooper, M. S., Gao, F., Sansom, D. M., … Thickett, D. R. (2015). Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax*, *70*(7), 617–624. https://doi.org/10.1136/thoraxjnl-2014-206680

Davison, G., Kehaya, C., & Wyn Jones, A. (2016). Nutritional and Physical Activity Interventions to Improve Immunity. *American Journal of Lifestyle Medicine*, *10*(3), 152–169. https://doi.org/10.1177/1559827614557773

de Groot, R. J., Baker, S. C., Baric, R. S., Brown, C. S., Drosten, C., Enjuanes, L., Fouchier, R. A. M., Galiano, M., Gorbalenya, A. E., Memish, Z. A., Perlman, S., Poon, L. L. M., Snijder, E. J., Stephens, G. M., Woo, P. C. Y., Zaki, A. M., Zambon, M., & Ziebuhr, J. (2013). Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. *Journal of Virology*, *87*(14), 7790–7792. https://doi.org/10.1128/JVI.01244-13

Desruisseaux, M. S., Nagajyothi, Trujillo, M. E., Tanowitz, H. B., & Scherer, P. E. (2007). Adipocyte, adipose tissue, and infectious disease. *Infection and Immunity*, *75*(3), 1066–1078. https://doi.org/10.1128/IAI.01455-06

Dinulovic, I., Furrer, R., Di Fulvio, S., Ferry, A., Beer, M., & Handschin, C. (2016). PGC-1α modulates necrosis, inflammatory response, and fibrotic tissue formation in injured skeletal muscle. *Skeletal Muscle*, *6*, 38. https://doi.org/10.1186/s13395-016-0110-x

Donath, M. Y., Dinarello, C. A., & Mandrup-Poulsen, T. (2019). Targeting innate immune mediators in type 1 and type 2 diabetes. *Nature Reviews. Immunology*, *19*(12), 734–746. https://doi.org/10.1038/s41577-019-0213-9

Donath, M. Y., Meier, D. T., & Böni-Schnetzler, M. (2019). Inflammation in the Pathophysiology and Therapy of Cardiometabolic Disease. *Endocrine Reviews*, *40*(4), 1080–1091. https://doi.org/10.1210/er.2019-00002

Drucker, D. J. (2020). Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. *Endocrine Reviews*, *41*(3). https://doi.org/10.1210/endrev/bnaa011

Dunachie, S., & Chamnan, P. (2019). The double burden of diabetes and global infection in low and middle-income countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *113*(2), 56–64. https://doi.org/10.1093/trstmh/try124

Eisele, P. S., Furrer, R., Beer, M., & Handschin, C. (2015). The PGC-1 coactivators promote an anti-inflammatory environment in skeletal muscle in vivo. *Biochemical and Biophysical Research Communications*, *464*(3), 692–697. https://doi.org/10.1016/j.bbrc.2015.06.166

Fernandes, M. R., & Barreto, W. D. R. J. (2017). Association between physical activity and vitamin D:

A narrative literature review. *Revista Da Associacao Medica Brasileira (1992)*, *63*(6), 550–556. https://doi.org/10.1590/1806-9282.63.06.550

Fernandes, P., de Mendonça Oliveira, L., Brüggemann, T. R., Sato, M. N., Olivo, C. R., & Arantes-Costa, F. M. (2019). Physical Exercise Induces Immunoregulation of TREG, M2, and pDCs in a Lung Allergic Inflammation Model. *Frontiers in Immunology*, *10*, 854. https://doi.org/10.3389/fimmu.2019.00854

Flynn, M. G., & McFarlin, B. K. (2006). Toll-like receptor 4: link to the anti-inflammatory effects of exercise? *Exercise and Sport Sciences Reviews*, *34*(4), 176–181. https://doi.org/10.1249/01.jes.0000240027.22749.14

Fossati, C., Torre, G., Borrione, P., Giombini, A., Fagnani, F., Turchetta, M., Albo, E., Casasco, M., Parisi, A., & Pigozzi, F. (2020). Biohumoral Indicators Influenced by Physical Activity in the Elderly. *Journal of Clinical Medicine*, *9*(4). https://doi.org/10.3390/jcm9041115

Gaddam, R. R., Chambers, S., & Bhatia, M. (2014). ACE and ACE2 in inflammation: a tale of two enzymes. *Inflammation & Allergy Drug Targets*, *13*(4), 224–234. https://doi.org/10.2174/1871528113666140713164506

Garg, M., Al-Ani, A., Mitchell, H., Hendy, P., & Christensen, B. (2020). Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North - supports vitamin D as a factor determining severity. Authors' reply. In *Alimentary pharmacology & therapeutics*. https://doi.org/10.1111/apt.15796

Gleeson, M., Bishop, N. C., Stensel, D. J., Lindley, M. R., Mastana, S. S., & Nimmo, M. A. (2011). The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Reviews. Immunology*, *11*(9), 607–615. https://doi.org/10.1038/nri3041

Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., & Bhattoa, H. P. (2020). Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, *12*(4). https://doi.org/10.3390/nu12040988

Gu, J., & Korteweg, C. (2007). Pathology and pathogenesis of severe acute respiratory syndrome. *The American Journal of Pathology*, *170*(4), 1136–1147. https://doi.org/10.2353/ajpath.2007.061088

Guan, W.-J., Liang, W.-H., Zhao, Y., Liang, H.-R., Chen, Z.-S., Li, Y.-M., Liu, X.-Q., Chen, R.-C., Tang, C.-L., Wang, T., Ou, C.-Q., Li, L., Chen, P.-Y., Sang, L., Wang, W., Li, J.-F., Li, C.-C., Ou, L.-M., Cheng, B., … He, J.-X. (2020). Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *The European Respiratory Journal*. https://doi.org/10.1183/13993003.00547-2020

Guan, W.-J., & Zhong, N.-S. (2020). Clinical Characteristics of Covid-19 in China. Reply. In *The New England journal of medicine* (Vol. 382). https://doi.org/10.1056/NEJMc2005203

Gupta, R., Ghosh, A., Singh, A. K., & Misra, A. (2020). Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes & Metabolic Syndrome*, *14*(3), 211–212. https://doi.org/10.1016/j.dsx.2020.03.002

Gupta, S., Koirala, J., Khardori, R., & Khardori, N. (2007). Infections in diabetes mellitus and hyperglycemia. *Infectious Disease Clinics of North America*, *21*(3), 617–638, vii. https://doi.org/10.1016/j.idc.2007.07.003

Hammami A, Harrabi B, Mohr M, K. P. (2020). No Title. *Managing Sport and Leisure*. https://doi.org/DOI: 10.1080/23750472.2020.1757494

Hashem, A. M., Alghamdi, B. S., Algaissi, A. A., Alshehri, F. S., Bukhari, A., Alfaleh, M. A., & Memish, Z. A. (2020). Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. *Travel Medicine and Infectious Disease*, 101735. https://doi.org/10.1016/j.tmaid.2020.101735

Hashizume, M., Tan, S.-L., Takano, J., Ohsawa, K., Hasada, I., Hanasaki, A., Ito, I., Mihara, M., & Nishida, K. (2015). Tocilizumab, a humanized anti-IL-6R antibody, as an emerging therapeutic option for rheumatoid arthritis: molecular and cellular mechanistic insights. *International Reviews of Immunology*, *34*(3), 265–279. https://doi.org/10.3109/08830185.2014.938325

Herold, T., Jurinovic, V., Arnreich, C., Hellmuth, J. C., von Bergwelt-Baildon, M., Klein, M., & Weinberger, T. (2020). Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. *MedRxiv*, 2020.04.01.20047381. https://doi.org/10.1101/2020.04.01.20047381

Hewison, M. (2012). An update on vitamin D and human immunity. *Clinical Endocrinology*, *76*(3), 315–325. https://doi.org/10.1111/j.1365-2265.2011.04261.x

Hill, D. A., Lim, H.-W., Kim, Y. H., Ho, W. Y., Foong, Y. H., Nelson, V. L., Nguyen, H. C. B., Chegireddy, K., Kim, J., Habertheuer, A., Vallabhajosyula, P., Kambayashi, T., Won, K.-J., & Lazar, M. A. (2018). Distinct macrophage populations direct inflammatory versus physiological changes in adipose tissue. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(22), E5096–E5105. https://doi.org/10.1073/pnas.1802611115

Holick, M. F. (2007). Vitamin D deficiency. *The New England Journal of Medicine*, *357*(3), 266–281. https://doi.org/10.1056/NEJMra070553

Honce, R., & Schultz-Cherry, S. (2019). Impact of Obesity on Influenza A Virus Pathogenesis, Immune Response, and Evolution. *Frontiers in Immunology*, *10*, 1071. https://doi.org/10.3389/fimmu.2019.01071

Hossain, M. J., Levinson, A., George, D., Canas, J., Kumar, S., & Balagopal, P. B. (2018). Vitamin D Status and Cardiovascular Risk in Obesity: Effect of Physical Activity in Nonvitamin D Supplemented Adolescents. *Metabolic Syndrome and Related Disorders*, *16*(4), 197–203. https://doi.org/10.1089/met.2017.0171

https://nextstrain. org/groups/blab/sars-like-cov. (n.d.).

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200414-sitrep-85-SARS-CoV2-19.pdf?sfvrsn=7b8629bb_4). (n.d.).

Jafar, N., Edriss, H., & Nugent, K. (2016). The Effect of Short-Term Hyperglycemia on the Innate Immune System. *The American Journal of the Medical Sciences*, *351*(2), 201–211. https://doi.org/10.1016/j.amjms.2015.11.011

Jamilloux, Y., Henry, T., Belot, A., Viel, S., Fauter, M., El Jammal, T., Walzer, T., François, B., & Sève, P. (2020). Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmunity Reviews*, 102567. https://doi.org/10.1016/j.autrev.2020.102567

Jia, H. P., Look, D. C., Shi, L., Hickey, M., Pewe, L., Netland, J., Farzan, M., Wohlford-Lenane, C., Perlman, S., & McCray, P. B. J. (2005). ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *Journal of Virology*, *79*(23), 14614–14621. https://doi.org/10.1128/JVI.79.23.14614-14621.2005

Kitamura, H., Shiva, D., Woods, J. A., & Yano, H. (2007). Beta-adrenergic receptor blockade attenuates the exercise-induced suppression of TNF-alpha in response to lipopolysaccharide in rats. *Neuroimmunomodulation*, *14*(2), 91–96. https://doi.org/10.1159/000107424

Knight, J. A. (2012). Physical inactivity: associated diseases and disorders. *Annals of Clinical and Laboratory Science*, *42*(3), 320–337.

Könner, A. C., & Brüning, J. C. (2011). Toll-like receptors: linking inflammation to metabolism. *Trends in Endocrinology and Metabolism: TEM*, *22*(1), 16–23. https://doi.org/10.1016/j.tem.2010.08.007

Kruglikov, I. L., & Scherer, P. E. (2020). The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. *Obesity (Silver Spring, Md.)*. https://doi.org/10.1002/oby.22856

Lackey, D. E., & Olefsky, J. M. (2016). Regulation of metabolism by the innate immune system. *Nature Reviews. Endocrinology*, *12*(1), 15–28. https://doi.org/10.1038/nrendo.2015.189

Laddu, D. R., Lavie, C. J., Phillips, S. A., & Arena, R. (2020). Physical activity for immunity protection: Inoculating populations with healthy living medicine in preparation for the next pandemic. In *Progress in cardiovascular diseases*. https://doi.org/10.1016/j.pcad.2020.04.006

Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J., & Hsueh, P.-R. (2020). Severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, *55*(3), 105924. https://doi.org/10.1016/j.ijantimicag.2020.105924

Lake, M. A. (2020). What we know so far: COVID-19 current clinical knowledge and research. *Clinical Medicine (London, England)*, *20*(2), 124–127. https://doi.org/10.7861/clinmed.2019-coron

Lancaster, G. I., & Febbraio, M. A. (2014). The immunomodulating role of exercise in metabolic disease. *Trends in Immunology*, *35*(6), 262–269. https://doi.org/10.1016/j.it.2014.02.008

Lancaster, G. I., Khan, Q., Drysdale, P., Wallace, F., Jeukendrup, A. E., Drayson, M. T., & Gleeson, M. (2005). The physiological regulation of toll-like receptor expression and function in humans. *The Journal of Physiology*, *563*(Pt 3), 945–955. https://doi.org/10.1113/jphysiol.2004.081224

Leary, P. F., Zamfirova, I., Au, J., & McCracken, W. H. (2017). Effect of Latitude on Vitamin D Levels. *The Journal of the American Osteopathic Association*, *117*(7), 433–439. https://doi.org/10.7556/jaoa.2017.089

Li, B., Yang, J., Zhao, F., Zhi, L., Wang, X., Liu, L., Bi, Z., & Zhao, Y. (2020). Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clinical Research in Cardiology : Official Journal of the German Cardiac Society*, *109*(5), 531–538. https://doi.org/10.1007/s00392-020-01626-9

Li, W., Shi, Z., Yu, M., Ren, W., Smith, C., Epstein, J. H., Wang, H., Crameri, G., Hu, Z., Zhang, H., Zhang, J., McEachern, J., Field, H., Daszak, P., Eaton, B. T., Zhang, S., & Wang, L.-F. (2005). Bats are natural reservoirs of SARS-like coronaviruses. *Science (New York, N.Y.)*, *310*(5748), 676–679. https://doi.org/10.1126/science.1118391

Lim, S., Choi, S. H., Jeong, I.-K., Kim, J. H., Moon, M. K., Park, K. S., Lee, H. K., Kim, Y.-B., & Jang, H. C. (2008). Insulin-sensitizing effects of exercise on adiponectin and retinol-binding protein-4 concentrations in young and middle-aged women. *The Journal of Clinical Endocrinology and Metabolism*, *93*(6), 2263–2268. https://doi.org/10.1210/jc.2007-2028

Liu, H.-W., & Chang, S.-J. (2018). Moderate Exercise Suppresses NF-κB Signaling and Activates the SIRT1-AMPK-PGC1α Axis to Attenuate Muscle Loss in Diabetic db/db Mice. *Frontiers in Physiology*, *9*, 636. https://doi.org/10.3389/fphys.2018.00636

Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., Li, W., Tong, Q., Yi, J., Zhao, L., Xiong, L., Guo, C., Tian, J., Luo, J., Yao, J., Pang, R., Shen, H., Peng, C., Liu, T., … Zheng, X. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*, *55*, 102763. https://doi.org/10.1016/j.ebiom.2020.102763

Ludvigsson, J. F. (2020). Systematic review of COVID-19 in children shows milder cases and a better

prognosis than adults. *Acta Paediatrica (Oslo, Norway : 1992)*. https://doi.org/10.1111/apa.15270

Luzi, L., & Radaelli, M. G. (2020). Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. *Acta Diabetologica*, 1–6. https://doi.org/10.1007/s00592-020-01522-8

Magee, M. J., & Narayan, K. M. V. (2013). Global confluence of infectious and non-communicable diseases -- the case of type 2 diabetes. *Preventive Medicine*, *57*(3), 149–151. https://doi.org/10.1016/j.ypmed.2013.05.027

Maier, H. E., Lopez, R., Sanchez, N., Ng, S., Gresh, L., Ojeda, S., Burger-Calderon, R., Kuan, G., Harris, E., Balmaseda, A., & Gordon, A. (2018). Obesity Increases the Duration of Influenza A Virus Shedding in Adults. *The Journal of Infectious Diseases*, *218*(9), 1378–1382. https://doi.org/10.1093/infdis/jiy370

Mathur, N., & Pedersen, B. K. (2008). Exercise as a mean to control low-grade systemic inflammation. *Mediators of Inflammation*, *2008*, 109502. https://doi.org/10.1155/2008/109502

McFarlin, B. K., Flynn, M. G., Campbell, W. W., Craig, B. A., Robinson, J. P., Stewart, L. K., Timmerman, K. L., & Coen, P. M. (2006). Physical activity status, but not age, influences inflammatory biomarkers and toll-like receptor 4. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*(4), 388–393. https://doi.org/10.1093/gerona/61.4.388

Metsios, G. S., Moe, R. H., & Kitas, G. D. (2020). Exercise and inflammation. *Best Practice & Research. Clinical Rheumatology*, 101504. https://doi.org/10.1016/j.berh.2020.101504

Misra, D. P., Agarwal, V., Gasparyan, A. Y., & Zimba, O. (2020). Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. *Clinical Rheumatology*, 1–8. https://doi.org/10.1007/s10067-020-05073-9

Morgan, O. W., Bramley, A., Fowlkes, A., Freedman, D. S., Taylor, T. H., Gargiullo, P., Belay, B., Jain, S., Cox, C., Kamimoto, L., Fiore, A., Finelli, L., Olsen, S. J., & Fry, A. M. (2010). Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PloS One*, *5*(3), e9694. https://doi.org/10.1371/journal.pone.0009694

Moser, J.-A. S., Galindo-Fraga, A., Ortiz-Hernández, A. A., Gu, W., Hunsberger, S., Galán-Herrera, J.-F., Guerrero, M. L., Ruiz-Palacios, G. M., & Beigel, J. H. (2019). Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. *Influenza and Other Respiratory Viruses*, *13*(1), 3–9. https://doi.org/10.1111/irv.12618

Mujumdar, P. P., Duerksen-Hughes, P. J., Firek, A. F., & Hessinger, D. A. (2011). Long-term,

progressive, aerobic training increases adiponectin in middle-aged, overweight, untrained males and females. *Scandinavian Journal of Clinical and Laboratory Investigation*, *71*(2), 101–107. https://doi.org/10.3109/00365513.2011.554995

Muñoz-Cánoves, P., Scheele, C., Pedersen, B. K., & Serrano, A. L. (2013). Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? *The FEBS Journal*, *280*(17), 4131–4148. https://doi.org/10.1111/febs.12338

Murai, K., Honda, M., Shirasaki, T., Shimakami, T., Omura, H., Misu, H., Kita, Y., Takeshita, Y., Ishii, K.-A., Takamura, T., Urabe, T., Shimizu, R., Okada, H., Yamashita, T., Sakai, Y., & Kaneko, S. (2019). Induction of Selenoprotein P mRNA during Hepatitis C Virus Infection Inhibits RIG-I-Mediated Antiviral Immunity. *Cell Host & Microbe*, *25*(4), 588-601.e7. https://doi.org/10.1016/j.chom.2019.02.015

Nicklas, B. J., Hsu, F.-C., Brinkley, T. J., Church, T., Goodpaster, B. H., Kritchevsky, S. B., & Pahor, M. (2008). Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *Journal of the American Geriatrics Society*, *56*(11), 2045–2052. https://doi.org/10.1111/j.1532-5415.2008.01994.x

Nieman, D. C., & Wentz, L. M. (2019). The compelling link between physical activity and the body's defense system. *Journal of Sport and Health Science*, *8*(3), 201–217. https://doi.org/10.1016/j.jshs.2018.09.009

Nigro, E., Scudiero, O., Ludovica Monaco, M., Polito, R., Schettino, P., Grandone, A., Perrone, L., Miraglia Del Giudice, E., & Daniele, A. (2017). Adiponectin profile and Irisin expression in Italian obese children: Association with insulin-resistance. *Cytokine*, *94*, 8–13. https://doi.org/10.1016/j.cyto.2016.12.018

Nigro, E., Scudiero, O., Monaco, M. L., Palmieri, A., Mazzarella, G., Costagliola, C., Bianco, A., & Daniele, A. (2014). New insight into adiponectin role in obesity and obesity-related diseases. *BioMed Research International*, *2014*, 658913. https://doi.org/10.1155/2014/658913

Nishimura, H., Itamura, S., Iwasaki, T., Kurata, T., & Tashiro, M. (2000). Characterization of human influenza A (H5N1) virus infection in mice: neuro-, pneumo- and adipotropic infection. *The Journal of General Virology*, *81*(Pt 10), 2503–2510. https://doi.org/10.1099/0022-1317-81-10-2503

Nold, M. F., Nold-Petry, C. A., Zepp, J. A., Palmer, B. E., Bufler, P., & Dinarello, C. A. (2010). IL-37 is a fundamental inhibitor of innate immunity. *Nature Immunology*, *11*(11), 1014–1022. https://doi.org/10.1038/ni.1944

Onder, G., Rezza, G., & Brusaferro, S. (2020). Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. https://doi.org/10.1001/jama.2020.4683

Orces, C. H. (2019). Association between leisure-time aerobic physical activity and vitamin D concentrations among US older adults: the NHANES 2007-2012. *Aging Clinical and Experimental Research*, *31*(5), 685–693. https://doi.org/10.1007/s40520-018-1031-9

Orrù, S., Nigro, E., Mandola, A., Alfieri, A., Buono, P., Daniele, A., Mancini, A., & Imperlini, E. (2017). A Functional Interplay between IGF-1 and Adiponectin. *International Journal of Molecular Sciences*, *18*(10). https://doi.org/10.3390/ijms18102145

Pagels, P., Wester, U., Söderström, M., Lindelöf, B., & Boldemann, C. (2016). Suberythemal Sun Exposures at Swedish Schools Depend on Sky Views of the Outdoor Environments - Possible Implications for Pupils' Health. *Photochemistry and Photobiology*, *92*(1), 201–207. https://doi.org/10.1111/php.12540

Papp, M., Li, X., Zhuang, J., Wang, R., & Uhal, B. D. (2002). Angiotensin receptor subtype AT(1) mediates alveolar epithelial cell apoptosis in response to ANG II. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *282*(4), L713-8. https://doi.org/10.1152/ajplung.00103.2001

Park, Y.-M., Myers, M., & Vieira-Potter, V. J. (2014). Adipose tissue inflammation and metabolic dysfunction: role of exercise. *Missouri Medicine*, *111*(1), 65–72.

Pecoraro, A., Nigro, E., Polito, R., Monaco, M. L., Scudiero, O., Mormile, I., Cesoni Marcelli, A., Capasso, M., Habetswallner, F., Genovese, A., Daniele, A., & Spadaro, G. (2017). Total and High Molecular Weight Adiponectin Expression Is Decreased in Patients with Common Variable Immunodeficiency: Correlation with Ig Replacement Therapy. *Frontiers in Immunology*, *8*, 895. https://doi.org/10.3389/fimmu.2017.00895

Pedersen, Bente K, & Febbraio, M. A. (2008). Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiological Reviews*, *88*(4), 1379–1406. https://doi.org/10.1152/physrev.90100.2007

Pedersen, Bente Klarlund. (2017). Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. *European Journal of Clinical Investigation*, *47*(8), 600–611. https://doi.org/10.1111/eci.12781

Perlman, S., & Netland, J. (2009). Coronaviruses post-SARS: update on replication and pathogenesis. *Nature Reviews. Microbiology*, *7*(6), 439–450. https://doi.org/10.1038/nrmicro2147

Perrotta, F., Matera, M. G., Cazzola, M., & Bianco, A. (2020). Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter? *Respiratory Medicine*, *168*(April), 105996. https://doi.org/10.1016/j.rmed.2020.105996

Pike, J. W., & Christakos, S. (2017). Biology and Mechanisms of Action of the Vitamin D Hormone. *Endocrinology and Metabolism Clinics of North America*, *46*(4), 815–843.

https://doi.org/10.1016/j.ecl.2017.07.001

Prata, L. O., Rodrigues, C. R., Martins, J. M., Vasconcelos, P. C., Oliveira, F. M. S., Ferreira, A. J., Rodrigues-Machado, M. da G., & Caliari, M. V. (2017). Original Research: ACE2 activator associated with physical exercise potentiates the reduction of pulmonary fibrosis. *Experimental Biology and Medicine (Maywood, N.J.)*, *242*(1), 8–21. https://doi.org/10.1177/1535370216665174

Prigent, H., Maxime, V., & Annane, D. (2004). Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. *Critical Care (London, England)*, *8*(4), 243–252. https://doi.org/10.1186/cc2878

Rada, I., Deldicque, L., Francaux, M., & Zbinden-Foncea, H. (2018). Toll like receptor expression induced by exercise in obesity and metabolic syndrome: A systematic review. *Exercise Immunology Review*, *24*, 60–71.

Radbel, J., Narayanan, N., & Bhatt, P. J. (2020). Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome: A Cautionary Case Report. In *Chest*. https://doi.org/10.1016/j.chest.2020.04.024

Richter, E. A., & Ruderman, N. B. (2009). AMPK and the biochemistry of exercise: implications for human health and disease. *The Biochemical Journal*, *418*(2), 261–275. https://doi.org/10.1042/BJ20082055

Ringseis, R., Eder, K., Mooren, F. C., & Krüger, K. (2015). Metabolic signals and innate immune activation in obesity and exercise. *Exercise Immunology Review*, *21*, 58–68.

Rizzo, M. R., Fasano, R., & Paolisso, G. (2020). Adiponectin and Cognitive Decline. *International Journal of Molecular Sciences*, *21*(6). https://doi.org/10.3390/ijms21062010

Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Gutiérrez-Ocampo, E., Villamizar-Peña, R., Holguin-Rivera, Y., Escalera-Antezana, J. P., Alvarado-Arnez, L. E., Bonilla-Aldana, D. K., Franco-Paredes, C., Henao-Martinez, A. F., Paniz-Mondolfi, A., Lagos-Grisales, G. J., Ramírez-Vallejo, E., Suárez, J. A., Zambrano, L. I., Villamil-Gómez, W. E., Balbin-Ramon, G. J., Rabaan, A. A., Harapan, H., … Sah, R. (2020). Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Medicine and Infectious Disease*, 101623. https://doi.org/10.1016/j.tmaid.2020.101623

Romeo, J., Wärnberg, J., Pozo, T., & Marcos, A. (2010). Physical activity, immunity and infection. *The Proceedings of the Nutrition Society*, *69*(3), 390–399. https://doi.org/10.1017/S0029665110001795

Rondanelli, M., Miccono, A., Lamburghini, S., Avanzato, I., Riva, A., Allegrini, P., Faliva, M. A., Peroni, G., Nichetti, M., & Perna, S. (2018). Self-Care for Common Colds: The Pivotal Role of Vitamin D,

Vitamin C, Zinc, and Echinacea in Three Main Immune Interactive Clusters (Physical Barriers, Innate and Adaptive Immunity) Involved during an Episode of Common Colds-Practical Advice on Dosages a. *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2018*, 5813095. https://doi.org/10.1155/2018/5813095

Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, *109*, 102433. https://doi.org/10.1016/j.jaut.2020.102433

Ruiz, P. L. D., Tapia, G., Bakken, I. J., Håberg, S. E., Hungnes, O., Gulseth, H. L., & Stene, L. C. (2018). Pandemic influenza and subsequent risk of type 1 diabetes: a nationwide cohort study. *Diabetologia*, *61*(9), 1996–2004. https://doi.org/10.1007/s00125-018-4662-7

Ryan, P. M., & Caplice, N. M. (2020). Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19. *Obesity (Silver Spring, Md.)*. https://doi.org/10.1002/oby.22843

Saltiel, A. R., & Olefsky, J. M. (2017). Inflammatory mechanisms linking obesity and metabolic disease. *The Journal of Clinical Investigation*, *127*(1), 1–4. https://doi.org/10.1172/JCI92035

Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica et Biophysica Acta*, *1813*(5), 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034

Scott, D., Ebeling, P. R., Sanders, K. M., Aitken, D., Winzenberg, T., & Jones, G. (2015). Vitamin d and physical activity status: associations with five-year changes in body composition and muscle function in community-dwelling older adults. *The Journal of Clinical Endocrinology and Metabolism*, *100*(2), 670–678. https://doi.org/10.1210/jc.2014-3519

Sigal, R. J., Kenny, G. P., Wasserman, D. H., Castaneda-Sceppa, C., & White, R. D. (2006). Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care*, *29*(6), 1433–1438. https://doi.org/10.2337/dc06-9910

Singhal, T. (2020). A Review of Coronavirus Disease-2019 (COVID-19). *Indian Journal of Pediatrics*, *87*(4), 281–286. https://doi.org/10.1007/s12098-020-03263-6

Spinelli, F. R., Conti, F., & Gadina, M. (2020). HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19. *Science Immunology*, *5*(47). https://doi.org/10.1126/sciimmunol.abc5367

Sun, Y., Wang, Q., Yang, G., Lin, C., Zhang, Y., & Yang, P. (2016). Weight and prognosis for influenza A(H1N1)pdm09 infection during the pandemic period between 2009 and 2011: a systematic review of observational studies with meta-analysis. *Infectious Diseases (London, England)*, *48*(11–12), 813–822. https://doi.org/10.1080/23744235.2016.1201721

Taguchi, T., & Mukai, K. (2019). Innate immunity signalling and membrane trafficking. *Current Opinion in Cell Biology*, *59*, 1–7. https://doi.org/10.1016/j.ceb.2019.02.002

Touvier, M., Deschasaux, M., Montourcy, M., Sutton, A., Charnaux, N., Kesse-Guyot, E., Assmann, K. E., Fezeu, L., Latino-Martel, P., Druesne-Pecollo, N., Guinot, C., Latreille, J., Malvy, D., Galan, P., Hercberg, S., Le Clerc, S., Souberbielle, J.-C., & Ezzedine, K. (2015). Determinants of vitamin D status in Caucasian adults: influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors. *The Journal of Investigative Dermatology*, *135*(2), 378–388. https://doi.org/10.1038/jid.2014.400

Uchida, M., Oyanagi, E., Kawanishi, N., Iemitsu, M., Miyachi, M., Kremenik, M. J., Onodera, S., & Yano, H. (2014). Exhaustive exercise increases the TNF-α production in response to flagellin via the upregulation of toll-like receptor 5 in the large intestine in mice. *Immunology Letters*, *158*(1–2), 151–158. https://doi.org/10.1016/j.imlet.2013.12.021

Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J. V, Pfeffer, M. A., & Solomon, S. D. (2020). Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *The New England Journal of Medicine*, *382*(17), 1653–1659. https://doi.org/10.1056/NEJMsr2005760

Valtueña, J., Dominguez, D., Til, L., González-Gross, M., & Drobnic, F. (2014). High prevalence of vitamin D insufficiency among elite Spanish athletes the importance of outdoor training adaptation. *Nutricion Hospitalaria*, *30*(1), 124–131. https://doi.org/10.3305/nh.2014.30.1.7539

van den Heuvel, E. G. H. M., van Schoor, N., de Jongh, R. T., Visser, M., & Lips, P. (2013). Cross-sectional study on different characteristics of physical activity as determinants of vitamin D status; inadequate in half of the population. *European Journal of Clinical Nutrition*, *67*(4), 360–365. https://doi.org/10.1038/ejcn.2013.22

Vásárhelyi, B., Sátori, A., Olajos, F., Szabó, A., & Beko, G. (2011). [Low vitamin D levels among patients at Semmelweis University: retrospective analysis during a one-year period]. *Orvosi hetilap*, *152*(32), 1272–1277. https://doi.org/10.1556/OH.2011.29187

Verheggen, R. J. H. M., Maessen, M. F. H., Green, D. J., Hermus, A. R. M. M., Hopman, M. T. E., & Thijssen, D. H. T. (2016). A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *17*(8), 664–690. https://doi.org/10.1111/obr.12406

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, *323*(11), 1061–1069. https://doi.org/10.1001/jama.2020.1585

Wanner, M., Richard, A., Martin, B., Linseisen, J., & Rohrmann, S. (2015). Associations between objective and self-reported physical activity and vitamin D serum levels in the US population. *Cancer Causes & Control : CCC*, *26*(6), 881–891. https://doi.org/10.1007/s10552-015-0563-y

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *174*(6), 801–809. https://doi.org/10.1503/cmaj.051351

Warren, K. J., Olson, M. M., Thompson, N. J., Cahill, M. L., Wyatt, T. A., Yoon, K. J., Loiacono, C. M., & Kohut, M. L. (2015). Exercise Improves Host Response to Influenza Viral Infection in Obese and Non-Obese Mice through Different Mechanisms. *PloS One*, *10*(6), e0129713. https://doi.org/10.1371/journal.pone.0129713

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., & Ferrante, A. W. J. (2003). Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of Clinical Investigation*, *112*(12), 1796–1808. https://doi.org/10.1172/JCI19246

Whooten, R., Kerem, L., & Stanley, T. (2019). Physical activity in adolescents and children and relationship to metabolic health. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *26*(1), 25–31. https://doi.org/10.1097/MED.0000000000000455

Wolfenden, L., Barnes, C., Jones, J., Finch, M., Wyse, R. J., Kingsland, M., Tzelepis, F., Grady, A., Hodder, R. K., Booth, D., & Yoong, S. L. (2020). Strategies to improve the implementation of healthy eating, physical activity and obesity prevention policies, practices or programmes within childcare services. *The Cochrane Database of Systematic Reviews*, *2*(2), CD011779. https://doi.org/10.1002/14651858.CD011779.pub3

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., … Song, Y. (2020). Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine*. https://doi.org/10.1001/jamainternmed.2020.0994

Xu, H., Barnes, G. T., Yang, Q., Tan, G., Yang, D., Chou, C. J., Sole, J., Nichols, A., Ross, J. S., Tartaglia, L. A., & Chen, H. (2003). Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *The Journal of Clinical Investigation*, *112*(12), 1821–1830. https://doi.org/10.1172/JCI19451

Xu, J., Zhao, S., Teng, T., Abdalla, A. E., Zhu, W., Xie, L., Wang, Y., & Guo, X. (2020). Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses*, *12*(2). https://doi.org/10.3390/v12020244

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of

SARS-CoV-2 by full-length human ACE2. *Science (New York, N.Y.)*, *367*(6485), 1444–1448. https://doi.org/10.1126/science.abb2762

Yang, J. K., Feng, Y., Yuan, M. Y., Yuan, S. Y., Fu, H. J., Wu, B. Y., Sun, G. Z., Yang, G. R., Zhang, X. L., Wang, L., Xu, X., Xu, X. P., & Chan, J. C. N. (2006). Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabetic Medicine : A Journal of the British Diabetic Association*, *23*(6), 623–628. https://doi.org/10.1111/j.1464-5491.2006.01861.x

Yang, J., Zheng, Y., Gou, X., Pu, K., Chen, Z., Guo, Q., Ji, R., Wang, H., Wang, Y., & Zhou, Y. (2020). Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *International Journal of Infectious Diseases : IJID : Official Publication of the International Society for Infectious Diseases*, *94*, 91–95. https://doi.org/10.1016/j.ijid.2020.03.017

Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *The Journal of Infection*. https://doi.org/10.1016/j.jinf.2020.03.037

Yu, C.-M., Wong, R. S.-M., Wu, E. B., Kong, S.-L., Wong, J., Yip, G. W.-K., Soo, Y. O. Y., Chiu, M. L. S., Chan, Y.-S., Hui, D., Lee, N., Wu, A., Leung, C.-B., & Sung, J. J.-Y. (2006). Cardiovascular complications of severe acute respiratory syndrome. *Postgraduate Medical Journal*, *82*(964), 140–144. https://doi.org/10.1136/pgmj.2005.037515

Zbinden-Foncea, H., Francaux, M., Deldicque, L., & Hawley, J. A. (2020). Does high cardiorespiratory fitness confer some protection against pro-inflammatory responses after infection by SARS-CoV-2? *Obesity (Silver Spring, Md.)*. https://doi.org/10.1002/oby.22849

Zhang, J., Dong, J., Martin, M., He, M., Gongol, B., Marin, T. L., Chen, L., Shi, X., Yin, Y., Shang, F., Wu, Y., Huang, H.-Y., Zhang, J., Zhang, Y., Kang, J., Moya, E. A., Huang, H.-D., Powell, F. L., Chen, Z., … Shyy, J. Y.-J. (2018). AMP-activated Protein Kinase Phosphorylation of Angiotensin-Converting Enzyme 2 in Endothelium Mitigates Pulmonary Hypertension. *American Journal of Respiratory and Critical Care Medicine*, *198*(4), 509–520. https://doi.org/10.1164/rccm.201712-2570OC

Zheng, Q., Cui, G., Chen, J., Gao, H., Wei, Y., Uede, T., Chen, Z., & Diao, H. (2015). Regular Exercise Enhances the Immune Response Against Microbial Antigens Through Up-Regulation of Toll-like Receptor Signaling Pathways. *Cellular Physiology and Biochemistry : International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, *37*(2), 735–746. https://doi.org/10.1159/000430391