PHYSICAL ACTIVITY, EXERCISE AND IMMUNE FUNCTION

Physical Activity, Exercise and Immune Function

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This factsheet has been developed by healthcare professionals and scientists, in response to the Coronavirus infectious disease-19 (COVID-19) pandemic, and is written for healthcare professionals to enhance their understanding of how physical activity/ exercise can support immune function and potentially minimise the severity of symptoms of COVID-19, if infected. It is one of a series of factsheets to increase health professionals knowledge of physical activity and relevant to all individuals.

Section 1: Background to exercise immunology

Researchers agree that regular bouts of moderate-to-vigorous intensity exercise (e.g. walking, running or cycling) can improve immune function and reduce systemic inflammation [1–3].
The anti-inflammatory effects of exercise relate to changes in both body composition (i.e. lower central fat mass) and a steady summation of changes to the immune system after each session of exercise [4]. Increases in cardiac output, blood flow and the release of stress hormones (e.g. adrenaline) during exercise result in immune cells with high functional capacity (i.e. neutrophils, natural killer cells and cytotoxic T-cells – see glossary) being mobilised into the bloodstream [5–7]. These cells migrate from the circulation towards various tissues to survey the body for damage, infection and/or tumour cells [8]. Each session of exercise therefore **primes the immune system** to 'patrol' the body and do its job effectively. Furthermore, the release of cytokines from muscle (termed myokines) induce an anti-inflammatory environment after each individual exercise bout [4,9,10]. These exercise-induced changes to the immune system are an important consideration for healthcare professionals.

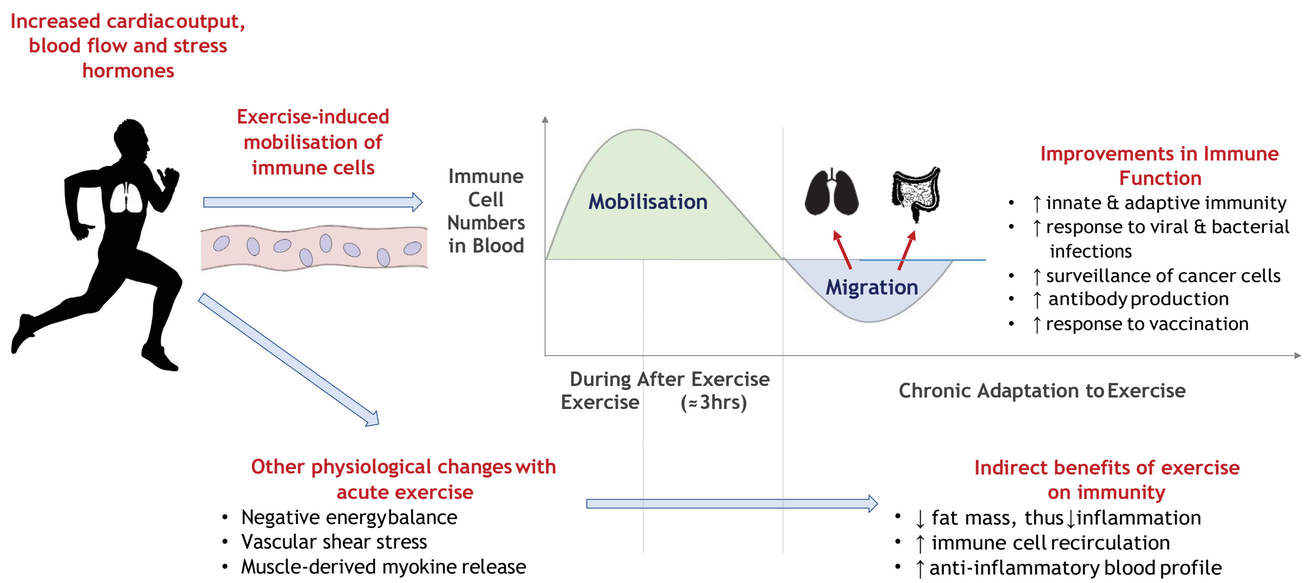
Over the longer-term, engaging regularly in physical activity is also linked with a reduction in the number (≈ 40-50%) [11] and severity of infectious episodes (e.g. common cold and flu) individuals experience throughout the year [11,12]. Collectively, over time, exercise can induce an array of benefits to the immune system (Figure 1) that optimise health and reduce the risk of infection and chronic disease.

Section 2: Can exercise suppress immune function?

Despite agreement by researchers that regular moderate-to-vigorous intensity exercise can improve host immunity, it is a very contentious issue as to whether arduous exercise *(see box 1 on next page)* can actually increase the risk of infection [3]. This is of particular interest in the context of the current COVID-19 pandemic (section 3).

Traditionally, the J-shaped model of immunity has proposed that regular moderate intensity exercise can lower the risk of upper respiratory tract infections (≈60% of infections experienced), whereas a high volume of vigorous intensity exercise might increase this risk, relative to sedentary individuals [13]. The evidence underpinning this model has been established from studies reporting a higher incidence of self-reported infections after competitive marathons [14] and heavy training periods in a variety of competitive team sports [15–17]. Since then, some data have indicated that aspects of immunity are impaired after single [18–21], consecutive [22–24], and regular sessions (i.e. week/ months) [25–27] of arduous exercise *(see box 1 on next page)*

Figure 1: Benefits of exercise on the immune system



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How much exercise is considered arduous for the immune system? (Box 1)

- A *moderate* amount of exercise is considered to be approximately 150 minutes per week at a moderate-to-vigorous intensity (≈60-70% of maximal oxygen consumption*), with individual sessions lasting less than 1 hour.
- An *arduous* amount of exercise is considered a volume of training far exceeding** the recommended 150 minutes per week for the general population, with individual sessions lasting over 2 hours at or above ≈60-70% of maximal oxygen consumption.

* the absolute intensity (i.e. workload) will be dependent on individual fitness levels

** studies reporting impaired immune function have involved both trained and untrained participants cycling or running up to 540 minutes over 3 consecutive days [28–30] and up to 630 minutes over 7 consecutive days [31].

From the studies conducted, exercise volume (intensity x duration) of individual and consecutive sessions appears to be the key factor driving alterations in markers of immune function. It is believed that these alterations relate to the depletion of muscle glycogen and/or depletion of energy reserves within immune cells, although these claims require further research to be substantiated [3,32]. The points of contention on this topic are multiple, but primarily relate to disagreements over study design, validity of the biomarkers examined, appropriate diagnosis of infection and the immunological techniques used [3]. It is important to emphasise that the data indicating that high volumes of training can **causatively** suppress immunity need to be considered in the context of a range of other factors that can adversely affect immunity *(see box 2)* [33]. **The body cannot distinguish between these different types of stress**, and many of these variables intertwine with exercise volume when 'suppressing' measures of immunity (e.g. stress induces cortisol release, which can suppress immune function). It is clear that heavy sessions of exercise, particularly if repeated over consecutive days, can dramatically alter markers of immune function [18–27]; however, the evidence does not support a direct relationship between exercise load and an increased risk of infection. Indeed, a recent consensus statement from the International Olympic Committee suggests that elite athletes who effectively manage their behavioural (i.e. minimise pathogen exposure) and lifestyle habits (i.e. stress, sleep and nutrition) are not more likely to have a higher risk of infection, despite their very high training volumes [34].

A key take home message for the general population is that there is no evidence to indicate that engaging in vigorous intensity exercise within or even slightly over the recommended guidelines of 150 minutes per week is detrimental to immune function. On the contrary, regular engagement in moderate-to-vigorous physical activity and structured exercise is critical to stimulating the immune system to perform its job effectively.

Non-exercise factors that influence immunity (Box 2)

1. Exposure to pathogen:
- Mass gatherings of people (touching eyes, nose or mouth)
- Sharing drinks bottles and equipment or living/training in close proximity to others
- Equipment/clothes (not washing regularly and effectively)
- Hand hygiene (not washing hands)

2. Psychological factors
- Lifestyle stress
- Anxiety
- Individual psychological traits, i.e. ability to regulate mood and psychological strain during prolonged bouts of exercise.

3. Lifestyle habits
- Quality of nutrition/hydration
- Quality of sleep
- Recovery between training sessions

4. Environmental factors
- Air travel – exposure to hypoxia, radiation, pollution, sleep disruption and dehydration
- Extremes of temperature, humidity and altitude
- Breathing cold, dry or polluted air
- Allergies

Section 3: Staying active during the COVID-19 pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus known to cause COVID-19, an infection of the lower respiratory tract that has caused widespread infection, morbidity and mortality worldwide. The government lockdown on March 23rd 2020 resulted in a new way of life for the British population. Isolation has confined individuals and families to their homes for prolonged periods, with restricted time outdoors. Emerging data from across the world are already indicating that lockdown resulted in reduced physical activity [35] and increased sedentary time [35,36]. Even as lockdown restrictions ease, it is possible that these habits are maintained, which in conjunction with the stress of the situation could be detrimental to immune function and the risk of further developing chronic health conditions [37]. Further, the likelihood of subsequent waves of infection may result in reinstatement of lockdown, so these forced lifestyle and habit changes may be ongoing.

Given that we are still in the infancy of what could be long-term changes to our way of life, **there is time** to alter daily activity and exercise habits to minimise the severity of symptoms of COVID-19, if infected. There are no empirical data to indicate that being more physically active or engaging in regular moderate-to-vigorous intensity exercise can **directly** reduce susceptibility to COVID-19 and/or the severity of its symptoms. However, by building on the literature described in *section 1*, we can intuitively suggest potential benefits of regular moderate-to-vigorous exercise that can enhance immune function and could reduce the severity of COVID-19 symptoms and shorten recovery times *(see box 3 on next page)*.

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Possible effects of physical activity and exercise on immunity against SARS-CoV-2 (Box 3)

1. **Healthy weight loss:** Obesity has been identified as a major risk factor for mortality associated with COVID-19 [38,39]. This is, in part, due to a heightened inflammatory response from excess adipose tissue that can promote vascular and thrombotic complications [39]. Therefore, increased exercise/ physical activity that results in a negative energy balance and subsequent weight loss (that is safe and gradual) may protect against the severity of COVID-19 symptoms.

2. **Stimulating immune cells to survey the body for pathogens:** Exercise mobilises immune cells with high functional capacity (i.e. anti-viral) after each session. The cumulative effect of this process is known to protect the body from common viruses that infect the respiratory tract, such as rhinovirus and influenza, and prevent reactivation of latent viruses, such as Epstein-Barr (EBV) [40,41].

3. **Contraction-induced release of immune-related proteins:** Skeletal muscle releases signalling proteins (termed myokines) in response to exercise that reduce inflammation (Interleukin (IL)-6) [4,9,10] and assists with lymphocyte proliferation (IL-7) [42,43]. In addition, it has been suggested that muscle-derived release of IL-15 may assist with trafficking of anti-viral natural killer cells towards vulnerable areas of the body that encounter pathogens 40, e.g. SARS-CoV-2 in the lungs.

4. **Improved blood vessel & lymphatic system health:** Improvements in vascular function are a well-established adaptation to regular exercise training [44]. Improvements in blood flow could assist with immune cell recirculation between the blood, lymphatic system and peripheral tissues in the event of infection. Furthermore, exercise increases the flow of immune cells through the lymphatic system (5-fold), with even mild activity stimulating this movement [45,46]. Thus, staying active is critical to enhancing immunity, particularly in sedentary individuals.

5. **Improved response to vaccination:** There is evidence that regular exercise can enhance the antibody titre after vaccination against influenza [47,48]. Potentially, this may enhance the response to a vaccination developed to combat COVID-19.

Section 4: Practical considerations for lockdown and beyond

Being more physically active and/or engaging in regular amounts of moderate-to-vigorous intensity exercise improves multiple aspects of immune function, which lowers one's risks for infection and chronic diseases. Some specific considerations about daily activity and exercise are highlighted below:

1. For more vulnerable population groups (older individuals and those shielding) at a higher risk), home-based exercise is recommended to minimize pathogen exposure risk. Adherence to government guidance on social distancing and personal hygiene (hand washing and avoiding touching eyes, nose and mouth) are critical to minimise virus exposure.

2. Any increase in physical activity is of benefit. While 150 minutes per week of moderate-to-vigorous intensity is a recommended target, regular bursts of exercise/activity for just a few minutes each day can benefit immune function and general health. Some examples include: walking around the garden, jogging on the spot, sit-to-stand exercises, or climbing the stairs in one's house/apartment.

3. If one is using this time to strive for personal performance goals by programming a high volume of training, they should pay special attention to their recovery time, nutrition, stress levels and sleep quality. Previous evidence allows us with some certainty to suggest that higher levels of aerobic fitness would likely reduce the severity of COVID-19 symptoms. However, it is conceivable that large volumes or large increases in training load could depress immune function, particularly if the variables outlined in Box 2 are not considered. It is a time to prioritise overall health and well-being, rather than performance.

Glossary

- *Innate immunity:* first line of defence against damage and/or infection
- *Adaptive immunity:* a delayed and coordinated response that develops memory for a more enhanced response to infection
- *Neutrophils:* most abundant innate immune cells in blood
- *Macrophages:* innate immune cells residing within tissues of the body
- *Natural Killer Cells:* innate immune cells that kill viruses and cancerous cells
- *T-cells:* adaptive immune cells (lymphocytes) produced in the thymus – kill viruses and cancerous cells
- *B-cells:* adaptive immune cells (lymphocytes) produced in the bone marrow – produce antibodies
- *Cytokines/ Interleukins:* proteins that convey signals between different immune cells
- *Myokines:* cytokines and other small proteins released from skeletal muscle in response to contraction
- *Antibodies:* proteins produced by B-cells in order to kill a previously encountered infection (found in blood, saliva, tears and the mucosal surfaces of certain tissues, e.g. gut and respiratory tract)

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