

# Low cardiorespiratory and mitochondrial fitness as risk factors in viral infections: implications for COVID-19

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Physical activity (PA) modulates immune system functions.<sup>1</sup> Susceptibility to viral infection thereby depends on the volume and intensity of PA: regular moderate PA (up to 60% of maximal oxygen uptake for no more than 1 hour/session) and an associated high cardiovascular fitness (CRF) boost immune system capacity and reduce inflammation, whereas exhausting PA transiently suppresses immune functions.<sup>1</sup>

It seems reasonable that the beneficial effects of regular PA on immune function are at least partly mediated by mitochondrial fitness, as outlined further. Both low mitochondrial fitness and low CRF may be important risk factors for the ongoing COVID-19 pandemic, possibly representing a link between established risk factors like age and various chronic diseases, such as obesity and diabetes mellitus.

## ENERGETIC BUG BUSTERS: MITOCHONDRIA

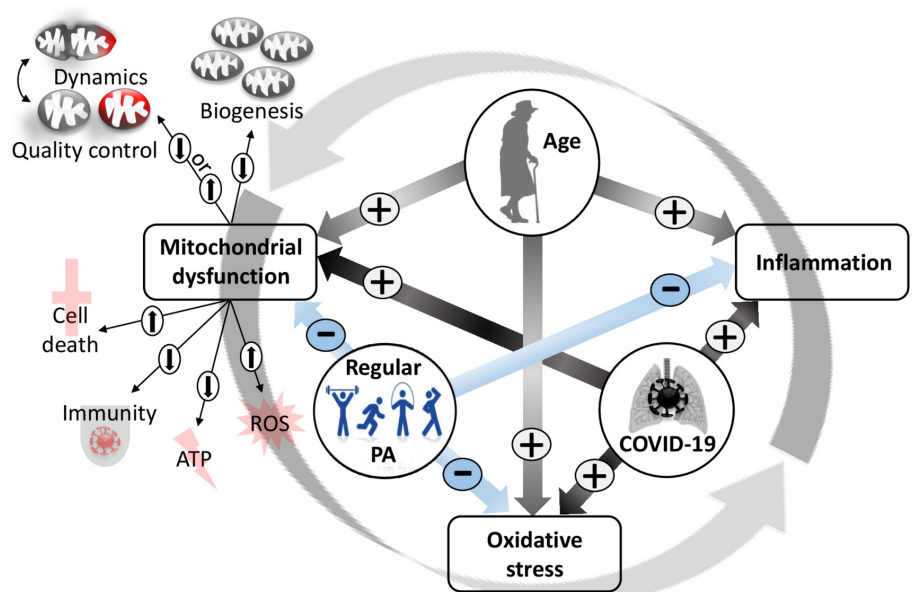
Mitochondria are cellular power generators and regulators of metabolism and are critically involved in the antiviral host response.<sup>2</sup> One important component in the innate immune defence is the mitochondrial antiviral signalling (MAVS) complex, a large protein complex

localised on the outer mitochondrial membrane. MAVS gets activated by a family of pathogen-detecting receptors, the retinoic acid inducible gene-like receptors (RLRs), and induces a response that includes the transcription of class 1 interferons, which serve as central molecules in the cellular defence against viruses. To impair cellular antiviral defence mechanisms, many viruses evolved mechanisms to evade cellular detection by RLR, or to reduce mitochondrial efficiency and

thereby inhibit the antiviral host response. Although the current experimental evidence for these effects occurring in patients with COVID-19 is sparse, it is highly likely that COVID-19 causes mitochondrial dysfunctions through viral invasion of host mitochondria.<sup>2</sup>

## PA KEEPS MITOCHONDRIA FIT

Mitochondria quickly respond to cell environmental conditions by modulating their metabolism, resulting in changes in energy production levels, oxidative stress signalling, immune defence efficiency and cell death regulation. These processes crucially depend on the mitochondrial integrity and quality control, as well as on the mitochondria's capacity to adequately change their morphology, increase their numbers or mass (mitochondrial biogenesis), and enhance their mobility and distribution throughout cells. Any measurable deficits of mitochondria in these capacities are termed mitochondrial dysfunctions. Their responsiveness to PA



**Figure 1** Inter-related mitochondrial dysfunction, oxidative stress and inflammation are modulated by age and physical activity in COVID-19. Mitochondrial dysfunctions include deficits in mitochondrial metabolic and structural integrity, oxidative phosphorylation, as well as in mitochondrial dynamics, biogenesis and quality control. They can lead to increased mitochondrial reactive oxygen species production (and oxidative stress), energy (ATP) deficiency, impaired immune defence and cell death.

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enables mitochondria to be 'trained'; the combination of their integrity, efficiency and dynamic adaptation to stressors is thus being referred to as their 'mitochondrial fitness'. The resulting benefits on mitochondrial fitness conferred by PA include improved mitochondrial biogenesis, mitochondrial respiration, mitochondrial protein synthesis, higher reliance of mitochondria on fatty acid substrates and better oxidative stress handling.<sup>3</sup>

### MITOCHONDRIAL AND CARDIORESPIRATORY FITNESS IN COVID-19 VULNERABILITY

High CRF has been suggested to be beneficial in COVID-19 by better controlling proinflammatory responses and potentially enhancing antiviral host responses following infection.<sup>4</sup> In line with this assumption, an inverse association of CRF with hospitalisation due to COVID-19 has recently been described<sup>5</sup>: women in the lowest quartile of peak metabolic equivalents of tasks had about twofold greater hospitalisation rates than those of the highest quartile. The effect for men was even more pronounced.<sup>5</sup>

Mechanistically, it has been hypothesised that the modulation of ACE 2,<sup>4</sup> a receptor integrally involved in cellular uptake of the virus in COVID-19, and of the angiotensin-(1-7)/MAS1 proto-oncogene, G protein-coupled receptor (GPCR) receptor (MAS receptor) axis<sup>6</sup> may be involved in conferring PA benefits in COVID-19. In addition, boosting mitochondrial fitness by PA enhances immune system function and anti-inflammatory effects, likely improves the host immune defence efficiency and may prevent the sometimes inappropriate cytokine responses in COVID-19 that can result in sepsis and COVID-19-related death.

### PA AS A PROTECTIVE FACTOR FOR COVID-19

COVID-19 more severely affects population groups characterised by reduced mitochondrial fitness, such as older people or patients with cardiovascular disease. Based

on the strong association between mitochondrial fitness and CRF, we put forth the hypothesis that enhancing mitochondrial fitness by regular PA is a protective factor in COVID-19 (figure 1). Regular PA and mitochondrial fitness enhance cellular energy, redox and inflammatory status, and improve the immune response to infection. In addition, PA and fitness have clear preventive potential on many chronic diseases that are considered to be risk factors for COVID-19 outcomes and counteract aging-related processes that may also be associated with higher COVID-19 risk.

Political measures to curb the COVID-19 pandemic include lockdowns, confinement and other means of physical isolation. These strategies raise concerns about dropping PA levels with associated negative health consequences. Many large studies have demonstrated the vast benefits conferred by PA, including a reduction of all-cause mortality.<sup>7</sup> Despite considerable knowledge of the associations between mitochondrial fitness and CRF and their impact on immune system function and antiviral host response, little attention has been paid on their potential to modulate COVID-19 susceptibility and severity. This hypothesis warrants future investigation in patient groups.

Finally, in times of internationally declining average population CRF levels,<sup>8</sup> every effort should be made to improve or maintain mitochondrial fitness and CRF, particularly in individuals most susceptible to COVID-19, by the promotion of appropriate PA. Indeed, several strategies to maintain CRF levels and metabolic health during the pandemic have recently been proposed.<sup>9</sup>

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