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The physiologic benefits of optimizing cardiorespiratory fitness and physical activity – From the cell to systems level in a post-pandemic world

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ABSTRACT

Cardiovascular (CV) disease (CVD) is a leading cause of premature death and hospitalization which places a significant strain on health services and economies around the World. Evidence from decades of empirical and observational research demonstrates clear associations between physical activity (PA) and cardiorespiratory fitness (CRF) which can offset the risk of mortality and increase life expectancy and the quality of life in patients. Whilst well documented, the narrative of increased CRF remained pertinent during the coronavirus disease 2019 (COVID-19) pandemic, where individuals with lower levels of CRF had more than double the risk of dying from COVID-19 compared to those with a moderate or high CRF. The need to better understand the mechanisms associated with COVID-19 and those that continue to be affected with persistent symptoms following infection (Long COVID), and CV health is key if we are to be able to effectively target the use of CRF and PA to improve the lives of those suffering its afflictions. Whilst there is a long way to go to optimise PA and CRF for improved health at a population level, particularly in a post-pandemic world, increasing the understanding using a cellular-to-systems approach, we hope to provide further insight into the benefits of engaging in PA.

Introduction

Cardiovascular (CV) disease (CVD) is the leading cause of premature death and hospitalization in the world,[1] and projections indicate >23 million annual deaths by 2030.[2] This places a significant financial burden on economies. For example, Public Health England estimates that CVD currently costs the United Kingdom (UK) economy £23.2 billion per annum.[3] The evidence from decades of research demonstrates a clear association between physical activity (PA) and cardiorespiratory fitness (CRF) that can significantly offset the impact of CVD. For example, the World Health Organization suggests that getting the population of the European Union (EU) to meet PA guidelines and improve CRF would save the EU €8 billion per annum.[4] The benefits of increasing CRF and PA are not just limited to an improved economic outlook. A positive association between increased CRF, PA, and health-related quality of life (HRQoL), and a reduction in CVD risk, has long been established.[5,6] A low CRF is associated with a greater risk of CVD mortality compared to a high CRF (Hazard Ratio [HR] 2.27; 95% CI 1.20–3.49).[7] Whilst the role of adopting increased CRF and PA as preventive medicine is effective and even desirable,[8] global attempts to improve them have largely been ineffective,[9] with the population of many countries continuing to spend less time engaging in PA and more

Abbreviations: BP, blood pressure; CI, Confidence Interval; CHD, coronary heart disease; COVID-19, Coronavirus disease 2019; CRF, Cardiorespiratory Fitness; CV, Cardiovascular; CVD, cardiovascular disease; DAMPs, Damage-associated molecular patterns; DM, diabetes mellitus; ECM, extracellular matrix; EU, European Union; HR, Hazard Ration; HRQoL, health-related quality of life; IFN-γ, Interferon gamma; IL, Interleukin; IPAQ, International Physical Activity Questionnaire; NCD, Non-communicable disease; PA, Physical Activity; PGC-1alpha, receptor-gamma coactivator-1-alpha; RNA, Ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus two; Th2, T-helper 2 cells; TNF, tumour necrosis factor-alpha; Treg, regulatory T cells; UK, United Kingdom.

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time being sedentary.[10] These negative trends worsened during,[11] and following the COVID-19 pandemic.[12]

Enhancing the understanding of the benefits of increasing PA and CRF from cells to systems has never been as important as it is now. As we learn lessons from the COVID-19 pandemic, evidence shows us that individuals with lower levels of CRF (<20th percentile) had more than double the risk of dying from COVID-19 compared to those with a moderate or high CRF,[13] and those with a higher CRF during early adulthood had a reduced likelihood of mortality, developing severe COVID-19 outcomes in later life, hospitalisations, and admission to intensive care units.[14] There is also evidence to suggest that sustained COVID-19, now termed Long-COVID, has a detrimental effect on CV function.[15] Whilst epidemiological data to highlight the advantageous relationship between CRF, PA and COVID-19 outcomes exists, there is a dearth of mechanistic data that underpins it, and as such it remains difficult to optimise CRF and PA to improve these disease outcomes. Preliminary research has suggested that compared to a healthy control group, COVID-19 significantly and meaningfully impairs endothelial function, both during initial infection [flow-mediated dilation (FMD) = −4.86%] and post 6-months infection (FMD = −1.24%).[15] Given that endothelial cells form a single layer in all the body's blood vessels, and are pivotal in helping to regulate blood flow, fluid filtration, vessel size, and substance transportation, this is an important finding which will likely affect multi-organ and multi-cellular systems. This is of particular importance because, in populations who do not have COVID-19 or Long-COVID, such as those with coronary heart disease (CHD) and diabetes mellitus (DM), increasing CRF and PA has repeatedly been shown to have a profound beneficial effect on endothelial function,[16] which is associated with a reduced CVD prevalence and mortality.[17] Fully understanding the mechanisms associated with COVID-19, Long COVID, and CV health is of key importance if we are to be able to effectively target the use of CRF and PA to improve the lives of those suffering its afflictions. We have a long way to go to optimise PA and CRF for improved health, especially in a post-pandemic world where the interaction of multi-systems and multi-dimensional complexity exists. However, in highlighting the benefits of increasing CRF and PA using a cellular-to-systems approach, we hope to provide further insight into the benefits of engaging in PA. As such, this review aims to highlight the multifaceted cells-to-system benefits of increasing both CRF and PA as we emerge from the COVID-19 pandemic.

Cell physiology and acute and chronic PA

Regular CV exercise, alongside a balanced diet, can help manage body composition, typically increasing/maintaining muscle mass, and decreasing overall adiposity. Lean adipose tissue houses immune cells including macrophages, eosinophils, regulatory T cells (Treg cells), and T-helper 2 (Th2) cells which express several anti-inflammatory, protective cytokines which include Interleukin-10 (IL), IL-4, IL-13, TGF-beta, IL-4, IL-5, IL-6, and IL-13).[18] Increased adiposity associated with obesity, results in phenotypic changes and an infiltration of inflammatory cells into adipose tissue, such as neutrophils and monocytes. This results in decreased anti-inflammatory markers, and an increase in inflammatory adipocytes and cytokines, including tumour necrosis factor (TNF-α), IL-1b, IL-6, IL-12, Interferon-gamma (IFN-γ), and IL-2.[18,19] The combination of increased pro-inflammatory and decreased anti-inflammatory cytokines results in chronic, systemic, low-grade inflammation which contributes to the development of non-communicable diseases (NCD). Obesity, typified by excess adiposity, therefore results in increased secretion of pro-inflammatory cytokines which negatively affects organ function.[18,20] Participation in regular PA has been shown to modulate inflammation, in turn contributing to a reduced risk of conditions such as obesity, CVD, Type 2 DM and some cancers.[17] In response to increased mechanical work during exercise, skeletal muscle cells undergo both acute and longer-term biological changes. Such changes enable skeletal muscle hypertrophy, increased vascularity/angiogenesis and structural changes within the extracellular matrix (ECM), which together improve the maximal aerobic capacity of the muscle allowing it to work harder. Remodelling of skeletal muscle in response to exercise occurs as a response to cells sensing changes in contractile activity leading to transcriptional changes within the skeletal muscle cells. Crucially transcriptomic changes cluster depending on whether the muscle is working acutely, during prolonged training or periods of inactivity whereas the type of activity (e.g., aerobic or resistance exercise) showed little transcriptomic difference.[21] This suggests that the type of exercise imposed has little difference on the transcriptional response on the muscle, but the amount of training has marked effects. A major mechanism by which skeletal muscle cells induce transcriptional changes in response to exercise is via peroxisome proliferator-activated receptor-gamma coactivator-1-alpha (PGC-1-alpha). Activation of PGC-1alpha in response to activity leads to transcriptional changes associated with glucose metabolism, mitochondrial biogenesis, lipid metabolism and angiogenesis.[22]

Remodelling and repair of skeletal muscle in response to exercise occurs in response to damage-associated molecular patterns (DAMPs) causing an influx of inflammatory and immune cells including neutrophils and macrophages.[23] Single-cell Ribonucleic acid (RNA) sequencing of skeletal muscle biopsies has recently shown that following exercise the number of circulating lymphocytes and monocytes increases twofold.[24] A crucial role for macrophages in promoting skeletal repair and remodelling has also been shown in vivo. Depletion of macrophages severely impairs the ability of skeletal muscle to regenerate following exercise.[25] It is clear that tight regulation of inflammation is required to promote effective skeletal repair since computational modelling has shown that excessive inflammation inhibits efficient repair.[26]

One cytokine of note which increases, acutely, in response to exercise is IL-6.[27] Several factors influence IL-6 elevation including exercise intensity, duration, and mode.[28] Despite IL-6 being a pro-inflammatory cytokine, the impaired cell-mediated immunity and increase in inflammation observed in response to exercise are thought to be some of the contributing factors to a reduced risk of chronic disease.[29] Increases in plasma IL-6 may increase fat oxidation and metabolism as well as induce the production of IL-1ra and IL-10, two anti-inflammatory cytokines.[30] IL-6 production has also been shown as a potential inhibitory mediator of TNF- α production. High plasma TNF- α is thought to be an important mechanism in insulin resistance and the development of CVD and therefore the increases in IL-6 that occur during and following PA, although pro-inflammatory, could be key to delaying or preventing the development of NCDs.[28]

Systems physiology and responses to PA

Cardiorespiratory

The cardiorespiratory system is comprised of the heart, blood vessels, airways, and lungs and primarily functions to provide the body with oxygen and nutrients whilst eliminating carbon dioxide and metabolic waste products. The system is also responsible for maintaining whole-body temperature and pH balance and the transportation of hormones. To accommodate the increased metabolic activity in skeletal muscle during exercise, the sympathetic nervous system is stimulated to produce a whole-body response causing an increase in demand for respiratory and CV efforts to maintain homeostasis. Such acute responses to exercise are accomplished through an increase in heart rate (HR), stroke volume, and ultimately cardiac output along with increases in blood pressure (BP) and blood flow redistribution.[31] In response to an increase in cardiac output, perfusion increases in each lung resulting in a greater surface area for gas exchange. With an increase in surface area and an increase in breathing frequency and tidal volume, there is an increase in oxygen uptake and transport to the working muscles and a greater rate of carbon dioxide removal. Following an acute bout of exercise, most factors return to resting levels relatively quickly, however, BP drops

below pre-exercise levels for 2–3 h postexercise which may be a key role of PA in helping control blood pressure, especially in hypertensive patients. Aside from acute responses to exercise, those who participated in PA regularly also benefit from numerous chronic cardiorespiratory adaptions. Regular PA over a prolonged period causes the heart to alter structurally through the increase in end-diastolic volume and left ventricular hypertrophy and mass.[32] Cardiac hypertrophy as a result of prolonged engagement in exercise has been associated with gene regulatory mechanisms and cellular signalling and results in improved cardiac function due to an increase in oxygen delivery to working muscles, reduced cardiac output at rest and improved cardiac output during exercise.[33] Further changes also include decreased resting HR, increased capillarisation at the lungs and muscles, increased oxidative capacity and the promotion of mitochondrial biogenesis.[33] The respiratory system also experiences chronic adaptations to exercise such as an increase in strength of the respiratory muscles. Additionally, with prolonged engagement in PA, there is an increase in the rate of pulmonary ventilation because of increases in tidal volume and respiration rate, and an increase in pulmonary diffusion at maximum workload which is primarily the result of increased pulmonary blood flow.

Neuromuscular

It is firmly established that prolonged inactivity and/or sedentarism causes a loss of function and efficiency within skeletal systems.[34] Within all skeletal muscles, there is a definitive loss of muscle mass and neuromuscular efficiency which affects strength and power and subsequently the ability to complete functional tasks and is closely linked to reduced functional status, frailty and independence.[35,36] A landmark study by Kyle et al (2004),[37] screened 6733 people aged between 18 and 98 years, the data highlighted a clear association between PA levels, fat-free mass and body fat when the data was normalised to height. Muscle wastage is widely reported to result from inactivity and to an extent this is true, but it is not a sole mechanism activity-related weakness. When changes in quadriceps muscle mass and strength of leg extensors were assessed over a 5-year period (n = 1678, 70–79-year-olds) it was observed that reductions in strength were greater when compared to those who reported a loss of muscle size when body mass was maintained.[38] Upon further inspection, those who gained weight during the trial (n = 333) demonstrated a slight increase in muscle size. Whilst they still demonstrated a reduction in strength and power, the findings highlight those reductions in muscle strength are not only attributed to atrophy but a much broader profile of skeletal muscle factors, which are eloquently discussed by Baumann et al. (2022). Whilst detailed biomolecular research has been responsible for pinpointing the important processes and mechanisms that are at result in systemic reductions in neuromuscular function, the subsequent and broader impact upon functional status, HRQoL and population health and wellbeing is incontrovertible.[39,40] Indeed, Busse and Ramdharry (2020) suggest that PA trials/research should be considered an important consideration within neurology practice as they have the potential to be effective and improve patient outcomes.[41] Despite widespread acknowledgement, there remains a dearth of research and/or public health agendas that have managed to reverse the physical inactivity pandemic.[42] Furthermore, this longstanding pandemic of physical inactivity has been augmented by COVID-19 restrictions through a potentially irreversible change in behaviours in the context of employment and lifestyle choices, both of which are compounded by reductions in human movement.

Methods to optimise CRF and PA

Owing to the plasticity of the body's physiologic processes, the importance of structured exercise and general PA to improve CRF is associated with widespread benefits for health and well-being. Subsequently, this area has been the subject of detailed investigations to optimise the prescription of structured activity and to maximise individual benefits. The development of PA programmes to follow the core principles of training (Fig. 1) has been developed and adopted by leading organisations such as the American College of Sports Medicine[9] to support rehabilitation health professionals. Recognising its significance, the core principles have been implemented by policies and reflected in guidelines published by leading health bodies such as the World Health Organisation[43] in an attempt to increase PA. In the context of increasing CRF for CV health, a notable consideration that co-exists alongside the principles of training is the mode of exercise (e.g., aerobic, resistance) which has been adopted by exercise scientists for decades.[44] As such, research has attempted to determine the most efficient and effective modes of increasing CRF.[45] For example, the effects of different types and intensities of PA on mortality were analysed in 58,537 adults, with a mean age of 73.9 years. The data presented by Kim *et al*[46] after a mean follow-up of 3.3 years demonstrated a reduction of 26% in all-cause mortality (95% CI 0.68–0.82) in participants that engaged in light PA, a reduction of 27% (95% CI 0.63–0.84) in those that completed light to moderate PA, and by 34% (95% CI 0.54–0.79) in those completing moderate PA when compared with those that self-reported being physically inactive. Furthermore, Wannamethee *et al*[47] investigated different types and intensities of PA on all-cause mortality in 5934 men with a mean age of 63 years. PA was scored using a 21-point system between inactive (1) to vigorous PA (>21). Relative risk of all-cause mortality was reduced as intensity of PA increased (light PA - 0.42, 95% CI 0.25–0.71 for light PA and 0.63, 95% CI 0.39–1.03 for vigorous PA) when compared to inactivity. Interestingly, participants who engaged in light PA later in the study also demonstrated a lower incidence of all-cause mortality (0.58 95% CI 0.33–1.030) compared to those who remained inactive.

Recent evidence demonstrates a dose-response relationship between PA and CV health which also indicates that engaging with regular exercise that is completed at a higher intensity may yield the biggest benefits to CV health.[48] Whilst acknowledging the broader benefits of high-intensity exercise and reports of low risks of adverse events,[49]

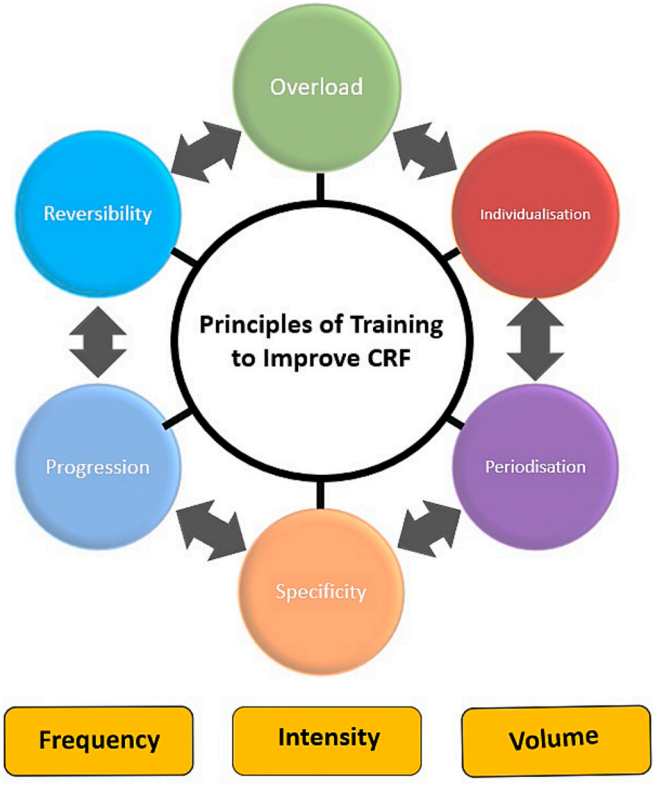

Fig. 1. Principles of training to improve cardiorespiratory fitness, adapted from Kasper (2019).[73]

prescribing high-intensity programmes in clinical exercise settings should be reviewed for appropriateness, suitability, and likely completion/attrition at an individual level. Whilst the widespread benefits of PA are acknowledged, the need to manage patient safety and mitigate adverse responses to exercise is paramount. Mittleman *et al*[50] highlighted in a cohort analysis of 1228 participants that those with little/no experience of exercise, who have predominantly led sedentary lifestyles, are at an increased risk of myocardial infarction compared to those who exercise at higher intensity and with increased frequency.

Benefits of optimizing CRF via PA

Although increased CRF is associated with increased health outcomes and HRQoL, there is a disparity in the degree of protection that PA can offer[5] possibly resulting from a lack of standardisation in the assessment and definition of CRF, which are unlikely to account for important descriptive characteristics such as age and ethnicity. The benefits of engaging in PA, and as a result having increased CRF, are far-reaching and stem far beyond the physical and mental well-being impacts, into important societal and economic areas.[51]

The beneficial effects of PA and exercise training on the vasculature have been repeatedly reported in patients with associated risk factors for chronic disease.[52] Mok et al.[53] evaluated 14,599 participants between the ages of 40–79 and a median follow-up duration of 12.5 years to determine an association between PA and all-cause mortality and risk of CVD. Self-report approaches were used to measure PA which was categorized relative to time (none, 0.1–3.5, 3.6–7.0, and $\geq$ 7.0 h/week) with the data demonstrating a clear association between PA and CVD risk. Specifically, moderate PA of around 150 min/week was associated with a decrease in all-cause mortality and CVD mortality [HR 0.76 (95% CI 0.71–0.82) and HR 0.71 (95% CI 0.62–0.82), respectively]. The data from Mok et al does not account for changes in PA over time, which is a known determinant of changing physical well-being. This was subsequently addressed by Aggio et al[54] who also completed a prospective cohort study of 3321 men between the ages of 40 and 59 years over a median follow-up time of 16.9 years. The data highlights those who were consistently engaged in light to moderate PA, were less likely to have been affected by all-cause mortality when compared to those with low (95% confidence interval 0.74–0.94) and declining levels of PA (95% CI 0.66–0.88). The data and evidence for engaging and maintaining PA volume and intensity and the impact upon CV function and mortality are compelling, yet physical inactivity remains a key threat to population health and wellbeing.[55] Arguably, the most comprehensive study in this area was a prospective cohort observation conducted by Lear *et al*[56] in ~130,000 adults from seventeen countries of differing (high-medium-low) economic statuses. Over the course of seven years, participants without pre-existing CVD completed the International Physical Activity Questionnaire (IPAQ) which was analysed across the intensity domains of low, moderate, and high to determine the risk of developing CVD. Their data showed that exercise intensity has a graded reduction in all-cause mortality (hazard ratio 0·80, 95% CI 0·74–0·87 and 0·65, 0·60–0·71; $p < 0·0001$ for trend), and major CVD event (0·86, 0·78–0·93; $p < 0·001$ for trend). Accordingly, higher intensities of PA were associated with lower risk of CVD and mortality in high-income, middle-income, and low-income countries. Importantly this is a repeated demonstration of the benefits of PA and while this does not represent new knowledge, there remains a global reduction in PA and a surge in non-communicable and chronic diseases, such as hypertension.

Hypertension is defined as systolic BP that is >130 and/or diastolic BP $\geq$85 mmHg and is associated with an increased risk of CHD, stroke, and heart failure.[57] Protogerou *et al* compared brachial mean arterial pressure and pulse pressure between two routine check-ups with a median follow-up duration of 5.8 years. By categorising changes in blood pressure as increased, decreased, or no change in 71,629 participants between the ages of 16–95 years of age, the authors were able to determine using all-cause Cox Mortality regression models, that when compared to the no-change group, those with increased brachial or central pulse pressure had an increase of 200% in the relative risk of being affected by all-cause mortality. Reductions in both brachial and central pressures were associated with a 15% reduction in relative risk. This highlights the importance of managing and/or preventing changes in BP and vascular function over the life course and demonstrates that mean arterial BP and pulse pressure are definite characteristics that affect all-cause mortality and risk to CV health. Longitudinal investigations have also determined that age-related changes in arterial stiffness and impaired vascular endothelial function are important age-related risk factors for CV health, and changes in these clinically relevant outcomes can be attenuated by engaging in positive lifestyle behaviours which includes increasing habitual PA.[58] A cohort analysis of 12,511 Chinese adults (female – 6525) between 1991 and 2015 demonstrates an increase in the incidence of hypertension (10.9% in 1991 and 20.3% in 2015) and a reduction in median PA (408 MET.h/week in 1991 to 104 MET.h/week in 2015), data that is consistent with global trends.[48,59] Once data were adjusted for confounding variables, PA in the highest quartiles were associated with a reduction in hypertension by 12 and 15% respectively when compared with PA in the lowest quartile.[60] Decreasing arterial stiffness from exercise reduces central aortic systolic BP and pulse pressure, which in turn decreases the detrimental effects on the CV system, which has been repeatedly demonstrated in older adults.[61,62] A positive association between the intensity and volume of PA and BP is established and literature has furthered our understanding with specific consideration also being given to the classification and intensity of exercise, which has been discussed previously.[63]

Post-pandemic considerations for improving CRF

The global health and well-being agenda has been subjected to unprecedented pressure in recent years, primarily resulting from the unforeseen COVID-19 pandemic.[64] Whilst political agendas are driving a return to pre-pandemic social and economic activities,[65] the complex and underlying aetiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provides an additional consideration for the screening and management of adopting methods to improve CRF. While other chronic conditions demonstrate a level of protection from increasing PA and CRF,[66] the protective effects of CRF in the context of COVID-19 and its associated persistent symptom profile, otherwise known as Long COVID remain unclear.[67] It has been established that COVID-19 contributes to a complex multiorgan pathophysiology, sustained systemic and dysregulated inflammatory profile[68] which impairs functional status and HRQoL.[39] Of significant importance here is what appears to be the entwining of a pre-COVID-19 issue of global health and the nuanced challenges presented by COVID-19,[69] especially when considering the observed impacts on CV function and status. Research has demonstrated an increase in the prevalence of CV-related issues including heart failure and stroke. Importantly, these risks are substantially higher in people who have recovered from a confirmed COVID-19 infection when compared to those people who have not had the disease.[70] Furthermore, an analysis of 154,000 veterans from the USA with confirmed SARS-CoV-2 infection found that in the year after recovering from the illness's acute phase, patients had increased risks of CVD problems which include abnormal heart rhythms, heart muscle inflammation, blood clots, stroke, myocardial infarction, and heart failure. What is concerning is that these increased risks were evident in those who were not admitted to the hospital but recuperated in community settings.[71] With the removal of all mitigation strategies and as the world seeks to 'live with COVID-19' the virus continues to evolve, transmit, infect, and re-infect people, therefore increasing the risk of substantive CV issues. In the design and implementation of effective models to improve CRF, there is a clear need to include detailed screening to determine the appropriateness of exercise in patients with a history of COVID-19 and to ensure safe and effective practice when engaging with PA to improve CRF.[72]

Conclusion

Sustaining a high CRF provides an array of benefits to population health and wellbeing and the benefits extend from cells to systems of the body. Whilst there is a clear rationale to increase CRF at a population level, physical inactivity remains one of the biggest risk factors for chronic disease. Strategies to improve CRF at a population level will have a widespread impact on global health and wellbeing, but such approaches need to consider broader determinants that impact the human's ability to engage in PA and improve CRF. Considering COVID-19, we must now consider the increased CV risk factors that are contributing to increased CV-related disease and mortality and establish global approaches to reduce an impending but avoidable risk to population health.

Declaration of competing interest

None.

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