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Physical activity and exercise in the context of SARS-Cov-2: A perspective from geroscience field

Philippe de Souto Barreto^{a,b,*}, Bruno Vellas^{a,b}, Yves Rolland^{a,b}

^a Gerontopole of Toulouse, Institute of Ageing, Toulouse University Hospital (CHU Toulouse), Toulouse, France

^b UPS/Inserm UMR1027, University of Toulouse III, Toulouse, France

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ABSTRACT

The recent pandemics of the SARS-Cov-2 has pushed physical activity (PA) and exercise at the forefront of the discussion, since PA is associated with a reduced risk of developing all the chronic diseases strongly associated with severe cases of SARS-Cov-2 and exercise is considered a complimentary therapeutics for the treatment of these age-related conditions. The mechanisms through which PA and exercise could contribute to reduce the severity of the SARS-Cov-2 infection would be multiple, including their capacity to boost the immune system, but also their global effect on slowing down the progression of the aging process. The present perspective presents a discussion on how PA and exercise might hypothetically be linked with SARS-Cov-2 infection, current scientific gaps and shortcomings as well as recommendations for advancing research in this area, placing the debate in the context of aging and gerosciences.

1. Introduction

Geroscience is a recent field of investigations in the broad gerontology discipline, born from the hypothesis that by manipulating biological aging it is possible to prevent or delay the onset of chronic conditions, as well as their severity (Sierra and Kohanski, 2017; Sierra, 2016a, b; Kennedy et al., 2014). Physical activity (PA) and exercise are considered powerful behaviors for reducing the risk of developing a myriad of chronic diseases (de Souto Barreto et al., 2017; Lee et al., 2012; Nyberg et al., 2020; Moore et al., 2016; Kivimäki et al., 2019) and to slow down the age-related progression of the disabling cascade, such as frailty (Abe et al., 2020), functional limitations and disability (GBD 2017 Risk Factor Collaborators, 2018; Sanchez-Sanchez et al., 2020; Tak et al., 2013), and early mortality (GBD 2017 Risk Factor Collaborators, 2018; Saint-Maurice et al., 2020). Since PA and exercise benefit so distinct diseases, such as cancer (Moore et al., 2016), Alzheimer's and related diseases (Kivimäki et al., 2019), heart conditions (Colpani et al., 2018), they can be seen as one of the best interventions for healthy aging from both epidemiological (Lin et al., 2020) and gerosciences perspectives (Ferrucci et al., 2016; Rebelo-Marques et al., 2018).

The recent pandemics of the SARS-Cov-2 has pushed PA and exercise at the forefront of the discussion, since PA is associated with a reduced risk of developing all the chronic diseases strongly associated with

severe cases of SARS-Cov-2, in particular hypertension, obesity, and diabetes (Wu et al., 2020; Palaiodimos et al., 2020; Huang et al., 2020; Wang et al., 2020; Aggarwal et al., 2020; Li et al., 2020; Zhang et al., 2020a, b), and exercise is considered a complimentary therapeutics for the treatment of these age-related conditions (de Souto Barreto, 2017; Eckel et al., 2013; Pescatello et al., 2004; Colberg et al., 2010; Marwick et al., 2009; Donnelly et al., 2009; Jensen et al., 2013). Researchers suggested different hypothesis about the fact exercise could reduce the severity of the infection (Zbinden-Foncea et al., 2020; Kenyon, 2020), and even decrease the risk of incident cases (Dixit, 2020). The ideas and hypothesis about PA and exercise in the context of the SARS-Cov-2 pandemics are, however, confused due to interconnected issues related with scientific terminology, study methodologies, and the lack of a precision medicine applied to PA and exercise sciences in a preventive perspective.

Therefore, how to disentangle true scientific evidence from hypothetical hopes around PA and exercise? The present perspective paper has the objective to discuss how PA and exercise might be linked with SARS-Cov-2 infection, placing such an association in the context of aging and gerosciences. For that, we first tried to clarify the sources of confusion, the potential mechanisms of the triad aging, PA/exercise and SARS-Cov-2, and then proposed how to advance the debate about the role of PA and exercise as an instrument protecting against infections

* Corresponding author at: Gérontopôle de Toulouse, Institut du Vieillissement, 37 Allées Jules Guesde, F-31000, Toulouse, France.

E-mail addresses: desouto-barreto.p@chu-toulouse.fr, philipebarreto81@yahoo.com.br (P. de Souto Barreto).

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through their potential for slowing down the progression of biological aging.

2. PA/exercise and SARS-Cov-2

2.1. Hypothesis and data

Researchers (Zbinden-Foncea et al., 2020; Kenyon, 2020; Dixit, 2020; Heffernan and Jae, 2020) advocate that exercise would have beneficial effects on the SARS-Cov-2 pandemics mainly because it is involved in the expression of the angiotensin conversion enzyme 2 (ACE2), which is used by the SARS-Cov2 as its receptor to enter the cells (Shang et al., 2020; Letko et al., 2020; Hoffmann et al., 2020). Simplifying the biological cascades and mechanisms, ACE2 is involved in a vasodilator axis of the renin-angiotensin system (RAS) that counteracts the vasoconstrictor RAS axis in which ACE is involved, alongside angiotensin II(AngII) and angiotensin type 1 (AT₁) receptor, and which is associated with cardiovascular diseases, in particular hypertension. Exercise would have a double effect, reducing the expression of the ACE-AngII-AT₁ vasoconstrictor axis and improving the expression of the vasodilator ACE2-Ang(1-7)-Mas receptor axis. These effects would ultimately lead to an anti-inflammatory action, reducing the risk of the so-called SARS-Cov-2-related cytokine storm, consequent hyperinflammation and lung, as well as distant organs like the kidneys, damage (Blagosklonny, 2020; Nikolich-Zugich et al., 2020; Ye et al., 2020). Moreover, exercise is involved in other anti-inflammatory cascades (Flynn et al., 2019), such as the downregulation of expression/activation of Toll like receptors (Flynn et al., 2003; Abbasi et al., 2014), which reduces the production of pro-inflammatory cytokines, as well as participation in AMPK activity which both inhibits NF-κB, reducing thus proinflammatory markers in airway epithelial cells, and promotes the activity of ACE2-Ang(1-7)-Mas receptor axis (Zbinden-Foncea et al., 2020). Added to these biological and physiological mechanisms, there is a massive and strong literature showing PA is associated with a reduced risk of developing aging-related cardiometabolic diseases (de Souto Barreto et al., 2017; Lee et al., 2012; Nyberg et al., 2020; Kivimäki et al., 2019) characterized by the low grade inflammation profile, inflammaging, as well as the recent report by Hamer and colleagues (Hamer et al., 2020) showing physical inactivity was associated with an increased hazard by 32 % for being hospitalized due to SARS-Cov-2, suggesting 9% of SARS-Cov-2 hospitalization cases were attributable to low PA.

2.2. Reducing confusion

Although, in theory, this simplified argumentation sounds extremely favorable for the effects of PA and exercise in decreasing both the incidence and severity of SARS-Cov-2 infection, a number of potential shortcomings must be highlighted.

- 1 **Scientific terminology:** PA and exercise are often used as synonyms, a mistake that may lead to confusion. Briefly, PA is the broad concept, referring to any movement performed through muscle contraction and associated energy expenditure; whereas exercise is a planned, repetitive and purposeful subtype of PA. PA is composed by all activities from four wide domains, ie, leisure-time (which includes exercise, but is not limited to), occupational, housework, and commuting/transportation. This differentiation is of major importance because when Hamer and colleagues (Hamer et al., 2020) found an association between physical inactivity (<150 min/week of moderate PA or <75 min/week of vigorous PA) and a raised hazard of SARS-Cov-2-related hospitalization, they used a questionnaire asking for all PAs (including housework and gardening) performed in the last week. Therefore, one could suggest that 30 min/day of housework (eg, moderate-intensity vacuuming/mopping), frequent PA during older adulthood especially among women (Lawlor et al.,

2002), would protect against SARS-Cov-2 infection, which is probably not the case since the links of housework PA and health outcomes is scarce and unclear (de Souto Barreto, 2015; Bellavia et al., 2013; de Souto Barreto et al., 2018). Similarly, all investigations of biological mechanisms through which exercise is related to anti-inflammatory profiles used exercise training (one bout or chronic exercise); no investigation being done on the associations of global PA and the mechanisms of inflammation that could reduce the strength of the cytokine storm in the SARS-Cov-2.

- 2 **Study methodologies:** most of the studies on the biological mechanisms through which exercise might bring benefits against the SARS-Cov-2 infection have been performed in mice and rats, particularly investigations focusing on the vasodilator ACE2-Ang(1-7)-Mas receptor axis (Nunes-Silva et al., 2017), with only one recent study (Magalhães et al., 2020) performed in humans. In that human study, Magalhães et al. (Magalhães et al., 2020) found a single bout of both high-intensity interval aerobic exercise and a moderate-intensity continuous aerobic exercise modulated the activity of both ACE (reducing its level in plasma) and ACE2 (increasing its level in plasma). Although these very preliminary findings suggest one bout of aerobic exercise (eg, walking, cycling, etc.) in humans leads to improvements in the ACE2-Ang(1-7)-Mas receptor axis, Magalhães et al.'s study was performed among only 10 men, aged 22 years-old in average. This conducts us to the second methodology-related issue: most studies investigating the effects of exercise on the human immune system were developed among younger adults. The immune response of younger adults may differ from those of older people, these latter already dealing with issues of immunosenescence and inflammaging (Salimi and Hamlyn, 2020; López-Otín et al., 2013). Since the most severe cases of SARS-Cov-2 are found in people ≥65 years-old, especially those with cardiometabolic-associated pathologies, we do not know if the anti-inflammatory effects of exercise on this population would be similar to the effects found in younger adults who are not suffering from any chronic condition.
- 3 **Lack of a precision medicine applied to PA and exercise:** Exercise refers to aerobic, strength, stretching, motor coordination and balance exercises; the benefits brought forth by the distinct exercise types are not the same. Most studies investigating the links between exercise and the immune system have used aerobic exercises (Niemann and Wentz, 2019), but some evidence also suggests strength training might improve the immune system (Yang et al., 2018; Sardeli et al., 2018). In a biological aging (Bolotta et al., 2020) perspective, strength training would have as much importance as aerobic exercise, especially in terms of metabolic benefits. It is interesting to highlight that, from a clinical viewpoint, experts suggest the best exercise combination for different aging populations (Colberg et al., 2010; Marwick et al., 2009; de Souto Barreto et al., 2016; Fletcher et al., 2013), with positive effects in numerous health outcomes, is a mix of aerobic and strength exercises, as disseminated in current PA guidelines (American College of Sports Medicine et al., 2009). Therefore, well-defined doses of exercise, specifying exercise type, frequency, duration, and intensity, as well as the global amounts of PA that might boost the immune system during different phases of biological aging are still to be established.

2.3. Global conclusion

Although PA and exercise anti-inflammatory effects might contribute to decrease the severity of SARS-Cov-2 and, even, to reduce the risk of incident cases of severe SARS-Cov-2 infections in humans, caution is needed since most of the scientific literature comes from animals, or human younger adults, and did not disentangle the components of PA and exercise (eg, type of activity) that would lead to the supposed protective effects. The potential role of PA and exercise on the severity of the SARS-Cov-2 infection remains thus hypothetical.

3. PA/exercise, severe SARS-Cov-2 infection and geroscience

Based on both epidemiology and biology of severe SARS-Cov-2 infections, some researchers have advocated this infection is an aging-related disease (Blagosklonny, 2020), and should thus be investigated using geroscience’s approaches (Blagosklonny, 2020; Salimi and Hamlyn, 2020; Sierra, 2020). Indeed, most of the hospitalization and death cases related to the infection occurred among older people. Moreover, most hosts of the severe SARS-Cov-2 cases have already been chronically touched by raised levels of pro-inflammatory cytokines before the infection, such as among people with cardiometabolic diseases characterized by low-grade chronic inflammation.

In such a geroscience perspective, PA and exercise might have helped the human organism to struggle against SARS-Cov-2 by several mechanisms, including mechanisms other than those directly linked to immunosenescence or inflammaging. The complex associations through which exercise would benefit each hallmark of aging has been discussed by Marquez-Rebello et al. (Rebello-Marques et al., 2018) and is not in the scope of the present article. The simplest and most illustrative examples are: a) the in/out energy balance; and b) increased cardiorespiratory reserves. Regarding energy balance, PA-related energy expenditure would reduce the risk of obesity (Cleven et al., 2020; Bell et al., 2014; Pavay et al., 2016); obesity is one of the most important risk factors for severe SARS-Cov-2 infections. For cardiorespiratory fitness, the SARS-Cov-2-associated hypoxemia pneumonia (Yang et al., 2020) is a major clinical sign of the infection; it is therefore plausible to think exercise, which is highly associated with increased cardiorespiratory fitness, including among older adults (Hurst et al., 2019), would reduce the risk of hypoxia and its deleterious effects because exercise increases cardiorespiratory reserves (improved heart and lung functioning), keeping infected individuals away from the cut-point below which low cardiorespiratory fitness is critical to help the organism fighting against the infection. It is worth mentioning people with hypertension, diabetes, and metabolic syndrome benefit more from the cardiorespiratory effects of exercise (Lin et al., 2015).

Moreover, exercise effects on molecular mechanisms involving (but not limited to) the regulation of nutrient sensing, loss of proteostasis, mitochondrial dysfunction (including redox signaling), and cellular

senescence (Rebello-Marques et al., 2018), all of them considered as hallmarks of biological aging (López-Otín et al., 2013), can also be cited. Exercise improves glucose metabolism, leading to improvements in insulin sensitivity (Mann et al., 2014), what may reduce the risk of both obesity and diabetes. Moreover, aerobic exercise stimulates autophagy by the modulation of IGF-1, protein kinase B (Akt)/mammalian target of rapamycin (mTOR), and Akt/Forkhead box O3A signaling pathways (Rebello-Marques et al., 2018), what induces the elimination of damaging proteins that are involved in neurodegeneration. Furthermore, mitochondrial oxidative capacity did not decline with age (comparing subjects aged in average 26 years-old with those 65 years-old) in aerobic exercise trained individuals (cycling or running for 60 min, 6 days/week, in the past ≥ 4 years) (Lanza et al., 2008), and a 14-week strength training (thrice/week) has been associated with improvements in oxidative stress in older people (Parise et al., 2005). Another potential mechanism is that exercise reduces the accumulation of senescent cells (Yang et al., 2018; Schafer et al., 2016) and then the expression of senescence-associated secretory phenotype (SASP), an important contributor to inflammaging, being considered markers of the aging process (Schafer et al., 2020).

Fig. 1 displays the mechanisms through which PA and exercise could help individuals’ body in struggling against SARS-Cov-2 and other infections. In sum, PA and exercise would have contributed to diminish the severity of SARS-Cov-2 not only through their direct anti-inflammatory effect, but also through a complex set of mechanisms linked to global biological aging, which would ultimately lead to a decreased hyperfunction of the immune system (Blagosklonny, 2020) (a characteristic linked to the SARS-Cov-2-related cytokine storm) when facing the pathogen. This global action of PA and exercise on biological aging would, in a life course perspective, lead to increased body reserves and individual’s resilience, which are used for both struggling against stressors of any type, including infections, and for body recovery (Ferrucci et al., 2019).

4. Advancing the debate

Although we recognize there is abundant literature showing PA and exercise promotes health in both sexes, different ages, in subjects from

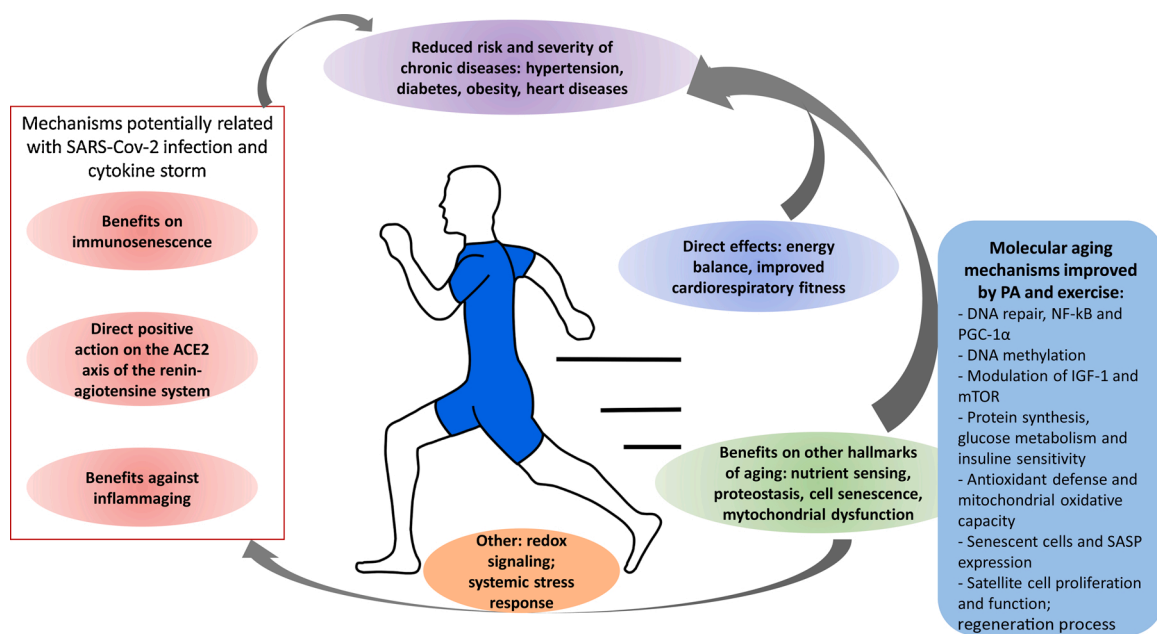


Fig. 1. Running against the SARS-Cov-2 and other infectious diseases. Potential mechanisms through which physical activity and exercise may help individuals’ body to fight against the SARS-Cov-2 and potentially other infections leading to hyperinflammation.

various geographical locations and cultures, among people with different socio-economic status, there is still much to be done to understand how these behaviors contribute to slowing down the progression of biological aging and how they can protect against severe epidemics such as the SARS-Cov-2. Among scientific actions to be developed in this regard, we recommend the following key aspects:

- 1 Using already existing observational cohorts with available biobanking in several time-points and collected data on global PA levels to disentangle the associations of the different types of PA (eg, leisure-time, occupational, commuting, and housework) with the dynamics of ACE2-Ang(1-7)-Mas receptor axis of the RAS, but also with markers of immunosenescence and other mechanisms that might have contributed to the hyperinflammation observed in severe SARS-Cov-2, such as SASP. Similar associations could be tested for other components of global PA, such as the minimum amount (time/week) and frequency (days/week) of PA. Similarly, undertaking subgroup analysis contrasting lifelong sedentary individuals to people who have been physically active (not athletes, who are extremely active individuals for whom adaptations in the immune system might be different from a globally active non-athlete person) in a life course perspective could shed light on the role of chronic PA in immunosenescence and inflammaging.
- 2 Using available data from randomized controlled trials (RCT) of long-term exercise in older people for testing the effects of chronic exercise training on markers of immunosenescence and inflammaging, disentangling the components of exercise, such as type (aerobic, strength training), and truly performed intensity, frequency and duration in exercise sessions. In this regard, exploring the data and biobanking of studies, such as LIFE (Pahor et al., 2014) and SPRINT-T (Landi et al., 2017), would be a good start; these exercise RCTs have non-negligible advantages, since older adults exercised in the long-term (over more than two years), applied simple exercises that could be adapted and performed at home, including during confinement periods.
- 3 Adding to current observational cohorts designed to study the aging process data on PA through the life course. This could be ideally inserted, for example, in the INSPIRE program (De Souto Barreto et al., 2020), developed in Toulouse, France, which develops a translational human cohort dedicated to investigating biomarkers of aging. Among the advantages of the INSPIRE translational cohort there are the longitudinal design, the large and comprehensive biobanking, composed of both bio-fluids and cells, as well as traditional clinical measurements, and maximal performance tests (eg, isokinetic strength and maximum volume of oxygen uptake (VO_2^{max})).

Although the above-mentioned recommendations focused on immunosenescence and inflammaging, they can be extended to investigate other molecular pathways (eg, redox signaling, systemic stress response) potentially involved in the links of PA and exercise with SARS-Cov-2 infection.

5. Conclusion

PA and exercise role in decreasing the severity of SARS-Cov-2 infections is a plausible, but still hypothetical, possibility, as well as are the biological mechanisms potentially involved. However, PA and exercise prevent or delay the onset of numerous aging-dependent phenotypic expressions (eg, chronic diseases, functional decline), being their positive effects on the immune system a major characteristic that may contribute to protect people against severe epidemics, such as SARS-Cov-2. Investigations are needed to establish the role of PA and exercise on global epidemics of infectious diseases in order to cross the barrier of hypothesis and become an evidence.

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Declaration of Competing Interest

The authors report no declarations of interest.

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