

step and develop evidence-based individualised treatments for post-COVID-19. We promote exercise as medicine as a treatment option for some patients post-COVID-19 and highlight current knowledge gaps in the literature as well as targets for future research.

Zusammenfassung

Dieser Beitrag ist ein Aufruf zum Handeln. Die Langzeitfolgen von COVID-19 stellen eine grosse Herausforderung für die öffentliche Gesundheit dar und haben erhebliche Auswirkungen auf das persönliche und berufliche Leben der Patienten. Es gibt immer mehr Evidenz für die möglichen Mechanismen von Post-COVID-19. Es ist an der Zeit, den nächsten Schritt zu tun und evidenzbasierte, individualisierte Behandlungen für Post-COVID-19 zu entwickeln. Wir werben für Bewegung als Medizin als Behandlungsmöglichkeit bei manchen Patienten nach COVID-19 und zeigen aktuelle Wissenslücken in der Literatur sowie Ziele für die zukünftige Forschung auf.

(Post-)COVID-19 as a public health burden

The long-term sequelae of coronavirus disease 2019 (post-COVID-19) have become a global public health challenge. Over the last two years, a large body of evidence has accumulated to underscore this. [1,2] Chen et al. [1] found a pooled prevalence estimate of 43% (95%CI, 39-46%) for having at least one persistent symptom at least 12 weeks post-infection in their meta-analysis of 31 studies. Symptoms of exhaustion (i.e. fatigue, dyspnoea, exercise intolerance), followed by cognitive problems, were the most common and debilitating. [1,2] In addition, Ceban et al. [2] reported in their meta-analysis a prevalence of post-COVID-19 fatigue of 32% (95%CI, 27-37%; N = 25,268 patients) and cognitive impairment of 22% (95%CI, 17-28%; N = 13,232 patients) in the same period. However, prevalence estimates of post-COVID-19 vary largely depending on population characteristics (sex, age, region), initial disease severity, and the time frame of interest. [1,2] Nevertheless, a substantial fraction of individuals suffer from post-COVID-19.

The disease manifests itself through a multitude of symptoms. [1,2] Not every patient with these symptoms is also diagnosed with post-COVID-19, but other chronic conditions more specific to the symptoms, i.e. myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or postural orthostatic tachycardia syndrome (POTS). [3,4] POTS is characterised by an excessive increase in heart rate following assuming an upright posture, accompanied by symptoms of orthostatic intolerance but without orthostatic hypotension. [4,5]

Using the U.S. as an example, conservative approximations (5% onset rate of post-COVID-19 ME/CFS) yield 3.1 million adult new cases of post-COVID-19 ME/CFS from 2020 to 2022. [3] Together with the pre-COVID-19 prevalence of ME/CFS (approximately 1.1 million cases in 2020), this adds up to a total of 4.2 million adult ME/CFS cases. [3] These approximations further provide an appraisal of the global public health challenge of post-COVID-19 and conditions with shared characteristics.

Post-COVID-19 and concomitant chronic conditions, in turn, drastically curtail patients' daily lives in many ways (*Figure 1*).

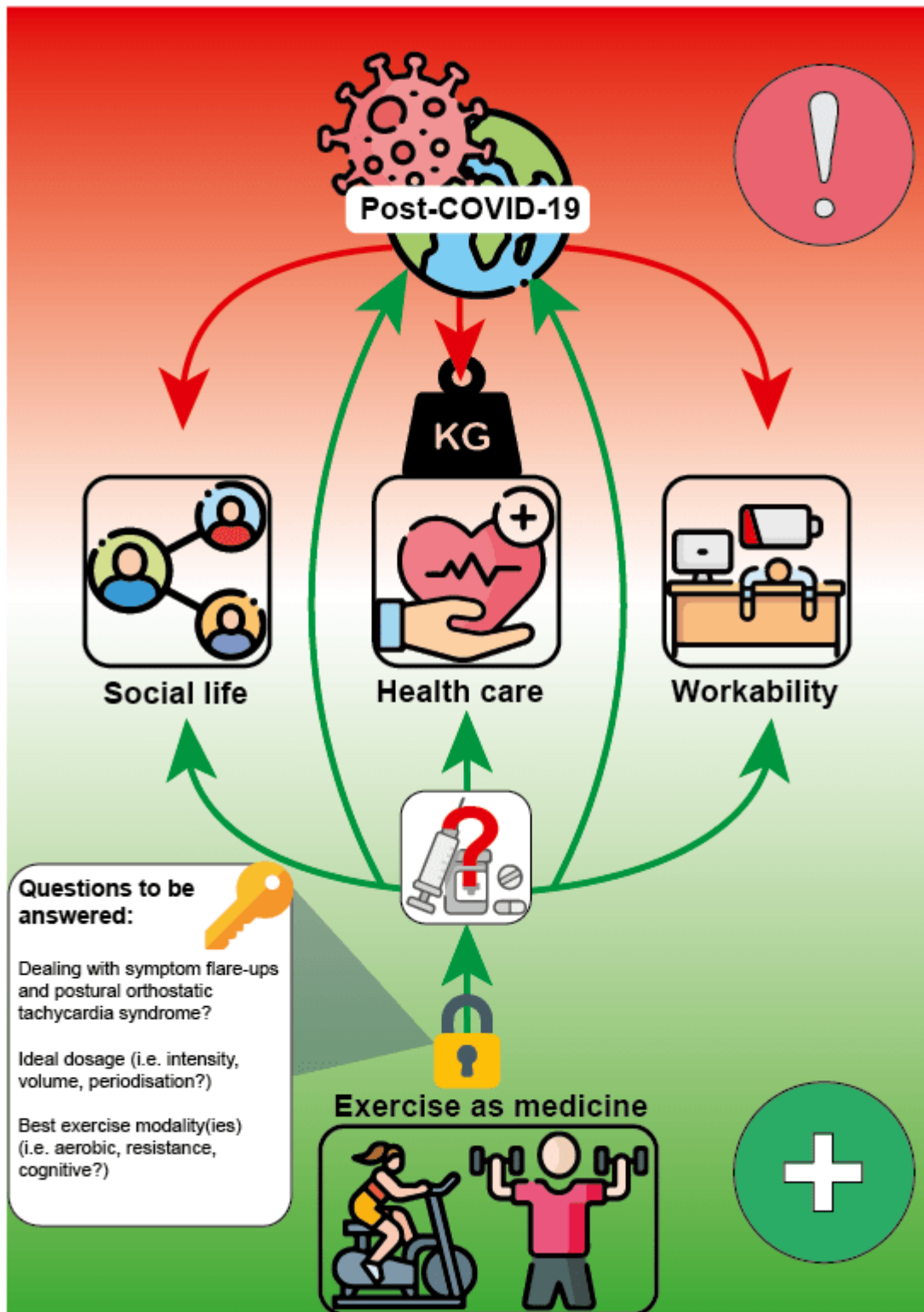


Figure 1

Exercise capacity, physical as well as cognitive function, and psychological health are often impaired in these patients. [1,2,6] As these parameters are important for daily life, the deficits reduce quality of life [2] and hinder participation in social as well as professional life. [2,7] The latter is reflected in reduced

workability and more frequent work absenteeism. [8,9] Without professional support and treatment, patients might enter a downwards spiral that promotes further exacerbation of the disease. Aside from these aspects, post-COVID-19 also poses a great economic burden. For instance, the previously reported increase in ME/CFS prevalence due to post-COVID-19 may be associated with an annual economic impact of 149-209 billion \$ in medical expenses and lost income for all ME/CFS cases in the U.S. [3] This does not consider the costs of disability benefits, social services, and lost wages of caregivers. [3] However, these costs may be only a small portion of the total economic impact of post-COVID-19. In short, the previous sections highlighted the significant sanitary and economic burden of post-COVID-19 on public health. There is an urgent need for action.

Treating post-COVID-19

There are currently few viable treatment options for post-COVID-19. This needs to change. Two recent reviews summarised the short- to long-term sequelae of COVID-19 on exercise capacity [6,10], contextualised these findings, and discussed the limiting role of various organ systems. [6] The authors concluded that low exercise capacity and exercise intolerance post-COVID-19 may not merely be explained by deconditioning but by limitations in several organ systems. [6] Another key message is that the one-size-fits-all principle is outdated because of the multitude of symptoms and organ limitations. [6] We thus need evidence-based and patient-centred treatment interventions. The available literature [6,10] provides an important starting point for the development of such interventions.

Exercise as medicine

To treat post-COVID-19, we should consider exercise as medicine. Given the abovementioned consequences of post-COVID-19 on social and professional life, exercise interventions could be a particularly suitable treatment option (possibly in combination with ongoing drug treatment). [11] Provided exercise is prescribed adequately, the following changes may be observable without severe side effects: a) reduced symptom burden, b) improved physical and cognitive function, and c) greater independence. [11] These changes may be paralleled by enhanced quality of life, participation in social life, workability, work presentism, and a reduction of the economic burden. [11]

To date, few studies offer insights into the feasibility and efficacy of exercise interventions in patients with post-COVID-19. [12] Most of the exercise interventions discussed in the review by Fugazzaro et al. [12] appear to offer some benefits regarding physical function, dyspnoea, and quality of life for these patients. All studies applied low to moderate intensity (<80% of maximum heart rate). [12] The feasibility and safety of different forms of acute high-intensity interval training (4×4 min, 6×1 min, 10-20-30 s) were examined in ten patients previously hospitalised due to COVID-19. [13] All exercise modalities in this sample were well tolerated. [13] While these results seem promising at first sight, several important issues need to be solved before exercise recommendations may be formulated (*Figure 1*):

How do we best deal with symptom flare-ups, post-exertion symptom exacerbation, and postural tachycardia syndrome?

In the latest version of the Clinical management of COVID-19: Living guideline, the WHO recommends

skills training on energy preservation techniques (i.e. pacing approaches) for patients with post-COVID-19 and modifying rehabilitation interventions in the presence of post-exertion symptom exacerbation and POTS. [14] This recommendation is based on low level of evidence. [14] Since studies on the feasibility and effects of exercise interventions in patients with post-COVID-19 and particularly with post-exertion symptom exacerbation or POTS are lacking, no recommendations for exercise therapy have been formulated to date. The high heterogeneity in this patient population further complicates this. [6] Pacing is an energy conservation technique that is considered safe [14] and might be effective for reducing fatigue in chronic conditions associated with fatigue. [15] There is also some evidence that the effects may be larger when pacing is combined with exercise therapy or cognitive behavioural therapy in these patients. [15] Whether this may also be the case in patients with post-COVID-19 needs to be further investigated. It should however also be noted that pacing might be more beneficial in some than in others, i.e. patients without post-exertion symptom exacerbation. Based on the large body of evidence in other chronic conditions with similar limitations [11], exercise interventions might harbour large potential in patients with post-COVID-19 not presenting with post-exertion symptom exacerbation. Yet, an important premise is that exercise is prescribed adequately.

The next steps to answer this question of how we best deal with symptom flare-ups in these patients may therefore be: 1) Specifically screening study cohorts for post-exertion symptom exacerbation and POTS, i.e. using questionnaires [5,16], to investigate whether and how exercise interventions need to be adapted for these sub-groups of patients. In our view, symptom-titrated exercise, not necessarily aiming at linear progression, has the greatest potential to be feasible and effective. 2) Carefully monitoring symptoms and their severity before, during, and after exercise interventions. 3) Conducting both acute and chronic exercise intervention studies in patients with post-COVID-19 in safe and controlled settings while considering points 1 & 2.

Which dosage (e.g. target intensity and volume) and exercise regimen (e.g. linear vs. non-linear periodisation) are ideal?

Depending on the recovery progress of a patient, one form of exercise periodisation may be preferred over the others. Patients experiencing considerable fluctuations in e.g. energy, fatigue, or pain levels might benefit from non-linear periodisation that takes into account the patient's form on the day of training. For those without fluctuations in symptom severity, linear periodisation might also be an option. Based on the multifaceted nature of post-COVID-19 sequelae, an individualised treatment approach, also with regard to exercise therapy, may be the most promising option. This needs to be examined in the future. Besides, research focussing on detecting which parameters (e.g. current level of fatigue, energy, symptom diaries) may be useful to adequately modify exercise intensity and volume.

Which exercise modalities should be performed (e.g. aerobic, resistance, cognitive)?

Peripheral limitations, impaired lung diffusion capacity, and cardiovascular limitations may contribute to exercise intolerance in patients with post-COVID-19. [6] Both aerobic and resistance training have been shown to elucidate improvements in chronic pulmonary, cardiovascular, and musculoskeletal diseases as well as other conditions (i.e. neurological diseases, chronic fatigue syndrome [17], depression). [11] Moreover, exercise training was shown to be effective in improving cognitive function. [18] It is to be determined which exercise modality or combination of modalities has the best benefit/risk ratio and

whether this may differ for certain patient characteristics.

How do we achieve high safety and patient compliance?

Exercise therapy needs to be safe for patients and have a good benefit/risk ratio. To achieve the best outcomes in the long run, high patient compliance is central. Whether an exercise intervention is safe and compliance is high will depend on the abovementioned questions. As for all studies applying exercise interventions in patients post-COVID-19, safety should always be the priority and be strictly monitored. Addressing these questions scientifically will ultimately yield a safe, feasible, and effective exercise therapy for post-COVID-19.

Conclusion

In summary, the prevalence of individuals affected by post-COVID-19 and the public health burden are significant. Evidence-based and patient-centred rehabilitation interventions are urgently needed. This is a call for action.

Practical implications

- Post-COVID-19 has extensive consequences for public health as well as social and professional life with currently no viable treatment options.
- Exercise may be beneficial for treating the multifaceted physiological and psychological sequelae of COVID-19 provided it is prescribed adequately and based on scientific evidence. Studies researching the feasibility and safety of different exercise regimes in these patients are needed.
- In our view, exercise therapy needs to be evidence-based and individualised to the patient's needs.

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Conflicts of interest

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FS conceptualised and wrote the manuscript. AST contributed to writing. All authors critically revised the manuscript and approved the final version.

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COVID-19 EXERCISE LONG-COVID POST-COVID-19 CONDITION TREATMENT