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REVIEW ARTICLE

Frailty after COVID-19: The wave after?

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Abstract

The COVID-19 pandemic poses an ongoing public health challenge, with a focus on older adults. Given the large number of older persons who have recovered from COVID-19 and reports of long-lasting sequelae, there is reasonable concern that the COVID-19 pandemic may lead to a long-term deterioration in the health of older adults, i.e., a potential "wave of frailty." Therefore, it is critical to better understand the circumstances surrounding the development of frailty as a result of COVID-19, as well as the underlying mechanisms and factors contributing to this development. We conducted a narrative review of the most relevant articles published on the association between COVID-19 and frailty through January 2023. Although few studies to date have addressed the effects of COVID-19 on the onset and progression of frailty, the available data suggest that there is indeed an increase in frailty in the elderly as a result of COVID-19. Regarding the underlying mechanisms, a multicausal genesis can be assumed, involving both direct viral effects and indirect effects, particularly from the imposed lockdowns with devastating consequences for the elderly: decreased physical activity, altered diet, sarcopenia, fatigue, social isolation, neurological problems, inflammation, and cardiovascular morbidity are among the possible mediators. Since the COVID-19 pandemic is leading to an increase in frailty in the elderly, there is an urgent need to raise awareness of this still little-known problem of potentially great public health importance and to find appropriate prevention and treatment measures.

KEYWORDS
COVID-19, frailty, health, older adults

1 | BACKGROUND AND RATIONALE

COVID-19 (coronavirus disease 2019) is an ongoing global challenge to public health and comes at a time when the challenges posed by aging populations (demographic change) are becoming ever more apparent.[1,2]

Frailty, a geriatric syndrome with major implications for clinical practice and public health, is on the rise. It is characterized by a decline in function across multiple physiological systems, accompanied by increased vulnerability to stressors.[2,3] Frailty is associated with an increased risk of adverse outcomes such as falls, hospitalization, and mortality, and is associated with higher health care costs.[3] The prevalence of frailty in community-dwelling men and women aged 65 years and older is in the range of 5% to 20%; estimates vary widely depending on the tool used and the population studied.[4-6] Pre-frailty, i.e. people at risk of frailty who meet some but not enough of the criteria for frailty, has a prevalence of about 1 in 3 people aged 65 years and older.

An increase in the number of frail older people experiencing disability and dependency is a critical aspect of demographic change and increasing life expectancy worldwide.[6] Prevention, early detection, and management of frailty are therefore critical at the level of the individual and for the sustainability of our health care systems.[7]

As discussed below, there is reason to believe that the COVID-19 pandemic will substantially increase the burden of multimorbidity, frailty, and disability in the older adult population (a potential "frailty wave"). A large proportion of older people have had one or more severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections, and given the reported persistent sequelae after acute COVID-19, many previously healthy individuals may be placed on a trajectory towards frailty and disability.[7,8] It is therefore crucial to better understand the association between COVID-19 and frailty.

The aim of this review is to provide a narrative overview of the existing evidence for a relationship between COVID-19 and frailty in older people and to identify the main mediators of this relationship, with a view to identifying preventive measures and appropriate therapies and raising awareness of this little-understood problem of potentially great public health significance.

2 | METHODS

All original articles available in PubMed/Medline, published until January 2023 and meeting the following inclusion criteria, were analyzed for the review of literature on COVID-19-associated frailty: (1) full text in English, (2) original or review article. The search terms used were "frailty" or "frail" and "COVID-19" or "COVID." In the second part, we reviewed the literature on potential mediating pathways. No systematic literature searches were carried out for this section.

3 | FRAILTY AFTER COVID-19

The concept of frailty is increasingly used in clinical care, and the COVID-19 pandemic has once again made a significant contribution to the awareness and clinical and scientific use of the concept of frailty.[9] As of 19 December 2022, a PubMed search for "COVID-19 AND Frailty" returned 952 hits.[10] Most of these articles examine the prognostic power of frailty, i.e. whether frailty is a risk factor for severe COVID-19, hospitalization, and death due to COVID-19.[11]

In addition, clinicians and researchers have primarily focused on the acute phase of COVID-19, and the focus is only gradually shifting to the long-term effects after recovery from the acute phase of COVID-19.[12] In fact, many people experience long-term effects of their infection, known as Long COVID, Post COVID-19 Conditions (PCC), or Post-Acute Sequelae of SARS-CoV-2 (PASC).[13] Studies have shown that up to 90% of patients who recovered from symptomatic COVID-19 reported persistence of at least one symptom or ongoing health problem. These included fatigue and dyspnoea that interfered with activities of daily living, as well as sleep problems, incident hypertension, memory problems, brain fog (difficulty thinking or concentrating), kidney damage, mental health problems, thromboembolism/hypercoagulability, arrhythmias/palpitations, cough, chest pain, neurological symptoms, dizziness, and joint and muscle pain.[8,14–18] According to data from the UK, an estimated 2.1 million people living in private households (3.3% of the population) had self-reported long COVID symptoms (lasting more than 4 weeks after the first confirmed or suspected coronavirus (COVID-19) infection and not explained by something else).[19] In fact, post-COVID-19 conditions can last for weeks, months, or years. In addition, data from previous coronavirus infections suggest that physical function and fitness may be impaired up to 2 years after infection.[16,20]

It is noteworthy that post-COVID-19 conditions share features with the frailty syndrome.[21] Likewise, post-COVID-19 neurological, cardiovascular, and musculoskeletal disorders may worsen functional status and contribute to the manifestation and progression of frailty.[18,22]

The role of COVID-19 in the development of frailty is currently not well understood.[12] Recently, preliminary studies have shown that the prevalence of frailty in the older adult population increased in the first and second years of the pandemic compared with the prepandemic situation.[23] For example, an Italian study of nursing home residents found a 19% greater decline in grip strength and a 22% greater decline in walking speed in COVID-19 cases compared with controls between pre- and post-COVID-19 assessments, and multivariable logistic regression showed that COVID-19 survivors had a fourfold increased risk of developing frailty compared with controls. Notably, there was a significant 10% decline in Mini-Mental State Examination scores over the study period in both cases and controls, which the authors attributed to social isolation and containment measures.[24] A recent prospective multicenter cohort study found that the Clinical Frailty Scale (CFS) increased significantly between pre-COVID-19 and follow-up.[25]

In fact, frailty status undergoes dynamic change. Recent data suggest that COVID-19 is associated with an increase in the rate of transition from robust to frail. Ferrara et al. showed that the rate of transition from robust to frail was 12.4% over a mean follow-up of 6 months in older patients previously hospitalized for COVID-19, whereas a prepandemic study found that the rate of transition from robust to frail was only 4.5% over a mean follow-up of 3.9 years[26,27] (Figure 1).

In addition, it has been shown that many older adults experienced a significant decline in physical and mental function during the COVID-19 pandemic, with multiple body systems affected at the same time.[28,29] As a geriatrician, the question is whether this isn't frailty. Indeed, many COVID-19 survivors exhibit the characteristics of frailty according to the original Fried frailty phenotype criteria (unintentional weight loss, self-reported fatigue, weakness, slow walking speed, and low physical activity) and exacerbated frailty according to the Clinical Frailty Scale (CFS).[5,29,30]

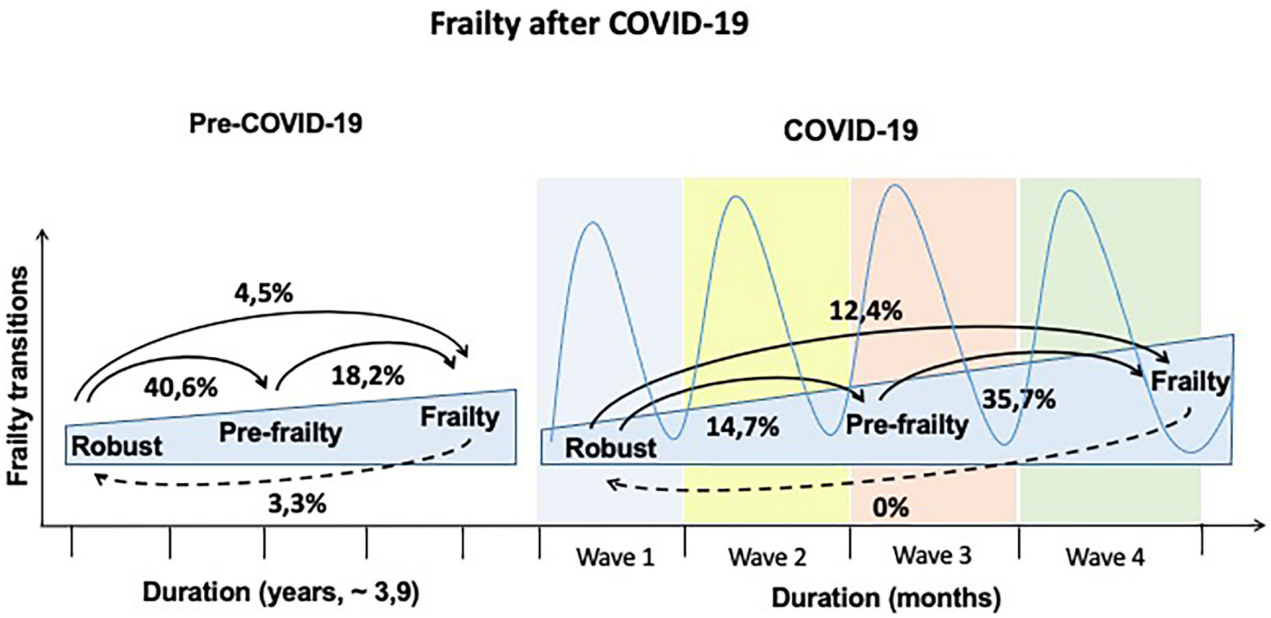
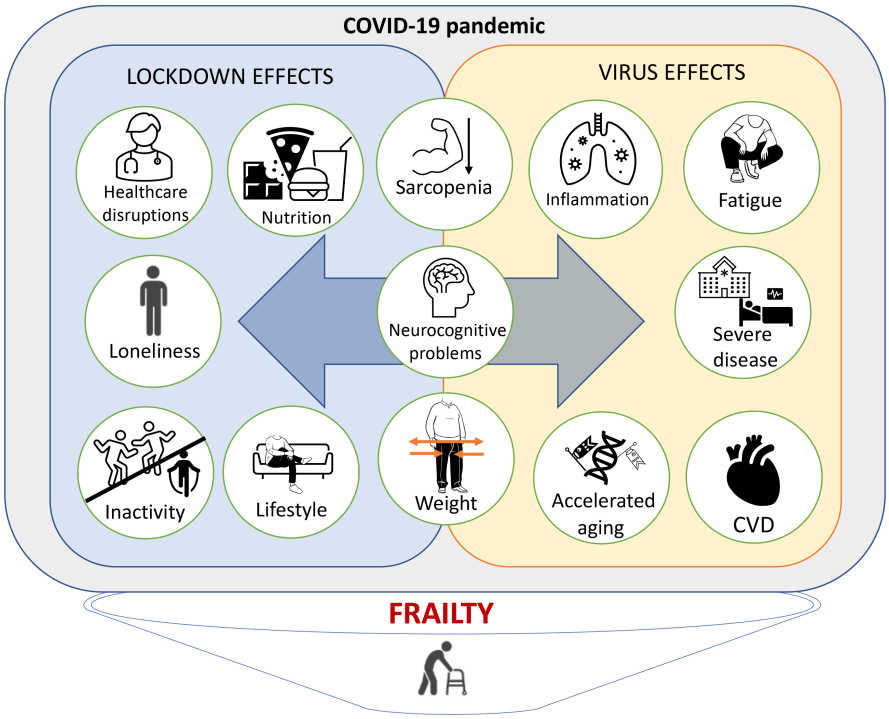


FIGURE 1 Frailty status undergoes dynamic change. Recent data suggest that COVID-19 is associated with an increase in the rate of transition from robust to frail. Ferrara et al. showed that the rate of transition from robust to frail was 12.4% during a mean follow-up of 6 months in older patients previously hospitalized for COVID-19.[26] A prepandemic study found that the rate of transition from robust to frail was only 4.5% during a mean follow-up of 3.9 years. Arrows show unfavorable transitions (robust → pre-frail → and frail). Dashed arrows show the reverse, favorable transition (frail → pre-frail → robust). These data support the hypothesis of a "frailty wave" after COVID-19.

FIGURE 2 Mediators of frailty. Several aspects of the COVID-19 pandemic favor the development of frailty in older people. These can be broadly categorized as lockdown-associated effects and direct viral effects, with many aspects being closely intertwined and partly interdependent.



4 | MEDIATORS OF FRAILTY IN THE COVID-19 PANDEMIC

Several aspects of the COVID-19 pandemic favor the development of frailty in older people. Mediators of frailty are listed in Figure 2. These can be broadly categorized into lockdown-associated effects and direct viral effects, with many aspects being closely intertwined and partly interdependent.

4.1 | Lockdowns

Frailty may be a possible consequence of lockdowns imposed during the COVID-19 pandemic, both in SARS-CoV-2 infected and uninfected older people.[30–32] Lockdowns resulted in widespread closures of sports facilities, exercise classes, social gatherings, etc. The *Effects of home Confinement on multiple Lifestyle Behaviors during the COVID-19 outbreak* (ECLB-COVID19) was a large multinational

web-based questionnaire study that examined the impact of the lockdown measures during the first wave of COVID-19 in 1047 people. The results showed that physical activity decreased by approximately 33% and sedentary time increased from 5 to 8 h per day.[33]

There is strong evidence that social isolation, loneliness, and resulting mental health problems, as well as physical inactivity (see below), are major risk factors for frailty, functional decline, and even mortality in older people.[3,33] For example, as shown in the *English Longitudinal Study of Aging* (2817 participants aged ≥60 years), older people who experienced high levels of loneliness were at increased risk of becoming physically frail.[34] There was a "modern behavioural epidemic of loneliness" before the COVID-19 pandemic, which was exacerbated during the lockdowns.[35,36] The results of a large prospective cohort study in Japan of 1953 community-dwelling older people aged 65 and over by Shinohara et al., which aimed to assess the impact of COVID-19 response measures on the development of frailty in older people and to identify factors associated with frailty, could confirm the negative impact of self-isolation in older people on the risk of development of frailty. However, this study was limited in that it did not consider the impact of SARS-CoV-2 infection itself on the risk of developing frailty.[37]

4.2 | Disruptions to health care

Many patients with chronic conditions have not received regular check-ups, and screening and preventive measures have been difficult or suspended due to the lockdowns, the workload on the medical system, and the reallocation of health care resources to combat the SARS-CoV-2 outbreak. In the long term, this can be fatal for some people, especially those with multiple or more severe conditions, that require regular monitoring of symptoms and adjustment of complex medication regimens.[38]

4.3 | Physical inactivity

Lack of physical activity during the COVID-19 pandemic may have contributed to the development of sarcopenia and frailty. Several studies have shown that physical activity decreased significantly by 30% or more during the pandemic waves compared to the time before the pandemic.[39,40] Specifically, physical activity decreased by 62% among older adults who lived alone and were socially inactive, leading to a significantly higher risk of incident frailty compared to those who did not live alone or were socially active.[39] In patients with symptomatic infection, weakness and symptoms of illness such as (persistent) dyspnoea, in addition to the effects of restrictions, may also lead to a reduction in physical activity.[41]

4.4 | Sarcopenia

Sarcopenia is highly prevalent in older COVID-19 survivors.[42,43] In a study of people who had recovered from symptomatic COVID-19 pneumonia, the majority had significantly reduced muscle strength and functionality (e.g. 69 and 54% of predicted normal for quadriceps and biceps strength, respectively).[44] Handgrip strength (HGS) is a good proxy for overall muscle strength, and low HGS is a diagnostic criterion for sarcopenia and frailty. In a large study, HGS was measured 3 months before (January 2020) and 9 months after the introduction of the virus into the population. The authors showed that SARS-CoV-2 seropositive individuals were 2.27 times more likely (95% CI: 1.33–3.87) to have a lower handgrip strength measurement at the time of follow-up than those who remained seronegative.[45] In addition, a small study from Japan ($n = 58$) found that participants in a frailty check program with examinations before and after the first COVID-19 wave had a reduction in handgrip strength that corresponded to different levels of social participation.[46] Different pathophysiological mechanisms may be involved in the development of post-COVID-19 sarcopenia (for a comprehensive review refer to[42,43]). Symptomatic COVID-19 infection regularly leads to prolonged immobilization, which may play a role in causing post-Covid-19 sarcopenia, and there is evidence of direct viral infiltration of SARS-CoV-2 into skeletal muscle, causing immune cell infiltration, muscle fiber atrophy, and metabolic changes.[47–49] Other factors include inactivity, medications, malnutrition, multimorbidity, deterioration of the antioxidant system, and a potent cytokine storm.[50–54] While the long-term effects of COVID-19 on muscle remain to be seen, there are indications that the adverse effects of COVID-19 on skeletal muscle may be long-lasting or permanent.[49,55]

4.5 | Malnutrition

Inappropriate diet is an important factor in the development of frailty. Lockdown measures have not only led to lower physical activity in the general population of older adults; lockdowns and stay-at-home restrictions have arguably also influenced eating behavior and habits, as well as body weight in the general population. There are reports of increased tobacco smoking, increased average food intake, increased consumption of high-calorie foods, more unbalanced diets, and poorer glycemic control.[56] Available data suggest that both weight gain and weight loss occurred during the pandemic.[57,58] For example, in a large Spanish cohort ($n = 1000$), 44.5% of participants reported weight gain during the lockdown period, whereas 6.4% of participants lost weight during the same period.[59] Similarly, a recent survey in Germany reported that 35% of respondents had gained weight since the start of the pandemic, in some cases significantly, while 15% of adults had lost weight since the start of the COVID-19 pandemic, in some cases drastically.[60] A US study found a significant increase in body weight (about 3 kg), body mass index (BMI), diastolic blood pressure, and total cholesterol levels, as well as a change in dietary habits (increased consumption of fats and oils and decreased consumption of fruits) compared with a control group before the COVID-19 pandemic.[61] The most commonly cited reasons include increased sedentary behavior, decreased physical activity, loss

of taste, increased snacking, increased alcohol consumption, decreased water intake, emotional eating, decreased sleep quality, and predisposition to overweight/obesity.[62] On the other hand, studies of patients with symptomatic COVID-19 tend to conclude that weight loss has occurred primarily as a direct result of the COVID-19 disease. For example, a post-hoc analysis of unintentional weight changes and malnutrition in 213 COVID-19 patients treated either in hospital or at home found a mean weight loss of 6.5 [5.0–9.0] kg and 8.1 [6.1–10.9] %, respectively, and recommended that nutritional assessment, counseling, and treatment be provided at baseline, throughout the course of the disease and after clinical remission.[63]

So far, the pandemic as a whole has tended to result in weight gain, while symptomatic disease has been more likely to result in weight loss and malnutrition.

4.6 | Fatigue

Fatigue (or exhaustion) is a hallmark of frailty and an item commonly included in frailty screening tools.[64] The *Global Burden of Disease Long COVID Collaboration* estimated, based on data from 1.2 million people, that the global proportion of people with persistent fatigue after symptomatic COVID-19 was 3.2%, controlling for pre-COVID-19 health status.[65] In fact, a study by Peter et al. showed that fatigue and neurocognitive impairment were the most important contributors to poor health after COVID-19.[66] Another study that followed 5406 participants 6 months or more after the test date found that 17.2% of those who tested positive for SARS-CoV-2 were still experiencing fatigue, which was twice the rate of those who tested negative for SARS-CoV-2.[67] A recent Italian study demonstrated the complex relationship between cognitive, psychological, and physical factors in the development of pandemic fatigue and subsequent changes in handgrip strength and gait speed in a normal aging elderly population.[32]

4.7 | Falls

The risk of falls increased as a result of stay-at-home restrictions, reduced physical activity, sarcopenia, malnutrition, and disruptions in health care. In addition, acute symptomatic COVID-19 may lead to falls (with or without traumatic consequences such as fractures), which in turn may limit physical activity and contribute to the development of frailty.[68,69]

4.8 | Inflammation

COVID-19 causes activated inflammation.[70] Likewise, chronic inflammation is one of the major mechanisms underlying the development of frailty.[71,72] The body's acute inflammatory response to COVID-19 is often associated with multi-organ damage, involving the lungs, but also the gut, central nervous system, cardiovascular system, kidneys, and muscle, among others. The uncontrolled and excessive release of inflammatory mediators can lead to multisystem organ failure and death ("cytokine storm"). There is also evidence that COVID-19 can lead to chronic, subclinical systemic inflammation of the type often seen in aging ("inflammaging"), leading to an increase and worsening of age-related diseases, including frailty, even in younger people.[73] The same markers and mediators are found to be elevated in COVID-19 as in frailty.[74] These include interleukins, inflammatory cytokines, and growth factors such as c-reactive protein (CRP), IL-6, IL-15, IL-2, CCL2, CXCL9, and TNF-alpha.[75] Recently, CXCL9 has been shown to play a key role in age-related chronic inflammation and may serve as a marker for early detection of age-related clinical phenomena.[76] Among the mechanisms that may underlie inflammation and frailty is activation of the NLRP3 inflammasome. Based on the literature, it is reasonable to consider NLRP3 inflammasome activation as a common pathogenic mechanism involved in a vicious cycle that triggers and perpetuates both COVID-19 and frailty.[77,78]

4.9 | Cardiovascular disease

Infection with SARS-CoV-2 has a high potential to cause cardiovascular complications, both in the short and long term. Current evidence suggests that the adverse cardiovascular effects of COVID-19 may persist for up to 2 years and beyond. Large US data showed that the 12-month risk of incident cardiovascular disease (all types) is significantly higher in COVID-19 survivors than in non-COVID-19 controls, even in individuals who were not hospitalized during the acute phase of infection.[79,80] The authors conclude that clinicians and patients with a history of COVID-19 should pay attention to their long-term cardiovascular health. Frailty and cardiovascular disease (CVD) are strongly (bidirectionally) associated.[80,81] Frailty is common in older adults with CVD, with prevalence estimates of up to 50% in people with heart failure.[82] Older adults with CVD or at increased cardiovascular risk are also at increased risk of frailty and cardiovascular events.[83] Frailty and CVD share common pathophysiological pathways.[77] These molecular pathways include the renin-angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2) pathways, oxidative stress, NLRP3 inflammasome activation, endothelial dysfunction, cell senescence and hypoxemia.[77,84] The inflammatory response associated with SARS-CoV-2 infection is likely to drive CVD and frailty, with CVD, inflammation and frailty reinforcing each other in a vicious cycle.[85]

4.10 | Neurocognitive impairment

Neurocognitive impairment is strongly associated with frailty.[86,87] Approximately 36% of SARS-CoV2 infections have been confirmed to develop neurocognitive and neuropsychiatric symptoms, which may persist long after the acute infection has resolved.[88,89] Studies have shown that the risk of cognitive deficits, dementia, psychotic

disorders, and epilepsy or seizures is still increased at the end of a 2-year follow-up period.[90] The most common neurocognitive symptoms after COVID-19 include, but are not limited to, "brain fog," dizziness, headache, impaired consciousness, seizures, myalgia, and encephalopathy.[88] In fact, brain fog is one of the most common long-term symptoms of COVID.[91] Most people who experience brain fog report forgetfulness, feeling confused, difficulty concentrating, making decisions, working, and carrying out daily activities, not to mention social relationships and communication or pursuing a job.[91,92] A decline in cognitive function, as in COVID-19, combined with muscular, proprioceptive factors can be thought of as cognitive frailty.[93] Proposed pathological mechanisms underlying neurocognitive symptoms range from neuroinflammation to gray matter loss, microvascular injury, brainstem dysfunction, a mild form of encephalopathy, perceptual dysfunction, and psychiatric disorders.[89,91] Direct viral encephalitis, microglial activation, peripheral organ dysfunction (liver, kidney, lung), damage to the blood–brain barrier, hypoxia, and cerebrovascular changes are considered as possible pathogenic mechanisms that may explain the adverse effect of COVID-19 on the nervous system.[94–99]

4.11 | Accelerated aging

There is great interest and intense research effort to identify a genuine, unifying biological basis of frailty. Advances in multi-omics platforms have provided, and will continue to provide, new information on the molecular mechanisms underlying frailty and a biological "signature of frailty."[100,101] Epigenetic changes are a hallmark of aging.[102] Indeed, individuals with COVID-19 have been found to have significant epigenetic (DNAm) age acceleration, as measured by epigenetic clocks, and significantly accelerated telomere length attrition compared to healthy individuals.[103] Irreversible epigenetic aging may serve as a biomarker for the risk of developing post-COVID-19 syndrome, or frailty.

We recognize that the review and listing of the areas and functions of the body that are affected by COVID-19 is not exhaustive.

5 | THERAPEUTIC APPROACHES TO FRAILTY POST-COVID-19

Frailty is a dynamic and potentially reversible process. There is currently no specific (targeted) therapy for frailty. There are also no ongoing trials aimed at reducing the endpoint of frailty according to https://clinicaltrials.gov, while numerous trials are underway to test different long-term COVID therapies.[104,105] However, there is good evidence that multimodal interventions are able to reduce frailty.[106,107] The appeal of such multimodal structured (home-based) interventions is that they start with the causes identified above, i.e. inactivity, sarcopenia, malnutrition, fatigue, loneliness. In this vein, a recent randomized controlled trial showed that nutritional therapy consisting of increased protein intake, specific probiotics and prebiotics, and specific physiotherapy improved the functional status of patients with recent COVID-19 infection.[47]

First and foremost, geriatrics as a clinical and scientific discipline is called upon to identify goals and clinically effective interventions against frailty after COVID-19.[56,77] Also, the importance of the multidimensional geriatric approach to older adults, implemented through the Comprehensive Geriatric Assessment (CGA), is again underscored by the COVID-19 pandemic.[108]

In addition, more public awareness campaigns such as the Canadian AVOID (Activity, Vaccinate, Optimize medications, Interact, and Diet/nutrition) campaign by the Canadian Frailty Network are urgently needed.[109]

6 | CONCLUSION

The COVID-19 pandemic remains an extraordinary public health challenge. Both the SARS-CoV-2 infection, which usually involves multiple organs and often leads to persistent multiple organ dysfunction, and the containment measures have the potential to set previously healthy older adults on a path of frailty and disease. The development of COVID-19-related frailty adds to the already high burden of disease and disability in older adults. If we now expect a significant increase in the incidence and prevalence of frailty, this underlines the need for prevention and early diagnosis of frailty in older adults, as well as the implementation of tailored therapeutic approaches.

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CONFLICT OF INTEREST STATEMENT

Maximilian König, Yulia Komleva, and Maik Gollasch declare that they have no conflicts of interest.

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