

**Title: Healthy ageing in the time of COVID-19: A wake-up call for action**

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Since 2020, COVID-19 has been ravaging the globe infecting and killing millions. People aged 60 years and over and those suffering from chronic illnesses are at particularly increased risk of severe infection and mortality [1, 2]. Marginalization and discrimination based on age have surfaced in the current situation with the need to establish a triage system in prioritizing the delivery of healthcare to those with better chances of survival, which implies that, often, those of older age might not receive optimal care amidst shortages of resources [3]. This raises many ethical concerns: have we been unable to provide adequate care for all and do no harm, and have our health systems been intrinsically arranged to inevitably fail our elderly population, whether before, during, or after the pandemic?

At the epicenter of this storm is the duty to protect and treat vulnerable populations who are disproportionately affected by the pandemic with the disruption of usual pathways of care. COVID-19 has affected all aspects of life, and perhaps one of the most worrying consequences of such disruptions is the effect it will continue to have on mental health and disease occurrence, progression, and prevention [4]. The current pandemic has again brought to the fore the fundamental role of maintaining optimal physical and mental health throughout life, adding quality of life to life and maintaining adequate trajectories of health and ageing. This is of particular importance with the overall increase in life expectancy and consequent demographic shifts in the global population, which have made of healthy ageing a prevailing concept.

In what follows, we draw on the literature to present the case for why healthy ageing is the foundational lifelong process upon which the adequate management of infectious diseases such as COVID-19 depends.

But first, what is healthy ageing? The concept of healthy ageing has evolved over time and the literature reports abundant attempts to operationalise it [5]. The WHO defines healthy ageing as “the process of developing and maintaining the functional ability that enables well-being in older age”, based on intrinsic capacity, enabling environment, and the interaction between them. This constitutes a longitudinal evaluation of the ageing trajectory and aims to support the individual intrinsic capacity and to promote behavioural activities that enhance the interaction between these constructs, away from the traditional disease-oriented models [6]. Nestola et al. describe the negative consequences of the pandemic on the five domains of intrinsic capacity in the aged, namely: locomotion, cognitive decline, psychological distress, sensory impairments, and vitality. The authors explain how COVID-19 is likely to deteriorate the ageing trajectories of the population with effects that will last beyond the pandemic [7].

Our knowledge of ageing and disease is constantly evolving. Underlying the ageing process are molecular, cellular, and physiological mechanisms such as telomere attrition and loss of proteostasis among others [8]. Complex homeodynamic systems for maintenance and repair come into play and determine the capacity of the body to age healthily [9]. In other words, hormesis, a term coined by Southam in 1943 and later contested by scientists seeking to use more accurate terms such as “adaptive homeostasis”, is the ability of the body to recover and maintain its structure and function following its exposure to multiple internal and environmental stressors. These adaptive mechanisms strengthen the capacity of living beings to resist stressors, maintaining health and survival [9]. It is when homeodynamic systems start failing progressively and the body loses its adaptive capacities and plasticity that damage accumulates, leading to frailty, disease, disability, and death [10]. Perhaps the most important factors that can feasibly enhance health in humans are behaviour and lifestyle [11]. Biogerontologists classify these factors into three categories: physical (exercise, oxidative stress reduction..), nutritional (micronutrients, caloric restriction..), and psychological (mentally stimulating activities..) [10]. Our understanding of the complex mechanisms underlying these protective effects against age-related diseases mainly originates from experimental studies, and these are well-elaborated in the literature [8-10]. For the purpose of this paper, we only mention that these beneficial effects stem from the activation of certain pathways, which would otherwise remain inactive. The hormetic effects on the immune response are of particular interest, knowing that chronic systemic inflammation and an increased production of pro-inflammatory cytokines have been linked to vascular ageing and the pathophysiology of diseases such

as atherosclerosis [12]. In addition to improving glucose and cell cycle regulation, reactive oxygen species control and stress resistance, caloric restriction has been shown to induce anti-inflammatory vascular effects through the inhibition of circulating factors such as pro-inflammatory transcription factor (NF- $\kappa$ B) and the attenuation of inflammatory gene expression [13, 14]. The hormetic effect of physical activity lies in its capacity to improve fitness and reduce inflammation, which is primarily modulated by the production of anti-inflammatory cytokines (IL-6, IL-1ra, IL-10) and the suppression of pro-inflammatory cytokine (TNF- $\alpha$ ) [15]. Reactive oxygen species that are generated during physical activity mediate antioxidant molecule upregulation and trigger a beneficial adaptive response [16]. Although the exact combination and level of these hormetins as well as exposure time and timing are yet to be unfolded in human interventional studies, experimental and observational studies are in considerable agreement with this concept [11, 13].

By examining how this pandemic has been unfolding and revisiting potential concepts underlying the intersection of healthy ageing with COVID-19, we argue that modifiable behavioural factors and their inherent capacities to stimulate the body's defense mechanisms and improve immunity need to be brought to the forefront of recommendations, not only for noncommunicable disease prevention and management, but equally for successfully dealing with challenges derived from infectious diseases across the lifespan.

Therefore, more stringent primary prevention policies are essential for improving the health and ageing trajectories of populations. This is of particular importance since:

*Our health spans are not inescapably determined by our genes:* How healthy we age is affected by the decisions we make every day, long before we reach old age. The effect of our genes on developing age-related diseases tend to decrease progressively after birth, paving the way for the effects of behaviour, lifestyle, and the environment in complex interactive mechanisms [17]. In addition to biological, demographic, and psychosocial determinants, a systematic review of longitudinal studies found that smoking was negatively associated with healthy ageing whereas physical activity and a healthy diet were positively associated with healthy ageing [11]. This places a great importance on behaviour and temporality, emphasizing the role of identifying and modifying risk factors to improve mental and physical capacities starting in early life and into old age.

*Poor health and comorbidities are major risk factors in the fight against COVID-19:* An abundance of data continues to emerge, consistently showing that physical and mental health status, age, sex, and BMI are among the main factors associated with COVID-19 severity and mortality [1]. Comorbidities that are also age-related including hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular, and cerebrovascular diseases are major risk factors for complications [2]. Halpern et al. outline the double burden of obesity and COVID-19 in low- and middle-income countries (specifically Latin America) and examine the underlying mechanisms [18]. Specifically, the dysregulation of lipid metabolism pathways results in an increased expression of angiotensin-converting enzyme 2 (ACE2) receptors, the main receptors used by SARS-CoV-2 virus to enter the host cells [19]. The effects of infection-containment strategies have also added a toll to general well-being and mental health, particularly in vulnerable populations and individuals with pre-existing mental health issues[20].

*The capacity of the immune system and inflammatory pathways to successfully eliminate the virus plays a vital role in the fight against COVID-19:* The immune response becomes life-threatening when dysregulated, as observed in the "Cytokine Storm Syndrome" in some patients [21]. Chen et al. hypothesized that the decline in immune function with age may contribute to adverse health outcomes in older COVID-19 patients. The exact mechanisms and associations with the propensity to experience the cytokine storm in this age group are yet to be elucidated in immunological studies [22]. As mentioned earlier, chronic inflammation, which contributes to ageing and disease, appears to be the culprit behind the increased risk of adverse outcomes in patients with cardiometabolic diseases and COVID-19 [23]. Adopting a healthier lifestyle contributes to healthy

ageing and has been shown to greatly improve cardiometabolic health and immunity in patients with COVID-19 [11, 23, 24].

History has shown that pandemics are inevitable, and we have limited immediate control over emerging infectious diseases. Perhaps one of the advantageous consequences of COVID-19 lies in its capacity to expose the faults both, in our individual behaviour and healthcare systems, which have long prioritized disease management over prevention. We have the opportunity and a collective responsibility to steer our focus towards health maintenance and disease prevention and play an active role in modifying our behaviour that can improve our health and, consequently, our preparedness for future pandemics. It is only by doing so that we can reap the health benefits within our reach. This pandemic will take its course as the global demographic shift into an older age group is happening, but one haunting question remains: when will the next pandemic take place and will we be better prepared next time? Perhaps we cannot predict the future, but we can create it.

### Contributors

Marilyne Menassa conceptualized the idea and drafted the manuscript. Esther MC Vriend revised the manuscript. Oscar H Franco conceptualized the idea and revised the manuscript. All authors approved the final version of the paper.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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