



# SFI TRANSMISSION

## COMPLEXITY SCIENCE FOR COVID-19

**STRATEGIC INSIGHT:** Physically active seniors are less susceptible to frailty, and thus to COVID-19 — and video gaming is here to help.

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*COVID spiraling frailty syndrome.* This was the term coined by the authors of a recent paper analyzing the unique vulnerability of the elderly to COVID-19 in Italy.<sup>1</sup> In the paper, they inform us that Italy is second only to Japan in terms of percentage of the population over 65 (22.4 percent). Along with the risk of increasing age, data from China and Italy implicate hypertension and type 2 diabetes as predictors of COVID-19 mortality, with these three factors defining the COVID spiraling frailty syndrome.

Frailty, outside the context of COVID-19, refers to a biological syndrome present in about 10 percent of Americans and indexed by three to five clinical components, including weakness from loss of muscle tissue (sarcopenia), slowed gait, low physical activity, sense of low energy or exhaustion, and unintentional weight loss.<sup>2</sup> The prevalence of frailty increases with age after 65, and this increases the risk of infections, the need for hospitalization for a given medical illness, and the risk for falls and disabilities. The causal components of frailty — to the degree that they have been identified — include age-related decline in gonadal hormones, increases in inflammatory mediators, and impaired insulin sensitivity.<sup>3,4</sup> Evidence suggests that the non-additive interaction of these failing systems leads to the emergence of the frailty phenotype, which has led it to be considered the consequence of disruption to a complex adaptive system. Critically, this dysregulated system lacks robustness, with the phenotype being unmasked and amplified by any external stressor or perturbation, e.g., infection by SARS-CoV-2. Notably, attempts to treat frailty with monotherapies — the one-system-at-a-time approach much beloved of mainstream medicine — have largely failed (for example, estrogen or testosterone replacement).<sup>5,6</sup>

In a recent article, Linda Fried, the investigator primarily responsible for first defining the frailty syndrome, makes a compelling case for physical activity as the kind of intervention needed to mitigate its effects. She states:

“This is because physical activity simultaneously upregulates many systems that mutually regulate each other in combination. Thus, the whole organism could be re-tuned to a higher functional level. This offers a model intervention that matches well a complex system problem. If monotherapies are not sufficient, then finding an intervention that ‘tunes’ a critical mass of systems would be critical.”<sup>7</sup>

The benefits of physical activity extend well beyond the special case of frailty, with well-proven links between lack of physical activity and vulnerability to numerous chronic diseases. There is overwhelming evidence, for example, that the two chronic diseases mentioned at the beginning of this piece, hypertension and type 2 diabetes, are highly responsive to physical activity,<sup>8</sup> an intervention that can have effect sizes as large as those seen with medications. Neuroscientist Peter Sterling in his recent book, *What Is Health?*, has this to say about hypertension:

“When the brain commands a rise in arterial pressure, blocking one peripheral mechanism leads the brain to drive the others harder, thereby requiring additional drugs. A therapeutic system based on blocking cerebral commands seems unlikely to succeed. A more promising strategy, we suggest, would concentrate on restoring social and psychological health, thereby reducing chronic conflicts between brain-centered and body-centered regulation. A therapeutic system based on brain-centered regulation would begin not with antihypertensive and antidiabetic polypharmacy (for example), but rather by enhancing sleep and exercise, both of which improve health.”<sup>9</sup>

Thus, a case can be made for reframing physical activity as either an emergent therapy or a complex medicine. If aging and chronic diseases are the consequences of a complex adaptive system gone awry, then perhaps a sustained complex perturbation is needed to fix it.

The high prevalence of frailty and chronic disease in the over-65 population, which is growing faster worldwide than all other age groups, highlights the urgent need to address the global consequences of inadequate levels of physical activity in this population pre-COVID-19 and the exacerbating effect that can be expected by the imposition of further limitations on exercise and movement post-COVID-19. At the WHO website, physical activity is defined as any bodily movement produced by skeletal muscle,<sup>10</sup> and includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, household chores, and recreational activities. The benefits are not just physical but also extend to mental health, cognitive function, and social and emotional well-being.

The WHO recommends that persons over 65 should do at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity throughout the week (or an equivalent combination of the two).<sup>11</sup> However, for many adults, there are several functional and motivational barriers to engaging in regular physical activity, barriers that are exacerbated in the setting of aging and chronic disease. Barriers range from limited access to safe and fun environments that encourage physical activity (not everyone can afford a gym membership) or difficulty engaging in daily physical activity at all. For example, brisk walking is beneficial if you can balance safely and have somewhere to walk. Even if one does have access, the fact is that exercise is boring — making this kind of behavioral intervention hugely difficult to sustain. It is perhaps unsurprising then that by age 75, about one in three men and one in two women engage in no physical activity at all.<sup>12</sup> Efforts to promote modest increases in physical activity among at-risk sedentary adults have met with only limited success in delaying frailty risk.<sup>13</sup>

The lockdown and self-quarantining recommendations being seen worldwide for COVID-19 and the lingering fear of going outside, even when these restrictions are lifted, will only exacerbate the myriad detrimental mental and physical consequences of inactivity on the aged. What is badly needed is a systematic approach that takes existing evidence and transforms it into an immersive, enjoyable, and gorgeous movement-based experience — human enrichment — for aging adults that is nevertheless realistic and scalable across locations and socioeconomic conditions. The one technology that we know keeps people on task is video-gaming. Indeed, about 50 percent of people over the age of 50 play video games.<sup>14</sup> We must take the impetus from the current crisis to accelerate innovation at the confluence of conventional video-gaming, virtual reality, real-time motion capture, and physical activity, with an emphasis on the over-65 population. Given that COVID-19 is disproportionately targeting those at higher socioeconomic risk, the development of such interventions is particularly urgent for those with few opportunities for safe, regular, and accessible physical activity.

## REFERENCES

- 1 Abbatecola, AM and Antonelli-Incalzi, R. COVID-19 Spiraling of Frailty in Older Italian Patients *J. Nutr Health Aging*. 2020: 1—3.
- 2 Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):3.
- 3 Chen Y, Liu S, Leng SX. Chronic Low-grade Inflammatory Phenotype (CLIP) and Senescent Immune Dysregulation. 2019 *Clin Ther*. (3):400-409
- 4 Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018 15(9):505-522.
- 5 Kenny AM, Dawson L, Kleppinger A, Iannuzzi-Sucich M, Judge JO. Prevalence of sarcopenia and predictors of skeletal muscle mass in non-obese women who are long-term users of estrogen-replacement therapy. *J Gerontol A Biol Sci Med Sci* 2003 58: M436—M440.

- 6 Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999 84: 2647—2653.
- 7 Fried LP. Interventions for Human Frailty: Physical Activity as a Model. *Cold Spring Harb Perspect Med* 2016 Jun 1;6(6):a025916.
- 8 Colberg SR, et al. Exercise and Type 2 Diabetes. The American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*. 2010 33(12): e147—e167.
- 9 Sterling P. *What is Health?*. MIT Press 2020.
- 10 <https://www.who.int/dietphysicalactivity/pa/en/>
- 11 [https://www.who.int/dietphysicalactivity/factsheet\\_olderadults/en/](https://www.who.int/dietphysicalactivity/factsheet_olderadults/en/)
- 12 <https://www.cdc.gov/nccdphp/sgr/olderad.htm>.
- 13 Maintenance of Physical Function 1 Year After Exercise Intervention in At-Risk Older Adults: Follow-up From the LIFE Study. Henderson RM et al, & LIFE Study Investigators. *J Gerontol A Biol Sci Med Sci*. 2018 73(5): 688-694.
- 14 <https://www.aarp.org/home-family/personal-technology/info-2019/report-video-games.html>

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