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Editorial

Resilience and the Future

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The term "resilience" has existed for many decades and defines the ability to bounce back after a stressful encounter or adversity in life (1). Resilience in older adults has gained increasing attention in recent years, and many countries are trying to build resilience at individual, community, and system levels, especially after the Covid-19 pandemic (2, 3). Resilience is dynamic and multidimensional, frequently distinguished into physical resilience and psychological (mental and/or cognitive) resilience (4, 5). Physical resilience is defined as "the ability to recover or optimize function in the face of age-related losses or disease" and is one of the top research priorities for the US National Institute on Aging (1, 6, 7). Declining resilience is considered a marker of accelerated aging and a risk factor for incident frailty. It is associated with adverse functional outcomes in later life. There are multiple risk and protective factors described with the mnemonic "PURPOSE OF LIFE" (Figure 1) (8).

Due to its dynamic and multidimensional nature, resilience is a difficult construct to measure (6, 8, 9). There is no mechanism in place to predict dose-response and tipping point for adverse outcomes (10). The response to stress and recovery is unpredictable due to the co-occurrence of chronic diseases and age-related declines in multiple physiological systems. A stressor can act alone (e.g., bedrest causing muscle wasting and delirium) or in combination with other multiple factors (e.g., osteoarthritis, sedatives and antihypertensives causing falls and fractures) in the onset of adverse outcomes. In addition, aging and resilience trajectories are determined by multiple interacting factors (including environment, exposure to toxins across lifespan, comorbidities, polypharmacy, genetics, lifestyle), all of which contribute to immune-senescence and decline in physical and biological reserves (11, 12). A recent study described four distinct trajectories of recovery in nursing home residents admitted to the emergency department, where those with good baseline function had better post-discharge functional recovery (13). Static evaluations, such as disease burden, geriatric assessment, frailty, gait speed and/or handgrip strength, may predict adverse outcomes but not sufficiently the capacity to recover. Multiple longitudinal assessments across the health trajectory may better estimate such capacity (9, 10). While it may be easier to measure physical resilience, this is often inseparable in real life from psychological resilience. To date, there is no scoring system incorporating both measures (14).

Adaptations to adversity are influenced by age, gender, ethnicity, generation differences, cultural variation, type and intensity of the stressor, and intended outcome (15-17). The New Mexico Aging Process Study focused on chronological age where the rate of decline in walking speed and cognition was much higher, and recovery was much lower in the old-old compared with the young-old (18). Age-related changes occur at the cellular, physiological system, and clinical level. A decline in resilience is possibly mediated through the dysregulated immune system, insulin resistance, mitochondrial dysfunction, impaired autophagy and endoplasmic reticulum stress, epigenetics, autonomic and vascular dysfunction (11, 19, 20). Similar dysfunction contributes to the development of frailty syndrome. One may argue that changes at the cellular level may be general changes with aging and not specific to physical resilience as a clinical phenotype (21). There are emerging studies exploring the contribution of biological mechanisms of aging to resilience trajectory in older adults. Higher Growth Differentiation Factor-15 and Tumor Necrosis Factor Receptor-1 levels are associated with frailty, decline in intrinsic capacity, mitochondrial dysfunction, and poor recovery after acute illness (20, 22, 23). In a group of patients with hip fracture, 27% of the differences in physical resilience or expected differential recovery could be explained by biomarkers (24). Various ongoing trials evaluate geroscience-based interventions, including pharmacotherapy and vaccinations on resilience trajectory (such as metformin, resveratrol, omega-3, senolytics - e.g., Dasatinib and Quertin, and low-dose mammalian Target of Rapamycin [mTOR] inhibitors) (25-28).

Frailty is a state of declining physiological reserves, and physical resilience can be described as the ability to mobilize reserves. While static measures, such as gait speed and handgrip strength can be used as a surrogate for underlying reserve, the intrinsic capacity framework proposed by the World Health Organization (WHO; including the assessment of cognition, vitality, mobility, psychological and sensory functions) has shown to predict functional recovery after exposure to adversity (29, 30). Intrinsic capacity can be considered an indirect measure of physical resilience through the physiologic reserve concept (31). The INSPIRE integrated

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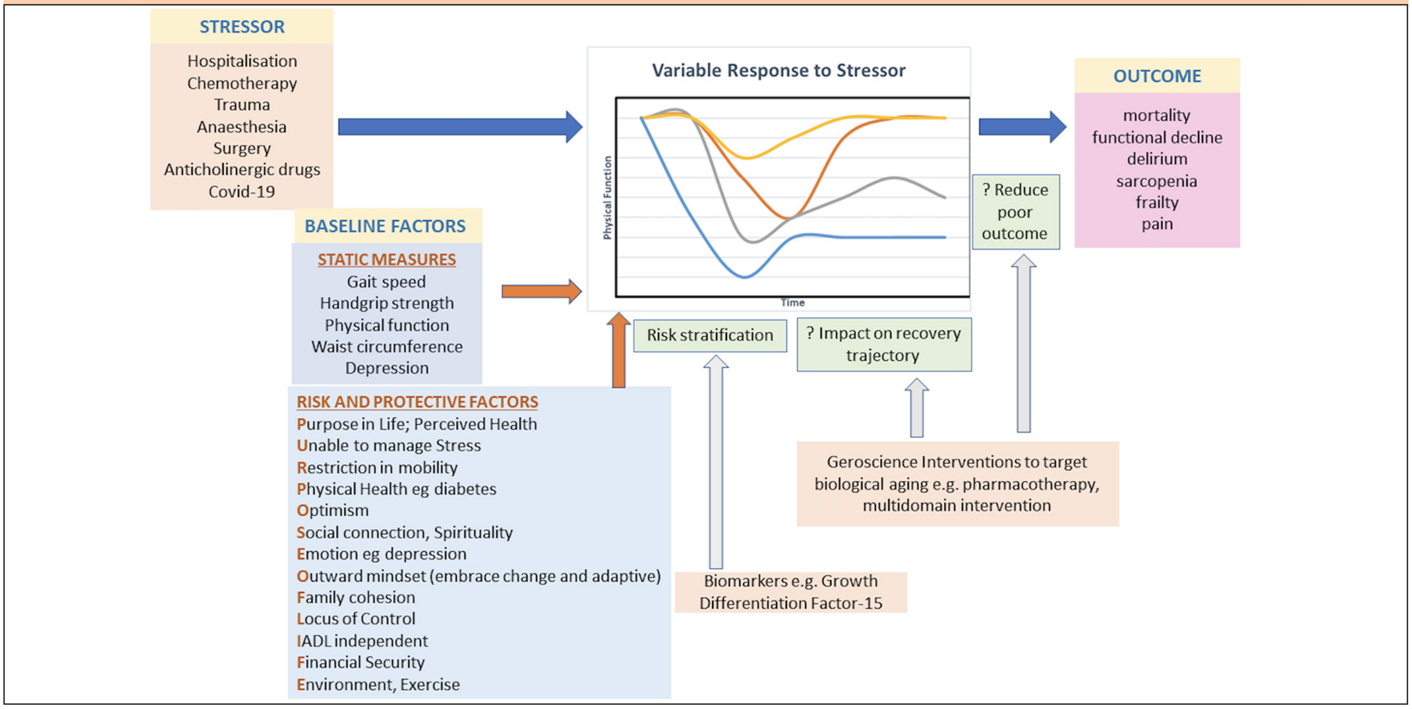
Figure 1. Variable Response to Stressors Influenced by Baseline Static Measures, Type of Stressor, Risk and Protective Factors, Biomarkers and Geroscience Interventions



care for older people (ICOPE)-CARE program conducted by the Gerontopole in Toulouse has recently introduced screening for intrinsic capacity using the ICOPE monitor and ICOPEBOT conversational robot with the aim of identifying high-risk older adults (32). Many countries are implementing programs such as frailty screening and multidomain interventions, incorporating nutrition and exercise at individual, community, and city levels to reverse, prevent, or delay the decline in physiological reserves, possibly improving resilience over the long term (33-38).

Incorporating resilience into the prognostication of hospitalized older patients is another evolving research area. Being able to measure baseline resilience, its magnitude, the type of stress (e.g., anesthesia or chemotherapy), the recovery trajectory, and predicting adverse outcomes will enable clinicians to provide cost-effective, personalized care. PRIME-KNEE is an ongoing prospective cohort study for elective knee replacement surgery where pre-stressor static and provocative tests will be validated, and the utility of biomarkers in predicting recovery will be measured (39).

Exercise and physical activity offer clinical benefits as a preventive strategy across a wide range of diseases and disabilities; improvement of muscular function, mental health, and quality of life; and reduction in mortality, with no upper age limit. Similarly, multicomponent exercise intervention programs, especially if including a cognitive task, effectively improve the hallmarks of frailty (i.e., low body mass, weakness, poor mobility, sedentariness, anergia) and cognition, thus optimising functional capacity (40-43). In older adults, the potential role of tailored physical exercise programs to maximize exercise-related effects on the ability to perform activities of daily living or promote resilience should also be explored. An individualized multicomponent exercise training program for older adults (VIVIFRAIL) (http://vivifrail.com/resources/) (44, 45) has shown to partially reverse sarcopenia and frailty (46-48) as well as loss in activities of daily living (i.e., toileting, transfers, mobility, and stair climbing), frequently occurring during and after hospitalisation (49).

In this issue of the Journal of Frailty and Aging, Cesari et al. provide a perspective from the International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force meeting on the biological and clinical significance of resilience in older adults. The authors have highlighted the challenges in measuring resilience due to its dynamic nature encompassing socioeconomic, environmental, clinical, and biological factors. Preliminary results of ongoing studies are also presented in the paper. It is discussed that future research is needed to develop appropriate tests of resilience in animal models within an aging context. However, the translation to human resilience trajectory may be challenging due to differences in life expectancy and difficulties in replicating the psychological, social, and physical environment, service provisions, and the whole host of social determinants of health throughout the life course. The authors concluded that future research should focus on identifying and validating biomarkers for different resilience phenotypes and developing prevention strategies before the onset of adverse events.

Conflicts of Interest: No conflict of interest.

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