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# Frailty, Vulnerability, and Plasticity: Towards a New Medicine of Complexity

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## Abstract

There is no single way of ageing, but different types of ageotypes have been identified. Frailty is the most problematic expression of the ageing population. The understanding of the route linking ageing, frailty and 2nd order criticalities open new and intriguing operational perspectives. Indeed, frailty might be reversible or attenuated by interventions put in place to avoid its evolution over time. This is most true when traditional therapeutic approaches are combined with the promotion of healthy lifestyles. Not only the European Innovation Partnership on Active and Healthy (EIP-AHA) is actively involved in the promotion of healthy and active ageing, but a more aware geriatric culture toward a new medicine of complexity is spreading. The fight against frailty takes place in a lifespan and multisystemic perspective. Indeed, every individual is a dynamic, interacting, adaptable system in which the disease triggers a cause-and-effect model that cannot be considered linear. Frailty in the elderly requires therefore a customized multidimensional approach according to the principle of “taking care of the patient and not only of the disease”. A bio-psycho-social model can help us to define the most appropriate interventions to promote health in terms of the best possible quality of life.

**Keywords:** ageing, ageotype, frailty, vulnerability, plasticity, prevention, comprehensive geriatric evaluation, medicine of complexity

## 1. Introduction

Ageing - whatever the age that characterizes it - cannot therefore be identified with a state of illness but must be considered a natural phenomenon that goes hand in hand with a progressive physiological and psychological transformation of the organism and that can determine - through an accentuated biological vulnerability - a greater propensity to illness [1].

Physical frailty is a condition of marked vulnerability to negative events caused by the reduction of functional reserves of multiple systems of the organism because of the ageing process and chronic polypathology. It is a condition that represents a risk factor of disability, hospitalization, institutionalization, and death [1]. But what determines frailty - not necessarily physical, but also cognitive or interpersonal - in an elderly person?

Biomedical sciences, neuroscience and epigenetics have increasingly analyzed the mechanisms that regulate structural-functional changes in the body in relation

to environmental influences. Each person has his/her own biography; each body and nervous system has its own development and use. Frailty and strength emerge in the course and within an individual story, according to a life-span perspective.

Frailty and strength constitute an oxymoron that often originates from the same semantic source. Paradoxically, it is the frailty condition that allows the discovery or rediscovery of resources and potentialities.

Frailty and strength are recognized, interwoven with affections, their formation and realization. It is the affective experiences that contribute in a decisive way to structuring an individual's personality, the feeling of security or precariousness, or the prevalence of one over the other.

Quintus Horatius Flaccus (Odi: IV, 4, v.65) argued that «*Merses profundo: pulchrior evenit*». It is frequent to observe how certain negative events allow the re-emergence of an inner strength, of a resilience, physical and motivating, which opens to new developments and opportunities. As an elderly person it is always possible, even in adverse conditions, to regain the ability to recover, to compensate, even for those who are less fortunate.

Frailty and strength interact, alternate and are continually shaped throughout life. Affectivity often represents its seismograph, but vulnerability can at the same time constitute the metronome of one's emotional instances, especially the deepest ones. The notions of "frailty" and "affectivity" recalls an ontological condition, as intrinsic to the human dimension, and offer original perspectives of investigation for multiple issues affecting the elderly. These perspectives are well highlighted by the analyses of numerous themes of both frailty-vulnerability and affectivity-emotivity in ageing developed by different disciplines (anthropology, sociology, philosophy, biology, psychology, neuroscience, medicine). It becomes relevant to understand how frailty and affectivity interact in the course of ageing, depending on what has been experienced and learned, and on what existence and life in society continue to offer.

The importance of a multidimensional assessment of the elderly to define their state of health and well-being has long been recognised. Indeed, cognitive, affective, behavioural and functional factors interact closely with somatic and socio-environmental ones.

A bio-psycho-social model can help us to define the most appropriate interventions to promote health in terms of the best possible quality of life. This approach attributes health to the intricate and variable interaction of biological, psychological, and social factors [1, 2].

## **2. There is not a single ageing: from successful ageing to frailty**

There is no single way of ageing, but there are as many different ageing processes as there are humans [2]. Indeed, ageing is a gradual and continuous process of natural mutation for which many bodily functions begin a gradual decline [2]. The life-span perspective recognizes changes in the functional state as characteristic of the human being ageing process [3] and are considered characteristic of the *pure ageing* [4].

Considering the continuum that goes from pure ageing to pathological ageing, one can define *successful ageing* as the situation in which the postponement or reduction of the unwanted effects related to advancing age occurs [2, 3]. The main features of successful ageing are the maintenance of physical health, an active and autonomous life; a full and satisfying emotional-relational life; prevention of ailments and disabilities. This perspective also applies to the neuropsychological domain: the label *successful cognitive ageing* can be used to refer to people whose physical health may or

may not be good, but whose cognitive profile remains exceptional [2]; at the same time, the label *typical cognitive ageing* can be used to refer to people who experience a slow loss of cognitive efficiency that does not result in a neurocognitive disorder and whose distinctive feature is the reduction of mental processing speed [3].

Different types of ageing patterns (*ageotypes*) have been identified, based on the molecular pathways that changed over time [5]: (1) metabolic (relating to the build-up and breakdown of substances in the body); (2) immune (relating to immune responses); (3) hepatic (relating to liver function); and (4) nephrotic (relating to kidney function) [5].

This type of classification provides a molecular assessment of individual ageing, reflective of personal lifestyle and medical history; indeed, ageotypes highlight the potential health risk factors and may ultimately be useful in monitoring the ageing process [2, 5]. Multimorbidity and polypharmacotherapy weakens the body and can predispose to accelerated ageing, resulting in frailty.

Frailty is certainly the most problematic expression of the ageing population [1, 2]. It is an integrated [6] and multidimensional [7] condition in which biological, functional, psychological, and social variables interact with each other. It may be relevant in identifying older people at risk of deteriorating mental health [8] and cognitive decline [9]. *Cognitive frailty* specifically refers to the co-occurrence of mild cognitive impairment and physical frailty in the absence of a major neurocognitive disorder diagnosis [10]. The presence of physical and/or cognitive frailty in the elderly increases the risk of negative outcomes and leads to greater use of health and care services [1, 2].

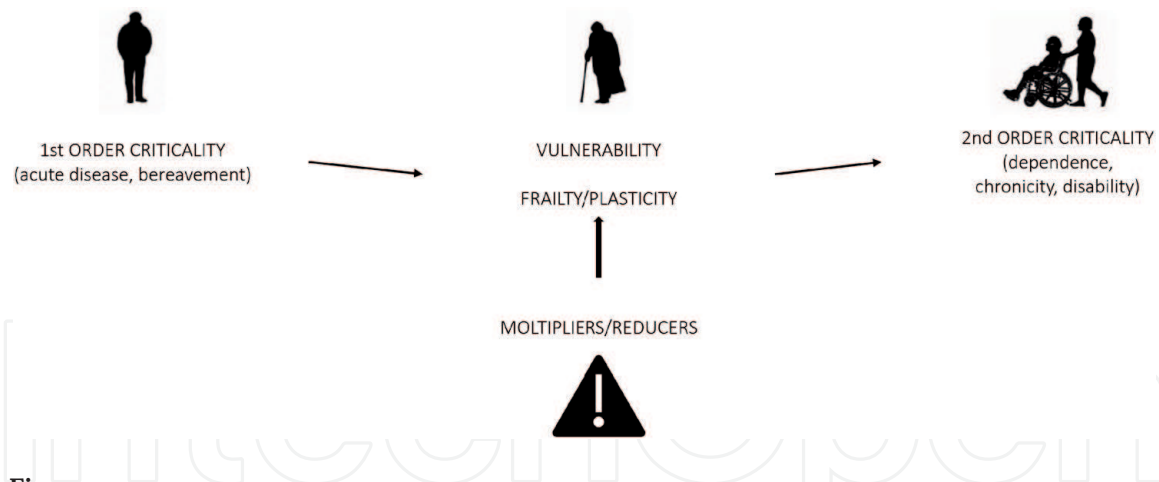
In the face of such a complex picture, there is yet no unambiguous operational definition of frailty that would make it possible to define a gold standard of evaluation. Experts belonging to the European Innovation Partnership on Active and Healthy (EIP-AHA) have identified two main approaches: the first concerns physical determinants (biomedical approach), while the second considers biological, cognitive, psychological, and socio-economic factors (bio-psycho-social approach). Indeed, a reliable assessment cannot be separated from the analysis of the affective, cognitive, and relational components [1].

### 3. From vulnerability to plasticity

Vulnerability should be considered as a predisposition of an individual exposed to a critical situation to slip into a more severe critical situation. Vulnerability and criticality define respectively a property of a process and a state within that process [11]. In this sense the definition of frailty proposed by Rozzini and Zanetti is explanatory [12]: «frailty is a condition of risk and vulnerability in the face of noxae of various kinds, which challenge the homeostatic balance of an organism. Frailty is predisposition to breakage, to damage when subjected to pressure».

Considering the above:

- *Criticality* is the condition experienced by an individual along a scale of severity and a scale of probability of occurrence. This concept is borrowed from the risk assessment process, a process from which all prevention and protection interventions for the individual are derived.
- *Vulnerability* is the degree of propensity of an individual, who experiences a less severe criticality (definable as *1st order criticality*: e.g., a bereavement, an acute illness), to slide towards a higher order of criticality (definable as *2nd order criticality*: e.g., dependence, chronicity, disability).



**Figure 1.** Logical concatenations between the concepts of criticality and vulnerability. Adapted by Micheli [11].

The shift towards higher order critical issues is the recurring scenario in the problems of the elderly population [11]. Indeed, chronicity can be considered the final state of a path of depletion of plastic capacity (**Figure 1**). According to a *life-span perspective*, the individual shows a substantial plasticity at any given time. This *developmental reserve capacity* is specific and variable for each age and for each functional domain [11].

The understanding of the route linking ageing, frailty and 2nd order criticalities and the distinction between frailty and 2nd order criticalities have not only a pathophysiological significance. They open operational perspectives. It has been demonstrated that the route from pure ageing to 2nd order criticalities is not a one-way street, and that a regression from frailty to pre-frailty and from the latter to a “non-frailty condition” is possible [13]. Indeed, frailty might be reversible or attenuated by interventions put in place to avoid its evolution over time [14]. Many conditions of (pre)frailty can reverse their direction, so that they can move in the direction of successful ageing. This is most true when traditional therapeutic approaches are combined with the promotion of healthy lifestyles. In old age, the potential and limits of plasticity are often monitored in the neurocognitive and rehabilitative fields. The prestigious *Nature* has dedicated a special issue to these themes. In the cover article “Prevention: activity is the best medicine” [15] you can see two people dancing. The evidence in favor of the protective role of healthy lifestyles for the maintenance of cognitive functions is well established.

The task now is to move from lifestyle factors to interventions to find out how what kind and much exercise, what kind of intellectual activity, what kind of diet, what kind of social support and engagement (and at what stage each of them) could influence the directions of ageing.

The question of how to promote healthy lifestyles in the adult and elderly population as a prevention intervention no longer arises only at a scientific level but at a social and political level.

#### 4. Promotion of healthy and active ageing

Recent studies have underlined the existence of a significant association between lifestyle and frailty [16, 17]. All older people are at risk of developing frailty, although risk levels are substantially higher among people with comorbidities, poor socio-economic status, poor nutrition and sedentary lifestyles [16]. However, inappropriate lifestyles and some clinical risk factors are potentially counteracted by specific interventions and preventive actions [16].

The EIP-AHA Action Group A3 has developed several multidimensional tools capable of predicting short-term negative outcomes [18]. Several factors have been highlighted as useful for proper health planning: malnutrition, polypharmaco-therapy, impairment of physical function and social isolation have been identified as those on which to act to mitigate fragility and its consequences [18].

Data from a recently published study [19] also point in this direction. The Barcelona Brain Health Initiative is a longitudinal cohort study initiated in 2017 that aims to understand and characterize the determinants of brain health and intellectual efficiency in middle-aged adults. A cohort of 4686 individuals aged between 40 and 65 has been established, with no history of neurological and/or psychiatric illness. The researchers collected demographic, socio-economic, clinical and health data, associating them with assessments of perceived health status and lifestyles (general health, physical activity, cognitive activity, socialization, sleep, diet and so on). The results underline the importance of healthy lifestyles to support brain health and intellectual efficiency [19].

Consistently with the above, it is believed that the prevention and treatment of frailty can only be based on:

- promotion of healthy lifestyles.
- promotion of social inclusion and social engagement
- promotion of emotional relationships.
- timely identification of clinical-functional fluctuations and “sentinel events” (falls, urinary incontinence, sensory deficit, delirium, ...), which must be considered potential 1st order criticalities
- diagnosis and treatment of all pathologies that can be responsible for asthenia, weight loss, reduced tolerance to effort, reduced physical strength and physical activity
- intensive and frequent clinical monitoring of the elderly at risk
- adaptation of daily living environments
- reduced exposure of the frail elderly to environmental stresses (including hospitalization and unnecessary medical procedures)

## **5. Monitoring health in the elderly: the Active Aging Index**

Active and healthy ageing is a multidimensional concept referring to a situation where the elderly persists to participate in the formal labour market, engage in voluntary activities, and live healthy, independent, and safe lives as they get older.

Active ageing policies therefore require addressing several factors: encourage healthy lifestyles, ensure social involvement, provide opportunities for independent living, and enable possibilities for longer working life. Monitoring such policy implementation requires a comprehensive tool that encompasses the multitude of aspects of active and healthy ageing. The European Commission has made the Active Aging Index (AAI) available precisely to meet this need.

The AAI captures various facets of active ageing by measuring 22 indicators grouped into 4 domains: employment, participation in society, independent



**Figure 2.** The AAI has been developed within the framework of the 2012 European Year for Active Ageing and Solidarity between Generations (EY2012). The index is made up by four domains each of which reflects a different aspect of active ageing.

health and secure living, and capacity and enabling environment for active ageing (Figure 2). The AAI also provides a breakdown of results by gender to highlight potential differences in ageing between men and women. The index values range from 0 to 100. Higher values indicate a greater capacity to realize the unexpressed potential in old age. AAI offers a flexible framework that can be applied to different countries and at national as well as regional/local levels. It depicts the current situation and highlights the areas where future gains can be made. If computed on a regular basis, AAI allows to measure progress over time and helps to identify effective policy actions. The 2018 Active Ageing Index Analytical report reveals that since 2008 most European countries have improved their overall AAI scores [20]. This progress is probably due to increased attention to the elderly by society and politics and to the spread of a multidimensional and bio-psycho-social approach to the fight against frailty.

## 6. Towards a new medicine of complexity

The implementation of a bio-psycho-social approach to frailty allows an active and proactive management of a condition strongly related to chronicity, disability, and mortality. Frailty early identification can prevent or slow down the evolution towards negative outcomes, with a significant positive impact on the quality of life of the ageing population and on the health system and society as a whole [1].

The question is what the best screening protocols are and what types of intervention to carry out given the uniqueness of everyone’s ageing and the type of ageo-type associated with it. Indeed, the lack of effectiveness of a purely pharmacological management of frailty should be analyzed in the light of its pathophysiology.

A progressive alteration of several physiological systems induced by the interaction between the ageing process (pure ageing) with several morbid processes and multiple psycho-social and environmental conditions are involved [2, 6, 7]. After all, if the pathogenesis of frailty is multifactorial, intervention on a single physiological system will not in itself resolve frailty or even prevent it [21]. The probability of becoming frail older people increases non-linearly in relation to the number of abnormal physiological systems, and the number of abnormal systems would seem to be more predictive than the individual abnormal system involved [21]. Notably, the non-linear relationship of accelerating likelihood of frailty as the number of abnormal systems escalates suggests that there could be a threshold beyond which

there is an adverse downward spiraling nature to frailty etiology and progression. Implications are that a threshold loss of complexity, as indicated by number of systems abnormal, may undermine homeostatic adaptive capacity, leading to the development of frailty and its associated risk for subsequent adverse outcomes [21]. It also indicates that the replacement of any defective system may not be sufficient to prevent or ameliorate the whole health condition [21].

What has been indicated refers to the importance of a multidimensional approach to the elderly - and especially to the frail elderly - both in the evaluation and in taking charge of the individuals. To date, the comprehensive geriatric evaluation (CGA) is the most fruitful process to assess elderly people to optimize their subsequent management. Indeed, CGA has consistently shown its significant benefits for over 30 years [22].

However, the high speed with which the world's population ages and is affected by chronic diseases, polyopathy and functional impairment is unfortunately not yet accompanied by a strong, competent, and aware geriatric culture. This unfulfilled need contributes to the further exponential increase in adverse outcomes (2° order criticalities) and to the loss of psychophysical well-being and health (which means complete happiness, as we have previously defined it) in older people.

It is increasingly evident that there is a dual need to put existing applied health research knowledge into practice (the "*know-do gap*") and the need to improve the evidence base (the "*know gap*") with respect to CGA [23].

Gladman et al. [23] discussed several barriers to the implementation of the GCA, including guiding factors, professional factors, patient factors, professional interactions, incentives, resources, capacity for organizational change, as well as social, political, and legal factors. There is little point in not actively working on *research co-production*, *practice communities* and *knowledge brokers* to overcome the main obstacles to the implementation of a multidimensional integrated approach that can bring its effectiveness in modern and novel settings. Applied health research and service innovation and development need to take place in parallel [22, 23]. These three action-domains are already inherent in the mindset of professionals as they reflect the method of academic medicine: research, clinical activity, and teaching [22]. Moreover, not only they could be realized in concerted actions of independent players/stakeholders, but they could be also greatly promoted by focusing on education and training, not only at the medical level (medical students and trainees) but also on the side of healthcare providers (multi-professional representatives of the geriatric team) [22].

Everything discussed urges geriatrics - nowadays a true medicine of complexity - to refine its cultural and operational tools and to make them available to a health system grappling with the growing problems posed by a progressively aging population.

The medicine of complexity suggests a model in which psychophysical well-being and disease are the result of complex, dynamic and unique interactions in the individual under examination: i.e., interactions between different components of the entire system. The human body is made up of interconnected, inter-reacting physiological systems, while the individual maintains a behaviour determined by experience and on the ability to adapt and interact with the environment.

The individual is therefore a dynamic, interacting, adaptable system in which the disease - and even more the polyopathy - triggers a cause-and-effect model that cannot be considered linear. To this follows a situation of complexity that requires a new type of taking charge of the elderly patient. This approach to the patient accepts unpredictability and proposes solutions based on elements that are sometimes imperceptible but emerging to the clinical sensitivity of the health professional. Considering the above, two elements become substantial for a successful



CGA: to conceive the individual frail elderly person as unique and complex; to put the clinical methodology at the heart of the patient approach. These concepts are having profound consequences, introducing working methodologies based on multidisciplinary, integration, implementation, contextualized work.

To make this a concrete reality, it is essential that geriatrics share with other professionals involved in the field the cultural values that belong to them, promoting multidisciplinary confrontation and integration, so that it is possible to build a vision of intent common to all specialists and operators of the multidisciplinary team that acts around the frail elderly.

## 7. Conclusions

Ageing has always affected and often frightened humans, which since ancient times has been well aware that the biological changes connected with the passing of the years induce a progressive weakening of functional capacities, a decay of physical or mental conditions, an increasing difficulty in carrying out tasks that were once easy to perform.

Publio Terenzio Afro (160 B.C.) referred to the physical ailments and privations that usually accompany senescence with the well-known sentence «*Senectus ipsa est morbus*» (Phormio: IV, v.575). This vision of old age is refuted by Cicero, who in the *Cato Maior de senectute* (40 B.C.) affirms: «each part of life has its own character, so that the weakness of children, the boldness of young people, the seriousness of manhood and the maturity of old age bear their own natural fruit which must be harvested in time». Cato begins his calm argument: he examines the criticism commonly levelled at old age and disproves it, with examples taken from Greek and Roman history. The accusations examined are physical weakness and decadence; the weakening of intellectual capacity; the impossibility of enjoying the pleasures of the senses; the bizarreness of character and avarice. Cicero explicitly extols the advantages of old age, which he calls not an involution but an evolution of the individual's biological capacities. Cicero emphasizes through the mouth of Cato the Censor the ability of the elderly to make a positive contribution to society and future generations, reassessing their social role and placing them in a position worthy of respect and consideration.

Health should be considered as the ability to identify and realize one's aspirations, to satisfy one's needs and to positively modify the surrounding environment. The elderly is in good health if they maintain a condition of self-sufficiency as much as possible, psychophysical well-being, and positive thinking about the future.

Frailty in the elderly requires a customized multidimensional approach that cannot be segmented into isolated interventions for each pathology, taking into account individual differences - not only clinical but also socio-relational and environmental differences - according to the principle of "taking care of the patient and not only of the disease".

There are many health problems in the elderly, and one wonders whether it is appropriate to take action not only as health professionals but also individually to counter them or to stem the consequences: if each of us adopted healthy habits and made ourselves the bearer of them we would have done something - perhaps modest on an individual level but important on a collective level to counter the "silver tsunami" which could jeopardize our old age and the stability of our society.

The fight against frailty takes place in a life-span perspective. A bio-psycho-social model can help us to define the most appropriate interventions to promote the best quality of life. This approach attributes health to the intricate and variable interaction of biological, psychological, and social factors.

Such a multidimensional approach is fundamental when it comes to the elderly and the promotion of healthy and active ageing.

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## Conflict of interest

The authors declare that the manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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There are many ways to age and grow old can be frightening: all sorts of losses to deal with, a body and mind less vigorous and brilliant than it once was, sometimes memory becomes clouded, self-awareness diminishes and loved ones disappear. However, there are older people who make you want to grow old. They have not been spared by life, but for them growing old is like continuing their adventure. They seem to keep in the form of inner riches those outer ones they have lost and discover new possibilities and freedom. I thank the senior students at the University of the Third Age of Turin for being a source of inspiration and teachers of life. To them, who taught me what it means to have a soul that is always young, every effort I make is dedicated.

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## References

- [1] Morese R, Palermo S, Defedele M, Nervo J, Borraccino A. Vulnerability and Social Exclusion: Risk in Adolescence and Old Age. In: Morese R, Palermo S, editors. *The New Forms of Social Exclusion*. London: IntechOpen Limited; 2019. p. 1-16. DOI: 10.5772/intechopen.85463
- [2] Palermo S. Covid-19 pandemic: Maximising future vaccination treatments considering ageing and frailty. *Front. Med.* 2020; 7:558835. DOI: 10.3389/fmed.2020.558835
- [3] Smith GE, Bondi MW. *Mild Cognitive Impairment and Dementia: Definitions, Diagnosis, and Treatment*. Oxford: OUP USA; 2013. 416 p. ISBN: 0199764182
- [4] Wise DA. *Analyses in the Economics of Aging*. Chicago: University of Chicago Press; 2005. 416 p. ISBN: 0-226-90286-2
- [5] Ahadi S, Zhou W, Schüssler-Fiorenza Rose SM, et al. Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat Med.* 2020; 26(1):83-90. DOI: 10.1038/s41591-019-0719-5
- [6] Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. In search of an integral conceptual definition of frailty: opinions of experts. *J Am Med Dir Assoc.* 2010; 11(5):338-343. DOI: 10.1016/j.jamda.2009.09.015
- [7] Sourial N, Wolfson C, Bergman H, et al. A correspondence analysis revealed frailty deficits aggregate and are multidimensional. *J Clin Epidemiol.* 2010; 63(6):647-654. DOI: 10.1016/j.jclinepi.2009.08.007
- [8] Ní Mhaoláin AM, Fan CW, Romero-Ortuno R, et al. Frailty, depression, and anxiety in later life. *Int Psychogeriatr.* 2012; 24(8):1265-1274. DOI: 10.1017/S1041610211002110
- [9] Nishiguchi S, Yamada M, Fukutani N, et al. Differential association of frailty with cognitive decline and sarcopenia in community-dwelling older adults. *J Am Med Dir Assoc.* 2015; 16(2):120-124. DOI: 10.1016/j.jamda.2014.07.010
- [10] Kelaiditi E, Cesari M, Canevelli M, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging.* 2013; 17(9):726-734. DOI: 10.1007/s12603-013-0367-2
- [11] Micheli GA. Vulnerabilità e radicamento. In: Cristini A, Cesa-Bianchi M, Porro A, Cipolli C, editors. *Fragilità e affettività nell'anziano*. Milano: Francoangeli; 2015. p. 79-96. ISBN: 978-88-917-1457-2
- [12] Rozzini R, Zanetti O. Fragilità e malattie. In: Rozzini R, Morandi A, Trabucchi M, editors. *Persona, salute, fragilità*. Milano: Vita e pensiero; 2006. p. 35-56. EAN: 9788834313862
- [13] Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med.* 2006;166(4):418-423. DOI: 10.1001/archinte.166.4.418
- [14] Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging.* 2014; 9:433-441. DOI:10.2147/CIA.S45300
- [15] DeWeerd S. Prevention: Activity is the best medicine. *Nature* 2011; 475: S16-S17. DOI: 10.1038/475S16a
- [16] Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet.* 2019; 394(10206):1365-1375. DOI: 10.1016/S0140-6736(19)31786-6
- [17] Wang X, Lu Y, Li C, et al. Associations of lifestyle activities and

a healthy diet with frailty in old age: a community-based study in Singapore. *Aging* (Albany NY). 2020; 12(1):288-308. DOI: 10.18632/aging.102615

[18] Liotta G, Ussai S, Illario M, et al. Frailty as the Future Core Business of Public Health: Report of the Activities of the A3 Action Group of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA). *Int J Environ Res Public Health*. 2018;15(12):2843. DOI: 10.3390/ijerph15122843

[19] Cattaneo G, Bartrés-Faz D, Morris TP, et al. The Barcelona Brain Health Initiative: Cohort description and first follow-up. *PLoS One*. 2020; 15(2): e0228754. DOI: 10.1371/journal.pone.0228754

[20] EU Commission. Active Ageing Index Analytical report 2018 [internet]. Available from: <https://www.unece.org/population/aai.html>

[21] Fried LP, Xue QL, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci*. 2009;64(10):1049-1057. DOI: 10.1093/gerona/glp076

[22] Polidori MC, Roller-Wirnsberger R. Chances and challenges of comprehensive geriatric assessment training for healthcare providers. *Geriatric Care* 2018; 4(4):79-83 DOI: 10.4081/gc.2018.7853.

[23] Gladman JR, Conroy SP, Ranhoff AH, Gordon AL. New horizons in the implementation and research of comprehensive geriatric assessment: knowing, doing and the 'know-do' gap. *Age Ageing*. 2016;45(2):194-200. DOI: 10.1093/ageing/afw012