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EDITORIAL

PREVENTION OF FRAILTY IN AGING

B. VELLAS[1,2], S. SOURDET[1]

1. Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; 2. INSERM UMR1027, Université de Toulouse III Paul Sabatier, Toulouse, France.
Corresponding author: Bruno Vellas, Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; email: vellas.b@chu-toulouse.fr

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Introduction

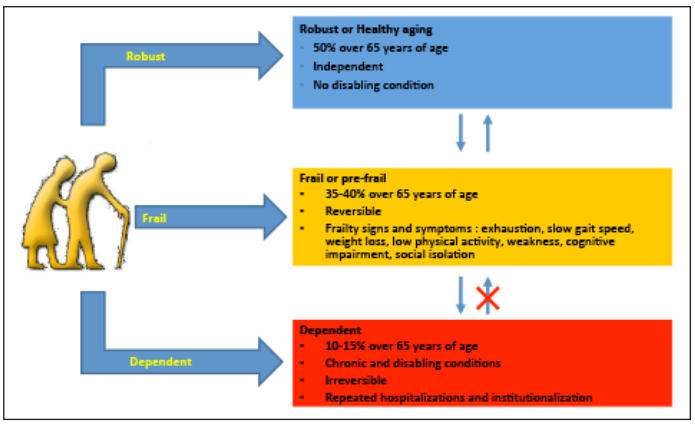
Worldwide, the number of people age 60 and older is expected to grow from nearly 900 million in 2015 to over 1.3 trillion in 2030 (1). Increased age is associated with gradual increases in molecular and cellular damage; impairment of bodily functions; decreased muscle mass and strength; loss of bone density; declining vision, hearing and cognition; multimorbidity; and frailty (2). Frailty has been conceptualized as a physiological syndrome of decreased reserve and resilience, resulting in progressive functional decline, increased vulnerability to many stressors, and an increase in negative health outcomes and dependence (3, 4). It has been recognized by the World Health Organization (2) and the U.S. National Academy of Sciences (5) as a major public health concern among the elderly, although consensus on a definition of frailty remains elusive (6). Nonetheless, research suggests that disability and dependence in the elderly may be preventable by targeting frail and pre-frail older adults (3, 7, 8).

Defining Frailty

In 2001, Linda Fried and colleagues proposed that the frailty phenotype is characterized by a constellation of symptoms including weakness, low energy, slow walking speed, low physical activity, and weight loss (9). Using this definition, older adults may be categorized into three groups along the disablement pathway (10): robust, frail or pre-frail, and dependent (Figure 1). Prevalence studies in several different populations have concluded that among those older than 65 years, approximately 50% are robust, 35-40% are frail or pre-frail, and 5-10% are dependent (11-13). Further studies have demonstrated that frailty and comorbidity are associated with increased hospital healthcare resource use and related costs (14).

The frailty syndrome results in a decline in many physiological systems, leading to increased vulnerability to loss of function following relatively minor illnesses such as urinary tract infections (4). The age-related loss of muscle mass and strength, known as sarcopenia, contributes to frailty (15), and loss of muscle mass has been shown to correlate with the risk of mortality in prefrail and frail older adults (16). Chronic inflammation has also been associated with both sarcopenia and frailty (17, 18). Physical frailty is also often associated with cognitive impairment, leading to the concept of "cognitive frailty" (19-22), which is associated with a high risk for developing dementia (23). Each of these physiologic contributors to frailty represents a potential therapeutic target.

Figure 1
Older adults: 3 categories – Robust, Frail/pre-frail, Dependent



Identifying frailty

Preventing frailty begins with identifying older persons at risk of becoming frail. In 2013, the Gérontopôle of Toulouse developed a screening tool to be implemented in primary care settings, the Gérontopôle Frailty Screening Tool (GFST) (24). This clinician-reported questionnaire asks six simple questions about whether the patient lives alone and has experienced weight loss, fatigue, mobility difficulties, memory problems, and gait speed. If any of these conditions are present, the questionnaire asks whether the clinician thinks the patient is frail and whether he or she is willing to be assessed at a frailty clinic. Other instruments developed to identify frail individuals include the Tilburg Frailty Indicator (TFI) (25), the Clinical Frailty Scale (CFS) (26), and the FiND (Frail, non-disabled) instrument, a self-reported questionnaire (27). In the future, biomarkers may also prove useful in the identification of frailty (28).

Also at the Gérontopôle in Toulouse, a Geriatric Frailty Clinic (GFC) was established in association with the University Department of General Medicine and the Midi-Pyrenees Regional Health Authority to support comprehensive and multidisciplinary assessment and management of frail older persons at an earlier stage of disability when it is still reversible. Among the first 1108 patients referred to the

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GFC following screening by their primary care physician, 93.6% were determined to be frail or pre-frail and in need of intervention (29).

Preventing frailty

Prevention of frailty encompasses three overlapping approaches across the lifespan: First, increasing intrinsic capacity reserves in early aging; second, preserving function in late aging, and third, restoring function in frail older adults. These approaches reflect WHO's concept of healthy aging as an interaction of intrinsic capacity and functional ability, with intrinsic capacity defined as the combination of an individual's physical and mental capacity (2). In the first wave of the WHO Study on global AGEing and adult health (SAGE), they combined data from physical and cognitive assessments and biometric measures to document a gradual decline in intrinsic capacity across the adult lifespan (30).

Intrinsic capacity can be explained by a combination of genetic factors, behavior, environmental exposures, and social determinants such as availability of resources (31, 32). The fact that many of these factors are modifiable implies that intrinsic capacity may be improved. Indeed, abundant evidence suggests that increasing physical activity and improving nutrition offers protection against age-related physical and cognitive decline across the lifespan (2, 33, 34). One study suggested that a diet high in protein and anti-oxidants could prevent frailty (35). However, additional studies are needed to show that nutrition can postpone frailty in older persons (36). Recent technological improvements including the accelerometers, voice analysis, and other technologies built into smart phones and other devices now offer the means to monitor physical activity, diet, sleeping patterns, and mental states across the lifespan, thus encouraging self-management (37-39).

The third pillar of frailty prevention involves restoring function in persons identified as frail. Treatments range from non-pharmacological (40) to pharmacologic approaches (41) aimed at ameliorating the loss of skeletal mass and strength associated with sarcopenia and frailty and improving function, cognition, and well-being.

Non-pharmacologic interventions typically combined physical exercise with nutritional approaches. These interventions build on studies showing, for example, that in older populations, physical activity intervention programs improve health quality and function, reduce major mobility disability, and may delay frailty onset (42-44); and that adherence to the Mediterranean diet is associated with higher physical performance (45). Other studies have suggested benefits from specific nutrients. For example, vitamin D (46) and essential amino acid (EAA) supplementation (47) have been shown to improve function; and the leucine metabolite, beta-hydroxy-beta-methylbutyrate may increase muscle mass and strength (48). Prebiotics that alter the composition of the microbiota have also been shown to improve some frailty criteria (49). And another study showed that long-term tea consumption was associated with improved mental health in older persons (50). A number of multi-modal prevention programs have been built upon these and other observations. These include:

- The Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies (SPRINTT) trial. This randomized controlled trial is testing a combined intervention of physical activity, nutritional counseling, and an information and communication technology intervention versus an educational program in older adults with physical frailty and sarcopenia (51).
- The Vitality, Independence, and Vigor 2 (VIVE2). This randomized controlled study demonstrated that a physical activity program improved mobility, with no additional benefit when combined with a nutritional supplement (52).
- A randomized controlled trial of exercise plus protein and vitamin D supplementation in community-dwelling frail older adults in Spain reversed frailty and improved functional performance, cognition, mood, social support, and quality of life (53).
- The Vitamin D3, Omega-3, Home Exercise – HeALTHy Aging and Longevity Trial (DO-HEALTH) is a large healthy aging study of whether the combination of nutritional supplements and a home exercise program will promote healthy aging (http://do-health.eu).
- The Multi-domain Alzheimer's Prevention Trial (MAPT). This randomized controlled study tested a multi-domain intervention combining nutrition, physical exercise, cognitive and social activities, and omega-3 polyunsaturated fatty acids in frail older adults at risk of cognitive decline (54).
- The Nolan trial is testing a Brain Protector Blend of nutritional supplements in older adults with memory complaints to see if it can improve cognition.

An improved understanding of the biological underpinnings of frailty and sarcopenia indicating changes in many physiologic systems including energy metabolism, muscle development, and hormonal and inflammatory functions (55) suggests several possible pharmacological approaches to treatment that are currently in development (41). These include a class of agents call myostatin inhibitors that promote muscle growth (56), androgens including testosterone (57), compounds called selective androgen receptor modulators (SARMs) that increase androgenic signaling (58), and anti-inflammatory compounds (59). Infusions of mesenchymal stem cells, which have potent anti-inflammatory properties, have also shown promise as a treatment for frailty (60).

Conclusions

There is an emerging consensus that preventing frailty in older adults could dramatically improve health outcomes and

quality of life, and enable a longer period of independent living. Integrated care offers perhaps the greatest opportunity for encouraging healthy aging across the lifecourse and preserving function in late aging. However, healthcare systems not currently not organized to deliver integrated care over the lifecourse, but rather to identify and treat acute illness. Change is needed at both the healthcare delivery and policy levels to emphasize integrated care across the lifecourse and to encourage health aging.

Conflict of Interests: None

References

1. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. World Alzheimer Report 2015: The Global Impact of Dementia. London; 2015.
2. World Health Organization. World Report on Ageing and Health. Luxembourg; 2015.
3. Cesari M, Prince M, Thiyagarajan JA, et al. Frailty: An Emerging Public Health Priority. J Am Med Dir Assoc. 2016;17(3):188-92.
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62.
5. Adams K, Corrigan JM, editors. Priority Areas for National Action: Transforming Health Care Quality. Washington, D.C.: National Academies Press 2003.
6. Rodriguez-Manas L, Feart C, Mann G, et al. Searching for an Operational Definition of Frailty: A Delphi Method Based Consensus Statement. The Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62-7.
7. Vellas B, Cestac P, Moley JE. Implementing frailty into clinical practice: we cannot wait. J Nutr Health Aging. 2012;16(7):599-600.
8. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7.
9. 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):M146-56.
10. Verbrugge LM, Jette AM. The disablement process. Soc Sci Med. 1994;38(1):1-14.
11. Buckinx F, Reginster JY, Gillain S, Petermans J, Brunois T, Bruyere O. Prevalence of Frailty in Nursing Home Residents According to Various Diagnostic Tools. J Frailty Aging. 2017;6(3):122-8.
12. Le Cossec C, Perrine AL, Beltzer N, Fuhrman C, Carcaillon-Bentata L. Pre-Frailty, Frailty, and Multimorbidity: Prevalences and Associated Characteristics from Two French National Surveys. J Nutr Health Aging. 2016;20(8):860-9.
13. Sanchez-Garcia S, Garcia-Pena C, Salva A, et al. Frailty in community-dwelling older adults: association with adverse outcomes. Clinical interventions in aging. 2017;12:1003-11.
14. Garcia-Nogueras I, Aranda-Reneo I, Pena-Longobardo LM, Oliva-Moreno J, Abizanda P. Use of Health Resources and Healthcare Costs associated with Frailty: The FRADEA Study. J Nutr Health Aging. 2017;21(2):207-14.
15. Landi F, Calvani R, Cesari M, et al. Sarcopenia as the Biological Substrate of Physical Frailty. Clin Geriatr Med. 2015;31(3):367-74.
16. Brown JC, Harhay MO, Harhay MN. Appendicular Lean Mass and Mortality among Prefrail and Frail Older Adults. J Nutr Health Aging. 2017;21(3):342-5.
17. Fougere B, Boulanger E, Nourhashemi F, Guyonnet S, Cesari M. Chronic Inflammation: Accelerator of Biological Aging. J Gerontol A Biol Sci Med Sci. 2017;72(9):1218-25.
18. Rossi AP, Budui S, Zoico E, et al. Role of Anti-Inflammatory Cytokines on Muscle Mass and Performance Changes in Elderly Men and Women. J Frailty Aging. 2017;6(2):65-71.
19. Fougere B, Delrieu J, Del Campo N, Soriano G, Sourdet S, Vellas B. Cognitive Frailty: Mechanisms, Tools to Measure, Prevention and Controversy. Clin Geriatr Med. 2017;33(3):339-55.
20. Halil M, Cemal Kizilarslanoglu M, Emin Kuyumcu M, Yesil Y, Cruz Jentoft AJ. Cognitive aspects of frailty: mechanisms behind the link between frailty and cognitive impairment. J Nutr Health Aging. 2015;19(3):276-83.
21. 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):726-34.
22. Sargent L, Brown R. Assessing the Current State of Cognitive Frailty: Measurement Properties. J Nutr Health Aging. 2017;21(2):152-60.
23. Shimada H, Makizako H, Tsutsumimoto T, Doi T, Lee S, Suzuki T. Cognitive frailty and incidence of dementia in older persons. J Prev Alz Dis. in press.
24. Vellas B, Balardy L, Gillette-Guyonnet S, et al. Looking for frailty in community-dwelling older persons: the Gerontopole Frailty Screening Tool (GFST). J Nutr Health Aging. 2013;17(7):629-31.
25. Pialoux T, Goyard J, Lesourd B. Screening tools for frailty in primary health care: a systematic review. Geriatr Gerontol Int. 2012;12(2):189-97.
26. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.
27. Cesari M, Demougeot L, Boccalon H, et al. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. PLoS One. 2014;9(7):e101745.
28. Calvani R, Marini F, Cesari M, et al. Biomarkers for physical frailty and sarcopenia. Aging Clin Exp Res. 2017;29(1):29-34.
29. Tavassoli N, Guyonnet S, Abellan Van Kan G, et al. Description of 1,108 older patients referred by their physician to the «Geriatric Frailty Clinic (G.F.C) for Assessment of Frailty and Prevention of Disability» at the gerontopole. J Nutr Health Aging. 2014;18(5):457-64.
30. World Health Organization. WHO Study on global AGEing and adult health (SAGE) [Available from: http://www.who.int/healthinfo/sage/en/.
31. Brooks-Wilson AR. Genetics of healthy aging and longevity. Hum Genet. 2013;132(12):1323-38.
32. Hong YC. Aging society and environmental health challenges. Environ Health Perspect. 2013;121(3):A68-9.
33. Qualls C, Waters DL, Vellas B, et al. Reversible States of Physical and/or Cognitive Dysfunction: A 9-Year Longitudinal Study. J Nutr Health Aging. 2017;21(3):271-5.
34. Handing EP, Small BJ, Reynolds SL, Kumar NB. Impact of dietary factors and inflammation on cognition among older adults. J Prev Alz Dis. 2015;2(4):220-6.
35. Kobayashi S, Suga H, Sasaki S. Diet with a combination of high protein and high total antioxidant capacity is strongly associated with low prevalence of frailty among old Japanese women: a multicenter cross-sectional study. Nutr J. 2017;16(1):29.
36. Kelaiditi E, Guyonnet S, Cesari M. Is nutrition important to postpone frailty? Curr Opin Clin Nutr Metab Care. 2015;18(1):37-42.
37. Corcoran MP, Chui KK, White DK, et al. Accelerometer Assessment of Physical Activity and Its Association with Physical Function in Older Adults Residing at Assisted Care Facilities. J Nutr Health Aging. 2016;20(7):752-8.
38. Forbes KE, Venneri A, Shanks MF. Distinct patterns of spontaneous speech deterioration: an early predictor of Alzheimer's disease. Brain Cogn. 2002;48(2-3):356-61.
39. Dorsey ER, Yvonne Chan YF, McConnell MV, Shaw SY, Trister AD, Friend SH. The Use of Smartphones for Health Research. Acad Med. 2017;92(2):157-60.
40. Lozano-Montoya I, Correa-Perez A, Abraha I, et al. Nonpharmacological interventions to treat physical frailty and sarcopenia in older patients: a systematic overview - the SENATOR Project ONTOP Series. Clinical interventions in aging. 2017;12:721-40.
41. Cesari M, Fielding R, Benichou O, et al. Pharmacological Interventions in Frailty and Sarcopenia: Report by the International Conference on Frailty and Sarcopenia Research Task Force. J Frailty Aging. 2015;4(3):114-20.
42. De Vriendt P, Peersman W, Florus A, Verbeke M, Van de Velde D. Improving Health Related Quality of Life and Independence in Community Dwelling Frail Older Adults through a Client-Centred and Activity-Oriented Program. A Pragmatic Randomized Controlled Trial. J

Nutr Health Aging. 2016;20(1):35-40.
43. Silva RB, Aldoradin-Cabeza H, Eslick GD, Phu S, Duque G. The Effect of Physical Exercise on Frail Older Persons: A Systematic Review. J Frailty Aging. 2017;6(2):91-6.
44. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA. 2014;311(23):2387-96.
45. Fougere B, Mazzuco S, Spagnolo P, et al. Association between the Mediterranean-style Dietary Pattern Score and Physical Performance: Results from TRELONG Study. J Nutr Health Aging. 2016;20(4):415-9.
46. Lopez J, Campa A, Lewis JE, et al. Assessing the relationship between vitamin D status and impairments in cognitive and physical performance in older adults using a dual task physical performance test. J Prev Alz Dis. 2017;4(1):29-36.
47. Ferrando AA, Paddon-Jones D, Hays NP, et al. EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. Clin Nutr. 2010;29(1):18-23.
48. Fitschen PJ, Wilson GJ, Wilson JM, Wilund KR. Efficacy of beta-hydroxy-beta-methylbutyrate supplementation in elderly and clinical populations. Nutrition. 2013;29(1):29-36.
49. Buiques C, Fernandez-Garrido J, Pruimboon L, et al. Effect of a prebiotic forumulation on frailty synddrome: a randomized, double-blind clinical trial. Int J Mol Sci. 2016;17(6).
50. Chan S-P, Yong PZ, Sun Y, et al. Associations of long-term tea consumptions with depressive and anxiety symptoms in community-living elderly: findings from the Diet and Healthy Aging Study. J Prev Alz Dis. 2017;in press.
51. Landi F, Cesari M, Calvani R, et al. The «Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies» (SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res. 2017;29(1):89-100.
52. Fielding RA, Travison TG, Kirn DR, et al. Effect of structured physical activity and nutritional supplementation on physical function in mobility-limited older adults: Results from the VIVE2 randomized trial. J Nutr Health Aging. 2017;in press.
53. Tarazona-Santabalbina FJ, Gomez-Cabrera MC, Perez-Ros P, et al. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. J Am Med Dir Assoc. 2016;17(5):426-33.
54. Vellas B, Carrie I, Gillette-Guyonnet S, et al. Mapt Study: A Multidomain Approach for Preventing Alzheimer's Disease: Design and Baseline Data. J Prev Alzheimers Dis. 2014;1(1):13-22.
55. Evans WJ, Paolisso G, Abbatecola AM, et al. Frailty and muscle metabolism dysregulation in the elderly. Biogerontology. 2010;11(5):527-36.
56. Parise G, Snijders T. Myostatin inhibition for treatment of sarcopenia. Lancet Diabetes Endocrinol. 2015;3(12):917-8.
57. Visvanathan R, Piantadosi C, Lange K, et al. The Randomized Control Trial of the Effects of Testosterone and a Nutritional Supplement On Hospital Admissions in Undernourished, Community Dwelling, Older People. J Nutr Health Aging. 2016;20(7):769-79.
58. Papanicolaou DA, Ather SN, Zhu H, et al. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. J Nutr Health Aging. 2013;17(6):533-43.
59. Manini TM, Anton SD, Beavers DP, et al. ENabling Reduction of Low-grade Inflammation in SEniors Pilot Study: Concept, Rationale, and Design. J Am Geriatr Soc. 2017.
60. Golpanian S, DiFede DL, Khan A, et al. Allogeneic Human Mesenchymal Stem Cell Infusions for Aging Frailty. J Gerontol A Biol Sci Med Sci. 2017.