Frailty in the older person: Implications for pharmacists

Am J Health-Syst Pharm. 2019; XX:XX-XX

Marta Gutiérrez-Valencia, Pharm.D., Pharmacy Department, Navarrabiomed, Universidad Pública de Navarra, Complejo Hospitalario de Navarra, Instituto de Investigación Sanitaria de Navarra, Pamplona Navarra, Spain.

Nicolás Martínez-Velilla, M.D., Ph.D., Geriatric Department, Navarrabiomed, Universidad Pública de Navarra, Complejo Hospitalario de Navarra, Instituto de Investigación Sanitaria de Navarra, Pamplona Navarra, Spain, Biomedical Research Networking Center of Frailty and Healthy Aging, Madrid, Spain.

Address correspondence to Dr. Gutiérrez-Valencia (marta.guva@gmail.com).

Keywords: frailty, older adults, pharmacists

DOI 10.1093/ajhp/zxz217

Frailty is an age-linked concept that defines a state of vulnerability characterized by the inability to adequately respond to stressors. Although primarily associated with the field of geriatrics, frailty has now been extended to multiple medical disciplines.[1] In recent years, the paradigm of frailty in the elderly has expanded in both research and clinical practice. Oncologists, surgeons, and cardiologists, among other professionals, have begun measuring frailty in their elderly patients; practitioners have recognized the potential for frailty as a predictor for adverse events and health outcomes and thus who will benefit most from an intervention.[2-6] Frailty has better predictive value for different adverse health outcomes than does chronological age, and the integration of this concept avoids ageism bias by allowing objective stratification according to needs and risks instead of exclusively by age.[7,8] A frailty prevalence of around 11% has been estimated in people older than 65 years.[9] Despite frailty conditions not being prevalent in community-dwelling elderly people, they are gaining importance at a public health level, attracting interest of policy makers, healthcare systems, and institutions such as the World Health Organization. This is because frailty is considered a potentially detectable and reversible step prior to disability and serves as a target for preventive interventions that contribute to successful aging in populations.[10]

Some clinical practice guidelines are beginning to incorporate specific recommendations for frail older patients.[11] The European Medicines Agency has recommended baseline characterization of frailty in patients older than 65 years who participate in clinical trials or other clinical investigations and the incorporation of this variable into subgroup analysis.[12] The International Conference on Frailty and Sarcopenia Research Task Force has analyzed the pharmacological approaches for the treatment of frailty and how the design of clinical trials to treat this condition could be improved (Table 1).[13-15]

Pharmacists must know well the concept of frailty and its implications, not only to communicate with other professionals but also because of the interaction between frailty and pharmacological treatment. In this commentary, we aim to review the concept of frailty, with a focus on the most relevant aspects for the profession of pharmacy.

History and concept

The increase in life expectancy over the last century has supported an accelerated aging of the population. This demographic transition has been accompanied by an epidemiological transition, with a modification of disease patterns towards chronic pathologies, and also initiates a clinical transition, which places the focus on functional capacity instead of on the disease.[16,17] Disability is the primary way in which health problems manifest in the elderly and what limits patients' well-being.[18] Therefore, the new challenge for health systems is to prolong disability-free survival and provide assistance to a growing number of dependent persons. Within this context, the concept of frailty emerged, as it was observed that there were people who were more predisposed to lose functional capacity when presenting an eventual health problem.[19] The term began to be used more frequently in the late 1990s, when Campbell and Buchner[20] defined it as "a condition or syndrome which results from a multisystem reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure, and that is associated to an increased risk of disability and death from minor external stresses." Since then, different definitions and measurement tools have been proposed, but 2 approaches or models stand out.

The frailty phenotype proposed by Fried and colleagues[14] in 2001, resulting from a prospective study, the Cardiovascular Health Study,[21] understands frailty as a clinical syndrome that is expressed in the following 5 domains: nutritional status, energy, physical activity, mobility, and strength.

There is also the cumulative deficit model proposed by Rockwood and Mitnitski[15] in 2007, from the Canadian Study of Health and Aging.[22] This model understands frailty as the cumulative effect of individual deficits expressed as signs, symptoms, abnormal laboratory values, disease states, and disabilities, such that a greater number of deficits corresponds to a greater degree of frailty. From this approach, frailty is a continuous variable which does not end with disability or dependence but increases progressively until death.

Both models have been shown to have predictive value for different adverse health outcomes and often overlap in their identification of frailty, but they

Table 1. Selected Recommendations Regarding Frailty[a]

Recommendation Topic	Recommendations by Source: EMA[12]	Recommendations by Source: ICFSR Task Force[13]
Measurements	Short Physical Performance Battery (preferred) Gait speed (alternative) Other validated scales in addition for specific populations	Fried et al.[14] criteria are the most widely used to define frailty and to classify individuals as frail or prefrail, but it may be necessary to define different stages of frailty itself (e.g., mild, moderate, and severe). In addition, the criteria focus only on physical frailty, yet there are also social, cognitive, or psychological forms of frailty. Rockwood and Mitnitski[15] approach captures additional elements to define frailty but may be somewhat onerous for clinicians and patients to administer.
Actions	Proposed scales to be used in clinical trials to assess baseline physical frailty. These instruments are intended for use in pre- and postauthorization studies across all therapeutic areas to support the inclusion of a representative population in the clinical trial development program as required by the epidemiology of the disease.	A regulatory pathway for frailty interventions would require a better understanding of the biological pathways that contribute to frailty and a clearer definition of frailty as an outcome. Lacking a consensus definition, it may be more productive to develop adjuvant treatments rather than target frailty itself. In the context of clinical trials, biomarkers can provide mechanistic insight or serve as intermediate or surrogate endpoints. Frailty may be too heterogeneous to be used as an intervention target, and functional measures, such as gait speed, chair rise, and stair climb performance, could be more reasonable outcomes to target. Given the heterogeneity of individuals with frailty, it would be helpful to define subgroups that can be tested with different interventions to see how they respond.

[a]EMA = European Medicines Agency, ICFSR = International Conference on Frailty and Sarcopenia Research.

cannot be considered equivalent, and it has been proposed that they could be useful in different circumstances.[23–25] There is no consensus on which is the best model or which can be more useful for the pharmacist. It has been suggested that the combined or sequential use of the 2 instruments is advisable because they provide distinct and complementary clinical information about the risk profile of an older person.

An attempt has been made to reach an operational definition of frailty through expert consensus. In 2013, a project led by Rodríguez-Mañas[26] defined frailty as a clinical syndrome characterized by decreased reserve and diminished resistance to stressors that increase vulnerability. In the same year, Morley et al.[27] defined frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death." Despite these attempts at a definition, different conceptual views remain, and there are difficulties in obtaining a single definition that satisfies all the experts. There seems to be consensus, however, that frailty is a state of multidimensional and multifactorial vulnerability, that is dynamic and potentially reversible, that is associated with functional capacity, and that can predict adverse health outcomes.[28]

Table 2. Criteria for Defining Frailty According to Fried et al.'s[14] Phenotype[a]

Frailty indicator	Measure
Weight loss	Self-reported weight loss of more than 10 pounds (4.5 kg) or recorded weight loss of ≥5% per yr
Self-reported exhaustion	Self-reported exhaustion on U.S. Center for Epidemiological Studies depression scale (3–4 days per wk or most of the time)
Low energy expenditure	Energy expenditure <383 kcal/wk (men) or <270 kcal/wk (women)
Slow gait speed	Standardized cutoff times to walk 15 ft (4.57 m), stratified by sex and height
Weak grip strength	Grip strength, stratified by sex and body mass index

[a]Adapted, with permission, from Clegg et al.[1] Copyright 2013, Elsevier.

Detection and diagnosis

Many tools have been proposed to detect or measure frailty.[29] Fried et al.'s[14] phenotype translates into 5 criteria, as follows: involuntary weight loss, exhaustion, low energy expenditure, slow gait speed, and weak strength (Table 2). Patients are considered prefrail when they meet 1 or 2 conditions and frail

when they meet 3 or more. The cumulative deficit model is demonstrated in the frailty index (FI), which assesses the total number of deficits as a proportion of the total number of items evaluated. An FI score of 0 represents full health, a score of >0.3 usually indicates frailty, and a score of 1 represents a theoretical "complete" frailty. Empirically, however, >99% of people have FI scores of <0.7, which is a clear marker of mortality risk. The deficit model also uses the Clinical Frailty Scale, which classifies individuals into 7 groups based on the frailty index.[22] For example, according to Fried et al. criteria, a 75-year-old woman presenting with an unintentional weight loss of >5% during the past year, who most days feels that everything she does is an effort or is limited for vigorous activities, and who walks 15 feet in more than 7 seconds is frail. According the Clinical Frailty Scale, this woman could be mildly frail if she is independent for basic activities of daily living but has limited dependence on others for instrumental activities of daily living. From these 2 models, various modifications have been proposed to develop numerous frailty scales, with some designed by pharmacists.[30] Some of the most well-known tools, in addition to those already indicated, are the Groningen Frailty Indicator,[31] the Tilburg Frailty Indicator,[32] the Edmonton Frail Scale,[33] different frailty indexes, and physical capacity tests, such as the Short Physical Performance Battery (SPPB).[34]

Mechanism and pathophysiology

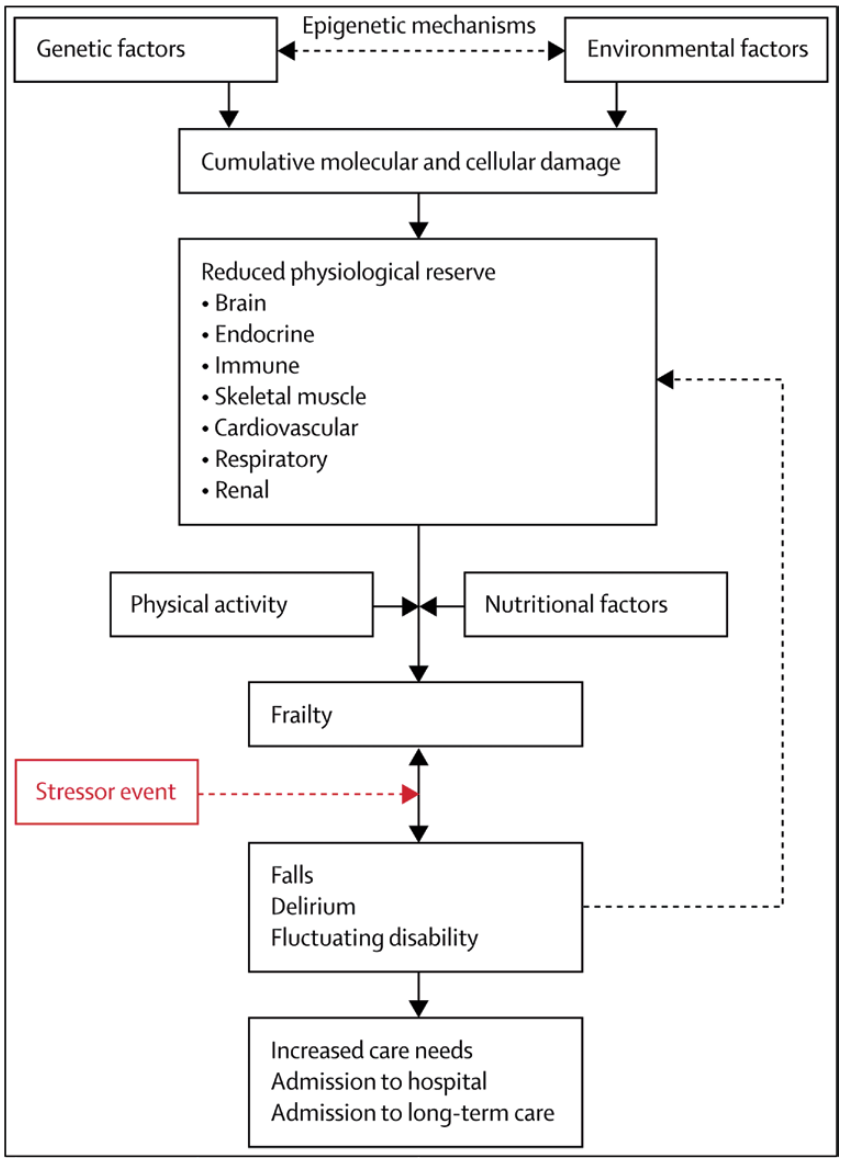
Frailty is a syndrome in which multiple interrelated physiological systems are involved. The decrease in physiological reserves is accelerated and the homeostatic processes begin to fail. The mechanisms involved in its development are complex and are determined by genetic, environmental, and epigenetic factors that produce cumulative damage at the cellular and molecular levels (Figure 1).[1] The nervous, endocrine, and immune systems, as well as skeletal muscle, are the systems that have been best studied in the development of frailty.[35,36] One example of this implication is sarcopenia, which is considered 1 of the main causes of frailty.[37] Some studies are currently being carried out to identify biomarkers for sarcopenia and frailty that can be applied at the clinical and research levels.[38] Malnutrition is another condition that is considered an important risk factor in the development of frailty.[39,40]

Recent studies have found that different chronic diseases, such as diabetes mellitus, chronic obstructive pulmonary disease, and atrial fibrillation, may play a role in the onset of frailty.[41–43] According to a recent review, frailty is also associated with the presence of multiple chronic diseases or multimorbidity.[44]

Frailty and medications

The relationship between frailty and drugs is highly complex due to the physiological, cellular, and molecular processes involved in the presentation of frailty and in the activity of drugs.[45] It seems plausible that the physiological changes that occur in frailty have an impact on drug pharmacokinetics

Figure 1. The pathophysiology of frailty. Reproduced, with permission, from Clegg et al.[1] Copyright 2013, Elsevier.



and pharmacodynamics. Corsonello et al.[46] found in a systematic review that glomerular filtration rate is associated with the degree of frailty. Aging has traditionally been associated with changes in drug pharmacokinetics, but this association seems to be stronger with frailty, especially for the processes of metabolism and excretion.[47–51] Older people also appear to be more sensitive to certain medications, but evidence of the role of frailty in pharmacodynamics or drug effectiveness is still underdeveloped.[52–54] Examples of altered pharmacodynamics include an increase in sedation produced by some drugs in frail patients and a greater susceptibility to drugs that increase the risk of falls.[55,56] There are also plausible mechanisms by which the use of medications can contribute to frailty. A relationship has been found between the number of medications taken and weight loss, impaired balance, poor nutritional status, and functional impairment, all of which are clinical features of frailty.[57] This points to polypharmacy as a possible mechanism that contributes to frailty.

Studies collected in recent systematic reviews have shown a clear association between frailty and polypharmacy in older adults.[58,59] The direction of this association is not clear, but it is suggested that it could be bidirectional, where polypharmacy could increase the risk of frailty, and frailty would increase the likelihood of receiving multiple drugs. Several frailty detection or measurement tools include an entry for polypharmacy, including the Edmonton Frail Scale, the Groningen Frailty Indicator,[31] and other frailty indexes.[33] It has been suggested that a reduction in polypharmacy could be a strategy to prevent and manage frailty, although there are no studies that have confirmed that reducing polypharmacy can delay or revert frailty.[27]

Other factors usually associated with polypharmacy could play a role in the development of frailty. It has been found that the use of drugs with anticholinergic properties is more frequent in frail patients, and that the risk of developing frailty increases proportionally to the anticholinergic load.[60–63] It has been argued that the possible explanation is the contribution of the anticholinergic load to the functional impairment that has been observed in different studies, this being 1 of the main features of frailty.[60]

The use of potentially inappropriate medications (PIMs) in elderly patients in relation to frailty has also been studied. Cullinan et al.[64] aimed to determine whether a positive relationship exists between patients' frailty status, the appropriateness of their medications, and their propensity to develop adverse drug reactions (ADRs); the predictive value of such a relationship was compared with that of polypharmacy. A frailty index was applied to a patient database, and a significant correlation between the frailty index and the number of STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria was found. Patients above a frailty index score threshold were more likely to experience a STOPP criterion and to develop an ADR, while patients taking more than 6 medications were more likely to experience a STOPP criterion but not to experience an ADR. Muhlack et al.[65] in a longitudinal study including community-dwelling adults at least 60 years old showed that patients with frailty had increased odds of both taking a PIM and getting PIM prescriptions in the future, according to Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. Maclagan et al.[66] performed a retrospective cohort study including older adults with cognitive impairment or dementia living in nursing homes. At admission to the nursing home, more frail patients were prescribed a PIM, according to Beers Criteria, than were those who were not frail, and frail patients were more likely to be taking newly prescribed benzodiazepines, antipsychotics, and anticholinergics. Martinot et al.[67] found in a prospective study in a large sample of community-dwelling older adults that the presence of PIMs according to the Laroche List (a French consensus panel list) increased the risk of becoming frail in a 3-year follow-up period. Two different studies have shown in older outpatients with cardiovascular disease and those living in nursing homes that frail patients could also be more exposed to underprescribing, according to the Screening Tool to Alert doctors to the Right Treatment criteria.[68,69] It has also been shown that frail patients present with more drug–drug interactions, perhaps in relation to the increase in polypharmacy.[56,70] This increase in polypharmacy, drug interactions, inappropriate prescriptions, and modifications to drug pharmacokinetics might explain why frail patients have more adverse drug events than do nonfrail patients.[71] This idea is closely associated with the concept of frailty as vulnerability, and shows how frailty can be applied to the use of medications most evidently. Sultana et al.[72] also emphasize that frailty could be important at a pharmacoepidemiological level as an effect modifier in the association between drug exposures and ADRs.

Several studies have found that frailty can affect the consumption of certain drugs, possibly due to associated conditions, the perception of risk, or a poor prognosis. For example, frailty has been associated with a higher prevalence of atrial fibrillation[43]; however, a recent meta-analysis showed that older patients with frailty at hospital admission are less likely to receive anticoagulants than are those without frailty.[73] This suggests that, in some cases, physicians' judgment of frailty may deter the prescription of anticoagulants, although this association has not been found at hospital discharge or in community-dwelling older adults.[73] Several authors also found an increased use of hypnotics and analgesics in frail patients than in nonfrail patients and a lower consumption of other drugs, such as multivitamins.[74–76]

Management and treatment

Because frailty is a multifactorial and heterogeneous condition, its management should also involve multidimensional interventions. Ongoing clinical trials are attempting to provide evidence on the benefits of this type of strategy, combining physical activity, nutritional counseling or dietary interventions, and information or educational programs.[77–80]

The main approaches to care have been directed towards controlling the causes and improving the systems that are most affected by frailty, such as chronic diseases, sarcopenia, and neuroendocrine disorders.[45] Exercise is 1 of the interventions that has shown the greatest benefit in preventing and treating frailty due to its effects on the brain, endocrine system, immune system, and skeletal muscle.[1,81,82] Many approaches have been suggested, but the most frequently used is the multicomponent program, combining endurance, flexibility, balance, and resistance training, performed with low to moderate intensity, in 30- to 45-minute sessions, 3 times a week.[83] Evidence-based materials are available for healthcare professionals and patients on individualized multicomponent exercise programs for older adults.[84] Given the relationship between malnutrition and frailty, interventions focused on nutrition have also been proposed and could have an important role.[85] Different pharmacological agents have been investigated to treat frailty. Vitamin D has been 1 of the most studied drugs due to its role in sarcopenia and the regulation of different systems, and it is 1 of the most accepted interventions, especially when there is a deficiency.[86] Prospective studies consistently report that low vitamin D status is associated with an increased risk of becoming frail.[87] However, large clinical trials are lacking to provide solid evidence of the clinical benefit of vitamin D supplementation. Some scientific societies have proposed a minimal serum 25-hydroxyvitamin D concentration of 75 nmol/L for frail elderly patients, requiring doses between 800 and 2,000 international units (IU)/day.[86] Studies have also been conducted with selective androgen receptor modulators, dehydroepiandrosterone, and testosterone, showing benefits in muscle mass and functional capacity; these studies demonstrate that adverse effects, such as prostate problems, edema, polycythemia, and gynecomastia, do not outweigh the potential benefits.[45,88] It has been suggested that angiotensin-converting enzyme inhibitors (ACEIs) may have a protective role in frailty due to the pleiotropic effects (e.g., improving muscular function) that some authors attribute to them.[89–92] A recent cohort study concluded that the use of ACEIs was associated with a lower risk of incident frailty in a large cohort of North American individuals,[93] although the possible benefit has not been confirmed by randomized controlled trials, and more robust data are needed to confirm the utility of ACEI in the prevention of frailty. Other agents have been proposed as possible treatments for frailty, such as hormonal treatments (e.g., growth hormone), but there is no evidence of their effectiveness. Finally, given the possible contribution of drugs to the establishment and development of frailty, periodic review of medication is one of the most accepted strategies for the management of frailty.

Importance for pharmacists

As part of the health teams, the pharmacist cannot be left behind in the knowledge and practice of the conceptual foundations of frailty. Although this term is not foreign to pharmacists, it is too often mistakenly applied to all patients of very advanced age, those who live in nursing homes, those who present with multimorbidity, and those who are terminally ill. These concepts are not equivalent, although they may overlap. Understanding frailty as a measurable entity and its associated characteristics, such as its potential reversibility or relationship to functional decline and adverse health outcomes, is essential. Frailty, as a risk predictor and prognostic measure, can help more precisely define the risk–benefit balance of drugs in each patient, with attention to individual needs. A better conceptual foundation of frailty will therefore allow pharmacists to participate more actively in the processes that favor the appropriate use of medications. It will also aid in the design of therapeutic optimization strategies in different settings and levels of care, ranging from epidemiological levels to hospitals and nursing homes.

The interaction between frailty and drugs is a recent study field that is increasingly attracting interest. A recent systematic review on the relationship between frailty and polypharmacy found that 80% of included studies were published in the last 5 years.[58] Given the novelty of knowledge in this subject, there is still no evidence on the implications that findings on frailty and medications may have for pharmacist interventions or the profession of pharmacy. As previously described, frail older patients are more prone to receive a greater number of medications and potentially inappropriate prescriptions, have greater susceptibility to sedatives and fall risk–increasing drugs, and are at higher risk of suffering adverse drug events than are nonfrail patients. Accordingly, it seems reasonable that the use of medications should be assessed with special caution in frail older adults when they are recognized. Frailty predicts better than polypharmacy future adverse drug events, so frailty status could be used to select the patients who can benefit most from targeted interventions by the pharmacist, such as comprehensive medication reviews, potentially inappropriate prescriptions, fall risk–increasing drug screening, and the use of anticholinergic risk scales. A pharmacist–geriatrician collaborative consultation service for frail patients could also be an interesting strategy to explore. Studies could be conducted to demonstrate whether frail patients can benefit more than others from these interventions, and whether adverse drug events or negative health outcomes can be reduced, as suggested by observational studies. A study by Bonaga et al.[94] showed that polypharmacy was associated with an increased risk of adverse events (disability, hospitalization, emergency department visits, and mortality) in prefrail and frail older adults, but not in nonfrail individuals, suggesting that reducing excessive polypharmacy could be especially important in these patients.

Furthermore, since polypharmacy may be recognized as a major contributor to the development of frailty, deprescribing strategies to reduce polypharmacy in older adults have been suggested as recommended measures for both the prevention and management of frailty. Further studies assessing deprescribing interventions and including frailty

measures as endpoints should be carried out to confirm these possible benefits.

Also, at a research level, frailty may pose new challenges regarding the inclusion of frail patients in clinical trials, the incorporation of frailty as a variable in subgroup analysis, and the development and research of drugs to treat frailty.

Conclusion

Frailty is a complex concept that is gaining research interest and is progressively being incorporated into clinical practice in many disciplines. Because of this interest and the important relationship between frailty and medicine at many levels, pharmacists must know the basic concepts of frailty in the elderly patient. Frailty must be gradually integrated into the professional practice of pharmacists. Challenges to this integration include uncertainty about various issues, including the different approaches and measurement tools for frailty, the effects of frailty on drug pharmacokinetics and pharmacodynamics, frailty's influence on the use and adverse effects of drugs, pharmacological possibilities for treatment and prevention, and the possible role of drugs in the development of frailty.

Disclosures

The authors have declared no potential conflicts of interest.

References

1. Clegg A, Young J, Iliffe S et al. Frailty in elderly people. *Lancet.* 2013; 381:752-62.
2. Hamaker ME, Jonker JM, de Rooij SE et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol.* 2012; 13:e437-44.
3. Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. *Age Ageing.* 2012; 41:142-7.
4. Freiheit EA, Hogan DB, Patten SB et al. Frailty trajectories after treatment for coronary artery disease in older patients. *Circ Cardiovasc Qual Outcomes.* 2016; 9:230-8.
5. Kojima G. Frailty as a predictor of nursing home placement among community-dwelling older adults: a systematic review and meta-analysis. *J Geriatr Phys Ther.* 2018; 41:42-8.
6. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. *Disabil Rehabil.* 2017; 39:1897-908.
7. Joseph B, Pandit V, Zangbar B et al. Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. *JAMA Surg.* 2014; 149:766-72.
8. Mandawat A, Mandawat A. Chronological age is just a number when it comes to percutaneous coronary intervention: why frailty may matter more. *JACC Cardiovasc Interv.* 2018; 11:1883-4.
9. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc.* 2012; 60:1487-92.
10. Cesari M, Prince M, Thiyagarajan JA et al. Frailty: an emerging public health priority. *J Am Med Dir Assoc.* 2016; 17:188-92.
11. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2015; 38:140-9.
12. Physical frailty: Instruments for baseline characterisation of older populations in clinical trials. 9 January 2018. EMA/CHMP/778709/2015. Committee for Medicinal Products for Human Use. Amsterdam, the Netherlands: European Medicines Agency; 2018.
13. Pahor M, Kritchevsky SB, Waters DL et al. Designing drug trials for frailty: ICFSR Task Force 2018. *J Frailty Aging.* 2018; 7:150-4.
14. Fried LP, Tangen CM, Walston J et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001; 56:M146-56.
15. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci.* 2007; 62:722-7.
16. Tinetti ME, Fried T. The end of the disease era. *Am J Med.* 2004; 116:179-85.
17. Rodriguez-Mañas L, Rodríguez-Artalejo F, Sinclair AJ. The third transition: the clinical evolution oriented to the contemporary older patient. *J Am Med Dir Assoc.* 2017; 18:8-9.
18. Manini T. Development of physical disability in older adults. *Curr Aging Sci.* 2011; 4:184-91.
19. Cesari M, Marzetti E, Thiem U et al. The geriatric management of frailty as paradigm of "the end of the disease era." *Eur J Intern Med.* 2016; 31:11-4.
20. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age Ageing.* 1997; 26:315-8.
21. Fried LP, Borhani NO, Enright P et al. The cardiovascular health study: design and rationale. *Ann Epidemiol.* 1991; 1:263-76.
22. Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005; 173:489-95.
23. Cigolle CT, Ofstedal MB, Tian Z, Blaum CS. Comparing models of frailty: the Health and Retirement Study. *J Am Geriatr Soc.* 2009; 57:830-9.
24. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci.* 2007; 62:738-43.
25. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age Ageing.* 2014; 43:10-2.
26. Rodríguez-Mañas L, Féart 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; 68:62-7.
27. Morley JE, Vellas B, van Kan GA et al. Frailty consensus: a call to action. *J Am Med Dir Assoc.* 2013; 14:392-7.
28. Junius-Walker U, Onder G, Soleymani D et al.; ADVANTAGE JA WP4 group. The essence of frailty: a systematic review and qualitative synthesis on frailty concepts and definitions. *Eur J Intern Med.* 2018; 56:3-10.
29. Buta BJ, Walston JD, Godino JG et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. *Ageing Res Rev.* 2016; 26:53-61.
30. Peris-Martí JF, Parro Martín MÁ, Fernández-Villalba E, Bravo José P. Approach to the development of a frailty index based on comprehensive geriatric assessment in nursing home. *Farm Hosp.* 2018; 42:159-62.
31. Steverink N. Measuring frailty: developing and testing the GFI (Groningen Frailty Indicator). *Gerontologist.* 2001; 41:236.
32. Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health care utilization, and quality of life in a population at risk. *Gerontologist.* 2012; 52:619-31.

33. Rolfson DB, Majumdar SR, Tsuyuki RT et al. Validity and reliability of the Edmonton Frail Scale. *Age Ageing.* 2006; 35:526-9.
34. Guralnik JM, Simonsick EM, Ferrucci L et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994; 49:M85-94.
35. Walston J, Hadley EC, Ferrucci L et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging research conference on frailty in older adults. *J Am Geriatr Soc.* 2006; 54: 991–1001.
36. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *Lancet Diabetes Endocrinol.* 2018; 6:743-52.
37. Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. *J Cachexia Sarcopenia Muscle.* 2014; 5:5-8.
38. Calvani R, Picca A, Marini F et al. The "BIOmarkers associated with Sarcopenia and PHysical frailty in ElderRly pErsons" (BIOSPHERE) study: rationale, design and methods. *Eur J Intern Med.* 2018; 56:19-25.
39. Gabrovec B, Veninšek G, Samaniego LL et al. The role of nutrition in ageing: a narrative review from the perspective of the European joint action on frailty - ADVANTAGE JA. *Eur J Intern Med.* 2018; 56:26-32.
40. Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N et al. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. *Maturitas.* 2016; 93:89-99.
41. Assar ME, Laosa O, Rodríguez Mañas L. Diabetes and frailty. *Curr Opin Clin Nutr Metab Care.* 2019; 22:52-7.
42. Marengoni A, Vetrano DL, Manes-Gravina E et al. The relationship between COPD and frailty: a systematic review and meta-analysis of observational studies. *Chest.* 2018; 154:21-40.
43. Villani ER, Tummolo AM, Palmer K et al. Frailty and atrial fibrillation: a systematic review. *Eur J Intern Med.* 2018; 56:33-8.
44. Vetrano DL, Palmer K, Marengoni A et al.; Joint Action ADVANTAGE WP4 Group. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci.* Epub ahead of print. 2018 May 3.
45. Palmer K, Marengoni A, Russo P et al. Frailty and drug use. *J Frailty Aging.* 2016; 5:100-3.
46. Corsonello A, Roller-Wirnsberger R, Di Rosa M et al.; Screening for Chronic Kidney Disease among Older people across Europe (SCOPE) Study Investigators. Estimated glomerular filtration rate and functional status among older people: a systematic review. *Eur J Intern Med.* 2018; 56:39-48.
47. Ballew SH, Chen Y, Daya NR et al. Frailty, kidney function, and polypharmacy: the Atherosclerosis Risk In Communities (ARIC) study. *Am J Kidney Dis.* 2017; 69:228-36.
48. Hilmer SN, Tran K, Rubie P et al. Gentamicin pharmacokinetics in old age and frailty. *Br J Clin Pharmacol.* 2011; 71:224-31.
49. Johnston C, Hilmer SN, McLachlan AJ et al. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. *Eur J Clin Pharmacol.* 2014; 70:549-55.
50. Williams FM, Wynne H, Woodhouse KW, Rawlins MD. Plasma aspirin esterase: the influence of old age and frailty. *Age Ageing.* 1989; 18:39-42.
51. Wynne HA, Cope LH, Herd B et al. The association of age and frailty with paracetamol conjugation in man. *Age Ageing.* 1990; 19:419-24.
52. Williamson JD, Supiano MA, Applegate WB et al.; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. *JAMA.* 2016; 315:2673-82.
53. Warwick J, Falaschetti E, Rockwood K et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med.* 2015; 13:78.
54. Nguyen TN, Pepperell D, Morel-Kopp MC et al. Effect of frailty and age on platelet aggregation and response to aspirin in older patients with atrial fibrillation: a pilot study. *Cardiol Ther.* 2016; 5:51-62.
55. Wynne HA, Yelland C, Cope LH et al. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. *Age Ageing.* 1993; 22:354-9.
56. Bennett A, Gnjidic D, Gillett M et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. *Drugs Aging.* 2014; 31:225-32.
57. Gnjidic D, Hilmer SN. Potential contribution of medications to frailty. *J Am Geriatr Soc.* 2012; 60:401.
58. Gutiérrez-Valencia M, Izquierdo M, Cesari M et al. The relationship between frailty and polypharmacy in older people: a systematic review. *Br J Clin Pharmacol.* 2018; 84:1432-44.
59. Palmer K, Villani ER, Vetrano DL et al. Association of polypharmacy and hyperpolypharmacy with frailty states: a systematic review and meta-analysis. *Eur Geriatr Med.* 2019; 10: 9-36.
60. Gnjidic D, Hilmer SN, Blyth FM et al. High-risk prescribing and incidence of frailty among older community-dwelling men. *Clin Pharmacol Ther.* 2012; 91:521-8.
61. Jamsen KM, Bell JS, Hilmer SN et al. Effects of changes in number of medications and drug burden index exposure on transitions between frailty states and death: the Concord Health And Ageing In Men Project Cohort Study. *J Am Geriatr Soc.* 2016; 64:89-95.
62. Moulis F, Moulis G, Balardy L et al. Exposure to atropinic drugs and frailty status. *J Am Med Dir Assoc.* 2015; 16:253-7.
63. Herr M, Sirven N, Grondin H et al. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the french population. *Eur J Clin Pharmacol.* 2017; 73:1165-72.
64. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. *Age Ageing.* 2016; 45:115-20.
65. Muhlack DC, Hoppe LK, Stock C et al. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study. *Eur J Clin Pharmacol.* 2018; 74:1633-44.
66. Maclagan LC, Maxwell CJ, Gandhi S et al. Frailty and potentially inappropriate medication use at nursing home transition. *J Am Geriatr Soc.* 2017; 65:2205-12.
67. Martinot P, Landré B, Zins M et al. Association between potentially inappropriate medications and frailty in the early old age: a longitudinal study in the GAZEL cohort. *J Am Med Dir Assoc.* 2018; 19:967-973.e3.
68. Meid AD, Quinzler R, Freigofas J et al. Medication underuse in aging outpatients with cardiovascular disease:

prevalence, determinants, and outcomes in a prospective cohort study. *PLoS One.* 2015; 10:e0136339.
69. Gutiérrez-Valencia M, Izquierdo M, Lacalle-Fabo E et al. Relationship between frailty, polypharmacy, and underprescription in older adults living in nursing homes. *Eur J Clin Pharmacol.* 2018; 74:961-70.
70. Thai M, Hilmer S, Pearson SA et al. Prevalence of potential and clinically relevant statin-drug interactions in frail and robust older inpatients. *Drugs Aging.* 2015; 32:849-56.
71. Poudel A, Peel NM, Nissen LM et al. Adverse outcomes in relation to polypharmacy in robust and frail older hospital patients. *J Am Med Dir Assoc.* 2016; 17:767.e9-767.e13.
72. Sultana J, Leal I, de Wilde M et al. Identifying data elements to measure frailty in a dutch nationwide electronic medical record database for use in postmarketing safety evaluation: an exploratory study. *Drug Saf.* 2019; 42:713-9.
73. Wilkinson C, Todd O, Clegg A et al. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. *Age Ageing.* 2019; 48:196-203.
74. Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. *Arch Gerontol Geriatr.* 2010; 50(Suppl 1):S43-7.
75. Woo J, Yu R, Wong M et al. Frailty screening in the community using the FRAIL scale. *J Am Med Dir Assoc.* 2015; 16:412-9.
76. Koponen MP, Bell JS, Karttunen NM et al. Analgesic use and frailty among community-dwelling older people: a population-based study. *Drugs Aging.* 2013; 30:129-36.
77. Landi F, Cesari M, Calvani R et al.; SPRINTT Consortium. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) randomized controlled trial: design and methods. *Aging Clin Exp Res.* 2017; 29:89-100.
78. Fernandes AL, Hayashi AP, Jambassi-Filho JC et al. Different protein and derivatives supplementation strategies combined with resistance training in pre-frail and frail elderly: rationale and protocol for the "pro-elderly" study. *Nutr Health.* 2017; 23:251-60.
79. Jadczak AD, Luscombe-Marsh N, Taylor P et al. The EXPRESS study: Exercise And Protein Effectiveness Supplementation Study supporting autonomy in community dwelling frail older people-study protocol for a randomized controlled pilot and feasibility study. *Pilot Feasibility Stud.* 2018; 4:8.
80. Vojciechowski AS, Biesek S, Melo Filho J et al. Effects of physical training with the Nintendo Wii Fit Plus and protein supplementation on musculoskeletal function and the risk of falls in pre-frail older women: protocol for a randomized controlled clinical trial (the WiiProtein study). *Maturitas.* 2018; 111:53-60.
81. Silva RB, Aldoradin-Cabeza H, Eslick GD et al. The effect of physical exercise on frail older persons: a systematic review. *J Frailty Aging.* 2017; 6:91-6.
82. Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med.* 2018; 179:28-36.
83. Theou O, Stathokostas L, Roland KP et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res.* 2011; 2011:569194.
84. Materials for the individualized prescription of a multicomponent program of physical exercise (VIVIFRAIL). http://www.vivifrail.com/resources.
85. Manal B, Suzana S, Singh DK. Nutrition and frailty: a review of clinical intervention studies. *J Frailty Aging.* 2015; 4:100-6.
86. Bruyère O, Cavalier E, Buckinx F, Reginster JY. Relevance of vitamin D in the pathogenesis and therapy of frailty. *Curr Opin Clin Nutr Metab Care.* 2017; 20:26-9.
87. Zhou J, Huang P, Liu P et al. Association of vitamin D deficiency and frailty: a systematic review and meta-analysis. *Maturitas.* 2016; 94:70-6.
88. Campbell S, Szoeke C. Pharmacological treatment of frailty in the elderly. *J Pharm Pract Res.* 2009; 39: 147-51.
89. Wzgarda A, Kleszcz R, Prokop M et al. Unknown face of known drugs - what else can we expect from angiotensin converting enzyme inhibitors? *Eur J Pharmacol.* 2017; 797:9-19.
90. Cranney A. Is there a new role for angiotensin-converting-enzyme inhibitors in elderly patients? *CMAJ.* 2007; 177:891-2.
91. Onder G, Penninx BW, Balkrishnan R et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet.* 2002; 359:926-30.
92. von Haehling S, Sandek A, Anker SD. Pleiotropic effects of angiotensin-converting enzyme inhibitors and the future of cachexia therapy. *J Am Geriatr Soc.* 2005; 53:2030-1.
93. Veronese N, Stubbs B, Smith L et al. Angiotensin-converting enzyme inhibitor use and incident frailty: a longitudinal cohort study. *Drugs Aging.* 2019; 36:387-93.
94. Bonaga B, Sánchez-Jurado PM, Martínez-Reig M et al. Frailty, polypharmacy, and health outcomes in older adults: the Frailty And Dependence In Albacete Study. *J Am Med Dir Assoc.* 2018; 19:46-52.