



PROMOTING ACCESS TO INNOVATION FOR FRAIL OLD PERSONS

IAGG (INTERNATIONAL ASSOCIATION OF GERONTOLOGY AND GERIATRICS), WHO (WORLD HEALTH ORGANIZATION) AND SFGG (SOCIETE FRANCAISE DE GERIATRIE ET DE GERONTOLOGIE) WORKSHOP - ATHENS JANUARY 20-21, 2012

G. BERRUT¹, S. ANDRIEU^{2,3}, I. ARAUJO DE CARVALHO⁴, J.P. BAEYENS⁵, H. BERGMAN⁶, B. CASSIM⁷, F. CERRETA⁸, M. CESARI^{2,3}, H.B. CHA⁹, L.K. CHEN¹⁰, A. CHERUBINI^{11,12}, M.Y. CHOU¹³, A.J. CRUZ-JENTOFT¹⁴, L. DE DECKER¹, P. DU¹⁵, B. FORETTE¹⁶, F. FORETTE¹⁷, A. FRANCO¹⁸, R. GUIMARAES¹⁹, L.M. GUTIERREZ-ROBLEDO²⁰, J. JAUREGUI²¹, V. KHAVINSON²², W.J. LEE²³, L.N. PENG²⁴, C. PERRET-GUILLAUME²⁵, M. PETROVIC²⁶, F. RETORNAZ²⁷, K. ROCKWOOD²⁸, L. RODRIGUEZ-MANAS²⁹, C. SIEBER³⁰, G. SPATHARAKIS³¹, O. THEOU²⁸, E. TOPINKOVA³², B. VELLAS^{3,33}, A. BENETOS²⁵

1. Pôle Hospitalo-Universitaire de Gérontologie Clinique, CHU Nantes, Nantes, France; 2. Gérontopole, Service de Santé Publique, CHU de Toulouse; 3. INSERM 1027, Toulouse, France; 4. Department of Gender, Women and Health, World Health Organization (WHO), Geneva, Switzerland; 5. Department of Geriatric Medicine, Damián General Hospital, Ostend, Belgium; 6. Department of Family Medicine, Mc Gill University, Montreal, Canada; 7. Department of Geriatrics, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa; 8. European Medicines Agency (EMA), London, United Kingdom; 9. Department of Social Welfare, Hallym University, Chuncheon, Gangwon-do, South Korea; 10. Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan; 11. Geriatrics, IRCCS-INRCA, Ancona, Italy; 12. Institute of Gerontology and Geriatrics, Department of Clinical and Experimental Medicine, Policlinico Santa Maria della Misericordia, University of Perugia Medical School, Perugia, Italy; 13. Geriatric Medicine Center, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan; 14. Geriatric Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; 15. Academic Research Office, Renmin University, Beijing, China; 16. Hôpital Sainte Perrine, Paris, France; 17. ILC-International Longevity Center, Paris, France; 18. Département de Médecine Gériatrique, CHU de Nice, Nice, France; 19. School of Health Sciences, Brasília, Brazil; 20. Instituto Nacional de Geriatria, Mexico City, Mexico; 21. Hospital Italiano, Buenos Aires, Argentina; 22. St Petersburg Institute of Bioregulation and Gerontology, St Petersburg, Russia; 23. Division of Geriatric Medicine, Taipei Veterans General Hospital, Yuanshan Branch, I-Lan, Taiwan; 24. Division of Geriatric Medicine, Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan; 25. Département de Médecine Gériatrique, CHU de Nancy, Vandoeuvre les Nancy, France; 26. Department of Geriatrics, Ghent University Hospital, Ghent, Belgium; 27. Centre Gérontologique Départementale, Marseille, France; 28. Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada; 29. Department of Geriatrics, Hospital Universitario de Getafe, Madrid, Spain; 30. Friedrich-Alexander-University, Erlangen-Nuernberg, Germany; 31. Public Primary Health Center of Itea, Phokida, Greece; 32. Department of Geriatrics, First Faculty of Medicine, Charles University, Prague, Czech Republic; 33. Gérontopôle, Service de Médecine Interne Gériatrique, CHU Toulouse, Toulouse, France. Corresponding author: Pr Athanase Benetos, MD, PhD, Département de Médecine Gériatrique, CHU de Nancy, Avenue de Bourgogne, BP 217, 54511 Vandoeuvre-les-Nancy, France, a.benetos@chu-nancy.fr

Abstract: Frailty tends to be considered as a major risk for adverse outcomes in older persons, but some important aspects remain matter of debate. *Objectives:* The purpose of this paper is to present expert's positions on the main aspects of the frailty syndrome in the older persons. *Participants:* Workshop organized by International Association of Gerontology and Geriatrics (IAGG), World Health Organization (WHO) and Société Française de Gériatrie et de Gérontologie (SFGG). *Results:* Frailty is widely recognized as an important risk factor for adverse health outcomes in older persons. This can be of particular value in evaluating non-disabled older persons with chronic diseases but today no operational definition has been established. Nutritional status, mobility, activity, strength, endurance, cognition, and mood have been proposed as markers of frailty. Another approach calculates a multidimensional score ranging from "very fit" to "severely frail," but it is difficult to apply into the medical practice. Frailty appears to be secondary to multiple conditions using multiple pathways leading to a vulnerability to a stressor. Biological (inflammation, loss of hormones), clinical (sarcopenia, osteoporosis etc.), as well as social factors (isolation, financial situation) are involved in the vulnerability process. In clinical practice, detection of frailty is of major interest in oncology because of the high prevalence of cancer in older persons and the bad tolerance of the drug therapies. Presence of frailty should also be taken into account in the definition of the cardiovascular risks in the older population. The experts of the workshop have listed the points reached an agreement and those must to be a priority for improving understanding and use of frailty syndrome in practice. *Conclusion:* Frailty in older adults is a syndrome corresponding to a vulnerability to a stressor. Diagnostic tools have been developed but none can integrate at the same time the large spectrum of factors and the simplicity asked by the clinical practice. An agreement with an international common definition is necessary to develop screening and to reduce the morbidity in older persons.

Key words: Older persons, frailty, vulnerability, diagnostic and workshop.

Introduction

Frailty is widely recognized as an important risk factor for adverse health outcomes in older persons, yet there is still a lack of consensus on the precise definition and the best means

of assessing frailty in the clinical setting. The vast majority of frail older persons are not seen by geriatricians but by primary care physicians or other specialists. The International Association of Gerontology and Geriatrics (IAGG), along with the World Health Organization (WHO) and the Société





JNHA: GERIATRIC SCIENCE

Française de Gériatrie et de Gériatologie (SFGG), convened a workshop in Athens, Greece, in January 2012 to map out a strategy to articulate a clinically valid concept of frailty, begin to develop validated screening and assessment tools, and consider whether frailty can be used as a tool in prevention campaigns.

Frailty: from concept to practice

The generally accepted definition of frailty, “A biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems and causing vulnerability to adverse outcomes” (1) mirrors the definition of aging, although chronological age is only one factor that predicts the risk of frailty. Susceptibility to stressors also is influenced by biological, behavioral, environmental, and social risk factors, with the main consequence being an increased risk for multiple adverse health outcomes, including disability, morbidity, falls, hospitalization, institutionalization, and death.

Frailty, which can be considered as one form of vulnerability, is a dynamic process, represented as a cycle influenced by multiple endogenous and exogenous factors that affect both the onset and trajectory over the lifetime of the individual (2). Women are more than twice as likely to develop the frailty syndrome as men, due to both physiologic reasons (e.g., lower muscle mass and differences in neuroendocrine and hormonal factors) and social/lifestyle factors such as level of activity and caloric intake. Among older people, frailty is further complicated by the presence of multiple other risk factors and comorbidities.

A standardized frailty phenotype was articulated in 2001 by Fried and colleagues based on data from the Cardiovascular Healthy Study (1), suggesting that with very simple tests and questions, one could identify frail individuals by the presence of three or more of the following criteria: unintended weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Moreover, Fried and colleagues found that the frailty was associated with an increased risk of death.

In 2008, Bergman et al. extended the frailty phenotype definition using a life course approach, which incorporates biological, social, clinical, psychological, and environmental determinants. Bergman and colleagues' definition thus identified seven markers of frailty – nutrition, mobility, activity, strength, endurance, cognition, and mood (3).

These last years several definitions and assessment tools on frailty in clinical practice and research were proposed combining evidence derived from a systematic review of literature along with expert opinions. There was no consensus on a definition of frailty but there was agreement to consider frailty as a pre-disability stage (4-6)

Establishing a definition of the frailty syndrome would improve our understanding of the aging process as well as our

ability to characterize the heterogeneity of health and functional status observed in older persons. Moreover, it would help identify a subset of vulnerable older adults at risk of experiencing adverse outcomes. This can be of particular value in evaluating non-disabled older persons with chronic diseases such as cancer or cardiovascular disease, where the presence of frailty can have important implications in treatment decision-making and care management.

However, there still remains no consensus on an operational definition of frailty (7). Thus, recently a Frailty Operative Definition Consensus Conference (FOD-CC) was convened by the European Commission to 1) develop a definition of frailty that would be useful in clinical practice and research, 2) identify biomarkers of frailty, and 3) provide guidelines to allow the early diagnosis of frailty. Using a modified Delphi process, the expert group reached consensus on the usefulness of defining frailty and its main dimensions, but recommended more research before an operative definition can be established (8).

Assessing frail older subjects

While there is consensus on the general definition of frailty, translation into practice has been more problematic. Multiple studies have attempted to capture and objectivize the frailty syndrome, each one translating the frailty theory according to somewhat different parameters, for example by clinical judgment (9), deficit accumulation (10), or the comprehensive geriatric assessment (11).

The model proposed by Fried and colleagues is limited by the fact that it lacks measures of cognition and mood, which improve the ability to predict adverse outcomes. However, this model is relatively easy and rapid to assess, and has shown its clinical prognostic interest in several epidemiological studies

In 2005, Rockwood et al. proposed the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale based on a Comprehensive Geriatric Assessment (CGA), with scores ranging from “very fit” to “severely frail,” (12). A more detailed evaluation quantifies health deficits in a Frailty Index (FI). A FI based on a CGA Frailty Index (FI-CGA) consists of a summary measure of deficit accumulation across functional, clinical, and physiological levels. Applied to a sample of 2,740 community-dwelling adults aged 65 to 102 in Canada, the FI-CGA estimated that 22.7% were frail, and that across all values of the FI, higher scores significantly increased the risk of death (13). Indeed, using an empirically derived cut-off score, the FI-CGA identified a group of individuals with 100% mortality 19 months after the baseline assessment (14).

While the multidimensional approach of the FI-CGA more accurately reflects the multidimensional nature of frailty it is difficult to apply in routine clinical practice. However, Rockwood and colleagues have suggested that deficits accumulate in a very orderly way and that frailty can be determined by counting up a smaller number of deficits with





INNOVATION FOR FRAIL PERSONS

similarly robust results (15).

This model is more complete but also more complicated than the Fried's model and probably less specific for "frailty".

In 2008, Ensrud et al. proposed the Study of Osteoporotic Fractures (SOF) index of physical frailty with three components: weight loss, weakness as measured by the inability to rise from a chair five times without using the arms to push off, and reduced energy as identified by answering the question "Do you feel full of energy?" (16). Subjects with two or three of these features were considered frail, those with one feature were considered prefrail, and those with none of these features were considered to be robust. Other indices have been developed based on self-report rather than objective criteria.

Physical performance measures such as the Short Performance Physical Battery (SPPB), which includes walking, balance, and chair stand tests, have also been used to assess frailty and predict negative health-related outcomes. Consistently, other objective measures of physical function, such as gait speed and hand grip strength, are strongly correlated with clinical outcomes, including survival (17). A growing body of evidence shows these instruments as able to capture the inner foundations of the frailty status beyond the mere evaluation of the physical status. Advantages of the physical performance tests are that they are extensively used in epidemiologic and clinical settings and can be performed easily and quickly, although some instrumentation and training are sometimes required. They represent extremely important screening tools for the overall health status, especially in community-dwelling and non-disabled older persons. For this reason, they may be particularly valuable for selecting subjects to enroll in interventional studies.

None of the aforementioned scales include social factors, such as socio-economic status (SES) and level of education, which also play important roles in the genesis and pathophysiology of frailty. Indeed, social vulnerability has been shown to correlate with frailty and mortality (18).

The usefulness of any measure of frailty depends on the reason for which the assessment is being done. For example, an oncologist or general surgeon may wish to evaluate frailty in a patient to determine whether he or she can tolerate a specific treatment or procedure. Moreover, in order to be useful, any measure of frailty needs to be easy to apply and of immediate understanding. Yet, since frailty is a multidimensional syndrome and frail elders so heterogeneous, a measure that captures such heterogeneity and the multiple phases of frailty has been difficult to establish.

It may well be that «one size does not fit all» and that different combination of frailty markers may be more predictive (remembering that risk and prediction are 2 inter-related but distinct concepts (19) depending on the type of population studied, the setting and the outcome of interest.

For use in clinical trials as an outcome measure, an instrument should adequately respond to specific clinimetric requirements, that are content validity, internal consistency, criterion validity, construct validity, reproducibility,

responsiveness, floor and ceiling effects, and interpretability (20) DeVries et al. compared 20 existing frailty instruments in terms of their clinimetric properties, concluding that only the FI covers all the frailty factors (21).

Mechanisms of frailty

There was general agreement that the core feature of frailty is increased vulnerability to stressors due to impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resiliency (7). Also, as defined by Rockwood and Mitnitski, frailty represents the accumulation of deficits over time, leading to increased risk for adverse health outcomes and death (22). Aging is also characterized by an accumulation of deficits at the cellular and subcellular level. How these deficits scale up is not yet fully understood. However, since frailty is a multifactorial condition, it is likely that there are multiple pathways leading to the same state. Frailty thus may be viewed as the manifestation of a multisystem dysfunction, implying the need of multidimensional tools to properly detect it. The FI-CGA, for example, provides clues about the mechanisms of frailty and health properties of populations. One of the critiques of the FI-CGA is that pathophysiology is not incorporated into the model. However, a study done in mice using a murine-based FI compared middle-aged to old rodents and showed that the FI corresponded to the degree of shortening of cardiac myocytes (23).

The deficit model of frailty also fits with hormonal changes occurring with aging. An alternative to the deficit model is the excess model, characterized by increases in interleukins, especially IL-6, tumor necrosis factor alpha (TNF- α), C-reactive protein (CRP), and adhesion proteins, all of which contribute to chronic inflammation, but also with increased levels of estrogens (24). These inflammatory markers are significantly associated with poor physical performance and reduced muscle strength in older persons (25), being the high levels of estradiol associated to an increased risk of frailty in older women, mainly if inflammation is also present (Carcaillon L et al., 2012). These markers may thus represent possible biomarkers of frailty as well as potential targets of intervention (26).

Social factors play an important role in modulating the adverse outcomes of frailty. For example, a meta-analysis of 19 published studies showed that lower childhood socioeconomic position (SEP) was associated with reduced physical performance in late life (27). Early childhood ill health and adverse SES were also shown to be related to frailty among older persons in Latin America (28). In a study utilizing Rockwood and colleagues' FI, non-white individuals and those living below the poverty level tended to have higher scores throughout life (29). Interestingly, social factors also appear to accumulate in a manner comparable to the way that health deficits do. Social factors thus appear to influence health outcomes at a number of levels – biological, health behaviors





JNHA: GERIATRIC SCIENCE

(including diet, exercise, and smoking), availability of social support, and access to quality healthcare. Yet despite strong evidence linking social factors to frailty, little is known about the interplay of molecular, clinical, and social factors, including how social stress could be expressed through epigenetic modulation or triggering of inflammatory processes throughout exposure to infectious agents (30).

Allostatic load is a cumulative index of wear and tear across multiple physiological systems involved in the body's effort to adapt to internal and external stressor over time. Recent analyses indicate higher allostatic load as a function of greater SES adversity cumulatively across the life course.

Weakness, slow walking speed, and lack of endurance are characteristics not only of frailty but also of sarcopenia, leading some to wonder if sarcopenia is the best determinant of physical frailty. Sarcopenia is defined by loss of muscle mass and muscle strength, leading to an increased risk of adverse outcomes such as physical disability, poor quality of life, and death. Sarcopenia may have a more clear pathophysiological definition (being organ-specific rather than multisystemic as the frailty syndrome). The study of sarcopenia in the context of the frailty scenario is an extremely interesting and promising field, especially taking into account that exercise and nutrition interventions have shown to prevent/delay muscle decline, and drugs specifically targeting sarcopenia are under development (31).

The identification of mechanisms associated with frailty suggests that it may be possible to identify biomarkers that would be useful in diagnosing frailty, predicting outcomes, and/or monitoring the effectiveness of treatments. Biomarkers may be useful in understanding the physical dimension of frailty, including factors that are also related to sarcopenia, i.e. low muscle mass and strength, (32), as well as inflammation. Other biomarkers that have been suggested as useful in identifying frailty or predicting outcome among frail individuals include hemoglobin (33) and HDL-cholesterol (34) concentrations. Multiple biomarkers of allostatic load may also be useful in assessing risk of becoming frail (35).

Clinical relevance of frailty in older persons

Oncologists are increasingly interested in frailty because of the aging population and the correlation between advanced age and prevalence of cancer: 60% of cancers are diagnosed and 70% of cancer deaths occur in patients over the age of 65 years. Moreover, advances in cancer therapy mean that many more patients survive at least five years, and an interaction exists between cancer treatment and the vulnerability of the patient (characterized by multiple comorbidities and geriatric syndromes). Thus, all of these factors need to be considered in the management of these patients. A frail patient with a slowly evolving cancer might not be able to tolerate aggressive treatment without significant deterioration of his quality of life. On the other hand, treating a frail patient with an aggressive cancer might improve symptoms and quality of life. The

question is whether frailty markers can help detecting vulnerability in cancer patients (36). Studies done to this point have been mixed on the question of whether frailty markers predict treatment toxicity or life expectancy (37-40). It may be that a frailty assessment specific to cancer patients is still needed.

Similarly, frailty needs to also be taken into account in the treatment of older patients with cardiometabolic diseases, a cluster of abnormalities that increase the risk of cardiovascular disease, chronic kidney disease, and type 2 diabetes. Cardiometabolic diseases and frailty are linked because they often co-exist in a patient and share common biological pathways, including chronic inflammation and insulin resistance. For example, the presence of frailty in patients with chronic kidney disease has shown to increase the risk of mortality (41); similarly, functional deficits of frailty increase the risk of mortality from a myocardial infarction (42). Frailty, along with comorbidity and quality of life, has also been shown to be an important risk factor for adverse outcomes following percutaneous revascularization (43). Among patients undergoing cardiac surgery, frailty has been shown to be better identify older subjects at risk of negative health-related events even better than scales traditionally adopted (44). Walking speed as a simple measure of frailty in these patients (45) has also been demonstrated to predict all-cause and cardiovascular mortality (46), even better than body mass index or measures of sarcopenia (47).

The therapeutic implications of these findings are not yet sufficiently clear. Frailty per se may be difficult to reverse; however, there have been some studies to suggest that early intervention may prevent the development of frailty. For example, in healthy older people, the angiotensin-converting-enzyme (ACE) inhibitor perindopril was shown to improve walking distance (48), higher protein consumption is associated with a lower risk of frailty (49), and resistance exercise has been shown effective in treating sarcopenia and osteoporosis, two conditions that contribute to the frailty syndrome (50). In addition, in the LIFE-P study, physical exercise was shown to alter SPPB score over 10 years among non-disabled community-dwelling sedentary persons at risk for disability based on SPPB scores <9 (51).

Conclusions

Our understanding of frailty has markedly improved over the last five years, yet there are many issues yet to be resolved. Speakers and observers at the conference reached agreement on a number of issues relevant to developing a research strategy that would move the field forward within the next five years by defining frailty markers and developing instruments that would be useful in various clinical settings. Ultimately, these tools will be relevant if they accompany effective health promotion, prevention, treatment, rehabilitation, and care interventions.

Agreement was reached on the following points:

- Although the mechanisms underlying frailty remain elusive,





INNOVATION FOR FRAIL PERSONS

it is still possible and necessary to develop clinically useful instruments.

- Early identification of frailty can lead to interventions to prevent worsening or reverse this condition components.
- Criteria to identify frail subjects and monitor frailty modifications are necessary to support the design of intervention trials.
- Identification of frailty is necessary for the planning of health care services. A single measure of frailty, such as gait speed or hand grip strength, while easy to apply in a clinical setting and correlated with clinical outcome, may be insufficient to capture the full multidimensional manifestations of the frailty syndrome. Nonetheless, simple measures of physical performance may represent a practical, clinically applicable, and widely understandable starting point for clinical assessment of frailty.
- From a public health point of view, it may be helpful to identify frail individuals, targeting them with interventions to reverse the condition or ameliorate their loss of functionality.
- Steps must be taken to ensure that frailty does not become an instrument to deny treatment or project a negative image on older people that could lead to stigmatization.
- Input from patients and their families should be incorporated into the planning and execution of studies.

Priorities for the coming years that were identified at the conference include:

- Establishing an internationally accepted definition of frailty that will convince practitioners to consider frailty in their patients.
- Developing a screening tool for frailty that can be administered quickly and easily by general practitioners, nurses, pharmacists, home health providers, social workers, and other health care workers. A positive screen would indicate the need of comprehensive geriatric assessment and design of tailored interventions.
- Linking the frailty screening tool to other risk assessment tools in order to reflect the entire spectrum of risks that affect health outcomes.
- Identifying biomarkers of frailty to improve screening, diagnosis, and prognosis of frailty in older individuals.
- Developing a tool to assess social frailty in order to add predictive power to any frailty assessment, particularly among persons who also possess physical frailty markers.
- Conducting longitudinal studies on the predictive capacity of frailty in different populations and settings and for different outcomes of interest.
- Conducting intervention studies aimed at delaying the onset of frailty or the onset of adverse outcomes.
- Conducting studies aimed at determining the public health costs of frailty
- Developing international collaborations to expedite research in this field and reach agreement in the currently

controversial issues of frailty.

Acknowledgements: The authors would like to thank Lisa J. Bain for editorial assistance with this manuscript.

References

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA: Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001, 56:M146-156.
2. Walston J, Fried LP: Frailty and the older man. *Med Clin North Am* 1999, 83:1173-1194.
3. Bergman H, Hogan D, Karunanathan S: Frailty: A clinically relevant concept? *Canadian J of Geriatrics* 2008, 11:124-128.
4. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *J Nutr Health Aging*. 2008;12:29-37.
5. Gobbens RJ, van Assen MA, Luijckx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc*. 2010;11:344-55.
6. Woo J, Leung J, Morley JE. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. *J Am Geriatr Soc*. 2012;60:1478-86.
7. Bergman H, Ferrucci L, Guralnik J, Hogan D, Hummel S, Karunanathan S, Wolfson C. Frailty, an Emerging Research and Clinical Paradigm: Issues and Controversies. *J Gerontol: Med Sci*. 2007; 62A: 731-737
8. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, Gonzalez-Colaco Harmand M, Bergman H, Carcaillon L, Nicholson C, 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* 2012.
9. Studenski S, Hayes RP, Leibowitz RQ, Bode R, Lavery L, Walston J, Duncan P, Perera S: Clinical Global Impression of Change in Physical Frailty: development of a measure based on clinical judgment. *J Am Geriatr Soc* 2004, 52:1560-1566.
10. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, Rockwood K: Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc* 2005, 53:2184-2189.
11. Jones DM, Song X, Rockwood K: Operationalizing a frailty index from a standardized comprehensive geriatric assessment. *J Am Geriatr Soc* 2004, 52:1929-1933.
12. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A: A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005, 173:489-495.
13. Song X, Mitnitski A, Rockwood K: Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010, 58:681-687.
14. Rockwood K, Rockwood MR, Mitnitski A: Physiological redundancy in older adults in relation to the change with age in the slope of a frailty index. *J Am Geriatr Soc* 2010, 58:318-323.
15. Rockwood K, Mitnitski A. How might deficit accumulation give rise to frailty? *J Frailty Aging* 2012;1:8-12
16. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, Hillier TA, Cauley JA, Hochberg MC, Rodondi N, et al: Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med* 2008, 168:382-389.
17. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, Brach J, Chandler J, Cawthon P, Connor EB, et al: Gait speed and survival in older adults. *JAMA* 2011, 305:50-58.
18. Andrew MK, Mitnitski AB, Rockwood K: Social vulnerability, frailty and mortality in elderly people. *PLoS One* 2008, 3:e2232.
19. Grady D, Berkowitz S. Why is a good clinical prediction rule so hard to find? *Arch Intern Med*. 2011;171(19):1701-02.
20. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC: Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007, 60:34-42.
21. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW: Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011, 10:104-114.
22. Rockwood K, Mitnitski A: Frailty defined by deficit accumulation and geriatricmedicine defined by frailty. *Clin Geriatr Med* 2011, 27:17-26.
23. Parks RJ, Fares E, Macdonald JK, Ernst MC, Sinal CJ, Rockwood K, Howlett SE: A procedure for creating a frailty index based on deficit accumulation in aging mice. *J Gerontol A Biol Sci Med Sci* 2012, 67:217-227.
24. Carcaillon L, García-García FJ, Tresguerres JA, Gutiérrez Avila G, Kireev R, Rodríguez- Mañas L.. Higher Levels of Endogenous Estradiol are Associated with Frailty in Postmenopausal Women from the Toledo Study for Healthy Aging. *J Clin*





JNHA: GERIATRIC SCIENCE

- Endocrinol Metabol 2012 Jun 7 (Epub ahead of print)
25. Ferrucci L, Penninx BW, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, Leveille SG, Fried LP, Md JM: Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc* 2002, 50:1947-1954.
 26. Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, Guralnik JM, Ferrucci L: Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2004, 59:242-248.
 27. Birnie K, Cooper R, Martin RM, Kuh D, Sayer AA, Alvarado BE, Bayer A, Christensen K, Cho SI, Cooper C, et al: Childhood socioeconomic position and objectively measured physical capability levels in adulthood: a systematic review and meta-analysis. *PLoS One* 2011, 6:e15564.
 28. Alvarado BE, Zunzunegui MV, Beland F, Bamvita JM: Life course social and health conditions linked to frailty in Latin American older men and women. *J Gerontol A Biol Sci Med Sci* 2008, 63:1399-1406.
 29. Yang Y, Lee LC: Dynamics and heterogeneity in the process of human frailty and aging: evidence from the U.S. older adult population. *J Gerontol B Psychol Sci Soc Sci* 2010, 65B:246-255.
 30. Mocchegiani E, Corsonello A, Lattanzio F: Frailty, ageing and inflammation: reality and perspectives. *Biogerontology* 2010, 11:523-525.
 31. Morley JE: Sarcopenia in the elderly. *Fam Pract* 2012, 29 Suppl 1:i44-i48.
 32. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al: Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010, 39:412-423.
 33. Landi F, Russo A, Danese P, Liperoti R, Barillaro C, Bernabei R, Onder G: Anemia status, hemoglobin concentration, and mortality in nursing home older residents. *J Am Med Dir Assoc* 2007, 8:322-327.
 34. Landi F, Russo A, Pahor M, Capoluongo E, Liperoti R, Cesari M, Bernabei R, Onder G: Serum high-density lipoprotein cholesterol levels and mortality in frail, community-living elderly. *Gerontology* 2008, 54:71-78.
 35. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA: Allostatic load and frailty in older adults. *J Am Geriatr Soc* 2009, 57:1525-1531.
 36. Retornaz, F*, Monette J, Batist G, Monette M, Sourial N, Small D, Caplan S, Wan-Chow-Wah D, Puts MTE*, Bergman H: Usefulness of frailty markers in the assessment of the health and functional status of older cancer patients referred for chemotherapy: a pilot study. *J Gerontol Med Sci*. 2008;63A.: 518-522
 37. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, Lichtman SM, Gajra A, Bhatia S, Katheria V, et al: Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011, 29:3457-3465.
 38. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, Takenaga R, Devgan L, Holzmueller CG, Tian J, Fried LP: Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010, 210:901-908.
 39. Puts MT, Monette J, Girre V, Wolfson C, Monette M, Batist G, Bergman H: Does frailty predict hospitalization, emergency department visits, and visits to the general practitioner in older newly-diagnosed cancer patients? Results of a prospective pilot study. *Crit Rev Oncol Hematol* 2009, 76:142-151.
 40. Tan KY, Kawamura YJ, Tokomitsu A, Tang T: Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. *Am J Surg* 2011.
 41. Wilhelm-Leen ER, Hall YN, M KT, Chertow GM: Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med* 2009, 122:664-671 e662.
 42. Krumholz HM, Chen J, Chen YT, Wang Y, Radford MJ: Predicting one-year mortality among elderly survivors of hospitalization for an acute myocardial infarction: results from the Cooperative Cardiovascular Project. *J Am Coll Cardiol* 2001, 38:453-459.
 43. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL: Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. *Circ Cardiovasc Qual Outcomes* 2011, 4:496-502.
 44. Afilalo J, Mottillo S, Eisenberg MJ, Alexander KP, Noiseux N, Perrault LP, Morin JF, Langlois Y, Ohayon SM, Monette J, et al: Addition of frailty and disability to cardiac surgery risk scores identifies elderly patients at high risk of mortality or major morbidity. *Circ Cardiovasc Qual Outcomes* 2012, 5:222-228.
 45. Afilalo J, Eisenberg MJ, Morin JF, Bergman H, Monette J, Noiseux N, Perrault LP, Alexander KP, Langlois Y, Dendukuri N, et al: Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol* 2010, 56:1668-1676.
 46. Chen PJ, Lin MH, Peng LN, Liu CL, Chang CW, Lin YT, Chen LK: Predicting Cause-Specific Mortality of Older Men Living in the Veterans Home by Handgrip Strength and Walking Speed: A 3-Year, Prospective Cohort Study in Taiwan. *J Am Med Dir Assoc* 2012.
 47. Cesari M, Pahor M, Lauretani F, Zamboni V, Bandinelli S, Bernabei R, Guralnik JM, Ferrucci L: Skeletal muscle and mortality results from the InCHIANTI Study. *J Gerontol A Biol Sci Med Sci* 2009, 64:377-384.
 48. Sumukadas D, Witham MD, Struthers AD, McMurdo ME: Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ* 2007, 177:867-874.
 49. Beasley JM, LaCroix AZ, Neuhauser ML, Huang Y, Tinker L, Woods N, Michael Y, Curb JD, Prentice RL: Protein intake and incident frailty in the Women's Health Initiative observational study. *J Am Geriatr Soc* 2010, 58:1063-1071.
 50. Sundell J: Resistance Training Is an Effective Tool against Metabolic and Frailty Syndromes. *Adv Prev Med* 2011, 2011:984683.
 51. Pahor M, Blair SN, Espeland M, Fielding R, Gill TM, Guralnik JM, Hadley EC, King AC, Kritchevsky SB, Maraldi C, et al: Effects of a physical activity intervention on measures of physical performance: Results of the lifestyle interventions and independence for Elders Pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci* 2006, 61:1157-1165.

