

REVIEW

Open Access



# An overview of osteoporosis and frailty in the elderly

Guowei Li<sup>1,2,3\*</sup>, Lehana Thabane<sup>1,2</sup>, Alexandra Papaioannou<sup>4</sup>, George Ioannidis<sup>4</sup>, Mitchell A. H. Levine<sup>1,2,3</sup> and Jonathan D. Adachi<sup>2,4,5\*</sup>

## Abstract

Osteoporosis and osteoporotic fractures remain significant public health challenges worldwide. Recently the concept of frailty in relation to osteoporosis in the elderly has been increasingly accepted, with emerging studies measuring frailty as a predictor of osteoporotic fractures. In this overview, we reviewed the relationship between frailty and osteoporosis, described the approaches to measuring the grades of frailty, and presented current studies and future research directions investigating osteoporosis and frailty in the elderly. It is concluded that measuring the grades of frailty in the elderly could assist in the assessment, management and decision-making for osteoporosis and osteoporotic fractures at a clinical research level and at a health care policy level.

**Keywords:** Osteoporosis, Osteoporotic fractures, Frailty, Geriatrics, Ageing

## Background

Osteoporosis is defined as a systemic skeletal disease with the characteristics of low bone mass and micro-architectural deterioration of bone tissues [1]. In clinical practice, osteoporosis is usually diagnosed by the bone mineral density (BMD) criteria or the occurrence of a fragility fracture. Based on the BMD criteria, osteoporosis is diagnosed by a BMD of 2.5 standard deviations or more below the mean of a young healthy adult women reference population ( $T\text{-score} \leq -2.5$ ) [2]. Osteoporosis results in increased bone fragility and subsequent accumulated fracture risk. With decreased BMD as people age, osteoporosis becomes more prevalent among older individuals [3]. As the population ages worldwide, the number of osteoporotic fractures is growing substantially. In western countries, the lifetime risk of any osteoporotic fracture remains very high, lying within the range of 40–50% for women and 13–22% for men [4]. For the year 2000, it was estimated that 9 million new osteoporotic fractures occurred globally, of which 1.6 million were hip fractures and 1.4 million were clinical vertebral fractures [5]. In the US, there are more than 2

million fractures annually attributed to osteoporosis, including 550,000 vertebral fractures and 300,000 hip fractures [6, 7]. Osteoporotic fractures in the elderly are usually followed by hospitalization, long-term care, impaired quality of life, disability and death [8]. Therefore osteoporosis and osteoporotic fractures remain significant public health challenges worldwide.

Recently, the concept of frailty in relation to osteoporosis in the elderly has been increasingly accepted, with emerging studies measuring frailty as a predictor of osteoporotic fractures [9]. Frailty is defined as a dynamic clinical condition with increased vulnerability which results from aging-related degeneration across psychological, physical and social functioning [10, 11]. Frailty is accelerating in the aging population, with an overall prevalence of 10.7% in community-dwellers aged  $\geq 65$  years worldwide [12]. Moreover, it is estimated that 25–50% of older adults aged  $\geq 85$  years are frail [9]. Frailty is mainly caused by the complex aging mechanisms that are determined by underlying genetic, epigenetic and environmental factors [9]. However, other multifactorial elements such as sarcopenia, inflammation, malnutrition, co-morbidities, hormonal insufficiency, etc., can also result in frailty in the elderly [13–15]. The fundamental of the relationship between frailty and osteoporosis relies on the fact that, the frailer an individual is, the greater the likelihood that the individual will have a prevalent osteoporotic fracture and the higher the risk of a

\* Correspondence: lig28@mcmaster.ca; jd.adachi@sympatico.ca

<sup>1</sup>Department of Clinical Epidemiology & Biostatistics, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada

<sup>2</sup>St. Joseph's Healthcare Hamilton, McMaster University, 25 Charlton Avenue East, Hamilton, ON L8N 1Y2, Canada

Full list of author information is available at the end of the article



fracture in the future [16, 17]. Quantifying the degree of frailty could aid in the assessment, management and decision-making for the elderly at a clinical research level and at a health care policy level [9].

### Measuring grades of frailty in assessing risk of osteoporotic fractures

A frailty instrument should be multidimensional, able to capture the grades of frailty, and qualified to serve as a screening or evaluation tool [18]. At present, two predominant approaches are being widely used in measuring the degree of frailty in the elderly: the phenotype model [19] and the frailty index of deficit accumulation [20]. Table 1 lists the respective components of the phenotype model and the frailty index of deficit accumulation. The phenotype model is calculated from five physical indicators (exhaustion, low physical activity, weakness, slow walking and unintentional weight loss) [19]. Each indicator is scored as either 0 or 1 and therefore the total score ranges from 0 to 5 points. The phenotype model categorizes the elderly into robust, pre-frail or frail groups by the cut-points of the total score of 0, 1–2 and  $\geq 3$  points respectively [19]. By contrast, the frailty index chooses a variety of individual health deficits to measure the cumulative effect and quantify the degree of frailty [20]. Generally, the deficits cover the domains of symptoms and signs, comorbidities, activities of daily living, and social relations and social support [21, 22]. Though each individual deficit may not carry an imminent threat of adverse health outcomes, the deficit accumulation contributes to the increased risk [23]. The frailty index approach does not require the same deficits or the same number of variables to build a frailty index [24]. Previous studies have selected 30 to 70 health deficits in creating a frailty index [25]. However it has been recommended to include at least 30 to 40 deficits in total to construct a frailty index [22]. Each

deficit is dichotomized or polychotomized and mapped on an interval scale between 0 and 1, in order to reflect the frequency or severity of the deficit [22]. Subsequently, the frailty index is calculated by summing up all the deficit values and dividing by the whole number of the deficits included. For example, if a frailty index includes 35 deficits, and an individual has 6 deficits with each scored as 1 point (6 point total), 2 deficits with each scored as 0.5 (1 point total), and the remaining 27 deficits with each scored of 0, then the frailty index would be 7 divided by 35 giving an index of 0.2.

Evidence has shown that both the phenotype model and the frailty index are predictive of osteoporotic fractures independent of chronological age in the elderly [26–29]. For instance, the Study of Osteoporotic Fractures (SOF) assessed the relationship between a phenotype model and risk of fractures in 6724 women aged  $\geq 69$  years with a mean follow-up of 9 years [26]. They reported higher hip fracture risk (hazard ratio (HR) = 1.40, 95% confidence interval (CI): 1.03–1.90) and non-spine fracture risk (HR = 1.25, 95% CI: 1.05–1.49) in frail women, compared with their robust peers. In addition, one study using data from the Canadian Multicentre Osteoporosis Study (CaMos) constructed a 30-item frailty index in 9423 adults with a mean age of 62 years and a 10-year follow-up [29]. Results indicated a significant HR of 1.18 for hip fractures and 1.30 for clinical vertebral fractures for every 0.10 increase in the frailty index.

In quantifying the risk of adverse health outcomes, even with statistical overlap and convergence, some studies argued that the continuous frailty index of deficit accumulation showed higher discriminatory ability than the categorical phenotype model [9, 30–32]. However, other comparative studies have found that the phenotype model was comparable with the frailty index in predicting risk of adverse outcomes [33–35]. For instance, results from a Chinese study presented similar predictive accuracy of the frailty index and the phenotype model for risk of mortality and physical limitation [33]. Likewise, our study using data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) 3-year Hamilton Cohort did not find a significant difference in predictive accuracy for risk of osteoporotic fractures, even though the frailty index approach tended to yield more precise estimates as compared with the phenotype model [35]. These findings may imply the flexibility in the choice of frailty models in population-based settings for the elderly. However, the frailty index is usually considered as a research tool because of the amount of information it requires to complete the assessment, while the phenotype model can be pragmatically applied in geriatric clinical practice [33, 35]. Indeed, it has been suggested that the combined or sequential use of the two approaches should be implemented for the elderly,

**Table 1** Components of the phenotype model and the frailty index of deficit accumulation

Approach to measuring grades of frailty	Components
The phenotype model <sup>a</sup>	Exhaustion
	Low physical activity
	Weakness
	Slow walking
	Unintentional weight loss
The frailty index of deficit accumulation <sup>b</sup>	Deficits of symptoms and signs
	Comorbidities
	Deficits of activities of daily living
	Deficits of social relations and social support

<sup>a</sup>The phenotype model is based on five physical indicators

<sup>b</sup>The frailty index of deficit accumulation is calculated from a variety of individual health deficits

given that the frailty index and the phenotype model provide complementary and distinct clinical information on the risk profiles [36].

#### **Current research investigating osteoporosis and frailty in the elderly**

There are some studies using derivations of the phenotype model or other categorical frailty models to measure the degree of frailty. Results from the comparisons between them and the original phenotype model have been published, with comparable model performances reported in different populations [3, 34, 37–40]. In addition, evidence indicates that the phenotype model may require model calibration or redevelopment. Some studies have raised concerns about the scoring algorithm for the phenotype model, with emerging reports showing that not all the components contributed equally to the prediction of adverse health outcomes [7, 41–43]. Previous findings have suggested that slow walking appears to be the most important risk factor for adverse outcomes among the five indicators included in the phenotype model [41, 42]. Moreover, low predictive accuracy of the phenotype model in the prediction of adverse outcomes has been reported [35, 37, 44]. For instance, one study found the phenotype model could not differentiate the healthy elderly from those with unplanned hospital admission and falls, with an area under the receiver operating characteristic curve (AUC) value of 0.50 and 0.52 respectively [44]. Similarly, another study reported an AUC value of 0.55 for non-spine fractures and 0.63 for hip fractures in 6701 women using the phenotype model [37].

Regarding the frailty index approach, much of the literature focuses on the comparison between the frailty index and the phenotype model in predicting risk of adverse outcomes [33–35, 38, 45–47]. Of note, it may be methodologically challenging to directly compare the continuous frailty index and the categorical phenotype model. One study based on the GLOW 3-year Hamilton Cohort used three strategies to perform direct comparisons between the frailty index and the phenotype model by (1) investigating the associations between the adverse outcomes and respective per one-fifth (20%) increase of the frailty index and the phenotype model; (2) trichotomizing the frailty index according to the overlap in the density distribution of the frailty index by the robust, pre-frail and frail groups defined by the phenotype model; and (3) trichotomizing the participants based on a predicted probability function of outcomes predicted by the frailty index [35]. All the three strategies yielded comparable predictive accuracy of the frailty index and the phenotype model in predicting risk of adverse outcomes. Additionally, some studies compare the frailty index with other existing tools for predictions of risk of osteoporotic fractures. For instance, there was one study comparing the frailty index

with the fracture risk assessment tool (FRAX) in prediction of risk of major osteoporotic fracture (spine, hip, upper arm or shoulder, or wrist) and hip fracture in 3985 elderly women [48]. The frailty index was found to be comparable with FRAX in predicting risk of major osteoporotic fractures and hip fracture, indicating that measuring grades of frailty may aid in fracture risk evaluation and fracture prevention for the elderly. Of note, we observed similar results in the women stratified by taking or not taking anti-osteoporotic treatments and/or supplementation, which indicated that the prediction of frailty index and FRAX in major osteoporotic fractures was not significantly influenced by the effect of anti-osteoporotic treatments and/or supplementation [48]. However, further studies are needed to evaluate whether the assessment of frailty would be a useful addition to FRAX to improve predictive accuracy for risk of fractures in the elderly. Furthermore, despite abundant studies investigating the trajectory nature of the frailty index in the elderly, limited evidence is available for the change of frailty before and after an osteoporotic fracture. In our study, we aimed to assess the change of the frailty index before and after onset of a major osteoporotic fracture during follow-up in the elderly women [46]. We found that the increase of the frailty index was significantly larger in the women who experienced a major osteoporotic fracture than their controls, indicating their greater deficit accumulation and accelerating frailty after a major osteoporotic fracture [46]. Investigating the transition nature by the change of frailty index before and after a major osteoporotic fracture may be useful to serve as an indicator for the effect of treatments or interventions [16]. For example, the change of frailty may be used to identify the minimally important differences (MIDs) in a fracture intervention study, taking into account the frailty transition nature [46]. Though results of the prediction of frailty status in risk of osteoporotic fractures are consistent in the literature, it still remains largely unknown whether frailty is a cause or a consequence of osteoporosis. For instance, some studies have reported no significant cross-sectional relationship between frailty and osteoporosis [49, 50], though frailty and osteoporosis share similar biological pathways and common risk factors such as advanced age, low physical activity, weight loss and cognitive decline [51]. More high-quality evidence is required to further clarify the association between frailty and osteoporosis dependently or independently of the aging process.

#### **Future research directions**

The phenotype model and the frailty index have been shown to be useful tools in predicting risk of osteoporotic fractures in the elderly. Future research may need to justify the validity and reliability of the frailty instruments in clinical settings and research studies, before they can be fully

used to guide clinical decision-making [16]. Moreover, measures of frailty need to be tested against the effect of treatments or interventions in studies aiming to prevent or treat frailty. Likewise, the effect of frailty on recovery after a fracture or prevention of a secondary fracture in the elderly warrants further investigation. Besides, given that there is lack of an operational definition for frailty and sarcopenia, it would be a worthwhile endeavor to investigate the combined or sequential use of the instruments (or risk assessment tools) for frailty and sarcopenia in the elderly. Information on assessing frailty and sarcopenia may, together or in parallel of an osteoporosis assessment tool, provide more comprehensive vision of the risks to develop hard clinical outcomes for osteoporotic patients. Other research areas needed to be examined in depth include: 1) the relationship between frailty and osteoporotic fractures in different populations; 2) integration of elements of frailty to FRAX to determine whether higher predictive accuracy can be achieved; and 3) whether interventions in the pre-frail older adults can prevent osteoporotic fractures.

In addition, more studies are warranted to evaluate the role of the frailty instruments as an outcome measure, rather than just a risk assessment tool. As the frailer an elderly is, the greater the risk of osteoporotic fractures, quantifying the degree of frailty may be also helpful as an outcome measure, especially for some short-term fracture intervention studies. Furthermore, understanding the complexity of aging and frailty in the elderly necessitates more exploration of the aging nature *per se*.

## Conclusion

In summary, we have presented an overview of the relationship between osteoporosis and frailty in the elderly. Measuring the degree of frailty in older adults by the frailty index and/or the phenotype model could assist in the assessment, management and decision-making for osteoporosis and osteoporotic fractures at a clinical research level and at a health care policy level. More evidence is needed to examine whether interventions in the pre-frail older adults can prevent osteoporotic fractures and to further support its usefulness and application of the frailty assessment in the elderly with osteoporosis in different populations.

## Abbreviations

AUC: Area under the receiver operating characteristic curve; BMD: Bone mineral density; CaMos: Canadian multicentre osteoporosis study; CI: Confidence interval; FRAX: Fracture risk assessment tool; GLOW: Global longitudinal study of osteoporosis in women; HR: Hazard ratio; MIDs: Minimally important differences; SOF: Study of osteoporotic fractures

## Acknowledgment

None.

## Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

## Availability of data and materials

The data appeared in this review are already publicly available in the literature.

## Authors' contributions

All the authors contributed to the study conception. GL was responsible for the draft of manuscript. LT, AP, GI, MAHL and JDA provided comments and made critical revision of the manuscript. All authors approved the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Author details

<sup>1</sup>Department of Clinical Epidemiology & Biostatistics, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada. <sup>2</sup>St. Joseph's Healthcare Hamilton, McMaster University, 25 Charlton Avenue East, Hamilton, ON L8N 1Y2, Canada. <sup>3</sup>Programs for Assessment of Technology in Health, Centre for Evaluation of Medicines, Hamilton, ON L8N 1Y3, Canada. <sup>4</sup>Department of Medicine, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4L8, Canada. <sup>5</sup>St. Joseph's Healthcare Hamilton, McMaster University, 25 Charlton Avenue East, Hamilton, ON L8N 1Y2, Canada.

Received: 15 September 2016 Accepted: 14 January 2017

Published online: 26 January 2017

## References

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001; 285(6):785–95.
2. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Orga Tech Rep Ser*. 1994; 843:1–129.
3. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the scientific advisory board of the osteoporosis society of Canada. 1. Introduction. *CMAJ*. 1996;155(7):921–3.
4. Johnell O, Kanis J. Epidemiology of osteoporotic fractures. *Osteoporos Int*. 2005;16 Suppl 2:S3–7.
5. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17(12):1726–33.
6. Ebeling PR. Clinical practice. Osteoporosis in men. *N Engl J Med*. 2008; 358(14):1474–82.
7. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359–81.
8. Beaupre LA, Jones CA, Saunders LD, Johnston DW, Buckingham J, Majumdar SR. Best practices for elderly hip fracture patients. A systematic overview of the evidence. *J Gen Intern Med*. 2005;20(11):1019–25.
9. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England)*. 2013;381(9868):752–62.
10. Gobbens RJ, Luijckx KG, Wijnen-Sponselee MT, Schols JM. Toward a conceptual definition of frail community dwelling older people. *Nurs Outlook*. 2010;58(2): 76–86.
11. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. 2011;27(1):1–15.
12. 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(8):1487–92.
13. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. *Am J Med*. 2007;120(9):748–53.
14. Morley JE, Haren MT, Rolland Y, Kim MJ. Frailty. *Med Clin N Am*. 2006;90(5): 837–47.
15. Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. *J Nutr Health Aging*. 1999;4(3):140–2.

16. Rockwood K, Theou O, Mitnitski A. What are frailty instruments for? *Age Ageing*. 2015;44(4):545–7.
17. van den Bergh JP, van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: implications for case finding and therapy. *Nat Rev Rheumatol*. 2012;8(3):163–72.
18. Rockwood K. What would make a definition of frailty successful? *Age Ageing*. 2005;34(5):432–4.
19. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–156.
20. 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(5):489–95.
21. De Vries N, Staal J, Van Ravensberg C, Hobbelen J, Olde Rikkert M, Nijhuis-Van der Sanden M. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev*. 2011;10(1):104–14.
22. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24.
23. Rockwood K, Mitnitski A. How might deficit accumulation give rise to frailty. *J Frailty Aging*. 2012;1:8–12.
24. 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(12):2184–9.
25. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):722–7.
26. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, Tracy JK, Hochberg MC, Rodondi N, Cawthon PM. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):744–51.
27. Tom SE, Adachi JD, Anderson Jr FA, Boonen S, Chapurlat RD, Compston JE, Cooper C, Gehlbach SH, Greenspan SL, Hooven FH, et al. Frailty and fracture, disability, and falls: a multiple country study from the global longitudinal study of osteoporosis in women. *J Am Geriatr Soc*. 2013;61(3):327–34.
28. Fang X, Shi J, Song X, Mitnitski A, Tang Z, Wang C, Yu P, Rockwood K. Frailty in relation to the risk of falls, fractures, and mortality in older Chinese adults: results from the Beijing Longitudinal Study of Aging. *J Nutr Health Aging*. 2012;16(10):903–7.
29. Kennedy C, Ioannidis G, Rockwood K, Thabane L, Adachi J, Kirkland S, Pickard L, Papaioannou A. A frailty index predicts 10-year fracture risk in adults age 25 years and older: results from the Canadian multicentre osteoporosis study (CaMos). *Osteoporos Int*. 2014;25(12):2825–32.
30. Kulminski AM, Ukraintseva SV, Kulminskaya IV, Arbeev KG, Land K, Yashin AI. Cumulative deficits better characterize susceptibility to death in elderly people than phenotypic frailty: lessons from the cardiovascular health study. *J Am Geriatr Soc*. 2008;56(5):898–903.
31. 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(7):738–43.
32. Jung HW, Kim SW, Ahn S, Lim JY, Han JW, Kim TH, Kim KW, Kim KI, Kim CH. Prevalence and outcomes of frailty in Korean elderly population: comparisons of a multidimensional frailty index with two phenotype models. *PLoS One*. 2014;9(2):e87958.
33. 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(8):1478–86.
34. Ravindrarajah R, Lee DM, Pye SR, Gielen E, Boonen S, Vanderschueren D, Pendleton N, Finn JD, Tajar A, O'Connell MD. The ability of three different models of frailty to predict all-cause mortality: results from the European Male Aging Study (EMAS). *Arch Gerontol Geriatr*. 2013;57(3):360–8.
35. Li G, Thabane L, Ioannidis G, Kennedy C, Papaioannou A, Adachi JD. Comparison between frailty index of deficit accumulation and phenotypic model to predict risk of falls: data from the global longitudinal study of osteoporosis in women (GLOW) Hamilton cohort. *PLoS One*. 2015;10(3):e0120144.
36. 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(1):10–2.
37. 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(4):382–9.
38. Malmstrom TK, Miller DK, Morley JE. A comparison of four frailty models. *J Am Geriatr Soc*. 2014;62(4):721–6.
39. Bandeen-Roche K, Xue Q-L, Ferrucci L, Walston J, Guralnik JM, Chaves P, Zeger SL, Fried LP. Phenotype of frailty: characterization in the women's health and aging studies. *J Gerontol A Biol Sci Med Sci*. 2006;61(3):262–6.
40. Boyd CM, Xue QL, Simpson CF, Guralnik JM, Fried LP. Frailty, hospitalization, and progression of disability in a cohort of disabled older women. *Am J Med*. 2005;118(11):1225–31.
41. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med*. 2006;166(4):418–23.
42. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. *J Am Geriatr Soc*. 2009;57(9):1532–9.
43. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. *J Am Geriatr Soc*. 2008;56(12):2211–16.
44. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, Rapp SR, Cesari M, Newman AB, Harris TB, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):844–50.
45. Ritt M, Schwarz C, Kronawitter V, Delinic A, Bollheimer LC, Gassmann KG, Sieber CC. Analysis of Rockwood et al's clinical frailty scale and Fried et al's frailty phenotype as predictors of mortality and other clinical outcomes in older patients who were admitted to a geriatric ward. *J Nutr Health Aging*. 2015;19(10):1043–8.
46. Dent E, Chapman I, Howell S, Piantadosi C, Visvanathan R. Frailty and functional decline indices predict poor outcomes in hospitalised older people. *Age Ageing*. 2014;43(4):477–84.
47. van Deudekom FJ, van de Ruitenbeek M, Te Water W, Smit JM, van Munster BC. Frailty index and frailty phenotype in elderly patients with cancer. *Acta oncologica (Stockholm, Sweden)*. 2016;55(5):644–6.
48. Li G, Thabane L, Papaioannou A, Adachi JD. Comparison between frailty index of deficit accumulation and fracture risk assessment tool (FRAX) in prediction of risk of fractures. *Bone*. 2015;77:107–14.
49. Gerdhem P, Ringsberg KA, Magnusson H, Obrant KJ, Akesson K. Bone mass cannot be predicted by estimations of frailty in elderly ambulatory women. *Gerontology*. 2003;49(3):168–72.
50. Sternberg SA, Levin R, Dkaidek S, Edelman S, Resnick T, Mencil J. Frailty and osteoporosis in older women—a prospective study. *Osteoporos Int*. 2014;25(2):763–8.
51. Rolland Y, Abellan Van Kan G, Benetos A, Blain H, Bonnefoy M, Chassagne P, Jeandel C, Laroche M, Nourhashemi F, Orcel P, et al. Frailty, osteoporosis and hip fracture: causes, consequences and therapeutic perspectives. *J Nutr Health Aging*. 2008;12(5):335–46.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

