FRAILTY: A Report from the 3rd Joint Workshop of IAGG/WHO/SFGG, Athens, January 2012

Kenneth Rockwood, MD, FRCPC, FRCP, FCAHS[1], Howard Bergman, MD, FCFP, FRCPC, FCAHS[2]

[1]Department of Medicine (Geriatric Medicine & Neurology), Dalhousie University and Capital District Health Authority, Halifax, NS; [2]Department of Medicine (Family Medicine and Oncology), McGill University and Jewish General Hospital, Montreal, QC

DOI: http://dx.doi.org/10.5770/cgj.15.35

ABSTRACT

Frailty represents a growing challenge to modern health-care systems. This paper reports on a conference on frailty held in Athens in January 2012. Papers from 11 groups, including those of the authors, were presented and discussed over two days. Several approaches to frailty and its operationalization (including biomarkers) and to social vulnerability were discussed. The search programs that incorporate multiple measures and allows them to be tested were encouraged.

Key words: frailty, phenotype, index, risk, aged, biomarkers, social vulnerability

How best to operationally define frailty for both clinical and research purposes remains a matter of debate. In January 2012, the authors took part in a consensus meeting jointly sponsored by the International Association of Geriatrics and Gerontology, the World Health Organization, and the Société Française de Gériatrie et Gérontologie. The meeting, convened in Athens, brought together 10 participants and more than 30 observers. The goals were to discuss how frailty might be studied, and how insights from frailty studies might be rapidly transmitted to the clinical and scientific communities. As the topic of frailty is of interest to Canadian geriatricians, the results of these deliberations are summarized here.

The introductory session, by Dr. Meropi Violaki, President of the Hellenic Association of Gerontology and Geriatrics, drew attention to the financial challenges now facing Greece. She pointed out that it would be elderly people (and others on fixed incomes) who would be hardest hit, and the frail who would find it hardest to cope. The opening introduction, therefore, drew to attention the link between frailty and social vulnerability, a theme explored in a subsequent paper by Prof. Luis Miguel Gutierrez-Robledo.

The first scientific session of the conference came from Prof. Howard Bergman, who outlined the broad clinical and scientific challenges of frailty. His paper underscored that understanding frailty has a clinical motivation: we need to help clinicians and we need to help scientists help clinicians. He drew attention to the fact that the vast majority of older people are not looked after by geriatricians, including older adults who are frail. Frailty research and debate has opened new horizons in understanding the aging process, the heterogeneity of older persons, and the potential to identify independent vulnerable older adults and prevent/delay adverse consequences.(1)

The presentation highlighted results from the FrData (International Database Inquiry on Frailty) project, which considers seven possible frailty domains. Prof. Bergman noted that the Fried model,(2) as well as most other models, robustly classify risk in relation to mortality and other adverse outcomes, such as disability. Most of the research in frailty has consisted of analyzing the explanatory ability (i.e., testing frailty as a significant risk factor for adverse outcomes within a given sample). However, little is known on the true predictive ability of frailty to predict accurate outcomes in new, out-of-sample subjects. Even highly significant risk factors can make poor predictors for a prognostic tool.(3)

Risk and prediction can also vary, based on the population, setting, and outcome that is studied. This is likely to be particularly true in clinical settings where, for example, medical oncology series with their likely high mortality will have systematically different accounts of the outcomes of frailty than would patients being evaluated for elective percutaneous coronary interventions, where mortality is much lower.

The presentation concluded that frailty research in general has opened up our understanding of frailty. What is needed now is a robust clinical instrument that can identify people at risk and, along with that, intervention research to either alter the cause of frailty or delay the onset of adverse outcomes—in particular, disability. The use of frailty markers per se, rather than their exact nature, may prove to be most important.(4) One size does not fit all with regard to the exact items used; our overarching goal must be to improve outcomes in our most vulnerable patients.

The second paper, presented by Dr. Matteo Cesari from Toulouse, France, looked first for consensus that frailty is a

syndrome (or at least a state) that increases vulnerability to endogenous and exogenous factors. He also underscored the fundamental nature of frailty as the basis for the practice of geriatric medicine, and compared our disciplined approach to patients with multiple disorders, which seeks to embrace their complexity, with the approach of single system (sub) specialties that aim to reduce the problem for their own area of concern.

Dr. Cesari proposed that it is important to define frailty as a disease, and focused on how social determinants typically define disease. Typically, a problem is identified as a disease from a consensus conference that holds two goals, which hopefully are not contradictory: to contrast normal from abnormal, and to contrast those who might benefit from treatment directed at that disease from those who would not.

For this reason, he proposed to focus on mobility and made the case that this is robust (spans from animals to humans).[5] He noted that we have data to build age-specific nomograms, and that in both cancer and cardiac surgery, mobility is the single best prediction of mortality. Such a measure could be used in busy clinical settings, although he cautioned that there is more to a frailty definition than mortality prediction.

In the general discussion that ensued from these two presentations, attention was drawn to the context dependence of any clinical frailty definition. The two papers were united in motivation, but at odds on operationalization. Prof. Bergman pointed out that the FrData analyses did not find that gait speed trumped other measures.[4] Likewise, timed mobility testing would be an unlikely frailty screening test for people about to undergo elective hip replacement.

The discussion was divided as to the urgency of the need to come up with a frailty measure that, if useful, could be widely taken up in other settings. The need not to be outflanked by other groups (in particular government officials) was raised. Likewise, an analogy was made with dementia, another common condition under the care of geriatricians. Prof. Bruno Vellas from France commented that the establishment of memory impairment dementia clinics had proved a boon to understanding dementia. In his view, a "frailty clinic" might likewise add dramatically to our understanding of how frailty operates. For this to happen, he proposed that some initial starting point definition should be adopted, with the expectation that it would be revised as our understanding improved.

Despite the controversy over how to proceed and whether an interim measure strategy would be worthwhile, there was support for an approach to frailty that was not binary or even tri-particle. Instead, the need to better grade the severity of frailty achieved near consensus.

Prof. Luis Miguel Gutierrez-Robledo from Mexico City presented on social factors and how they might determine frailty.[6] He noted that social factors are non-controversial determinants of health, including those that arise from early life. Incorporating this into a model of frailty is conceptually straightforward in that, in general, social factors predispose and even precipitate frailty.

But how are they modulated? For example, low socioeconomic statistics give rise to certain comorbidities (obesity and its consequences), which interact to predispose to frailty. Further, diabetic control and medication access are lower amongst the poor. Similarly social inequality increases the risk of adverse outcomes amongst the frail.[4]

Prof. Gutierrez-Robledo proposed allostatic load ("a cumulative index of wear and tear across multiple physiological systems"[7]) as a mediation. In other words, if frailty (especially phenotypic frailty) reflects impaired reserve, it may be captured by the notion of allostatic load, which might also express how social vulnerability exerts its impact. Similar to the notion of reduced mobility as a useful single indicator, he noted the concept of life space assessment[8]—being the physical distance a person routinely travels to perform activities—as holding out the possibility of a single measure that might capture social vulnerability. He concluded that the existing evidence makes it clear that physical frailty and social vulnerability are linked.

Prof. Antonio Cherubini from Perugia, Italy looked at scales which could quantify frailty. He began by noting that frailty is a dynamic process, which gives rise to the possibility that it could be a focus for intervention. In consequence, frailty measures must be able to be useful as screening tools and as responsive measures. Like some other speakers, he distinguished between two main approaches—the frailty phenotype[1] and the deficit accumulation approach.[9]

The frailty phenotype is a uni-dimensional construct, and notably does not include impairments in cognition and affect, and may not be readily operationalized in clinical practice. The deficit accumulation approach was seen to capture the multidimensional nature of frailty and to be soundly based in the mathematics of complex systems.[10] Even so, it was felt to be time-consuming and thereby difficult to apply in routine practice, and to lack a pathophysiological model. Instead, a short physical performance measure was proposed as a frailty screening method that could also be responsive enough for use in clinical trials. Its widespread use in primary care was seen as providing strong support for its use.

Prof. Leocadio Rodriguez Manas from Madrid, Spain presented the results of the frailty operative definition-consensus conferences. The results are embargoed but a paper is forthcoming. Initially, there was no consensus amongst more than 50 experts. The final version is expected to propose a half-dozen key components to frailty. Validation of the approach, and assessment of its reliability and responsiveness, is already under way. Some nuance is likely to be needed to fully appreciate all the points on which consensus was achieved.

A second part of this presentation outlined the design of a study to investigate the impact of a multi-model intervention on frailty in diabetes. Patients aged 70 years and older will be targeted. The questions will focus on how a

frailty intervention can affect function, cognition, mobility, and quality of life. Finally, Prof. Manas noted the growing recognition of the importance of studying frailty. For example, the European Union's Future Age program set as a key question, "What is frailty?" In this regard, he saw as essential the frailty operational definition consensus conferences recommendation.

In the ensuing discussion on the use of clinical scales, ethical issues in particular were raised. It was underscored that frailty scales should not be punitive, used to deny treatment, or negatively affect the self-image of people who now are to be labeled as frail. Instead, frailty measures should be employed to optimize treatment, and especially to adapt treatment routines to maximize benefit and to prevent harm from the "whole person" perspective afforded by a focus on frailty. It was also emphasized that a frailty measure should be used as a means to optimize treatment for everyone, both fit and frail.

Next, Prof. Kenneth Rockwood presented on the question of "how deficit accumulation gives rise to frailty".[11] Prof. Rockwood proposed that frailty is a multiply determined vulnerability state. People who are frail are at risk of many adverse health outcomes, including death. For any individual, this risk can only be expressed probabilistically. Even very fit people can suddenly die or become catastrophically disabled, but their risk of both is much lower than that of a very frail person who might nevertheless suddenly succumb without worsening health.

Frailty occurs with ageing, a stochastic, dynamic process of deficit accumulation. Deficits occur ubiquitously at subcellular levels, ultimately affecting tissues, organs, and integrated organ action, especially under stress. Some people are disposed to accumulate deficits at higher rates but, on average, deficit accumulation varies across the life course and likely is mutable. In this way, the clinical definition of frailty is distinct from the statistical definition, which sees frailty as a fixed factor for an individual.

Recent, early animal work links subcellular deficits to whole body frailty.[12] In humans, clinically detectable health deficits combine to increase the risk of adverse health outcomes. The rate of deficit accumulation occurs with remarkable regularity around the world, as does a limit to frailty. Of note, when more than 20 deficits are counted, these characteristics are indifferent to which deficits are considered.

The expression of risk in relation to deficit accumulation varies systematically. For example, at any given level of deficit accumulation, men are more susceptible to adverse health outcomes than are women. Likewise, in China, the lethality of deficit accumulation appears to be higher than in Western countries.[13] As a consequence, it may be necessary to better distinguish between frailty and physiological reserve; the latter may apply chiefly in relation to microscopic deficits. The expression of frailty risk in relation to deficit accumulation depends on the environment, including both the physical and social circumstances in which people find themselves.

Prof. Cornel Sieber from Germany presented on biomarkers in relation to frailty. Biomarkers were defined as a characteristic that is objectively measured and evaluated as an indication of a normal biological process which can be used to monitor the effect of an intervention.[14] He first reviewed the idea that the physical aspects of frailty (and not the psychological or social aspects) would be the object of inquiry of a biomarker. Provocatively, he proposed that the frailty phenotype reduces to sarcopenia, a point elaborated elsewhere.[15]

Prof. Sieber contrasted two approaches to biomarkers: those which accumulate with age, and those that diminish with age. The ageing deficit model would be clearly the case if there are multiple neuroendocrine pathways. Likewise, biomarkers that assayed nutrients and anti-oxidants might be expected to decline with age. The ageing excess model says that there are too many bad factors—especially pro-inflammatory protein factors. A growing literature has documented the correlation between inflammatory markers and frailty (e.g., IL-6[16]). Likewise TNF alpha antibody levels correlate with muscle strength and respond to an exercise intervention.[17] Other frailty parameters might include hemoglobin, HDL, and neopterin, several nutritional parameters (Vitamins D, B, C and E), transcobalamin, and carotinoids.[18] In general, however, although each measure is correlated with frailty, none is specific; in any case, they usually go unmeasured. Finally, Prof. Sieber drew attention to the biomarkers associated with cachexia, and how the clinical definition of cachexia[19] overlaps with the Fried frailty definition.[2] It also includes commonly used biomarkers (CRP, IgG, anemia). On these grounds, he proposed that biomarkers may become more likely to be used clinically.

Prof. Alfonso J. Cruz-Jentoft from Madrid, Spain proposed that frailty is best described as a geriatric syndrome. He then asked, "What is a geriatric syndrome?". Borrowing from casuistry, he said that it could then be understood as arising from the description of typical clinical scenarios of people who would readily be recognized as frail. (In this, he echoed HB's opening statement to the conference that, for clinicians, frailty was like pornography: hard to define but easy to recognize when they saw it.) He quoted one proposition that frailty scenarios had in common, their being "multifactorial state of accumulated deficits that leads to increase vulnerability." He noted that delirium, by way of an example, had multiple complex causes but still was a recognizable entity.

Frailty as a multicomponent syndrome mandates a multifactorial intervention, perhaps best directed to shared risk factors.[20] According to this view, frailty can be seen as an intermediate path by which the adverse effects of typical geriatric syndromes are mediated. Prof. Cruz-Jentoft proposed, however, that functional decline was present at all steps of the model and thereby entangling frailty with disability. By contrast, he proposed that sarcopenia and

frailty are intrinsically linked through shared risk factors. Sarcopenia, the decline in lean body mass, is a syndrome characterized by progressive and generalized loss of skeletal muscle mass, predisposing to adverse outcomes. Studies that investigate whether sarcopenia was at the base of all frailty would be of great use in understanding frailty mechanisms.

His proposition rests on frailty as a risk model (more than as a clinical entity), and on the most useful insights coming from studying frailty as a pre-disability state. In this way, subclinical sarcopenia might occur before the other parts of the frailty phenotype, and be readily linked to biomarkers. Cognition, he noted, is not well modeled by sarcopenia, so this needs work. Intriguingly, mild motor deficits, especially in gait, have been linked to the development of dementia. This may provide a useful link. Further, sarcopenia is the subject of a drug study, and its treatment may well improve frailty.

Prof. Jean-Pierre Baeyens from Brussels, Belgium proposed a competency model, which focused on the ways in which people adapt to their deficits to maintain their own functionality. Its assessment requires the assessment of the individual's functionality, plus the functionality of the environment. How to assess individual functionality would therefore be a key component of frailty assessment.

The classic models of adding years to life are supplemental by increasing the quality of life of the years that remain (i.e., adding life to years). Prof. Baeyens emphasized that doctors need something that they can use in seconds, and therefore he endorsed the Study of Osteoporotic Fractures three-item approach to frailty (weight loss > 5 lbs between two examinations), inability to rise from chair (five times without using the arms), and the answer to the question, "Are you feeling full of energy?"[21] This can be done by a family physician, nurse or pharmacist—even social workers or home help personnel. (Who gets home help without being frail?) After this screening, he proposed that the MDS-Inter RAI should be employed.[22]

The discussion about these two papers was of some interest. It revealed a split within the audience of experts: those who saw frailty as a "pre-clinical disability" state, and those who saw it as a continuously distributed process in which frailty would be staged across a range of severity states, many of which would be staged by the degree of disability. Those who see frailty chiefly as a pre-clinical disability argue that, from a public health standpoint, the biggest gain comes from people who are at an increased risk (and in this way frail) but without frank disability. People with frank disability, they argue, are known to be at risk, are readily recognized as being disabled, and do not benefit from being re-named as frail. Those who view frailty as a continuously distributed process see things differently: frailty is a vulnerability state, and people who are disabled can almost always be worse (i.e., "disability" does not adequately grade their vulnerability state).

Dr. Frederique Retornaz from Marseilles discussed the heterogeneity in health status of older adults' referral to a medical oncology service. Clearly, some patients will be too frail to benefit from toxic chemotherapy regimes. But weight loss, fatigue, reduced activity, and even slowing can be part of any concern, so that some will be misclassified as frail on this basis. She reviewed a Canadian pilot study of frailty markers that were found to be common in older adults referred for chemotherapy who were not otherwise clearly disabled or who had much co-morbidity.[23] Of these, impaired grip strength predicted toxicity. She reviewed a second recent paper from a surgical oncology series that showed a dose response in relation to frailty markers. It was noted, however, that the paper used a non-standard classification, with 0 or 1 frailty marker being the "non-frail" group, 2–3 being intermediate group, and 4 or 5 being the frail group.[24]

Dr. Retornaz presented data from her own clinic which showed that 84% of older adults had at least one frailty marker, so that this did not change management. Only a Comprehensive Geriatric Assessment identified those who needed their treatment course adjusted and for that, cognition and mobility were the most important considerations. She called for a specific Oncology Geriatric Assessment.

Dr. Liang-Kung Chen from Taipei presented on how frailty might be taken into account in older patients treated for cardio-metabolic diseases. He noted that frailty and all cardio-metabolic diseases occur quite often, in the range of 25%–50%, and that frailty influences the outcome of the disease. For example, in chronic kidney disease, the presence of frailty, measured using the frailty phenotype, was as powerful as the presence of microalbuminaria in predicting adverse outcomes.

He proposed that adding frailty to risk scoring in cardio-metabolic disease (where such risk stratification is routine) could be beneficial. He noted further that ACE-Inhibitors, already a mainstay in cardio metabolic diseases, may offer independent benefit in frailty,[25] although negative trials are also present,[26] and, in general, neither case of ACE inhibitors nor statins is associated, on a population basis, with less mobility impairment.[27] Further protein supplementation might also be beneficial in both frailty and cardio-metabolic diseases, as might exercise.

CONCLUSION

To promote access to innovation and clinical research for frail old persons are worthy goals and important challenges. Whether they will be helped or harmed by coming rapidly to an international consensus definition of frailty is a matter on which intelligent people of goodwill will disagree: one person's instinct to avoid premature specification will be another's desire for letting the perfect be the enemy of the good. In the absence of a single consensus definition, it will be important for researchers to specify

exactly which approach they used, and ideally to use more than one approach.

The conference heard something approaching a consensus on the clinical need for a rapid screening measure for frailty and a more detailed assessment for those who screen positive. There is no consensus on what would constitute an ideal screening test (e.g., self-report versus performance measures, or some combination), only that it be short. Even so, there is a rich literature on how to screen for any condition, and the frailty community likely would benefit for the standard, formal assessments for when and how to screen (and how to compare screening with case findings).[28]

The conference attendees were also reminded of the rationale to understand frailty. It offers a means of understanding heterogeneity in relation to age, so that age alone is not used as a means to stratify risk. What is more is the discipline introduced by understanding frailty. To do so requires clinicians to look at patients as whole people and not just as single illnesses. An urgent need now is to move more frailty studies to the clinical domains. This is where the need is, and this is where the clinical and scientific communities can leverage the fairly limited resource of frailty researchers by partnering with other clinical studies across a full range of medical and surgical subspecialties. Likewise, primary intervention studies (directed at frailty itself) are needed, so that we know what helps and what harms in frailty. The problem facing all health-care systems for ageing populations is not the burden of single illnesses. Rather it is that these illnesses are occurring in people with many other things wrong, yet people are being treated by health-care systems designed for people who only have one illness active at a time. This is a worthy challenge for geriatricians, requiring as it does the needs for scholarship, patient-centered care, and advocacy.

That is why the authors strongly believe that Canadian and international geriatric and gerontological societies need to call for the development of a research strategy, from cell to society, on frailty. For this to happen, health research funding agencies must invest in targeted research programs.

ACKNOWLEDGEMENTS

Kenneth Rockwood is supported by the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research. The work reported here was funded by the Fountain Innovation Fund of the Queen Elizabeth II Health Sciences Foundation, and by operating grants from the Canadian Institutes of Health Research, including these now held: MOP-62823; MOP-150940 and MOP-61270. Howard Bergman receives career funding as the Dr. Joseph Kaufmann Professor of Geriatric Medicine at McGill University and the Jewish General Hospital. The work reported here is funded by the Canadian Initiative on Frailty and Aging, and a Canadian Institutes of Health Research Team Grant on Frailty and Ageing.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

REFERENCES

1. Bergman H, Ferrucci L, Guralnik J, *et al*. Frailty, an emerging research and clinical paradigm: issues and controversies. *J Gerontol Biol Sci Med Sci*. 2007;62A(7):731–37.
2. Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol Biol Sci Med Sci*. 2001;56(3):146–57.
3. Grady D, Berkowitz S. Why is a good clinical prediction rule so hard to find? *Arch Inter Med*. 2011;171(19):1701–02.
4. Sourial N, Bergman H, Karunananthan S, *et al*. Contribution of frailty markers in explaining differences among individuals in five samples of older persons. *J Gerontol Biol Sci Med Sci*. [Epub ahead of print]
5. Carter CS, Sonntag WE, Onder G, *et al*. Physical performance and longevity in aged rats. *J Gerontol A Biol Sci Med Sci*. 2002;57(5):B193–97.
6. Avila-Funes JA, Helmer C, Amieva H, *et al*. Frailty among community-dwelling elderly people in France: the three-city study. *J Gerontol A Biol Sci Med Sci*. 2008;63(10):1089–96.
7. Seeman TE, Singer BH, Rowe JW, *et al*. Price of adaptation—allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med*. 1997;157(19):2259–68.
8. Xue QL, Fried LP, Glass Ta, *et al*. Life-space constriction, development of frailty, and the competing risk of mortality: the Women's Health and Aging Study I. *Am J Epidemiol*. 2008;167(2):240–48.
9. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Scientific World J*. 2001;1:323–36.
10. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med*. 2011;27(1):17–26.
11. Rockwood K, Mitnitski A. How might deficit accumulation give rise to frailty? *J Aging Frailty*. 2012;1(1):8–12.
12. Parks RJ, Fares E, MacDonald JK, *et al*. A procedure for creating a frailty index based on deficit accumulation in aging mice. *J Gerontol A Biol Sci Med Sci*. 2011. [Published online] doi: 10.1093/gerona/glr193.
13. J Shi, X Song, P Yu, *et al*. Analysis of frailty and survival from late middle age in the Beijing Longitudinal Study of Aging. *BMC Geriatrics*. 2011;11(1):17.
14. Heppner HJ, Bauer JM, Sieber CC, *et al*. Laboratory aspects relating to the detection and prevention of frailty. *Int J Prev Med*. 2010;1(3):149–57.
15. Bauer JM, Sieber CC. Sarcopenia and frailty: a clinician's controversial point of view. *Exp Gerontol*. 2008;43(7):674–78.
16. Ferrucci L, Penninx BW, Volpato S, *et al*. 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(12):1947–54.
17. Bruunsgaard H, Bjerregaard E, Schroll M, *et al*. Muscle strength after resistance training is inversely correlated with baseline levels of soluble tumor necrosis factor receptors in the oldest old. *J Am Geriatr Soc*. 2004;52(2):237–41.
18. Ensrud KE, Blackwell TL, Cauley JA, *et al*. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc*. 2011;59(1):101–06.
19. Evans WJ, Morley JE, Argilés J, *et al*. Cachexia: a new definition. *Clin Nutr*. 2008;27(6):793–99.
20. Inouye SK, Studenski S, Tinetti ME, *et al*. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007;55(5):780–91.
21. Ensrud KE, Ewing SK, Taylor BC, *et al*. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med*. 2008;168(4):382–89.
22. Hirdes JP, Ljunggren G, Morris JN, *et al*. Reliability of the interRAI suite of assessment instruments: a 12-country study of an integrated health information system. *BMC Health Serv Res*. 2008; 8: 277. Available from: tp://www.biomedcentral.com/1472-6963/8/277
23. Puts M, Monette J, Girre V, *et al*. Are frailty markers useful for predicting treatment toxicity and mortality in older newly diagnosed cancer patients? Results from a prospective pilot study. *Crit Rev Oncol Hematol*. 2011;78(2):138–49.
24. Makary MA, Segev DL, Pronovost PJ, *et al*. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg*. 2010;210(6):901–08.
25. Sumukadas D, Witham MD, Struthers AD, *et al*. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ*. 2007;177(8):867–74.
26. Morley JE. Developing novel therapeutic approaches to frailty. *Curr Pharm Des*. 2009;15(29):3384–95.
27. Gray SL, Boudreau AB, Newman SA, *et al*. Angiotensin-converting enzyme inhibitor and statin use and incident mobility limitation in community-dwelling older adults: the health, aging and body composition study. *J Am Geriatr Soc*. 2011;59(12):2226–32.
28. Stephan BC, Kurth T, Matthews FE, *et al*. Dementia risk prediction in the population: are screening models accurate? *Nat Rev Neurol*. 2010;6(6):318–26.

Correspondence to: Kenneth Rockwood, MD, FRCPC, FRCP, FCAHS, Department of Medicine (Geriatric Medicine & Neurology), Dalhousie University, 6299 South Street, Halifax, NS B3H 3J5, Canada
E-mail: Kenneth.rockwood@dal.ca