

## Unconventional Views of Frailty

### Special Article

# Frailty: An Emerging Research and Clinical Paradigm—Issues and Controversies

Howard Bergman,<sup>1</sup> Luigi Ferrucci,<sup>2</sup> Jack Guralnik,<sup>3</sup> David B. Hogan,<sup>4</sup> Silvia Hummel,<sup>5</sup>  
Sathya Karunanathan,<sup>5</sup> and Christina Wolfson<sup>6</sup>

<sup>1</sup>Division of Geriatric Medicine, Jewish General Hospital, McGill University, Montreal, Quebec, Canada.

<sup>2</sup>Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.

<sup>3</sup>Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland.

<sup>4</sup>Division of Geriatric Medicine, University of Calgary, Alberta, Canada.

<sup>5</sup>Canadian Initiative on Frailty and Aging, Solidage Research Group, McGill/Université de Montreal/  
Jewish General Hospital, Quebec, Canada.

<sup>6</sup>Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada.

Clinicians and researchers have shown increasing interest in frailty. Yet, there is still considerable uncertainty regarding the concept and its definition. In this article, we present perspectives on key issues and controversies discussed by scientists from 13 different countries, representing a diverse range of disciplines, at the 2006 Second International Working Meeting on Frailty and Aging. The following fundamental questions are discussed: What is the distinction, if any, between frailty and aging? What is its relationship with chronic disease? Is frailty a syndrome or a series of age-related impairments that predict adverse outcomes? What are the critical domains in its operational definition? Is frailty a useful concept? The implications of different models and approaches are examined. Although consensus has yet to be attained, work accomplished to date has opened exciting new horizons. The article concludes with suggested directions for future research.

**F**RILITY is “one of those complex terms . . . with multiple and slippery meanings” (1). Notwithstanding uncertainty about its definition, frailty has attracted increasing attention in the medical literature (2) and was recently the subject of an article in the *New York Times* (3).

Clinicians generally agree that frailty is a useful concept. In a survey of 356 Canadian health care professionals, administrators, and researchers, two thirds felt that frailty was a useful term, incorporating three qualities: a state of risk or vulnerability; a precarious balance between demands and capacity to cope; and impending or current disability (4). According to another survey of 62 American geriatricians (5), most felt that disability and frailty differed. More than half cited the following as features of frailty: undernutrition, dependence, prolonged bed rest, pressure ulcers, gait disorders, generalized weakness, extreme old age, weight loss, anorexia, fear of falling, dementia, hip fracture, delirium, confusion, going outdoors infrequently, and polypharmacy. In focus groups, older patients and their caregivers emphasized emotional and social domains of frailty, in addition to the physical ones (6).

Researchers have shown increasing interest in frailty. The term “frail elderly” has been a Medline Medical Subject Heading (MeSH) term since 1991 and is defined as “older adults or aged individuals who are lacking in general

strength and are unusually susceptible to disease or to other infirmity.” The number of publications with the “frail elderly” subheading has increased exponentially over the last 30 years (7).

Both clinicians and researchers should realize that there is still considerable uncertainty around the concept of frailty. Conflicting ideas abound on the definition of frailty, what criteria should be used for its recognition, and its relationships with aging, disability, and chronic disease (5,7). In this article, we present perspectives on key issues and controversies discussed by scientists from 13 different countries, representing a diverse range of disciplines, at the Second International Working Meeting on Frailty and Aging held in Montreal in March 2006. The objectives of the meeting were to advance our understanding of frailty through a multidisciplinary perspective, to identify a series of cogent research questions regarding frailty, and to establish mechanisms for collaboration among investigators. This meeting builds upon the First International Working Meeting held in 2003, as well as on the 2004 American Geriatrics Society/National Institute on Aging (AGS/NIA) Conference on a Research Agenda on Frailty in Older Adults (8).

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 (9–11). The main consequence is an increased risk for multiple adverse health-related outcomes (9,12–14). Frailty and disability, while related, are distinct concepts (5). Although there does remain overlap between frailty and both instrumental activities of daily living (IADL) and mobility disability, researchers have, for the most part, disentangled frailty from disability in basic activities of daily living (ADL) (9,15).

Although agreement on the main features of frailty is a good starting point, this is far from establishing a comprehensive definition of frailty, and says almost nothing about its unique characteristics, causes, and clinical course. The contrasting viewpoints about the nature of frailty are spread along a continuum. At one end, frailty is interpreted as accelerated aging (16). At the other, frailty is conceptualized as an entity with its own distinct pathophysiology (17).

The following fundamental questions remain unanswered and were discussed at the meeting: What is the distinction, if any, between frailty and aging? What is its relationship with chronic disease? Is frailty a syndrome or a series of age-related impairments that predict adverse outcomes? What are the critical domains that should be included in its operational definition? How can it be measured? Is frailty a useful concept?

#### WHAT IS THE DISTINCTION, IF ANY, BETWEEN FRAILTY AND AGING?

Many of the attributes of frailty also apply to the aging process—so much so that a clear-cut distinction between aging and frailty is likely impossible. As people age, they accumulate impairments in multiple physiological systems and become increasingly vulnerable to adverse outcomes. This process of vulnerability and decline is inextricably linked to the aging process (5,18–20). Studies have shown that some degree of functional loss is inevitable in very old age (21,22). For instance, almost all centenarians have at least some functional deficits. None of the 138 centenarians evaluated in the Sardinia Study of Extreme Longevity (AKEntAnnos) had the maximum possible score on a standard performance test of lower extremity function (22). If frailty is simply the cumulative impact of age-related physiological changes and subclinical or clinical pathology, frailty would be essentially synonymous with these existing concepts and of questionable added value.

Nevertheless, the conceptualization of frailty may help in understanding the heterogeneity of functional decline observed with chronological aging. Chronological age alone is only a rough proxy of a person's vulnerability to adverse outcomes. Some people appear to be frail (however defined) at age 70 years, whereas others only reach this state in their 90s. If the concept of frailty allows a more direct quantification of vulnerability, then it has many potential applications in gerontological research and geriatric practice. Varying susceptibility may result from genetic traits and behavioral, environmental, and social risk factors. Some studies have reported that a measure of frailty that incorporates a diverse range of deficits including functional limitations, morbidity, psychosocial status, and cognitive ability is a better predictor of autonomy, institutionalization, and mortality than is chronological age alone (23,24).

In contrast, other studies suggest that some or all the manifestations of frailty are caused by an underlying process, separate from aging, but most likely to develop and progress with aging (25–27). The proposed mechanism leads to multisystem damage that tends to emerge as a cluster of symptoms and impairments that can be identified as part of a syndrome. Elements of the syndrome are linked in a pathophysiological chain that generates a downward spiral, and also serve as criteria for its diagnosis. Identification of the underlying process may offer the opportunity to intervene, by altering its course (17).

#### WHAT IS THE RELATIONSHIP BETWEEN FRAILTY AND CHRONIC DISEASE?

The relationship between frailty and chronic disease(s) is complex and poorly understood. In one study, only 7% of older persons categorized as frail had none of the nine most common chronic diseases whereas > 90% of those with two diseases or more were not frail (9). The terms “primary” and “secondary” frailty have been used to refer to frailty in the absence or presence of chronic diseases, respectively (17). Whether such a distinction is important for research or clinical practice is uncertain, as the number of individuals with primary frailty is probably very small. Perhaps more important is that the development of acute and chronic disease can precipitate frailty because they require the organism to mobilize available resources with the potential consequence of exhausting the reserve function of organ systems. Accordingly, most frail persons *do* have chronic disease(s). There is a statistically significant trend of an increasing prevalence of frailty in persons with more diseases (9). In advanced stages of many conditions such as severe congestive heart failure or advanced renal failure, the development of the characteristics of frailty is virtually an inevitable outcome of the disease (28). In these persons, sorting out disease from frailty may be possible only at an early stage if at all.

Certain conditions (such as depression and obesity) may share some of the same characteristics as frailty, leading to the potential for misclassification. When persons with depression or obesity have symptoms that meet the criteria for frailty it is difficult to know if they are truly frail. Older persons with cardiovascular disease (28), renal impairment (29), stroke, hip and/or knee osteoarthritis, and depression are significantly more likely to be classified as frail than are persons without these conditions, even after adjusting for age and sex. Elucidating the relationship between frailty and disease is likely to prove difficult.

If frailty results from a defect in some critical homeostatic mechanism, it is possible that this defect will also increase the general susceptibility to disease. This mechanism may explain why the co-occurrence of multiple chronic diseases in older persons is greater than expected by chance alone. This finding is consistent with either frailty and chronic disease sharing the same root causes or frailty as a homeostatic dysregulation *causing* certain individuals to be more susceptible to disease.

Another possibility is that frailty is merely the manifestation of clinical and subclinical or undiagnosed chronic

disease, and that frailty in the absence of chronic disease does not exist. Frailty occurring among persons without known chronic disease might be explained by the presence of either subclinical or undiagnosed disease (or conditions) (28).

Whether frailty is a direct consequence of chronic diseases cannot be definitively refuted, but several lines of evidence are inconsistent with this supposition. Only a small proportion of persons with at least two chronic diseases are frail, and some older persons with little or no disease show the classic signs of frailty (9). Older individuals unable to cope with stress when challenged (e.g., surgery, chemotherapy, other aggressive therapeutic procedures) cannot be easily identified by their presenting baseline clinical characteristics. Finally, studies have demonstrated that the assessment of disease status is a poor marker of health status in older individuals, even when indicators of disease severity are considered (30).

### IS FRAILITY A SYNDROME?

A medical syndrome has been defined as “the aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease” (31). A classical example is Cushing’s syndrome, where the disruption of a single physiological process (excessive cortisol secretion) results in multiple clinical manifestations. In geriatrics, however, the term syndrome has commonly been used to indicate the “accumulated effect of impairments in multiple domains” that together result in a particular adverse outcome (32,33). Typical examples are falls and incontinence.

In keeping with this interpretation of a “geriatric syndrome,” one group of researchers has proposed that frailty is a measure of the number of age-related deficits that predicts multiple adverse outcomes. These researchers have demonstrated that the accumulation of a set of age-related deficits can predict mortality and institutionalization independent of the nature and precise number of deficits, assuming that a large enough number of deficits is assessed (34,35). They propose that these data support the hypothesis that physiological and behavioral traits that are affected by the aging process are highly correlated and together could represent the syndrome of frailty. This operational definition of frailty has appealing conceptual and computational properties. A drawback of this approach is that the large number of deficits that have to be assessed make it impractical for use, at least in clinical practice. In addition, little information is provided on the specific factors leading to the adverse outcomes and what the underlying pathophysiology may be.

Other researchers have suggested that frailty may be a medical syndrome (like Cushing’s), with a specific pathophysiological process underlying and linking the different manifestations. Factors thought to be important components of frailty have been linked through already established pairwise associations to envision a hypothetical cycle of frailty (9). It is hypothesized that there is an underlying biological process, which is not yet well understood, that drives or precipitates this cycle.

A recent study evaluated the construct validity of the five frailty measures originally studied in the Cardiovascular Health Study (CHS). Findings showed that these criteria aggregate in a pattern consistent with a medical syndrome (12). However, as pointed out by the authors of the study, several questions regarding the construct validity of the frailty syndrome have yet to be addressed. For example, certain measures included in the CHS definition of frailty may be in the causal pathway to declining physical function. This may partially explain why frailty predicts adverse outcomes. Furthermore, there is a need to determine if the aggregate of the frailty measures adds predictive value above the independent contributions of individual criteria (12).

### WHAT ARE THE CRITICAL DOMAINS OF FRAILITY?

The conceptual model of frailty that is adopted will affect which characteristics are selected as components and diagnostic criteria. If frailty is viewed as a medical syndrome, all the components must have a plausible link to the underlying biological pathway. Widely used criteria include shrinking (weight loss, sarcopenia), weakness, exhaustion (poor endurance), slowness, and low activity. Although this operationalization of frailty fits a coherent model and has proven predictive validity, questions have been raised about specific criteria. For example, studies indicate that obese people are a substantial subset of the frail population (14,36,37), and therefore utilizing weight loss as a measure may underestimate the prevalence of frailty in the obese.

There is also a strong rationale for the inclusion of additional components such as cognition and mood, which may be affected by the same biological processes that lead to the manifestations of “physical” frailty. For example, chronic inflammation is believed to play a central role in the pathogenesis of frailty (25,38). Increased levels of inflammatory cytokines are also associated with both a lower Mini-Mental State Examination score (39) and an increased risk of developing dementia (40,41). Furthermore, in longitudinal studies, physical performance measures (i.e., slow motor performance and walking speed) independently predict the time to onset of persistent cognitive impairment (42,43). Specific aspects of cognitive decline such as psychomotor speed have been associated with frailty. Although there may be a common biological basis for frailty, there may be multiple pathways for its development. The trajectory of frailty that begins with cognitive decline may differ from the trajectory that begins with physical components.

Clinicians and older persons and their families often perceive aspects of mood, such as apathy, as the result of physical frailty (6). However, the relationship is most likely bidirectional. Depressive symptoms predict declines in physical function (standing balance, walking speed, chair rises) (44,45) and older persons with impaired physical function are more likely to be depressed or develop depression. Interestingly, a variety of cytokine abnormalities seen in patients with major depression are similar to those seen in frail older persons (46). It is also noteworthy that, although depression was not included as one of the five characteristics in a widely recognized model of frailty, items

from a depression scale were used to measure one of the characteristics: exhaustion (9,15).

Those who think that “the more things someone has wrong with them, the more likely that person is to be frail” are less concerned about the biological relationship between the proposed components. They therefore pull together variables as different as sensory impairments, poor social conditions, chronic diseases, and disability in the same model. The resulting measure of frailty is an indicator of an older person’s global health status (13,35).

#### HOW CAN FRAILTY BE MEASURED IN A CLINICAL AND RESEARCH CONTEXT?

For the concept of frailty to be of practical utility, its theoretical conceptualization must be translatable into an operational definition (19). In a traditional medical syndrome, most symptoms will be present in affected patients. To avoid overdiagnosing the syndrome, a person with only one or two of the symptoms, which may have arisen from other causes, would not be considered to have it (though they may be considered at risk for its development). The underlying assumption of an operational definition based on symptoms is that the domains that are used for the diagnosis do not represent all possible manifestations of the syndrome, but rather, they are the important domains that can be easily and reliably measured. Because all the true components of the pathologic process are associated with each other, it is not necessary to require the presence of all of them to make the diagnosis.

One consideration in the determination of frailty is whether static criteria, measured at a single point in time, are appropriate for a condition that, by definition, is a dynamic process, involving change over time. One study comparing static and dynamic measures of frailty found the former to be more predictive of functional decline (47). However, another recent study demonstrated that older persons with even a small increase in gait speed (e.g., 0.1 m/s) experienced a lower mortality rate than did those whose gait speed remained stable, whereas those whose gait speed slowed down had the highest mortality rate. This finding suggests that older persons who retain the capacity to improve still have considerable reserves and are therefore not frail (or “less frail”) (48).

When considering research findings, the wide variability in the interpretation of the nature of frailty needs to be recognized. For example, the prevalence of frailty in a sample of 125 elderly people ranged from 33% to 88%, depending on the criteria used (49).

#### THE LIFE COURSE APPROACH

In a life course approach to the epidemiology of chronic conditions, biological, behavioral, and environmental risk factors in early, adult, and late life are all felt to contribute to health in old age (50). For example, it is increasingly appreciated that the likelihood of developing certain chronic conditions (e.g., type 2 diabetes) depends in part on environmental influences and behaviors in early life (51). Thus, it is conceivable that a stimulus at a critical or sensitive

period in early life may be associated with the risk of developing disability and/or frailty in old age (52,53).

There is evidence suggesting that midlife depression, self-rated health, physical activity, chronic medical conditions, and chronic symptoms, alcohol intake, and body mass index predict the development of frailty later in life (54). The Medical Research Council National Survey of Health & Development (the 1946 birth cohort) and the Hertfordshire cohort study both found a direct relationship between birth weight and grip strength in middle age (55,56). Analysis of data from the 1946 birth cohort has shown that postnatal growth and childhood development of motor and cognitive abilities are also associated with midlife performance (standing balance, chair rise time, grip strength) (57,58). Exposure to chronic stress in early life and the cumulative exposure to infections may play a role in the development of frailty. In this cohort, children raised in households supported by manual labor were more likely than others to have poor physical performance scores at age 53. Conversely, those raised by more highly educated mothers were much more likely to be in the top 10% of performance (59).

#### IS FRAILTY A USEFUL CONCEPT?

Frailty provides a conceptual basis for moving away from organ- and disease-based approaches toward a health-based, integrative one. Frailty may represent a key approach to improving the clinical care provided for at least a subset of older persons.

Health status in older persons has typically been described with measures of morbidity, mental status, and/or disability in ADL. Using this approach, clinicians may overlook older persons who are functionally independent with apparently normal cognitive function, even if they have identifiable frailty markers and are highly vulnerable for adverse health outcomes and increased utilization of health services. Frailty may provide new opportunities for prevention, health promotion, and improved care at both the population and clinical level by improving our understanding of the heterogeneity of vulnerability in the older population.

The potential to identify older persons at risk of disability may lead to exciting applications. For example, exercise and rehabilitation have the potential to improve functional state (60). Compared to their nonfrail counterparts with the same conditions, it has been suggested that frail older persons with cancer undergoing chemotherapy or with congestive heart failure are more vulnerable to developing complications and adverse outcomes from both their underlying disease and the treatment prescribed for it (61). This may be true as well for frail patients who suffer major trauma (e.g., hip fractures), undergo major surgical procedures, or are admitted to hospital. The capacity to identify these frail older persons should not lead to denying treatment but rather to modulating the interventions proposed so as to prevent or minimize complications.

Some of the recent literature on the metabolic syndrome provides elements of discussion that are relevant for frailty. The metabolic syndrome is postulated to be the result of genetic, hormonal, and lifestyle factors and has been defined



not as a disease but as a clinical entity with a clustering of metabolic abnormalities that are each associated with the risk of coronary heart disease, stroke, and cardiovascular mortality. It is held that this clustering is associated with a risk greater than the additive risk conferred by the individual components (62).

More recently, there has been a vehement, ongoing debate in the literature on whether the metabolic syndrome is a true clinical entity. Grundy (63) maintains that the metabolic syndrome is “a powerful hypothesis that unifies the metabolic factors underlying the development of both atherosclerotic cardiovascular disease and diabetes” that facilitates the detection and clinical management of patients despite the variable clinical presentation. In contrast, in a recent editorial, Reaven (64), who was pivotal in the development of the metabolic syndrome concept, strongly argues that defining the metabolic syndrome does not in fact bring much in the way of advancing our understanding of the pathophysiology or clinical utility. He holds that it may lead to withholding treatment to individuals with fewer than three of the five arbitrarily chosen diagnostic criteria.

This same controversy may apply to frailty. There is a danger of missing the trees for the forest. Focusing on frailty may lead to denying treatment to older persons affected by only one of the frailty components (i.e., poor muscle strength), which may in itself be an important predictor for adverse outcomes. At the same time, individuals with diseases that mimic the features of frailty may be erroneously considered to be frail. Ultimately, it may turn out that a single measurement such as grip strength or gait speed may be an adequate, practical screen for vulnerability in non-disabled persons and that the complexity of diagnosing frailty may be unnecessary.

In addition, the inappropriate “labeling” of older persons as frail can alter their self-concept and the way others view them. This may have deleterious effects on their physical (65) and cognitive performance (66) and affect health-related decision making (67).

# MOVING FORWARD ON FRAILITY RESEARCH

The research agenda is full of exciting opportunities. The 2004 AGS/NIA conference proposed a detailed research agenda (8). Other research programs and projects have been proposed (12,19,68,69). Nevertheless, the identification of priorities is necessarily arbitrary and beyond the scope of our meeting and this article. However, several key research issues and approaches emerged from the discussions at the meeting.

An operational definition of frailty should further our understanding of its underlying biology and pathophysiology to identify potential targets for prevention or treatment. Ultimately, to better understand the molecular mechanisms that lead to frailty we need to develop animal models and perform small-scale intervention studies testing specific hypotheses.

An operational definition of frailty should also further our understanding of the dynamic relationship between frailty, its biological basis, impairments, and longitudinal changes in physical function as well as the contribution of social,

environmental, and behavioral factors. Until now, the hypotheses that frailty is a syndrome with its own pathophysiology or a cumulative index of impairments that describes biological aging rather than chronological age have been examined in longitudinal epidemiological studies designed for other purposes, at a time when frailty had not been fully conceptualized. Although it is still valuable to explore data from completed studies, it is now time to design new cohort studies that put the frailty concept at the center of their scientific paradigm. In these prospective cohort studies, frailty domains and their aggregation in syndromic algorithms should be hypothesized a priori. Research on diagnostic criteria should examine if and how the risk of adverse outcomes associated with the cluster of components is greater than that of any single component or the additive risk associated with the combination of components (12,70).

Optimization of treatment and management of chronic diseases may be different in frail and nonfrail individuals. Diseases such as cancer or congestive heart failure or treatments such as chemotherapy and surgery offer the opportunity through observational clinical research to study if and how frail individuals are in fact more vulnerable to adverse outcomes of these conditions and treatments than are nonfrail individuals. The results of clinical trials testing the effectiveness of treatment for these and other medical conditions cannot be extended to older frail individuals unless frail individuals are included in the trials (68).

To bring together the original contributions of the different perspectives and methodologies, further progress will require the implementation of collaborative networks and interdisciplinary research projects.

# Conclusion

The work done to date on frailty has opened exciting new horizons. It has the potential of furthering our understanding of the aging process and offers the hope that we can identify vulnerable older adults with the goal to prevent or delay adverse consequences. More work is necessary to advance our understanding of the difference between frailty and aging, its relationship to chronic disease, its determinants and pathophysiology, and the identification of its core components. At this time, it is too early to “close the discussion” on the issue of whether frailty is a medical syndrome with its own pathophysiology. Despite the debate on the exact nature of frailty, there is no disagreement on its catastrophic impact on older individuals, their families (particularly those involved in providing support to the older individual), and on society as a whole. Ultimately, work on frailty will only be relevant if effective health promotion, prevention, treatment, rehabilitation, and care interventions can be identified.

# ACKNOWLEDGMENTS

The Second International Working Meeting on Frailty and Aging was supported by the Max Bell Foundation; Quebec Network for Research on Aging (Fonds de la recherche en santé du Québec); Institute of Aging-Canadian Institutes of Health Research (CIHR); CIHR International Opportunity Program-Development Grant 68739; the Gustav Levinschi Foundation; and The Dr. Joseph Kaufmann Chair in Geriatric Medicine, McGill University.

We thank Rebecca Rupp for her invaluable contribution to the organization of the meeting.

The following scientists participated in the Second International Working Meeting on Frailty and Aging (in no particular order): Marcel Arcand, Tamas Fulop, Réjean Hébert, Hélène Payette, *Université de Sherbrooke, Sherbrooke, Canada*; Audrey Attia, Michèle Monette, *Solidage Research Group, Montreal, Canada*; Chantal Autexier, Howard Bergman, Martin Chasen, Stéphanie Chevalier, Liette Lapointe, Johanne Monette, José Morais, Martine Puts, Jaqueline Quail, Sandra Richardson, Ernesto Schiffrin, Doreen Wan-Chow-Wah, Deborah Weiss, Christina Wolfson, Bin Zhu, *McGill University, Montreal, Canada*; Karen Bandeen-Roche, *Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland*; Benedetta Bartali, *Cornell University, Ithaca, New York*; François Béland, Pierrette Gaudreau, *Université de Montréal, Montreal, Canada*; David Bennett, *Rush University Medical Center, Chicago, Illinois*; Netta Bentur, Jenny Brodsky, *Myers-JDC-Brookdale Institute, Jerusalem, Israel*; Christophe Büla, *Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*; A. Mark Clarfield, *Ben-Gurion University, Beersheva, Israel*; Kenneth Covinsky, *University of California, San Francisco, San Francisco, California*; Dorly J. H. Deeg, *Vrije Universiteit Medical Centre, Amsterdam, The Netherlands*; Geoff Fennie, Gary Naglie, *University of Toronto, Toronto, Canada*; Luigi Ferrucci, Jack M. Guralnik, *National Institute on Aging, Baltimore, Maryland*; Linda P. Fried, Jeremy Walston, *Johns Hopkins Medical Institutions, Baltimore, Maryland*; David Gass, Susan Kirkland, Christopher MacKnight, Arnold Mitnitski, Kenneth Rockwood, *Dalhousie University, Halifax, Canada*; Thomas Gill, *Yale University School of Medicine, New Haven, Connecticut*; J. Alberto Àvila-Funes, Luis Miguel Gutiérrez-Robledo, *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*; Klaus Hauer, *Universität Heidelberg, Heidelberg, Germany*; Russell T. Hepple, David Hogan, Colleen J. Maxwell, Heidi Schmaltz, *University of Calgary, Calgary, Canada*; François Herrmann, Jean-Pierre Michel, *Geneva University Hospitals, Geneva, Switzerland*; Silvia Hummel, Sathya Karunanathan, Nadia Sourial, *Canadian Initiative on Frailty and Aging, Montreal, Canada*; Koichi Kozaki, Kenji Toba, *Kyorin University School of Medicine, Tokyo, Japan*; Diana Kuh, *Royal Free and University College London Medical School, United Kingdom*; Lewis A. Lipsitz, *Harvard Medical School, Boston, Massachusetts*; Anne Martin-Matthews, *Institute of Aging, Canadian Institutes of Health Research, Ottawa, Canada*; Jiro Okochi, *Kyushu University, Fukuoka, Japan*; Ángel Otero, *Universidad Autónoma de Madrid, Madrid, Spain*; Fred Paccaud, Brigitte Santos-Eggimann, *Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland*; Christopher Patterson, Parminder Raina, *McMaster University, Hamilton, Canada*; Margaret Penning, *University of Victoria, Victoria, Canada*; Frédérique Retornaz, *Hopital Sainte Marguerite, Marseille, France*; Darryl B. Rolfson, *University of Alberta, Edmonton, Canada*; Brandi Row, *Sunnybrook & Women's College, Toronto, Canada*; Olivier Saint-Jean, *Hôpital Européen Georges Pompidou, Paris, France*; Catherine A. Sarkisian, *University of California, Los Angeles, Los Angeles, California*; Shelley Sternberg, *Maccabi Health Systems, Jerusalem, Israel*; Stephanie Studenski, *University of Pittsburgh, Pittsburgh, Pennsylvania*; René Verreault, *Université Laval, Quebec, Canada*; Chek Hooi Wong, *Singapore General Hospital, Singapore*.

#### CORRESPONDENCE

Address correspondence to Howard Bergman, MD, Division of Geriatric Medicine, Jewish General Hospital/McGill University, 3755 Côte-Ste-Catherine, Montreal, QC, Canada H3T 1E2. E-mail: howard.bergman@mcgill.ca

#### REFERENCES

- Kaufman SR. The social construction of frailty: an anthropological perspective. *J Aging Stud.* 1994;8:45–58.
- Swinne C, Cornette P, Schoevaerdts D, et al. Frailty in the medical literature. *Age Ageing.* 1998;27:411–413.
- Kolata G. Old but not frail: a matter of heart and head. *The New York Times.* October 5, 2006:A1.
- Kaethler Y, Molnar FJ, Mitchell SL, Soucie P, Man-Son-Hing M. Defining the concept of frailty: a survey of multi-disciplinary health professionals. *Geriatr Today.* 2003;6:26–31.
- Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol Biol Sci Med Sci.* 2004;59A:255–263.
- Studenski S, Hayes RP, Leibowitz RQ, et al. Clinical global impression of change in physical frailty: development of a measure based on clinical judgment. *J Am Geriatr Soc.* 2004;52:1560–1566.
- Hogan DB, MacKnight C, Bergman H. Models, definitions, and criteria of frailty. *Aging Clin Exp Res.* 2003;15(Suppl 3):1–29.
- Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc.* 2006;54:991–1001.
- Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Med Sci.* 2001;56A:M146–M156.
- Bortz WM. The physics of frailty. *J Am Geriatr Soc.* 1993;41:1004–1008.
- Lipsitz LA, Goldberger AL. Loss of ‘complexity’ and aging. Potential applications of fractals and chaos theory to senescence. *JAMA.* 1992;267:1806–1809.
- Bandeen-Roche K, Xue QL, Ferrucci L, et al. Phenotype of frailty: characterization in the Women’s Health and Aging Studies. *J Gerontol Biol Sci Med Sci.* 2006;61A:262–266.
- Mitnitski AB, Graham JJ, Mogilner AE, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr.* 2002;2:1–11.
- Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women’s Health Initiative Observational Study. *J Am Geriatr Soc.* 2005;53:1321–1330.
- Ottensbacher KJ, Ostir GV, Peek MK, Snih SA, Raji MA, Markides KS. Frailty in older Mexican Americans. *J Am Geriatr Soc.* 2005;53:1524–1531.
- Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The accumulation of deficits with age and possible invariants of aging. *ScientificWorldJournal.* 2002;2:1816–1822.
- Fried LP, Walston J. Frailty and failure to thrive. In: Hazzard WR, Blass JP, Halter JB, et al., eds. *Principles of Geriatric Medicine and Gerontology.* 5th Ed. New York: McGraw Hill; 2003:1487–1502.
- Izaks GJ, Westendorp RG. Ill or just old? Towards a conceptual framework of the relation between ageing and disease. *BMC Geriatr.* 2003;3:7.
- Rockwood K. What would make a definition of frailty successful? *Age Ageing.* 2005;34:432–434.
- Isaacs B, Gunn J, McKechnan A, McMillan I, Neville Y. The concept of pre-death. *Lancet.* 1971;1:1115–1118.
- Gondo Y, Hirose N, Arai Y, et al. Functional status of centenarians in Tokyo, Japan: developing better phenotypes of exceptional longevity. *J Gerontol Biol Sci Med Sci.* 2006;61A:305–310.
- Deiana L, Ferrucci L, Pes GM, et al. AKEntAnnos. The Sardinia Study of Extreme Longevity. *Aging (Milano).* 1999;11:142–149.
- Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. *J Am Geriatr Soc.* 2006;54:975–979.
- Schuermans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? *J Gerontol Biol Sci Med Sci.* 2004;59A:M962–M965.
- Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med.* 2002;162:2333–2341.
- Leng SX, Cappola AR, Andersen RE, et al. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. *Aging Clin Exp Res.* 2004;16:153–157.
- Buchner DM, Wagner EH. Preventing frail health. *Clin Geriatr Med.* 1992;8:1–17.
- Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol Med Sci.* 2001;56A:M158–M166.

29. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis*. 2004;43:861–867.
30. Hogan DB, Ebly EM, Fung TS. Disease, disability, and age in cognitively intact seniors: results from the Canadian Study of Health and Aging. *J Gerontol Med Sci*. 1999;54A:M77–M82.
31. *Stedman's Medical Dictionary*. 27th Ed. Philadelphia: Lippincott Williams & Wilkins; 2000.
32. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA*. 1995;273:1348–1353.
33. Flacker JM. What is a geriatric syndrome anyway? *J Am Geriatr Soc*. 2003;51:574–576.
34. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The mortality rate as a function of accumulated deficits in a frailty index. *Mech Ageing Dev*. 2002;123:1457–1460.
35. Mitnitski AB, Song X, Rockwood K. The estimation of relative fitness and frailty in community-dwelling older adults using self-report data. *J Gerontol Biol Sci Med Sci*. 2004;59A:M627–M632.
36. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc*. 2005;53:927–934.
37. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol (Oxf)*. 2005;63:403–411.
38. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc*. 2002;50:1268–1271.
39. Ravaglia G, Forti P, Maioli F, et al. Serum C-reactive protein and cognitive function in healthy elderly Italian community dwellers. *J Gerontol Biol Sci Med Sci*. 2005;60A:1017–1021.
40. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol*. 2004;61:668–672.
41. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc*. 2002;50:2041–2056.
42. Camicioli R, Howieson D, Oken B, Sexton G, Kaye J. Motor slowing precedes cognitive impairment in the oldest old. *Neurology*. 1998;50:1496–1498.
43. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol*. 2002;59:601–606.
44. Lenze EJ, Schulz R, Martire LM, et al. The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal findings from the Cardiovascular Health Study. *J Am Geriatr Soc*. 2005;53:569–575.
45. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA*. 1998;279:1720–1726.
46. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol*. 2004;19:397–403.
47. Puts MT, Lips P, Deeg DJ. Static and dynamic measures of frailty predicted decline in performance-based and self-reported physical functioning. *J Clin Epidemiol*. 2005;58:1188–1198.
48. Perera S, Studenski S, Chandler JM. Ability to improve physical performance predicts long-term survival. *Gerontology*. 2005;45(Suppl 2):331.
49. van Iersel MB, Rikkert MG. Frailty criteria give heterogeneous results when applied in clinical practice. *J Am Geriatr Soc*. 2006;54:728–729.
50. Ben Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002;31:285–293.
51. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. *Science*. 2004;305:1733–1736.
52. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr*. 2001;4:611–624.
53. Bergman H, Béland F, Karunanathan S, Hummel S, Hogan D, Wolfson C. Développement d'un cadre de travail pour comprendre et étudier la fragilité. *Gerontol Soc*. 2004;109:15–29.
54. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *J Gerontol Soc Sci*. 1998;53B:S9–S16.
55. Kuh D, Bassey J, Hardy R, Aihie SA, Wadsworth M, Cooper C. Birth weight, childhood size, and muscle strength in adult life: evidence from a birth cohort study. *Am J Epidemiol*. 2002;156:627–633.
56. Sayer AA, Syddall HE, Gilbody HJ, Dennison EM, Cooper C. Does sarcopenia originate in early life? Findings from the Hertfordshire cohort study. *J Gerontol Biol Sci Med Sci*. 2004;59A:930–934.
57. Kuh D, Hardy R, Butterworth S, et al. Developmental origins of midlife grip strength: findings from a birth cohort study. *J Gerontol Biol Sci Med Sci*. 2006;61A:702–706.
58. Kuh D, Hardy R, Butterworth S, et al. Developmental origins of midlife physical performance: evidence from a British birth cohort. *Am J Epidemiol*. 2006;164:110–121.
59. Guralnik JM, Butterworth S, Wadsworth ME, Kuh D. Childhood socioeconomic status predicts physical functioning a half century later. *J Gerontol Biol Sci Med Sci*. 2006;61A:694–701.
60. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med*. 2002;347:1068–1074.
61. Ferrucci L, Guralnik JM, Cavazzini C, et al. The frailty syndrome: a critical issue in geriatric oncology. *Crit Rev Oncol Hematol*. 2003;46:127–137.
62. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. 2004;110:1245–1250.
63. Grundy SM. Point: the metabolic syndrome still lives. *Clin Chem*. 2005;51:1352–1354.
64. Reaven GM. The metabolic syndrome: requiescat in pace. *Clin Chem*. 2005;51:931–938.
65. Hausdorff JM, Levy BR, Wei JY. The power of ageism on physical function of older persons: reversibility of age-related gait changes. *J Am Geriatr Soc*. 1999;47:1346–1349.
66. Levy B. Improving memory in old age through implicit self-stereotyping. *J Pers Soc Psychol*. 1996;71:1092–1107.
67. Levy B, Ashman O, Dror I. To be or not to be: the effects of aging stereotypes on the will to live. *Omega (Westport)*. 1999;40:409–420.
68. Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc*. 2004;52:625–634.
69. Ferrucci L, Mahallati A, Simonsick EM. Frailty and the foolishness of Eos. *J Gerontol Biol Sci Med Sci*. 2006;61A:260–261.
70. Bergman H, Wolfson C, Sourial N, et al. Frailty Data (FrData): examining candidate domains of frailty in the elderly. *Can J Geriatr*. 2006;9:70.

Received October 13, 2006

Accepted December 20, 2006

Decision Editor: Darryl Wieland, MD, MPH