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Frailty: A Review of the First Decade of Research

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Abstract

Frailty is an emerging geriatric syndrome that refers to a state of increased vulnerability to adverse events including mortality, morbidity, disability, hospitalization, and nursing home admission. Despite its long conceptual and operational history in research and publications, frailty and mechanisms of frailty development are still poorly understood. In this review, we describe a number of conceptual models—reliability, allostatic load, and complexity—that have been put forward to explain the dynamic nature of frailty. We illustrate a consolidated pathophysiological model of frailty, taking into consideration the large and exponentially growing body of studies regarding predictors, indicators, and outcomes of frailty. The model addresses cellular (e.g., oxidative damage and telomere length) and systemic mechanisms (e.g., endocrinal, inflammatory, coagulatory, and metabolic deficiencies) of frailty, moderating or risk factors (e.g., ethnicity, lifestyle, and comorbidities), and outcomes (morbidity, disability, and cognitive decline). Finally, we identify the weaknesses of traditional epidemiological approaches for studying complex phenomena related to frailty and propose areas for future methodological and physiological inquiry.

Keywords

frailty, biological mechanism, aging, review, methodological perspectives, longitudinal modeling, multilevel models

Advanced age is associated with an inevitable sequence of structural, functional, and physiological changes (e.g., decreased number of myocardial cells, decreased collagen levels, and reduced muscle mass). For some individuals, these changes are accentuated and lead to increased morbidity and mortality, whereas other older adults remain physically and functionally robust up to a fairly advanced age. In an attempt to understand the heterogeneous nature of human aging, researchers have turned to the concept of frailty. Frailty, as distinct from normal aging, usually refers to a state of increased vulnerability to external and internal stressors resulting from a significant reduction in physiological reserves (Fried et al., 2001; Lang, Michel, & Zekry, 2009). When exposed to environmental challenges, frail individuals demonstrate an increased risk of hospitalization, nursing home placement, and mortality compared with nonfrail older adults (Ensrud et al., 2007; Rockwood & Mitnitski, 2007).

In this article, we focus on conceptual models proposed to explain the dynamics and development of frailty. We elucidate pathophysiological changes that have been studied as etiological mechanisms of frailty. We also identify risk factors that initiate these pathophysiological changes, the downward spiral of events leading to frailty and its clinically relevant health outcomes. Finally, we graphically illustrate a framework for the development of frailty and its outcomes and point to directions for future research.

Operational Definition

Conceptual and operational definitions of frailty have transformed over time, culminating with the scientific recognition

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of the construct as a medical syndrome with important etiological, symptomatic, and pathophysiological considerations. The concept of frailty first appeared in the research literature in 1968, when O'Brien and colleagues, in a cross-sectional study of 48 community-dwelling older adults, outlined the gradual development of frailty as an excessive, disproportionate reaction of older adults to adverse events (O'Brien, Roberts, Brackenridge, & Lloyd, 1968). After this first publication, the concept of frailty rarely appeared in the medical literature until the late 1980s, when Winograd, Gerety, Brown, and Kolodny (1988) defined its first quantitative measurement. According to their operational definition, frail older adults had 1 or more of 15 common geriatric clinical conditions.

Fried and colleagues' (2001) introduction of a phenotypical (rule-based) operational definition of frailty based on a large sample of community-dwelling older adults participating in the Cardiovascular Health Study (CHS) initiated considerable progress in understanding and exploring the pathophysiology of frailty. They defined frailty as the display of three or more of five physiological deficits (muscle weakness, low gait speed, unintentional weight loss, exhaustion, and low physical activity). Findings from the CHS showed that frailty was independently associated with incident falls, worsened mobility, activities of daily living disability, incident hospitalization, and death. The Frailty Task Force of the American Geriatrics Society adopted Fried's working definition of frailty as its conventional operational definition (Lang et al., 2009).

Conceptual Models

Since frailty was operationalized, researchers have directed their efforts at uncovering its biological and physiological underpinnings, proposing reliability, allostatic load (AL), and complexity theories to explain the dynamic nature of frailty and its development.

Reliability Theory

Reliability theory argues that all living organisms inherently possess a limited number of redundant biological systems to maintain homeostasis. As one ages, there is an inevitable but gradual process of deficit accumulation (e.g., genetic damages, comorbidities, and stresses), which in turn leads to an exhaustion of available physiological reserves and increased mortality (Gavrilov & Gavrilova, 2001). This loss of system redundancy (i.e., decline in the number and function of homeostatic mechanisms) and the cumulative effect of cell loss over time have been observed in several biological studies (Andersen, Gundersen, & Pakkenberg, 2003; Leeuwenburgh, 2003; Wallace & Kelsey, 2010). Mitnitski, Mogilner, and Rockwood (2001) demonstrated the application of reliability theory in frailty research by operationalizing frailty as an accumulation of aging-associated deficits across multiple physiological systems. These researchers showed that the frailty index (FI)—based on a set of 20 symptoms, signs, and impairments—is a sensitive predictor of 5-year survival. This view of frailty in relation to deficit accumulation has been further validated internationally in several large-scale cohort studies (Goggins, Woo, Sham, & Ho, 2005; Kulminski, Ukraintseva, Akushevich, Arbeev, & Yashin, 2007; Rockwood, Andrew, & Mitnitski, 2007).

Allostatic Load

AL theory postulates that a critical mass of wear and tear processes across physiological systems affects biological equilibrium. Beyond a certain critical mass, an individual is at increased risk for adverse health outcomes (Seeman, McEwen, Rowe, & Singer, 2001). Szanton, Allen, Seplaki, Bandeen-Roche, and Fried (2009) have suggested an AL index including biomarkers of cardiovascular, metabolic, endocrine, and inflammatory regulatory systems as a preclinical marker of frailty. Findings of an association between AL and the frailty phenotype in longitudinal and cross-sectional studies suggest that the major regulatory systems represented in the AL index are linked to individual indicators of frailty. For example, a decline in muscle strength has been associated with inflammation (Schaap et al., 2009), and low energy levels have been linked to endocrine misbalance (Kop et al., 2002). On the multisystem level, among a large sample of older adults who were high functioning at baseline in the MacArthur Study of Successful Aging, higher levels of AL were associated with a greater incidence of frailty, after 3 years of follow-up (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009). Additional support for the linkage between AL and frailty came from a secondary analysis of a large cohort of aging participants in the Women's Health and Aging Study (WHAS; Fried et al., 2009). In that study, Fried and colleagues confirmed an association between the phenotype of frailty and a number of abnormal physiological systems, independent of specific system abnormalities. The authors also indicated that three systems functioning at an abnormal level emerged as a potential threshold for a critical mass of wear and tear processes.

Complexity Theory

Complexity theory draws attention to the dynamic interplay across regulatory systems that govern the homeostatic adaptive response to external and internal stressors. This theory focuses on both the quality of interactions among biological systems and the quantity of accumulated physiological abnormalities (Lipsitz, 2004). According to this theory, ''Deterioration of the complex network of interacting physiological signals . . . may compromise the capacity to mount compensatory physiological adaptations in response to stressors and lead to greater clinical vulnerability—or frailty'' (Chaves et al., 2008, p. 1699). Researchers have proposed a number of biological markers as surrogate measures for impaired physiological complexity. For example, heart rate variability, a natural fluctuation in the intervals between normal heartbeats based on autonomic nervous system inputs to the sinus node, reflects a continuous exchange of regulatory signals for maintaining cardiovascular

homeostasis. The approximate entropy for a heart rate (ApEnHR), a statistic that quantifies the regularity of heart rate fluctuations over time, has been found to correlate with older age (Beckers, Verheyden, & Aubert, 2006; Pikkujamsa et al., 1999) and greater morbidity and mortality (Makikallio et al., 2004; Tapanainen et al., 2002). Chaves and colleagues (2008) conducted a cross-sectional analysis of WHAS data aimed at testing the link between frailty and loss of physiological complexity, as indicated by low ApEnHR. They found that individuals who had lower ApEnHR were twice as likely to be diagnosed as frail as those without lower ApEnHR (odds ratio [OR] = 1.99, 95% confidence interval [CI] = [1.1, 3.7]).

Summary of Conceptual Models

Frailty is independently associated with an absolute number of impaired physiological systems; as more systems show abnormal function, frailty increases, and a dysregulation in a complex network of interaction occurs between its biological elements. Further research, though, is needed to determine the hierarchical, chronological, and causal sequence of physiological events that initiate the downward spiral of pathophysiological processes terminating with a state of increased vulnerability. An integrative model of frailty—one that incorporates both quantitative measurements (that estimate the number of systems functioning abnormally) and an assessment of the quality of interaction between two or more of its defining elements—may help close gaps among alternative conceptual models.

Pathophysiological Mechanisms

Level I—Cellular Changes

Although researchers have identified no specific cause for frailty, efforts to outline its molecular and systemic mechanisms are ongoing. At the cellular level, cumulative oxidative damage has received scientific support as one of the plausible causal pathways leading to frailty (Walston, 2004). The loss of telomeres, with resultant alterations in cell division and protein production, has been strongly associated with physiological decline in older adults. Cawthon, Smith, O'Brien, Sivatchenko, and Kerber (2003) reported that the mortality rate of aging individuals with shorter telomeres was nearly twice that of those with longer telomeres. However, a later cross-sectional study found no relationship between a FI (defined as the ratio of actual-to-possible deficits in an individual) and telomere length (Woo, Tang, Suen, Leung, & Leung, 2008). These researchers concluded that, although telomere length may be a biomarker of cellular senescence, this relationship might not extrapolate to a higher level representing frailty. Additional research is needed to further explore the molecular foundations of frailty.

Level II—System Dysregulation

On a higher level (i.e., system dysregulation), a number of studies have helped to establish inflammation, hormonal dysregulation, activation of blood clotting pathways, and metabolic abnormalities as important correlates of frailty (Cappola, Xue, & Fried, 2009; Reiner et al., 2009; Walston et al., 2006).

Inflammatory pathway dysregulation. Previous research has shown that certain inflammatory markers (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], and leukocytes) are more elevated in frail individuals than in age-matched counterparts. Cross-sectional data from the CHS cohort revealed that frail versus nonfrail participants had significantly increased levels of CRP (Walston et al., 2006). Longitudinal analyses assessing the risk of frailty after 5 and 9 years of follow-up yielded similar results, demonstrating that CRP levels at baseline were significantly associated with incident frailty (hazard ratio [HR] = 1.16, 95% CI = [1.02, 1.32]; Barzilay et al., 2007). Similarly, investigators in the Longitudinal Aging Study of Amsterdam, designed to assess predictors and consequences of change in physical, cognitive, emotional, and social functioning, found that moderately elevated levels of CRP predicted 3-year incident frailty. In that study, researchers operationalized frailty as the presence of at least three of nine frailty indicators: low body mass index (BMI), low peak expiratory flow, impaired cognitive function, poor distant vision, hearing problems, incontinence, low sense of mastery, depressive symptoms, and low physical activity (Puts, Visser, Twisk, Deeg, & Lips, 2005). This evidence suggests that inflammatory pathway alterations play a crucial pathophysiological role in the development of frailty. However, further research is needed to draw definitive conclusions about the effects of inflammatory signals on biological and physiological indicators of frailty. In addition, although anti-inflammatory cytokines such as IL-4 and IL-10 have been studied extensively in aging research (van den Biggelaar et al., 2004; Walston et al., 2008), their effects on the development of frailty in humans have yet to be determined.

Endocrine dysregulation. Alterations in anabolic hormones are theorized to contribute to aging and frailty. In fact, given the impact of endocrine dysfunction on biological senescence, much of the research on frailty has focused on these hormones. Cappola, Xue, and Fried (2009) showed that WHAS participants who had two or more deficiencies in anabolic hormones were significantly more likely to be frail than their counterparts with no hormonal deficiencies. Moreover, the authors demonstrated that the absolute burden of anabolic hormonal deficiencies is a stronger predictor of frailty than the type of hormonal deficiency.

In a large cross-sectional study, Voznesensky, Walsh, Dauser, Brindisi, and Kenny (2009) demonstrated a negative correlation between dehydroepiandrosterone sulfate (DHEA-s) levels and frailty status. DHEA-s levels show a gradual decline throughout the life span, reaching as low as 5–10% of the peak values achieved in early adulthood (Heineman, Hamrick-King, & Sewell, 2010). Very low levels of DHEA-s have also been observed in a variety of age-related conditions including

Alzheimer's disease, cardiovascular disease, and various cancers.

Similar to findings regarding DHEA-s, growth hormone insulin-like growth factor-1 (IGF-1), and sex steroids decline with age (Heineman et al., 2010). Puts, Visser, Twisk, Deeg, and Lips (2005) demonstrated a significant cross-sectional association between low serum IGF-1 and the presence of at least four of nine physical and psychological indicators of frailty in a large sample of older Dutch individuals. Research on steroid hormones in gender-specific cohorts has, however, provided more ambiguous results. A research team from the New England Research Institute found no association between total and free testosterone levels and frailty in a sample of 646 community-dwelling men, aged 50 years and older (Mohr et al., 2007). Conversely, in the longitudinal Australian Health in Men study, researchers found that low free testosterone was independently associated with frailty at baseline as well as after a follow-up period of 4–7 years (Hyde et al., 2010). In that study, the authors operationalized frailty using a FRAIL scale comprising five physiological indicators: fatigue, difficulty climbing a flight of stairs, difficulty walking more than 100 m, more than five illnesses present, or weight loss greater than 5%.

In summary, endocrine studies indicate that lower levels of anabolic hormones are closely linked to a state of multisystem senescence and therefore frailty. Cappola et al. (2009) have suggested that these effects are mediated through musculoskeletal impairment; however, further confirmatory research is needed.

Hematocoagulatory dysregulation. Excessive activation of the coagulation system has been associated with aging (Pieper, Rao, Currie, Harris, & Chen, 2000), functional decline, and increased mortality (Cohen, Harris, & Pieper, 2003). Moreover, age-associated changes in coagulation markers occur earlier than in other aging biomarkers (Kanapuru & Ershler, 2009), leading to the hypothesis that biomarkers of coagulation (e.g., D-dimer, factor VIII, and fibrinogen) and fibrinolysis (e.g., tissue-type plasminogen activator [t-PA]) signal important physiological mechanisms in the development of frailty. Evidence in support of this idea includes cross-sectional findings by Walston and colleagues (2002), who reported that increased mean levels of factor VIII and fibrinogen were associated with frailty status. However, recent prospective studies on the associations between inflammation, coagulation and fibrinolysis and frailty have been inconsistent. Barzilay and colleagues (2007) found a mere borderline association between factor VIII levels and incidence of frailty in the CHS cohort. Conversely, using a nested case–control design with 900 randomly selected enrollees in the Women's Health Initiative (WHI) who developed frailty cross-matched for age and ethnicity with those who did not, Reiner and colleagues (2009) found that the former showed higher levels of D-dimer and t-PA at baseline. Thus, activation of coagulation and fibrinolytic systems seems to play a role in the pathophysiology of frailty in older adults. Additional prospective studies are needed to further explore possible synergistic biological connections among coagulation system activation, inflammation, and risk of frailty.

Metabolic dysregulation. There is growing evidence that a rise in insulin resistance (IR) occurs as individuals grow older, resulting in impaired uptake of glucose by skeletal muscle (Heineman et al., 2010). Previous research has described a relationship between elevated IR and many of the clinical indicators of frailty, such as skeletal muscle weakness, lower extremity mobility problems, physical disability, and cognitive impairment (Abbatecola & Paolisso, 2008). IR, therefore, has been suggested as a metabolic disorder likely to have a direct impact on frailty. Gradual replacement of lean tissue with fat is partly responsible for the increased IR and glucose intolerance seen in older individuals (Chevalier, Gougeon, Choong, Lamarche, & Morais, 2006). In addition, chronic overproduction of cortisol in response to stress can result in suppressed immune function, increased IR, increased adipose tissue mass, and loss of lean mass (Goulet et al., 2009).

Examining the association between impaired metabolic state and frailty in a cross-sectional analysis of WHAS data, Blaum et al. (2009) demonstrated that hyperglycemia, itself, is associated with greater prevalence of frailty, independent of complications from diabetes mellitus, obesity, and high IL-6. Barzilay and colleagues (2007), using data from the CHS cohort, demonstrated similar results by showing an association between IR and a 1.15-fold increased risk (95% CI = [1.02, 1.31]) of frailty. Thus, future interventions aimed at correcting IR may have a significant role in preventing or at least slowing the downward cascade toward frailty.

Summary of system dysregulation. In summary, it has become apparent that inflammatory, endocrine, coagulation, and metabolic pathways are increasingly disrupted with advanced age and to a greater extent in those who meet criteria for frailty. The coexistence of these unbalanced factors suggests their synergistic role in pathophysiological mechanisms leading to frailty. For example, researchers have shown that there is bilateral interplay between inflammatory cytokines and procoagulant factors in a wide range of age-related conditions (Kanapuru & Ershler, 2009). Similarly, Cappola et al. (2003) reported an interaction between endocrine factors (e.g., IGF-1) and IL-6 in relation to disability and mortality. While these findings provide important new insights into the physiological correlates of frailty and indicate that these factors exist simultaneously in aging individuals, more questions about multisystem dysregulation remain to be explored.

Level III—System Impairment

A consideration of high-level or multisystem impairment (i.e., Level III) in frailty is consistent with the wide range of studies on different factors associated with its development. Musculoskeletal and neurocognitive changes are key indicators

for frailty in the research literature and represent a high level of impairment in the chain of pathophysiological events.

Musculoskeletal impairment. Sarcopenia, or loss of muscle mass and functioning, occurs with aging and is one of the major components of the frailty phenotype. Sarcopenia is of great consequence to older adults because it is associated with an increased risk of functional impairment and disability (Hairi et al., 2010). The biology of sarcopenia remains elusive; however, authors have proposed a few etiological mechanisms to explain this age-related decline in muscle mass (Heineman et al., 2010). In an extensive literature review encompassing several decades of frailty research, we noted that most studies include a functional decline in muscle mass (e.g., upper muscle strength, gait speed, and total physical activity) as a fundamental indicator of frailty (Zaslavsky, Thompson, & Demiris, 2012).

The age-related loss of muscle mass may not be an isolated phenomenon but rather may be strongly connected with a parallel increase in fat mass. The fat mass increase and muscle mass decrease may act synergistically and lead to sarcopenic obesity. In the Invecchiare in Chianti study of 923 participants aged 65 years and older, frail subjects had lower muscle density and muscle mass and higher fat mass than did their nonfrail counterparts (Cesari et al., 2006). The authors observed this difference in both genders and it was independent of the concentration of inflammatory markers such as IL-6, CRP, and tumor necrosis factor-α. Sarcopenic obesity is particularly ominous, being associated with worse functional outcomes (e.g., climbing stairs, rising from a chair or bed, and lifting heavy objects) and disability (Baumgartner et al., 2004; Rolland et al., 2009). A prospective study of 3,075 well-functioning older adults aged 70–79 years participating in the Health ABC cohort showed that greater fat infiltration into muscle, as measured by computed tomography, was associated with an almost twofold risk of mobility loss in 2.5 years of follow-up (Visser et al., 2005). Research has also demonstrated a positive correlation between fat infiltration into the muscle and overall body weight as well as changes in body composition (Ryan & Nicklas, 1999). In fact, body weight can be sustained or increased as a result of the accumulation of adipose tissue, despite a loss of lean body mass (Koster et al., 2011). In the Koster et al. study excess body fat was a stronger determinant of impaired physical function in older adults than was inadequate lean body mass. More importantly, fat in older adults is preferentially accumulated in a central distribution. This central distribution of adipose tissue mass, similar to relative weight or other measures of obesity, is a major risk factor for many age-related metabolic abnormalities (Hubbard, Lang, Llewellyn, & Rockwood, 2010). Researchers have used impaired nutrition status, as measured by change in BMI or total body weight over 1–3 years, in multiple studies as one of the well-established frailty criteria (Ensrud et al., 2009; Fried et al., 2001; Woods et al., 2005). Yet, additional research is needed to clearly establish which indicators will provide the more sensitive measure of these age-related pathophysiological processes in frail elderly: loss of lean mass, change in fat mass as indicated by an increase or decrease in BMI, or a direct measurement of central obesity (e.g., waist circumference).

Neurocognitive impairment. Investigators have previously reported the association between neurocognitive impairment and functional decline (Lenze et al., 2001; Spiers et al., 2005). Although these factors have been associated with frailty (Avila-Funes et al., 2009; Rothman, Leo-Summers, & Gill, 2008), their pathophysiological role in the process of frailty development has yet to be determined. In frailty research, neurocognitive indicators have included a wide array of measures such as cognition, sensory impairment (e.g., visual or hearing loss), and psychological factors (depression; Zaslavsky et al., 2012). Avila-Funes and colleagues (2009) examined 6,030 participants aged 65–95 years in the French Three-City Study and clearly demonstrated that cognitive impairment, as measured by the Mini-Mental State Examination (MMSE) and the Isaac Set test, improved the predictive validity of the CHS-based frailty phenotype for adverse health outcomes (e.g., dementia, functional decline, and hospitalization). The OR of incident 4-year hospitalization in frail individuals without cognitive impairment was not statistically significant (OR = 1.26, 95% CI = [0.91, 1.74]) compared to a nonfrail group without cognitive deficits. However, frail individuals with cognitive impairment had 1.9 times increased risk (95% CI = [1.09, 3.31]) compared to the same reference group. Rothman, Leo-Summers, and Gill (2008) had similar findings in their longitudinal analysis of 754 initially nondisabled, community-dwelling persons aged 70 and older. These researchers sought to determine the individual prognostic effect of each of Fried's five frailty criteria as well as cognitive impairment (measured by the MMSE) and depressive symptoms (measured by the Center for Epidemiological Studies Depression Scale) on clinically relevant geriatric outcomes (e.g., disability, institutionalization, injurious falls, and death). Rothman et al. found that cognitive impairment was independently and strongly associated with chronic disability (HR = 1.82, 95% [CI = 1.4, 2.38]), long-term nursing home stay (HR = 2.64, 95% CI = [1.75, 3.99]), and death (HR = 1.54, 95% CI = [1.13, 2.1]) over 7.5 years of follow-up.

Sensory loss, such as decline of visual function, has also been linked to increased mortality in older adults (Klein, Klein, Knudtson, & Lee, 2005; Knudtson, Klein, & Klein, 2006). Longitudinal data indicate that older individuals with reduced visual acuity have a 70% increased mortality risk compared to persons without visual impairment (Wang, Mitchell, Simpson, Cumming, & Smith, 2001). Thus, it has been argued that visual impairment may also be a useful indicator of frailty. Testing this hypothesis, Klein, Klein, Knudtson, and Lee (2005) demonstrated that greater frailty status, as measured by a modified FI that included best corrected visual acuity in addition to musculoskeletal indicators, was associated with poorer survival among community-dwelling Midwestern older adults.

Mood disturbance (e.g., depression) is another neurocognitive parameter that predicts functional disability in older

adults (Lenze et al., 2001) and has been suggested as an indicator of frailty (Lang et al., 2009). Longitudinal analysis of CHS data showed that persistently depressed older individuals had a 5.3-fold (95% CI = [3.03, 9.16]) increased risk for functional disability compared to nondepressed individuals over 3 years of follow-up (Lenze et al., 2005). However, despite mounting evidence on the effect of mood disorder on aging-related outcomes, findings regarding an independent effect of depressive symptoms on frailty have been inconsistent (Rothman et al., 2008). For instance, Rothman et al. found that depressive symptoms failed to independently predict risk of chronic disability, long-term nursing home stay, injurious falls or death, after adjusting for age, sex, race, education, chronic conditions, and the presence of other frailty criteria.

Summary of Pathophysiological Mechanisms

Numerous researchers have argued that frailty is a multidimensional and multisystem process that cannot be comprehensively captured by applying physical criteria only, as there are other cognitive, neurological, and biological domains that ought to be taken into consideration (Lang et al., 2009). A number of authors have discussed this lack of consensus on the definition of the construct of frailty and its components (Abellan van Kan et al., 2008; Lang et al., 2009), prompting continued efforts to identify a comprehensive model of frailty. Furthermore, it is apparent that no single system impairment characterizes frailty. Instead, an intertwined network of biological abnormalities is likely to be part of the pathophysiological chain of events leading to frailty. In particular, based on multiple studies and literature reviews, we suggest including measures of cognition and sensory loss as defining criteria of frailty, thus extending Fried's phenotypical definition into the neurocognitive dimension.

Moderating/Risk Factors

Ethnicity, comorbidities, lifestyle, and poor nutrition have been proposed as plausible risk factors of frailty and increased risk of mortality. Numerous studies have shown their independent and synergistic effects on frailty development (Alvarado, Zunzunegui, Beland, & Bamvita, 2008; Newman et al., 2001; Woods et al., 2005).

Ethnicity

Cross-sectional analysis of CHS cohort data has shown that African Americans have fourfold greater odds of frailty than their White counterparts (Hirsch et al., 2006). The authors hypothesized that race serves as a marker for the differential genetic polymorphisms that affect the expression of the frailty phenotype. However, it is also likely that an increased risk for frailty among African Americans closely relates to their experience of cumulative disadvantage (decreased health care access, poorer quality education, and fewer employment choices) for the current generation of older African American adults. Addressing the effect of ethnicity on frailty, Espinoza and Hazuda (2008) conducted a secondary analysis of baseline data from a random sample of community-dwelling Mexican Americans ($n = 394$) and European Americans ($n = 355$) aged 65–80 years. The prevalence of frailty among Mexican Americans was 4.3% higher ($p = .045$) than among European Americans when applying Fried's screening tool for frailty. The authors argued, however, that the observed ethnic differences in frailty might be attributed in part to screening criteria that are inherently biased and do not take into account the unique biological and psychosocial characteristics of ethnically diverse groups. The standardization of frailty indicators according to racially sensitive cutoff points (e.g., that take into consideration the higher incidence of obesity, malnutrition, and comorbidities in some racial–ethnic minority populations) as well as concerns about racial disparities deserve further investigation in gerontological research.

Comorbidities

Comorbidities increase the risk for frailty. In a prospective longitudinal study of 40,657 women aged 65–79 years participating in the WHI's observational study, Woods and colleagues (2005) found that history of coronary heart disease (CHD), stroke, hip fracture, chronic obstructive pulmonary disease, treated diabetes mellitus, and arthritis were significantly related to a 3-year incident frailty. Moreover, in a cross-sectional analysis of participants in the CHS, cardiovascular morbidity and vascular abnormalities were independently associated with increased prevalence of frailty (Newman et al., 2001). Thus, it is clear now that subclinical and chronic health conditions are strongly linked to the development and prevalence of frailty.

Lifestyle Factors

Lifestyle, health-related behaviors, and socioeconomic status have also been recognized as contributors to the risk of developing frailty. For example, in a cross-sectional study of 10,661 Latin American and Caribbean men and women aged 60 years and older, poor health, little education, and poor socioeconomic conditions were associated with higher odds of frailty (Alvarado et al.,, 2008).

Impaired Nutrition

Finally, various aspects of poor nutritional intake are also considered important biological mechanisms in the development of frailty (Fried et al., 2009; Walston et al., 2006). One sign of impaired nutrition is daily energy intake. The Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging (Florence, Italy) linked calorie intakes of 21 kcal/kg/day or less to frailty (as defined by Fried et al., 2001) in a prospective population-based analysis of 1,155 participants aged 65–102 years (Bartali et al., 2006).

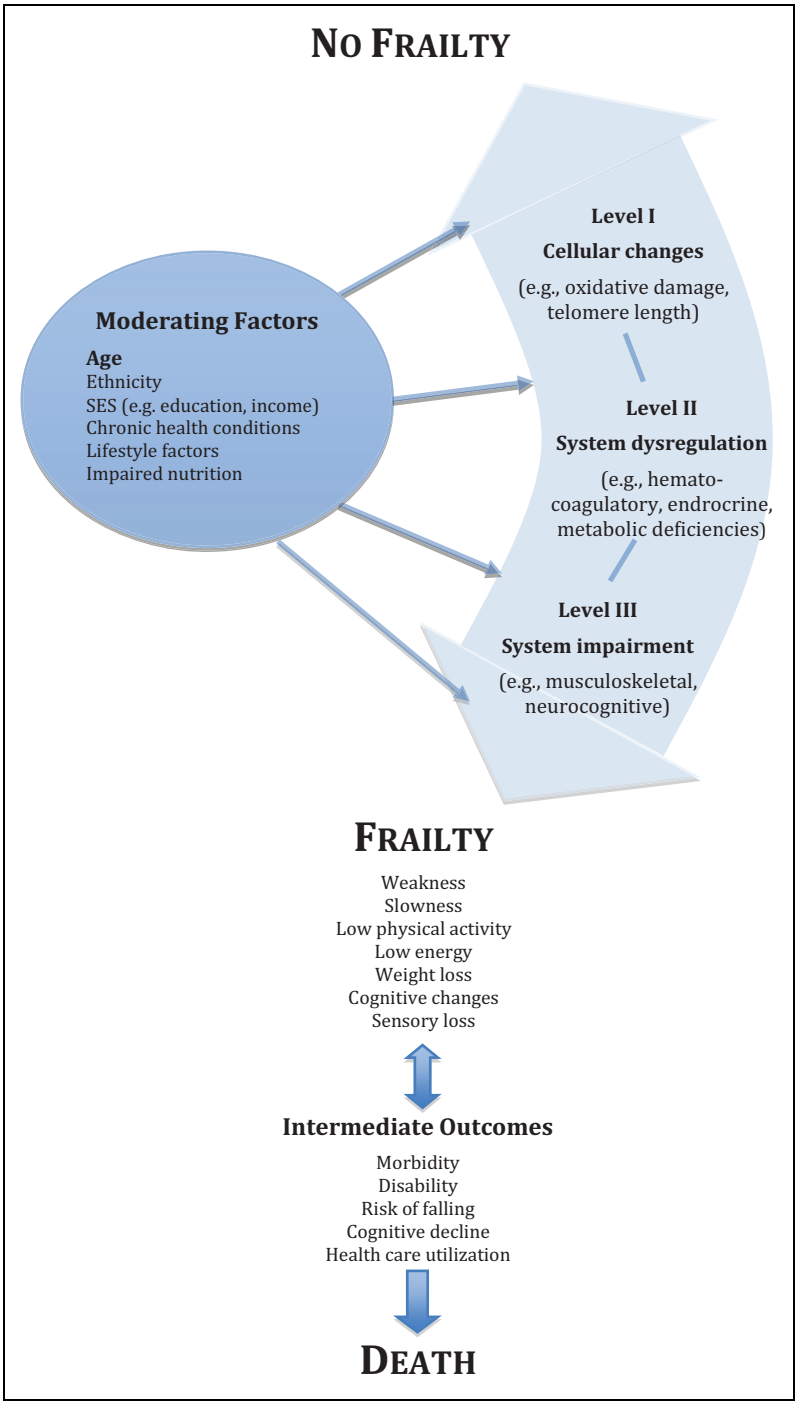

Figure 1. Integrative model for the development of frailty in older adults. Aging is a biological factor that is likely to contribute to a cascade of pathophysiological responses of an individual to a set of behavioral and environmental risk factors by modulating that individual's molecular and systemic mechanisms. This disruption of physiological processes, in turn, is associated with a chain of multisystem dysregulation, pronounced functional and neurocognitive impairment, and poor health-related outcomes observed in the frail elderly. SES = socioeconomic status.

In that study, a poor nutritional score (low intake of more than three nutrients, such as protein, vitamins A, C, and E, calcium, folate, and zinc), independent of energy intake, was also significantly associated with frailty. Walston and colleagues (2006) proposed the anti-inflammatory effects of dietary antioxidants as a plausible mechanism linking micronutrient deficiency and frailty.

An Integrative Model of Frailty Development

In Figure 1, we illustrate a biological model that integrates the various conceptual models of frailty as well as research on the multilevel/nested pathophysiological processes leading to frailty and their moderating/risk factors. Although potential interactions among these multiple physiological deficits have

been recognized, to date no unifying causal mechanism has been established from which to derive a more mathematical model of frailty. This figure provides an integrative conceptual framework for examining the cascade of pathophysiological events leading to frailty and can help researchers generate testable hypotheses about the complex intra- and interlevel dynamics involved in its development. Analytic approaches like multilevel modeling (Singer & Willet, 2003) have the capacity to allow investigators to examine and estimate the multilevel, nonlinear longitudinal trends expected in such complex biological phenomena. For example, one research question that can be derived from the integrative model would be to estimate the extent to which variability in longitudinal dynamics of musculoskeletal indicators (Level III) could be explained by lower level (i.e., Level II) factors (e.g., hematocoagulatory and metabolic), which in turn could be a function of Level I factors (i.e., oxidative damage and telomere length).

Conclusions and Areas for Future Research

Based on research to date, frailty develops as a result of impairment in musculoskeletal and neurocognitive systems. The etiology of such impairment is multifactorial and includes progressive dysregulation in a number of main physiological systems (e.g., hematocoagulatory, metabolic, and endocrine) and their complex interconnected network. The process of frailty development starts with the prolonged exposure of an individual to a set of behavioral and environmental risk factors such as unhealthy lifestyle, low socioeconomic status, and abnormal health conditions that initiate a downward spiral of molecular- and system-level pathological events. Frailty is expressed as an accumulation of musculoskeletal and neurocognitive limitations. The indicators of frailty include weakness, slowness, low physical activity, low energy, weight loss, cognitive changes, and sensory loss; thus its multidimensional nature stretches beyond mere physical function.

The main focus in frailty research has been to find its ultimate constellation of biological indicators and physiological markers. In addition to the "conventional" criteria developed by Fried et al. (2001), we suggest including indicators of neurosensory loss (i.e., cognition and sensory loss). However, a more complete understanding of the biological processes involved in frailty development requires a deeper examination of its structural components and their unique longitudinal dynamics. In other words, to better understand the etiological processes in the development of frailty, it is important to extend unilevel analyses to more comprehensive multilevel models. Given such efforts, we will be able to explicitly model complex structural and longitudinal dynamics involved in the pathophysiology of frailty. As an illustration of one important venture for future research, we suggest examining the longitudinal patterns of change in frailty indicators and evaluating the effect of aggregate physiological abnormalities on these trajectories. The results of such analyses are likely to explicate the heterogeneous nature of frailty and its development and identify directions for future intervention development.

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References

Abbatecola, A. M., & Paolisso, G. (2008). Is there a relationship between insulin resistance and frailty syndrome. *Current Pharmaceutical Design*, *14*, 405–410.

Abellan van Kan, G., Rolland, Y., Bergman, H., Morley, J. E., Kritchevsky, S. B., & Vellas, B. (2008). The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *Journal of Nutrition, Health, and Aging*, *12*, 29–37.

Alvarado, B. E., Zunzunegui, M. V., Beland, F., & Bamvita, J. M. (2008). Life course social and health conditions linked to frailty in Latin American older men and women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*, 1399–1406.

Andersen, B. B., Gundersen, H. J., & Pakkenberg, B. (2003). Aging of the human cerebellum: A stereological study. *Journal of Comparative Neurology*, *466*, 356–365.

Avila-Funes, J. A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., . . . Dartigues, J. F. (2009). Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The three-city study. *Journal of the American Geriatrics Society*, *57*, 453–461.

Bartali, B., Frongillo, E. A., Bandinelli, S., Lauretani, F., Semba, R. D., Fried, L. P., & Ferruci, L. (2006). Low nutrient intake is an essential component of frailty in older persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *61*, 589–593.

Barzilay, J. I., Blaum, C., Moore, T., Xue, Q. L., Hirsch, C. H., Walston, J. D., & Fried, L. P. (2007). Insulin resistance and inflammation as precursors of frailty: The cardiovascular health study. *Archives of Internal Medicine*, *167*, 635–641.

Baumgartner, R. N., Wayne, S. J., Waters, D. L., Janssen, I., Gallagher, D., & Morley, J. E. (2004). Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obesity Research*, *12*, 1995–2004.

Beckers, F., Verheyden, B., & Aubert, A. E. (2006). Aging and nonlinear heart rate control in a healthy population. *American Journal of Physiology Heart and Circulatory Physiology*, *290*, H2560–H2570.

Blaum, C. S., Xue, Q. L., Tian, J., Semba, R. D., Fried, L. P., & Walston, J. (2009). Is hyperglycemia associated with frailty status in older women? *Journal of the American Geriatrics Society*, *57*, 840–847.

Cappola, A. R., Xue, Q. L., Ferrucci, L., Guralnik, J. M., Volpato, S., & Fried, L. P. (2003). Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *Journal of Clinical Endocrinology and Metabolism*, *88*, 2019–2025.

Cappola, A. R., Xue, Q. L., & Fried, L. P. (2009). Multiple hormonal deficiencies in anabolic hormones are found in frail older women: The women's health and aging studies. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *64*, 243–248.

Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet*, *361*, 393–395.

Cesari, M., Leeuwenburgh, C., Lauretani, F., Onder, G., Bandinelli, S., Maraldi, C., … Ferruci, L. (2006). Frailty syndrome and skeletal muscle: Results from the invecchiare in chianti study. *American Journal of Clinical Nutrition*, *83*, 1142–1148.

Chaves, P. H., Varadhan, R., Lipsitz, L. A., Stein, P. K., Windham, B. G., Tian, J., … Fried, L. P. (2008). Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. *Journal of the American Geriatrics Society*, *56*, 1698–1703.

Chevalier, S., Gougeon, R., Choong, N., Lamarche, M., & Morais, J. A. (2006). Influence of adiposity in the blunted whole-body protein anabolic response to insulin with aging. *Journals of Gerontology. Series A, Biological Science and Medical Science*, *61*, 156–164.

Cohen, H. J., Harris, T., & Pieper, C. F. (2003). Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *American Journal of Medicine*, *114*, 180–187.

Ensrud, K. E., Blackwell, T. L., Redline, S., Ancoli-Israel, S., Paudel, M. L., & Cawthon, P. M., … Osteoporotic Fractures in Men Group. (2009). Sleep disturbances and frailty status in older community-dwelling men. *Journal of the American Geriatrics Society*, *57*, 2085–2093.

Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., & Cauley, J. A., … Osteoporotic Fractures in Men Group. (2007). Frailty and risk of falls, fracture, and mortality in older women: The study of osteoporotic fractures. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *62*, 744–751.

Espinoza, S. E., & Hazuda, H. P. (2008). Frailty in older Mexican-American and European-American adults: Is there an ethnic disparity? *Journal of the American Geriatrics Society*, *56*, 1744–1749.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., & Gottdiener, J., … Cardiovascular Health Study Collaborative Research Group. (2001). Frailty in older adults: Evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *56*, M146–M156.

Fried, L. P., Xue, Q. L., Cappola, A. R., Ferrucci, L., Chaves, P., Varadhan, R., … Bandeen-Roche, K. (2009). Nonlinear multisystem physiological dysregulation associated with frailty in older women: Implications for etiology and treatment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *64*, 1049–1057.

Gavrilov, L. A., & Gavrilova, N. S. (2001). The reliability theory of aging and longevity. *Journal of Theoretical Biology*, *213*, 527–545.

Goggins, W. B., Woo, J., Sham, A., & Ho, S. C. (2005). Frailty index as a measure of biological age in a Chinese population. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*, 1046–1051.

Goulet, E. D., Hassaine, A., Dionne, I. J., Gaudreau, P., Khalil, A., Fulop, T., … Morais, J. A. (2009). Frailty in the elderly is associated with insulin resistance of glucose metabolism in the postabsorptive state only in the presence of increased abdominal fat. *Experimental Gerontology*, *44*, 740–744.

Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., & Sarkisian, C. A. (2009). Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society*, *57*, 1525–1531.

Hairi, N. N., Cumming, R. G., Naganathan, V., Handelsman, D. J., Le Couteur, D. G., Greasey, H., … Sambrook, P. N. (2010). Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: The concord health and ageing in men project. *Journal of the American Geriatric Society*, *58*, 2055–2062.

Heineman, J. M., Hamrick-King, J., & Sewell, B. S. (2010). Review of the aging of physiological systems. In K. L. Mauk (Ed.), *Gerontological nursing* (2nd ed., pp. 172–177). Sudbury, MA: Jones and Bartlett.

Hirsch, C., Anderson, M. L., Newman, A., Kop, W., Jackson, S., & Gottdiener, J., … Cardiovascular Health Study Research Group. (2006). The association of race with frailty: The cardiovascular health study. *Annals of Epidemiology*, *16*, 545–553.

Hubbard, R. E., Lang, I. A., Llewellyn, D. J., & Rockwood, K. (2010). Frailty, body mass index, and abdominal obesity in older people. *Journals of Gerontology. Series A, Biological Science and Medical Science*, *65*, 377–381.

Hyde, Z., Flicker, L., Almeida, O. P., Hankey, G. J., McCaul, K. A., Chubb, S. A., & Yeap, B. B. (2010). Low free testosterone predicts frailty in older men: The health in men study. *Journal of Clinical Endocrinology and Metabolism*, *95*, 3165–3172.

Kanapuru, B., & Ershler, W. B. (2009). Inflammation, coagulation, and the pathway to frailty. *American Journal of Medicine*, *122*, 605–613.

Klein, B. E., Klein, R., Knudtson, M. D., & Lee, K. E. (2005). Frailty, morbidity and survival. *Archives of Gerontology and Geriatrics*, *41*, 141–149.

Knudtson, M. D., Klein, B. E., & Klein, R. (2006). Age-related eye disease, visual impairment, and survival: The beaver dam eye study. *Archives of Ophthalmology*, *124*, 243–249.

Kop, W. J., Gottdiener, J. S., Tangen, C. M., Fried, L. P., McBurnie, M. A., Walston, J., … Tracy, R. P. (2002). Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. *American Journal of Cardiology*, *89*, 419–424.

Koster, A., Ding, J., Stenholm, S., Caserotti, P., Houston, D. K., & Nicklas, B. J., … Health ABC study. (2011). Does the amount of fat mass predict age-related loss of lean mass, muscle strength, and muscle quality in older adults? *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *66*, 888–895.

Kulminski, A. M., Ukraintseva, S. V., Akushevich, I. V., Arbeev, K. G., & Yashin, A. I. (2007). Cumulative index of health deficiencies as a characteristic of long life. *Journal of the American Geriatrics Society*, *55*, 935–940.

Lang, P. O., Michel, J. P., & Zekry, D. (2009). Frailty syndrome: A transitional state in a dynamic process. *Gerontology*, *55*, 539–549.

Leeuwenburgh, C. (2003). Role of apoptosis in sarcopenia. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*, 999–1001.

Lenze, E. J., Rogers, J. C., Martire, L. M., Mulsant, B. H., Rollman, B. L., Dew, M. A., . . . Reynolds, C. F., 3rd. (2001). The association of late-life depression and anxiety with physical disability: A review of the literature and prospectus for future research. *American Journal of Geriatric Psychiatry*, *9*, 113–135.

Lenze, E. J., Schulz, R., Martire, L. M., Zdaniuk, B., Glass, T., Kop, W. J., . . . Reynolds, C. F., 3rd. (2005). The course of functional decline in older people with persistently elevated depressive symptoms: Longitudinal findings from the Cardiovascular Health Study. *Journal of the American Geriatrics Society*, *53*, 569–575.

Lipsitz, L. A. (2004). Physiological complexity, aging, and the path to frailty. *Science of Aging Knowledge Environment*, *2004*, pe16.

Makikallio, A. M., Makikallio, T. H., Korpelainen, J. T., Sotaniemi, K. A., Huikuri, H. V., & Myllyla, V. V. (2004). Heart rate dynamics predict poststroke mortality. *Neurology*, *62*, 1822–1826.

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *Scientific World Journal*, *1*, 323–336.

Mohr, B. A., Bhasin, S., Kupelian, V., Araujo, A. B., O'Donnell, A. B., & McKinlay, J. B. (2007). Testosterone, sex hormone-binding globulin, and frailty in older men. *Journal of the American Geriatrics Society*, *55*, 548–555.

Newman, A. B., Gottdiener, J. S., McBurnie, M. A., Hirsch, C. H., Kop, W. J., & Tracy, R., . . . Cardiovascular Health Study Research Group. (2001). Associations of subclinical cardiovascular disease with frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *56*, M158–M166.

O'Brien, T. D., Roberts, J., Brackenridge, G. R., & Lloyd, W. H. (1968). Some aspects of community care of the frail and elderly: The need for assessment. *Gerontologia Clinica*, *10*, 215–227.

Pieper, C. F., Rao, K. M., Currie, M. S., Harris, T. B., & Chen, H. J. (2000). Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *55*, M649–M657.

Pikkujamsa, S. M., Makikallio, T. H., Sourander, L. B., Raiha, I. J., Puukka, P., Skytta, J., . . . Huikuri, H. V. (1999). Cardiac interbeat interval dynamics from childhood to senescence: Comparison of conventional and new measures based on fractals and chaos theory. *Circulation*, *100*, 393–399.

Puts, M. T., Visser, M., Twisk, J. W., Deeg, D. J., & Lips, P. (2005). Endocrine and inflammatory markers as predictors of frailty. *Clinical Endocrinology*, *63*, 403–411.

Reiner, A. P., Aragaki, A. K., Gray, S. L., Wactawski-Wende, J., Cauley, J. A., Cochrane, B. B., . . . LaCroix, A. Z (2009). Inflammation and thrombosis biomarkers and incident frailty in postmenopausal women. *American Journal of Medicine*, *122*, 947–954.

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *62*, 738–743.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *62*, 722–727.

Rolland, Y., Lauwers-Cances, V., Cristini, C., Abellan van Kan, G., Janssen, I., Morley, J. E., & Vellas, B. (2009). Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: The EPIDOS (EPIDemiologie de l'OSteoporose) Study. *American Journal of Clinical Nutrition*, *89*, 1895–1900.

Rothman, M. D., Leo-Summers, L., & Gill, T. M. (2008). Prognostic significance of potential frailty criteria. *Journal of the American Geriatrics Society*, *56*, 2211–2116.

Ryan, A. S., & Nicklas, B. J. (1999). Age-related changes in fat deposition in mid-thigh muscle in women: Relationships with metabolic cardiovascular disease risk factors. *International Journal of Obesity and Related Metabolic Disorders*, *23*, 126–132.

Schaap, L. A., Pluijm, S. M., Deeg, D. J., Harris, T. B., Kritchevsky, S. B., Newman, A. B., & Health, ABC study. (2009). Higher inflammatory marker levels in older persons: Associations with 5-year change in muscle mass and muscle strength. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *64*, 1183–1189.

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 4770–4775.

Singer, J. D., & Willet, J. B. (2003). *Applied longitudinal data analysis*. Oxford, England: Oxford University Press.

Spiers, N. A., Matthews, R. J., Jagger, C., Matthews, F. E., Boult, C., Robinson, T. G., & Brayne, C. (2005). Diseases and impairments as risk factors for onset of disability in the older population in England and Wales: Findings from the medical research council cognitive function and ageing study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*, 248–254.

Szanton, S. L., Allen, J. K., Seplaki, C. L., Bandeen-Roche, K., & Fried, L. P. (2009). Allostatic load and frailty in the women's health and aging studies. *Biological Research for Nursing*, *10*, 248–256.

Tapanainen, J. M., Thomsen, P. E., Kober, L., Torp-Pedersen, C., Makikallio, T. H., Still, A. M., . . . Huikuri, H. V. (2002). Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *American Journal of Cardiology*, *90*, 347–352.

van den Biggelaar, A. H., Huizinga, T. W., de Craen, A. J., Gussekloo, J., Heijmans, B. T., Frolich, M., & Westendorp, R. G. (2004). Impaired innate immunity predicts frailty in old age. The Leiden 85-plus study. *Experimental Gerontology*, *39*, 1407–1414.

Visser, M., Goodpaster, B. H., Kritchevsky, S. B., Newman, A. B., Nevitt, M., Rubin, S. M., . . . Harris, T. B. (2005). Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *60*, 324–333.

Voznesensky, M., Walsh, S., Dauser, D., Brindisi, J., & Kenny, A. M. (2009). The association between dehydroepiandosterone and frailty in older men and women. *Age and Ageing*, *38*, 401–406.

Wallace, W. H., & Kelsey, T. W. (2010). Human ovarian reserve from conception to the menopause. *PLoS One*, *5*, e8772.

Walston, J. (2004). Frailty—the search for underlying causes. *Science of Aging Knowledge Environment*, *2004*, pe4.

Walston, J., Fedarko, N., Yang, H., Leng, S., Beamer, B., Espinoza, S., … Becker, K. (2008). The physical and biological characterization of a frail mouse model. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *63*, 391–398.

Walston, J., McBurnie, M. A., Newman, A., Tracy, R. P., Kop, W. J., & Hirsch, C. H., … Cardiovascular Health Study. (2002). Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: Results from the Cardiovascular Health Study. *Archives of Internal Medicine*, *162*, 2333–2341.

Walston, J., Xue, Q., Semba, R. D., Ferrucci, L., Cappola, A. R., Ricks, M., … Fried, L. P. (2006). Serum antioxidants, inflammation, and total mortality in older women. *American Journal of Epidemiology*, *163*, 18–26.

Wang, J. J., Mitchell, P., Simpson, J. M., Cumming, R. G., & Smith, W. (2001). Visual impairment, age-related cataract, and mortality. *Archives of Ophthalmology*, *119*, 1186–1190.

Winograd, C. H., Gerety, M. B., Brown, E., & Kolodny, V. (1988). Targeting the hospitalized elderly for geriatric consultation. *Journal of the American Geriatrics Society*, *36*, 1113–1119.

Woo, J., Tang, N. L., Suen, E., Leung, J. C., & Leung, P. C. (2008). Telomeres and frailty. *Mechanisms of Ageing and Development*, *129*, 642–648.

Woods, N. F., LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., & Brunner, R. L., … Women's Health Initiative. (2005). Frailty: Emergence and consequences in women aged 65 and older in the women's health initiative observational study. *Journal of the American Geriatrics Society*, *53*, 1321–1330.

Zaslavsky, O., Thompson, H., & Demiris, G. (2012). The role of emerging information technologies in frailty assessment. *Research in Gerontological Nursing*, *5*, 216–228.