Journal of Nutrition in Gerontology and Geriatrics

ISSN: 2155-1197 (Print) 2155-1200 (Online) Journal homepage: http://www.tandfonline.com/loi/wjne21

The Frailty Syndrome: A Comprehensive Review

Roschelle A. Heuberger PhD, RD

To cite this article: Roschelle A. Heuberger PhD, RD (2011) The Frailty Syndrome: A Comprehensive Review, Journal of Nutrition in Gerontology and Geriatrics, 30:4, 315-368, DOI: 10.1080/21551197.2011.623931

To link to this article: https://doi.org/10.1080/21551197.2011.623931

Journal of Nutrition in Gerontology and Geriatrics, 30:315–368, 2011

ISSN: 2155-1197 print/2155-1200 online
DOI: 10.1080/21551197.2011.623931

Routledge
Taylor & Francis Group

Review

The Frailty Syndrome: A Comprehensive Review

ROSCHELLE A. HEUBERGER, PhD, RD

Department of Human Environmental Studies, Central Michigan University, Mt. Pleasant, Michigan, USA

The frailty syndrome is defined as unintentional weight and muscle loss, exhaustion, and declines in grip strength, gait speed, and activity. Evidence with respect to the clinical definition, epidemiology, mechanisms, interactions, assessment, prevention, and treatment of frailty in the older adult is reviewed.

KEYWORDS frailty, nutrition, older adult

INTRODUCTION

Frailty has only recently been defined as a clinical syndrome with criteria for diagnosis. Prior to the mid-1990s, the term frail was used to describe older persons who were disabled, failed to thrive, were institutionalized, or were near the end of life. There was no consensus as to what defined "frailty." In the mid-to-late 1990s, Rockwood and colleagues proposed that frailty be defined as a state in which there was a dependence on others for performing functions of daily living. Later this group developed a Frailty Index, a longer Clinical Frailty Scale, and a brief screening tool known as FRAIL, which was amended to include the following criteria: fatigue, disease, weight loss, inability to walk a short distance, and inability to climb a flight of stairs (Table 1) (1–3). Strawbridge and associates, at about the same time, proposed that frailty be "diagnosed" if two or more impairments were noted in any one of the following four areas: physical functioning, nutritional adequacy, cognition, and sensory ability (4).

Address correspondence to Roschelle A. Heuberger, PhD, RD, Department of Human Environmental Studies, Central Michigan University, 106A Wightman Hall, Mt. Pleasant, MI 48859, USA. E-mail: heube1ra@cmich.edu

TABLE 1 FRAIL Scale[†]

F	Fatigue
R	Resistance (inability to group a flight of stairs)
A	Ambulation (inability to walk a short distance)
I	Illness (more than 5 comorbid conditions)
L	Loss (of more than 5% total body weight)

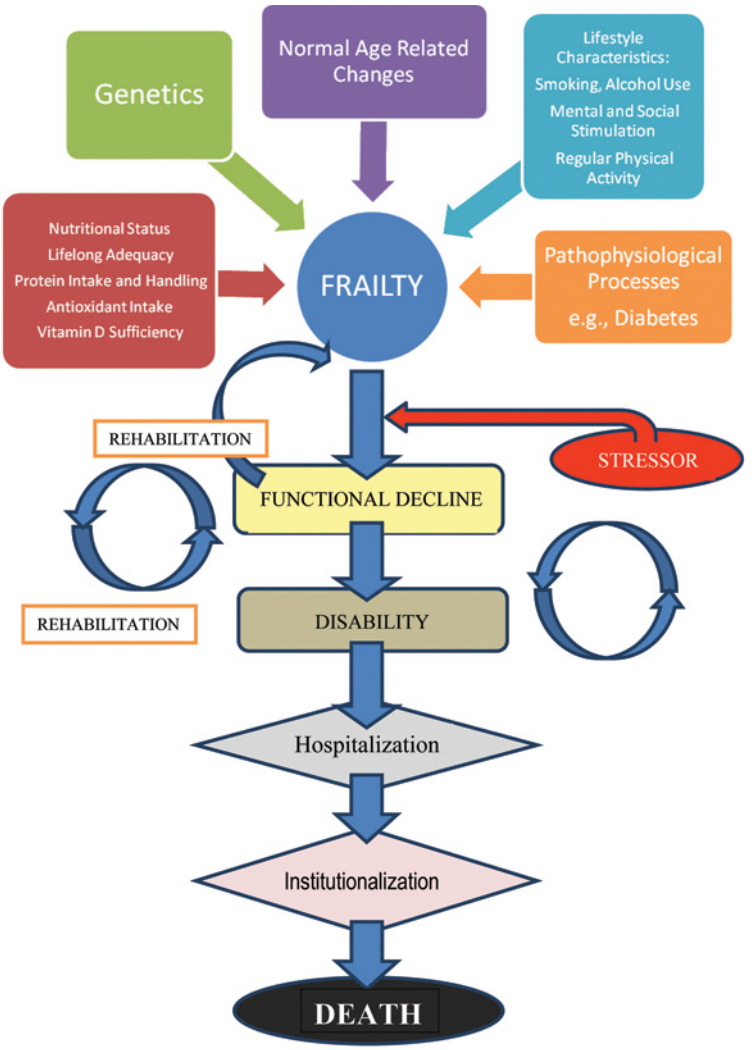
[†]Adapted from Rockwood K, Stadnyk K, McKnight C, McDowell I, Herbert R, Hogan D. A brief clinical instrument to classify frailty in elderly people. Lancet. 1999; 353:205–6.

In early 2000, the phenotype of frailty was described by Fried and colleagues, who put forth objective diagnostic measures in an effort to separate the concept of frailty from disability and comorbidity. The criteria established for frailty included the loss of 10 pounds or more in a year, self-reported exhaustion, and weakness as measured by a progressive decrease in grip strength, reductions in gait speed, and declines in physical activity (5–7). Frailty was distinguished from frank disability in that (1) it was a predecessor to disability, (2) there was an event or stressor that catapulted the frail older adult into frank disability, and (3) the syndrome was a complex interaction between several factors, including but not limited to natural physiological alterations seen in aging, comorbid disease inception and/or progression, nutriture and nutritional inadequacy, cumulative negative environmental impact, genetics, and lifestyle choices (8, 9). Recent investigations have focused on the cumulative role of inflammatory processes on the development and progression of frailty in the older adult (10). Proinflammatory cytokines, dysregulation of the immunological redundancy pathways, and activation of promoter genes having catabolic effects are thought to be pivotal in the frailty syndrome (11, 12).

Frailty is often correlated with the presence of pathological conditions in the older adult. These include anemia, orthostasis, weight loss, sarcopenia, anorexia, polypharmacy, congestive heart failure, diabetes mellitus, osteopenia, hypovitaminosis D, testosterone deficiency, low protein intake, deficits in protein trafficking, declines in cognitive functioning, inflammation with increased cytokine production, and decreased regulatory peptides, among others (13). While weight loss and sarcopenia are central to the clinical manifestations of frailty, the older obese population is equally at risk. Obese persons are generally not thought of as frail, which results in low rates of screening and detection. Obesity in the absence of physical activity leads to sarcopenia and increases in fat mass, which in turn leads to conditions correlated with frailty and its progression to frank disability. The frail obese or "sarcopenic obese" are a rapidly growing segment of the older adult population, and the condition is associated with the greatest health care burdens. Central obesity is of particular concern, with its associations to metabolic syndrome and rapid deterioration in physical functioning (14). In 2007, the

European, Canadian, and American Geriatric Advisory Panel failed to reach consensus on a universal definition of frailty or on a single tool to be used in assessing the syndrome (15). Several working clinical definitions and tools were considered useful and appropriate for frailty in the obese and nonobese older adult.

Frailty in the older adult and the easy progression to disability with the addition of another stressor results in a domino effect that increases mortality



†Adapted from: Morley JE, Haren MT, Rolland Y, Kim MJ. Frailty. Med *Clin N Am*. 2006;90(5):837–47‡Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: towards a clinical definition. *J Am Med Direct Assoc*. 2008; 9(2):71–2§Bortz W. Understanding Frailty. *J Gerontol A Biol Sci Med Sci*. 2010; 65A(3): 255–6.

FIGURE 1 The etiology and progression of clinical frailty in the older adult. (Color figure available online.)

(Figure 1). Prevention is far more cost-effective than treatment and should be the first line of defense. Screening and early intervention are key. Due to the difficulties in getting accurate measurements that screen for and/or index the degree of frailty, such as with self-reports of fatigue, several tools and rating scales have been developed over the past decade (16). Education of practitioners regarding the frailty syndrome, screening and indexing, prevention, intervention, and progression, is essential to curtail the rapid increases in disability and health care expenditures expected with the burgeoning aging population (17).

The clinical definitions, epidemiology, mechanisms, interactions, assessment, prevention, and treatments pertaining to frailty in older adults will be addressed in this review.

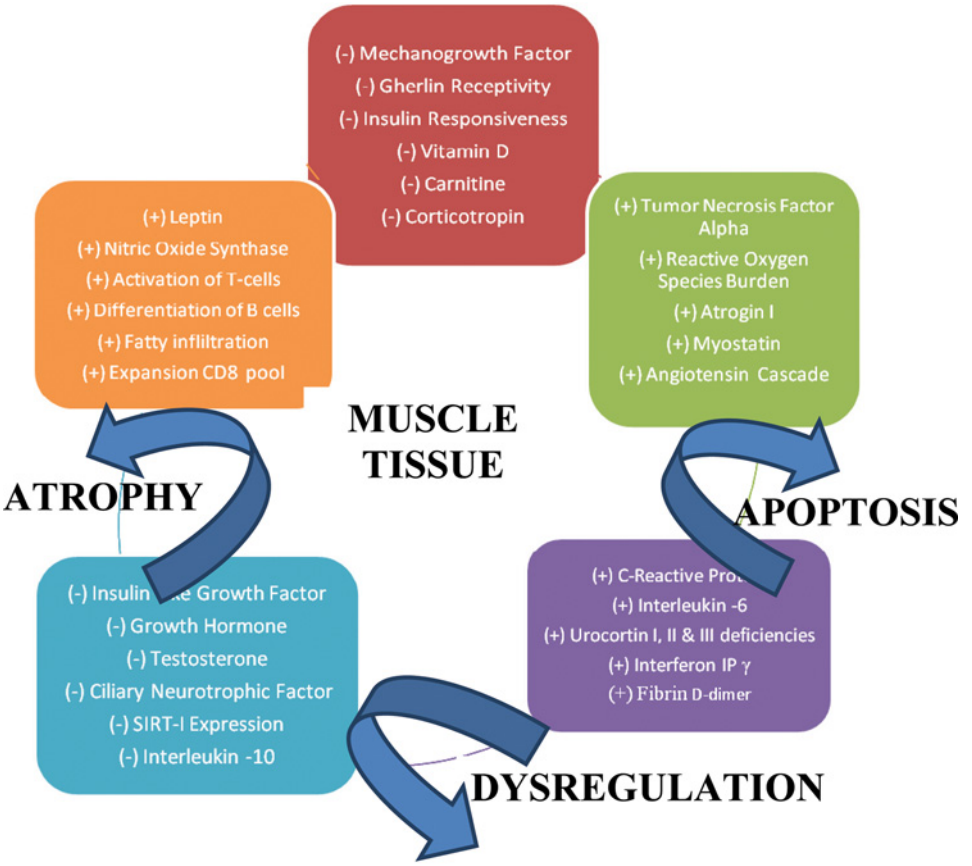
CLINICAL DEFINITIONS

Frailty, as explained by the Geriatric Advisory Panel of the International Academy of Nutrition and Aging, involves weight loss, exhaustion, weakness, slowness, and inactivity but excludes frank disability, which is defined as "impairment that interferes with the ability to perform activities of daily living (ADLs)." Frailty assumes "increased vulnerability to stressors" in "susceptible individuals" and predicts adverse outcomes and ultimately death (18, 19). A stressor can be defined as an event, stimulus, or change to which there is a response; it is often thought of as negative (distress), but positive stimuli can also elicit systemic reactions (20).

Sarcopenia is a fundamental component of the frailty syndrome. Sarcopenia is the age-related loss of lean body tissue (LBM) or muscle mass. Muscle loss is part of the normal aging process; however, LBM losses are greatly exaggerated when there is little physical activity. Sarcopenia in older adults is defined as "LBM less than two standard deviations from the mean of a younger healthy individual of the same gender" (21). In addition to LBM loss, there is a decline in muscle fiber strength and an infiltration of adipose cells, which causes a "decline in overall functionality of remaining muscle." The impact of sarcopenia is heightened when it occurs along with obesity; the term "sarcopenic obesity" refers to individuals who are obese and also meet the criteria for sarcopenia as well as those for whom the decline in muscle mass relative to their total body mass is sufficient to produce disability and other negative health outcomes. In sarcopenic obesity, the adipocytes produce peptides that contribute to heightened inflammation, acceleration of muscle diminution, and insulin resistance. These changes trigger a host of pathophysiological events, which further reduce activity levels and thus increase muscle loss (22). In older adults with sarcopenic obesity, the extent of functional decline is an excellent predictor of morbidity and mortality (23–25).

There are many contributing factors to sarcopenia and frailty in obese and nonobese older adults. Allostatic load, or the "cumulative burden of chronic exposures and elevated response to stressors, mediated by neuroendocrine systems and regulatory feedback mechanisms," is highly correlated with sarcopenia and ultimately with frailty (26, 27). The number of abnormalities rather than their nature determines frailty (Figure 2).

Another contributor to frailty is cachexia or wasting. Cachexia is defined as "a complex metabolic syndrome associated with underlying illness and



† Adapted from: Le Couteur DG, Benson VL, McMahon AC, et al. Determinants of serum-induced SIRT1 expression in older men: the CHAMP Study. *J Gerontol A Biol Sci Med Sci*. 2011; 66A(1): 3–8.
‡ 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(7): 1268–71.
§ Leng SX, Hung W, Cappola AR, et al. White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women. *J Gerontol A Biol Sci Med Sci*. 2009; 64A(4): 499–502.
‖ Marcell TJ. Sarcopenia: causes, consequences, and prevention. *J Gerontol A Biol Sci Med Sci*. 2003;58(10):911–6.

FIGURE 2 Inflammatory cascades linked to frailty in older persons. (Color figure available online.)

characterized by loss of muscle with or without loss of fat mass" (28). Clinically, it involves muscle loss and is often accompanied by "anorexia, inflammation, insulin resistance and muscle protein breakdown" (29). It is associated with the dysregulation of appetitive control peptides such as leptin and neuropeptide Y (NPY) as well as gherlin and orexin through the nitric oxide synthase pathways in the brain and should not be confused with muscle loss due to advanced age, starvation, cognitive disorders, gastrointestinal illnesses that result in malabsorption, and orthyroid abnormalities. Declines in hormones such as testosterone result in hyperleptinemia, which promotes anorexia. Hypogherlinemia fosters the anorectic effects of proinflammatory cytokines. These changes are associated with increased morbidity and mortality over time and belie a complex cascade of metabolic anomalies (30, 31).

Malnutrition and immobility are key to the development of frailty, and alterations in these components are central to its reversal. As an "emergent" or synergistic syndrome, a multifaceted approach is required to combat frailty. The outcome with respect to synergism dictates that the sum of the contributory factors greatly outweighs their presumed additive effects (e.g., one plus one yields a sum of four). Older persons are at risk for "malnutrition" due to decrements in metabolic rate, lean body mass, gastrointestinal function, sensory perception, and fluid and/or electrolyte homeostasis. Poor oral health, chronic disease, polypharmacy, social isolation, hospitalization, cognitive impairment, and pain are contributory. The ability to consume, digest, absorb, utilize, traffic, and excrete is central to nutritional adequacy and ultimately to overall nutriture. Nutritional adequacy becomes a "chicken or egg" dilemma, as frailty imposes decrements in adequacy, and malnutrition contributes to frailty's development (7, 32). Malnutrition speeds LBM loss and decreases competence and therefore underlies declining grip strength, gait speed, and physical function in the frail older adult (33).

Bales and colleagues coined the phrase "nutritional frailty" to represent the phenomenon of unintentional, marked weight loss in older adults that comes strictly from declining oral intake and that is distinct from sarcopenia and cachexia. Nutritional frailty as defined in this way occurs in a smaller subset of all frail individuals and its etiology is complex; age-related physiological and pathophysiological changes are central to its development and other contributory factors include but are not limited to sensory deficits, economic hardship, mental status changes, or polypharmacy (34). Nutritional frailty is associated with decrements in physical function that arise from the loss of both lean and fatty tissues.

Declining physical function, as assessed by weakness indicators, is a risk factor for morbidity, disability, and mortality in older adults. The presentation of weakness in frailty, with declining grip strength, gait speed, and physical activity, is due to the nutritional, sarcopenic, and/or cachectic nature of the syndrome in older adults. Poor grip strength, as measured by dynamometry,

and handgrip fatigue, as measured by vigorimetry, are predictive of poorer long-term outcomes, greater disability, and higher levels of proinflammatory cytokines, such as IL-6 (35). Grip strength deficits are related to perceptions of weakness and often to fatigue and exhaustion (Table 2).

Fatigue, exhaustion, and perceptions of weakness can be measured using a variety of self-report scales, such as the Visual Analogue Scale of Fatigue, Mobility Tiredness Scales, and items from the Quality of Life Comprehensive Questionnaire developed by the World Health Organization (www.who.int/mental_health/who_qol_field_trial_1995.pdf, accessed 2 April 2011). Perceived weakness and fatigue are manifestations of sarcopenia, cachexia, and inflammation.

The Fried criteria for frailty established that weight loss, exhaustion, and weakness were objective measures that heralded a progressive decline in functioning but were distinguishable from comorbid conditions and frank disability. Weakness was evaluated using decrements in grip strength and gait speed as well as physical activity. This paved the way for further refinements in objective criteria. Decrements in gait speed and lower extremity physical functioning have been defined and measured by the International Academy on Nutrition and Aging (IANA) through a comprehensive, systematic review of available literature (36). In an effort to determine a simple, safe way to gauge the predictive ability of gait speed for adverse outcomes in free living older adults, the IANA task force used the following criteria:

- Short distance walk
- Single measurement
- Baseline evaluation
- Longitudinal assessment of outcomes

Using the published results of 27 large cohort studies, the task force determined that having a slow, usual gait speed, defined as less than 1 ms^{-1} over a short distance (4–6 meters), is a consistent predictor of adverse

TABLE 2 Grip Strength Measurements Derived from Cardiovascular Health Study Data[§]

Weakness as determined by measurements of grip strength	
Females	Males
≤17 kg for BMI ≤ 23	≤29 kg for BMI ≤ 24
≤17.3 kg for BMI = 23.1–26	≤30 kg for BMI = 24.1–26
≤18 kg for BMI = 26.1–29	≤30 kg for BMI = 26.1–28
≤21 kg for BMI > 29	≤32 kg for BMI > 28

[§]Pel-Little RE, Schuurmans MJ, Emmelot-Vonk MH, Verhaar HJ. Frailty: defining and measuring of a concept. J Nutr Health Aging. 2009; 13(4):390–4.

outcomes and mortality. While gait speed diminishes by up to 20% with advanced age (in comparison to younger persons), a rapid diminution of pace is also associated with cognitive impairment. It has been hypothesized that declining gait speed is a surrogate measure of inflammation, neurological deficit, sarcopenia, and vulnerability to stressors (37).

Slowing gait is a function of longer stance and support phases of the walk cycle and is the result of neurological and musculoskeletal deficits linked with reductions in motor discharge rate, lower activation of muscle fibers, and poor balance in an individual with reduced LBM in their lower extremities. The long-term effect of declining mobility is the inability to perform ADLs and thus frank disability (38).

There has been a concerted effort to reexamine the components of the clinical definition of frailty. Recently, expert panels have suggested that the operational definition include strength, balance, nutrition, endurance, mobility, activity, cognition, and psychosocial measures (39).

EPIDEMIOLOGY

Age adjusted prevalence from the NHANES 1999–2002 Surveys revealed that females, the oldest age groups, and minorities commonly report problems with physical function (Table 3) (40). Although rates of functional decline in persons older than 65 years have decreased by 2.2% and associated Medicare expenditures have declined 0.9% per annum over the past two decades, it is thought that the trend will reverse with increases in obesity (41). These declines are attributed to better education, nutrition and sanitation, preventative health services, and technological advance (42). While these influences

TABLE 3 Functional Deficits in Older Persons: National Health and Nutrition Examination Surveys 1999–2002 and National Health Interview Survey 2009 of Adults[‡§]

Characteristics	NHANES 1999–2002 Data age adjusted % difficulty					NHIS 2009 data age adjusted % difficulty			
Gender	Males	Females	Males/ Females	Males/ Females	Males/ Females	Males/ Females	Males/ Females	Males/ Females	Males/ Females
Age category	60+	60+	60–69	70–79	80+	65–74	75+	65+ Medicare	65+ Private
Walk a quarter mile	24	34	21	30	49	13	28	21	18
Climb 10 stairs	18	31	18	26	41	9	21	16	12
Stand for 2 hours.	37	47	32	43	63	16	33	25	22

[‡]Summary Health Statistics for U.S. Adults: NHIS 2009, Tables 18, 19 (www.nchs/data/series/sr_10/sr10_249.pdf) pp. 69–71.

[§]Ervin RB. U.S. 1999–2002. Advance Data from Vital and Health Statistics: No. 375. Hyattsville, MD: National Center for Health Statistics; 2006.

remain operational, there are indications that the rapidly growing segments of the oldest old, older, poorer minorities, and obese persons entering the older age brackets will shift current trends toward an increase in malnutrition, functional impairment, and sarcopenic obesity with a concomitant rise in basic functional difficulties, frailty, and care expenditures (Figure 3).

It is estimated that there are currently more than 22 million persons in the United States older than 65 years who experience difficulties with a basic activity, such as walking. Xue and colleagues reported on difficulties walking and other manifestations of frailty in the longitudinal Women's Health and Aging Observational Study, which followed 420 community-dwelling women in the United States for more than 8 years. The incidence for the development of frailty was 9% and reported weakness at baseline heralded frailty in 76% of women. Those who reported weight loss and exhaustion were approximately 4 times more likely to develop all criteria of clinical frailty ($p < 0.05$). The Relative Risk (RR) and Confidence Intervals (CI) for weakness ($RR = 3.7$, $CI = 2.5–5.5$, $p < 0.05$), slow gait ($RR = 1.7$, $CI = 1.1–2.5$, $p < 0.01$), and low activity ($RR = 1.9$, $CI = 1.3–2.9$, $p < 0.05$) in those who had no signs at baseline showed that the development of the syndrome is heterogeneous, with differing entry points into the frailty cycle among aging women (43).

Frailty and mortality has been clinically and spatially modeled using a variety of techniques (44). In the Precipitating Events Project, a longitudinal study of 754 community-dwelling persons older than 70 years, it was found that frail persons easily transition from states of lesser to greater frailty (43%) and, depending on the degree of frailty, 13%–20% will die within 1.5 years (45). Change in circumstance, such as illness or hospitalization, increases risk

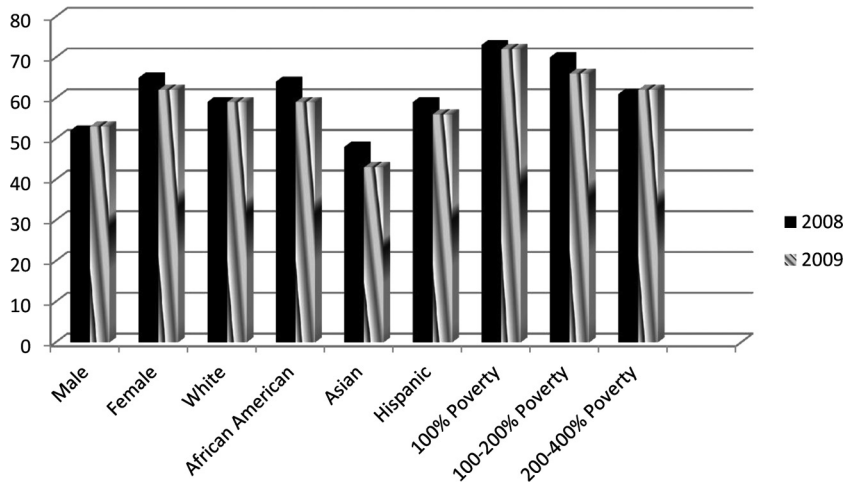


FIGURE 3 Age-adjusted percentages of basic functional difficulty in older persons by demographic characteristics for 2008–2009. Source: Adapted from CDC/NCHS. Health, United States, 2010, Table 54 (www.nchs/data/hus/hus10.pdf#054).

for frailty, disability, and death. A one month hospitalization transitioned the frail to disabled at a 12.4% rate (CI = 12.1–12.7, $p < 0.005$) and to death at 5.1% (CI = 4.9–5.3, $p < 0.01$) (46). In the SAFES study, a longitudinal study of 1,300 frail patients in 9 European hospitals, cox modeling evidenced that gait (RR = 1.7, CI = 1.3–2.3, $p < 0.001$), older age (RR = 1.6, CI = 1.3–2.0, $p < 0.001$), comorbidities (RR = 2.4, CI = 1.5–3.9, $p < 0.001$), and recent hospitalization (RR = 1.4, CI = 1.1–1.7, $p < 0.004$) accurately predicted mortality over a two-year period (47). Analyses of data from the IlSIRENTE study, a longitudinal study of subjects older than 80 years in central Italy, revealed that poor appetite and lower food intake was a strong predictor of frailty, disability, and mortality after adjustment for potential confounders, such as age, gender, body mass index, comorbid diseases, and depression. The disability risk in a two-year period was ~2 times that of older adults with better diets (HR = 2.25, CI = 1.2–4.4, $p < 0.05$) (48).

The frailty index (FI) was constructed as a composite measure of deficits and was evaluated for its predictive capacity for morbidity and mortality. Change, as a function of the progressive worsening of any of four domains, included alterations in strength, gait, body composition, and fatigue. A change of 1° was modeled against morbidity and mortality while controlling for age, gender, and education. Results indicated that for every 1° change per year there was a 5-fold increase in risk for death in frail older persons (HR = 5, CI = 3.1–8.0, $p < 0.01$). Similarly, the FI predicted disability, with an 85% increased risk. Age modified the rate of change so that older age steepened the trajectory of morbidity and mortality (49–51). When the FI was applied to data from the National Population Health Survey of Canada (which followed 2,740 persons older than 65 years, for >10 years) age or gender alone strongly influenced the progression of frailty to disability and death, with women being at greatest risk. Models were then adjusted for age, gender, and other sociodemographic variables, and risk of death was significantly higher with higher FI scores (ARR = 1.6, CI = 1.4–1.7, $p < 0.01$) (52).

Cumulative deficit scoring, or the Deficit Index (DI), was compared with FI. The DI scores the quantity of disorders and signs and symptoms accumulated over the life-course, including variables measured by the FI (which determines phenotypic frailty), but is much broader and may be a better prognosticator for mortality. Data from the Cardiovascular Health Study was used to construct both the FI and DI, using measures from a longitudinal investigation of 5,201 Medicare eligible persons. The results showed that the DI was 55% more precise in its prediction of death than the FI but was not as specific to frailty (53).

In the Women's Health Initiative Studies, a prospective study of 47,657 women aged 65–79 years, incident frailty in a 3-year period was approximately 15%. Strong associations were found between frailty and older age ($p < 0.01$), poverty ($p < 0.01$), less education ($p < 0.01$), African American or Hispanic race ($p < 0.01$), very low or high body mass index (BMI)

($p < 0.01$), chronic physical and/or mental illnesses ($p < 0.01$), smoking ($p < 0.01$), and alcohol use ($p < 0.01$). The Odds Ratio (OR) for underweight women developing frailty was OR = 1.7 (CI = 1.1–2.5, $p < .01$), which was less than those women who had BMI >30, with OR = 4.0 (CI = 3.5–4.5, $p < 0.01$) (54). Similarly, results from the InCHIANTI study, a 6-year longitudinal investigation of outcomes in 934 persons older than 65 years, found that slow gait speed, sarcopenia, and high BMI predicted mortality after adjustment for confounders (HR = 2.2, CI = 1.2–3.8, $p < 0.05$) (55).

Izawa and colleagues investigated the relationships between data on body weight and mortality in 952 frail community-dwelling older adults in Japan. The study was undertaken to see if having consecutive measurements documenting body weight and weight change decreased mortality. Lack of data on weight was associated with increased mortality over a 2-year period (HR = 1.5, CI = 1.1–1.8, $p < 0.001$). The authors concluded that early intervention and treatment was associated with having more information regarding weight status and change in frail elders that lived at home (56).

Weight, sarcopenia, and inactivity are known correlates for mortality in the frail older adult. In the Elderly Health Centers of Hong Kong Study, 54,088 older adults were followed for 4 years and the relationship between obesity, sarcopenia, and death was modeled. In the absence of comorbid conditions, higher BMI groups were at greater risk than those of normal weight (HR = 1.5, CI = 1.1–2.3, $p < 0.001$) and, in the presence of morbidity, the lowest BMI groups had the highest mortality rates (HR = 1.8, CI = 1.6–12.0, $p < 0.01$) (57). In a study of 660 older veterans in the United States, weight changes were highly correlated with mortality. Loss of 3 kg or more increased the adjusted relative risk (ARR) for death to 3.6 (CI = 2.6–5.0, $p < 0.05$) and gain of 3 kg or more resulted in an ARR = 3.7 (CI = 2.3–5.9, $p < 0.05$) (58).

Obesity and overweight alone are known to precipitate morbidity and disability. Obesity has been hypothesized to be a confounder for frailty since it may directly result in slow gait and weakness. The "frail obese" would also have higher levels of inflammatory markers as a result of both obesity and frailty. To compensate, multinomial logistic models should be run controlling for confounders. Analyses of the Women's Health and Aging Studies I and II revealed that obesity was independently related to frailty phenotype, with an OR = 2.2 (CI = 1.3–3.8, $p < 0.01$) for prefrailty and OR = 3.5 (CI = 1.3–9.1, $p < 0.05$ for frailty (59).The position of the North American Association for the Study of Obesity states that obesity in the older adult leads to frailty, and weight loss should be encouraged in those at risk. The percentage of older adults in the United States who are obese has increased in the past decade, with estimates of a 56% and 36% increase among the 60–69 and 70+ age groups respectively. Sarcopenic obesity's relationship to (a) disease, (b) declines in physical function, (c) quality of life, and (d) increased mortality must be considered in relation to the development of frailty and the overlapping benefits of weight loss treatment (60).

Multimorbidity in frail older adults is high. Estimates range upward of 70% and the mean number of chronic diseases is ~2. Wong and associates (61) and Weiss and colleagues (62) in two separates studies found that the most common chronic disease among frail older persons of both genders was hypertension (52% and 60% respectively) and the most common in women was osteoarthritis (78% and 80% respectively). Frailty is not disease specific but is mechanistically specific, with loss of function, malnutrition, and inflammation being hallmarks. Anemia and depression are thought to be two diseases that increase risk through these mechanistic effects (61, 62). Increased mortality has been associated with poor physical function and psychosocial factors, such as depression or low income (63). Bilotta and colleagues found that correlates of frailty in older persons living alone were social isolation, less caregiving, and financial vulnerability. Depression was highly related to frailty in this sample ($OR = 10.4$, $CI = 2.3–47.1$, $p < 0.002$) (64). Being homebound was also associated with psychosocial deficit, depression, frailty, and fiscal vulnerability at much higher levels than the general population, as was institutionalization (65, 66). This is in sharp contrast to Day Care for elders, which was shown to decrease risk for mortality. A longitudinal investigation of 1673 Japanese elders evidenced that after adjusting for confounders such as sociodemographics, the use of Day Care two times ($HR = 0.37$, $CI = 0.2–0.7$, $p < 0.01$) or three times ($HR = 0.56$, $CI = 0.3–0.9$, $p < 0.01$) per week reduced risk of death by 63% and 44% respectively (67).

In the Women's Health and Aging Studies, the odds of being frail were three times greater for older persons with less than a high school education ($OR = 3.0$, $CI = 2–4.5$, $p < 0.05$), were uninsured ($OR = 2.4$, $CI = 1.4–4$, $p < 0.05$), or had lower incomes ($OR = 2.7$, $CI = 1.8–3.9$, $p < 0.05$) (68). In addition to socioeconomic status, neighborhood deprivation was found to be related to frailty and its progression. Using the FI or DI against the Index of Multiple Deprivation (geographic area index of income, employment, health care, education, housing, services, and crime) it was found that frailty was independently related to poverty and neighborhood deprivation after adjustments for age, gender, and education. Older adults who were poorest and living in the most deprived circumstances were more than three times likely to be frail. This was also found in a cohort of British middle-aged adults followed into older age (69, 70). An interesting finding was related to the investigation of "life space" and its ability to accurately predict risk of frailty in women. "Life Space" is defined as the "size of spatial area people purposefully travel through in daily life as well as the frequency with which it occurs". Women who almost never left their homes were 3 times more likely to become frail, and those who infrequently left were at a 1.7 times greater risk (71).

Gender has a marked influence on prevalence and development of frailty. Female gender is associated with heightened fear of falling and avoidance of activity. Fear of falling was associated with increased falls, accidents, disability, and death in frail persons (72, 73). In the Study of Osteoporotic Fractures, a

longitudinal study of 6724 women older than 70 years, frailty was independently associated with falls (OR = 1.4, CI = 1.02–1.9, $p < 0.01$), hip fracture (OR = 1.4, CI = 1.03–1.9, $p < 0.01$), and death (OR = 1.8, CI = 1.6–2.1, $p < 0.01$) regardless of BMI and after adjustment for multiple confounders (74).

In general, frailty, fear of falling, and changes in fitness with aging are greater in women, with men better able to maintain relative levels of fitness over the life-course, with subsequent delays in hospitalization and institutionalization. However, men are still at greater risk for all-cause mortality despite being less frail, regardless of age category (75, 76). When older males were exclusively considered in the longitudinal Osteoporotic Fractures in Men Studies (N = 5,993), frailty increased mortality risk in underweight and overweight groups two-fold, with frail "normal" weight males experiencing the highest risk ratio of 2.4 (CI = 1.5–3.8, $p < 0.01$). Progression from robust to prefrail status in males was 25% and from prefrail to frail was 10%. Forty-two percent of those classified as frail at baseline died in the 4.5-year follow-up period (77). Frail males had greatest risk for adverse outcomes; recurrent falls (OR = 3.0, CI = 2.3–4.1, $p < 0.01$), disability (OR = 5.3, CI = 3.8–7.3, $p < 0.01$), and death (OR = 2.6, CI = 1.8–3.7, $p < 0.01$) (78). Frailty at baseline was associated with lower testosterone levels, sleep disturbances, and sleep disordered breathing (79–81). In other investigations it was found that low testosterone due to androgen deprivation treatment is also highly correlated with frailty, sarcopenic obesity, falls, progression to disability, and deficit accumulation, as is depression. Frail men were shown to have significant increased (46%) prevalence of depression ($p < 0.0001$) and were far more likely to use health and other services and thus incur greater costs (82–84).

In addition to gender, the relationship between race and frailty has been investigated in several large-scale studies. In the Cardiovascular Health Study, African American race was found to be independently related to frailty across all age categories at prevalence rates two times that of Whites. Frail African Americans had less education, less income, and were more frail in the nonobese classifications (males [OR = 7.7, CI = 3.8–15.7, $p < 0.05$]; females [OR = 6.6, CI = 3.1–14.1, $p < 0.05$]) than Whites (85).

Several predisposing factors were identified for development of frailty in Hispanic populations—childhood poverty and malnutrition, adulthood lack of education and employment, and poverty in older age. Being underweight, overweight, or obese was related to frailty in both Hispanic men and women, with women being at greater risk than men across all categories (86). In the Hispanic HANES, frailty was significantly associated with education such that persons with less than 8 years of schooling were 67% more likely to be frail (87). The authors postulated that education was a surrogate for access to health care, health behaviors, self-efficacy, childhood circumstance, and income. Interestingly, in the Hispanic Established Population for the Epidemiological Study of the Elderly, a longitudinal investigation following 3050 noninstitutionalized Mexican Americans older than 65 years, there was

a significant differential in mortality rates between frail men and women (OR = 3.0, CI = 2.2–4.3 versus OR = 1.9, CI = 1.4–2.7, $p < 0.01$) after controlling for sociodemographics, such as education, as well as health behaviors (88). Using data from this cohort, frailty status was found to increase (2x) the progression to disability over a 10-year follow-up period and increase mortality risk by 1.8 (CI = 1.4–2.3, $p < 0.01$). The trajectory from robust to frail appears less steep for Hispanics than those of non-Hispanic cohorts (89–91).

There has been controversy regarding the grouping of results obtained from Latin subgroups (e.g., Mexican, Puerto Rican, Cuban) as one "race" as well as regarding the application of the same frailty criteria to Hispanics as to Caucasians of European decent. The application of ethnic-specific criteria changes the prevalence rates, lowering the number of older Hispanic elders deemed frail versus European Americans, when matched on other demographic variables. The phrase "Hispanic Paradox" has been coined as a result, although acculturation narrows the risk gap between Americans of Hispanic versus European decent (92–95). Cognition and perceived mental and physical health, as measured by Health Related Quality of Life (HRQOL) Index, impacts mortality in frail Caucasians, but in Hispanics only certain facets of the HRQOL were found to be significant (96). Pain was associated with poorer HRQOL, frailty, and mortality; impaired cognitive status was associated with risk and progression of frailty in Hispanics, to the exclusion of other components of the HRQOL (97–99).

In sum, there are differential influences across gender and racial groups with respect to frailty, disability, and mortality. Other sociodemographic and lifestyle variables, mental and physical health, perceived quality of life and health, as well as anthropometrics are all integral to elucidating the risk and relationships surrounding this complex syndrome (100, 101). These findings generate hypotheses form echanistic investigations into frailty.

MECHANISMS

Mechanistically, frailty is a synergistic, multifactorial, complex phenomenon. Many of the factors thought to be influential have yet to be thoroughly studied and their pathways elucidated. The lack of biological resilience in aging is of research interest (102).

Activation of inflammatory and coagulative processes is known to increase with age but can also be independently associated with frailty. Markers for activation of these pathways include the Interleukins (IL), C-Reactive Protein (CRP), Factor VIII, fibrin D-dimer (FDD), and others (103). With regards to the etiology of frailty, it has been hypothesized that inflammation maybe (a) a primary cause, (b) a response to some insult or infection, or (c) a surrogate for some other set of pathophysiological processes associated with dysregulation of cellular, nuclear, transcription, and other homeostatic controls (104). If frailty

is the manifestation of the cumulative damage wreaked by oxidative stress over time or a failure of homeostatic and systemic redundancy controls that result from a lifetime of "insults," the outcome remains the same. The frail system no longer has the ability to handle any additional stress (105).

Increased levels of IL-6, Tumor Necrosis Factor-α (TNF-α), CRP, and FDD have consistently been related to frailty and mortality in older adults. These proinflammatory factors are injurious to muscle and are thought to be central to sarcopenia since they decrease the rate of muscle repair and protein anabolism and increase catabolism through their inhibition of Insulin like Growth Factor-1(IGF-1), or in the case of TNF-α, directly trigger apoptosis (preprogrammed cell death) (106, 107). Frailty is correlated with increased levels of white blood cells, particularly neutrophils (OR = 6.2, CI = 2.6–14.8, $p < 0.01$), monocytes (OR = 2.8, CI = 1.3–5.9, $p < 0.01$), and T-lymphocytes, such as CD8 and CD28 (OR = 3.61, CI = 1.6–5.0, $p < 0.01$), denoting abnormal immune response. Frailty is also associated with decreased levels of anti-inflammatory cytokines, such as IL-10. The dysregulation of immunity is mediated in part by IL-6, but may also be a function of a subclinical viral or bacterial infection (108–111).

There has been evidence of chronic, subclinical Cytomegalovirus (CMV) infections in frail older persons. This may be representative of a trigger for the inflammatory and dysregulated immune response observed. In the Women's Health and Aging Studies, 87% were seropositive for CMV, which, when coupled with high IL-6 levels, drastically increased the odds (20x) for frailty (112, 113). Infection and inflammation change protein kinetics, thus increasing protein degradation and decreasing nitrogen balance. Stress results in an irreversible destruction of essential amino acids to provide substrates for gluconeogenesis. There is an increase in hepatic protein turnover, and alterations in blood coagulation systems, including FDD. Reiner and colleagues investigated the inflammatory response and biomarkers of thrombosis in frail older women, using a nested case control study within the Women's Health Initiative. Frailty was significantly associated with FDD (OR = 1.6, CI = 1.1–2.2, $p < 0.04$) and tissue plasminogen activator (OR = 1.5, CI = 1.1–2.1, $p < 0.03$) (114).

Cytokine production, while a normal response to infection, trauma, and so on, can also be heightened through genotypic anomalies, where a single nucleotide polymorphism (SNP) results in a "pro-inflammatory genotype" that may exaggerate responsivity and explain why some become frail while others do not (115). Alterations in T cell–dependent immunity with aging or cumulative insult or infection is less well characterized. Analyses of antigen-presenting cells called dendritic cells that induce T cells showed that in the presence of cytokines, maturation and antigenic presentation abilities are diminished in frail, aged persons, but not in healthy older adults (116). In an investigation of IL-6, monocytes, chemokine ligands, and stressors that upregulate gene expression it was found that frail persons have a two times

greater expression of stress responsive genes that mediate inflammation through monocytes and cytokines. They also had a greater risk of chemokine ligand 10 overexpression than robust persons, with concomitant rise in IL-6 and monocyte stimulation. Chemokine ligand 10 is also known as interferon γ inducible protein and is a potent proinflammatory compound (117, 118).

Inflammation has also been seen in conjunction with subclinical normocytic anemia in frail older subjects, where hemoglobin and hematocrit are reduced. Increases in IL-6 are associated with abnormal hematopoiesis and chronic disease or infection in addition to muscle catabolism (119). Hematological parameters and known acute phase proteins, such as high alpha-2 macroglobulin and fibrinogen and low albumin, are thought to predict frailty and its progression (120). These alterations may be a result of or the response to another pathophysiological set of processes related to oxidative stress or accumulations of insult from reactive oxygen species (ROS) (121). ROS causes muscle damage, stimulates the apoptotic effects of TNF-α, and is thought to be central to the deficits of aging and sarcopenia.

Oxidative stress is known to be causal for a number of pathological processes, including atherosclerosis, with increased oxidation of Low Density Lipoproteins (LDL-Ox), for example (122). Oxidative stress within the mitochondria leads to the increased production of ROS by damaged mitochondria, resulting in a vicious cycle. Antioxidant nutrients and defense mechanisms such as superoxide dismutase, glutathione peroxidase, or catalase systems must be robust to quench the free radicals. Each of these enzyme systems are dependent on specific minerals, such as Selenium, and aging results in less available antioxidants and anti-oxidant enzyme systems (123).

A marker of oxidative stress, serum-8OHdG, was associated with frailty ($OR = 1.9$, $CI = 1.1–3.5$, $p < 0.03$) and CRP ($OR = 1.9$, $CI = 1.2–3.3$, $p < 0.01$) in a large cohort of older Chinese subjects (124). Frailty was associated with oxidized Glutathione ($OR = 1.8$, $CI = 1.2–2.5$, $p < 0.02$), Malonaldehyde ($OR = 2.8$, $CI = 1.6–4.7$, $p < 0.001$), and HNE protein adducts ($OR = 1.5$, $CI = 1.2–1.8$, $p < 0.001$), as well as TNF-α, which are measures of cell membrane breakdown due to oxidative damage (125). Smoking, which generates considerable oxidative stress, has long been known to increase deficits, frailty, disability, and mortality (126).

Aging affects muscle, with declines in mass, strength, functionality, endurance, and protein synthesis. Mitochondrial dysfunction and concomitant decreases in muscle mitochondrial ATP production, along with alterations in neuropeptides, such as Orexin, Melanocortin, NPY, Leptin, insulin, Gherlin, and triiodothyronine, serve to reduce spontaneous physical activity and reverse the permissive effects of activity on muscle (127). Protein depletion, both visceral and skeletal, is of concern in frailty. Malnutrition and physical inactivity are two areas where intervention may stay declines in function (128).

Skeletal muscle decrements are a function of cachexia, sarcopenia, and atrophy. Protein degradation rates increase, synthesis decreases, and function

is lost with myosteatosis. Specific nutritional issues are related to impairment, such as hypovitaminosis D, protein malnutrition, and abnormal glucose handling with insulin resistance (IR). Age-related IR is an independent determinant of poor muscle strength and function, myosteatosis, and catabolism (129).

Some studies have shown that sarcopenia exists despite normal or even elevated rates of biosynthesis of proteins in muscle with aging (130). Age-related declines in the integrity and function of skeletal muscle persist despite efforts to increase physical stressors on the tissue, which normally improves strength and contractility due to Heat Shock Protein 70 and Ciliary Neutrophic Factor (CNTF). CNTF is a member of the IL-6 family and increases neuronal and muscle growth. Persons who have SNPs for less CNTF are frailer regardless of external influence (131, 132).

Exercise positively influences protein metabolism in skeletal muscle in the aged by changing oxidation rates of key amino acids, such as leucine, and increasing hypertrophy in the presence of adequate protein nutriture. In particular, resistance training greatly enhances the ability of aging muscle to retain fiber strength, decrease adipocyte infiltration, and increase metabolic function. Inactivity greatly exacerbates catabolism and atrophy in skeletal muscle, with deficits in specific (myosin and actin) force producing proteins and abnormal accumulations of collagen and fat (133–135). Efforts to stay the decrements in functionality, strength, and amount of skeletal muscle should be two pronged, involving both diet and resistance exercise. The improvements are related in part to Growth Hormone (GH) and IGF-1 increases and declines in angiotensin II (136, 137).

Heritability of total lean body mass is strong, with linkage of the trait to loci on chromosomes 12 and 14. The genetic predisposition for maintenance of skeletal muscle mass with age has been related to the heritability of androgen receptors in myocytes and the lack of an Apo_{e4}allele (138–140). Despite the clear genetic predisposition to sarcopenia and frailty, the percent decline related to modifiable factors is still greater. Management through behavioral modification, pharmacological approaches, and nutritional interventions are required.

Anorexia, cachexia, and protein calorie malnutrition are central to the frailty syndrome and to sarcopenia. Alterations in the levels of proinflammatory cytokines, hormones, neuropeptides, and nutrients such as vitamin D, zinc, B-12, and leucine increase these in the older adult (141–143). The operational definition of cachexia as a wasting disease implies that anorexia is a key feature and malnutrition is an outcome of reduction in appetite and intake (28). The underlying mechanisms for the "anorexia of aging" are multifactorial (144, 145).

Gherlin is a neuropeptide that is produced by the stomach, stimulates feeding, and has reciprocity with GH and IGF-1. Gherlin, GH, and IGF-1 responsiveness decrease with age and frailty. Exogenous Gherlin administration should stimulate GH and IGF-1 responsiveness while improving body composition and appetite (146–148).

Hormonal change with aging affects body composition and nutriture. Testosterone decreases by 1% every year in men and decreased sex hormone binding globulin intensifies this effect with age (149, 150). Androgens also decline in females and both genders experience significant losses of dehydroepiandosterone (DHEA) with frailty (151). These losses are associated with decrements in muscle mass, increased Leptin levels, and depressed appetite and food intake (152). Cortisol increases with age and the normal diurnal fluctuations are blunted in frailty. Cortisol is a stress hormone and regulates a myriad of homeostatic control mechanisms, including inflammatory pathways, glucose disposition, and hypothalamic control of appetite (153). An interesting finding was that subjects in the Women's Health Initiative, who had autoantibodies against thyroglobulin or thyroid peroxidase, exhibited almost one-third the risk of frailty. Thyroid hormones regulate metabolism and energy balance and indirectly impact appetite and intake (154).

Protein nutriture is of interest in frailty. It is thought that nitrogen retention is low and protein requirements are higher in frail persons. Due to changes in protein kinetics and increased turnover, there is evidence for an increased requirement of 1.1–1.5 g/kg/d with a high proportion of leucine, an essential amino acid (155). Muscle carnitine levels are diminished with age, and carnitine is an amine central to skeletal muscle metabolism as well as the production of energy for T-cells and deactivation of cytokines. Frailty is manifested in myopathy and anorexia, and carnitine supplementation improves both. Carnitine deficiency disrupts energy metabolism, endocrine control, and immunologic response. Because it is responsible for movement fatty acids across the mitochondria with carnitine palmitoyltransferase II (CPII), an investigation into CP II's influence on frailty was undertaken. It appears that CP II deficiency may also play a role in age related decline and frailty (156). Alanine transferase, the protein responsible for conversion of alanine to alpha ketoglutarate, the first step in gluconeogenesis, is also decreased in frail persons ($OR = 3.4$, $CI = 2.5–5.1$, $p < 0.01$) and is associated with a higher rates of mortality (157).

Micronutrients, such as zinc, have been implicated in the anorexia and cachexia of frailty. The Zinc transporter ZnT5 has a corresponding gene called SLC30A5, which can be down-regulated by methylation. This methylation seems to occur more with advancing age, thus decreasing Zn transport and contributing to zinc deficiency (158). Zinc is essential for the regulation of gene expression, inflammatory and immune responsivity, and antioxidant enzyme system activity. Zinc is involved in the transcription of IL-6 and other cytokines. High IL-6, particularly in SNP overexpression, leads to low metallothionine (zinc transporter protein), which in turn decreases available zinc and thus decreases immunity. Low zinc alters the ratio of copper to zinc and results in increased anorexia, cachexia, frailty, and mortality. A high copper to low zinc ratio has been proposed as a screening tool for mortality in frail elderly (159, 160). Similarly, B_{-12}, B_{-12} transport proteins

(Transcobalamin I, II, III) and their genetic polymorphisms have been implicated in much the same way (161). Low and high vitamin D levels were associated with frailty in older adults. Activated vitamin D is a super-hormone with far reaching systemic regulatory capabilities. Authors have postulated a "threshold effect" for the hormone but admit that confounding and inconsistencies across measures and studies could have resulted in spurious findings (162–165).

Caloric restriction has been shown to increase longevity and decrease frailty. The response is thought to be mediated by a class of compounds called "Sirtuins" (SIRT) that are responsible for deacetylation and transfer with NAD and ADP. If the Sirtuins are activated, particularly SIRT1, metabolic responses are coordinated to heighten glucose tolerance, insulin sensitivity, mitochondrial adaptation, and fatty acid oxidation, which are decreased in aging and frailty (166–168). Increases in B-type natriuretic peptide levels (protein responsible for decreasing blood volume) and elevations in the concentrations of glucose, sodium, and potassium in the blood have been correlated with frailty and its progression to disability and mortality. A composite index of plasma tonicity was modeled against frailty and adjusted for sociodemographic, lifestyle, and other confounders. Hypertonicity increased the risk of frailty (2.1, CI = 1.2–3.6, $p < 0.05$), disability (OR = 2.7, CI = 1.3–5.6, $p < 0.05$), and mortality (OR = 1.4, CI = 1.0–1.9, $p < 0.05$) in a 10-year longitudinal study of persons (N = 561) older than 70 years (169–172).

Many of the findings are mechanistically difficult to separate from one another. Due to the inter-related nature of dysregulation that occurs on multiple molecular, cellular, and physiologic systems in frailty, an attempt to account for multidimensionality resulted in the term "allostasis," which refers to an additive load of long-term stress that results in heightened pathophysiological responsivity. In addition to "allostasis" in frailty, specific morbidities must also be considered.

INTERACTION OF CHRONIC DISEASE WITH FRAILTY

Dysregulation of many systems results in a "critical mass" that induces frailty (173). "Allostatic Load" is the conceptualization of multisystem dysfunction and a composite measure has been proposed, using the additive effects of 13 biomarkers (Table 4). For every one unit increase in the Allostatic Load Score there is a 10% increased risk for frailty. The components of the scoring system include measures that might indicate hypertension, cardiovascular disease, diabetes, neuroendocrine abnormality, coagulation dysfunction, and inflammatory processes, among others (174).

Interactions within the multidimensional conceptualization of frailty are numerous. Frailty often presents alongside several indicators of pathogenesis, despite these not being included in the criteria that defines the syndrome.

TABLE 4 Biomarkers Used to Calculate Allostatic Load[‡]

Biomarker	High risk cut point
Systolic blood pressure mmHg	≥148
Diastolic blood pressure mmHg	≥83.33
HDL cholesterol mg/dL	≤36.00
Total/HDL cholesterol	≥5.92
Glycosylated hemoglobin %	≥7.10
Waist to hip ratio	≥0.94
Dehydroepiandosterone sulfate mg/dL	≤5.00
Urinary cortisol μg/g creatinine	≥25.69
Urinary norepinephrine μg/g creatinine	≥48.12
Urinary epinephrine μg/g creatinine	≥5.00
Fibrinogen mg/dL	≥336.00
C-Reactive protein mg/L	≥3.19
Interleukin-6 pg/mL	≥4.65

[‡]Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker for cumulative biological risk: MacArthur Studies of Successful Aging. Proc Natl Acad Sci USA. 2001; 98:4770–5.

Several large-scale investigations have found relationships between frailty status and chronic diseases, such as:

- Anemia
- Hypertension
- Cardiovascular Disease
- Chronic Kidney Disease
- Diabetes Mellitus
- Osteopenia, Fractures, Falls
- Cancer
- HIV Infection
- Oral Health
- Eye Disease
- Cognitive Impairment
- Parkinson Disease
- Depression
- Sleep Disorders

The treatment of these disease states is also associated with frailty, particularly with polypharmacy. Conversely, classification of frailty results in alterations of pharmacokinetics and dynamics and requires alterations in drug dosing and greater vigilance regarding drug-drug, drug-nutrient, and drug-disease interactions. Inflammation, abnormalities in immune function, and loss of redundancy in homeostatic systems of the frail adult are integral to all the chronic diseases described.

Anemia

Anemia is prevalent in community-dwelling older adults, with estimates of 26% and 20% in men and women, respectively. The World Health Organization defines age-specific anemia as Hemoglobin (HgB) values less than 13 g/dL

for men and less than 12 g/dL in women. Institutionalization increases prevalence 2–3 fold. African Americans are at 1.5 times the risk of Whites, and frailty and mortality rates are 2 times as high with diagnosed anemia (175). In an examination of the Women's Health and Aging cohort, frailty was estimated at 14% with the greatest proportion in the lowest quintile of HgB, with adjusted odds of 1.9 (CI = 1.1–3.4, $p < 0.05$) (176). It is hypothesized that approximately one-third of frail anemic older persons have an anemia of unexplained etiology, one-third have an iron deficiency, and one-third have anemia of "chronic disease." Chronic inflammation is known to impact normal hemopoietic capacity and poor oxygenation results in diminished muscle capacity and increases sarcopenia and fatigue, which then furthers frailty (177).

Hypertension

Hypertension is the chronic disease most frequently associated with frailty in older adults. Interestingly, treatment with angiotensin-converting enzyme inhibitors (ACE) significantly decreases frailty incidence in some studies but not in others (178–180). The Renin-Angiotensin System (RAS) regulates blood pressure, electrolytes, inflammation, proliferation, and apoptosis in many vascular and muscular tissues. Aging dysregulates the ratio of RAS receptor activation, which increases proinflammatory cytokine production, oxidative stress, and apoptosis. This mechanistically influences the inception and progression of frailty, particularly in those predisposed by SNPs for exaggerated inflammatory response (181). ACE inhibitors modify RAS receptivity.

Cardiovascular Disease

Frailty's association with CVD has been investigated in several large-scale studies. In a systematic review it was found that CVD was associated with frailty prevalence (OR = 2.8, CI = 2.1–3.7, $p < 0.01$) with decreased survival (−30%) and a 1.5 times greater risk for development in those who were not frail at baseline (182). Using slow gait as a surrogate, frailty accurately predicted mortality in patients with congestive heart failure (CHF), such that after adjustment for confounders the ARR was 1.6 (CI = 1.2–2.3, $p < 0.01$) (183). Profiling frailty in CHF patients and targeting intervention to frailty per se, decreases mortality and results in significant health care cost savings (184). Several authors have postulated that CHF is the clinical manifestation of frailty's progression. The same processes, namely dysregulation of inflammatory, coagulative, and homeostatic controls, are operational in both (185–187).

The presence of frailty in persons with subclinical CVD is high and higher still in those with complicated CVD. Multimorbidity is far more frequently seen in those who are frail (188, 189). Screening and diagnosing frailty in CVD patients is important for determining outcomes with any treatment modality (190). A three-fold greater risk for death is observed for frail patients

undergoing cardiac surgery; advanced age, female gender, and frailty increased the risk to eight-fold. Frail CVD patients who were not treated using newer transcatheterization techniques had greatly elevated risks for long-term institutionalization (OR = 6.3, CI = 4.2–9.4, $p < 0.01$) if they did survive (191–193).

Chronic Kidney Disease

Renal disease is correlated with frailty and vice versa. Frailty was shown to be related to renal insufficiency (OR = 1.8, CI = 1.3–2.4, $p < 0.05$), CKD Stages I/II (OR = 2.2, CI = 1.5–3.9, $p < 0.05$), CKD Stage III (OR = 2.5, CI = 1.6–3.9, $p < 0.05$), and CKD Stages IV/V (OR = 5.9, CI = 3.4–10.1, $p < 0.05$) (194, 195). The mechanistic processes that underlie frailty also underlie renal disease, and the previously described contribution of RAS dysfunction that occurs with aging may be key (196).

It has also been hypothesized that thyroid hormone abnormalities may have a significant role in frailty and CKD. The kidney metabolizes and excretes thyroid hormone; thyroid abnormalities are present at much higher rates in frailty and CKD. Thyroid hormone replacement and GH administration have been mildly effective in combating several of the common pathophysiological features of both frailty and CKD (197, 198).

Diabetes Mellitus

Glucose intolerance, insulin resistance, and DM are associated with frailty (199). Hyperglycemia is independently associated with frailty status after adjustments for all confounders, including BMI and levels of pro-inflammatory cytokines. A glycosylated hemoglobin (Hgb1Ac) > 6.5% was associated with an OR = 2.0 (CI = 1.5–2.6, $p < 0.01$) and an HgB1Ac>9% increased risk to OR = 2.6 (CI = 2.0–3.3, $p < 0.01$) (200). Diagnosed diabetes was associated with frailty (OR = 2.7, CI = 1.7–4.2, $p < 0.05$) and a two-fold increase in risk of progression to disability. Frail diabetics were shown to have 1.6 times the risk for falls and 1.7 times the risk for fracture with a fall. Insulin resistance decreases GH, IGF-1, and Mechanogrowth factor and alters myostatin, Il-6, TNF-α, Gherlin, RAS, and androgen levels, leading to inflammation, sarcopenia, neuropathy, osteopathy, and furthers oxidative damage caused by glycation products in the microvasculature (201, 202).

Osteopenia, Fractures, Falls

Frailty, osteoporosis, falls, and fracture are known correlates in the aged. Frailty increases risk for bone mineral density (BMD) deficit (OR = 1.9, CI = 1.2–2.9, $p < 0.01$), falls (OR = 2.4, CI = 1.9–3.1, $p < 0.01$), and fracture (OR = 1.7, CI = 1.4–2.1, $p < 0.01$) (203, 204). Hip fracture risk is 25 times

higher in frail women with low BMD and a history of falls. Fall characteristics are strongly related to fracture (OR = 5.7, CI = 1.7–13.0, $p < 0.01$), as is sarcopenia. More than 50% of women with low BMD are sarcopenic and frail (205–207).

Frailty, fracture, and subsequent fear of falling serve to hasten the progression to disability and mortality (208, 209). Fracture risk and mortality is associated with higher rates of bone resorption in frail older adults in some studies (HR = 1.7, CI = 1.4–2.0, $p < 0.001$), but not others (210–212). Balance, number of prior fractures, cognitive impairment, polypharmacy, and serum vitamin D concentrations modified these relationships (213–215). Malnourished frail older adults were more likely to fall repeatedly (RR = 3.1, CI = 1.1–10.9, $p < 0.02$) and have a prolonged hospitalization (OR = 5.3, CI = 1.4–20.0, $p < 0.001$) (216, 217). Malnutrition, balance, and lower extremity strength significantly influences falling and fracture risk and accounts for 10% of emergency department visits and 6% of all urgent hospitalizations among older adults (218, 219).

Cancer

Frailty is common among older cancer patients. Prevalence is estimated as high as 88% and frailty predicts adverse outcomes and mortality (220–222). Androgen deprivation therapy for prostate cancer is shown to accelerate frailty and progression to disability and death in older men. Testosterone losses increase fatigue, osteopenia, and sarcopenia (223). Frailty modifies cancer diagnoses with negative effects on prognosis. Both populations tend to be fatigued, sarcopenic, have impaired homeostasis, and little ability to withstand additional stressors. Treatment for cancer may lead to cross infection, disability, and death (224). Nosocomial infection is greatly increased with frailty (RR = 2.1, 1.1–3.8, $p < 0.001$) and further increased with cancer. Cancer and frailty have significant synergistic interactions and must be managed with a tailored approach (225, 226).

HIV

As more HIV-positive persons move into older age brackets, the relationship between HIV seropositivity and frailty is being investigated. Prevalence of frailty in middle age is approximately 9% and rises to almost 50% within the oldest HIV patient population (227). Frailty is thought to increase comorbidity and mortality in this group. CD4-T cell count was independently associated with frailty (228, 229). Interestingly, vitamin D levels appear to be significantly lower in the HIV-positive population. Immunocompromise, depression, malnutrition, frailty, and polypharmacy serve to synergistically hasten progression and worsen outcomes (230). Several factors have been shown to increase comfort and ameliorate progression in the HIV-positive

frail older adult population: social support, continual follow-up, compliance with treatment protocols, and use of care services (231, 232).

Oral Health

Poor oral health is a known risk factor for malnutrition, inflammation, and infection. Pathogenic oral flora enters the bloodstream and the inflammation that ensues contributes to disease. Poor mouth care and decreased fluid consumption and lubrication increase bacterial colonization in the oral cavity (233–235). Frail women in the Women's Health and Aging Studies were far more likely to wear dentures (73%), and denture use was associated with decreased survival rates ($HR = 1.4$, $CI = 1.1–2.0$, $p < 0.05$). Denture wearers who were frail also had much lower fat soluble and B vitamin levels (236). Poor oral health and frailty may interact to synergistically increase inflammation and worsen outcomes (237). Screening for oral health issues should be performed in all frail older adults.

Eye Disease

Age-related macular degeneration (ARMD) has been weakly associated with frailty status in older adults, and age-related cataract has been significantly associated with frailty in both women and men (238, 239). Age adjusted analyses show that frailty is associated with nuclear, cortical, and posterior subscapular cataract. Inflammatory processes are known to be contributory to both ARMD and cataract as well as to frailty.

Cognitive Impairment

Frailty is almost exclusively used to described physical deficit in the aged; the term "complexity" encompasses physical and mental status changes often seen in older adults. There has been a significant push to include cognitive status in the definition of "frailty" for screening and treatment purposes (240). Prevalence of cognitive impairment was more than 50% of very frail patients in one study, while others have shown rates of approximately 20%, with 5 times the risk for disability, 1.9 times the rate of prolonged hospitalization, 1.9 times risk of death, and 5 times the risk of future dementia (241, 242).

Weight loss, malnutrition, and cognitive impairment are strongly associated and synergistic with poorer outcomes and increased mortality risk. Cognitive impairment may reduce intake for a number of reasons, and conversely, several key nutrients have been shown to influence its development. Anti-inflammatory compounds, such as Omega-3 FAs and antioxidants such as the carotenoids, may be preventative in both frailty and cognitive deficit (243–245). Dual tasking ability (performance of a motor task such as walking and a cognitive task such as speaking) is decreased in frailty. It is thought that this decline in dual tasking leads to falls. Fall risk increases with cognitive

impairment among frail persons who dual task (246). Frail, cognitively impaired persons less often improve or stabilize compared with nonfrail persons, and mortality risk is greater (RR = 4.7, CI = 4.5–5.0, $p < 0.05$). Episodes of delirium further increase institutionalization and mortality, with 58.5% dying within 2 years (247, 248).

Parkinson Disease

Frailty seems to be more prevalent in Parkinson disease (PD), but few studies have been done. An investigation of 50 ambulatory PD patients was performed (age $\mu = 71$) and 33% met the criteria for frailty. Statistically significant deficits were observed in frail PD patients versus nonfrail in grip strength ($p < 0.03$), gait speed ($p < 0.002$), and exhaustion ($p < 0.02$). Severity of PD was greater in frail patients; however it is important to note that a PD diagnosis does not imply that frailty is inevitable (249, 250).

Depression

In terms of psychopathology, depression has been reported frequently in noncognitively impaired frail older adults at levels of greater than 14% in community dwellers and greater than 32% of those residing in facilities (251). Mild to moderate cognitive impairment has been associated with even greater depressive symptomatology (+12%, +15%, respectively) (252). Mortality rates in frail depressed persons were almost 70% higher, and women with more depressive symptoms had 2.5 times the risk of death versus women with fewer symptoms (253). Persistence of depression among those diagnosed was greater than 61%, with men much more likely to remain depressed despite treatment (254).

Predictors for depression in frailty included pain, loneliness, and negative life events; perceived inadequacies of care; functional limitation; and cognitive and visual impairment. Depression is a risk factor for anorexia (255). Also of interest are the higher risk rates for depression and anxiety seen among persons who care for the frail older adult population (256, 257).

Sleep Disorders

Sleep wake disturbances are categorized by symptoms of hypersomnia or insomnia. Both are associated with frailty, adverse outcomes, and death in older persons. Drowsiness was increased (OR = 3.8, CI = 2.3–6.3, $p < 0.05$) as was insomnia (OR = 2.8, CI = 1.4–5.7, $p < 0.05$) in frailty. Sleep efficiency lowers with age and is further disrupted by changes in melatonin, GH, cortisol, IL-6, RAS, and a variety of neuropeptides. Depression, cognitive impairment, polypharmacy, pain, and other comorbidities can also significantly affect sleep. Sleep disorders and their treatment also significantly increase falls. Sleep disordered breathing is also increased in frailty, with an age adjusted

risk of 4.9 (CI = 1.4, 16.8, $p < 0.05$) and a 2.8-fold increase in progression to disability (CI = 1.4, 5.4, $p < 0.05$) (258–260).

Polypharmacy

Older adults, particularly those who are frail, use more prescribed and over-the-counter compounds than any other demographic. While there have been reports of certain agents actually decreasing incident frailty (e.g., ACE inhibitors, low dose statin use) due to their inhibition of inflammatory pathways, the vast majority of drugs do not have an ameliorating effect on the incidence or progression of frailty in the aged (261). It has been established by several expert panels that pharmacodynamics and kinetics are dramatically altered with advanced age. These changes are due to decreases in renal clearance, liver function, total body water pools, agent and/or metabolite distribution, LBM:Fat Mass ratios, gastrointestinal absorption, and function of drug metabolizing enzyme systems. These changes also increase drug-nutrient interactions, as they do interactions between drug and disease progression (262). Exogenous drug administration may be classified as a "stressor," which may destabilize the frail person. Falls, confusion, GI blood losses, motility changes, neuroleptic effects, and other adverse outcomes may hasten progression to disability and death in frail older adults (263).

Investigation of drug-drug and drug-disease interactions among frail older adults revealed an increased likelihood of adverse events (OR = 2.7, 1.1–6.6, $p < 0.05$ and OR = 2.1, CI = 1.1–3.9, $p < 0.05$ respectively) (264). Frailty resulted in the omission of prescribed medications after discharge (OR = 2.2, CI = 1.3–3.7, $p < 0.01$), and patient knowledge of adverse events of prescribed medicines was poorer (265, 266). One recent study in Canada found that the average number of medications taken by the very frail older adult (age $\mu = 81.5$ years) in geriatric "day hospitals" was 15, with an average of 8 drug-related problems per person. Many drugs, drug-drug, and drug-disease interactions and their adverse effects have a marked impact on nutritional and functional status (267, 268).

In summary, many chronic disease states have commonalities that underlie both the condition and the syndrome of frailty. Polypharmacy and interactions may constitute significant dangers to the frail demographic. In an effort to improve quality of life and prevention and treatment strategies as well as to decrease health care costs and burden, appropriate screening and assessment of frail persons is essential.

ASSESSMENT OF FRAILTY

The assessment of frailty in the older adult population has been controversial (269, 270). The previously described Fried criteria are dramatically different

from the operational criteria put forward by the American Geriatric Society, for example, where sociodemographics, mental status, and ADLs are used. Even the criteria for assessment of the various components of frailty are debated, such as with sarcopenia (271–273).

Many scales, such as the FI (previously described), rely on comprehensive geriatric assessments; they may require medical personnel, adequate time, and specialized tools or equipment. In an effort to construct and validate a clinically useful, short tool that could be administered by untrained personnel, the Edmonton Frail Scale (EFS) was developed. The EFS was shown to have good face validity, inter-rater reliability, and practicality (274). Armstrong and colleagues investigated the predictive potential of three frailty scales: the Changes in Health End Stage Disease and Signs and Symptoms Scale, the EFS and the FI. All three exhibited excellent prognostic abilities for adverse outcomes in the home health arena (275).

Using components of several scales, domains designated as "Functional," "Biological," and "Burden" were constructed and each tested for its predictive value against the Fried definition of frailty. Each domain captured groups of "frail" older adults within the 11,113 participants of the Health and Retirement Study, and the authors postulated that frailty among older adults took different pathways, each of which was captured by a different "Domain" (276). In another large-scale trial, when "inactivity" was combined with "low energy intake," "weight loss," or "low BMI" and used for predictive purposes, "inactivity + weight loss" was the operational criteria that best identified persons at risk for disability, disease, or death in a population-based sample (277).

In a systematic review of the literature, de Vries and associates evaluated 20 different instruments for their clinimetric properties. Instruments with multiple domains were included so that social, demographic, mental status, nutritional, physical, and mobility constructs were evaluated. It was concluded that the FI was best suited for clinical use and covered all the necessary domains using a continuous scoring system for greater discrimination (278). When the Study of Osteoporotic Fractures Index (SOF) was compared with the Cardiovascular Health Study Index (CHS), it was found that both had excellent predictive potential, but the SOF was shorter and easier to use. The SOF evaluates weight loss, low energy, and inability to rise from a chair (279, 280). However, the case has been made that quick and easy may not be best, and detection of frailty by more comprehensive measures is in the best interest of both the patient and provider, in addition to the researcher (281).

In an investigation comparing the FI versus the Conselice Study of Brain Aging Score (CSBAS), both were found to be specific, sensitive, and predictive of mortality, with the CSBAS using only 7 factors versus FI's evaluation of more than 40 deficits (282). The Tilburg Frailty Indicator (TFI) was constructed to include physical, psychological, social, and QOL domains. It was found to be reliable, valid, and predictive, particularly with respect to QOL and the need for future care (283). Three self-report screening instruments were

evaluated for identification of frailty in a community setting: the Groningen Frailty Indicator (GFI), TFI, and Sherbrooke Postal Questionnaire (SPQ) were examined. The authors found that the GFI and TFI were superior in their screening potential versus the SPQ (284).

Another multidimensional rating scale, the Marigliano-Cacciafesta Polypathological Scale, was developed as an early detection tool for frailty in European elders. A particularly sensitive and quantitative instrument, it presents a mechanism for both identifying and describing the extent of deficits in several domains related to frailty. It was later modified so that a portion could be completed by self-report, thus increasing its ease of use and decreasing the time required to complete the assessment (285, 286). The Ravaglia scale was developed to include nine predictive variables from a variety of domains. The data were easily collected from the medical record and through self-report, and did not require trained personnel. The scale accurately identified frail persons and predicted adverse outcomes (287). Another scale, the Self-Rated Scale of Health Deficits (SRHDI), was developed from the Canadian Study of Health and Aging. The SRHDI was contrasted with the FI and was found to similarly predict mortality in frail older adults. The authors maintained that the self-reported perception of health and social well being accurately reflected their condition and frailty status (288).

Scales using mobility assessment parameters exclusively have been developed to detect frailty. The DeMorton Mobility Index was developed and validated in community-dwelling Australian participants and was found to be both reliable and valid, although the predictive potential for progression and mortality was not adequately assessed (289). Several authors have determined that slow gait speed is the most reliable screener and predictor variable for frailty.

Often, a combination of definitions and measures are used to detect frailty, and the heterogeneity of the frailty syndrome and the variable entry of an individual into the frail state require that different approaches be considered for assessment (290). It has been postulated that population-specific tools should be used so that for any given population of older persons, specific domains, and specific variables within those domains would be highlighted. This tailors the assessment to a more homogenous group of frail persons (291). In contrast, it has been proposed that frail individuals present with standard deficits that are consistent and valid across populations (292). This issue was explored in a comparison between the FI and the British FI. It was determined that the British FI was a "better population metric" (293). There may be differences between assessment from an epidemiological research standpoint and the utility and prognostic ability of a tool in clinical practice. The Clinical Frailty Scale (CFS) was developed for clinicians in an effort to make use of clinical judgment and data that were already being collected in the office visit (294). The CFS only used 7 parameters as opposed to the more than 40 of the FI (295).

Cumulative deficits are the cornerstone of the relationship between frailty and progression to disability and death. Operationalizing definitions and prognostic indicators is key to developing prevention and treatment strategies (296, 297). Clinicians are often reluctant to test and use static measures. Development of a Clinical Global Impression of Change in Physical Frailty was undertaken to account for asymptomatic features, changes over time, and weighting of specific components based on clinical judgment. The European counterpart was made available on the Web (298–300). Hubbard and colleagues, in an exploration of the clinical utility of a variety of indices, determined that significant research remains to be done on which tools are best suited for the clinician (301).

An additional set of issues are presented by the standards currently used for the evaluation of parameters assessed in the diagnoses of frailty. The older adult population, which is so heterogeneous, should have a variety of referent categories for what constitutes "within normal limits." For example, reevaluation of biochemistry and vital sign referent data may be warranted. There may be other features, such as dizziness, senescent swallow, or poor heat or exercise tolerance that require standardization for assessment purposes (302–307). Several investigators have tried to tailor differential standards for assessment to particular populations, such as with CVD patients (308).

In addition to assessment tools for specific patient populations, general tools for frailty identification in hospitalized patients exist. However, many believe that comprehensive geriatric assessment must be coupled with other measures prior to clinical decision making (309–311). This is particularly true of patients entering the surgical arena. Frailty measures, inflammatory biomarkers, and instruments that detect level of cognitive impairment are important in preoperative assessment. Determination of risk levels and potential surgical complications via a comprehensive assessment improves decision making and care, as frail older patients pose a significantly greater surgical risk (312–315).

Nutritional assessment is an extremely important component of the identification of frailty in older adults. Almost all the instruments developed for screening and assessment have a nutritional or at least an anthropometric component. Several screening tools specific to nutrition are available for use in the older adult population, including the Nutritional Risk Index (NRI), Nutritional Risk Score, Nutrition Risk Assessment Scale, Prognostic Nutritional Index (PNI), Patient Generated Subjective Global Assessment (PG-SGA), and the Mini Nutritional Assessment (MNA), among others. All these tools have been validated. Some were designed for specific populations, such as the PNI for surgical inpatients, some are more cumbersome (PG-SGA) and require trained personnel, and some are neither specific nor sensitive enough (NRI) (316). The British Association for Parenteral and Enteral Nutrition has developed a Protein Energy Malnutrition (PEM) specific tool, called the MAG-Tool, which uses BMI, weight loss, clinical factors such as anorexia,

dysphagia, and psychosocial attributes (317). The use of biochemical indicators in addition to age-specific anthropometry and measures of dietary quality are important to nutritional assessment (318–320).

The use of the MNA for frailty assessment has been the subject of considerable inquiry. Scores of 17–23 have been significantly associated with frailty in several studies (321, 322). The MNA was evaluated versus the predictive capacity of the Barthel Index—an indicator of functional status and frailty in older adults. The results indicated that the MNA reliably identified at-risk individuals, adverse events, and mortality, although its specificity required some improvement (323–325). The MNA has been translated into many languages, utilized in many different countries, and has performed well in many different settings (community, long-term care, hospitalized) and across many different subgroups (cognitively impaired, surgical inpatients) (326, 327).

BMI, weight loss, and central adiposity can be used as indicators of functional status, decline, frailty, morbidity, and mortality. There is a U-shaped distribution of BMI associations with adverse outcomes (328–330), indicating the complexity of the relationship and emphasizing the importance of recent weight history and changes in body composition. Various methods have been employed to assess anthropometrics and body composition in older adults. The amount of LBM, Fat Mass (FM), Total Body Water, and Bone Mineral Density (BMD) are all of interest. These can be assessed using dual x-ray absorptiometry, which is expensive and often impractical in some settings (331–333). Utility of Bio-electrical Impedance Analysis (BIA) has been investigated. BIA is noninvasive, easy to use, and does not require specialized personnel. Using geometric modeling equations, estimates of body compartments may be obtained, although age, gender, and hydration greatly influence accuracy. Resting energy expenditure calculation is also important in the nutritional needs assessment of the frail older person and should be a part of a comprehensive work-up (334–338).

Mobility, balance, and physical exertion assessments are critical in determination of frailty and adverse outcome (339, 340). There are several performance tests, Chair Sit to Stand (STS), Timed Up and Go, Timed Rapid Gait (TRG), and Usual Gait Speed (UGS), among others. TRG was found to have the highest specificity and sensitivity. The STS was found to have relatively good predictive potential, and variability of gait within the TRG and UGS had the best predictive capacity. Interestingly, the heterogeneity of mobility characteristics among frail older adults, including variation in gait, is thought to be of mechanistic significance (341–345).

Heterogeneity among the frail and differences in entry points within the frailty cycle have led to a concept titled "variable frailty." Variable frailty implies stratification of the mechanistic underpinnings by unknown factors. Elucidation of these factors would explain why some become frail and others do not, and why frailty is seen more in women, for example (346–348). Understanding the mechanistic and phenotypical differences among frail

persons, and how, when, and where individuals enter the frailty cycle would increase the targeting and efficacy of screening, intervention, and ultimately quality of life in this population (349, 350). This also has implications for formal and informal caregiving, insurance underwriting, and overall health care costs and burden (351–355).

PREVENTION AND TREATMENT

Physical Activity

Physical activity has been investigated for the prevention, delay of inception, treatment and reversal of frailty, and more specifically, sarcopenia in older persons (356–358). Several regimens and types of activity have been studied in this population (359–361). Mechanistically, this is due (in part) to a number of potential benefits, including amelioration of chronic low level inflammation, stemming the loss of type II muscle fibers, decreasing myosteatosis, and increasing muscle strength, among others (362–364). Several large epidemiological studies have found that consistent physical activity over the life-course is protective against frailty. Intervention studies have shown that consistent ($\geq$3 times per week), long-term ($\geq$6 months), multicomponent programs (which include resistance training), along with increased intake of high quality dietary protein and micronutrients, can have a marked, positive impact on frailty's inception and progression in older adults, with or without cognitive impairment (365–371) (Table 5).

Nutrition

Many studies have investigated PEM, micronutriture, and overall nutritional status of frail persons, with the aim of providing recommendations and guidance for preventing, staying, and/or reversing the syndrome (407–409). Many areas have been identified as impacting intake and status, such as sensory diminution; changes in hypothalamic cues for hunger and thirst; and inability to prepare, acquire, or afford high quality, nutrient dense foods, among others. Risk for general malnutrition or deficits in specific macro- or micronutrients have been independently associated with poorer outcomes, poor quality of life, and mortality (410–414).

Risk for PEM has been reported as high as ~15% of community dwellers and ~65% hospitalized and ~75% institutionalized frail older adults. Protein administration has been of interest in combating sarcopenia and frailty (415–419). In the Women's Health Initiative Observational Study significant associations were found between protein intake and frailty. Food Frequency Questionnaires were analyzed and corrected with values derived from 24-hour urinary nitrogen measurements and doubly labeled water. The results indicated that protein, corrected for energy, was related in a dose-responsive

TABLE 5 Physical Activity With and Without Nutrition Interventions in Frail Older Adults (371–406)[†]

Reference	N, μ Age	Study type[‡]	Intervention[§]	Outcome measures[¶]	Benefit
Bates et al., 2009	110, 68	PP	PRTLI, 1x/week for 10 weeks	SF-36, Fitness, Gait, Performance, QOL	↑ strength, agility, flexibility, wellbeing, QOL
Binder et al., 2005	91, 83	RTC	MC, 3x/week for 36 weeks	SF-36, QOL, Balance, Performance, ADLs, DXA, FR	↑ LBM, strength
Blanc-Bisson et al., 2008	76, 85	RTC	PRTLI 5x/week, 4 weeks	ADLs, FR, Hand grip, Performance	↑ strength, protein intake, ADLs
Bonnefoy et al., 2003	57, 72	RTC	FMC 3x/week, 36 weeks + ↑ protein oral supplements	DLH_2O, BMI, REE, MNA, Mobility, Gait, Performance	↑ BMI, strength
Boshuizen et al., 2005	49, 79	RTC	PRTLI 3x/week, 10 weeks	Gait, Activity, Balance, Performance, Speed	↑ strength, speed
Chin et al., 2002	139, 79	RTC	MC 2x/week, 17 weeks + ↑ micronutrient supplements	Fitness, Performance, Balance, Flexibility, Gait, Hand Grip, Biochemical Markers	↑ fitness, micronutrient status
Dehail et al., 2005	28, 86	PP	FMI 5x/week, 4 weeks + ↑ pro-protein ↑ micronutrient oral supplement	BMI, FR, Performance, Biochemical Markers	↑ strength, nutritional status
De Jong et al., 2000	159, 79	RTC	MC 2x/week, 17 weeks + ↑ micronutrient supplements	Fitness, Performance, Balance, Flexibility, Gait, Hand Grip, BMI, DXA, FR	↑ LBM, kcal Intake
De Jong et al., 2001	130, 78	RTC	MC 2x/week, 17 weeks + ↑ micronutrient supplements	Fitness, Performance, Response Time, Biochemical Markers, BMI, SF-36 Equivalent	↑ micronutrient status
Frimel et al., 2008	30, 70	PP	PRTLI 3x/week, 24 weeks + ↓ Kcal diet	Fitness, Performance, DXA	↑ strength, LBM
Hennessey et al., 2001	31, 71	RTC	PRTLI 3x/week, 24 weeks + Growth Hormone	Muscle biopsy, IGF-1, Performance	↑ strength, type II muscle fibers, IGF-1
Hess et al., 2006	27, 82	RTC	PRTHI 3x/week, 10 weeks	Performance, MMSE, Balance, Gait	↑ strength, balance

Kenny et al., 2010	99, 77	RTC	MC 2x/week, 24 weeks + DHEA, Calcium, Vitamin D	Performance, Balance, Gait, Fitness, SF-36, Biochemical markers, DXA	↑ strength, hormone levels
Kryger et al., 2007	11, 89	RTC	PRTLI 3x/week, 12 weeks	Performance, Muscle biopsy, MRI	↑ strength, type I and II muscle fibers, x-sectional area of muscle
Lambert et al., 2008	16, 69	RTC	FMCI 3x/week, 12 weeks	Performance, DXA, Biochemical markers, Muscle biopsy	↑ strength, type II muscle fibers, LBM, Mechanogrowth Factor; ↓ TNF-α, IL-6
Landi et al., 2004	30, 81	RTC	FMCI 3x/week, 4 weeks	Equivalents of SF-36, MMSE	↓ behavioral issues
LaStayo et al., 2003	21, 80	RTC	PRTHI 3x/week, 11 weeks	Performance, Balance, Agility, Muscle Size, Perceived Exertion	↑ strength, balance
Littbrand et al., 2006	91, 85	PP	PRTHI 3x/week, 13 weeks	MMSE, Performance, ADLs, Balance, Equivalent of SF-36, MNA, BMI	↑ strength
Lord et al., 2003	551, 80	RTC	PRTHI 2x/week, 52 weeks	Gait, Performance, Balance, Reaction Times	↑ strength, gait, reaction time
Miller et al., 2006	100, 84	RTC	PRTHI 3x/week, 12 weeks + ↑ kcal micronutrient oral supplement	SF-36, MMSE, QOL equivalents, Anthropometrics, Biochemical indicators	↑ weight
Onambele et al., 2008	24, 70	RTC	PRTHI 3x/week, 12 weeks	Performance, Balance, MRI	↑ strength, balance
Rosendahl et al., 2006	191, 85	RTC	PRTHI 3x/week, 12 weeks + ↑ kcal, protein, micronutrient supplement	Performance, Balance, Gait, ADL, MMSE, MNA	↑ strength, balance
Rydwik et al., 2008,10	96, 83	RTC	MC 3x/week, 12 weeks+Nutrition Counseling Individual Tailored	Performance, Balance, Gait, ADL, Health beliefs	↑ strength, gait, ADL
Schulte et al., 2001	17,84	PP	PRTHI 3x/week, 24weeks	Performance, Leucine Isotope Kinetics	↑ protein synthesis
Seynnes et al., 2004	22, 82	RTC	PRTHI 3x/week, 10 weeks	Performance, Gait, ADL	↑ strength, gait, ADL
Sullivan et al., 2005	71, 78	RTC	PRTLI 3x/week, 12 weeks + Testosterone	Performance, Muscle X-section, ADL, CT Scan, Air Plethysmography, Gait, Balance	↑ strength

(*Continued*)

TABLE 5 Continued

Reference	N, μ Age	Study type[‡]	Intervention[§]	Outcome measures[¶]	Benefit
Sullivan et al., 2007	29, 80	RTC	PRTHI 3x/week, 12 weeks + Megestrol Acetate	Performance, Muscle X-section, ADL, CT Scan, Air Plethysmography, Gait, Balance, FR	↓ strength
Villareal et al., 2003	28, 81	RTC	PRTLI 3x/week, 36 weeks + Hormone Replacement Therapy	Performance, FR, DXA, BMI	↑ strength, bone density ↓ fat mass, BMI
Villareal et al., 2006	27, 70	RTC	PRTLI 3x/week, 24 weeks + Weight Loss Counseling	Performance, FR, BMI, Gait, Balance, ADL, DXA, SF-36, QOL	↑ strength, ADL, gait, balance, health ↓ fat mass, BMI
Villareal et al., 2010	9, 70	RTC	FMI 3x week, 12 weeks	Performance, Balance, Gait, Endurance, Flexibility, Leucine Isotope Kinetics, DXA, Biochemical Markers	↑ strength, LBM, gait, balance, speed, muscle protein synthesis ↓ fat mass,
Villareal et al., 2010	27, 70	RTC	FMI 3x/week, 52 weeks + ↓ Kcal diet + Behavior Modification	Performance, Balance, Gait, Endurance, Flexibility, BMI, DXA, Biochemical Markers	↓ fat mass, BMI, Bone Mineral Density, Osteocalcin, Leptin, Estradiol, Vitamin D
Villareal et al., 2011	93, 70	RTC	FMI 3x/week, 52 weeks + ↓ Kcal diet + Behavior Modification	Performance, Balance, Gait, Endurance, Flexibility, BMI, DXA, SF-36, VO_{2Max}	↑ strength, LBM, gait, balance, speed, VO_{2Max}, ↓ fat mass, Bone Mineral Density
Yareshki, 2003	17, 82	RTC	PRTLI 3x/week, 24 weeks	Performance, Leucine Isotope Kinetics, DXA, ADL, VO_{2Max}	↑ strength, $VO_{2Max,}$ muscle protein synthesis
Zak et al., 2009	91, 79	RTC	FMI 5x/week, 7 weeks + ↑ kcal micronutrient oral supplement	Performance, ADL, MMSE, MNA, FR, BMI, Balance, Gait, Endurance, Biochemical Markers	↑ strength, gait, balance

[†]Citations appear in bibliography. [‡]PP: Pre- versus Postintervention Single, RTC: Randomized Controlled Trial. [§]FMC: Functional Multicomponent Intervention (resistance training, balance, flexibility, and coordination), MC: Multicomponent Intervention (resistance, balance, aerobic), PRTLI: Strength Training (Progressive Resistance Training: Low Intensity, PRTHI: Progressive Resistance Training: High Intensity. [¶]ADL: Activities of Daily Living, DLH_2O: Doubly Labeled Water, DXA: Dual X-Ray Absorptiometry for Body Composition, FR: Food Records, MMSE: Mini Mental Status Exam, MNA: Mini Nutritional Assessment, QOL: Quality of Life Scale, REE: Resting Energy Expenditure, SF-36: Medical Outcomes Short Form 36.

manner to decreased risk for frailty, so that a 20% increase resulted in a 32% lower risk. This translates into highly bioavailable protein levels of 1.5 g/kg body weight or 20% of total calories being protective (420). In a randomized controlled trial of 41 subjects with sarcopenia, oral essential amino acid mixtures increased body weight, decreased insulin resistance, decreased TNF-α, and increased IGF-1and LBM without negatively influencing renal function (421). In a small group of frail women, a 42% increase in protein intake resulted in positive nitrogen balance but had no significant impact on whole body protein turnover. The supplementation of 1.25 g/kg/d for 12 days did not result in accretion of LBM, but the authors concluded that the trial was too short and the sample too small to determine efficacy (422). Similarly, in another small-scale trial, feeding high protein–enriched foods did not result in statistically significant improvements in muscle function but did show some positive effects on nutritional and body composition parameters (423). Previous reviews of studies using high protein oral supplements for sarcopenia and frailty have also shown mixed results (424, 425).

As a result of the high risk rates for malnutrition, improving energy and overall nutrient intake has been investigated in a variety of settings using a number of different strategies such as supplements, Meals on Wheels, flavor augmentation, assisted feeding, and meal-time environment enhancements (426–429). Use of supplements has been shown to reduce mortality by as much as 34% (OR = 0.66, CI = 0.49, 0.90, $p < 0.01$) in malnourished frail persons whose energy requirements are estimated as 20–30 kcal/kg body weight/day (430–432). Several studies have noted an increase in total energy intake and weight gain, without corresponding increases in LBM or muscle strength indices, after supplementation with a nutrient-dense, high energy nutritional drink (433–435). In a randomized controlled study of a high calorie, micronutrient enriched supplement, a significant increase in immune competence ($p < 0.01$) and biochemical markers of antioxidant capacity ($p < 0.05$) was observed after 6 months (436, 437).

Aging affects taste, smell, and swallowing. Flavor augmentation was shown to increase food intake in some studies but not others. In those studies that observed significant effects of flavor enhancements, body weight as well as intake of food, energy, and micronutrients increased (438–440). Treatment that accounts for senescent swallowing and provides appealing foods that have modified textures and consistencies will aid in maintaining more appropriate food intake and caloric, protein, and micronutrient levels. Compassionate assistive feeding by staff, family, and friends improves intake and quality of life in those unable to adequately feed themselves due to neurological impairments, deficits in swallowing reflex, or other issues, such as depression, early satiety, or medication induced changes. Assisted feeding is time and staff intensive but has been shown to significantly improve nutritional and anthropometric indices. Preference for oral intake over placing a tube and initiating enteral feedings should always be carefully considered (441–448).

Meal patterns, timing, preparation, and eating environment have profound impact on nutritional status, particularly in frail elders who have little tolerance for stressors or deficit. Difficulty with shopping, cooking, cleaning up, and enjoying the mealtime environment is cited as a deterrent to obtaining adequate macro- and micronutrients (449, 450). The use of programs such as Meals on Wheels (MOW) improves dietary intake but often does not overcome or prevent deficiencies. The addition of a breakfast delivery as well as the lunch meal delivered by MOW significantly improved nutrient intake, food security, and quality of life in a sample of frail older homebound adults (451, 452). Greater variation in food preferences and foods is also associated with significant improvements in nutritional status. The greater the numbers of different fruits and vegetables and preferences for varied food items, the better the nutrient density, body composition, and biochemical marker profile of the individual (453, 454). Allowing a more liberal diet and greater offerings of foods or the provision of fortified or genetically enhanced foods also improves nutritional status in frail older persons. For example, in a study of low-lactose milk powder use in Chinese elders, an increase in nutrient density was observed, without a concomitant decrease in overall intake (455–459). Making meals pleasurable, attractive, and social and offering snacks and smaller, highly palatable portions enhances intake (460–462). The use of nutrition education for patients, caretakers, and staff as a means of improving intake among frail persons is beneficial and should be employed (463, 464). Educators should note that there are several cultural determinants that may influence nutritional status of older adults, particularly older women. For example, in certain African cultures, elders who care for children are required to give their food away to the young (465).

Micronutriture has been investigated in relationship to frailty and adverse outcome. Low serum levels of vitamins and minerals such as fat soluble vitamins A, D, and E; water soluble vitamins, such as B_6, B_{12}, folate, and C; and minerals such as calcium, zinc and selenium have been independently associated with frailty indicators (466). In the InCHIANTI Study ($N = 802$) low vitamin D ($OR = 2.4$, $CI = 1.5–3.7$, $p < 0.001$), E ($OR = 2.1$, $CI = 1.3–3.3$, $p < 0.003$), C ($OR = 2.2$, $CI = 1.3\text{-}3.5$, $p < 0.001$), and folate ($OR = 1.8$, $CI = 1.2–3.0$, $p < 0.01$) were associated with frailty. Similarly in the Women's Health and Aging Studies, highly significant associations were found between frailty risk and vitamin D, the carotenoids, the B vitamins, calcium, zinc, and selenium (467–469). Mechanistically, these nutrients play an important role in inflammation, quenching free radicals, neuromuscular function, systemic homeostasis, and bone health.

Zinc is known to affect IGF-1, bone turnover, protein transport, protein utilization, and assimilation. In a RTC, zinc was administered along with essential amino acids to frail older adults and was significantly associated with decreased bone resorption indices, increased IGF-1 responsivity and better overall physical functioning (470). Subclinical B_{-12} deficiency has also

been associated with decrements in bone health in frail older persons. Mechanistically, this is due to B_{-12}'s permissive effect on osteoblast proliferation. Folate was found to be protective against falls, such that for every 1 ng increase in serum concentrations, there was a 19% decrease in falls. These findings point to higher levels of B_{-12}, zinc, folate, and vitamin D being associated with lower levels of physical frailty (471, 472).

Several studies have investigated the relationship of vitamin D to frailty. In an analysis of NHANES data, low serum levels of vitamin D, defined as less than 15 ng/mL were associated with a 3.7-fold increased risk of frailty, after adjustment for all confounders (473). A loading dose of vitamin D (200,000 IU) administered to frail patients older than 75 years (N = 323), followed by 800 IU daily for a month, failed to increase serum concentrations to levels known to prevent adverse outcomes (474). In another loading dose trial, 500,000 IUs of vitamin D was administered followed by continued supplementation of 500,000 IU per month. This resulted in an increase in active serum vitamin D, followed by a plateau. No changes were observed in serum calcium levels or PTH among the 63 frail participants (475). In a 6-month trial of vitamin D supplementation, frail older patients had no appreciable decreases in inflammatory or coagulative biomarker concentrations or in markers of bone metabolism and turnover, despite elevations in their circulating levels of activated vitamin D (476).

Vitamin D influences calcium absorption, retention, utilization, and trafficking. Advanced age, along with high levels of phosphorus, phytates, and dietary acid load, among other factors, decrease absorption, while the requirements for the mineral increase. Levels of vitamin D are generally low in frailty, while other factors that diminish calcium absorption are higher, leading to poor bone health and furthering disability. This is particularly dangerous in the older, sarcopenic obese population, where there are pronounced decreases in mobility and no benefit is derived from the extra shear force of body weight on bone (477–480).

The treatment of frailty in obese older adults must be considered, as underweight is no longer the only prognosticator of poor outcomes. Higher protein and micronutrient density on a low calorie diet is far more difficult to achieve. Dietary interventions in the sarcopenic obese population must be tailored and individualized. Intervention should be initiated as part of a multimodal program, which may include exercise and pharmacotherapy (481–483).

Pharmacotherapeutics

The complexity of frailty requires a multifaceted approach to treatment. Pharmacological intervention, with or without other modalities, has been investigated with varying degrees of success (484–487). Low testosterone levels have been independently associated with frailty in some studies but not in all. Testosterone administration has been shown to increase BMD,

muscle mass, and strength in some trials, but these improvements did not necessarily translate into better functional status over time (488–492). Estrogen use in postmenopausal women is also protective for BMD, skeletal muscle integrity, and strength but is known to increase risk for worse cancer outcomes; as is the administration of GH. DHEA, another anabolic steroid, has failed to show clinical effects in either gender. Similarly, Myostatin antagonists and Gherlin secretagogues failed to show long-term clinical improvement upon administration to frail older adults in randomized trials (493–495).

Nonsteroidal selective androgen receptor modulators (SARMS) bind androgen receptors and have skeletal muscle specificity. SARMS increase anabolism in skeletal muscle and bone, without negative effects on prostate and cardiovascular outcomes (496–499). Oxandrolone has been studied in a variety of wasting disorders, and results in improvements in body composition, muscle strength and mass, and functionality, but is associated with significant, far reaching, adverse effects (500).

Orexigenic drugs, such as GH, testosterone, SARMS, megestrol, and dronabinol, have been used, off-label, for the treatment of poor appetite in frail older persons. Megestrol is a synthetic form of progesterone. It has appetite-enhancing effects and has been used for wasting diseases such as cancer cachexia and HIV/AIDS. It has antineoplastic effects for endometrial carcinoma and is also known for its ability to decrease estrogen-mediated carcinogenesis. Megesterol has glucocorticoid effects and long-term administration is known to induce cushinoid syndromes and diabetes. It is also known to have the potential for nephrotoxicity in older adults and has been associated with deep vein thrombosis. Other adverse effects include malaise, dyspnea, sweating, hypertension, and edema. Dronabinol is a synthetic form of tetrahydrocannabinol (one of the active compounds in marijuana) and its adverse effects include paranoia, dizziness, amnesia, and ataxia, which can be particularly problematic in older adults but has been shown to improve appetite and result in weight gain (501–508).

Other

Biofeedback has been utilized with some success for the improvement of balance and gait in frail older persons. Auditory, visual, and "virtual reality" types of biofeedback may be utile when combined with a comprehensive approach to treatment (509, 510). Memory training and psychotherapy has been shown to be beneficial, as has social integration and productive activities, such as volunteering (511–516). Comprehensive interventions are more successful than single intervention approaches.

The use of multimodal assessment, prevention, and intervention strategies, which combine physical activity, nutritional, psychological, medical, pharmacological, social, and environmental components have greater demonstrated efficacy, applicability to varied subgroups, and overall health care cost savings,

in addition to enhancing the quality of life for those they reach (517–529). In addition to developing and maintaining comprehensive prevention and intervention programs, targeting, recruiting, and retaining older persons into these programs is essential. The use of incentives, exemptions, marketing, and advocacy may be warranted to decrease the progression from frailty to states requiring institutionalization, hospitalization, or greater in-home care needs (530–537). Several studies have emphasized the difficulty in preventing these transitions, and even greater deficits in providing coordinated communication and care either within a clinical setting or in the community (538–541). Future research should be aimed at the systematic integration of knowledge from a variety of disciplines to elucidate the best, most comprehensive approach for the prevention and treatment of frailty to reduce health care costs and improve quality of life for frail older adults (542).

CONCLUSIONS

Frailty in older adults is a complex syndrome, characterized by loss of lean body mass, weakness, exhaustion, and decrements in physical function and activity. The frailty syndrome results in an increased vulnerability to stressors, which may propel the progression to disability, comorbidity, and mortality. Mechanistically, the syndrome is mediated through inflammatory and coagulative dysregulation, with alterations in a variety of hormones, peptides, and other homeostatic controls. Adequate assessment and the institution of multicomponent programs for prevention and treatment, involving nutrition, physical activity, and other modalities, is required to reduce health care burdens and improve quality of life for older adults who are frail (543–547).

TAKE AWAY POINTS

- Frailty rates are increasing with shifts in demographics; frailty and obesity may occur in tandem and are not mutually exclusive.
- Frailty has been defined as a clinical syndrome characterized by:
  - Weight and muscle loss
  - Physical exhaustion and weakness
  - Slow gait and lower levels of activity and functionality
- Frailty is not identical to disability, although with the addition of a stressor, frailty easily progresses to disability.
- Frailty assumes the excessive loss of lean body mass, or sarcopenia, as a result of the interaction between many factors: genetics, disease, aging processes, environment, lifestyle, and nutrition.
- Frail older persons are at greater risk for falls, fractures, and complications, thus increasing the likelihood for institutionalization and greater health care expenditures.

- Frailty in older persons is associated with poorer prognosis for comorbid conditions, polypharmacy, and drug interactions.
- A tailored, in-depth assessment of the frail person is crucial to successful intervention.
- Frailty can often be prevented, delayed, and treated if caught early and appropriate interventions are applied.
- A multidisciplinary approach is required for prevention, assessment, and treatment.
- Exercise prescription, adequate nutriture, early treatment of comorbid conditions, amelioration of inflammation, and environmental and lifestyle modifications can offset the pathway from frailty to disability to death in the older adult.

REFERENCES

1. Rockwood K, Abeysundera MJ, Mitniski A. J Am Med Dir Assoc. 2007; 8(9):595–603.
2. Rockwood K, Fox RA, Stolee P, et al. Can Med Assoc J. 1994; 150(4):489–95.
3. Rockwood K, Stadnyk K, McKnight C, et al. Lancet. 1999; 353:205–6.
4. Strawbridge W, Shema SJ, Balfour JL, et al. J Gerontol Psychol Sci Soc Sci. 1998; 53B(1):S9–S16.
5. Fried L, Tangen CM, Walston J, et al. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M146–56.
6. Fried LP, Fernucci I, Darer J, et al. J Gerontol Med Sci. 2004; 59:255–63.
7. Bortz W. J Gerontol A Biol Sci Med Sci. 2010; 65A(3):255–6.
8. Morley JE, Haren MT, Rolland Y, et al. Med Clin N Am. 2006; 90(5):837–47.
9. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. J Am Med Dir Assoc. 2010; 11(5):338–43.
10. Yao X, Li H, Leng SX. Clin Geriatr Med. 2011; 27(1):79–87.
11. Candore G, Caruso C, Colonna-Romano G. Biogerontol. 2010; 11(5):565–73.
12. Hubbard RE, Woodhouse KW. Biogerontol. 2010; 11(5):635–41.
13. Abellan van Kan G, Rolland YM, Morley JE, et al. J Am Med Direct Assoc. 2008; 9(2):71–2.
14. Hubbard RE, Lang IA, Llewellyn DJ, et al. J Gerontol A Biol Med Sci. 2010; 65A(4):377–1.
15. Abellan van Kan G, Rolland Y, Houles M, et al. Clin Geriatr Med. 2010; 26(2):275–86.
16. Pepersack T. J Nutr Health Aging. 2008; 12(5):348–52.
17. Mühlberg W, Sieber CZ. Gerontol Geriatr. 2004; 37(1):2–8.
18. Morley JE, Kim MJ, Haren MT, et al. Aging Male. 2005; 8(3–4):135–40.
19. Abellan van Kan G, Rolland YM, Bergman H, et al. J Nutr Health Aging. 2008; 12:29–37.
20. Paddon-Jones D. J Nutr. 2006; 136(8):2123–6.
21. Morley JE. Nutr. 2001; 17(7–8):660–3.
22. Villareal DT, Banks M, Siener C, et al. Obes Res. 2004; 12(6):913–20.

23. Cruz-Jentoft AJ, Landi F, Topinková E, et al. Curr Opin Clin Nutr Metab Care. 2010; 13(1):1–7.
24. Kirchengast S, Huber J. Anthropol Anz. 2009; 67(2):139–51.
25. Jarosz PA, Bellar A. Geriatr Nurs. 2009; 30(1):64–70.
26. Kuchel GA. J Am Geriatr Soc. 2009; 57(9):1704–6.
27. Barzilay JI, Blaum C, Moore T, et al. Arch Intern Med. 2007; 167(7):635–41.
28. Evans WJ, Morley JE, Argilés J, et al. Clin Nutr. 2008; 27(6):793–6.
29. Morley JE, Farr SA. Nutr. 2008; 24(9):815–9.
30. Krasnow S, Marks D. Curr Opin Support Palliat Care. 2010; 4:266–71.
31. Morley JE. Curr Opin Clin Nutr Metab Care. 2001; 4(1):9–13.
32. Brownie S. Int J Nurs Pract. 2006; 12(2):110–8.
33. Lesourd B. J Nutr Health Aging. 2004; 8(1):28–37.
34. Bales CW, Ritchie CS. Redefining nutritional frailty: Interventions for weight loss due to undernutrition. In: Nutrition and Health: Handbook of Clinical Nutrition and Aging. 2nd ed. New York: Humana Press; 2009:157–83.
35. Bautmans I, Gorus E, Njemini R, et al. BMC Geriatr. 2007; 7:5.
36. Abellan van Kan G, Rolland Y, Andrieu S, et al. J Nutr Health Aging. 2009; 13(10):881–9.
37. Abellan van Kan G, Rolland Y, Bergman H, et al. J Nutr Health Aging. 2008; 12(1):29–37.
38. Thomas EE, Stewart D, Mitchell S, et al. Gait Posture. 2011; 33(3):356–60.
39. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, et al. J Health Nutr Aging. 2010; 14(3):175–81.
40. Ervin RB. Adv Data. 2006; 23(375):1–7.
41. Manton KG. Ann Rev Pub Health. 2008; 29:91–113.
42. Manton KG, Lamb VL, Gu XL. J Aging Health. 2007; 19:359–81.
43. Xue QL, Bandeen-Roche K, Varadhan R, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(9):984–90.
44. Banerjee S, Wall MM, Carlin BP. Biostatistics. 2003; 4(1):123–42.
45. Gill TM, Gahbauer EA, Allore HG, et al. Arch Intern Med. 2006; 166(4):418–23.
46. Gill TM, Allore HG, Gahbauer EA, et al. J Am Med Assoc. 2010; 304(17): 1919–28.
47. Dramé M, Novella JL, Lang PO, et al. Eur J Epidemiol. 2008; 23(12):783–91.
48. Landi F, Russo A, Liperoti R, et al. J Am Dir Assoc. 2010; 11(4):268–74.
49. Rockwood K, Rockwood MR, Eng D, et al. J Am Geriatr Soc. 2010; 58(2):318–23.
50. Buchman AS, Wilson RS. Exp Aging Res. 2009; 35(1):61–82.
51. Fries BE, Morris JN, Skarupski KA, et al. J Gerontol A Biol Sci Med Sci. 2000; 55(6):M336–41.
52. Song X, Mitnitski A, Rockwood K. J Am Geriatr Soc. 2010; 58(4):681–87.
53. Kulminski AM, Ukraintseva SV, Kulminskaya IV, et al. J Am Geriatr Soc. 2008; 56(5):898–903.
54. Woods NF, LaCroix AZ, Gray SL, et al. J Am Geriatr Soc. 2005; 53(8):1321–30.
55. Cesari M, Pahor M, Lauretani F, et al. J Gerontol A Biol Sci Med Sci. 2009; 64(3):377–84.
56. Izawa S, Enoki H, Hirakawa Y, et al. Clin Nutr. 2007; 26(6):764–70.
57. Schooling CM, Lam TH, Li ZB, et al. Arch Intern Med. 2006; 166(14):1498–504.

58. Sullivan DH, Liu L, Roberson PK, et al. J Am Geriatr Soc. 2004; 52(10):1696–701.
59. Blaum CS, Xue QL, Michelon E, et al. J Am Geriatr Soc. 2005; 53(6):927–34.
60. Villareal DT, Apovian CM, Kushner RF, et al. Am J Clin Nutr. 2005; 82(5): 923–34.
61. Wong CH, Weiss D, Sourial N, et al. Aging Clin Exp Res. 2010; 22(1):54–62.
62. Weiss CO. Clin Geriatr Med. 2011; 27(1):39–52.
63. Bowling A. Age Aging. 2009; 38(5):527–30.
64. Bilotta C, Casè A, Nicolini P, et al. Aging Ment Health. 2010; 14(8):1024–36.
65. Qiu WQ, Dean M, Liu T, et al. J Am Geriatr Soc. 2010; 58(12):2423–8.
66. Lee JS, Chau PP, Hui E, et al. Eur J Public Health. 2009; 19(3):308–12.
67. Kuzuya M, Masuda Y, Hirakawa Y, et al. J Am Geriatr Soc. 2006; 54(9):1364–71.
68. Szanton SL, Seplaki CL, Thorpe RJ, et al. J Epidemiol Community Health. 2010; 64:63–7.
69. Lang IA, Hubbard RE, Andrew MK, et al. J Am Geriatr Soc. 2009; 57(10):1776–80.
70. Kuh D, Bassey EJ, Butterworth S, et al. J Gerontol A Biol Sci Med Sci. 2005; 60(2):224–31.
71. Xue QL. Clin Geriatr Med. 2011; 27(1):1–15.
72. Kempen GI, van Haastregt JC, McKee KJ, et al. BCM Public Health. 2009; 9(1):170–7.
73. Kent R, Trowbridge M, Lopez-Valdes FJ, et al. Ann Adv Automotive Med. 2009; 53:41–50.
74. Ensrud KE, Ewing SK, Taylor BC, et al. J Gerontol A Biol Sci Med Sci. 2007; 62(7):744–51.
75. Rockwood K, Song X, Mitnitski A. Canad Med Assoc J. 2011; 183(8):487–94.
76. Mitnitski A, Song X, Skoog I, et al. J Am Geriatr Soc. 2005; 53(12):2184–9.
77. Cawthon PM, Marshall LM, Micheal Y, et al. J Am Geriatr Soc. 2007; 55(8):1216–23.
78. Ensrud KE, Ewing SK, Cawthon PM, et al. J Am Geriatr Soc. 2009; 57(3):492–8.
79. Cawthon PM, Ensrud KE, Laughlin GA, et al. J Clin Endocrinol Metab. 2009; 94(10):3806–15.
80. Wu IC, Lin XZ, Liu PF, et al. Maturitas. 2010; 67(4):348–52.
81. Ensrud KE, Blackwell TL, Redline S, et al. J Am Geriatr Soc. 2009; 57(11):2085–93.
82. Bylow K, Hemmerich J, Mohile SG, et al. J Urolog. 2011; 77(4):934–40.
83. Rantanen T, Penninx BW, Masaki K, et al. J Am Geriatr Soc. 2000; 48(6):613–7.
84. Rochat S, Cumming RG, Blyth F, et al. Age Aging. 2010; 39(2):228–33.
85. Hirsch C, Anderson ML, Newman A, et al. Ann Epidemiol. 2006; 16(7):545–53.
86. Alvarado BE, Zunzunegui MV, Béland F, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(12):1399–406.
87. Leigh JP, Fries JF. J Health Care Poor Underserved. 2002; 13(1):112–27.
88. Berges IM, Graham JE, Ostir GV, et al. J Womens Health. 2009; 18(10):1674–51.
89. Al Snih SA, Graham JE, Ray LA, et al. J Rehabil Med. 2009; 41(11):892–7.
90. Graham JE, Al Snih SA, Berges IM, et al. Gerontol. 2009; 55(6):644–51.
91. Ottenbacher KJ, Graham JE, Al Snih S, et al. Am J Public Health. 2009; 99(4):673–9.
92. Ottenbacher KJ, Ostir GV, Peek MK, et al. J Am Geriatr Soc. 2005; 53(9):1524–31.
93. Espinoza SE, Hazuda HP. J Am Geriatr Soc. 2008; 56(9):1744–9.
94. Espinoza SE, Jung I, Hazuda H. J Am Geriatr Soc. 2010; 58(11):2142–8.
95. Masel MC, Howrey B, Peek MK. J Aging Health. 2011; 23(4):704–13.

96. Masel MC, Ostir GV, Ottenbacher KJ. J Am Geriatr Soc. 2010; 58(11):2149–53.
97. Weaver GD, Kuo YF, Raji MA, et al. J Am Geriatr Soc. 2009; 57(6):992–9.
98. Raji MA, Al Snih S, Ostir GV, et al. J Gerontol A Biol Sci Med Sci. 2010; 65A(11):1228–34.
99. Samper-Ternent R, Al Snih S, Raji MA, et al. J Am Geriatr Soc. 2008; 56(10): 1845–52.
100. Hackstaff L. Soc Work Health Care. 2009; 48(8):798–811.
101. Klein BE, Klein R, Knudtson MD. Arch Gerontol Geriatr. 2005; 41(2):141–9.
102. De Alfieri W, Costanzo S, Borgogni T. Med Hypotheses. 2011; 76(2):304–5.
103. Cohen HJ, Harris T, Pieper CF. Am J Med. 2003; 114(3):180–7.
104. Fedarko NS. Clin Geriatr Med. 2011; 27(1):27–37.
105. Francheschi C, Capri M, Monti D, et al. Mech Aging Dev. 2007; 128:92–105.
106. Leng SX, Cappola AR, Anderson RE, et al. Aging Clin Exp Res. 2004; 16(2):153–7.
107. Hubbard RE, O'Mahony MS, Savva GM, et al. J Cell Mol Med. 2009; 13(9B):3103–9.
108. Van den Biggelaar AH, Huizinga TW, de Craen AJ, et al. Exp Gerontol. 2004; 39:1407–14.
109. Walston J, Fedarko N, Yang H, et al. J Gerontol A Biol Sci Med Sci. 2008; 63:391–8.
110. de Fanis U, Wang GC, Fedarko NS, et al. J Am Geriatr Soc. 2008; 56(5):904–8.
111. Leng SX, Xue QL, Tian J, et al. J Am Geriatr Soc. 2007; 55(6):864–71.
112. Schmaltz HN, Fried LP, Xue QL, et al. J Am Geriatr Soc. 2005; 53(5):747–54.
113. Leng SX, Xue QL, Tian J, et al. Exp Gerontol. 2009; 44(8):511–16.
114. Reiner AP, Aragaki AK, Gray SL, et al. Am J Med. 2009; 122(10):947–54.
115. Soeters PB, Grimble RF. Clin Nutr. 2009; 28(6):583–96.
116. Uyemura K, Caste SC, Makinodan T. Mech Aging Dev. 2002; 123(8):955–62.
117. Qu T, Yang H, Walston JD, et al. Cytokine. 2009; 46(3):319–24.
118. Qu T, Walston JD, Yang H, et al. Mech Aging Dev. 2009; 130(3):161–6.
119. Leng S, Chaves P, Koenig K, et al. J Am Geriatr Soc. 2002; 50(7):1268–71.
120. Mayot G, Vidal K, Martin JF, et al. Exp Gerontol. 2007; 42(6):498–505.
121. Kanapuru B, Erschler WB. Am J Med. 2009; 122(7):605–13.
122. Lenaz G. IUBMB Life. 2001; 52(1):159–64.
123. Romano AD, Serviddio G, de Matthaeis A, et al. J Nephrol. 2010; 23:S29–36.
124. Wu IC, Shiesh SC, Kuo PH. J Am Geriatr Soc. 2009; 57(9):1666–1671.
125. Serviddio G, Romano AD, Greco A, et al. Int J Immunopathol Pharmacol. 2009; 22(3):819–27.
126. Hubbard RE, Searle SD, Mitnitski A, et al. J Nutr Health Aging. 2009; 13(5): 468–72.
127. Nair KS. Am J Clin Nutr. 2005; 81(5):953–63.
128. Vanitallie TB. Metabolism. 2003; 52(10) Suppl 2:22–6.
129. Evans WJ, Paolisso G, Abbatecola AM, et al. Biogerontol. 2010; 11(5):527–36.
130. Kimball SR, O'Malley JP, Anthony JC, et al. Am J Physiol Endocrinol Metab. 2004; 287(4):E772–80.
131. Kayani AC, Close GL, Jackson MJ, et al. Am J Physiol Regul Integr Comp Physiol. 2008; 294(2):R568–76.
132. Arking DE, Fallin DM, Fried LP, et al. J Am Geriatr Soc. 2006; 54(5):823–6.
133. Evans WJ, Campbell WW. Diabetes Nutr Metab. 2000; 13(2):108–12.

134. Osowska S, Duchemann T, Walrand S, et al. Am J Physiol Endocrinol Metab. 2006; 291(3):E582–6.
135. Lemoine JK, Haus JM, Trappe SW, Trappe TA. Muscle Nerve. 2009; 39(4):463–71.
136. Fiatarone-Singh M, Ding W, Manfredi TJ, et al. Am J Physiol. 1999; 277(1) Pt 1:E135–43.
137. Giovannini S, Marzetti E, Borst SE, et al. Mech Aging Dev. 2008; 129(10):593–601.
138. Livshits G, Kato BS, Wilson SG, et al. J Clin Endocrinol Metab. 2007; 92(8):3171–6.
139. Ophoff J, van Proeyen K, Callewaert F, et al. Endocrinology. 2009; 150(8): 3558–66.
140. Passarino G, Montesanto A, DeRango F, et al. Biogerontol. 2007; 8:283–90.
141. Morley JE. J Nutr Health Aging. 2008; 12(7):452–6.
142. Rolland Y, Czerwinski S, Abellan van Kan G, et al. J Nutr Health Aging. 2008; 12(7):433–50.
143. Roubenoff R. Curr Opin Clin Nutr Metab Care. 2003; 6(3):295–9.
144. Morley JE. J Am Med Direct Assoc. 2010; 11(4):225–8.
145. van Staveren WA, de Graaf C, de Groot LC. Clin Geriatr Med. 2000; 18(4):675–84.
146. Sun Y, Garcia JM, Smith RG. Endocrinology. 2007; 148(3):1323–9.
147. Nass R, Pezzoli SS, Oliveri MC, et al. Ann Intern Med. 2008; 149(9):601–11.
148. Serra-Prat M, Palomera E, Clave P, et al. Am J Clin Nutr. 2009; 89(5):1410–7.
149. Morley JE. Rev Endocr Metab Disord. 2005; 6(2):101–8.
150. Mohr BA, Bhasin S, Kupelian V, et al. J Am Geriatr Soc. 2007; 55(4):548–55.
151. Voznesensky M, Walsh S, Dauser D, et al. Age Aging. 2009; 38(4):401–6.
152. Hubbard RE, O'Mahony MS, Calver BL, et al. J Am Geriatr Soc. 2008; 56(2): 279–84.
153. Varadhan R, Walston J, Cappola AR, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(2):190–5.
154. Wang GC, Talor MV, Rose RN, et al. J Clin Endocrinol Metab. 2010; 95(3):1161–8.
155. Morais JA, Chevalier S, Gougeon R. J Nutr Health Aging. 2006; 10(4):272–83.
156. Crentsil V. Aging Res Rev. 2010; 9(3):265–8.
157. Le Couteur DG, Blyth FM, Creasey HM, et al. J Gerontol A Biol Sci Med Sci. 2010; 65(7):712–7.
158. Coneyworth LJ, Mathers JC, Ford D. Proc Nutr Soc. 2009; 68(2):142–7.
159. Mocchegiani E, Basso A, Giaccoini R, et al. Biogerontol. 2010; 11(5):589–95.
160. Mocchegiani E, Corsonello A, Lattanzio F. Biogerontol. 2010; 11(5):523–5.
161. Matteini AM, Walston JD, Bandeen-Roche K, et al. J Nutr Health Aging. 2010; 14(1):73–7.
162. Shardell M, Hicks GE, Miller RR, et al. J Gerontol A Biol Sci Med Sci. 2009; 64(1):69–75.
163. Ensrud KE, Ewing SK, Fredman L, et al. J Clin Endocrinol Metab. 2010; 95(12):5266–73.
164. Nakamura K, Nishiwaki T, Ueno K, et al. J Bone Miner Metab. 2007; 25(4):232–6.
165. Rosen CJ, Manson JE. J Clin Endocrinol Metab. 2010; 95(12):5210–2.
166. Imai S. Curr Opin Clin Nutr Metab Care. 2009; 12(4):350–6.
167. Goulet ED, Hassaine A, Dionne IJ, et al. Exp Gerontol. 2009; 44(11):740–4.
168. Goulet ED, Khursigara Z, Gougeon R, et al. Appl Physiol Nutr Metab. 2010; 35(4):526–33.
169. Lebourgeois F, Golmard JL, Piette F. J Am Geriatr Soc. 2009; 57(2):365–6.

170. Witbam MD, Gillespie ND, Hutcbeon SD, et al. J Am Geriatr Soc. 2005; 53(11): 1991–5.
171. Ritz P, Vol S, Berrut G, et al. Clin Nutr. 2008; 27(5):740–6.
172. Stookey JD, Purser JL, Pieper CF, et al. J Am Geriatr Soc. 2004; 52(8):1313–20.
173. Szanton SL, Allen JK, Seplaki CL, et al. Biol Res Nurs. 2009; 10(3):248–56.
174. Gruenewald TL, Seeman TE, Karlamangla AS, et al. J Am Geriatr Soc. 2009; 57(9):1525–31.
175. Steensma DP, Tefferi A. Mayo Clin Proc. 2007; 82(8):958–66.
176. Chaves PH, Semba RD, Leng SX, et al. J Gerontol A Biol Sci Med Sci. 2005; 60(6):729–35.
177. Artz AS. Semin Hematol. 2008; 45(4):261–6.
178. Onder G, Penninx BW, Blakrishnan R, et al. Lancet. 2002; 359:926–30.
179. Di Bari M, vande Poll-Franse LV, Onder G, et al. J Am Geriatr Soc. 2004; 52:961–6.
180. Gray SL, LaCroix AZ, Aragaki AK, et al. J Am Geriatr Soc. 2009; 57(2):297–303.
181. Abadir PM. Clin Geriatr Med. 2011; 27(1):53–65.
182. Afilalo J, Karunananthan S, Eisenberg MJ, et al. Am J Cardiol. 2009; 103(11): 1616–21.
183. Boxer R, Kepplinger A, Ahmad A, et al. Congest Heart Fail. 2010; 16(5):208–13.
184. Pulignano G, Del Sindaco D, Di Lenarda A, et al. J Cardiovasc Med. 2010; 11(10):739–47.
185. Foebel AD, Hirdes JP, Heckman GA, et al. Chronic Dis Can. 2011; 31(2):49–57.
186. Phan HM, Alpert JS, Fain M. Am J Geriatr Cardiol. 2008; 17(2):101–7.
187. Folsom AR, Boland LL, Cushman M, et al. J Gerontol A Biol Sci Med Sci. 2007; 62(1):79–82.
188. Newman AB, Gottdiener JS, McBurnie MA, et al. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M158–66.
189. McGann PE. Clin Geriatr Med. 2000; 16(3):631–48.
190. Singh M, Alexander K, Roger VL, et al. Mayo Clin Proc. 2008; 83(10):1146–53.
191. Cleveland Jr JC. J Am Coll Cardiol. 2010; 56(20):1677–8.
192. Chikwe J, Adams DH. Seminars Thorac Cardiovasc Surg. 2010; 22(2):109–10.
193. Lee JS, He K, Harbaugh CM, et al. J Vascular Surg. 2011; 53(4):912–17.
194. Shlipak MG, Stehman-Breen C, Fried LF, et al. Am J Kidney Dis. 2004; 43(5):861–7.
195. Wilhelm-Leen ER, Hall YN, Tamura MK, et al. Am J Med. 2009; 122(7): 664–71.e2.
196. Törner A, Odar-Cederlöf I, Kallner A, et al. Aging Clin Exp Res. 2008; 20(3):216–25.
197. Abdel-Rahman EM, Mansour W, Holley JL. Endocrinolog Dialysis. 2010; 23(3):317–23.
198. Abdel-Rahman E, Holley JL. Endocrinolog Dialysis. 2009; 22(5):532–8.
199. Willey KA, Fiatarone Singh MA. Diabetes Care. 2003; 26(5):1580–8.
200. Blaum CS, Xue QL, Tian J, et al. J Am Geriatr Soc. 2009; 57(5):840–7.
201. Morley JE. Clin Geriatr Med. 2008; 24(3):455–69.
202. Araki A, Ito H. Geriatr Gerontol Int. 2009; 9(2):105–14.
203. Ma SL, Oyler J, Glavin S, et al. Osteoporo Int. 2009; 20(11):1837–46.
204. Rolland Y, Abellan van Kan G, Benetos A, et al. J Nutr Health Aging. 2008; 12(5):335–46.
205. de Cullier E, Couris CM, Beauchet O, et al. J Nutr Health Aging. 2010; 14(7):602–8.

206. Janssen HC, Samson MM, Meeuwsen IB, et al. Aging Clin Exp Res. 2004; 16(2):122–5.
207. Frisoli Jr A, Chaves PH, McNeill-Ingham SJ, et al. Bone. 2011; 48(4):952–7.
208. Visschedijk J, Achterberg W, van Balen R, et al. J Am Geriatr Soc. 2010; 58(9):1739–48.
209. Jang SN, Chung HU, Kwon IS, et al. Arch Gerontol Geriatr. 2009; 48(1):89–94.
210. Hignett S, Sands G, Griffiths P. Age Aging. 2011; 40(1):135–8.
211. Sambrook PN, Cameron ID, Chen JS, et al. Osteoporos Int. 2007; 18(5): 603–10.
212. Chen JS, Seibel MJ, Zochling J, et al. Calcif Tissue Int. 2006; 79(1):37–42.
213. Chen JS, Simpson JM, March LM, et al. Age Aging. 2008; 37(5):536–41.
214. Campbell JW, Degolia PA, Fallon WF, et al. Geriatrics. 2009; 64(1):8–13.
215. Pramyothin P, Techasurungkul S, Lin J, et al. Osteoporos Int. 2009; 20(11): 1955–62.
216. Vivanti AP, McDonald CK, Palmer MA, et al. Emerg Med Aust. 2009; 21(5):386–94.
217. Kinney JM. Curr Opin Clin Nutr Metab Care. 2004; 7(1):15–20.
218. Johnson CS. J Nutr Health Aging. 2003; 7(4):247–50.
219. Sambrook PN, Chen CJ, March L, et al. J Bone Miner Res. 2006; 21(4): 549–55.
220. Retornaz F, Monette J, Batist G, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(5):518–22.
221. Flood KL, Carroll MB, Le CV, et al. J Clin Oncol. 2006; 24(15):2298–303.
222. Puts MT, Monette J, Girre V, et al. Crit Rev Oncol Hematol. 2010; 76(2):142–51.
223. Bylow K, Mohile SG, Stadler WM, et al. Cancer. 2007; 110(12):2604–13.
224. Michel JP, Pautex S, Aapro M, et al. J Nutr Health Aging. 2009; 13(1):31–3.
225. Cosquéric G, Sebag A, Ducolombier C, et al. Br J Nutr. 2006; 96(5):895–901.
226. Gosney M. Royal Coll Radiol. 2009; 21(2):86–91.
227. Onen NF, Agbebi A, Shacham E, et al. J Infect. 2009; 59(5):346–52.
228. Ruiz M, Cefalu C. J Int Assoc Physicians AIDS. 2011; 10(2):138–43.
229. Desquilbet L, Margolick JB, Fried LP, et al. J Acquir Immune Syndr. 2009; 50(3):299–306.
230. Ruiz M, Cefalu C. Clin Geriatr. 2011; 19(2):46–9.
231. Carey EC, Covinsky KE, Lui LY, et al. J Am Geriatr Soc. 2008; 56(1):68–75.
232. Boockvar KS, Meier DE. J Am Med Assoc. 2006; 296(18):2245–53.
233. Leibovitz A, Plotnikov G, Habot B, et al. J Gerontol A Biol Sci Med Sci. 2003; 58(1):52–5.
234. Mentes JC. J Gerontol Nurs. 2006; 32(1):13–9.
235. Mojon P, Budtz-Jørgensen E, Rapin CH. Age Aging. 1999; 28(5):463–8.
236. Semba RD, Blaum CS, Bartali B, et al. J Nutr Health Aging. 2006; 10(2):161–7.
237. Jepsen R, Kuchel GA. J Clin Periodontol. 2006; 33(5):309–11.
238. Klein BE, Klein R, Knudtson MD, et al. Am J Opthalmol. 2005; 140:129–30.
239. Klein BE, Klein R, Knudtson MD. Ophthalmology. 2006; 113(12):2209–12.
240. McGeorge SJ. J Psychiatric Ment Health. 2010; 18(1):67–73.
241. Aguilera A, Pi-Figuews M, Arellano M, et al. Arch Gerontol Geriatr Suppl. 2004; 9:7–11.
242. Avila-Funes JA, Amieva H, Barberger-Gateau P, et al. J Am Geriatr Soc. 2009; 57(3):453–61.

243. Gillette-Guyonnet S, Abellan van Kan G, Andrieu S, et al. J Nutr Health Aging. 2007; 11(2):132–52.
244. Shatenstein B, Kergoat MJ, Nadon S. Can J Public Health. 2001; 92(2):143–9.
245. Bhat RS, Chiu E, Jeste DV. Curr Opin Psychiatry. 2005; 18(6):609–14.
246. Lamoth CJ, van Deudekom FJ, van Campen JP, et al. J Neuroengineering Rehabil. 2011; 8:2–10.
247. Mitnitski A, Nader F, Rockwood K. Ann Epidemiol. 2011; 21(7):507–16.
248. Pitkala KH, Laurila JV, Strandberg TE, et al. Dement Geriatr Cogn Disord. 2005; 19(2–3):158–63.
249. Ahmed NN, Sherman SJ, VanWyck D. Parkinsonism Relat Disord. 2008; 14(4):334–7.
250. Powell C. Parkinsonism Relat Disord. 2008; 14(4):271–2.
251. Antsey KJ, von Sanden C, Sargent-Cox K, et al. Am J Geriatr Psych. 2007; 15(6):497–505.
252. McCabe MP, Davison T, Mellor D, et al. Int J Geriatr Psych. 2006; 21:633–44.
253. Yaffe K, Edwards ER, Covinsky K, et al. Am J Geriatr Psych. 2003; 11(5):561–7.
254. Harris T, Cook DG, Victor C, et al. Age Aging. 2006; 35:25–32.
255. Jongenelis K, Pot AM, Eisses AM, et al. J Affect Dis. 2004; 83(2–3):135–42.
256. de Bernardini L, Innamorati M. Arch Gerontol Geriatr. 2007; 44 Suppl 1:139–42.
257. Aggar C, Ronaldson S, Cameron ID. Int J Ment Health Nurs. 2010; 19:409–15.
258. Cochen V, Arbus C, Soto ME, et al. J Nutr Health Aging. 2009; 13(4):322–9.
259. Endeshaw YW, Unruh ML, Kutner M, et al. Am J Epidemiol. 2009; 170(2): 193–202.
260. Vaz Fragoso CA, Gahbauer EA, Van Ness PH, et al. J Am Geriatr Soc. 2009; 57(11):2094–100.
261. LaCroix AZ, Gray SL, Aragaki A, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(4):369–75.
262. Komajda M, Hanon O, Aupetit JF, et al. J Nutr Health Aging. 2006; 10(5):434–44.
263. Huisman-Baron M, van der Veen L, Jansen PA, et al. Drugs Aging. 2011; 28(5):391–402.
264. Hanlon JT, Sloane RJ, Pieper CF, et al. Age Aging. 2011; 40(2):274–7.
265. Wright RM, Sloane R, Pieper CF, et al. Am J Geriatr Pharmacother. 2009; 7(5):271–80.
266. Modig S, Kristensson J, Kristensson-Ekwall A, et al. Eur J Clin Pharmacol. 2009; 65(2):151–5.
267. Farrell B, Szeto W, Shamji S. Can Fam Physician. 2011; 57(6):168–9.
268. Juby AG, Davis P. Clin Rheumatol. 2008; 27(9):1191–4.
269. Conroy S. J Nutr Health Aging. 2009; 13(4):389.
270. Conti AA, Conti A. Med Hypotheses. 2010; 74(6):1090.
271. Katsikas JL, Nelson FV, Bacchus S, et al. Semin Dial. 2009; 22(1):22–4.
272. Drey M, Pfeifer K, Sieber CC, et al. Gerontol. 2011; 57(1):11–8.
273. Abellan van Kan G, André E, Bischoff-Ferrari HA, et al. J Nutr Health Aging. 2009; 13(8):700–7.
274. Rolfson DB, Majumdar SR, Tsuyuki RT, et al. Age Aging. 2006; 35(5):526–9.
275. Armstrong JJ, Stolee P, Hirdes JP, et al. Age Aging. 2010; 39(6):755–8.
276. Cigolle CT, Ofstedal MB, Tian Z, et al. J Am Geriatr Soc. 2009; 57(5):830–9.
277. Chin A, Paw MJ, Dekker JM, et al. J Clin Epidemiol. 1999; 52(11):1015–21.

278. de Vries NM, Staal JB, van Ravensberg CD, et al. Aging Res Rev. 2011; 10(1): 104–14.
279. Ensrud KE, Ewing SK, Taylor BC, et al. Arch Intern Med. 2008; 168(4):382–9.
280. Kiely DK, Cupples LA, Lipsitz LA. J Am Geriatr Soc. 2009; 57(9):1532–9.
281. Filho STR, Lourenço RA, Moreira VG. J Am Geriatr Soc. 2010; 58(2):383–5.
282. Lucicesare A, Hubbard RE, Fallah N, et al. J Nutr Health Aging. 2010; 14(4):278–81.
283. Gobbens RJ, van Assen MA, Luijkx KG, et al. J Am Med Dir Assoc. 2010; 11(5):344–55.
284. Metzelthin SF, Daniëls R, van Rossum E, et al. BMC Public Health. 2010; 10:176–84.
285. Amici A, Baratta A, Linguanti A, et al. Arch Gerontol Geriatr. 2008; 46(3):327–34.
286. Amici A, Pecci MT, Linguanti A, et al. Arch Gerontol Geriatr. 2011; 52(1):e60–5.
287. Ravaglia G, Forti P, Lucicesare A, et al. Age Aging. 2008; 37(2):161–6.
288. Lucicesare A, Hubbard RE, Searle SD, et al. Aging Clin Exp Res. 2010; 22(3): 255–60.
289. Davenport SJ, Hons BP, de Morton NA. Arch Phys Med Rehabil. 2011; 92:51–8.
290. Avila-Funes JA, Helmer C, Amieva H, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(10):1089–96.
291. Montesanto A, Lagani V, Martino C, et al. Age. 2010; 32(3):385–95.
292. Jones D, Song X, Mitnitski A, et al. Aging Clin Exp Res. 2005; 17(6):465–71.
293. Kamaruzzaman S, Ploubids GB, Fletcher A, et al. Health Quality Life Outcomes. 2010; 8(1):123–37.
294. Rockwood K, Song X, Macknight C, et al. Can Med Assoc J. 2005; 173(5):489–95.
295. Searle SD, Mitnitski A, Gahbauer EA, et al. BMC Geriatr. 2008; 8:24.
296. Rockwood K, Mitnitski A. Clin Geriatr Med. 2011; 27(1):17–26.
297. Rothman MD, Leo-Summers L, Gill TM. J Am Geriatr Soc. 2008; 56(12):2211–6.
298. Studenski S, Hates RP, Leibowitz RQ. J Am Geriatr Soc. 2004; 52(9):1560–6.
299. De Lepeleire J, Iliffe S, Mann E, et al. Br J Gen Pract. 2009; 59(562):e177–82.
300. Romero-Ortuno R, Walsh CD, Lawlor BA, et al. BMC Geriatr. 2010; 10:57–68.
301. Hubbard RE, O'Mahony MS, Woodhouse KW. Age Aging. 2009; 38(1):115–9.
302. Cowan DT, Roberts JD, Fitzpatrick JM, et al. Int J Nurs Stud. 2004; 41(3):225–37.
303. Bourdel-Marchasson I, Laksir H, Puget E. Maturitas. 2010; 66(1):39–45.
304. Chester JG, Rudolph JL. J Am Med Dir Assoc. 2011; 12(5):337–43.
305. Gomez F, Curcio CL, Duque G. J Nutr Health Aging. 2011; 15(6):490–7.
306. van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, et al. J Am Med Direct Assoc. 2011; 12(5):344–54.
307. Goodlin SJ. J Cardiac Failure. 2010; 16(5):396–7.
308. Kim H, Choi SE. J Am Geriatr Soc. 2011; 59(2):373–4.
309. Freiheit EA, Hogan DB, Eliasziw M, et al. J Am Geriatr Soc. 2010; 57(8):1526–31.
310. Hoogerduijn JG, Schuurmans MJ, Duijnstee MS, et al. J Clin Nurs. 2007; 16(1): 46–57.
311. Mallery LH, Moorhouse P. J Med Ethics. 2011; 37(2):126–8.
312. Mathias JM. OR Manager. 2010; 26(11):23–4.
313. Pimlot BJ, Jones CA, Beaupre LA, et al. Arch Gerontol Geriatr. 2011; 53(1):90–4.
314. Ronning B, Wyller TB, Seljeflot I, et al. Age Aging. 2010; 39(6):758–61.
315. Robinson TN, Eiseman B, Wallace JI, et al. Ann Surg. 2009; 250(3):449–55.
316. Vellas B, Lauque S, Andrieu S, et al. Curr Opin Clin Nutr Metab Care. 2001; 4(1):5–8.

317. Todorovic V. Br J Community Nurs. 2001; 6(2):54–60.
318. Matteini AM, Walston JD, Fallin MD, et al. J Nutr Health Aging. 2008; 12(5):303–8.
319. Alter G. Popul Stud. 2004; 58(3):265–79.
320. Freisling H, Elmadfa I. Ann Nutr Metab. 2008; 52 Suppl 1:43–6.
321. Abellan van Kan G, Vellas B. J Nutr Health Aging. 2011; 15(3):159–61.
322. Oliveira MRM, Fogaça KCP, Leandro-Merhi VA. Nutr J. 2009; 8(1):54–61.
323. Cereda E, Valzolgher L, Pedrolli C. Clin Nutr. 2008; 27(5):700–5.
324. Donini LM, de Felice MR, Tassi L, et al. J Nutr Health Aging. 2002; 6(2):141–6.
325. Donini LM, Savina C, Rosano A. J Nutr Health Aging. 2003; 7(5):282–93.
326. Izawa S, Kuzuya M, Okada K, et al. Clin Nutr. 2006; 25(6):962–7.
327. Tsai AC, Ku PY. Br J Nutr. 2008; 100(1):152–8.
328. Apovian CM, Frey CM, Wood GC, et al. Obes Res. 2002; 10(8):740–7.
329. Chin A, Paw MJ, de Groot LC, et al. J Nutr Health Aging. 2003; 7(1):55–60.
330. Jensen GL. Clin Geriatr Med. 2005; 21(4):677–87.
331. Ritz P, Sallé A, Audran M, et al. Diabetes Res Clin Pract. 2007; 77(3):405–11.
332. Kyle UG, Genton L, Gremion G, et al. Clin Nutr. 2004; 23(1):79–88.
333. Hansen RD, Williamson DA, Finnegan TP, et al. Am J Clin Nutr. 2007; 86(4): 952–8.
334. Lupoli L, Sergi G, Coin A, et al. Clin Nutr. 2004; 23(6):1371–80.
335. Davidson J, Getz M. J Nutr Elder. 2004; 23(4):47–63.
336. Khalaj-Hedayati K, Bosy-Westphal A, Müller MJ, et al. Nutr Res. 2009; 29(8): 531–41.
337. Gaillard C, Alix E, Salle A, et al. J Nutr Health Aging. 2008; 12(4):277–80.
338. Clegg A, Young J. Clin Med. 2011; 11(1):72–5.
339. Dunlop DD, Semanik P, Song J, et al. Arthritis Rheum. 2005; 52(4):1274–82.
340. Davis DHJ, Rockwood MRH, Mitnitski AB, et al. Arch Gerontol Geriatr. 2011; 53(1):79–83.
341. Kim MJ, Yabushita N, Kim MK, et al. Arch Gerontol Geriatr. 2010; 51(2):192–8.
342. Fallah N, Mitinitski A, Searle SD, et al. J Am Geriatr Soc. 2011; 59(3):524–9.
343. Benton MJ, Alexander JL. Am J Phys Med Rebabil. 2009; 88(7):579–83.
344. Montero-Odasso M, Muir SW, Hall M, et al. J Gerontol A Biol Sci Med Sci. 2011; 66A(5):568–76.
345. Montero-Odasso M, Bergman H, Béland F, et al. Arch Gerontol Geriatr. 2009; 49(2):272–7.
346. Yang Y, Lee LC. J Gerontol B Psychol Sci Soc Sci. 2010; 65B(2):246–55.
347. Sarkisian CA, Gruenewald TL, John Boscardin W, et al. J Am Geriatr Soc. 2008; 56(12):2292–7.
348. Topinková E. Ann Nutr Metab. 2008; 52 Suppl 1:6–11.
349. Booth J, Leadbetter A, Francis M, et al. Nurs Older People. 2005; 16(10):26–8.
350. Booth J, Leadbetter A, Francis M, et al. Nurs Older People. 2005; 17(1):22–4.
351. Chevalier S, Saoud F, Gray-Donald K, et al. J Nutr Health Aging. 2008; 12(10): 721–6.
352. Challa S, Sharkey JR, Chen M, et al. J Nutr Health Aging. 2007; 11(2):179–84.
353. McPhail S, Comans T, Haines T. Clin Rehabil. 2010; 24(11):1036–44.
354. Jenkins KR, Kabeto MU, Fultz NH, et al. J Gerontol Nurs. 2007; 33(4):42–51.
355. Bennett AK. J Insur Med. 2004; 36(1):74–83.
356. Roth SM, Ferrell RE, Hurley BF. J Nutr Health Aging. 2000; 4(3):143–55.

357. Taaffe DR. Aust Fam Physician. 2006; 35(3):130–4.
358. Cesari M, Leeuwenburgh C, Lauretani F, et al. Am J Clin Nutr. 2006; 83(5):1142–8.
359. McCarthy ME. Provider. 2003; 29(8):36–8.
360. Liu CK, Fielding RA. Clin Geriatr Med. 2011; 27(1):101–10.
361. Dziura J, Mendes de Leon C, Kasl S, et al. Am J Epidemiol. 2004; 159(8):759–67.
362. Nicklas BJ, Brinkley TE. Exerc Sport Sci Rev. 2009; 37(4):165–70.
363. Theou O, Jones GR, Overend TJ, et al. Appl Physiol Nutr Metab. 2008; 33(4):651–65.
364. Theou O, Jones GR, Vandervoort AA, et al. Exp Gerontol. 2010; 45(12):909–17.
365. Tager IB, Haight T, Sternfeld B, et al. Epidemiology. 2004; 15(4):479–93.
366. Peterson MJ, Giuliani C, Morey MC, et al. J Gerontol A Biol Sci Med Sci. 2009; 64A(1):61–8.
367. Theou O, Stathokostas L, Roland KP, et al. J Aging Res. 2011; 2011:1–19.
368. Campbell WW, Leidy HJ. J Am Coll Nutr. 2007; 26(6):696S–703S.
369. Fiatarone Singh MA. Asia Pac J Clin Nutr. 2002; 11 Suppl 3:S642–52.
370. Hébuterne X, Bermon S, Schneider SM. Curr Opin Clin Nutr Metab Care. 2001; 4(4):295–300.
371. Heyn PC, Johnson KE, Kramer AF. J Nutr Health Aging. 2008; 12(6):401–9.
372. Bates A, Donaldson A, Lloyd B, et al. Health Promot J Austr. 2009; 20(1):42–7.
373. Binder EF, Yarasheski KE, Steger-May K, et al. J Gerontol A Biol Sci Med Sci. 2005; 60(11):1425–31.
374. Blanc-Bisson C, Dechamps A, Gouspillou G, et al. J Nutr Health Aging. 2008; 12(6):395–9.
375. Bonnefoy M, Cornu C, Normand S, et al. Br J Nutr. 2003; 89(5):731–9.
376. Boshuizen HC, Stemmerik L, Westhoff MH, et al. J Aging Phys Nutr. 2005; 13(1):5–22.
377. Chin A, Paw MJ, de Jong N, et al. Br J Sports Med. 2002; 36(2):126–31.
378. Dehail P, Joseph PA, Faux P, et al. J Nutr Health Aging. 2005; 9(5):356–63.
379. de Jong N, Chin A Paw MJ, de Graaf C, et al. Br J Nutr. 2000; 83(6):605–13.
380. de Jong N, Chin A Paw MJ, de Groot LC, et al. Am J Clin Nutr. 2001; 73(2):338–46.
381. Frimel TN, Sinacore DR, Villareal DT. Med Sci Sports Exerc. 2008; 40(7):1213–9.
382. Hennessey JV, Chromiak JA, DellaVentura S, et al. J Am Geriatr Soc. 2001; 49(7):852–8.
383. Hess JA, Woollacott M, Shivitz N. Aging Clin Exp Res. 2006; 18(2):107–15.
384. Kenny AM, Boxer RS, Kleppinger A, et al. J Am Geriatr Soc. 2010; 58(9):1707–14.
385. Kryger AI, Andersen JL. Scand J Med Sci Sports. 2007; 17(4):422–30.
386. Lambert CP, Wright NR, Finck BN, et al. J Appl Physiol. 2008; 105(2):473–8.
387. Landi F, Russo A, Bernabei R. Arch Gerontol Geriatr Suppl. 2004; 9:235–41.
388. LaStayo PC, Ewy GA, Pierotti DD, et al. J Gerontol A Biol Sci Med Sci. 2003; 58(5):M419–24.
389. Littbrand H, Rosendahl E, Lindelöf N, et al. Phys Ther. 2006; 86(4):489–98.
390. Lord SR, Castell S, Corcoran J, et al. J Am Geriatr Soc. 2003; 51(12):1685–92.
391. Miller MD, Crotty M, Whitehead C, et al. Clin Rehabil. 2006; 20(4):311–23.
392. Onambélé GL, Mganaris CN, Mian OS, et al. J Biomech. 2008; 41(15):3133–8.
393. Rosendahl E, Lindelöf N, Littbrand H, et al. Aust J Physiother. 2006; 52(2):105–13.
394. Rydwik E, Lammes V, Frändin K, et al. Aging Clin Exp Res. 2008; 20(2):159–70.
395. Rydwik E, Lammes V, Frändin K, et al. Arch Gerontol Geriatr. 2010; 51(3):283–9.

396. Schulte JN, Yarasheski KE. Int J Sport Nutr Exerc Metab. 2001; 11 Suppl:S111–8.
397. Seynnes O, Fiatarone Singh MA, Hue O, et al. J Gerontol A Biol Sci Med Sci. 2004; 59(5):503–9.
398. Sullivan DH, Roberson PK, Johnson LE, et al. Med Sci Sports Exerc. 2005; 37(10):1664–72.
399. Sullivan DH, Roberson PK, Smith ES, et al. J Am Geriatr Soc. 2007; 55(1):20–8.
400. Villareal DT, Banks M, Sinacore DR, et al. Arch Intern Med. 2006; 166(8):860–6.
401. Villareal DT, Binder EF, Yarasheski KE, et al. J Am Geriatr Soc. 2003; 51(7):985–90.
402. Villareal DT, Chode S, Parimi N, et al. N Engl J Med. 2011; 364(13):1218–29.
403. Villareal DT, Shah K, Banks MR, et al. J Clin Endocrinol Metab. 2008; 93(6): 2181–7.
404. Villareal DT, Smith GI, Sinacore DR, et al. Obesity. 2011; 19(2):312–8.
405. Yarasheski KE. J Gerontol A Biol Sci Med Sci. 2003; 58(10):M918–22.
406. Zak M, Swine C, Grodzicki T. BMC Public Health. 2009; 9:39.
407. Cherniack EP, Florez HJ, Troen BR. Altern Med Rev. 2007; 12(3):246–58.
408. Tolson D, Schofield I, Booth J, et al. Nurs Times. 2002; 98(28):38–40.
409. Pepersack T. Acta Clin Belg. 2009; 64(2):85–91.
410. Ferry M. Nutr Rev. 2005; 63(6):Pt 2:S22–9.
411. Johansson L, Sidenvall B, Malmberg B, et al. J Nutr Health Aging. 2009; 13(10):855–61.
412. Keller HH, Østbye T, Goy R. J Gerontol A Biol Sci Med Sci. 2004; 59(1):68–74.
413. Lesourd B. Proc Nutr Soc. 2006; 65(3):319–25.
414. Lindberg M, Saltvedt I, Sletvold O, et al. Am J Clin Nutr. 2008; 88(3):722–9.
415. Kaiser MJ, Bandinelli S, Lunenfeld B. Acta Biomed. 2010; 81(1):37–45.
416. Keller HH. J Nutr Health Aging. 2004; 8(4):245–52.
417. Kagansky N, Berner Y, Koren-Morag N, et al. Am J Clin Nutr. 2005; 82(4):784–91.
418. Allard JP. Curr Opin Clin Nutr Metab Care. 2001; 4(4):293–4.
419. Lesourd BM. J Nutr Health Aging. 2004; 8(1):28–37.
420. Beasley JM, LaCroix AZ, Neuhouser ML, et al. J Am Geriatr Soc. 2010; 58:1063–71.
421. Solerte S, Gazzaruso C, Bonacasa R, et al. Am J Cardiol. 2008; 101(11A):69E–77E.
422. Chevalier S, Gougeon R, Nayar K, et al. Am J Clin Nutr. 2003; 78(3):422–9.
423. Smoliner C, Norman K, Scheufele R, et al. Nutrition. 2008; 24(11–12):1139–44.
424. Bales CW, Ritchie CS. Ann Rev Nutr. 2002; 22:309–23.
425. Reuben DR. J Am Geriatr Soc. 2007; 55 Suppl 2:S438–42.
426. Vikstedt T, Suominen MH, Joki A, et al. J Am Med Direc Assoc. 2011; 12(4):302–7.
427. Visvanathan R, Chapman IM. Gastroenterol Clin North Am. 2009; 38(3):393–409.
428. Wells JL, Dumbrell AC. Clin Interv Aging. 2006; 1(1):67–79.
429. van Staveren W, de Groot L. J Nutr Health Aging. 2009; 13(9):759.
430. Gaillard C, Alix E, Sallé A, et al. Clin Nutr. 2007; 26(1):16–24.
431. Gaskill D, Black LJ, Isenring EA, et al. Australas J Aging. 2008; 27(4):189–94.
432. Labossiere R, Bernard MA. Curr Opin Clin Nutr Metab Care. 2008; 11(1):1–6.
433. Payette H, Boutier V, Coulombe C, et al. J Am Diet Assoc. 2002; 192(8):1088–95.
434. Payette H. Can J Physiol Pharmacol. 2005; 83(11):1061–70.
435. Fiatarone-Singh MA, Bernstein MA, Ryan AD, et al. J Nutr Health Aging. 2000; 4(1):5–12.
436. Wouters-Wesseling W, Vos AP, van Hal M, et al. J Nutr Health Aging. 2005; 9(4):281–6.

437. Wouters-Wesseling W, Wagenaar LW, de Groot LC, et al. J Am Coll Nutr. 2003; 22(3):232–8.
438. van Wymelbeke V, Jiang T, Pfitzenmeyer P. J Nutr Health Aging. 2009; 13(1):40–5.
439. de Jong N. Nutrition. 2000; 16(7–8):537–41.
440. Mathey MF, Siebelink E, de Graaf C, et al. J Gerontol A Biol Sci Med Sci. 2001; 56(4):M200–5.
441. Ney DM, Weiss JM, Kind AJ, et al. Nutr Clin Pract. 2009; 24(3):395–413.
442. Germain I, Dufresne T, Gray-Donald K. J Am Diet Assoc. 2006; 106(10):1614–23.
443. Simmons SF, Keeler E, Zhuo X, et al. J Am Geriatr Soc. 2008; 56(8):1466–73.
444. Donini LM, Savina C, Cannella C. J Nutr Health Aging. 2010; 14(6):494–6.
445. Khalaf A, Berggren V, Westergren A. Nurs Ethics. 2009; 16(1):5–18.
446. Dorner B, Posthauer ME, Friedrich EK, et al. Nutr Clin Pract. 2011; 26(3):261–72.
447. Dyck MJ, Schumacher JR. J Gerontol Nurs. 2011; 37(3):22–34.
448. Pauly L, Stehle P, Volkert D. Z Gerontol Geriatr. 2007; 40(1):3–12.
449. Porter EJ. ANS Adv Nurs Sci. 2007; 30(2):159–74.
450. Saletti A, Johansson L, Yifter-Lindgren E, et al. Gerontology. 2005; 51(3):192–8.
451. Roy MA, Payette H. J Nutr Health Aging. 2006; 10(6):554–60.
452. Gollub EA, Weddle DO. J Am Diet Assoc. 2004; 104(8):1227–35.
453. Bernstein MA, Tucker KL, Ryan ND, et al. J Am Diet Assoc. 2002; 102(8): 1096–104.
454. Engelheart S, Lammes E, Akner G. J Nutr Health Aging. 2006; 10(2):96–102.
455. Niedert KC. J Am Diet Assoc. 2005; 105(12):1955–65.
456. Leslie WS. Nutr Soc. 2011; 70:263–7.
457. de Jong N, Adam SG, de Groot LC, et al. Int J Food Sci Nutr. 2000; 51(4):247–57.
458. Kwok T, Woo J, Kwan M. J Nutr Health Aging. 2001; 5(1):17–21.
459. van Staveren WA, Steijns JM, de Groot LC. J Am Coll Nutr. 2008; 27(6):747S–54S.
460. Nazarko L. Prof Nurse. 2002; 18(4):211–4.
461. Ödlund Olin A, Koochek A, Cederholm T, et al. J Nutr Health Aging. 2008; 12(5):295–301.
462. Ödlund Olin A, Koochek A, Ljungqvist O, et al. Eur J Clin Nutr. 2005; 59(2):263–70.
463. Noel M, Reddy M. Prim Care. 2005; 32(3):659–69.
464. Gaskill D, Isenring EA, Black LJ, et al. J Nutr Health Aging. 2009; 13(10):913–7.
465. Kikafunda JK, Lukwago FB. Nutr. 2005; 21(1):59–66.
466. Kaiser MJ, Bandinelli S, Lunenfeld B. Aging Male. 2009; 12(4):87–94.
467. Bartali B, Frongillo EA, Bandinelli S, et al. J Gerontol A Biol Sci Med Sci. 2006; 61(6):589–93.
468. Ble A, Cherubini A, Volpato S, et al. J Gerontol A Biol Sci Med Sci. 2006; 61(3):278–83.
469. Ray AL, Semba RD, Walston J, et al. J Nutr. 2006; 136:172–6.
470. Rodondi A, Ammann P, Ghilardi-Beuret S, et al. J Nutr Health Aging. 2009; 13(6):491–7.
471. Dhonukshe-Rutten RA, Lips M, de Jong N, et al. J Nutr. 2003; 133(3):801–7.
472. Shahar D, Levi M, Kurtz I, et al. Ann Nutr Metab. 2009; 54(1):59–66.
473. Wilhelm-Leen ER, Hall YN, deBoer IH, et al. J Intern Med. 2010; 268(2):171–80.
474. Deschasse G, Dardaine-Giraud V, Constans T. J Am Geriatr Soc. 2009; 57(11): 2155–7.
475. Bacon CJ, Gamble GD, Horne AM, et al. Osteoporosis Int. 2009; 20(8):1407–9.

476. Bjorkman MP, Sorva AJ, Tilvis RS. J Nutr Health Aging. 2009; 13(5):435–9.
477. Zochlin J, Chen JS, Seibel M, et al. Clin Rheumatol. 2005; 24(6):576–82.
478. Nieves JW. Clin Geriatr Med. 2003; 19(2):321–35.
479. Jacobs Jr DR, Hohe C, Mursu J, et al. Br J Nutr. 2010; 104:1537–43.
480. Wynn E, Lanham-New SA, Krieg MA, et al. J Nutr. 2008; 138(7):1349–54.
481. Miller MD, Thomas JM, Cameron ID, et al. Br J Nutr. 2009; 101(9):1300–5.
482. Johnson CS, Begum MN. Nutr Elder. 2008; 27(1–2):65–82.
483. Chau S, Cho LM, Jani P, et al. Curr Opin Clin Nutr Metab. 2008; 11(1):27–31.
484. Rocchiccioli JT, Sanford JT. J Gerontol Nurs. 2009; 35(1):18–24.
485. Ko FC. Clin Geriatr Med. 2011; 27(1):89–100.
486. Lang PO, Michel JP, Zekry D. Gerontol. 2009; 55(5):539–49.
487. McMinn J, Steel C, Bowman A. Br Med J. 2011; 342:1732–41.
488. Kenny AM, Kleppinger A, Annis K, et al. J Am Geriatr Soc. 2010; 58(6):1134–43.
489. Morley JE. Aging Male. 2011; 14(1):1–3.
490. O'Connell MD, Roberts SA, Srinivas-Shankar U, et al. J Clin Endocrinol Metab. 2011; 96(2):454–8.
491. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. J Clin Endocrinol Metab. 2010; 95(2):639–50.
492. Bhasin S. J Clin Endocrinol Metab. 2010; 95(2):509–11.
493. Jeffe DB, Binder EF, Williams DB, et al. Menopause. 2001; 8(2):127–34.
494. Nass R, Johannsson G, Christiansen JS, et al. Growth Horm IGF Res. 2009; 19(2):89–100.
495. Morley JE. J Am Med Direct Assoc. 2010; 11(8):533–6.
496. Morley JE. Curr Pharm Des. 2009; 15(29):3384–95.
497. Bhasin S, Jasuja R. Curr Opin Clin Nutr Metab Care. 2009; 12(3):232–40.
498. Morley JE. Curr Pharm Des. 2007; 13(35):3637–7.
499. Vajda EG, Hogue A, Griffiths KN, et al. J Bone Miner Res. 2009; 24(2):231–40.
500. Orr R, Fiatarone-Singh M. Drugs. 2004; 64(7):725–50.
501. Robertson RG, Montagnini M. Am Fam Physician. 2004; 70(2):343–50.
502. Quinlan N, O'Neill D. Arch Intern Med. 2008; 168(19):2171–2.
503. Golden AG, Daiello LA, Silverman MA, et al. Am J Ther. 2003; 10(4):292–8.
504. Raney MS, Anding R, Fay V, et al. J Am Med Dir Assoc. 2000; 1(4):154–8.
505. Simmons SF, Walker KA, Osterweil D. J Am Med Dir Assoc. 2004; 5(1):24–30.
506. Simmons SF, Walker KA, Osterweil D. J Am Med Dir Assoc. 2005; 6(3) Suppl:S5–11.
507. Yeh S, Lovitt S, Schuster M. J Nutr Health Aging. 2009; 13:448–54.
508. Marshall LL. Consult Pharm. 2003; 18(9):764–73.
509. Zijlstra A, Mancini M, Chiari L, et al. J Neuroengineering Rehabil. 2010; 7(1):58–73.
510. Sihvonen SE, Sipilä S, Era PA. Gerontol. 2004; 50(2):87–95.
511. Gillette-Guyonnet S, Abellan van Kan G, Andrieu S, et al. J Nutr Health Aging. 2008; 12(8):520–9.
512. Sherman FT. Geriatr. 2009; 64(2):6–7.
513. Park-Lee E, Fredman L, Hochberg M, et al. J Am Geriatr Soc. 2009; 57(4):627–33.
514. Hawton A, Green C, Dickens AP, et al. Qual Life Res. 2011; 20(1):57–67.
515. Jung Y, Gruenewald TL, Seeman TE, Sarkisian CA. J Gerontol B Psychol Sci Soc Sci. 2009; 65B(2):256–61.
516. Vernooij-Dassen M, Leatherman S, Rikkert M. Br Med J. 2011; 342:1062–3.

517. Fairhall N, Sherrington C, Kurrle SE, et al. Physiotherapy. 2011; 97(1):26–32.
518. Fairhall N, Aggar C, Kurrle SE, et al. BMC Geriatr. 2008; 8:27.
519. Wells JL, Seabrook JA, Stolee P, et al. Arch Phys Med Rehabil. 2003; 84(6):890–7.
520. Wells JL, Seabrook JA, Stolee P, et al. Arch Phys Med Rehabil. 2003; 84(6): 898–903.
521. Fillit H, Butler RN. J Am Geriatr Soc. 2009; 57(2):348–52.
522. Shore WS, deLateur BJ. Phys Med Rehabil Clin N Am. 2007; 18(3):609–21.
523. Vliek S, Melis RJ, Faes M, et al. J Nutr Health Aging. 2008; 12(5):319–22.
524. Ljubuncic P, Globerson A, Reznick AZ. J Nutr Health Aging. 2008; 12(2):139–43.
525. Weening-Dijksterhuis E, de Greef MH, Scherder EJ, et al. Am J Phys Med Rehabil. 2011; 90(2):156–68.
526. Meils RJ, van Eijken MI, Teerenstra S, et al. J Gerontol A Biol Sci Med Sci. 2008; 63(3):283–90.
527. Melis RJ, van Eijken MI, Borm GF, et al. BMC Health Serv Res. 2005; 5:65.
528. Metzelthin SF, van Rossum E, de Witte LP, et al. BMC Public Health. 2010; 10:511–22.
529. Keating N, Dosman D. Can Rev Sociol. 2009; 46(4):301–8.
530. Heckman GA. Healthc Pap. 2011; 11(1):62–8.
531. Banghwa LC, van Vulpen KS, Davis SL. J Aging Health. 2011; 23(3):529–53.
532. Verghese J, Xue X. Age Aging. 2010; 39(3):382–5.
533. Stineman MG, Strumpf N, Kurichi JE, et al. Gerontologist. 2011; 51(1):S59–72.
534. Pereira SRM, Chiu W, Turner A, et al. BMC Geriatr. 2010; 10(1):82–7.
535. Kristensson J, Hallberg IR, Kristensson-Ekwall A. J Gerontol Nurs. 2010; 36(10): 20–8.
536. Wilson M. BMJ. 2011; 342:1948.
537. Wong WC, Sahadevan S, Ding YY, et al. Ann Acad Med. 2010; 39(11):830–6.
538. Monsen KA, Westra BL, Oancea SC, et al. Res Nurs Health. 2011; 34(2):160–8.
539. Mitty E. Geriatr Nurs. 2010; 31(5):368–74.
540. Kergoat MJ, Latour J, Julien I, et al. BMC Geriatr. 2010; 10(1):69–79.
541. Bauer M, Fitzgerald L, Haesler E, et al. J Clin Nurs. 2009; 18:2539–46.
542. Fulop T, Larbi A, Witkowski JM, et al. Biogerontol. 2010; 11(5):547–63.
543. Beswick AD, Rees K, Dieppe P, et al. Lancet. 2008; 371(9614):725–35.
544. Chang SS, Weiss CO, Xue QL, et al. J Gerontol A Biol Sci Med Sci. 2010; 65(4): 407–13.
545. Roubenoff R. J Nutr Health Aging. 2000; 4(3):140–2.
546. Hickson M, Frost G. Clin Nutr. 2004; 23(2):213–21.
547. Espinoza S, Walston JD. Cleve Clin J Med. 2005; 72(12):1105–12.