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Frailty: Pathophysiology, Phenotype and Patient Care

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Preface

The demographic shift of the average age of the population worldwide mandates that careful attention be paid to the nutritional and health needs of all segments of our older adult population. Well-defined changes in body composition occur with advancing age. Characteristic of this change is the expanding pool of subcutaneous and visceral adipose tissue and the age-associated decline in skeletal muscle mass and function, sarcopenia. Sarcopenia has been linked to declines in physical function, loss of independence and mortality. In addition, dysregulation of host defense mechanisms and cellular senescence, all accumulate with advancing age. The functional declines associated with these changes are mediating factors that contribute to the syndrome of frailty with advancing age. Frailty has been defined as a geriatric syndrome that is characterized by a reduction in physiologic reserve required for an individual to respond to endogenous and exogenous stressors. Using a discrete definition of frailty that includes: sedentarity, involuntary weight loss, fatigue, poor muscle strength and slow gait speed, ‘frailty’ has been associated with increased disability, postsurgical complications and increased mortality. Despite the strong associations between frailty and subsequent poor outcomes, limited attention to this common geriatric condition has been paid in clinical settings. While multiple syndromes overlap with and are likely contributors to frailty, several lines of evidence suggest that ‘frailty’ is a distinct phenotype that has important clinical significance in the care and treatment of older adults.

This monograph includes summaries of talks presented at the 83rd Nestle Nutrition Institute Workshop held in Barcelona, Spain, on the 14th and 15th of March, 2014. The speakers in the symposium addressed our current understanding of the biological basis, clinical presentation and therapeutic interventions that target frailty.

Clearly, multiple underlying biological factors, including dysregulation of inflammatory processes, oxidative stress, mitochondrial dysfunction and cellular senescence, contribute to the clinical presentation of frailty. In addition, the
frailty criteria of sedentariness, involuntary weight loss, fatigue, poor muscle strength and slow gait speed are all components of other common geriatric syndromes. Emerging evidence suggests that both behavioral (nutrition and physical activity) and pharmacologic (myostatin antagonists, selective androgen receptor modulators, skeletal activators, angiotensin inhibitors and anti-inflammatory agents) interventions may be efficacious in the treatment and prevention of the frailty syndrome. This workshop has highlighted the translational nature of research on the frailty syndrome and identified key unmet needs and areas for future investigation in this expanding field.

Roger A. Fielding
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Foreword

Worldwide, the population aged 65 years and more is expected to grow from near 500 million people in 2004 to an estimated 2 billion people by 2050. The geriatric syndrome of frailty is likely to affect a large number of elderly living in the community, as approximately 14% of those are frail and 43% are prefrail based on findings of the Survey of Health, Aging and Retirement in Europe (SHARE) conducted in 10 major European countries.

In a frail state, older adults are at greater risk for adverse outcomes, including falls and admissions to hospitals and nursing homes. Early action is warranted in vulnerable individuals because frailty is a predisabled condition, disability is costly, and initiating intervention may modify the frailty trajectory. Yet, today it is more common for older adults to progress to a worsened level of frailty than to transition to an improvement. The development and application of evolving science is important for better patient-centric health care.

Due to the multifactorial etiology of frailty, the comprehensive needs of patients are best treated by a multidomain intervention. In an effort to spread the use of science-based clinical practices, the 83rd Nestlé Nutrition Institute Workshop, entitled ‘Frailty: Pathophysiology, Phenotype and Patient Care’ was organized. The 2-day event in Barcelona, Spain, was an interactive forum to share state-of-the-art concepts from a broad range of specialties to help advance frailty management and influence active aging.

A major success of the Workshop was to bring together a diverse group to connect and spread best practices from across the world, including:

- Health care professionals with a clinical specialty in geriatric medicine, physical therapy, and dietetics
- Medical school faculties
- Professors in departments of aging and geriatric research
- Experts in epidemiology and public health

The program stimulated thinking beyond the current approach and inspired consideration of different viewpoints. Robust discussion took place. Participants
learned about novel, validated methods that could be applied in daily practice, as well as emerging theories and therapies. To help build awareness and educate new groups of clinicians on the latest evidence to address frailty, sarcopenia, and impaired mobility, the Workshop lectures and discussions were made freely available, first streamed as a live broadcast, and later posted online at www.nestlenutrition-institute.org.

The interest and efforts of many made it possible to take these steps forward as a result of the Workshop. Our thanks go to: the 83rd Nestlé Nutrition Institute Workshop Chairmen, Prof. Roger Fielding (USA), Dr. Cornel Sieber (Germany), and Dr. Bruno Vellas (France), who each exemplify the strong multidisciplinary team collaboration essential for understanding the complexity of frailty management and best treatment strategies. We are grateful to all the presenters, session facilitators, and attendees, who shared their expertise and perspectives during and after the Workshop to help educate, activate, and advance practices in frailty.

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Abstract
Frailty is an important construct in aging which allows for the identification of the most vulnerable subset of older adults. At least two conceptual models of frailty have been developed that have in turn facilitated the development of multiple frailty screening tools. This has enabled the study of populations of frail and nonfrail older adults, and facilitated the risk assessment for adverse health outcomes. In addition, using the syndromic approach to frailty, numerous biological hypotheses have been tested, which have identified chronic inflammatory pathway activation, hypothalamic-pituitary-adrenal axis activation, and sympathetic nervous system activity as important in the development of frailty. In addition, age-related molecular changes related to autophagy, mitochondrial decline, apoptosis, senescent cell development, and necroptosis likely contribute to the heterogeneous phenotype of frailty. The recent development of a frail mouse model with chronic inflammatory pathway activation has helped to facilitate further whole organism biological discoveries. The following article attempts to create an understanding of the connections between these age-related biological changes and frailty.

Introduction
Frailty has long been recognized by health care providers as a syndrome of vulnerability that marks a subset of older adults as being at high risk for adverse health care outcomes, such as functional decline, disability, worsening chronic illnesses, and mortality. Over the past several years, research interest
in frailty has grown exponentially as has the interest in integrating frailty into clinical practice models. In addition, marked progress in understanding age-related biological changes has helped to unravel the biology that likely underlies frailty and related biological vulnerability. The purpose of this chapter is to provide a state-of-the-art conceptual overview of frailty and to describe the known physiological and molecular changes that associate with and drive the development of frailty. Further research in this area will help to (1) identify those older adults at highest risk of adverse outcomes, (2) facilitate improved understanding of the biological underpinnings of frailty-related vulnerability, and (3) foster the development of improved preventive and intervention strategies aiming to improve health outcomes and quality of life of older adults.

**Frailty Conceptualization**

Over the past 20 years, the definitions of frailty have evolved from generalized observations by clinicians that frail individuals were vulnerable, weak, and failing to multiple definitions that have helped to bring scientific rigor to the field of frailty research. At present, two major conceptualizations of frailty have emerged in the literature. The most commonly utilized conceptualization is that frailty is an age-related syndrome with a deep biological basis that becomes manifest during periods of stress [1]. This concept has been further refined into a cycle of decline in energy, skeletal muscles and nutrition that can be triggered by disease, medications, or environmental stressors (fig. 1). This cycle of decline, further influences medical illnesses, mobility, functionality, and cognition. Importantly, this conceptualization has been operationalized into the most commonly utilized frailty screening tool [1] and has allowed for hypothesis testing related to etiology and for intervention development period.

In addition to this biological conceptualization, a cumulative burden conceptualization of frailty has evolved. In this model, frailty is defined by a number of related and unrelated health, biological, social, functional, and cognitive variables that are tallied in an index. Those that are most frail are those with the highest tally of variables [2]. This model has been widely tested for predictive validity and has been shown to capture vulnerability as well as the biological model described above. However, frailty index was not constructed with an underlying biological theory in mind, and hence has not been extensively utilized to test biological hypotheses [2]. Further, because it was not conceptualized around a potential etiology, targeted preventive and intervention strategies have not been developed or tested to date using this model.
Frailty Measurement

Dozens of studies have been published over the past two decades that detail specific frailty measurement tools [3]. The vast bulk of these tools have been developed to study the risk of adverse outcomes in populations of older adults, and for the most part were developed utilizing aggregate measures of physical function, fatigue, and activity [3]. To date, no clear gold standard for the measurement of frailty has emerged and it is becoming increasingly apparent that none of these tools is adequate for all of the emerging clinical practice, risk assessment, biological research, and intervention development purposes that require frailty screening tools [4]. To date, most of the tools that have been developed can be divided into two groups that match the conceptualization of frailty articulated in the section above, i.e. either tools that attempt to capture essence of a biologically based, syndromic frailty or those that work to capture a tally of deficits or problems that in sum define a level of frailty. A brief summary of commonly utilized measurement tools are discussed below.

Fried et al. [1] previously developed a screening tool that consists of measured grip strength, walking speed, and weight loss along with subjective reporting of activity and fatigue levels. A score of 0–5 is generated based on a series of

Fig. 1. Cycle of frailty that underlies one of the primary conceptualizations of frailty, demonstrating a reinforcing downward physiological spiral that facilitates the development of adverse health outcomes. Reproduced with permission from Walston and Fried [26].
cutoff points for each measure, with 0 being robust, 1–2 being prefrail, and 3–5 being frail. This tool and adaptations to this tool have been used in population studies of community dwelling older adults to determine demographic information about older adults, and to identify individuals that are at significantly higher risk of adverse health outcomes such as disability, hospitalization, functional decline, and mortality compared to age-matched nonfrail individuals. In addition to this commonly utilized tool, many others have been developed that have a similar construct around syndromic frailty with weight loss, physical function, and skeletal muscle weakness measures most often included in these adaptations. While many have been validated by their ability to predict adverse outcomes in older adults, few have been utilized to test biological hypotheses or interventions.

A second common approach to detecting and measuring frailty comes from Rockwood and Mitnitski [2]. Building on the conceptualization of frailty as a condition that arises from cumulative declines, the tool consists of up to 71 measures of function, illness, cognition, and social mobility. A tally is taken, and those with the highest number of tallies are deemed most frail, and those with the lowest number of tallies are deemed least frail. This tool or similar indexing approaches do not require de novo measurements as information can be abstracted from medical records. Hence, it has been most commonly utilized to assess the risk of an adverse outcome, especially mortality in older adults. Importantly, numerous studies have attempted to include social or cognitive variables into screening tools in order to better capture frailty and its incumbent risk for adverse outcomes in broader population contexts. This will continue to be an important area of development in frailty research [5].

The Biology That Underlies Frailty

In order to better understand the etiology of frailty and late-life vulnerability, and in order to facilitate the development of treatment and prevention strategies, an improved understanding of the connections between age-related biological changes and frailty is required. As mentioned above, the most commonly utilized frailty construct was conceptualized around age-related biological and physiological changes with potential influence from poor nutrition and medical conditions [1]. In older adults, it is apparent that these changes do not exist in isolation; rather they exist together in a variety of constellations, which in sum contribute to frailty and the inherent biological vulnerability observed in frail, older adults [6]. We and others have helped to develop model pathways that have helped to conceptualize the interconnections between age-related
biological changes, physiological system changes, and disease states with frailty and adverse outcomes [6]. The following sections detail studies of chronic disease, physiology, and biology that have been performed related to frailty.

**Disease States and Frailty**

Multiple investigators have attempted to identify important relationships between disease states and frailty in older adults. Early work identified a strong correlation between glucose intolerance and type 2 diabetes mellitus and frailty in older adults [7]. In addition, vascular disease, especially congestive heart failure, has been shown to be highly related to frailty in older adults [8]. Although associations between frailty and disease states do not prove causality, they suggest that a common underlying biological mechanism ties some diseases and frailty together. For example, an important biological commonality that has been identified in frailty and chronic disease is the chronic activation of inflammatory pathways and the strong relationship between inflammation and frailty as detailed below. Other studies have shown heightened activation of clotting pathways and more clotting events in frail older adults, further supporting biological commodity [7, 9]. Many studies demonstrate a substantial overlap between inflammation, frailty, and chronic disease states, including congestive heart failure, hypertension, and diabetes mellitus [7, 8, 10].

**Physiological System Dysregulation and Frailty**

Dysfunction in multiple physiological systems is thought to play an important role in late-life vulnerability. As biological understanding rapidly evolved, the distinction between physiological and molecular biological systems is blurred. For the purposes of this text, we will refer to physiological changes as those related to stress response systems that bridge between organs and tissues. The multiple chronic disease states including diabetes, vascular disease, chronic obstructive pulmonary disease, depression, and congestive heart failure that often coexist in frail, older adults likely contribute to the underlying biological vulnerability of many tissues and organs in older adults [11]. Many of these disease states have been demonstrated to chronically activate physiological systems, including the innate immune system, the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis.

The identification of major physiological systems also thought to drive late-life vulnerability comes in part from the literature on frailty. Altered heart rate
variability is a key measure of dysregulated sympathetic nervous system activity and is associated with aging, frailty, and cardiac arrhythmias [12]. Significantly higher levels of salivary cortisol during the afternoon nadir period have been observed in frail older adults compared to the nonfrail, suggesting chronically increased activity of the hypothalamic-pituitary-adrenal axis [13]. Multiple studies demonstrate a consistent and strong relationship between multiple inflammatory cytokines, C-reactive protein, and adverse outcomes of functional decline, frailty, chronic disease, and mortality [7]. The inflammatory cytokine interleukin (IL)-6 is most often used as a serum marker of inflammation in research studies involving older adults. Both of these measures are highly biologically active molecules and are the best predictors of mortality in at least two large population studies of older adults. Chronic, long-term exposure to IL-6 likely negatively impacts stem and satellite cells, which in turn may influence the development of chronic anemia and age-related declines in skeletal muscle (sarcopenia) and bone mass (osteopenia) commonly observed in frail, older adults [14].

Importantly, the activation of each of these systems helps to reinforce the activation of chronic activation of the other stress response systems [14]. This in turn facilitates the local and systemic release of a broad array of bioactive molecules, such as cortisol, IL-6, and norepinephrine. Although each of these bio-mediators triggers critical stress responses and plays signaling roles that are vital for health and well-being, chronic activation of these systems is likely to have a negative impact on many organs, tissues, and stem cells that may replenish these organs and tissues. This in turn can further exacerbate aging-related clinical conditions such as osteoporosis and hypertension and increase vulnerability to other adverse health outcomes. Figure 2 illustrates the interacting stress response systems described above and chronically secreted bioactive mediators that may influence vulnerability late in life.

Age-Related Cellular and Molecular Changes and Frailty

Over the past decade, marked improvement in the understanding of age-related biological changes has been realized, including advances in the understanding of apoptosis, necroptosis, mitochondrial dysfunction, cell senescence, autophagy, and inflammatory pathway activation. This in turn has often facilitated the understanding of the role of these aging-related changes in the development of aging-related disease states, such as Parkinson’s disease and type 2 diabetes mellitus [15]. These biological changes are also likely highly relevant to the multi-system changes observed in frailty, as well as the multiple disease states that are highly associated with frailty. Like the physiological changes, the molecular
changes likely do not exist in isolation but contribute across systems, organs, and tissues to frailty and its incumbent vulnerability to adverse outcomes such as functional decline, acute and chronic illness, and ultimately to mortality.

An example of this comes from attempts to understand the underlying etiology of the age-related activation of inflammatory pathways and its relationship to a host of disease states and functional decline [16]. The etiology of the activation of inflammatory pathway activation comes from several age-related biological sources. Increasing evidence suggests that senescent cell populations arise with increasing age, and may lead to alterations in tissue and immune system function that contribute to frailty. For example, fibroblasts and fat cells evolve towards a phenotype whereby reproduction and cell death are less likely to take place, and survival persists in an altered, less functional state [17]. These senescent cells no longer function normally and chronically secrete inflammatory cytokines and other bioactive molecules that negatively impact surrounding tissues [17]. Beyond this inflammatory impact, senescent T-cell populations also increase in number with increasing age, perhaps related to early-life cytomegalovirus or other viral exposure [18]. Age-related changes in mitochondrial function are also thought to play an important role in the development of activated inflammatory pathways through the increased production of proinflammatory free-radical by-products [19].

**Fig. 2.** Model of interacting stress response systems that likely drive pathophysiological changes in frailty. HPA = Hypothalamic-pituitary-adrenal; SNS = sympathetic nervous system.
Many other altered molecular processes are also thought to contribute to broad systemic changes in older frail adults. Autophagy, an intracellular process responsible for the recycling of damaged or redundant organelles or proteins, becomes less effective with age [15]. This results in an intracellular accumulation of dysfunctional mitochondria and proteins, which in turn can trigger cellular dysregulation via increased levels of free radicals, lower mitochondrial energy production, and programmed cell death or apoptosis [19, 20]. Next, it is evident that some tissues become more sensitive to apoptosis or programmed cell death. Apoptosis is a normal cellular program that serves to kill and dissemble damaged or redundant cells in all tissues. However, it appears to accelerate and likely contributes to the vulnerability to chronic disease states such as Parkinson’s disease and congestive heart failure, or to the generalized loss of cells in many tissues [15]. Another potential molecular contributor to frailty and late-life vulnerability is increased TGF-β signaling, which likely plays an important role in the fibrotic changes that are observed in heart and lung tissue [21]. Importantly, these aging-related molecular and cellular changes are heterogeneous, and may contribute to frailty at different ages and through different disease states.

Building on the need to identify animal models to study aging-related physiological and biological changes and how they affect frailty and vulnerability to adverse outcomes, a frail mouse model was recently characterized [22]. Given the strong relationship between frailty and chronic activation of inflammatory pathways, the IL-10^tm/tm^ mouse was chosen for further study because of the mild activation of inflammation associated with loss of the anti-inflammatory cytokine IL-10 [22]. Like frail humans, the IL-10^tm/tm^ mouse has been found to develop modest elevations in serum inflammatory markers with increasing age, age-related declines in muscle strength and activity levels, and premature all-cause mortality compared to age- and gender-matched background control strain mice [22, 23]. In addition, the mouse develops decreased cardiac ejection fraction without substantial myocardial loss, consistent with the strong relationship noted between frailty and congestive heart failure in humans [8, 24]. The underlying molecular etiology that drives this multisystem decline has not yet been completely characterized. However, there is evidence for skeletal muscle mitochondrial dysfunction in the older IL-10^tm/tm^ mouse through studies that demonstrate lower levels of ATP flux in frail compared to control mice [25]. Although characterization of this mouse model is not complete, early evidence suggests that it may be a good model for testing additional mechanistic and biological hypotheses related to aging, chronic inflammation and frailty, as well as a model to test intervention strategies.

In summary, frailty in older adults is a rapidly emerging clinical construct that likely has age-related biological underpinnings, and stress response systems
and especially inflammation activation appear to drive declines in function and health. New discoveries related to apoptosis, necroptosis, cellular senescence, and mitochondrial decline are now being implemented in frailty research using novel cellular and animal models. Future interventions targeting specific biological pathways may slow these pathophysiological changes and improve health and well-being in older adults.

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References


Abstract
Population aging simultaneously highlights the remarkable advances in science, medicine, and public policy, and the formidable challenges facing society. Indeed, aging is the primary risk factor for many of the most common chronic diseases and frailty, which result in profound social and economic costs. Population aging also reveals an opportunity, i.e. interventions to disrupt the fundamental biology of aging could significantly delay the onset of age-related conditions as a group, and, as a result, extend the healthy life span, or health span. There is now considerable evidence that cellular senescence is an underlying mechanism of aging and age-related conditions. Cellular senescence is a process in which cells lose the ability to divide and damage neighboring cells by the factors they secrete, collectively referred to as the senescence-associated secretory phenotype (SASP). Herein, we discuss the concept of cellular senescence, review the evidence that implicates cellular senescence and SASP in age-related deterioration, hyperproliferation, and inflammation, and propose that this underlying mechanism of aging may play a fundamental role in the biology of frailty.

Introduction
Population aging results from the many remarkable achievements in science, medicine, and public policy. Indeed, in developed countries, innovations in antibiotics, vaccines, medications, sanitation, hygiene, and working conditions have increased the average life expectancy at birth from roughly 45 years in the
early 1900s to approximately 80 years today. By 2050, over 21% of the global population, or two billion persons, will be over 60 years of age [1].

This remarkable accomplishment also poses a formidable challenge to public health. Aging is the major risk factor for cardiovascular disease, cancer, Alzheimer’s disease, diabetes, arthritis, osteoporosis, blindness, and several other chronic conditions with profound consequences and enormous medical costs. For many, aging also leads to the incapacity to respond to stress and return to homeostasis (fig. 1a). The age-related loss of resiliency and increased vulnerability is now widely considered a geriatric health condition, termed frailty [2, 3]. The clinical definition and measurement of frailty are not universally agreed upon; however, it is clear that patients deemed frail by the existing tools suffer a host of adverse health outcomes, including perioperative complications, increased length of hospital stay, disability, loss of independence, institutionalization, and death [4–7].

On the one hand, age-related chronic disease and frailty are enormous financial and social threats to society. On the other hand, with aging at their root, they represent an exciting opportunity. Specifically, interventions that disrupt the fundamental biology of aging have the potential to (i) delay the onset of age-related chronic diseases and frailty as a group, (ii) significantly extend the healthy life span, and (iii) compress end-of-life morbidity (fig. 1b). This concept has recently developed into the interdisciplinary field of geroscience. The objective of this chapter is to outline the evidence that supports the biological process of cellular senescence as a unifying mechanism of aging, age-related disease, and frailty. The potential for therapies that target senescent cells to delay aging and the onset of age-related disease and frailty will also be discussed.
Aging is a consequence of the gradual lifelong accumulation of molecular and cellular impairments that manifest as deterioration (e.g. as evidenced by the cardiovascular, metabolic, musculoskeletal, and the nervous system), hyperproliferation (i.e. as in the aberrant growth of malignant cells), and chronic, low grade, sterile inflammation (inflammaging). These phenotypes of aging have fueled a search for a unifying mechanism. In the 1960s, Hayflick and Moorehead [8] introduced the term cellular senescence to describe the state of permanent cellular growth arrest that occurred in normal human fibroblasts after extensive serial passaging in culture. Although they postulated that replicative senescence might play a role in aging, it has been more widely appreciated as a fundamental anticancer defense. Subsequent studies have demonstrated that in addition to replication-induced senescence, cellular senescence is associated with diverse stimuli, including telomere erosion, DNA lesions, reactive oxygen species, and other mitogenic and metabolic stressors [9]. The induction of ‘stable’ growth arrest is associated with activation of the tumor suppressor pathways, p16^INK4a/retronblastoma protein (Rb) and/or p53/p21. Together these mechanisms of senescence limit excessive or aberrant growth of malignant cells. Intriguingly, several senescence-inducing stressors are also the foundation of several theories of aging (i.e. telomere erosion, DNA damage and mutation, protein aggregation, and reactive oxygen species). However, instead of preventing the growth of cancers, the accumulation of senescent cells with advancing age negatively affects tissue structure and function, and ultimately leads to tissue pathology, as discussed herein. Thus, cellular senescence is an example of antagonistic pleiotropy, i.e. a biological mechanism that was selected through the evolution to enhance early-life fitness that has late-life costs.

How do senescent cells lead to age-associated tissue deterioration, hyperproliferation, and inflammation? The abundance of senescent cells increases in multiple tissues with chronological aging [10, 11]. Senescent cells were first distinguished from quiescent and terminally differentiated cells by their expression of a pH-dependent β-galactosidase (SA-β-Gal) [12]. Now, elements of the Rb and p53 signaling pathways, including p16^INK4a and p21^Cip1/Waf1 encoded by Cdkn2a and Cdkn1a, respectively, are mediators and also biomarkers of senescence [13, 14]. Though they are quite modest in number, senescent cells contribute to aging through three paths. First, the net accumulation of senescent cells, which have a markedly altered morphology and gene expression profile, may reach a point that compromises the functionality of a tissue. Specifically, senescent cells reorganize chromatin, which results in heterochromatin forma-
tion, increased cell size and protein content, and changes in organelles and cell shape [15, 16]. Second, senescence limits the regenerative potential of stem cell pools and undifferentiated progenitor cell pools [thoughtfully reviewed in ref. 17]. As a result, the capacity to regenerate damaged and atrophic tissues declines. Moreover, senescent cells could be of great consequence to tissues that require ‘homeostatic cellular replication’, including the bone marrow, thymus, and endocrine pancreas [9]. Third, and potentially most interesting with regard to the etiology of age-related diseases and frailty, senescent cells are active factories that secrete a broad repertoire of cytokines and chemokines, matrix-remodeling proteases, and growth factors, collectively referred to as the senescence-associated secretory phenotype (SASP) [reviewed in ref. 18]. Importantly, SASP factors vary in distinct cell types and under different senescence-inducing stressors [19]. This plasticity within SASP composition predicts variability with respect to the biological processes impacted by the different kinds of senescent cells. Recent data further suggest that senescence likely spreads to neighboring cells through components of the SASP, which, in turn, intensifies age-related tissue deterioration [20]. Together, these consequences of cellular senescence lead to age-related tissue deterioration (due to accumulation and spread of senescent cells, the loss of regenerative potential, and degradation of the extracellular matrix), hyperproliferation, or the growth and spread of cancers (paradoxically through components of the SASP including growth factors and matrix-remodeling proteases), and inflammaging (as cytokines and chemokines are prominent features of the SASP). Thus, cellular senescence has emerged as a potential unifying mechanism of aging, age-related diseases, and frailty.

**Cellular Senescence and Age-Related Disease and Frailty**

Inflammation is a hallmark of age-related chronic diseases and frailty. Factors such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and acute-phase proteins such as C-reactive protein are now recognized as pathogenic factors in the development of cardiovascular disease, diabetes, cancer, depression, and dementia, as well as frailty [21–27]. The cause and source of inflammation in these conditions has remained elusive. Although the immune system plays a major role in modulating the levels of pro- and anti-inflammatory factors, it is not the only source of these factors. It is plausible that cellular senescence and the SASP could serve as a significant source of inflammation and play a substantial role in the genesis and/or progression of age-related diseases and frailty.

In support of this concept, biomarkers of senescent cells, including p16<sup>INK4a</sup> and SA-β-Gal, and components of the SASP, including TNFα, IL-6, matrix me-
talloproteinases, monocyte chemoattractant protein-1, and insulin-like growth factor binding proteins, increase in multiple tissues with chronological aging [10, 14, 18, 28]. Even more noteworthy is that SA-β-Gal, p16<sup>ink4a</sup>, and/or p21 are elevated in the affected tissues of patients with age-related conditions, including osteoarthritis, pulmonary fibrosis, atherosclerosis, and Alzheimer’s disease [extensively reviewed in ref. 29]. However, the extent to which senescent cells residing at the site of active pathology account for the onset and/or progression of these diseases is unknown, but is an active area of investigation by our laboratories and others. With regard to frailty, ongoing work will help to determine what tissues (e.g. adipose tissue or spleen) and systems (e.g. immune or endocrine system) are affected by senescence, and whether or not senescent cells and the SASP negatively affect resiliency, functional reserves, and systemic inflammation. Answers to these questions and others will help to determine the therapeutic potential of therapies to selectively remove senescent cells and/or suppress the SASP.

**Interventions Targeting Senescent Cells and the Senescence-Associated Secretory Phenotype**

In light of the growing body of data implicating senescent cells in age-related disease and frailty, a number of strategies are being considered to mitigate their deleterious effects. First, the cell stresses and signaling pathways that lead to senescence-associated growth arrest could be targeted by therapeutic interventions. On the one hand, preventing cell damage could be an effective means to limit senescent cell accumulation. On the other hand, however, interfering with tumor suppressor pathways such as Rb, p16<sup>INK4A</sup> or p53 would compromise fundamental anticancer mechanisms and pose significant risks. Second, interventions could be devised to selectively eliminate senescent cells and, in turn, reduce tissue dysfunction and inflammation. As proof of concept, we designed a transgenic mouse model in which senescent cells could be inducibly eliminated. In this model, which we termed INK-ATTAC, a transgene that encodes caspase 8 fused to a mutated FKBP domain version, is selectively expressed in p16<sup>INK4A</sup>-positive senescent cells. Upon administration of the synthetic drug AP20187, FKBP-caspase 8 fusion proteins homodimerize and activate a chain of events that triggers apoptosis of p16<sup>ink4a</sup>-positive cells. Recently, we demonstrated that in a BubR1 progeroid (rapid aging) mouse background, INK-ATTAC removes p16<sup>ink4a</sup>-positive senescent cells upon drug treatment [30]. In tissues – such as adipose tissue, skeletal muscle, and eye – in which p16<sup>ink4a</sup> contributes to the acquisition of age-related pathologies, life-long removal of p16<sup>ink4a</sup>-expressing cells delayed the onset of
these phenotypes and improved physical function. Furthermore, late-life clearance attenuated the progression of already established age-related disorders. The findings demonstrate that senescent cells and the SASP contribute to age-related tissue dysfunction. Importantly, we observed no overt side effects of senescent cell clearance in our model, even though it has been postulated that senescent cells might enhance certain types of tissue repair. The translation of these findings to humans is contingent upon the ability to specifically target senescent cells using biological or small-molecule ‘senolytic’ therapies. We have very recently shown that deletion of p16^{INK4a}-expressing cells through a pharmacological strategy can improve multiple aging-related phenotypes, including cardiac function, vascular reactivity, bone microarchitecture, and exercise capacity, in mouse models of aging [31]. The unique morphology and gene expression profile of senescent cells suggest they may either harbor unique epitopes that could be exploited by antibody-based therapies or be more sensitive than nonsenescent cells to small-molecule senolytic agents. The third approach to prevent the deleterious effects of senescent cells is to prevent or ameliorate the effects of the SASP. This is an attractive approach given senescent cells are a major source of tissue inflammation, which, in turn, is a fundamental component of several age-related diseases and frailty. Moreover, the SASP could theoretically be disrupted without interfering with the anti-oncogenic pathways activated in senescent cells.

In parallel with the research and development of interventions to eliminate senescent cells and diminish the SASP, the clinical opportunities to test the effectiveness of senolytic agents are being discussed. Frailty offers a unique indication, and we are actively researching the association, if not the fundamental contribution, of cellular senescence to the frailty syndrome. If, in fact, patients with high compared to low senescent cell burden experience worse short-term outcomes (e.g. more complications, higher incidence of delirium, or longer hospitalization) and longer-term outcomes (more readmissions, greater dependence in activities of daily living, delayed recovery of function, or higher institutionalization) following a medical intervention, then the efficacy of senolytics at improving these clinically important and patient-centered metrics could be evaluated. While tantalizing, several obstacles need to be overcome before this can be achieved. For example, biomarkers of senescent cell burden and SASP activity in humans need to be developed and validated. Moreover, the frequency and duration of treatment regimens to reduce senescent cell number and SASP activity, without unwanted side effects, need to be defined. In fact, it is plausible that senescent cell removal could actually impair an older person’s response to infection, wound healing, and other stressors. Nonetheless, frailty offers a possible scenario in which eliminating senescent cells or SASP components would result in a rapidly detectable, clinically meaningful response.
Conclusions

Aging has long been appreciated to be the major risk factor for most chronic diseases and frailty, but deemed unalterable. However, recent and transformative breakthroughs in the biology of aging have challenged this assumption. In particular, significant advances in our understanding of cellular senescence and the SASP along with proof-of-concept studies in preclinical models suggest that interventions to disrupt this fundamental mechanism of aging could have a profound effect on the health span by delaying age-related conditions as a group. By compressing late-life morbidity, such interventions could have a transformative effect on public health. While the search is on for pharmacological strategies to delay aging, significant work is needed to further understand the biology of cellular senescence and its role in the pathogenesis of age-related diseases and frailty. Moreover, understanding how lifestyle choices, including diet and physical activity, can be optimized to counter the biology of aging may simultaneously provide a readily implementable and scalable means to extend the health span.

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Disclosure Statement

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References

Abstract
Late-life aging in humans is often associated with severe frailty. This suggests catastrophic events reaching an undeniable biological threshold in cellular stability and a rapidly diminished homeostasis. The driving force of the syndrome is likely 'genetic instability' or 'genomic instability', a high frequency of mutations and deletions within the genome (both nuclear and mitochondrial DNA) of bodily somatic cells caused by DNA damage and inefficient repair. Reactive oxygen species, calcium deregulation, and iron dyshomeostasis are potential chemical triggers of nucleic acid sequence alterations and chromosomal rearrangements. These include mutations, deletions, translocations, chromosomal inversions, and single- and double-strand DNA breaks. Nuclear damage, such as telomere shortening, also appears to cause an abnormal expression of several proteins, including p53, which leads to impaired mitochondrial biogenesis, mitochondrial permeability transition pore opening, apoptosis, and other biological events. Moreover, mitochondrial DNA damage could produce inaccurate translation and synthesis of proteins important for energy production in the inner mitochondrial membrane. Another cause of genomic instability may be a reduced expression and function of DNA repair genes, especially when stressful events trigger slow responses. With late-life frailty, overall endogenous damage occurs much more frequently and repair is much less efficient, which further accelerates genomic instability.

Introduction
Frailty increases an individual’s susceptibility to age-associated cardiovascular, metabolic, and inflammatory disorders. Moreover, a strong association between frailty and cognitive impairment was observed in elderly human populations,
suggesting frailty is not just limited to pathophysiological impairment, but also attributes to psychological weakness caused by hormonal/neural changes. Phenotypic characteristics of frailty, therefore, accompany multidimensional impairments in immune/inflammatory control and hormonal/neuromuscular regulation, and are associated with alterations in cellular metabolic/redox responses that occur during aging [1].

**Cellular and Mitochondrial Mechanisms of Nuclear Genome Instability**

Several lines of correlative evidence indicate that genomic instability gradually increases with increasing age in humans. Thought to be a causative driver of frailty, genomic instability reprograms nuclear gene expression, thereby impairing cellular homeostatic maintenance/repair function (reviewed by Bellizzi et al. [2]). Various in vitro studies suggest that alterations in genomic integrity by abnormal DNA methylation deregulate genes related to cell cycle/death regulation, DNA damage repair, and cell metabolic homeostasis in aging humans [3]. Besides this epigenetic deregulation, intrinsic chromosomal DNA instability generates an extrachromosomal DNA structure, potentially decreasing nuclear genome stability, but these mechanisms are not yet understood. A recent study reported that microDNA (extrachromosomal DNA structure) occurs in mouse/human cell lines and adult brain tissues [4], suggesting a potential risk factor that increases nuclear genome instability during the human aging process. A similar deteriorative role of extrachromosomal DNA structures in nuclear genome integrity is well described in a budding yeast-replicative aging model [5]. Ribosomal DNA (rDNA) circles, which inherently form due to yeast genomic instability of the rDNA locus, propagate while yeast cells undergo asymmetric division cycles. This asymmetric cell division unequally accumulates rDNA circles mostly in mother cells, and rDNA circles diminish their nuclear genome stability and cell viability. Interestingly, preventing abnormal accumulation of this extrachromosomal circular DNA by genetic, pharmacological, or metabolic means (e.g. redistribution of sirtuin proteins to the nucleolus, rapamycin, and calorie restriction) significantly increases the mitotic capacity and viability of cells. This suggests that intrinsic risks in nuclear DNA possibly increase chromosomal abnormality with advancing age in humans. Whether extrachromosomal DNA directly or indirectly impacts nuclear genome instability and drives frailty in human aging remains to be tested.

Another genetic factor that directly compromises eukaryotic genome integrity is the progressive loss of telomeres (repetitive nucleotide sequences at each end of the chromatids). Telomeres protect chromosomes from being progressively shortened or fused into adjacent chromosomes while cells replicate their nuclear DNA.
Loss of telomeric tails perturbs genomic DNA replication and promotes cell death signals, especially in the non-germ line stem cell population; this is due to the lack of telomerase (the enzyme that extends telomere length) activity. Shortening telomeres can also increase chromosome abnormality by inappropriate DNA recombination and thus increase the cancer risk [6]. Loss of telomere integrity during aging or aging-related disease processes, therefore, possibly forms a cellular basis for the mechanisms of frailty. Indeed, few studies have attempted to reveal a biological association between telomere length and frailty phenotype in humans [7].

A recent remarkable study by DePinho and colleagues further connects telomere abnormality to subcellular organellar dysfunction by identifying a mechanistic link between telomere instability and mitochondrial dysfunction [8]. Using telomerase reverse transcriptase knockout (Tert−/−) mice, whose telomere becomes extremely short due to the lack of telomere biogenesis after several generations, the authors found that telomere dysfunction deactivates peroxisome proliferator-activated receptor-γ co-activator (PGC) 1α and PGC1β, and accelerates aging phenotypes across different tissues in premature Tert−/− mice. Since PGC1α and PGC1β regulate mitochondrial protein and genome (mitochondrial DNA, mtDNA) biogenesis, Tert−/− mice exhibit defective mitochondrial biogenesis and metabolic activity. Surprisingly, activation of p53 caused by telomere dysfunction transcriptionally represses both PGC1α and PGC1β activities. These data indicate that loss of telomere integrity can lead to mitochondrial dysfunction through the negative effect of p53 on mitochondrial biogenesis. It is therefore possible that loss of nuclear genome integrity activates p53 and represses mitochondrial biogenesis while accumulating damaged mitochondria in aging cells and tissue (fig. 1). This would diminish mitochondrial metabolic function and lead to a gradual decline in overall cell/tissue functions in aged organisms. To the best of our knowledge, this report is the first to link and unify the important theories of aging, such as the mitochondrial and nuclear damage event theories.

A master regulator of programmed cell death pathways, p53, functions either by increasing the levels of apoptosis inducers such as AIP1, Bax, and Fas, or by modulating the activities of Bcl-2 family signals [9]. In addition to having these canonical roles in the regulation of apoptosis, p53 can directly impact mitochondrial signals and their metabolic function. Recently, Vaseva et al. [10] reported that p53 activation upon DNA damage redistributes cytosolic p53 into the mitochondrial matrix, and mitochondrial p53 destabilizes the mitochondrial permeability transition pore (mPTP) complex by interacting with one of the mPTP components (i.e. cyclophilin D). A nonselective pore that resides on mitochondrial inner and outer membranes, mPTP, regulates mitochondrial membrane potential by channeling nonorganic ions, such as calcium. This p53-cyclophilin D interaction triggers mPTP opening, increases cytosolic calcium levels, and
Fig. 1. Homeostatic interplay between mitochondria and nucleus for the maintenance of genomic integrity in aging cells. Age-associated mitochondrial damage (e.g. mtDNA mutations and deletions) gradually increase mtDNA instability, which eventually augment nuclear DNA damage and genomic instability along with telomere shortening in aging cells. Without successful DNA damage repair, accumulating abnormalities in the genome (both mitochondria and nucleus) activate p53. Then, activated p53 increases cellular susceptibility towards cell death by inducing apoptosis-regulatory genes (e.g. Bax/Bak) and triggering mitochondrial permeability transition through opening of a channel, the mPTP. As a transcriptional repressor, p53 decreases mitochondrial biogenesis by inhibiting PGC1α and PGC1β activity, leading to a global loss of mitochondrial structural/functional fidelity. Dysfunctional mitochondria also directly affect nuclear genome integrity by perturbing ISC biogenesis or activating regulators in subcellular endonuclease pathways [e.g. apoptosis-inducing factor (AIF), endonuclease G (EndoG), and poly(ADP-ribose) polymerase (PARP)]. In contrast, keeping healthy/functioning mitochondria allows aging cells to increase genome stability by homeostatic defense pathways. A coordinated interplay between mitochondrial dynamics, mitochondrial biogenesis, and degradation (i.e. mitophagy) would play a pivotal role in maintaining mitochondrial quality and genomic stability. CypD = Cyclophilin D.
induces necrotic cell death, although cyclosporine A (an mPTP inhibitor) abolishes this cascade of cell death reactions. A direct interplay, therefore, exists between nuclear DNA damage, p53 activation, and mitochondrial dysfunction. Augmented nuclear genomic instability caused by telomere shortening or other damage occurring in DNA can initiate p53 activation and subsequently turn on cell death signaling (fig. 1a). Concurrently, p53 activation diminishes mitochondrial function by destabilizing mPTP, eventually resulting in overall physical, physiological, or psychological weakness in the old and frail.

Given the fact that even healthy mitochondria inevitably leak electrons during metabolic activity, mitochondrial dysfunction can significantly proliferate cellular reactive oxygen species and damage various subcellular compartments, including endogenous nuclear DNA. This can gradually increase nuclear genome instability. In addition, recent studies suggest that defective mitochondrial activity can increase nuclear genome instability independent of the redox status, which is regulated by low-weight molecular compounds, such as NADPH, GSH, and key antioxidant enzymes. Veatch et al. [11] reported that defective iron-sulfur cluster (ISC) biogenesis due to mtDNA loss decreases cytosolic ISC and impairs the assembly of ISC-containing protein(s) specifically required to maintain nuclear genome stability in yeasts. A similar mechanism by which ISC availability affects nuclear genome stability is conserved in higher organisms [12], suggesting that a decrease in mitochondrial function can directly impair nuclear genome integrity through defective ISC synthesis by mitochondria. These findings provide another cell mechanism by which mitochondrial metabolic function, although not necessarily limited to energy metabolism, plays a pivotal role in the maintenance of nuclear genome stability.

Taken together, intrinsic defects in genomic DNA structures (e.g. telomere shortening) and extrinsic damage to the nuclear genome due to defective mitochondrial function (e.g. impaired redox status, metabolic function, and cell death homeostasis) seem to be largely responsible for the age-dependent loss of nuclear genomic stability. Thus, keeping healthy mitochondria during the cell senescence process is critical not only for enhancing the mitochondrial canonical function in cell metabolism and survival, but also for maintaining an intact nuclear genome (fig. 1).

**Mitochondrial Quality Control and Nuclear Genome Stability**

While there are multidimensional processes required for maintaining healthy mitochondrial pools in cells, at least three different pathways must interplay correctly: mitochondrial fusion and fission dynamics, biogenesis, and degradation
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Recent studies reveal that mitochondria are highly motile and remarkably plastic in their structure. This dynamic property, which is regulated by the fusion and fission processes, is critical for active changes in mitochondrial function under various environmental stimuli (i.e. oxidative stress and apoptotic signals). Without this structural dynamic, mitochondria immediately lose their genomic integrity, increase redox and cell death stress, and become metabolically dysfunctional. Thus, it is not surprising to observe that genetic defects in the fusion and fission processes are often related to severe developmental abnormalities, neuromuscular degeneration, and metabolic disorders in various animal models and in humans. Furthermore, gradual deregulation of mitochondrial dynamics might be one of the intrinsic causes of mitochondrial malfunction in the aging process. How the fusion and fission dynamics modulate mitochondrial function, however, is still unclear, and whether this structural dynamism can directly or indirectly induce any changes in nuclear genome integrity in aging cells remains unknown.

An aberrant mitochondrial structure caused by defective fusion and fission events potentially impairs mitochondrial quality control. By accumulating unrepaired (malfunctioning) mitochondria in aging cells, this indirectly diminishes nuclear genomic stability, as suggested previously. To remove dysfunctional mitochondria, cells operate a lysosome-mediated degradation pathway called autophagy. Autophagy degrades entire mitochondria when autophagosomes (specialized double-membrane structures) encapsulate and deliver them into the lysosome. During this process, mitochondria must undergo constant division and fusion cycles to isolate the damaged mitochondria from the healthy ones. Unopposed mitochondrial fusion leads to mitochondrial enlargement and inhibits autophagic mitochondrial turnover, since autophagosomes cannot engulf enlarged mitochondria that are larger than their physical limit [14]. Indeed, enlarged (or swollen) mitochondria often accumulate in aging cells and exhibit diminished metabolic activity, possibly due to inefficient mitochondrial turnover [15]. On the other hand, mitochondrial fusion must follow immediately after mitochondrial division to protect isolated healthy mitochondrial pools from being randomly digested by nonselective autophagic activity [14]. Without fusion, unwanted mitochondrial degradation would occur, which can accelerate mitochondrial loss in aging organisms. Therefore, both mitochondrial fission and fusion play an important role in degrading and protecting mitochondria during the organellar quality control and in maintaining their function (fig. 1b), thus securing nuclear genome integrity.

While mitochondrial fission increases the organellar number, the fusion process might be involved in mitochondrial biogenesis [13]. Since fused mitochondria can synchronize their electrochemical gradient potential, which is
required for active import and/or exchange of genetic/enzymatic materials between organelles, mitochondrial biogenesis should be more efficiently facilitated in the fused mitochondrial network than the unfused ones. Furthermore, the fact that some mitochondrial fusion components (e.g. MFN2) colocalize onto both endoplasmic reticulum and mitochondria suggests that mitochondrial fusion might help their biogenesis by forming a direct bridge between mitochondria and endoplasmic reticulum by enhancing the protein import efficiency of nuclear-encoded mitochondrial gene products to newly growing mitochondria. Reinforcing this, activation of AMP-activated protein kinase, which is the master regulator of mitochondrial biogenesis, concurrently promotes mitochondrial fusion activity by posttranslational deactivation of fission machineries [unpubl. data]. Moreover, PGC1α directly regulates mitochondrial fusion gene (i.e. MFN2) expression together with triggering mitochondrial biogenesis genes, which suggests that mitochondrial fusion and biogenesis potentially depend on each other [16]. Given the fact, then, that proper mitochondrial biogenesis is necessary for maintaining healthy mitochondria, mitochondrial quality control relies on a well-balanced mitochondrial fission and fusion activity. In support of this, impaired mitochondrial fusion and fission activities coincide with diminished mitochondrial quality, content, and function in age-related metabolic diseases (e.g. obesity and type 2 diabetes) [17].

Taken together, a coordinated interplay between mitochondrial fission and fusion dynamics, degradation, and biogenesis allows aging cells to maintain mitochondrial repair and quality control (fig. 1b). This delicate balance is lost in old age, and especially in frail elderly under acute stress, leading to comorbidities and increased mortalities. Several combination therapies (nutritional, hormonal, and pharmaceutical) implemented earlier in life could alter the number of comorbidities and improve the quality of life of the elderly.

**Concluding Remarks**

Late-life aging in humans is often associated with severe frailty, which increases an individual’s susceptibility to age-associated cardiovascular, metabolic, and inflammatory disorders as well as cognitive and physical weakness. Although cellular mechanisms underlying the frailty syndrome are still largely unknown, an altered balance between damage repair of mitochondrial and nuclear material as well as associated altered cellular signaling play a driving force to aging and frailty. Upon augmented nuclear genome instability, nuclear DNA signals (e.g. p53, Bax, and Bak) become overactivated, resulting in impaired
mitochondrial biogenesis, mPTP opening, apoptosis, and an overall rapid decline in cellular viability. The healthy interaction between the mitochondria and nuclear events (mitochondrial dynamics/mitophagy) are lost during cellular aging. These are critical processes for maintaining an intact nuclear genome, preventing loss of mtDNA and nuclear DNA content, and quality. In this review, we briefly discussed potential molecular mechanisms related to changes in genomic instability (mitochondria/nucleus) and their interactive roles in the causes of frailty.

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References

Abstract
Older people are at risk of developing frailty with advancing age. The prevalence of frailty increases from 2.5–3% in adults aged 65 years to 30–35% in those older than 85 years. These results suggest that an association exists between longevity and frailty. However, at the same time, even at advanced age, the majority of older adults are free of frailty, suggesting that factors different from those contributing to or produced by the life length are involved in producing frailty. Genetic and epigenetic factors, nutrient-sensing systems, mainly the so-called insulin/insulin-like growth factor-1 signaling pathway, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, inflammation, and some hormonal systems are involved in longevity. However, factors involved in frailty are mainly inflammation and hormones, with an anecdotal role for genetic and other potential factors, but even these two common factors seem to regulate longevity and frailty in different ways. Moreover, their effect on frailty seems to change when they are acting in combination.

Introduction
During the last century, life expectancy and prevalence of disability have increased in parallel. Life expectancy has increased from 30–35 years at the beginning of the last century to figures approaching 85 years in many of the more industrialized countries [1]. At the same time, and especially during the second half of the 20th century, there has been an increase in the prevalence of disability in those same
countries [2]. Although in the last decades the rate of increase in life expectancy has apparently started to decline and the prevalence of disability has begun to stabilize or smoothly decrease [2–4], there is still a tendency to believe that the changes that promote and accompany the extension of longevity are the same as those underlying disabling processes in general, and frailty in particular. If this holds true, frailty and disability should be an inevitable consequence of the aging process, an inexorable result of prolonging the duration of our life. If this is not true, i.e. longevity and frailty only share some common mechanisms but they are regulated in different ways to increase longevity or, on the opposite, to produce frailty, increasing longevity without experiencing relevant frailty will be feasible. However, disentangling longevity and frailty can be a tricky task because one of the characteristics of frailty, no matter the chosen conceptual model, is to predict death.

Both longevity and frailty share some common facts, with the loss of functional reserve being the most relevant [5, 6]. Although frailty is more prevalent with increasing age, the majority of the people never reach a state of frailty even when they reach advanced age. Thus, at a first glance, it looks like longevity and frailty share some causes that act by similar mechanisms (i.e. involved both in longevity and frailty); other causes (e.g. sexual hormones) produce beneficial effects prolonging longevity but increasing the risk of frailty, and, finally, some exclusive causes that operate independently are based on different mechanisms.

Furthermore, while the mechanisms involved in longevity seem to exert their effects in the majority of cells, organs, and systems (although at a different rate and intensity), the mechanisms involved in frailty seem to be of importance in the organs and systems related to energy consumption and mobility, mainly the osteo-muscle-skeletal system and the peripheral nervous system.

Finally, some chronic diseases and conditions have been especially related to frailty: ischemic heart disease, heart failure, chronic obstructive pulmonary disease, type 2 diabetes mellitus, cognitive dysfunction/dementia, and arthritis. The majority of them show some common pathophysiological characteristics that involve inflammation, insulin resistance, nutritional deficits, and musculoskeletal deficits affecting mobility and function.

**Longevity and Functional Reserve**

As previously stated, one of the most important changes accompanying the aging process is a progressive loss of functional reserve. This process starts at the end of the maturational phase and lasts until death. Only after losing around 70% of our functional capacity, we are at risk of experiencing frailty or disability [7]. When the loss exceeds 80%, the risk of death occurs. During lifetime, function declines at a
rate of 0.5% per year in all systems, with most data being available for those aged 30–70 years [8], although data from the Baltimore Longitudinal Study, measuring peak treadmill oxygen consumption, suggest that this rate can be accelerated with advancing age, reaching rates of 2% per year in the 70s and beyond [9]. This general, basal rate, which is based on intrinsic aging and insusceptible to changes (including leisure time physical activity), makes it unlikely to cross the line of 30% of remaining function that determines the presence of frailty or disability. But this basal rate can be accelerated under different extrinsic circumstances, with a rate ranging from a mean of 1% per week to 2% per year, leading to catastrophic or slowly accumulating decrements that will lead to different rates of aging. These different rates have a high interindividual variability, which is one of the main factors contributing to the high phenotypic heterogeneity that is typical in older people. Moreover, the differences in the rate of aging may also explain the differences in the trajectories of people during their last year of life. In this regard, it is noteworthy that frail decedents are more than 8 times more likely than sudden-death decedents to be dependent on help in activities of daily living [10], which illustrates the proximity of frailty to disability, with low functional reserve (a characteristic of frailty) being one of the most important risk factors for disability.

**Disease, Functional Reserve, and Frailty**

Having in mind this general scheme, which is the role for disease and other conditions, and which are the mechanisms increasing the rate of functional loss? Although there are several models to explain this relationship, probably a more comprehensive one was released in the Report of the National Institute on Aging on Comorbidity [11]. According to this report, aging produces few generalized changes (inflammation, oxidative stress, apoptosis, hypoxia, and hormonal changes). When diseases or conditions that exhibit all or some of these changes among their pathophysiological mechanisms coexist with aging, they aggravate these physiological impairments to finally produce clinical consequences that ultimately affect the functional status of older people (fig. 1a).

In other words, and according to our scheme, chronic disease accelerates the rate of functional loss, acting as the precipitating factor of frailty and disability (fig. 2). At the same time, once the disease(s) has produced its effect, its consequences (frailty or disability) evolve independently (fig. 1b). In fact, in very old people, the accuracy of comorbidity for predicting death and disability is lower than that of frailty. As a consequence, if you only treat the diseases/conditions but not the functional deterioration produced by them, the clinical symptoms of the diseases will improve but functional impairment will remain unchanged.
Frailty is in essence the final product of the interrelation between the aging process and different chronic diseases and conditions. Thus, several of the changes accompanying the aging process and some of the causes and mechanisms underlying them should be also present in frailty (table 1). In some way, these are the longevity-associated mechanisms predisposing to the development of frailty.
Longevity
In a recent review paper on the causes and mechanisms of aging [12], four main causes have been identified as the 'primary hallmarks' of aging by determining the original damage: genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis. All of them produce damage in nuclear and mitochondrial DNA or changes in the proteasome resulting in proteotoxic effects.
due to the accumulation and aggregation of unfolded proteins. Consequently, and in response to this damage, the other three sets of mechanisms try to mitigate this damage, but in case of persistent damage, these initially protective mechanisms become deleterious. These so-called ‘antagonistic hallmarks’ are deregulated nutrient-sensing, mitochondrial dysfunction, and cellular senescence. The main component of the first of them is the insulin/insulin-like growth factor (IGF)-1 signaling pathway, including all its downstream components. This pathway is associated with higher longevity when its performance is reduced at any level [13], and it is probably responsible for the life-prolonging effect of dietary restriction that has been shown in many species, including (although with controversial findings) nonhuman primates [14].

Mitochondrial dysfunction, whatever the responsible mechanism (e.g. mitochondrial DNA mutation or mitophagy), increases the generation and release of reactive oxygen species (ROS). At low concentrations, ROS play a significant role in cellular and intercellular signaling that facilitates cell survival and the occurrence of many significant cellular processes, whereas irreversible damage to different cell structures is caused above a certain threshold [15]. Finally, cellular senescence has been regarded as a defensive mechanism against malignant cell transformation. However, with aging, the clearance of these senescent cells is decreased; decreased clearance that in addition to a decreased capacity of progenitor cells to reestablish well-functioning cell numbers results in the accumulation of senescent cells with the ensuing consequences. One of these consequences is an increase in the production of cytokines [16]. In this regard, the role of p53 and p16\textsuperscript{INK4a} seems to be of importance, and their levels are associated with chronological age [17]. Interestingly, however, the suppression of p16\textsuperscript{ink4a} in transgenic mice has shown to have an effect which does not prolong longevity but rather delay the onset of some phenotypes associated with disorders that typically appear in older animals [18].

The interaction between the four mechanisms causing the original damage and the three ones trying to tackle it, is going to produce consequences on two main systems that will be finally responsible for the aging phenotype: stem cell exhaustion and altered intercellular communication, which are controlled by changes in immune and inflammatory responses (inflammaging) [19] and the endocrine system.

\textit{Frailty}
Several systems and factors have been involved in the generation of frailty. The loss of functional capacity and functional reserve that is characteristic of frailty is mainly due to changes in two systems: hormonal dysregulation and inflammation, which, in turn, can be modulated by both genetic and environmental
influences. The changes in these physiological systems, in addition to the compromise in several regulatory functions, finally impact on different target organs (bone, brain, vessels, and muscle). Among these organs, the effect on skeletal muscles and its energetic mechanisms (both energy production and energy expenditure, with a predominance of catabolism over anabolism) has a pivotal role in producing the clinical phenotype.

Before looking at some of these changes, it should be underscored that one of the main characteristics of frailty is its multidimensional nature, with an increasing risk of frailty when several systems are involved in a dose-dependent relationship [20]. Thus, when facing the biological basis of frailty, we should consider the effect of the combination of several factors instead of the individual effect of each one alone.

**Inflammation.** Frailty has been associated with several traditional markers of inflammation [21] (e.g. IL-6, TNF-α, C-reactive protein, fibrinogen, D-dimer, and leukocytes). The origin of this low-grade inflammatory status that accompanies frailty is an issue of controversy, and among the different candidates are the increase in senescent cells, decreased response to Toll-like receptor ligation [22], decreased muscular activity, and upregulated expression of some stress-responsive inflammatory pathway genes [23]. However, the role of the adipose tissue seems to be predominant. Several sources of evidence have found a possible connection between the adipose tissue and muscular fibers, with a fluent dialogue between both tissues by means of adipokines and myokines [24]. Two short comments to this issue: although the relationship between adipose tissue has been mainly established with visceral adipose tissue, one of the changes in the body composition during the aging process is a progressive infiltration of skeletal muscles by adipose tissue, with the metabolic characteristics of this adipose tissue being similar to those of the visceral adipose tissue. In this regard, it should be highlighted that the amount of intermuscular fat is not affected by physical activity [25]. The second comment concerns the relationship of obesity with both longevity and frailty. The relationship between body mass index (BMI) and mortality changes with age. Although a high BMI in young adults increases the risk of death, this relationship is U-shaped in older people, with the optimal BMI being in the range of overweight and stage-1 obesity, probably reflecting the changing proportion between muscle mass and fat mass with age.

However, the effect of BMI on frailty seems to be more linear, with a direct relationship between frailty and BMI, with the paradigm of this relationship being the one observed in sarcopenic obesity. Furthermore, both overweight and obesity during adulthood have been associated with the development of prefrailty and frailty in the elderly [26].
Hormonal Changes: Frailty is associated with an impairment in different anabolic hormones. Although some disparate effects of inflammation on longevity and frailty have been cited previously, it is in the field of hormones where these disparate effects are probably more relevant. Three main groups of hormones are involved in frailty: growth hormone (GH)/IGF-1 and insulin, sexual hormones (testosterone and estradiol), and cortisol/dehydroepiandrosterone (DHEA) [27].

DHEA is a steroid precursor of testosterone. DHEA and its sulfated form DHEA-S are produced by the adrenal cortex, and the biological role of these hormones is not yet well defined. Observational cohort studies have demonstrated that plasma levels of DHEA and its sulfated form decline by 80% between the ages of 25 and 75 years, and this decrease is greater after 80 years. In parallel, muscle mass and strength also decline with age, and both low DHEA plasma levels and a high cortisol/DHEA ratio predict the risk of developing frailty [28]. Published data about DHEA replacement in older people are confusing and conflicting. In fact, there are few studies on DHEA supplements and evaluation of muscle function. Moreover, most of them are performed in small cohorts aged between 50 and 70 years, making extrapolation of the results to the general population of older people a major issue [29]. In addition to its association with frailty, serum DHEA-S is also a predictive factor for long-term longevity, as higher plasma concentrations have been associated with greater longevity [30].

It has been well established that in subjects over 65 years of age serum testosterone levels tend to be considerably reduced, a state that has become known as andropause. Free testosterone levels begin to decline at a rate of 1% per year after age 40 years. It is estimated that 20% of men aged 60–80 years have levels below the lower limit of normality of adult men. This decrease has been directly associated with low longevity [31] in men and frailty in older men and women [32]. In women, although low testosterone levels seem to be also related to frailty [32], the most important issue from a hormonal point of view is menopause, which causes a sudden drop in sex steroid hormones resulting in loss of bone density but also in muscle weakness. Moreover, a recent study [33] suggested that the relationship between frailty and estrogens could be opposite to the one expected: frailty seems to be associated with high estrogen levels in older (i.e. postmenopausal) women. In addition, and in contrast to what occurs with testosterone, high levels of estrogen are associated with increased longevity, but also with frailty, especially if they are associated to inflammation. So the beneficial effect of estradiol on survival [34] is opposed to the effect on frailty.

GH levels also decrease with age. Compared with nonfrail older adults, frail older adults have lower levels of IGF-1, a GH-stimulated messenger molecule. In this same regard, insulin resistance is also associated with frailty, supporting the
contribution of low-functioning insulin/IGF-1 signaling to a prolonged survival but, at the same time, to the presence of frailty. In addition, mitochondrial dysfunction in skeletal muscles seems to be one of the factors involved in the generation of insulin resistance in older people due to a poor utilization of glucose secondary to impaired oxidative phosphorylation, which results in increased ROS levels. Furthermore, sirtuins also have disparate relationships with longevity and frailty. In mice, while sirtuin 1 does not produce any effect on longevity but improves the health status, sirtuin 6 prolongs longevity by an effect mediated by IGF-1 without having any effect on the health status. Finally, sirtuin 3 seems to be involved in the beneficial effects of caloric restriction on longevity in mammals.

Interestingly, the role of the combination of these factors in the association with frailty has been extensively studied, and some relationships with frailty are stronger (which is the case for estradiol and inflammation, previously commented) or subject to changes. In this later case, among the different combinations of factors, it is worthy to mention the association between inflammation (assessed by white blood cell counts) and IGF-1. The highest odds ratio for the association with frailty was observed when both inflammation and IGF-1 were in the high tertile, changing the relationship of isolated IGF-1 with frailty [35].

Finally, genetic factors have also been involved in the development of frailty. With longevity being a familial trait, some authors have tried to associate longevity of the parents with frailty (or less frailty) in the offspring, and found a relationship between the age of the parents and the performance in some functional tasks (but not in all of them) [36]. Although there are few studies on the genetic background of frailty, polymorphisms in some groups of human genes related with apoptosis and transcription regulation could be involved [37].

Telomere length has also been studied with disparities in the results. While some authors have found a marginal association between telomere length and longevity in older people, the majority of works have reported an absence of associations between mean telomere length and percentage of short telomeres with longevity. However, one group has found a relationship between telomere length in leukocytes and disability (i.e. in activities of daily living) in nondiabetic subjects [38].

Finally, some factors with no potential direct relationship with longevity, e.g. glycoproteins (including HbA1c) [39] and vitamin D, have also been related with a higher risk of developing frailty in humans.

In summary, longevity and frailty share some of their underlying mechanisms. This fact may explain why they are closely related and the association between advanced age and a higher prevalence of frailty, but at the same time longevity and frailty differ in some characteristics. First, while aging/longevity is a universal and intrinsic phenomenon, frailty is modified by external factors...
and has its main impact on four organs. Second, some factors that prolong longevity (favorable effect on the duration of life) increase the risk of frailty (unfavorable effect on the quality of life), while others protecting from frailty shorten the life expectancy. These different characteristics may explain the different courses of longevity and the functional status in many older people, opening opportunities for intervention.

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References

Abstract
Frailty has been defined as a geriatric syndrome that is characterized by a reduction in the physiological reserve required for an individual to respond to endogenous and exogenous stressors. Using a discrete definition of frailty that includes sedentariness, involuntary weight loss, fatigue, poor muscle strength, and slow gait speed, ‘frailty’ has been associated with increased disability, postsurgical complications, and increased mortality. Despite the strong associations between frailty and subsequent poor outcomes, limited attention to this common geriatric condition has been paid in clinical settings. A more fundamental basic understanding of the biological factors that contribute to the frailty phenotype has begun to emerge. Multiple underlying biological factors such as dysregulation of inflammatory processes, genomic instability, oxidative stress, mitochondrial dysfunction, and cellular senescence appear to contribute to the clinical presentation of frailty. This chapter summarizes the papers presented on the biological basis of frailty from the 83rd Nestlé Nutrition Institute Workshop on ‘Frailty, Pathophysiology, Phenotype and Patient Care’ held in Barcelona, Spain, in March 2014.

Introduction
The demographic shift in the average age of the population worldwide mandates that careful attention be paid to the nutritional and health needs of all segments of our aging society. Well-defined changes in body composition
occur with advancing age. Characteristic of this change is the age-associated decline in skeletal muscle mass and function (sarcopenia). Sarcopenia has been linked to declines in physical function, loss of independence, and mortality. The functional declines associated with sarcopenia are factors that contribute to the syndrome of frailty with advancing age (fig. 1). Frailty has been operationalized as a geriatric syndrome that is characterized by a reduction in the physiological reserve required for an individual to respond to endogenous and exogenous stressors [1]. Using a discrete definition of frailty that includes sedentariness, involuntary weight loss, fatigue, poor muscle strength, and slow gait speed, Fried et al. [1] have been able to associate states of frailty with increased disability, postsurgical complications, and increased mortality. Recent work in this area has focused on the underlying biological mechanisms associated with the phenotype of frailty and the components of the frailty syndrome.

The conceptual basis for the clinical phenotype of frailty has coalesced into five distinct features including sedentary lifestyle, involuntary weight loss, muscle weakness, fatigue, and slow gait speed [1]. Hypotheses about the cellular alterations that drive this syndrome have focused on changes in the proinflammatory environment, altered hypothalamic-pituitary axis functioning, increased sympathetic nervous system activity, and increased renin-angiotensin system activation [2]. These systemic changes appear to be driving intracellular regulatory systems related to mitophagy/autophagy, apoptosis, senescence,
mitochondrial dysfunction, and epigenetic modifications. Recent work has focused on developing animal models that best reflect the frailty phenotype. Among these, the interleukin-$10^{-/-}$ transgenic mouse model has emerged as a promising model of human frailty [3]. Future studies will require additional model systems to elucidate the underlying mechanisms driving frailty with the ultimate goal being the successful development of therapeutics for the prevention or treatment of frailty.

Cellular senescence, the process by which cells lose the ability to divide and impart damaging secretory products to neighboring cells, the senescence-associated secretory phenotype, has been implicated in age-related chronic disease and aspects of frailty. While cellular senescence may be an important anticancer defense during growth and development, the accumulation of senescent cells in tissues during aging has resultant negative consequences, including increased inflammatory burden, functional changes, and pathology. A key feature of cellular senescence in relation to age-related chronic diseases and frailty is the secretion of a number of proinflammatory cytokines, chemokines, matrix remodeling proteases, and growth factors (the senescence-associated secretory phenotype) [4]. With the development of model systems that allow for the manipulation of senescent cells [5] to determine the role of cell senescence in frailty, the development of targeted therapeutics for this process is on the horizon [6].

Genomic instability refers to the high frequency of mutations and deletions within the genome (both nuclear and mitochondrial DNA) caused by DNA damage and inefficient repair [7]. Evidence for a role of increased reactive oxygen species, altered intracellular calcium homeostasis, and iron dysregulation in advancing age has been proposed to induce age-related alterations in nuclear and mitochondrial DNA and may play a role in frailty.

Finally, questions have arisen about the distinction between cellular mechanisms associated with frailty and those specifically related to life span or longevity. Longevity appears to be controlled by a combination of genetic and epigenetic factors, nutrient-sensing systems, IGF-1 signaling, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, inflammation, and other hormonal axes [8], whereas frailty appears to be controlled by systemic inflammation and key regulatory hormones [9].

In summary, a consolidation of the components underlying frailty, the development of powerful biological tools in model systems to evaluate mechanisms, and the continuing approach to target therapeutics have pushed knowledge on the cause and treatment for the frailty syndrome to the forefront. Promising innovative therapies loom on the horizon and will do much to address the largely unmet clinical need of frailty in our aging society.
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References

Abstract
There is little written in the geriatric literature about the concept of psychological frailty which encompasses cognitive, mood, and motivational components. The concept is intended to consider brain changes that are beyond normal aging, but not necessarily inclusive of disease, that result in decreased cognitive or mood resilience in the presence of modest stressors, and may eventually lead to negative health outcomes in a manner parallel to physical frailty, an entity well known to clinicians. Most work exploring the interface between cognition, mood, and physical frailty has demonstrated a bidirectional association between the two domains. Psychological symptoms or deficits have been described as either worsening the degree of physical frailty, or physical frailty has been viewed as a risk to a worsening cognition or depression. However, psychological frailty, a consequence of age-altered brain function, has not been studied for itself. By what possible mechanism does the brain reveal its loss of resiliency under modest stress and how can this be visualized? Are there markers that predate a psychological decline that might permit a preventive intervention which could delay the appearance of negative health outcomes such as reduced functional capacity or increased dependency? The present review will explore these concepts and possibilities.

Introduction
There is little reference in the medical literature to the term ‘psychological frailty’ in the context of aging adults. The term ‘psychological’ is taken to refer to particular products of brain function that result in conscious and unconscious
experiences and complex, usually directed behavior. There are, of course, other important aspects of brain activity which are critical to the individual but are not deemed to be psychological per se. These include multiple autonomic regulations of body functions needed to maintain homeostasis and activity. In the following discussion, we will consider the concept of frailty as it specifically pertains to three important psychological functions: cognition, mood, and motivation.

**Frailty**

The concept of frailty has been broadly characterized as a multisystem geriatric syndrome involving an increased vulnerability to stressors and loss of resilience in the face of internal or environmental challenges in different but interlinked physiological systems. This enhanced vulnerability to challenge, beyond that seen in usual aging, is believed to be linked to a higher risk for poor health outcomes such as falls, hospitalizations, institutionalization, and death. After more than 15 years of clinical research, no consensus operational definition has been reached nor have definitive assessment tools or biological markers been established. In landmark research, Fried et al. [1] developed the concept of a physical frailty phenotype, offering an operational definition of the condition based on an assumed state of negative energy balance, sarcopenia, diminished strength, and low tolerance for exertion. The phenotype originally consisted of five practically measurable clinical symptoms: exhaustion, weight loss, weak grip strength, and slow walking speed, three of which had to be present for the frail diagnosis. Cognition and mood were excluded. In subsequent studies, the phenotype was able to predict consistently various negative clinical outcomes such as falls, low mobility, hospitalization, and death in vulnerable populations [2]. Other groups using adapted phenotype criteria predicted similar outcomes. Recently, gait speed has become the most used marker of frailty among many clinicians due to its simplicity and predictive power [3, 4].

Other researchers have argued for a broader, more inclusive account of frailty which in addition to physical factors would include cognitive, emotional, motivational, and social characteristics given the multisystem nature of biological changes underpinning the frail condition [5]. These workers have emphasized a cumulative deficit approach which incorporates a large number of candidate factors ranging from disease states, symptoms, signs, to abnormal laboratory values. When combined and divided by the total number of deficits, these yield a frailty index. Although longer to administer, this approach offers some advantages over the frail phenotype method because it is more comprehensive and has the ability to produce a graded version of frailty rather than the bicategorical characterization of the
phenotypic model. Rockwood et al. [6] and others have produced a frailty index that has been highly predictive of the outcomes of death and institutionalization in identified frail subjects [7]. However, in spite of the considerable progress to date in the development of both the phenotypic and index models, the observational identification of frailty in the absence of the demonstrated pathophysiological mechanisms and biologic markers may occur too proximal to poor health outcomes to permit earlier, more effective interventions.

**Psychological Frailty**

*Cognitive Frailty*

The use of this construct is relatively new in the geriatric literature, having to date attracted little attention from clinicians and gerontologists. The term ‘cognitive frailty’ suggests a parallel to physical frailty, a loss of resilience and adaptability in the domain of brain function and implies a linkage to physical frailty. Numerous studies on expanded physical frailty have implicated cognition as a possible factor influencing health outcome [8, 9]. Furthermore, in many of these studies, frailty was explored as a manifestation of some class of cognitive impairment or, more frequently, frailty was viewed as a predictor of cognitive impairment. The concept of cognitive frailty is not examined in and of itself. What then is it and how can its presence be determined? In the recent literature, only Panza et al. [10] and Keleiditi et al. [11] have attempted to develop the construct, albeit in different clinical contexts. Most recently, Keleiditi et al. [11] made a direct attempt to open a dialogue about what cognitive frailty should comprise, of what should constitute a basic operational definition of the condition? They raised important considerations and suggested that cognitive frailty should be (1) linked to a reduction in cognitive ‘reserve’; (2) independent of specific brain diseases but at the same time coexist with the presence of physical frailty (in this concept, cognitive frailty is to be distinguished from the presence of cognitive impairment found in individuals without physical frailty), and (3) represented by a score of 0.5 on the well-established Clinical Dementia Rating (CDR) Scale, a score that is often associated with predementia, but not dementia conditions. These framing concepts deserve further consideration.

*Cognitive Frailty as a Reduction in Cognitive Reserve.* The link between the notion of cognitive reserve and the emergence of cognitive frailty would benefit from further development. As used by Keleiditi et al. [11], cognitive reserve implies a passive process similar to the concept of brain reserve capacity first proposed by Katzman [12] and Satz [13] where reserve is defined in terms of the amount of brain damage that can be sustained before reaching a threshold of
clinical expression. Analogously, per Keleiditi et al. [11], the appearance of cognitive frailty would be established with a CDR score of 0.5. In contrast, an active model of cognitive reserve would suggest that the brain actively attempts to manage brain damage or age-related changes by either using preexisting cognitive processing approaches or by using compensatory mechanisms [14, 15]. That is, an active model of cognitive reserve implies that underlying it are neural networks and neuronal connectivity that are more efficient, have a greater capacity, or are more flexible in individuals with greater reserve than those with less, thus high-reserve persons may be better capable of coping with challenges imposed by age-related brain changes or systemic or brain disease. Significant variability exists in cognitive reserve among individuals, and epidemiologic studies have suggested that good proxies for the amount of cognitive reserve include measures of economic attainment, level of education, IQ, and degree of literacy [16].

With the recent development of more sophisticated brain imaging techniques such as functional MRI, diffusion tensor imaging, and optical imaging, for example, and in combination with the application of new, highly sensitive cognitive tasks during imaging, there has been accelerating activity in the functional imaging of cognitive reserve and compensatory cognitive operations in healthy younger and older persons. Functional neuroimaging is providing many useful insights into the field of cognitive aging besides improving information on the localization of particular cognitive operations. It has furnished evidence in aging for increased recruitment of the prefrontal cortex in diverse cognitive tasks, probably the area with most plastic capacity in the brain [17]. It has also revealed that functional interactions between the prefrontal cortex and other brain regions, such as the mesial temporal lobe, which are important in encoding new information, are associated with better memory performance in older adults [18]. These changes are likely compensatory in nature. Reuter-Lorenz and Cappell [19] have shown evidence supporting the observation that older adults display regions of greater prefrontal activity than younger adults when task demands are low, suggesting that older adults recruit more neural circuits than younger adults at lower levels of task demand. As demand increases, younger adults also begin to engage additional circuitry, whereas older adults plateau and then begin to decline, probably because they are no longer able to engage task-related circuitry, that is, they can no longer compensate for the challenge of the added cognitive load.

One could possibly consider then, as a more biologically based marker of cognitive frailty, the inability to exhibit a minimal level of compensation for a cognitive task that had been previously established to produce a compensating response in most healthy older persons. From a more practical standpoint, an office proxy for the imaging evidence could be a successful completion of that image-linked task in a given amount of time. An approach of this type would
have improved validity over the more arbitrary selection of a particular CDR
score as a cutoff point for cognitive frailty. Its prognostic value would need to be
determined in subsequent longitudinal studies, but it could have the advantage
of a longer lead time before negative health outcomes became imminent.

It can already be foreseen that through the future use of state-of-the-art cog-
nitive testing and imaging techniques, improved understanding of the neural
mediation of various aspects of cognitive reserve can be attained. The imaging
approach to measuring cognitive reserve could be important for understanding
an aged individual’s true clinical status which would reflect a combination of
underlying age-related brain changes and that individual’s cognitive reserve in
the context of those changes. Individuals with similar clinical appearances could
differ substantially in their neural measures of reserve and this could have sig-
nificant implications for a timely prognosis and treatment.

Can Cognitive Frailty Exist Independently of Brain Disease and Must It
Co-Occur with Some Evidence of Physical Frailty? A major question in the study
of brain aging is the boundary between age-related changes and disease. More
recently, the questions of what distinguishes ‘normal’ aging from cognitive frail-
ity and how is frailty different from disease have arisen. Our ability to answer
these questions has improved recently as a consequence of better imaging tech-
niques and cognitive characterization of patients, but certainly is not yet com-
plete. Many now suggest that aging is not just the aggregation of disease, but that
other time-related factors and subtle but pervasive accumulation of damage to
homeostatic mechanisms can account for aging changes and that some brain
structures are more vulnerable than others to this process. In making the distinc-
tion between age-related brain changes and age-related brain disease, Small et
al. [20] have been able to demonstrate, using human and nonhuman primate
species, that memory decline is different in aging than in Alzheimer’s disease
(AD), and is mediated by damage to different hippocampal structures in each
condition, e.g. the entorhinal cortex in AD and the dentate gyrus in normal ag-
ing. Their work supports the proposition that aging per se and AD are distinct
but possibly related processes since sporadic AD appears to be age dependent
with the risk of it increasing exponentially after 65 until about 95 years of age,
yet there are very old individuals who do not develop AD.

Where to situate cognitive frailty in relationship to normal or ‘usual’ aging
cognition and disease is a more complicated issue and has been viewed differ-
ently by clinicians from different disciplines. Application of emerging imaging
techniques and new cognitive testing approaches should help to bring clarity
and evidence of more subtle brain dysfunctions into better view. If we assume
that primary cognitive frailty can develop intrinsically in the brain, perhaps from
a loss of protective factors still operative in normal aging, and as a result of non-
disease-specific, age-related physiological degradation of neural network communications evidenced by a reduction in cognitive reserve and an inadequate compensatory response to a challenge, we can affirm that in at least some cases cognitive frailty can be dissociated from an identifiable disease processes such as, for example, predementia AD. As we become more able to image occult brain diseases (e.g. amyloid imaging in asymptomatic AD) and confirm the presence of preclinical disease with biomarkers (e.g. amyloid β42 and phosphorylated tau), we will be able to separate those individuals who are developing intrinsic primary cognitive frailty, as evidenced by challenge test results, from those who harbor occult disease and may also underperform during a challenge paradigm. This would have important intervention implications as the absence of disease would permit the frail brain to respond much better to cognitive and behavioral stimulation of its inherent plasticity.

Primary cognitive frailty will be worsened by the presence of brain and systemic disease, preclinical or not, as cognitive reserve and compensatory mechanisms would be additionally challenged by disease-specific neurodegenerative or vascular processes with a predilection for particular brain circuitry and areas beyond what is likely to be affected in nondiseased aging. Examples of these are the early damage in AD to the entorhinal cortex and posterior cingulate, and in systemic hypertension by the deep white and deep grey matter lesions due to damage of the thin, deep, penetrating arteries of the posterior and anterior circulation. Consequently, disease-specific damage would be additive to the physiological degradation of age-vulnerable areas such as the prefrontal cortex, a structure likely to be involved in reduced reserve and compensatory capacity in primary cognitive frailty.

Lastly, the relationship between the state of intrinsic primary cognitive frailty and disease needs to be considered. As with much of the preceding discussion, little is factually known currently and many of the ensuing comments will necessarily be conjectural, yet eventually testable. It is appealing to hypothesize that primary cognitive frailty is an intermediary between ‘normal aging’ and brain disease. For example, the molecular changes in neurons and glial cells that characterize the subtle loss of functionality from ‘normal’ aging to primary cognitive frailty are but part of a continuum of changes that as further degradation takes place permit the pathogenic mechanisms of a particular disease to become more fully activated and expressed. The additional burden of systemic disease and physical frailty may actually hasten the process. This could at least partially explain why the emergence of sporadic, late-onset AD seems to accelerate exponentially with age as individuals become more frail and ill. If this were the case, then it would be important to identify primary cognitive frailty and develop interventions to reduce it to delay the risk of acquiring age-related diseases.
Cognitive Frailty May Indicate a Higher Risk for Adverse Long-Term Health Outcomes. Based on the assumption that frailty is driven by the same basic age-related processes in all organs and systems in the body, its presence in the brain is bound to have functional consequences as it develops and these will likely lead to undesirable health outcomes. However, it is important to note that all organs or systems in the body will not have developed the same degree of frailty at the same point in the individual’s history. A number of recent studies have shown links between cognitive deficits and physical frailty [9]. The pattern emerging from these studies suggests that gait speed or grip strength are the components of frailty most strongly associated with cognitive function. Executive dysfunction and impaired attention are the cognitive domains most consistently linked to frailty. This may be best understood by the strong relationship of gait to the functioning of prefrontal executive and motor circuits. More subtle brain dysfunction such as a reduction in cognitive compensation mechanisms under challenge has not been examined as a predictor of gait speed or strength or longitudinally as a possible indicator of future negative health outcomes.

Mood and Motivational Frailty

As with the term cognitive frailty, the concept of ‘mood or motivational frailty’ in aging also suggests a parallel to physical frailty in the domain of brain function and implies a linkage between the two. The term mood describes a relatively persistent state of emotion such as depression, fear, anxiety, or anger. Motivation, the drive toward a goal, or lack thereof (apathy), is linked to mood but can be largely independent of it as is noted, for example, in nondepressed individuals with dementia. This is probably the case because reward and motivation are subserved by different but overlapping neural networks and circuits. Generally, the elaboration of emotion and mood is dependent on particular brain circuitry involving limbic and neocortical structures such as the amygdala, hippocampus, hypothalamus, anterior cingulate, ventral striatum, and orbital and medial prefrontal cortices, possibly explaining why thoughts are so colored by mood and moods influenced by thought. Single-source divergent networks primarily originating in the locus ceruleus, raphe’ nuclei, and ventral tegmentum of the brain stem innervate and modulate the above networks via noradrenergic, serotonergic, and dopaminergic input. The experience of particular emotions appears dependent on the activation/suppression and modulation of key structures in a circuit. There is usually circuit overlap between emotions, but there are also differences. This may explain why in the presence of a disorder such as depression, other emotions such as anxiety and irritability can also be present. The development of mood disorders appears dependent on the interaction of genetic circuitry predispositions and a variety of stressors.
Much of the work examining the relationship of physical frailty to mood has focused on depressive symptoms. Depression and physical frailty share several clinical characteristics such as loss of energy, fatigability, poor sleep, and reduced interest. A number of clinical studies have strongly suggested a bidirectional association between depression in later life and physical frailty [21], but have not explored the possibility of the existence of a primary, intrinsic vulnerability to emotional stressors with age that might signal mood frailty, a possible precursor to depression and its negative health outcomes. A state of mood frailty could possibly be demonstrated by monitoring a subject’s response to an emotional challenge test such as visualizing or imagining a sad situation, then being able to quickly revert to positive thoughts. Failure to make a rapid switch could have the potential to invite an earlier preventive intervention. As is the case with cognitive frailty, stressors, either external or internal, such as the presence of disease, will likely augment mood frailty.

The frailty and depression studies noted above also have not been able to disentangle frailty and depression, i.e. whether they are separate etiological entities or are simply variants in the expression of the same underlying pathology. Recent basic work has demonstrated that the pathophysiology of psychological stress-induced illnesses such as depression is associated with atrophy of vulnerable neurons and decreased expression of neurotrophic factors such as brain-derived neurotrophic factor [22, 23]. It has also been shown that the NMDA receptor antagonist ketamine, which has been found to produce rapid antidepressant actions in treatment-resistant depressed patients, also rapidly increases synaptogenesis and reverses the atrophy caused by depression-induced chronic stress [24]. Further studies on the clinical applicability and safety of this agent in diverse populations are needed. However, future studies using new imaging techniques combined with ketamine-stimulated synaptogenesis and brain-derived neurotrophic factor production may show differences or similarities between low-energy, fatigued, but nondepressed or demented frail elders, and others who display similar symptoms but are found to be depressed. Thus future studies involving functional neuroimaging and biomarkers to the study of cognition, mood, and frailty will help us gain greater insight into the biological similarities and differences between physical frailty and brain-based cognitive, motivational and mood frailty.

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References


Abstract

Frailty is recognized as a clinical geriatric syndrome used to describe the weakest or most vulnerable older adults. Although the term frailty is commonly used in clinical practice, and the theoretical phenomenon is well accepted, it remains an evolving concept that lacks a universally accepted definition and specific diagnostic criteria. Different perspectives on frailty have led to two distinct viewpoints of this phenomenon in the literature. The first describes the phenomenon based solely on physical attributes and capabilities. In contrast, more recent perspectives describe the phenomenon in broader, multidimensional terms by incorporating the concept of cognitive frailty. In support of this view, there is increasing evidence that consideration of both cognitive and physical factors can better improve the ability to predict adverse health outcomes among frail older adults over physical factors alone. The recent recognition of the importance of cognitive factors has increased the complexity of this phenomenon and difficulty in developing a consensus definition. To add to this challenge, frailty can present in different stages of severity (from mild to severe), and there appears to be a dynamic relationship between these stages. Despite these challenges, a consensus on an international definition of frailty including physical and cognitive criteria is essential in order to advance research and treatment of this condition.

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Introduction

Frailty is a term frequently used by practitioners to describe the weakest or most vulnerable older adults. Frailty has been described as a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of adverse health outcomes, including fall-related injuries, delirium, hospitalization, disability, and even death [1, 2]. Accordingly, frailty is associated with high utilization of health care resources, especially within the last 2 years of life [3]. Thus, there is great importance in identifying and treating individuals who are frail, or at risk of becoming frail, to maximize their functional independence for as long as possible.

It is widely accepted that the prevalence of frailty increases dramatically with age [4], and appears to be a result of a vicious cycle influenced by endogenous and exogenous factors. The United States Census Bureau has predicted that by 2050, Americans aged 65 years or older will number nearly 89 million people, which is more than double the number of older adults in the United States in 2010 [5]. Given these projections, it is critical that health care practitioners are able to identify individuals with this condition or at risk for this condition. Without intervention, the number of frail older adults is likely to dramatically increase in the next few decades. Thus, there is an urgent need for interventions that can assist frail older adults in maintaining independence and reducing adverse health outcomes associated with frailty.

Although the term frailty is commonly used in clinical practice, and the theoretical phenomenon is well accepted, it remains an evolving concept that lacks a consensus definition and specific diagnostic criteria [6]. Because there is no universal and accepted definition of frailty, this phenomenon can mean different things to different health care practitioners. Without an operational definition available in clinical practice, the health practitioner’s ability to recognize and provide care for this phenomenon is limited [1, 6].

The challenge in developing a consensus definition of frailty is due in large part to the complexity of the phenomenon, which involves many different physiological, cognitive, and psychological systems. Because no single manifestation of frailty can encompass the whole of the symptoms or signs present, there is growing evidence that defining frailty in clinical practice and research remains paradoxically difficult. Different definitions have been proposed for a variety of reasons including: (1) differences in health care systems across countries; (2) debate over whether frailty is fundamentally distinct from sarcopenia or dynapenia; (3) ambiguity surrounding diagnosing a person with loss of independence; (4) novelty of the inclusion of the roles of cognitive and social function in the frailty process, and (5) variations in the tools used to assess frailty. To add even more
complexity to this process, frailty presents in different stages of severity (from mild to severe) and is characterized by the dynamic relationship between these stages. Despite these challenges, a universally accepted operational definition of frailty is critical for continued clinical care, research, and health policy. As suggested by Rockwood and Hubbard [4] in 2004, frailty needs to be understood as a quantifiable entity, rather than viewed as a subjective and imprecise concept. Therefore, there is an important need to come to a consensus definition of frailty.

As noted above, one of the primary reasons that there is not a universally accepted definition of frailty is that there is ongoing debate among experts over the concept of frailty itself. Past definitions of frailty have tended to focus exclusively on a physical phenotype, but more recent definitions are broader and combine physical indicators with cognitive, functional, and psychosocial indicators of frailty [7]. For example, impairments in cognition are beginning to be considered as critical components of this condition and may lead to a more holistic approach to treatment [7, 8]. These different perspectives on frailty have led to two distinct definitions of this phenomenon in the literature. The first perspective on frailty describes the phenomenon based solely on physical capabilities. The second perspective on frailty describes the phenomenon in broader, multidimensional terms. Based on this second definition, different presentations of frailty can be encountered by the clinician, since the individual may experience impairments in one domain but not another.

Inconsistent operationalization of the frailty status has resulted in widely varying prevalence estimates between studies. The prevalence of frailty is around 11%; 10% regarding physical frailty and 14% regarding the broad phenotype of frailty [7]. However, geriatric frailty has been reported in 20–30% of adults over 75 years, and its occurrence increases with advancing age [9]. Furthermore, women tend to develop the frailty syndrome more than men [7]. In the following sections, we present information on the use of the physical phenotype of frailty in clinical practice and then describe more novel cognitive approaches to defining and treating frailty.

**Physical Frailty: From Concept to Clinical Practice**

The *physical frailty* syndrome has been proposed to be a clinical condition characterized by an abnormal decline in physiologic reserves that increases stress and reduces an individual’s ability to maintain homeostasis and thus leads to vulnerability [2]. The differentiation between normal aging and frailty appears to be indistinct because some factors, such as the loss of muscle mass (sarcopenia) and strength (dynapenia), occur throughout the process of aging. To distinguish
physical frailty from aging, the widely used domains include ‘shrinking’ with weight loss and sarcopenia, weakness with low grip strength, exhaustion or poor endurance, slow motor performance (e.g. slow walking speed and decreased balance), and decreased physical activity as a marker of low-energy expenditure [2].

Although there is not a universally accepted operational definition of physical frailty, the most commonly used definition of a physical phenotype of frailty comes from Fried et al. [10] who proposed identifying frailty by using the Fried Frailty Index. The Fried Frailty Index is used to assess the presence of physical frailty if three or more symptoms are observed: (1) shrinking (i.e. a nutritional/metabolic component assessed by unintentional weight loss); (2) weakness (i.e. indicated by muscle strength); (3) poor endurance and energy (i.e. self-reported exhaustion); (4) slowness (i.e. demonstrated by slow walking speed), and (5) low amounts of physical activity [10]. Strong associations have been observed between the physical frailty phenotype, as defined by Fried et al. [10], and the risk of developing certain health-related outcomes. Thus, physical frailty could be partially explained by the occurrence of age-related body composition changes, loss of muscle mass, reduced muscle quality, and increased fat mass, which altogether precipitate the development of the frailty syndrome in older adults.

The Fried Frailty Index has shown its clinical application by diagnosing frailty in epidemiological studies [10]. It is relatively easy to use and allows for rapid assessment of physical frailty; however, administration of certain measurements, such as those for muscle strength and gait speed, could be difficult to implement in some clinical settings due to lack of proper equipment, time, and/or space to conduct the assessments. It is also not possible to use the Fried model for the assessment in the presence of disability or cognitive impairment, which seems to affect the reliability. With the exception of objectively measured gait speed, which is a strong predictor of poor clinical outcomes in different populations [11], the added value of the other criteria used in Fried’s definition is not known. Furthermore, the heterogeneous constellation of the Fried criteria includes very diverse phenotypes of frailty, making the syndrome difficult for targeting with specific pharmacologic interventions. From the interventional perspective, a more restrictive definition of frailty, involving, for example, only physical performance, would be of more practical utility.

Cognitive Frailty: From Concept to Operational Definition

While physical frailty is a widely recognized problem in the elderly, only in recent years has the term cognitive frailty emerged in the literature. Although many researchers study age-related cognitive decline and dysfunction, it is not
typically conceptualized in a manner consistent with current definitions of frailty. The term cognitive frailty has been used as a general descriptor for cognitive impairment occurring as people reach advanced age, or to refer to cognitive disturbances or pre dementia occurring in association with other medical conditions [12]. The current working definition of cognitive frailty, however, provides a foundation for clinical studies aimed at establishing an operational definition of this phenomenon.

A growing body of literature suggests a significant association between age-associated declines in both physical and cognitive function [13–15]; however, until recently, cognitive frailty lacked a working operational definition in the literature. Motivated by the growing awareness that many people with physical frailty are also prone to cognitive difficulties, an international consensus group comprised of investigators from the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics recently established a working definition for cognitive frailty in older adults [16]. The consensus group summarized cognitive frailty as a heterogeneous clinical manifestation characterized by the simultaneous presence of physical frailty and cognitive impairment in the absence of dementia [16].

The term cognitive frailty implies a parallel with physical frailty. The definition of cognitive frailty, however, is dependent on its diagnostic criteria. Unlike physical frailty, the primary criteria for cognitive frailty are the presence of mild cognitive impairment as defined by a Clinical Dementia Rating (CDR) score of 0.5, without Alzheimer’s disease or another progressive brain disturbance leading to dementia. The recently proposed definition of cognitive frailty has not yet been empirically tested, and past investigators have focused on a variety of different phenomena related to the concept of cognitive frailty [17].

Several questions must be addressed in future clinical studies: How do we characterize phenotypic differences among people with cognitive frailty? A CDR score of 0.5 is likely too narrow to capture the heterogeneity of cognitive frailty in older adults, and individuals without cognitive impairment may still be vulnerable to functional decline under certain conditions. This occurs commonly during hospitalization, or in response to extreme stress or changes in the physical environment in the elderly [18]. As such, vulnerability to alterations in cognitive function under such conditions may be an essential feature of cognitive frailty. What is the relationship between cognitive frailty and cognitive reserve? Cognitive reserve refers to the capacity of a person to resist cognitive impairment or decline [17]. While cognitive reserve and cognitive frailty are likely to be associated, their relationship is not well understood. Is there value in excluding brain disorders from cognitive frailty? Excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that...
the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Accordingly, there may be value in dichotomizing cognitive frailty between people with or without preexisting brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

The current working definition of cognitive frailty provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. The construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability for cognitive functional decline among people with or without physical frailty. Though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors, growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, is independently associated with a cognitive decline [13–15]. Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Prospective clinical studies are needed to assess the reliability and predictive validity of the operational measure of cognitive frailty.

Redefining Frailty: Emerging Definitions

Based on a growing body of literature, it seems that it is no longer satisfactory to define frailty in terms of physical attributes and capabilities alone since there are other factors involved in the frailty syndrome. A limitation of the Fried model is that it does not account for the role of cognition and other psychosocial factors in determining the frailty status. There is increasing evidence that such factors need to be considered and could improve the ability to predict adverse health outcomes. Pilotto et al. [19] examined the prognostic accuracy of frailty assessment inventories for mortality among hospitalized older adults and found that both cognitive and physical factors were important in predicting this outcome.

Numerous other definitions of frailty have added to the current controversy related to which components should be included in the frailty syndrome, in addition to physical manifestations. For example, in 1996, Rockwood et al. [20] conceptualized frailty as a multidimensional construct with both physical and
cognitive origins. In 2006, Panza et al. [21] attempted to specify different models of frailty in predementia and dementia syndromes. More recently, Rockwood and Mitnitski [22] proposed a comprehensive definition of the frailty syndrome that is based on an ‘accumulation of deficits’. For this definition, a frailty index is determined based on the total number of impairments or deficits present in the individual. The frailty index is based on the accumulation of up to 70 deficits that are coded as binary variables. This frailty index predicts health outcomes, such as mortality, progression of disability, and institutionalization in different populations [23]. Since the model contains 70 assessment items, its utility in clinical practice may be limited; however, it may be useful to ascertain the effectiveness of any intervention. Yet, even this frailty index lacks the ability to discriminate across the frailty spectrum (i.e. mild, moderate, or severe). Finally, the choice of components to be included in the frailty definition continues to be a contentious issue with important implications. For example, some authors have included disability and functional decline as components of frailty [24, 25], while others regard disability and functional decline as outcomes [10, 26].

With the increasing number of older adults, research interests in gerontology are growing. An additional challenge with defining frailty is distinguishing it from related concepts from other fields of study (e.g. muscle quality vs. muscle strength vs. muscle power vs. muscle mass), particularly as they relate to physical function in older adults. For example, the European consensus definition of sarcopenia [27], which now includes criteria for gait speed and muscle strength, is close to and/or overlaps with the Fried frailty phenotype. The lack of ability to distinguish between sarcopenia and frailty could have important research and treatment implications.

**Conclusion**

Frailty is widely recognized as a specific, clinical geriatric syndrome, yet there are no universally accepted definitions or clinical screening tools for this condition. The development of a consensus operational definition of frailty is essential to advance the understanding of the causes and improve the treatment of this syndrome. Such a definition should be helpful in characterizing subsets of vulnerable older people (i.e. those with chronic disease conditions), who are not evaluated for the disability risk in the clinical health care process. The following factors will contribute to advancing research and treatment of this condition: (1) a consensus on an international definition of frailty including physical and cognitive criteria; (2) the development of simple screening tools for frailty; (3) longitudinal studies of factors that predict frailty and its consequences in diverse
populations; (4) interventional studies to delay frailty and its adverse health outcomes, and (5) translation into clinical practice of the scientific findings regarding the predictors and treatments for this condition.

Acknowledgments

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References

Clinical Phenotype of Frailty

Abstract
Aging is characterized by the catabolism of muscles leading to sarcopenia and frailty. These are two geriatric syndromes with partly overlapping phenotypes. Primary sarcopenia, i.e. loss of muscle mass and function related to aging alone, usually precedes frailty. Thus, robustness passes from sarcopenia over frailty to disability leading eventually to a mortal outcome. Frailty (defined according to the phenotype model) encompasses states as exhaustion, weakness, and slowness, whereas sarcopenia, combining mass and function, is more strictly focused on muscles. Frailty is age related, whereas sarcopenia is also related to disease, starvation, and disuse. In general, the criteria for the two conditions overlap, but frailty requires weight loss, whereas sarcopenia requires muscle loss. Both gait speed and hand grip strength are suggested to be used as diagnostic measures for the two conditions since muscle function is crucial for any of the two syndromes. It is suggested that frailty screening should be part of the geriatric comprehensive assessment starting with measuring walking capacity and complemented by taking a history of fatigue and low activity. For younger adults (i.e. <70 years), sarcopenia screening could first register gait speed or hand grip strength and then body composition measurements. Simple questionnaires are feasible clinical alternatives. Treatment of frailty and sarcopenia overlaps, i.e. provide adequate protein and vitamin D supplementation, and encourage resistance exercise.

Overlaps between Frailty and Sarcopenia Definitions
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Sarcopenia, Frailty, and Aging Well

Advanced aging is characterized by the catabolism and degeneration of organs and organ functions. Reserve capacities in major organ systems are absorbed and finally depleted. Impaired activities of daily living ensue, followed by disability, i.e. severe limitations in major life activities, and eventually death.

Aging well is usually characterized by the ability to live independently, move freely in- and outdoors without the support of others and to have good memory and intellectual capacity [1]. When these conditions prevail, social interaction with family and friends is facilitated, which may enhance quality of life. From this description, it is easy to recognize muscles and brain functions as crucial for quality of life at advanced age. Brain dysfunction with aging leads to dementia, whereas muscle dysfunction with aging leads to sarcopenia and frailty.

Sarcopenia or Frailty – Which Comes First?

Sarcopenia and frailty are two fairly recently defined geriatric syndromes [2, 3], meaning that they are commonly occurring, have a strong clinical impact, have a multitude of underlying etiologic mechanisms, and they have fairly well-described phenotypes. Interestingly, the two phenotypes show considerable overlapping, especially if physical frailty is meant by frailty, as it has been defined by most authors over the last 15 years.

Defining frailty may follow the ‘index’ model or the ‘phenotype’ model [4]. The original index model is based on an accumulation of health deficits that mounts to a score, i.e. the ratio (0–1) of deficits present to the number of deficits counted [5, 6]. The somewhat more accepted phenotype model requires that some (i.e. three) criteria of the following five criteria are met: weight loss, exhaustion, low activity, slowness, and weakness [7].

Primary sarcopenia, i.e. loss of muscle mass and function related to aging alone [8], precedes frailty, whereas frailty is a risk factor for disability. Thus, the aging trajectory from a state of robustness and good health passes from sarcopenia over frailty to disability and death. Frailty may be viewed as a more complex condition mainly related to advanced age. The features of frailty defined by the frailty phenotype model [7] encompass terms as exhaustion, weakness, and slowness, which are conditions that are not strictly and exclusively related to muscle function. On the other hand, the concept of sarcopenia is rather focused on the muscle itself and, according to the more recently launched definitions [8–10], not only related to aging. The features of sarcopenia are the combined
Overlaps between Frailty and Sarcopenia Definitions

Table 1. Diagnostic criteria for frailty and sarcopenia

<table>
<thead>
<tr>
<th>Frailty</th>
<th>Sarcopenia</th>
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<tbody>
<tr>
<td>Walking capacity</td>
<td>Gait speed</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Muscle loss</td>
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<tr>
<td>Exhaustion, fatigue</td>
<td>Grip strength</td>
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finding of the more muscle-specific conditions of reduced muscle mass and impaired strength or function [11]. Thus, sarcopenia may also be related to disease, starvation, and disuse, i.e. secondary sarcopenia [8].

Definition of Sarcopenia versus Frailty

The distinction between frailty and sarcopenia is also reflected by the different use of the ‘loss of mass’ criterion. Frailty requires weight loss, which could be either muscle or fat loss, as one of its five criteria according to the frailty phenotype [7]. On the other hand, sarcopenia requires muscle loss as one criterion. The other criterion of sarcopenia is directly related to muscle strength or power as it is suggested to be measured by gait speed or hand grip strength. Slowness and weakness of frailty are also measured by walking speed and hand grip strength, whereas exhaustion and low activity are related to self-reported fatigue and walking capacity, respectively. Thus, there are great overlaps between the definitions and diagnostic criteria of the two conditions (table 1).

Obviously, muscles are crucial for any of the two syndromes, strongly implicating the important impact of good muscle function for independent aging as well as well functioning despite suffering from a disease.

Is There a Clinical Implication of a Distinction between Frailty and Sarcopenia?

A question that may arise in clinical settings is whether the screening and diagnostic efforts should focus on identifying frailty or sarcopenia in order to identify individual cases that need to be further assessed and offered treatment.

A model that could be suggested is to partly separate the efforts for geriatrics and elderly care on one hand and health care for adults on the other. For geriatric and elderly care, there is already a quite strong acceptance to use the model of the geriatric comprehensive assessment, which usually takes the mental (Geriatric Depression Scale), cognitive (Mini Mental State Examination), and
nutritional status (short form of the Mini Nutritional Assessment) into account. An assessment of physical function should be integrated as a natural part of the geriatric comprehensive assessment. Thus, gate speed or walking capacity should be assessed. If reduced it is fairly simple to combine with information on weight loss (from the short form of the Mini Nutritional Assessment) and anamnestic information on fatigue and low activity, which are integral parts of any frailty screening model [7, 12, 13]. Perhaps this could be information enough to start treatment for muscle anabolism, i.e. to provide adequate proteins and vitamin D, and to start resistance exercise.

For those younger than 70 years where the risk of frailty is not yet imminent, a more focused sarcopenia screening could be advised. Step one is as for frailty screening to register gait speed or hand grip strength. If reduced it could be advised to do a body composition measurement, most likely by bioimpedance analysis or dual-energy X-ray absorptiometry, to decide on the sarcopenia diagnosis. A questionnaire alternative has been proposed by Malmstrom and Morley [14]; i.e. the SARC-F questionnaire for a rapid diagnosis of sarcopenia. The SARC-F screening tool provides responses (from 0 to 2 points) to 5 questions related to strength, assistance in walking, rising from a chair, climbing stairs, and fall frequency. This simple approach is validated [15].

Treatment for the sarcopenic somewhat younger individual would still be the same as for the frail older individual; i.e. adequate protein and vitamin D supplementation, and resistance exercise.

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**References**

Recovery after Hip Fracture: Interventions and Their Timing to Address Deficits and Desired Outcomes – Evidence from the Baltimore Hip Studies

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Abstract
Hip fracture is a significant public health problem affecting an estimated 1.6 million persons annually. The consequences of hip fracture are also significant, with more than half of those who sustain a fracture either dying or not returning to functional abilities present before fracture required to function independently. The Baltimore Hip Studies (BHS) is a program of research that for more than 30 years has been doing investigations to identify, develop, and evaluate strategies to optimize recovery from hip fracture. This paper provides an overview of known outcomes and recovery patterns following a hip fracture, which are derived primarily from the BHS. Target areas and timing for interventions based on this recovery sequence are suggested. The paper concludes with a discussion of some of the areas that the next generation of studies needs to concentrate on in order to advance knowledge about the care of hip fracture patients to maximize their recovery.

Introduction
Hip fractures are a health problem of major significance, affecting over 1.6 million adults annually worldwide [1]. The worldwide annual incidence of hip fractures is projected to increase to 3.9 million by 2050 [2–4]. Outcomes following hip fracture include increased risk of mortality, subsequent hip and nonvertebral fractures, loss of independent function, and other adverse health and economic
consequences for patients, families and the health care system [5–11]. The care given to hip fracture patients after discharge is often provided by a spouse, adult child, another family member, or a friend. These informal caregivers face significant burden in the early phases of recovery when the patient is first discharged from the hospital [12–14], which is important since the specific needs of these caregivers have been shown to affect the recovery of the patient [15].

**Framework for Research on Hip Fracture Consequences**

A framework for examining consequences of hip fracture considers the progression of clinical research which evolves from clinical observation, to description of those who have the condition, understanding of the etiology or causes of the condition, and eventually to understanding underlying mechanisms; the ultimate aim is to use this information to design, implement, and test treatments to ameliorate or reduce the burden of the condition. With hip fracture, we can use this framework and categorize consequences or outcomes into three groups: survival, recovery of functionality, and other consequences. Survival includes survival versus death, time until death, and causes of death. Functional areas of recovery include physical, instrumental, affective, social, and cognitive function, as well as strength, physical capacity, and pain. Other consequences that have been examined include refracture, changes in body composition, including bone mineral density (BMD) and muscle and fat mass, costs, rehospitalizations, health care, and community service use, caregiver burden, complications, and re-operations. More recently, emphasis has been placed on changing systems of care delivery to improve outcomes and reduce costs. The increase in utilization of patient-focused care models throughout the health care system has introduced a new challenge for clinical practice and research. It is now necessary to design and evaluate the efficacy and cost-effectiveness of patient-focused/need-based interventions that can be implemented in diverse health care delivery systems that are changing, and to evaluate the effectiveness of these new treatment and management strategies.

**Overview of the Baltimore Hip Studies**

The goal of the research program of the Baltimore Hip Studies (BHS) is to identify, develop, and evaluate strategies to optimize recovery from hip fracture. The BHS have enrolled and followed more than 3,500 hip fracture patients admitted to 25 hospitals in the Baltimore area over the past 30 years, and BHS leaders have participated in multiple single- and multisite studies of hip fracture treatments.
and outcomes conducted outside of the BHS hospital network. BHS have assessed many diverse outcomes after hip fracture, including mortality and functional recovery, as well as changes in BMD, muscle mass and composition, and strength, balance, falls, medical complications, caregiver burden, and costs. The study designs have progressed from observational, etiological, mechanistic, and interventional over time. This paper provides an overview of known outcomes following a hip fracture derived primarily from the BHS, with a discussion of some of the areas that the next generation of studies needs to focus on to advance the knowledge and care of hip fracture patients.

**Survival**

Currently, 75% of hip fractures occur among women [2]. While the incidence of hip fracture in women appears to be stabilizing, the incidence in men is expected to increase over the next several decades [16]. Mortality rates are almost double in men compared to women [17]. One year after fracture, the probability of survival is 86% for women and 68% for men [17]. Similarly, 2 years after fracture, the probability of survival is 77% for women and 58% for men [17]. Even though men are often younger when they sustain a fracture, one explanation for the disparity in the mortality rate is that men are often sicker at the time of the fracture than women [17]. Interestingly, both men and women are dying at a higher rate due to infectious causes compared to the general population matched for age and sex, but the excess rate of deaths from infectious causes in men is 2–3 times higher than in women when compared to the general population of older men and women [17].

**Physiological Losses after Fracture**

Body composition changes have been assessed in the BHS through 12 months after fracture. From 3 to 10 days after fracture, there are minimal changes in total hip and femoral neck BMD [10]. Greater decreases occur from 10 days to 2 months after fracture [18], with significant decreases in total hip BMD (1.3%) and femoral neck BMD (2.0%) [18], and continued decreases through 12 months after fracture with approximate BMD losses of 2.5% in total hip and 4.5% at the femoral neck [19]. When these losses are compared to BMD loss in older women with the same average age (79 years) and with total hip BMD in the same low range (average total hip in hip fx = 0.595 g/cm²; comparison group from the Study of Osteoporotic Fractures = 0.610 g/cm²), the loss of femoral neck BMD
in hip fracture patients is more than 12 times greater than expected over the year following hip fracture [19]. In contrast, lean mass experiences a minimal increase from 3 to 10 days after fracture, followed by a steady decrease of 5.4% from 10 days to 2 months after fracture and little change thereafter [18, 20]. Interestingly, fat mass decreases minimally from 3 to 10 days, and continues to decrease until 2 months after fracture [18, 20]. However, from 2 through 12 months, fat mass steadily increases by about 7%, exceeding levels before fracture (need reference here). Sarcopenia, a condition of muscle loss and muscle wasting is prevalent in about 35% of female hip fracture patients within a week of hip fracture and increases to about 50% between day 10 and 2 months, and to about 60% by 1 year after fracture [21].

Additionally, an inflammatory response occurs after fracture. IL-6 levels 3–10 days after fracture are higher than in those of the same age group with functional limitations but no fracture, decrease by 2 months, and remain low through 12 months, but still do not reach the level of similar comparison subjects matched for age and sex [22]. Further, these changes in inflammation are associated with lower levels of physical performance on tests that assess tasks that are relevant to hip fracture patients and their caregivers, such as walking, getting up from a chair, and picking something up from the ground [22, 23].

**Functional Recovery**

The functional consequences of a hip fracture can be assessed through self-report of Activities of Daily Living (ADLs). Many hip fracture patients who had ADL limitations before fracture experience new limitations that persist for 1 year or more after fracture. While there is steady recovery in ADL from 2 to 12 months, a range of 20–90% of participants who were not impaired in specific tasks prior to their fracture are still experiencing limitations in those tasks 12 months after fracture [10].

Specifically, 20% of participants who were able to put on their own pants prior to fracture are now unable to do so without assistance. For those able to perform tasks without assistance before fracture, 50% used assistance to walk across a room, 50% used assistance to rise from a chair, 55% used assistance to walk a block, 66% used assistance to get on and off of the toilet, and a striking 90% used assistance to climb stairs 1 year later. These disability levels remain through 24 months after fracture. Similarly, participants experience increased limitations with Instrumental ADLs (IADLs), including shopping and housework. We also assessed the percentage of participants after fracture with a dependency in walking 10 feet or across a small room and found that 2 months
after fracture, over 90% of participants had a dependency [10]. By 6 months after fracture, the percentage of dependent patients decreased to around 60% but remained at around 55% through 2 years after fracture [10].

Beyond physical disabilities, 50% of patients after a hip fracture experience increases in cognitive deficits in the hospital, and 25% have cognitive deficits 2 months after fracture. Depressive symptoms are similarly experienced among 50% of patients in the hospital, and 25% of patients 2 months after fracture [10]. Further, those who are persistently impaired in cognitive function and who have persistent depressive symptoms do the most poorly in functional recovery over the following 10 months [24–26]. Changes in social function are also experienced, with many patients visiting with others and participating in activities less often than before their fracture [8].

The overall time to maximal recovery under usual care conditions differs across several areas of functioning [10] (fig. 1). While depression, upper-extremity ADLs, and cognition require around 4 months for recuperation, the time is greater for balance and gait recovery at approximately 9 months, and greatest for social function, IADLs, and lower-extremity ADLs, which peak at around 12 months following fracture. From these findings, it can be deduced that the hip fracture recovery process evolves first from recovery from the hip fracture itself at the level of the bone and muscle, then recovery in functional limitations including gait and balance, cognition, and strength, and finally recovery in lower-extremity ADLs and IADLs and social activities [10].
Intervention Timing

Older adults are expected to experience a gradual loss of function over time (fig. 2a). After a hip fracture, however, older adults experience a sudden loss of function (fig. 2b). With usual care, as described above, there is variation in the rate of recovery by specific area of function and the point at which peak recovery
is reached in each. It is also apparent that with usual care, most patients never recover to the functional levels present before the fracture (fig. 2c, dot-dash). With an intervention, the goal is to help patients restore functional levels and, if possible, continue intervening to improve function to surpass functional levels they had before fracture (fig. 2c, dots). While we have an understanding of the losses that occur following a hip fracture, as well as knowledge of how recovery progresses across several physiologic and functional domains, there is, as yet, only limited evidence on what specific interventions to deliver and when to provide interventions to get maximal benefit.

**Treatment and Intervention Options**

We know that hip fractures are a multifaceted problem requiring multiple treatments and/or interventions. Again, the goal of treatment and interventions is to return patients to or beyond the function levels they had prior to their fracture. In addition to the limited evidence on when treatments should be provided, there is also limited evidence on what specific treatments should be provided.

Several treatments have been suggested for hip fracture patients based on the deficit and recovery sequence, including bone-strengthening medications; other pharmacologic agents, and nutritional and vitamin supplements to address some of the preexisting and emerging deficits in BMD and muscle mass; surgical management to repair the broken bone so that patients have less pain and can stand again; psychological treatments to help re-orient patients from cognitive losses and help them to feel better, which in turn may lead to better adherence to other interventions; gait, balance, and strength training to further increase bone and muscle mass and to help patients regain their ability to stand, walk, and carry out tasks of daily living, and physical, and occupational therapy to help patients perform tasks of daily living. A list of possible treatment areas appears in table 1.

Patient-, provider-, and intervention-specific considerations exist for designing efficacious and cost-effective interventions for hip fracture patients. Due to the multifaceted nature of hip fracture recovery, a multidisciplinary/multicomponent intervention program may be best. The content of this multifaceted program is a work in progress. To be effective, we believe it needs to include multiple components, yet we have not yet determined which specific components are best, nor at what point following the fracture they are most suitably introduced to the recovering hip fracture patient. Most of what we know and do is based on what clinicians and teams of clinicians believe will work best for individual patients; evidence for multimodal programs is limited at best.
Rehabilitation Programs

The multidisciplinary rehabilitation team has been suggested as one way to address the many deficits and needs of hip fracture patients. This team could consist of a geriatrician, specially trained general practitioner, geriatric nurse practitioner, geriatric nursing staff, occupational therapist, physical therapist, social worker, and neuropsychologist. By the team approach, intervention programs should include geriatric assessments with the team, accelerated rehabilitation for the patient, and discharge planning with the multidisciplinary team, the patient, and caregivers. There also should be an assessment of the home environment before discharge, as well as in-home and long-term rehabilitation either in the home or at an outpatient or fitness facility.

We have conducted an extensive review of the recent literature on multidisciplinary hip fracture rehabilitation interventions and found mixed results. We reviewed both early multidisciplinary interventions that include physical activity, as well as long-term interventions that emphasize physical activity. For the early interventions, some studies did show improvements in strength, gait speed, and functional performance. For the long-term interventions, some studies showed improvements in strength, faster walking speed, and functional performance. Center- or community-based programs were usually more beneficial than home-based programs as they were more intensive. Neither center- nor

---

**Table 1.** Hip fracture treatments suggested by recovery sequence

<table>
<thead>
<tr>
<th>Recovery process</th>
<th>Possible treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat pathology</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bone-strengthening medications</td>
</tr>
<tr>
<td>Chronic conditions</td>
<td>Stabilize exacerbations/control complications</td>
</tr>
<tr>
<td>Sarcopenia</td>
<td>Anabolic agents/protein/nutritional supplements</td>
</tr>
<tr>
<td>Treat impairment</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>Surgical management to repair bone</td>
</tr>
<tr>
<td></td>
<td>Pain management</td>
</tr>
<tr>
<td>Reduce functional limitations</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Gait, balance, and strength training</td>
</tr>
<tr>
<td>Cognitive</td>
<td>Medical stabilization, orientation therapy</td>
</tr>
<tr>
<td>Affective</td>
<td>Medication, psychological therapy</td>
</tr>
<tr>
<td>Minimize disability</td>
<td></td>
</tr>
<tr>
<td>ADL</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>IADL</td>
<td>Occupational therapy</td>
</tr>
<tr>
<td>Social activity</td>
<td>Social engagement therapies</td>
</tr>
</tbody>
</table>
home-based intervention programs demonstrated strong benefits for ‘real-world’ functioning, e.g. ADL, IADL, or quality of life.

The results from the reviews of rehabilitation programs were also not consistent. Some of the studies suggested that interventions with physical activity are beneficial in proximal outcomes, such as strength, gait speed, and functional performance. Studies also did not usually provide precise descriptions of the interventions, which makes it difficult to know what was done and which aspects of interventions are most beneficial.

**Conclusion**

Hip fracture results in significant mortality and, for those who do not die, significant impairment and functional deficits across multiple physiological and functional areas, all of which need to be considered when designing an effective rehabilitative program. Multidisciplinary/multicomponent interventions have the greatest potential to improve long-term outcomes. Apparent gaps in investigating interventions for hip fracture patients include attention to the optimal timing for specific interventions and the way interventions should be combined to yield the best outcomes. There is also a dearth of information on extended treatment options and long-term outcomes of extended treatment. Ultimately, given the multifaceted losses and changes that take place after a hip fracture, there is a need to identify components of multidisciplinary/multicomponent interventions that have the greatest impact on these deficits at different times during the recovery period after fracture. There also is a need to design programs using effective components that target individual patient needs and evaluate their combined effects. With the growing emphasis on care pathways for hip fracture patients, and the major changes that are taking place across the globe in the way care systems manage hip fracture patients using the best evidence available, there is an ongoing need to develop better evidence that addresses the needs of hip fracture patients, their families, and caregivers. With this information, care systems can include improved strategies for increasing the likelihood that hip fracture patients will recover more fully.

**Acknowledgments**

The authors would like to thank the National Institute on Aging for their support of research on hip fracture recovery for more than 25 years, which has allowed investigators in the BHS to address issues relevant to recovery from hip fracture. We also would like to thank the orthopedic surgery, medical, nursing, social work, and physical therapy
providers in the 25 hospitals in the BHS network who have enabled us to pursue this important work, and of course, the many patients and families of patients who have participated in this research.

Disclosure Statement

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References


Interventions for Frailty


Abstract
Longitudinal studies demonstrate that regular physical exercise extends longevity and reduces the risk of physical disability. Decline in physical activity with aging is associated with a decrease in exercise capacity that predisposes to frailty. The frailty syndrome includes a lowered activity level, poor exercise tolerance, and loss of lean body and muscle mass. Poor exercise tolerance is related to aerobic endurance. Aerobic endurance training can significantly improve peak oxygen consumption by \( \sim 10\% - 15\% \). Resistance training is the best way to increase muscle strength and mass. Although the increase in muscle mass in response to resistance training may be attenuated in frail older adults, resistance training can significantly improve muscle strength, particularly in institutionalized patients, by \( \sim 110\% \). Because both aerobic and resistance training target specific components of frailty, studies combining aerobic and resistance training provide the most promising evidence with respect to successfully treating frailty. At the molecular level, exercise reduces frailty by decreasing muscle inflammation, increasing anabolism, and increasing muscle protein synthesis. More studies are needed to determine which exercises are best suited, most effective, and safe for this population. Based on the available studies, an individualized multicomponent exercise program that includes aerobic activity, strength exercises, and flexibility is recommended to treat frailty.

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Introduction
The population aged 65 years and older is expected to more than double between 2012 and 2060 (from 43.1 to 92 million) [1]. The continuing increase in the older population has generated interest toward investigations of older adults who are ‘frail’. Frailty is a state of vulnerability that carries an increased risk for
adverse outcomes [2]; it can be viewed as a transition phase in older people between good health and poor health. Frail older adults are less capable of tolerating the stress of medical illness, hospitalization, and immobility. Common signs and symptoms are fatigue, weight loss, muscle weakness, and progressive decline in function. Frailty is more prevalent in older people and in those with multiple medical conditions.

Concomitant with age, there is a decline in voluntary physical activity which is associated with decreases in numerous measures of exercise capacity, including peak oxygen consumption (VO$_{2peak}$), muscle strength, and fatigability, ultimately leading to frailty [3]. Recently, it has been recognized that most older adults who are obese also meet criteria for frailty because of decreased muscle mass and strength that occurs with aging (sarcopenia) and a need to carry greater body mass due to obesity [4]. Because frailty increases the risk for loss of functional independence and decreases the quality of life, the identification of cost-effective interventions to prevent or ameliorate frailty is one of the most important public health challenges. Accordingly, exercise may be an effective strategy to prevent and treat frailty as it can target four of the five commonly used criteria: weakness, low physical activity, slowed motor performance, and poor exercise tolerance [5]. Frailty is not a contraindication to physical activity, rather it maybe one of the most important indications to prescribe physical exercise. Longitudinal studies have demonstrated that regular physical activity extends longevity and reduces the risk of physical disability. In fact, cardiopulmonary fitness has been found to be a significant mortality predictor in older adults, independent of overall or abdominal obesity [6]. In more than 10,000 older adults participating in the EPESE (Established Populations for Epidemiologic Studies of the Elderly) studies, an almost twofold increased likelihood of dying without disability was found among those most physically active compared to those who were sedentary [7].

**Aerobic Endurance Training**

After age 30 years, aerobic capacity, often measured as VO$_{2peak}$, declines with age and contributes to a decrease in the older adult’s ability to perform activities of daily living. This is largely due to three major causes: (1) a decline in the ability of the cardiopulmonary system to deliver O$_2$; (2) a decline in the ability of the working muscles to extract O$_2$, and (3) a decline in metabolic muscle mass and a parallel increase in metabolically inactive fat mass [3]. Indeed, probably one of the most notable effects of endurance training is on VO$_{2peak}$, which is an important determinant of frailty in older adults [4]. The improvement in VO$_{2peak}$ with
endurance exercise training would be thought to reduce frailty in older adults and thus counter the decline in VO_{2peak} with aging and physical inactivity. Whereas VO_{2peak} declines \sim 1\% / \text{year} in nontraining individuals [8], this decline is \sim 0.5\% / \text{years} in master athletes who participate in aerobic activities [3]. Another important adaptation to endurance exercise training is an increase in muscle oxidative capacity, which results in fatigue resistance or increased muscle endurance. In an interventional trial of 64 frail older men and women, a 9-month program of strength training and walking exercise at 78\% of peak heart rate increased endurance by improving VO_{2peak} by \sim 14\% [9]. A similar exercise program for 12 months in 107 frail obese older men and women also increased VO_{2peak} by \sim 10\% [10]. On the other hand, in healthy elderly (77–87 years old), 9 months of endurance training at 83\% of peak heart rate increased VO_{2peak} by 15\%, as compared to increased VO_{2peak} by 24–30\% in healthy elderly 60–71 years old, indicating that the adaptations in aerobic power may be attenuated in advancing age [11]. Data from meta-analyses [12] also showed that endurance training may help to conserve fat-free mass (FFM) during weight loss, although it is probably less effective than resistance exercise. We recently reported that compared to weight loss induced by diet, weight loss induced by aerobic exercise preserved lower-extremity muscle mass (measured by magnetic resonance imaging) and physical work capacity, although the amount of exercise was large [13].

**Progressive Resistance Training**

It is well known that muscle strength and mass decreases with advancing age. A 30\% reduction in strength between 50 and 70 years of age is generally found, with muscle strength losses being most dramatic after age 70 [14]. Most of the decline in strength can be explained by selective atrophy of type II muscle fibers and the loss of neuronal activation. Based on body composition techniques such as dual-energy X-ray absorptiometry and computed tomography, the relative annual decline in muscle mass was estimated to be between –0.64 and –1.29\% per year for older men and –0.53 and –0.84\% per year for older women [15]. Although a decline in muscle quality is also involved, several studies have found that the decline in strength in the older adult is primarily due to loss of muscle quantity with age. Several studies have shown that resistance exercise training increases muscle mass and thus muscle strength in both younger and older adults. However, the response to resistance training appears to be attenuated in older adults with mobility limitations or other comorbidities. In healthy older adults, 4 months of progressive resistance training increased muscle mass by 16–23\%, whereas it increased muscle mass by 2.0–9\% in frail older adults [10,
Other studies showed that the gain in FFM in older women and men was only $\sim 58\%$ of that for younger men and women in response to resistance training [19]. Nonetheless, resistance training has still been found to significantly increase strength in older men and women. Several studies have demonstrated that these changes can occur even in the late stages in life [20, 21]. Indeed, based on two recent systematic reviews of randomized controlled trials (RCT) involving resistance training in older adults, it was concluded that resistance training results in significant improvement in muscle strength in older adults [22, 23]. These reviews included studies in both healthy and older adults. Of particular interest is that in frail institutionalized patients, Fiatarone et al. [16] demonstrated that 10 weeks of resistance exercise training increased muscle strength by $\sim 113\%$ as compared to $\sim 3\%$ in nonexercising subjects. Moreover, our group has shown that in frail older men and women, resistance training added to diet reduced FFM loss (from 3.5 to 1.8 kg) during voluntary weight loss and increased both upper- and lower-extremity muscle strength (by 17–43%) despite FFM loss [24]. With respect to aspects of functional limitations, resistance training has been shown to improve gait speed in healthy and frail elders (weighted mean differences = 0.07 m/s based on 14 trials; $n = 798$) [22]. Specifically, in frail older adults living in a nursing home and community, 10 weeks of resistance training have been shown to significantly improve gait speed [16].

**Combined Aerobic and Resistance Training**

The physiological adaptations to aerobic exercise and to resistance exercise are distinctly different and both types of exercise also target specific components of frailty. Therefore, the few exercise interventions conducted in frail older populations have mostly used combined aerobic and resistance exercise. A 9-month RCT intervention of aerobic and resistance exercise concomitantly improved scores in VO$_{2\text{peak}}$ (95% confidence interval 0.9–3.6 ml/kg/min) and a modified physical performance test (95% confidence interval 1.0–5.2 points) [25]. In addition, a recent 12-month RCT of aerobic and resistance exercise also improved scores in VO$_{2\text{peak}}$ and in a modified physical performance test in frail obese older adults, which were additive to the effects of diet-induced weight loss [10]. Finally, the LIFE-P (Lifestyle Intervention and Independence for Elders Pilot) study also reported that a 12-month program of walking, resistance exercise, and flexibility training resulted in a clinically meaningful improvement in physical performance assessed by using the Short Physical Performance Battery [26]. This study also presented promising evidence on the effectiveness of exercise in the prevention of the disability in walking as assessed by the capacity to complete a 400-meter walk.
Effect on Frailty as an Outcome Measure

Most exercise intervention trials studied the effects on features of frailty and the adverse outcomes of frailty. There have been relatively few studies designed to determine whether physical exercise can reverse frailty (frail reverse to nonfrail) or if older adults can convert from a greater state of frailty to a lesser state of frailty with exercise. The FIT (Frailty Intervention Trial) study examined whether a multifactorial intervention that included balance, strength, and endurance exercise could reduce frailty and improve mobility [27]. After 12 months of the intervention, there was a lower prevalence of frailty in the intervention group compared with the control group (between-group difference 14.7%), which was associated with a significant improvement in the Short Physical Performance Battery (between-group difference 1.44 points), suggesting that it is possible to successfully ‘treat’ frailty.

Molecular and Cellular Mechanisms Underlying Exercise Training

Aging and physical inactivity are associated with increased levels of chronic inflammation. Inflammatory cytokines have direct catabolic effects on skeletal muscle: Tumor necrosis factor (TNF)-α suppresses muscle protein synthesis (MPS) [28], while interleukin (IL)-6 inhibits the anabolic effects of insulin-like growth factor (IGF)-1 [29]. These cytokines also induce insulin resistance, which contributes to sarcopenia and frailty by reducing MPS. High concentrations of TNF-α or IL-6 are associated with lower muscle mass or strength and mobility disability [30] and high IL-6 and low IGF-1 levels contribute synergistically to impaired mobility [31]. Accordingly, an important mechanism by which exercise training reduces frailty is by suppressing muscle inflammation and promoting anabolism which leads to an increase in MPS (fig. 1). We previously reported that in frail obese older adults 12 weeks of exercise (aerobic and resistance) but not 12 weeks of weight loss (~7% reduction) decreased IL-6 and TNF-α and increased mechanogrowth factor mRNA of skeletal muscles, which was associated with positive effects on functional status [32]. Moreover, in these frail obese older adults, a multicomponent exercise program increased the mixed muscle protein fractional synthesis rate in the basal, postabsorptive state without affecting the magnitude of the muscle protein anabolic response to feeding [33]. These changes in muscle protein anabolism were accompanied by increases in FFM, appendicular lean body mass, strength, and VO_{2peak}, all of which are important determinants of frailty. There appears to be sexual dimorphism in muscle protein anabolism in that (1) older women have a greater MPS rate in the basal state.
but less anabolic response to mixed meal than older men [34] and (2) older women have less MPS rate increase in response to exercise training in the basal state than older men [35]. These findings may explain not only the lower muscle mass in older women but also perhaps the need for greater exercise stimuli to achieve the same anabolic response seen in older men [36].

**Recommendations and Future Directions**

In a systemic review of the effectiveness of exercise interventions for the management of frailty, it was found that even though the participants were frail, the exercise adherence was high with no adverse events in most reported studies, supporting that exercise was safe and feasible in this older population [37]. Although exercise uniformly had a positive impact on functional measurements, exercise seemed to be more beneficial in frail people living in long-term care.
facilities compared to the community (probably due to floor and ceiling effects of some outcome measurements) and in the earlier stages of frailty compared to the later stages of frailty (probably due to less ability to exercise with greater degree of frailty). With respect to the specific types of exercises, a multicomponent training was found to have a more positive effect on the functional ability and adverse health consequences of the frail people. Interventions lasting longer than 5 months seemed to result in greater benefits on the adverse health consequences of the frail people. The duration for each session of exercise that was most beneficial was 30–45 min, which is less than what is usually recommended for healthier older adults. Clearly, more RCT are required that include robust sample sizes and participants with different degrees of frailty, and examine age and potential sex dimorphism of the positive effects of exercise in frail older adults. More studies are also needed to determine which exercises are best suited, most effective, and safe (type, setting, duration, frequency, and intensity) for this population. Whether these exercise interventions would require supervision by rehabilitation personnel or could be safely and effectively conducted in the community or even at home needs further investigation. Based on currently available evidence, a multicomponent exercise program that includes aerobic activity, strength exercises, and flexibility is recommended in frail older adults (table 1).

**Table 1. Exercise recommendations for frail older adults**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic exercise</strong></td>
<td>Moderate-to-vigorous activity enough to raise the pulse rate to 70–80% of the maximum heart rate. Activity performed for a minimum of 20–30 min at least 3 days per week.</td>
</tr>
<tr>
<td><strong>Resistance exercise</strong></td>
<td>The progressive resistance program should involve all major muscle groups of the upper and lower extremities and trunk. One set of 8–10 different exercises, with 10–15 repetitions per set, performed 2–3 nonconsecutive days per week. Moderate-high intensity training is recommended, in which moderate intensity is 5 or 6 on a scale from 0 to 10.</td>
</tr>
<tr>
<td><strong>Flexibility and balance exercise</strong></td>
<td>Stretching to the point of tightness and holding the position for a few seconds. Flexibility activities are performed on all days that aerobic or muscle strengthening activity is performed. Balance training exercise 2–3 times per week.</td>
</tr>
</tbody>
</table>

The exercise program should be individualized according to an older individual’s medical conditions and disability. The program should start at a low-to-moderate intensity, duration, and frequency to promote compliance and minimize musculoskeletal injuries.
It is worth mentioning that changes in the lifestyle habits of frail, older persons may present special challenges. Multiple medical problems, depression, sensory impairments, and cognitive dysfunction may make it difficult to change lifestyle. The increase in chronic disabilities with aging reduces physical activity and exercise capacity. To facilitate adherence to lifestyle changes that include regular physical exercise, program participation by the spouse or caregivers may need to be encouraged. In addition, special consideration should be given to hurdles faced during learning by frail older adults, such as impaired vision and hearing, orthopedic conditions, multiple comorbidities, and limited financial resources.

Acknowledgments

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Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

References


Interventions for Frailty


Frailty in Clinical Practice

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Abstract

Frailty is a geriatric syndrome characterized by reduced homeostatic reserves, exposing the organism to extreme vulnerability to endogenous and exogenous stressors. Since disability is considered as an almost irreversible condition at advanced age, frailty has been indicated as a promising target for specific interventions in order to prevent disability. From a theoretical viewpoint, the concept of frailty has been well established, but its operationalization is still subject to controversy. This impediment leads to the postponement of the integration of frailty in the clinical setting. In the present article, we discuss the main issues regarding the frailty syndrome in the clinical setting, describe possible solutions (especially on the basis of our experience derived from the frailty clinic we have set up in Toulouse, France), and present the most relevant research perspectives in the field.

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Introduction

The urgent need of solutions against the threats that disabling conditions at old age pose to the sustainability of health care systems has concurred with increasing interest in the frailty syndrome. Frailty is a geriatric syndrome characterized by reduced homeostatic reserves, exposing the organism to extreme vulnerability to endogenous and exogenous stressors [1]. It has been associated with major negative health-related events (including disability, institutionalization, and mortality) [2]. Moreover, since disability is considered as an almost irreversible condition at advanced age [3], it has been indicated as a promising target for specific interventions to prevent disability [4, 5].
From a theoretical viewpoint, the concept of frailty has been well established, but its operationalization is still subject to controversy. In fact, several assessment instruments have been developed over the last years to evaluate this risk condition. The problem is that each instrument has its specific peculiarities and perceives different aspects of the frailty condition [6]. This often leads to a heterogeneous selection of the target population according to the adopted instrument. Such ambiguity may be perceived as a major issue before frailty can be completely integrated in the clinical setting. In fact, the lack of a universally accepted operational definition potentially affects the capacity to standardize possible health care services devoted to the assessment of frailty, identification of its underlying causes, and development of personalized plans of intervention.

In the present article, we discuss the main issues regarding the integration of the frailty syndrome in the clinical setting, describe possible solutions (especially on the basis of our experience derived from the frailty clinic we have set up in Toulouse, France [7]), and present the most relevant research perspectives in the field. Of note, the paper will deal with frailty in terms of a condition preceding disability only and as a means for preventing disability. Other operational interpretations of frailty nonexclusive of disabling conditions will not be part of this article.

**Methodological Issues**

Recently, an international panel of experts published a consensus paper soliciting action against frailty [4]. The existing limitations and controversies in the field were acknowledged. At the same time, it was explained that the epidemiological scenario of our societies (characterized by the relative and absolute increase in older persons) as well as the high health care expenditures due to disabling conditions [8] somehow forced the development of rapid and shared initiatives in the clinical field. The consensus paper has been widely diffused and raised discussion in the scientific community. It has been argued that the clinical integration of frailty might still be premature given the limited knowledge (after all, we have started talking about frailty less than 20 years ago) and lack of standardization in the assessment and treatment procedures [9]. Such criticisms are surely legitimate. However, as discussed in a preceding article [10], it is unlikely that deferring a systematic adoption of frailty in clinics will help to clarify which is the most robust or feasible assessment instrument to use. There is the serious risk that we might spend another 20 years discussing the best assessment and developing new instruments without taking action against a pressing need. The reason for urgent action in the field is based on the fact that frailty is now a
well-established risk condition [2] and established as highly prevalent in community-dwelling older persons [11]. Waiting may indeed mean that we accept that clinical needs of a large part of the elderly in our society are not met. In contrast, we believe it is important to take action while preserving the most conservative approach if possible in order to allow future accommodations in the methodology of the clinical ‘take in charge’ of the frail individual.

Since October 2011, the Gérontopôle of the Centre Hospitalier Universitaire de Toulouse has established an innovative day hospital unit exclusively devoted to the treatment of frailty [7, 12]. In collaboration with the general practitioners of the area, nondisabled frail elders were assessed regarding their overall health status using a comprehensive geriatric assessment; causes of their frailty condition were determined using a multidisciplinary approach, and a person-tailored plan of preventive interventions was then proposed. The model replicates a traditionally and well-established approach which has shown positive results in different settings (e.g. home care) [13–16]. To date, more than 1,200 persons have been evaluated in our clinic. Since all the subjects have been assessed in a standardized and objective way, a clinical database has been developed in parallel providing us the possibility to analyze frailty in the ‘real world’. This has led to modifications and improvements of the instruments originally adopted based on ‘pure research’ findings.

The ‘Overdiagnosis’ Issue

It might be argued that the development of a health care service around a clinical condition which is not yet optimally developed could simply mean ‘overdiagnosis’ [17]. In other words, there might be the risk of medicalizing an otherwise healthy individual. After all, the persons with frailty are not yet disabled and still able to conduct independent lives in the community. From available evidence and our personal experience, this may not be the case for several reasons.

First, the frail older person perceives the modification of his/her health status due to the syndrome of interest. They realize that their organism is no longer the one it used to be and report a poorer quality of life [18, 19]. Nevertheless, such perceptions are apparently not yet considered sufficient for taking clinical action. This is probably due to the lack of awareness (by both the general population and health care professionals) of the frailty syndrome and the absence of specific settings where the necessary ad hoc evaluation is conducted.

Second, frailty represents still a reversible condition we can target with interventions before the onset of physical disability (i.e. the ‘gold standard’ outcome for geriatric medicine). In a very simplistic way, frailty and disability may represent
in geriatrics what hypertension and myocardial infarction are in cardiology. Hypertension at old age is often undiagnosed [20, 21], although some vague symptoms might be present. The treatment of hypertension is not aimed at simply reducing the objective blood pressure values, but at improving the risk profile for their possible devastating consequences (e.g. myocardial infarction). A proof of this is that the risk thresholds defining hypertension have been repeatedly modified (with a tendency to lower levels) over the years. This obviously implies that (1) in itinere corrections of operational definitions adopted in clinics are possible, and (2) treatment of a risk condition may prevent the ‘hard outcome’.

Third, it is noteworthy that almost half of the frail older persons assessed at our frailty clinic were found to have at least one undiagnosed condition [unpubl. data, available upon request]. This means that the presence of the general practitioner (who refers the individual to our clinic) may not be sufficient to comprehensively assess the older person’s clinical complexity. A coordinated and multidisciplinary approach is indeed required to identify the inner causes of the frailty condition. The detection of a previously unknown clinical condition will surely conduct to the need of a specific treatment. On the other hand, the early intervention may signify (1) preventing more serious consequences in the future, and (2) potentially solve (part of) the individual’s complaints.

Last but not least, it should never be forgotten what posing a diagnosis means to the patient. The individual may find out for the first time to be ‘officially’ sick or to have one more condition to treat. Such information does not only deal with the physical aspect of the disease, but touches the personal feelings of the person. In other words, every action anticipating a diagnosis presents serious ethical repercussions. The screening of a clinical condition makes sense and is justified if, in case of positive results, we are able to provide effective solutions. In the case of frailty, evidence exists about the possibility of treating signs of disability. Moreover, the model of the comprehensive geriatric assessment and integrated care has been well established in the literature for a long time.

The Cost-Effectiveness Issue

Of course, doing more diagnoses also involves more economic costs. Our frailty clinic has costs. Both have to be justified, especially during an economic crisis. The presentation of our activities devoted to the prevention of disability often leads to the question: ‘Who pays for this?’ Our service is funded as a geriatric day hospital unit by the health care system. In our case, public health authorities have decided to invest in such a project in order to identify potential risk factors leading to the ultimate problem: disability. Nevertheless, cost-effectiveness anal-
yses supporting the long-term implementation of the model are needed and currently under development.

The time variable has to be taken into account when performing cost-effectiveness analyses of preventive interventions. In fact, in order to conduct a fair cost-effectiveness analysis, the time needed to correctly appreciate the capacity of the intervention to prevent the unwanted outcome has to be considered. In the case of disability, the evaluation cannot be limited to the few months of observation, considering that the disabling process may take some time before reaching the most catastrophic scenarios. Three to 5 years are probably necessary to understand whether the intervention and its relatively high initial expenditures are cost-effective. The new diagnoses we have made are associated with an immediate rise in health care expenses in terms of previously unforeseen extra examinations, additional evaluations, and/or specific treatments. On the other hand, the early intervention may reverse the frailty status by acting at a very preliminary phase of the clinical conditions responsible for it. This potentially means restoring the individual’s robustness (or at least reducing the severity of his/her frailty status) and extending independent life. We do not exclude that hospitalizations, requests of social support, and/or implementation of specific health care services might increase. Nevertheless, we believe that such an immediate rise in costs may indeed be balanced against relevant long-term savings [5].

Conclusions

Frailty represents a unique opportunity to study the aging process and its consequences [12]. At the same time, it is the ideal outcome for the structuring of clinical actions devoted to the prevention of disabling conditions in older persons. Surely, a huge amount of work is in front of us for clarifying existing ambiguities and reinforcing evidence on specific aspects. Nevertheless, the critical decision of diverting some health care resources to specific actions against disability and the burden of age-related disabling conditions has to be urgently made. Too many community-dwelling older persons are with unmet clinical needs, and therefore procrastination or avoidance of the problem can no longer be justified.

Disclosure Statement

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References

Interventions for Frailty


Abstract
Geriatric medicine started to be developed approximately 40 years ago when the increasing number of older adults with disability and dementia admitted to hospital emergency units threatened the sustainability of the healthcare organizations. Today, almost 90% of the geriatric medicine forces are devoted to the care of age-related disabilities. The epidemiological scenario and the high healthcare costs required for the management of dependent individuals require the adoption of strategies aimed at preventing the loss of physical function and anticipate the take in charge of older persons at risk of negative outcomes. Major medical specialties (e.g., oncology, cardiology, neurology…) have already moved to an early stage of the diseases to be more effective. Geriatric medicine must do the same moving to frailty an early stage of disability were intervention are more likely to be effective.

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Integrating Frailty into Clinical Practice to Prevent the Risk of Dependency in the Elderly

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Abstract
Geriatric medicine started to be developed approximately 40 years ago when the increasing number of older adults with disability and dementia admitted to hospital emergency units threatened the sustainability of the healthcare organizations. Today, almost 90% of the geriatric medicine forces are devoted to the care of age-related disabilities. The epidemiological scenario and the high healthcare costs required for the management of dependent individuals require the adoption of strategies aimed at preventing the loss of physical function and anticipate the take in charge of older persons at risk of negative outcomes. Major medical specialties (e.g., oncology, cardiology, neurology…) have already moved to an early stage of the diseases to be more effective. Geriatric medicine must do the same moving to frailty an early stage of disability were intervention are more likely to be effective.

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With increasing life expectancy, the risk of developing severe dependency increases dramatically in our society. It is important to realize that geriatric medicine was introduced almost 40 years ago because older adults with severe disability and dementia were discharged to hospital emergency rooms. Nobody was able or wanted to take care of them. For these reasons, it was decided to build
long-term care facilities, subacute care units, acute care units, and day hospitals. Today, the number of geriatric departments is on the increase, with increasing numbers of beds and hospitals. However, in view of the prolonged life expectancy of our population and the dramatic increase in the oldest old, geriatric medicine needs revision in order to improve the management of the elderly and control the accelerating increase in the number of geriatric facilities required. However, the required funding could probably become a major barrier. Interventions should target conditions well before disability presents, since the only approach to keep adequate levels of functioning in the elderly is to prevent severe disabilities which cannot be restored.

In fact, there are three categories of older persons, and each of these categories requires different interventions.

The older adults with generally good health conditions represent approximately 50–60% of those aged more than 65 years. They present diseases such as high blood pressure, diabetes, high cholesterol levels, or a history of malignancy, which are all well controlled diseases.

The severely dependent older adults represent between 7 and 10% of older adults; they need assistance for basic activities of daily living such as walking, eating, and washing, and 95% of geriatric medicine tasks are dedicated to these patients. Of course, it is really important to take care of these patients, but at this stage their health status is often considered to be irreversible.

The frail subjects represent between 10 and 15% of older adults and those in a stage preceding frailty amount to almost 20% of those aged 65 years or more. These frail and prefrail older adults represent an important target population because they are in a condition that may be reversible at this stage but are at risk of progressing to dependency if left untreated.

We now need to target our interventions towards these frail and prefrail older adults in our aging population in order to avoid the development to severe dependency [1–9]. This was not done in the past. Most of our actions focused on dependent or healthy individuals, but frail older adults were neglected.

To provide significant action in medicine, particularly in geriatric medicine, we need to launch a strong and sustained interventions.

**Targeting the Frail**

Several tools have been developed in the field of frailty. They all have their advantages and disadvantages, and are very similar. We do not need a general consensus to choose the same tool. Our knowledge progresses and, similar to many other diseases, definitions are constantly adjusted. What we now need is a tool
that is useful in clinical practice. In Toulouse, we used the Gérontopôle screening tool (table 1), which consists of two parts: the first section reminds the physician or health care professional of the risk factors for frailty, and the second section invites the health professional to classify patients as frail/at risk of further dependency according to his own experience and subjective impression. When using this tool, more than 94% of the patients referred to the geriatric Gérontopôle frailty clinics were reported to be frail or prefrail.

### The Causes of Frailty

It is important to look after the causes of frailty. In fact, many age-related diseases as well as loss of functions can be associated with frailty. In table 2, the results of patients presenting at the Gérontopôle frailty clinics are summarized. It must be underlined that the mean age of the subjects is 83 years, i.e. 3 years younger than the mean age for nursing home entry in the EU, a period that is crucial to promote useful interventions. Slow gait speed, cognitive decline, weight loss, sarcopenia, undernutrition, and vision and hearing impairments are common in this population [10–18]. It is also important to note that 40% of this population live alone. A new disease was observed in nearly half of the patients and drug prescription was changed in more than one third of the subjects.

---

**Table 1.** The Gérontopôle screening tool (from Vellas et al. [9], with permission) for the detection of frailty in the elderly

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your patient live alone?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Has your patient involuntarily lost weight in the last 3 months?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Has your patient been more fatigued in the last 3 months?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Has your patient experienced increased mobility difficulties in the last 3 months?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Has your patient complained of memory problems?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Does your patient present slow gait speed (i.e. &gt;4 s to walk 4 m)?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If you have answered yes to one or more of these questions:
- Do you think your patient is frail? ☐  ☐
  - If yes, is your patient willing to be assessed for his/her frailty status at the frailty clinic? ☐  ☐

Patients aged 65 years and older without functional disability (Activities of Daily Living score ≥5/6) and with no current acute disease.
Table 2. Baseline characteristics of the patients (n = 1,108) presenting at the geriatric frailty clinics (GFC) (from Tavassoli et al. [20], with permission)

<table>
<thead>
<tr>
<th>Characteristic (n = 1,108)</th>
<th>GFC population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty status (n = 1,082)</td>
<td></td>
</tr>
<tr>
<td>Not frail</td>
<td>69 (6.4)</td>
</tr>
<tr>
<td>Prefrail (1–2 criteria)</td>
<td>423 (39.1)</td>
</tr>
<tr>
<td>Frail (≥3 criteria)</td>
<td>590 (54.5)</td>
</tr>
<tr>
<td>Frailty criteria (n = 1,082)</td>
<td></td>
</tr>
<tr>
<td>Involuntary recent weight loss (n = 1,098)</td>
<td>358 (32.6)</td>
</tr>
<tr>
<td>Feeling of exhaustion (n = 1,083)</td>
<td>353 (32.6)</td>
</tr>
<tr>
<td>Slow gait speed (n = 1,065)</td>
<td>547 (51.4)</td>
</tr>
<tr>
<td>Decreased muscle strength (n = 1,084)</td>
<td>722 (66.6)</td>
</tr>
<tr>
<td>Sedentariness (n = 1,096)</td>
<td>665 (60.7)</td>
</tr>
<tr>
<td>MMSE score (/30) (n = 1,071)</td>
<td>24.6±4.9</td>
</tr>
<tr>
<td>CDR score (n = 1,039)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>353 (34.0)</td>
</tr>
<tr>
<td>0.5</td>
<td>531 (51.1)</td>
</tr>
<tr>
<td>1</td>
<td>111 (10.7)</td>
</tr>
<tr>
<td>≥2</td>
<td>44 (4.2)</td>
</tr>
<tr>
<td>MIS score (/8) (n = 1,038)</td>
<td>6.6±1.9</td>
</tr>
<tr>
<td>MIS-D score (/8) (n = 1,036)</td>
<td>6.0±2.3</td>
</tr>
<tr>
<td>ADL score (/6) (n = 1,102)</td>
<td>5.5±1.0</td>
</tr>
<tr>
<td>IADL score (/8) (n = 1,094)</td>
<td>5.6±2.4</td>
</tr>
<tr>
<td>SPPB score (/12) (n = 1,063)</td>
<td>7.3±2.9</td>
</tr>
<tr>
<td>Good performance (SPPB = 10–12)</td>
<td>272 (25.6)</td>
</tr>
<tr>
<td>Medium performance (SPPB = 7–9)</td>
<td>388 (36.5)</td>
</tr>
<tr>
<td>Poor performance (SPPB = 0–6)</td>
<td>403 (37.9)</td>
</tr>
<tr>
<td>Gait speed, m/s (n = 1,065)</td>
<td>0.78±0.27</td>
</tr>
<tr>
<td>Wrist strength, kg (n = 1,083)</td>
<td>20.6±8.2</td>
</tr>
<tr>
<td>MNA score (/30) (n = 1,048)</td>
<td>23.2±4.1</td>
</tr>
<tr>
<td>Good nutritional status (MNA &gt;23.5)</td>
<td>550 (52.5)</td>
</tr>
<tr>
<td>Risk of malnutrition (MNA = 17–23.5)</td>
<td>414 (39.5)</td>
</tr>
<tr>
<td>Malnourished (MNA &lt;17)</td>
<td>84 (8.0)</td>
</tr>
<tr>
<td>Vitamin D concentration, ng/ml (n = 1,065)</td>
<td>18.1±11.3</td>
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<tr>
<td>≤10 ng/ml</td>
<td>343 (32.2)</td>
</tr>
<tr>
<td>11–29 ng/ml</td>
<td>563 (52.9)</td>
</tr>
<tr>
<td>≥30 ng/ml</td>
<td>159 (14.9)</td>
</tr>
<tr>
<td>GDS score (/15) (n = 424)</td>
<td>4.8±3.1</td>
</tr>
<tr>
<td>Presence of depressive symptoms (GDS ≥5)</td>
<td>155 (36.6)</td>
</tr>
<tr>
<td>Abnormal distance vision (n = 1,019)</td>
<td>840 (82.4)</td>
</tr>
<tr>
<td>Abnormal near vision (n = 1,039)</td>
<td>232 (22.3)</td>
</tr>
<tr>
<td>Abnormal Amsler grid (n = 1,060)</td>
<td>177 (16.7)</td>
</tr>
<tr>
<td>HHIE-S score (/40) (n = 1,055)</td>
<td>9.5±9.8</td>
</tr>
<tr>
<td>Significant hearing impairment (HHIE-S &gt;21)</td>
<td>330 (31.3)</td>
</tr>
<tr>
<td>Urinary incontinence score (/6) (n = 280)</td>
<td>1.7±1.4</td>
</tr>
<tr>
<td>Urinary disorders causing discomfort in everyday life (score ≥1)</td>
<td>215 (76.8)</td>
</tr>
<tr>
<td>OHAT score (/16) (n = 271)</td>
<td>2.8±2.4</td>
</tr>
<tr>
<td>The mouth not considered healthy (OHAT &gt;4)</td>
<td>44 (16.2)</td>
</tr>
</tbody>
</table>

Means ± SD or numbers of patients (%). ADL = Activities of Daily Living: from 0 = low (patient very dependent) to 6 = high (patient independent); CDR = Clinical Dementia Rating: 0 = no dementia, 0.5 = very mild dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia; GDS = Geriatric Depression Scale; HHIE-S = Hearing Handicap Inventory for the Elderly-Screening; IADL = Instrumental Activities of Daily Living; from 0 = low (patient very dependent) to 8 = high (patient independent); MIS = Memory Impairment Screen, free recall; MIS-D = Memory Impairment Screen, delayed recall; MNA = Mini Nutritional Assessment; MMSE = Mini Mental State Examination; OHAT = Oral Health Assessment Tool; SPPB = Short Physical Performance Battery.
Sustained Interventions

To be effective, and because aging and age-related diseases are still progressing, we need to implement long-term and sustained interventions [19]. Therefore, we need the participation of the family physician and all other health care professionals. Approaches should also include physical and cognitive exercises as well as nutritional support (table 3).

One month after assessing the patient at the geriatric frailty clinics, a follow-up visit is scheduled to determine whether the frail patient has implemented the interventions. At the 3-month follow-up, the patient’s activities of daily living are assessed and evaluated. These actions are always carried out in close collaboration with the family physician.

During the workshop, the option of hormonal therapy and research issues were discussed with Prof. S. Bhasin from Harvard, Boston, MA, USA, and vitamin D supplementation with Prof. H. Bishop Ferrari from Zurich, Switzerland. Rehabilitation programs and physical exercises were presented by Prof. J. Magaziner from Baltimore, MD, and Dr. Dennis Villareal from Albuquerque, NM, USA. Papers of their presentations are also included in this book.

Disclosure Statement

Consultancy to Nestlé.
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