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Successful Aging: Advancing the Science of Physical Independence in Older Adults

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Abstract

The concept of 'Successful Aging' has long intrigued the scientific community. Despite this long-standing interest, a consensus definition has proven to be a difficult task, due to the inherent challenge involved in defining such a complex, multi-dimensional phenomenon. The lack of a clear set of defining characteristics for the construct of successful aging has made comparison of findings across studies difficult and has limited advances in aging research. The domain in which consensus on markers of successful aging is furthest developed is the domain of physical functioning. For example, walking speed appears to be an excellent surrogate marker of overall health and predicts the maintenance of physical independence, a cornerstone of successful aging. The purpose of the present article is to provide an overview and discussion of specific health conditions, behavioral factors, and biological mechanisms that mark declining mobility and physical function and promising interventions to counter these effects. With life expectancy continuing to increase in the United States and developed countries throughout the world, there is an increasing public health focus on the maintenance of physical independence among all older adults.

Keywords

age; mobility; obesity; sarcopenia; healthspan; longevity

1. Introduction

The concept of "Successful Aging" has intrigued philosophers and scientists for hundreds of years. For example, in the ancient treatise *De Senectute*, Cicero contemplates the extent to which individuals can remain active and experience vitality in later life. Despite this long standing interest, scientific attempts to define the phenomenon of successful aging have primarily occurred during the past century. This term was first introduced in the scientific literature by Robert J. Havighurst in 1961(Havighurst 1961) in which he states that the science of gerontology has the practical purpose of "adding life to the years" with the goal of increasing enjoyment and satisfaction during the latter stages of an individual's lifespan. To achieve such an objective, he argues that it is essential to have a theory of successful aging. However, this has proven to be a difficult task, due to the inherent challenge involved

in defining this complex, multi-dimensional phenomenon which comprises biological, physical, cognitive, affective, and social components.

Many of the initial definitions of successful aging were in line with the *biomedical model*, which conceptualizes health, and by extension successful aging, largely based on the absence of chronic disease conditions and reduction in risk factors for disease. Within this model, individuals are typically classified into distinct dichotomous categories of healthy or diseased, such that successful aging is represented by good health, independence, and high levels of cognitive and physical functioning. The role of lifestyle and/or psychosocial factors in contributing to good or poor health, however, is not recognized by this model. Due to the increasing recognition of the complex interplay among biological, psychological, and social factors in affecting an individual's health status and disease risk, a new model for understanding the development of disease, termed the *biopsychosocial model*, was proposed in the 1970s.(Engel 1977;Schwartz 1982) As applied to the construct of successful aging, this model views an individual's health and functional status later in life not as a dichotomous classification of healthy or diseased but rather as occurring along a spectrum across multiple dimensions.(Coyne and Downey 1991)

Consistent with the biopsychosocial approach, biological and psychosocial concepts have been successfully integrated in many recent models of successful aging.(Bowling 2007;Glass 2003;Hung, Lee, Chen, and Huang 2010;Pruchno, Wilson-Genderson, and Cartwright 2010;Pruchno, Wilson-Genderson, Rose, and Cartwright 2010) For example, Rowe and Kahn's model of successful aging, (Rowe and Kahn 1997) one of the most widely accepted and applied models,(Dillaway and Byrnes 2009) views "better than average" aging as a combination of three components: avoiding disease and disability, high cognitive and physical function, and engagement with life. Recent models continue to support the multidimensional nature of this construct and have incorporated both objective and subjective dimensions in their definitions of successful aging.(Pruchno, Wilson-Genderson, Rose, and Cartwright 2010) For example, Pruchno and colleagues (2010) have proposed a two-factor model of successful aging, which incorporates both objective criteria (i.e., functional abilities, pain, and diagnosed health conditions) and subjective criteria (i.e., perceptions of quality of life and successful aging).(Pruchno, Wilson-Genderson, and Cartwright 2010)

In order to determine the most suitable theory of successful aging, the majority of experts in aging and gerontology would need to agree on an operational definition and methods to measure the degree to which an individual fits this definition. Such a consensus definition does not currently exist, and the construct of successful aging remains an evolving concept without a clear set of metrics to define this phenomenon.(Cosco, Prina, Perales, Stephan, and Brayne 2014) In the absence of an accepted definition and commonly used metrics, a diverse array of measures are being used to assess different aspects the construct of successful aging.(Depp and Jeste 2006) This has had the unintended consequence of limiting advances in aging research since comparisons of findings across studies are not possible without clearly defined constructs and standardized measures to assess them.(Depp and Jeste 2006)

To determine the effectiveness of treatment approaches targeting agreed upon markers of successful aging, outcome measures are needed that can be directly translated to measureable improvements in both health and functional abilities. The strongest evidence of such markers can be found within the physical domain of the multidimensional construct of successful aging. Within this domain, there is a growing consensus of indicators of successful aging (i.e., mobility performance and physical function), measures to assess these markers, and metrics for evaluating performance on such measures. For example, mobility performance (i.e., walking speed) has emerged as a surrogate marker of overall health and functional ability among older adults.(Cesari 2011) Mobility performance is frequently measured based on time to complete a distance walk ranging from 4 meters to 400 meters or distance covered within a pre-specified time period, typically 6 min. Accumulating evidence indicates slow walking speed (<1 m/sec indicating a high risk and < 0.8 m/sec indicating a very high risk), as well as reductions in walking speed, strongly predict functional decline, major health outcomes, and mortality in older adults.(Abellan Van, Rolland, Andrieu, Bauer, Beauchet, Bonnefoy, Cesari, Donini, Gillette, Inzitari, Nourhashemi, Onder, Ritz, Salva, Visser, and Vellas 2009;Cesari, Kritchevsky, Penninx, Nicklas, Simonsick, Newman, Tylavsky, Brach, Satterfield, Bauer, Visser, Rubin, Harris, and Pahor 2005;den Ouden, Schuurmans, Arts, and van der Schouw 2011;Menant, Schoene, and Lord 2014;Studenski, Perera, Patel, Rosano, Faulkner, Inzitari, Brach, Chandler, Cawthon, Connor, Nevitt, Visser, Kritchevsky, Badinelli, Harris, Newman, Cauley, Ferrucci, and Guralnik 2011) In line with this clinical evidence, a close relationship between mobility performance and longevity has been documented in preclinical models.(Carter, Sonntag, Onder, and Pahor 2002;Demontis and Perrimon 2010)

Another commonly used and well validated measure of physical function in older adults is the Short Physical Performance Battery (SPPB).(Guralnik, Simonsick, Ferrucci, Glynn, Berkman, Blazer, Scherr, and Wallace 1994) The SPPB assesses multiple aspects of lower extremity function including balance, strength, and walking speed and incorporates performance on these three dimensions into an overall physical function score (range = 0 – 12 points). Scores on the SPPB and walking speed have been found to predict onset of difficulty in activities of daily living (Wennie Huang, Perera, VanSwearingen, and Studenski 2010) and disability in community-dwelling older adults.(Albert, Bear-Lehman, and Anderson 2014;Carter, Sonntag, Onder, and Pahor 2002;Demontis and Perrimon 2010;Guralnik, Ferrucci, Pieper, Leveille, Markides, Ostir, Studenski, Berkman, and Wallace 2000;Guralnik, Ferrucci, Simonsick, Salive, and Wallace 1995;Guralnik, Simonsick, Ferrucci, Glynn, Berkman, Blazer, Scherr, and Wallace 1994) Moreover, small improvements in walking speed ($\Delta > 0.05$ m/sec) and performance on the SPPB ($\Delta > 0.5$ points) have been found to translate to meaningful improvements in performance of activities of daily living (e.g., stair climbing, walking a block).(Perera, Mody, Woodman, and Studenski 2006) Such findings suggest that performance on these objective and easy to administer measures of physical function (e.g., SPPB) and mobility (e.g., 400 meter walk) constitute useful indicators of health status and risk for disease and functional decline in older adults.(Bua, Johnson, Herbst, Delong, McKenzie, Salamat, and AIKEN 2006)

With the growing population of older adults in the United States and developed countries throughout the world, there is an increasing public health focus on the maintenance of

physical independence in aging. An increased understanding of the biological and behavioral mechanisms contributing to functional decline can aid in the development of future interventions designed to improve mobility and function or attenuate declines in physical function in older adults.(Lonergan and Krevans 1991) As such, the purpose of the present article is to provide an overview of specific health conditions, behavioral factors, and biological mechanisms that are strongly related to mobility and physical function during aging. In addition, we summarize promising interventions that have been shown to enhance mobility and physical function in older adults by targeting one or more biological or behavioral factors contributing to functional decline (see **Conceptual** Figure 1). This review is divided into four main sections. In the first section, we review specific health conditions that contribute to functional decline. Next, we describe key behavioral and social factors that can affect physical function and risk for functional decline in older adults. We then discuss the biological mechanisms that show a strong link with physical function (**see** Figure 2). In the final section, we discuss promising interventions for enhancing mobility and physical function in older adults (**see** Figure 3 **and** Table 1), as well as important statistical considerations in evaluating such interventions.

2. Discussion

2.1 Contribution of Specific Health Conditions to Reductions in Physical Function

A number of health conditions which we briefly review in this section have been shown to contribute to reductions in physical function during aging and may affect successful aging. (Anton, Karabetian, Naugle, and Buford 2013;Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010a) Specifically, a growing body of evidence indicates specific conditions including cognitive decline, obesity, sarcopenia, dynapenia, chronic pain, are strongly linked to physical function. In this section, we briefly review the contribution of each of these factors to reductions in physical function during aging.

2.1.1 Cognitive Decline—A broad range of cognitive functions decline with advanced age, such as memory, attention, and executive functions. (Salthouse 2012;Woods, Cohen, and Pahor 2013;Woods, Mark, Pitts, and Mennemeier 2011) Yet, other elements of cognitive function, like vocabulary, remain stable over the lifespan.(Botwinick and Storandt 1973;Salthouse 2010) In addition to experiencing changes in cognitive function over time, many older adults may also be susceptible to transient episodes of cognitive decline (e.g., delirium). A growing body of evidence suggests that age-related and transient declines in cognitive function significantly contribute to functional decline and eventual development of physical disability.(Atkinson, Cesari, Kritchevsky, Penninx, Fried, Guralnik, and Williamson 2005;Brummel, Jackson, Pandharipande, Thompson, Shintani, Dittus, Gill, Bernard, Ely, and Girard 2014;Deshpande, Metter, Bandinelli, Guralnik, and Ferrucci 2009;Dodge, Mattek, Austin, Hayes, and Kaye 2012;Fitzpatrick, Buchanan, Nahin, Dekosky, Atkinson, Carlson, and Williamson 2007;Jedrziewski, Lee, and Trojanowski 2007;Raji, Kuo, Snih, Markides, Peek, and Ottenbacher 2005;Woods, Cohen, and Pahor 2013;Woods, Mark, Pitts, and Mennemeier 2011) Given the association between cognitive decline and increased rates of injury, hospitalization, dependence on assisted living, and mortality,(Boockvar, Signor, Ramaswamy, and Hung 2013;Brummel, Jackson,

Pandharipande, Thompson, Shintani, Dittus, Gill, Bernard, Ely, and Girard 2014;Woods, Mark, Pitts, and Mennemeier 2011) an improved understanding of the link between cognitive and physical function is important for the development of multidisciplinary interventions that are effective at combating age-related physical decline.

2.1.2 Obesity—The prevalence of obesity has increased dramatically during the past few decades, particularly among older adults.(Main, Rao, and O'Keefe 2010;Ogden, Carroll, and Flegal 2014) Obese, older adults currently represent 33 percent of American older adults (age > 60 years).(Flegal, Carroll, Kit, and Ogden 2012) Obesity is a multifactorial, complex chronic disease, including age-related or adult-onset obesity, and its burden will likely increase as the population of older American adults increases over the coming decades. (Manson and Bassuk 2003;Vastag 2004) Although the initial onset and progression of functional decline is typically associated with the progressive loss of skeletal muscle mass (i.e., sarcopenia),(Hyatt, Whitelaw, Bhat, Scott, and Maxwell 1990;Janssen, Heymsfield, and Ross 2002) age-related changes in muscle composition appear to be even more pronounced in obese individuals. (Barbat-Artigas, Pion, Leduc-Gaudet, Rolland, and Aubertin-Leheudre 2014;Koster, Ding, Stenholm, Caserotti, Houston, Nicklas, You, Lee, Visser, Newman, Schwartz, Cauley, Tylavsky, Goodpaster, Kritchevsky, and Harris 2011) The combination of muscle loss and fat gain may act synergistically to increase risk of physical disability in obese, older adults.(Baumgartner 2000b;Blaum, Xue, Michelon, Semba, and Fried 2005a;Cesari, Kritchevsky, Baumgartner, Atkinson, Penninx, Lenchik, Palla, Ambrosius, Tracy, and Pahor 2005) Moreover, obesity has been identified as a contributor to the progression of sarcopenia (Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010a) and directly linked to an increased risk of physical disability.(Figaro, Kritchevsky, Resnick, Shorr, Butler, Shintani, Penninx, Simonsick, Goodpaster, Newman, Schwartz, and Harris 2006) Excess adiposity leads to an increased production of reactive oxygen species and inflammatory cytokines, damaging mitochondria and adversely affecting cellular quality control processes, (Bayeva, Gheorghiade, and Ardehali 2013;Verdejo, del, Troncoso, Gutierrez, Toro, Quiroga, Pedrozo, Munoz, Garcia, Castro, and Lavandero 2012) which can further accelerate the process of functional decline in older adults.(Naugle, Higgins, and Manini 2012;Peeters, Bonneux, Nusselder, Laet, and Barendregt 2004;Rillamas-Sun, LaCroix, Waring, Kroenke, LaMonte, Vitolins, Seguin, Bell, Gass, and Manini 2014) Obesity also contributes to cognitive decline, (Bhargava, Weiner, Hynan, Diaz-Arrastia, and Lipton 2006;Riekse, Leverenz, McCormick, Bowen, Teri, Nochlin, Simpson, Eugenio, Larson, and Tsuang 2004) which in turn contributes to increased risk of disability.(Deshpande, Metter, Bandinelli, Guralnik, and Ferrucci 2009;Dodge, Mattek, Austin, Hayes, and Kaye 2012)

2.1.3 Sarcopenia—Individuals tend to lose muscle mass at a rate of 1–2% per year after the age of 50 years.(Hiona and Leeuwenburgh 2008;Lauretani, Russo, Bandinelli, Bartali, Cavazzini, Di, Corsi, Rantanen, Guralnik, and Ferrucci 2003;Marcell 2003) The age-related loss of muscle mass and quality, otherwise known as sarcopenia, is primarily due to the progressive atrophy and loss of type II muscle fibers and motor neurons.(Larsson, Sjodin, and Karlsson 1978) However, other morphological changes occur during the atrophy process including increased variability in fiber size, accumulation of non-grouping, scattered

and angulated fibers, expansion of extracellular space, and deposition of protein aggregates within the interstitial matrix.(Kim, Kwak, Leeuwenburgh, and Lawler 2008) These morphological changes occur in conjunction with increased infiltration of non-contractile material such as adipose and connective tissues.(Brooks and Faulkner 1994;Goldspink, Fernandes, Williams, and Wells 1994;Goodpaster, Chomentowski, Ward, Rossi, Glynn, Delmonico, Kritchevsky, Pahor, and Newman 2008;McNeil, Doherty, Stashuk, and Rice 2005;Petersen, Befroy, Dufour, Dziura, Ariyan, Rothman, DiPietro, Cline, and Shulman 2003) These changes contribute to declines in functional capacity of the muscle, which in turn contribute to functional disability.(Evans 1997;Janssen, Heymsfield, and Ross 2002;Muhlberg and Sieber 2004;Rolland, Czerwinski, Abellan Van, Morley, Cesari, Onder, Woo, Baumgartner, Pillard, Boirie, Chumlea, and Vellas 2008;Visser, Goodpaster, Kritchevsky, Newman, Nevitt, Rubin, Simonsick, and Harris 2005)

Sarcopenia is a major healthcare concern for older adults, (Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010a) as it is associated with the development of functional disability (Janssen, Shepard, Katzmarzyk, and Roubenoff 2004;Visser, Goodpaster, Kritchevsky, Newman, Nevitt, Rubin, Simonsick, and Harris 2005) and may lead to the loss of independence. Because of the costs associated with caring for an individual with compromised function, sarcopenia has been linked to elevated healthcare costs.(Janssen, Shepard, Katzmarzyk, and Roubenoff 2004) Moreover, the absolute costs associated with sarcopenia are likely to rise sharply in the coming decades considering that the total number of persons over 65 years is expected to double over the next 25 years.(Federal Interagency Forum on Aging-Related Statistics. 2009)

While impaired locomotion is certainly the hallmark concern of sarcopenia, muscle atrophy may impair other physiological functions including glucose regulation, hormone production, and cellular communication.(Moon 2014) Moreover, muscle tissue provides the body's only major "reserve" of readily available amino acids. Thus, inadequate muscle mass prior to the onset of a disease condition may be dangerous in patients who need a large protein reservoir to recover. As a result, patients with sarcopenia prior to disease diagnosis may face impaired recovery from surgery (Rutan and Herndon 1990) or increased risk of mortality.(Prado, Baracos, McCargar, Reiman, Mourtzakis, Tonkin, Mackey, Koski, Pituskin, and Sawyer 2009) While the contributions of sarcopenia to functional impairments are well documented, data regarding the importance of skeletal muscle in the recovery from life-threatening situations, such as severe burns or traumatic surgeries, are limited.

Currently, there are several recommendations for criteria and the inclusion of cut-points for defining low muscle mass and low grip strength. The European Working Group on Sarcopenia and The Society of Sarcopenia, Cachaexia and Wasting Disorders both define sarcopenia using a multifactorial approach of combining low walking speed and low muscle mass.(Cruz-Jentoft, Baeyens, Bauer, Boirie, Cederholm, Landi, Martin, Michel, Rolland, Schneider, Topinkova, Vandewoude, and Zamboni 2010;Morley, Abbatecola, Argiles, Baracos, Bauer, Bhasin, Cederholm, Coats, Cummings, Evans, Fearon, Ferrucci, Fielding, Guralnik, Harris, Inui, Kalantar-Zadeh, Kirwan, Mantovani, Muscaritoli, Newman, Rossi-Fanelli, Rosano, Roubenoff, Schambelan, Sokol, Storer, Vellas, von, Yeh, and Anker 2011) These definitions take advantage of the strong association between low walking speed and

health outcomes in elders and thus are expected to serve as a primary indicator of sarcopenia.

2.1.4 Dynapenia—Dynapenia, a term coined by Manini and Clark (Manini and Clark 2012), is the age-related loss of muscle strength.(Clark and Manini 2008;Manini, Hong, and Clark 2013) In contrast to sarcopenia, dynapenia may or may not be related to age-related changes in muscle mass. Rather, dynapenia can be multifactorial including deficits in muscle quality and neuromuscular control. The presence of dynapenia can be assessed by measurements of isometric maximal voluntary force, one-repetition maximum force, rate of force production and other related measures.(Clark and Manini 2008)

While muscle mass seems to have little relationship to mobility impairments (Cruz-Jentoft, Baeyens, Bauer, Boirie, Cederholm, Landi, Martin, Michel, Rolland, Schneider, Topinkova, Vandewoude, and Zamboni 2010;McLean, Shardell, Alley, Cawthon, Fragala, Harris, Kenny, Peters, Ferrucci, Guralnik, Kritchevsky, Kiel, Vassileva, Xue, Perera, Studenski, and Dam 2014), dynapenia has been shown to be independently associated with loss of mobility function.(Bassey, Fiatarone, O'Neill, Kelly, Evans, and Lipsitz 1992;Bean, Kiely, Herman, Leveille, Mizer, Frontera, and Fielding 2002;Bean, Leveille, Kiely, Bandinelli, Guralnik, and Ferrucci 2003;Clark, Patten, Reid, Carabello, Phillips, and Fielding 2010;Clark, Patten, Reid, Carabello, Phillips, and Fielding 2011;Foldvari, Clark, Laviolette, Bernstein, Kaliton, Castaneda, Pu, Hausdorff, Fielding, and Singh 2000;Suzuki, Bean, and Fielding 2001). For example, older adults with muscle loss, and no strength loss, do not have mobility impairment. (McLean, Shardell, Alley, Cawthon, Fragala, Harris, Kenny, Peters, Ferrucci, Guralnik, Kritchevsky, Kiel, Vassileva, Xue, Perera, Studenski, and Dam 2014) This association only becomes more consistent when loss of muscle mass co-occurs with loss of muscle strength. (McLean, Shardell, Alley, Cawthon, Fragala, Harris, Kenny, Peters, Ferrucci, Guralnik, Kritchevsky, Kiel, Vassileva, Xue, Perera, Studenski, and Dam 2014;Studenski, Peters, Alley, Cawthon, McLean, Harris, Ferrucci, Guralnik, Fragala, Kenny, Kiel, Kritchevsky, Shardell, Dam, and Vassileva 2014) For example, grip strength less than 26kg or 16kg for men and women respectively is highly predictive of mobility disability. (Alley, Shardell, Peters, McLean, Dam, Kenny, Fragala, Harris, Kiel, Guralnik, Ferrucci, Kritchevsky, Studenski, Vassileva, and Cawthon 2014) A ten year follow-up with participants revealed that muscle weakness is also associated with higher mortality rates in both older men and women, to a degree much higher than a cohort who only has low lean mass. In fact, this study indicated that low lean mass in women was not associated with elevated mortality rates. (McLean, Shardell, Alley, Cawthon, Fragala, Harris, Kenny, Peters, Ferrucci, Guralnik, Kritchevsky, Kiel, Vassileva, Xue, Perera, Studenski, and Dam 2014) This suggests that at some level, there is a disconnect between muscle mass and weakness that may theoretically be explained by other factors such as age-dependent inter- and intramuscular fat infiltration (Goodpaster, Carlson, Visser, Kelley, Scherzinger, Harris, Stamm, and Newman 2001;Visser, Kritchevsky, Goodpaster, Newman, Nevitt, Stamm, and Harris 2002), excitation-contraction coupling, (Delbono 2000) or dysfunctions of the central nervous system or neuromuscular junctions. (Vandervoort 2002) In support of this, evidence suggests that neither the measurement of muscle mass nor muscle index (appendicular lean mass relative to BMI) is consistently associated with adverse outcomes.

2.1.5 Chronic Pain—Chronic pain is a highly prevalent condition in older adults with estimates as high as 70% in community settings and up to 80% in nursing homes.(Ferrell, Whedon, and Rollins 1995;Helme and Gibson 2001;Karttunen, Turunen, Ahonen, and Hartikainen 2014) Of the types of pain experienced, knee osteoarthritis represents the most common chronic pain condition and the leading cause of disability among older adults. (Neogi and Zhang 2013) Chronic pain significantly contributes to functional decline and activity limitation, (Fletcher, Guthrie, Berg, and Hirdes 2010;Pisters, Veenhof, van Dijk, Heymans, Twisk, and Dekker 2012;Rossi, Pereira, Driusso, Rebelatto, and Ricci 2013;White, Felson, Niu, Nevitt, Lewis, Torner, and Neogi 2011) adversely affects quality of life, and is associated with increased morbidity and mortality.(Andersson 2004;Bruckenthal, Reid, and Reisner 2009;Torrance, Elliott, Lee, and Smith 2010) Multiple factors inevitably influence age-related increases in pain vulnerability, including greater frequency of chronic medical conditions as well as multiple changes in biological and psychosocial functioning.(Cruz-Almeida, King, Goodin, Sibille, Glover, Riley, Sotolongo, Herbert, Schmidt, Fessler, Redden, Staud, Bradley, and Fillingim 2013) Indeed, as has been proposed for gerontology in general (Alkema and Alley 2006), age-related changes in pain are best conceptualized in the context of the biopsychosocial model, which posits that the experience of pain is sculpted by dynamic interactions between biological and psychosocial forces.(Kerns, Sellinger, and Goodin 2011) Complicating matters, older adults are also at increased risk for under treatment of pain and for adverse effects when pain treatment is provided.(Helme and Gibson 2001) (Karttunen, Turunen, Ahonen, and Hartikainen 2014) Despite the prevalence and adverse impact of pain among older adults, the mechanisms underlying age-related increases in pain and their contribution to functional decline remain poorly understood, and treatments designed to reduce pain and pain-related disability among older adults are woefully underdeveloped.

Given the relationship between pain and aging is multifaceted and dynamic, research efforts are needed across numerous pathways and from multiple directions. Age-related changes in sensory (i.e., increased central sensitization, pain facilitation, reduced pain inhibition)(Cruz-Almeida, Sibille, Goodin, Petrov, Bartley, Riley, III, King, Glover, Sotolongo, Herbert, Schmidt, Fessler, Staud, Redden, Bradley, and Fillingim 2014;Riley, III, Cruz-Almeida, Glover, King, Goodin, Sibille, Bartley, Herbert, Sotolongo, Fessler, Redden, Staud, Bradley, and Fillingim 2014) and immune (i.e., increased pro-inflammatory profiles) function, (Naugle, Cruz-Almeida, Vierck, Mauderli, and Riley, III 2015) as well as central and peripheral changes in structure of the nervous system (i.e., decreased number of myelinated afferents, decreased cortical and subcortical connectivity) can contribute to both pain and functional decline among older adults.(Cruz-Almeida, Black, Christou, and Clark 2014) Moreover, premorbid cognitive dysfunction contributes to the development and/or persistence of chronic pain, (Lavand'homme 2011;Solberg, Roach, and Segerstrom 2009;Williams 2010) although few studies have examined age-specific differences. (Oosterman, Gibson, Pulles, and Veldhuijzen 2013) Additionally, the contribution of pain to the development of sarcopenia and/or dynapenia is not currently known. Accumulating evidence indicates that recurring pain (via its associated somatosensory dysfunction) can induce long-term adaptation of the motor system, including reorganization of neural motor control (Tsao, Galea, and Hodges 2008;Tsao, Galea, and Hodges 2010) as well as

biochemical and morphological changes to muscle tissue.(Gerdle, Lemming, Kristiansen, Larsson, Peolsson, and Rosendal 2008;Gerdle, Soderberg, Salvador, Rosendal, and Larsson 2010;Rosendal, Larsson, Kristiansen, Peolsson, Sogaard, Kjaer, Sorensen, and Gerdle 2004) Further research is needed to elucidate the complex interactions between pain, functional decline, age related disability, sarcopenia, and dynapenia. Additionally, living with chronic pain is stressful further burdening biological system functioning, and ultimately contributing to allostatic overload, accelerated cellular aging, and increased morbidity and mortality. (Andersson 2004;Sibille, Witek-Janusek, Mathews, and Fillingim 2012;Szanton, Allen, Seplaki, Bandeen-Roche, and Fried 2009;Torrance, Elliott, Lee, and Smith 2010) Identifying risk factors, including resilience and vulnerability factors, that impact the onset and/or consequences of chronic pain will permit development of targeted interventions for reducing pain, improving physical functioning and enhancing quality of life in our aging population.

2.2 Emerging Evidence of Behavioral Risk Factors for Functional Decline

A number of behavior factors have been associated with the pathogenesis of functional decline and physical disability (in non-acute disease conditions) in older adults.(Anton, Karabetian, Naugle, and Buford 2013;Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010a) An increased understanding of such factors can assist in identifying at risk older adults. In this section, we will briefly review the contribution of each of these factors to reductions in physical function during aging.

2.2.1 Under/Over Nutrition—Both humans and rodents demonstrate a steady increase in body weight and adiposity through early senescence followed by a decline in later life. The development of leptin resistance, as seen in senescent rats, may be one factor contributing to increased adiposity with age.(Scarpace and Tumer 2001) Leptin behaves as a potent anorexic and energy-enhancing hormone in most young or lean animals, but its effects are diminished or lacking in the aged or obese state. Emerging evidence suggests that leptin resistance predisposes animals to exacerbated diet-induced obesity.(Scarpace and Zhang 2009) Recent studies have found that aged rats consume a greater amount of highly palatable high-fat (HF) diet than young rats, leading to exacerbated weight gain mostly in the form of fat. These finding indicate that susceptibility to diet-induced obesity increases with age.(Petervari, Rostas, Soos, Tenk, Miko, Furedi, Szekely, and Balasko 2014)

The findings described are concerning as epidemiological studies indicate that the *per capita* energy intake has significantly increased by approximately 300 kcal/d from 1985 to 2000, despite remaining fairly constant for the previous 75 years.(Finkelstein, Ruhm, and Kosa 2005) If left unchecked, a constant oversupply of energy and nutrients can contribute to increased adiposity during aging, which can accelerate functional decline and significantly increases risk for disability.(Baumgartner 2000a;Blaum, Xue, Michelon, Semba, and Fried 2005b) For example, higher fat mass has been associated with reductions in functional abilities in both healthy, postmenopausal women and older men.(Broadwin, Goodman-Gruen, and Slymen 2001;Lebrun, van der Schouw, de Jong, Pols, Grobbee, and Lamberts 2006) These changes occur even when body weight remains stable (Delmonico, Harris, Visser, Park, Conroy, Velasquez-Mieyer, Boudreau, Manini, Nevitt, Newman, and Goodpaster 2009) and are associated with increased fat depots within the muscle, as well as

loss of muscle strength (Delmonico, Harris, Visser, Park, Conroy, Velasquez-Mieyer, Boudreau, Manini, Nevitt, Newman, and Goodpaster 2009) and power.(Tuttle, Sinacore, and Mueller 2012) Compared to older adults with a body mass index (BMI; kg/m^2) in the healthy range (i.e., 20 – 24.9 kg/m^2), obese, older adults have been found to be significantly more likely to experience impairments in activities of daily living.(Peeters, Bonneux, Nusselder, Laet, and Barendregt 2004) Such findings suggest that obese, older adults appear are at greater risk of functional decline compared to peers with a BMI in the healthy range, and therefore represent a high-risk group.(Vincent, Horodyski, Gearen, Vlasak, Seay, Conrad, and Vincent 2012)

2.2.2 Sedentary Lifestyle—In the US, comprehensive reports indicate daily energy expenditure in work-related physical activity has fallen by more than 100 calories per day during the past 50 years.(Brownson, Boehmer, and Luke 2005) Most adults in affluent countries live sedentary lifestyles and spend more than half their waking hours in sedentary pursuits. (Cohen, Matthews, Signorello, Schlundt, Blot, and Buchowski 2013;Maher, Mire, Harrington, Staiano, and Katzmarzyk 2013) Moreover, the amount of time engaged in sedentary behavior appears to increase with age.(Troiano, Berrigan, Dodd, Masse, Tilert, and McDowell 2008) These trends are concerning as physical inactivity is currently the most common behavioral risk factor for obesity in the United States.(2008;Physical activity guidelines for Americans 2008) Despite a growing body of evidence indicating time spent in sedentary pursuits represents an independent disease risk factor,(Henson, Yates, Biddle, Edwardson, Khunti, Wilmot, Gray, Gorely, Nimmo, and Davies 2013) most adults are currently unaware of the potential insidious health risks associated with high levels of sedentary behavior.(Shuval, Hebert, Siddiqi, Leonard, Lee, Tiro, McCallister, and Skinner 2013) Such findings raise a new concern regarding the health consequences of sedentary time that potentially have major clinical and public health significance.

Individuals have traditionally been defined as ‘active’ or ‘inactive’ based on whether or not they achieve minimum physical activity recommendations (i.e., 150 min of moderate intensity or 90 min of vigorous intensity exercise per week) as described by physical activity guidelines. (Physical activity guidelines for Americans 2008)

Although health risks associated with lack of engagement in moderate-to-vigorous intensity physical activity are clear,(WHO 2009) current definitions comingle the health consequences associated with lack of moderate-to-vigorous intensity activity with potential adverse health effects of extended periods of physical inactivity (sitting, reclining). (Sedentary Behaviour 2012) An important consequence of the current approach for classifying individuals as ‘active’ or ‘inactive’ is that the potential physiological effects of the types of activities that most adults engage in during the vast majority of their day, namely sedentary (sitting) and non-exercise light activities (standing, walking), are not well understood.(Hamilton, Hamilton, and Zderic 2007)

For over a quarter century, experts have differing opinions regarding the contribution of a sedentary lifestyle to age-related muscle loss.(Faulkner, Larkin, Claflin, and Brooks 2007) These differences in opinion are not surprising given inherent difficulties understanding the heterogeneity of physical activity patterns across the lifespan as well as challenges in

measuring free-living activity. These challenges can be addressed through the development and standardization of assessment techniques for measuring the energy expended during physical activity. Recently, Manini et al. utilized the doubly-labeled water technique to measure energy expenditure during free-living activity in older adults.(Manini, Everhart, Anton, Schoeller, Cummings, Mackey, Delmonico, Bauer, Simonsick, Colbert, Visser, Tylavsky, Newman, and Harris 2009) Participants were divided into equal thirds based on energy expended through physical activity, and individuals in the highest third of daily activity energy expenditure had the greatest amount of lean mass. The rate of muscle loss across the most active individuals over five years was similar to those in the lowest third of free-living activity. These data suggest that high levels of physical inactivity may not *directly* accelerate the trajectory of sarcopenia; however, a sedentary lifestyle certainly adds to the risk of numerous pathological conditions, many of which do appear to accelerate sarcopenia progression.(Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010a)

2.2.3 Poor Sleep—Sleep problems are commonly underdiagnosed (Roth, Coulouvrat, Hajak, Lakoma, Sampson, Shahly, Shillington, Stephenson, Walsh, and Kessler 2011) and are a significant source of concern in older adults.(Ory, Smith, Ahn, Jiang, Lorig, and Whitelaw 2014) In older adults poor sleep has been associated with reduced physical function.(Foley, Ancoli-Israel, Britz, and Walsh 2004) Several diverse factors may contribute to sleep disturbances in a large percentage of older adults including retirement, health problems, death of spouse/family members,(Jackowska, Dockray, Hendrickx, and Steptoe 2011;Luo, Zhu, Zhao, Guo, Meng, Hong, and Ding 2013) and changes in circadian rhythm. Changes in sleep patterns may be part of the normal aging process; older adults generally have decreased sleep efficiency (time asleep divided by time in bed), stable or decreased total sleep time, and increased sleep latency (time to fall asleep).(Grandner, Martin, Patel, Jackson, Gehrman, Pien, Perlis, Xie, Sha, Weaver, and Gooneratne 2012) Older adults also report an earlier bedtime and earlier morning awakening, more awakenings during the night, more wakefulness during the night, and more daytime napping.(Grandner, Martin, Patel, Jackson, Gehrman, Pien, Perlis, Xie, Sha, Weaver, and Gooneratne 2012;Pace-Schott EF and Spencer RMC 2013) Abnormal sleep patterns were reported by over 15% of older adults who also reported limitations in ambulatory function. (Rantanen, Volpato, Ferrucci, Heikkinen, Fried, and Guralnik 2003) Notably, many of these disturbances may be related to pathological processes that are not considered a normal part of aging.(Orozco-Solis and Sassone-Corsi 2014) Epidemiologic studies in older adults have demonstrated an association between sleep complaints and risk factors for sleep disturbance (e.g., chronic illness, multiple medical problems, mood disturbance, less physical activity, physical disability) but little association with older age, suggesting that these risk factors, rather than aging per se, account for much of the increase in insomnia with age.(Luo, Zhu, Zhao, Guo, Meng, Hong, and Ding 2013) Functional limitations related to poor sleep have been reported as difficulty performing 6 instrumental activities of daily living (IADLs) which included walking 2–3 blocks, walking up or down 10 steps, preparing meals, heavy housework, and shopping.(Gregg, Mangione, Cauley, Thompson, Schwartz, Ensrud, and Nevitt 2002) In addition to affecting quality of life because of excessive daytime sleepiness, as well as physical, psychological, and cognitive problems, sleep disorders have been

associated with increased mortality.(Kripke, Langer, Elliott, Klauber, and Rex 2011) There is a lower mortality risk when individuals sleep 6–7 hours per night.(Patel, Ayas, Malhotra, White, Schernhammer, Speizer, Stampfer, and Hu 2004) The relationship between sleep and physical limitation based on neuromuscular performance is complex, but it has been shown that poor sleep as measured by actigraphy may be associated with functional limitations. (Goldman, Stone, Ancoli-Israel, Blackwell, Ewing, Boudreau, Cauley, Hall, Matthews, and Newman 2007) In addition, the number of medications used tends to increase with age, which can lead to increased morbidity, mortality, and side effects such as falls, cognitive impairment, and even sleep disturbances.(Huang, Mallet, Rochefort, Eguale, Buckeridge, and Tamblyn 2012)

2.2.4 Environmental Stress—Environmental stressors are a major contributor to mortality and declining health in older individuals.(Leahy and Crews 2012) Among numerous environmental stressors, three have been extensively researched and appear to have the greatest impact: air pollution, extreme temperature fluctuations, and mobility barriers within living environments.

In the last 10 years there has been a call to focus on the impact of air pollution research in older adults.(Sandstrom, Frew, Svartengren, and Viegi 2003) Outdoor air pollution (i.e., particulate and chemical), in major population centers around the world, is directly responsible for increased mortality and declining health, especially with regards to respiratory illness.(Bentayeb, Simoni, Baiz, Norback, Baldacci, Maio, Viegi, and Annesi-Maesano 2012;Kunzli, Kaiser, Medina, Studnicka, Chanel, Filliger, Herry, Horak, Jr., Puybonnieux-Texier, Quenel, Schneider, Seethaler, Vergnaud, and Sommer 2000;Pope, III, Ezzati, and Dockery 2009;Saldiva, Pope, III, Schwartz, Dockery, Lichtenfels, Salge, Barone, and Bohm 1995;Wen and Gu 2012;Zhang, Mauzerall, Zhu, Liang, Ezzati, and Remais 2010) Older individuals are particularly susceptible given their compromised immune systems (Bentayeb, Simoni, Baiz, Norback, Baldacci, Maio, Viegi, and Annesi-Maesano 2012) and predisposition to respiratory infections, and as such are vulnerable to increased risk for chronic obstructive pulmonary disease (COPD).(Bentayeb, Simoni, Baiz, Norback, Baldacci, Maio, Viegi, and Annesi-Maesano 2012) There are limited studies measuring mobility issues and more globally disability; however, due to the scope of the problem in developing countries such China, where there are fewer regulations for monitoring and controlling air pollution, this population has been better characterized. Using the Chinese Longitudinal Health Longevity Survey cohort, Wen & Gu designed a multilevel prospective cohort study based on a nationally representative sample of older Chinese men and women, comparing those individuals living in provinces with good versus poor air quality. Whereas women were shown to have a higher mortality rate than men in poor air quality zones, both sexes experienced a 42–47% odds increase for being deficient in at least one of six measured activities of daily living (ADLs) (Wen and Gu 2012). Indeed, ADL was the most affected health outcome measured (among 20) in this study.

Acute temperature extremes experienced in the context of heat/cold waves are responsible for increased mortality in a variety of vulnerable subgroups including older adults.(Pan, Li, and Tsai 1995) The real threat of global climate change has hastened the need for evaluation and prediction of societal healthcare costs and particularly in vulnerable populations

including the elderly.(Keatinge and Donaldson 2004;McGeehin and Mirabelli 2001;O'Neill and Ebi 2009;Zanobetti, O'Neill, Gronlund, and Schwartz 2012) Regardless of race and gender, individuals over the age of 65 are more susceptible than their younger counterparts to heat-related mortality.(Astrom, Forsberg, and Rocklov 2011;McGeehin and Mirabelli 2001) Fewer studies address the relationship to declining physical function; however, this was internationally highlighted by the heat wave experienced in August 2003 across Europe. A study conducted in Modena, Italy (Foroni, Salvioli, Rielli, Goldoni, Orlandi, Zauli, Guerzoni, Maccaferri, Daya, and Mussi 2007) demonstrated that older individuals with deficiencies in ADLs were more likely to succumb to the effects of the heat wave than those with no deficiencies in ADLs. The relationship between extremely cold winters is inconsistent with some studies showing increased mortality in the elderly and others not finding this relationship. (Conlon, Rajkovich, White-Newsome, Larsen, and O'Neill 2011) The Chinese Longitudinal Health Longevity Survey demonstrated that very low seasonal temperature increased the odds of ADL disability by 44% and increased mortality by 32%. (The CLHLS Research Team 2008) There was no effect of high temperatures on ADLs, however. These data demonstrate that environmental temperature regulation (i.e., air conditioning in the summer; heating in the winter) may serve as a frontline intervention for preventing and/or protecting older adults with or at risk of disability.

Finally, community mobility barriers and facilitators may influence the ability of older individuals to ambulate in their social environment and hence remain independent/dependent in their activities of daily living. Much of this research has come from the Multi-center Osteoarthritis Study (MOST), a prospective study of community-dwelling adults with or at risk for developing systemic knee osteoarthritis.(Keysor, Jette, LaValley, Lewis, Torner, Nevitt, and Felson 2010) The Home and Community Survey was used to ascertain daily activity limitation and daily activity frequency with the Late-Life Disability Instrument. Approximately one third of individuals in this cohort were more likely to have high mobility barriers and low transportation facilitators. Interestingly, individuals with functional limitations living in restrictive communities felt limited in their daily activities but did not perform tasks less frequently. Furthermore, investigators demonstrated that those individuals living in neighborhoods with no parks or walking areas engaged less frequently in regular fitness whereas those with neighborhoods with adequate handicap parking were more likely to engage in social and work activities.(Gray, Hollingsworth, Stark, and Morgan 2008;White, Jette, Felson, LaValley, Lewis, Torner, Nevitt, and Keysor 2010) Thus, social engineering of communities and neighborhoods that provide walking areas adequate handicap parking and public transportation may prevent and/or provide access to older individuals with or at risk for mobility disability.

2.2.5 Depression and Other Psychosocial Factors—Aging is associated with an increased risk for depressive symptoms (Alexopoulos 2005), which have been linked with functional decline. In fact, the World Health Organization estimates that depression is the leading cause of functional disability worldwide. A recent review identified a positive, and potentially bidirectional, association between depressive symptoms and functional impairment. (Mezuk, Edwards, Lohman, Choi, and Lapane 2012) In particular, cross-sectional studies provide evidence that older adults with functional deficits experience more

depressive symptoms than robust individuals. (Chang and Chueh 2011;Ni Mhaolain, Fan, Romero-Ortuno, Cogan, Cunningham, Lawlor, and Kenny 2012)

The effect may be linear, such that increasing severity of depressive symptoms is associated with increasing functional deficits (St John, Tyas, and Montgomery 2013), and functional ability scores improve as depressive symptoms remit. (Ormel, Oldehinkel, Brilman, and vanden Brink 1993). In addition, longitudinal investigations have shown that depression predicts future frailty (Fried, Tangen, Walston, Newman, Hirsch, Gottdiener, Seeman, Tracy, Kop, Burke, and McBurnie 2001;Woods, LaCroix, Gray, Aragaki, Cochrane, Brunner, Masaki, Murray, and Newman 2005) and functional disability. (Carbonare LD, Maggi S, Giannini S, Rozzini R, Cascio VL, Crepaldi G, and ILSA Working Group 2009;Hybels, Pieper, and Blazer 2009) In turn, there is evidence that onset of functional decline leads to increased depressive symptoms over time in older adults. (Kennedy, Kelman, and Thomas 1990;Lyness, Chapman, McGriff, Drayer, and Duberstein 2009;Roberts, Kaplan, Shema, and Strawbridge 1997;Yang and George 2005)

The relationship between depression and functional decline does not appear to be fully explained by somatic comorbidities. In an investigation of symptom dimensions of depression, which included symptoms of negative affect, lack of positive affect, somatic symptoms, and interpersonal difficulties, all symptoms were associated with frailty except for interpersonal difficulties. (St John, Tyas, and Montgomery 2013) This suggests that affective symptoms of depression contribute to the depression–functional ability relationship. There also is evidence that anhedonia and apathy, common non-somatic symptoms of depression that are also prevalent in non-clinically depressed populations (Ishii, Weintraub, and Mervis 2009;Ritchie, Hearld, Gross, Allman, Sawyer, Sheppard, Salanitro, Locher, Brown, and Roth 2013) confer risks for physical disability, functional impairment, and death independent of depression (Covinsky, Cenzer, Yaffe, O'Brien, and Blazer 2014;Holtta, Laakkonen, Laurila, Strandberg, Tilvis, and Pitkala 2012). Evidence that depression increases the risk for functional decline independent of the presence or severity of medical illness (Ng, Niti, Zaw, and Kua 2009;Patten 1999;Steffens, Hays, and Krishnan 1999) further suggests that somatic comorbidities do not fully explain the relationship between depressive symptoms and functional ability.

The mechanisms underlying the relationship between depressive symptoms and functional decline have not been fully elucidated, but likely involve a complex interrelationship of psychosocial, cognitive, and brain changes. Depressed individuals may be at risk for functional decline due to poor self-care, including poor nutritional intake and disengagement from daily activities. (Katon 2011) Conversely, functional decline may lead to depression by limiting participation in social, leisure, and physical activities, thereby increasing chronic stress and social isolation. (Carriere, Villebrun, Peres, Stewart, Ritchie, and Ancelin 2009;James, Wilson, Barnes, and Bennett 2011) This hypothesis is supported by evidence that the diversity of social networks, availability of confidants, satisfaction with social support, sense of control and self-esteem mediate the relationship between depression and functional decline. (Escobar-Bravo, Puga-Gonzalez, and Martin-Baranera 2012)

Biological factors might also have an important role. For example, depression-related changes in the hypothalamic–pituitary–adrenal (HPA) axis and the immunological system may aggravate medical illnesses, leading to functional decline. (Furtado and Katzman 2015). Furthermore, depression is also associated with cognitive and brain changes, (Dotson, Resnick, and Zonderman 2008;Dotson, Szymkowics, Kirton, McLaren, Green, and Rohani 2014;Dotson, Zonderman, Davatzikos, Kraut, and Resnick 2009;Dotson, Zonderman, Kraut, and Resnick 2013) which are also known to impact functional abilities.

In addition to depression, psychosocial influences pertaining to self-regulatory and emotion-regulatory strategies, personality, social isolation, stress, and psychiatric symptoms and disorders have recently been identified as contributing to risk for functional decline. (Baltes and Baltes 1993;Dark-Freudeman, Ebner, and West 2014;Ebner and Freund 2007;Freund and Ebner 2005) Psychosocial influences may become particularly relevant in old age possibly due to the experience of increasing physical ailments, dependency, and age-related social losses.(Ebner, Maura, Macdonald, Westberg, and Fischer 2013) For example, self-efficacy and control beliefs are associated with fear of falling, gait speed, balance, worse pain management, and limitations in ADLs.(Dark-Freudeman, Ebner, and West 2014) Heightened levels of negative emotions predict worse cardiovascular health, (Suls and Bunde 2005) and inefficient emotionregulatory strategies are associated with increased levels of inflammation.(Appleton, Buka, Loucks, Gilman, and Kubzansky 2013) Goal orientation and selection appears to affect well-being with goal orientation towards maintenance being associated with well-being in older adults.(Ebner, Freund, and Baltes 2006)

2.3 Evolving Concepts on Biological Mechanisms Underlying Functional Decline

Several biological factors have been associated with the pathogenesis of functional decline during aging and physical disability (in non-acute disease conditions), but the exact mechanisms contributing to age-related functional decline remain largely undefined. In this section, we will briefly review specific biological mechanisms that have been directly linked with physical function and appear to play an important role in maintenance of physical function in older adults. These mechanisms, which are described below, include mitochondrial function and dynamics, autophagy, oxidative stress, chronic inflammation, muscle composition, hormonal factors, and neurodegeneration.

As diverse as the etiologies of physical disability are, a growing body of evidence strongly implicates the mitochondria (Mt) as playing a key role in the initial onset and progression of functional decline in many individuals.(Garnier, Fortin, Zoll, N'Guessan, Mettauer, Lampert, Veksler, and Ventura-Clapier 2005a;Safdar, Hamadeh, Kaczor, Raha, and Tarnopolsky 2010) Mitochondria are dynamic organelles responsible for the plasticity of skeletal muscle and its ability to adapt to the ever changing metabolic demands of the cell. Given that Mt are the main energy producing organelles of the body, it is not surprising that they play a central role in the maintenance of muscle mass and that their dysfunction may contribute to sarcopenia. Abundant evidence points to mitochondrial dysregulation in aging tissues including altered gene expression pathways, aberrant quality control processes, and activation of myonuclear cell death.(Calvani, Joseph, Adhihetty, Miccheli, Bossola,

Leeuwenburgh, Bernabei, and Marzetti 2013) Additionally, accumulating evidence from both preclinical studies and recent human clinical trials strongly suggests that Mt have a key role in the pathogenesis of age-related functional decline, marked by slower walking speed. (Hiona and Leeuwenburgh 2008;Studenski, Perera, Patel, Rosano, Faulkner, Inzitari, Brach, Chandler, Cawthon, Connor, Nevitt, Visser, Kritchevsky, Badinelli, Harris, Newman, Cauley, Ferrucci, and Guralnik 2011) Abnormalities in mitochondrial enzyme activity, (Rooyackers, Adey, Ades, and Nair 1996;Short, Bigelow, Kahl, Singh, Coenen-Schimke, Raghavakaimal, and Nair 2005a) lower mitochondrial protein synthesis rates,(Rooyackers, Adey, Ades, and Nair 1996) oxidative capacity, and adenosine triphosphate (ATP) synthesis(Short, Bigelow, Kahl, Singh, Coenen-Schimke, Raghavakaimal, and Nair 2005a) have been observed in the skeletal muscle of older persons. In addition, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a powerful regulator of mitochondrial oxidative metabolism,(Liang and Ward 2006;Russell 2005;Spiegelman 2007) shows marked declines with aging.(Corton and Brown-Borg 2005;Ling, Poulsen, Carlsson, Ridderstrale, Almgren, Wojtaszewski, Beck-Nielsen, Groop, and Vaag 2004) Specifically, declines in PGC-1α have been associated with reductions in mitochondrial oxidative metabolism which is associated with poor muscle quality and function.(Garnier, Fortin, Zoll, N'Guessan, Mettauer, Lampert, Veksler, and Ventura-Clapier 2005b;Little, Safdar, Bishop, Tarnopolsky, and Gibala 2011;Safdar, Hamadeh, Kaczor, Raha, Debeer, and Tarnopolsky 2010)

To date, reasons for the decrease in mitochondrial function with aging remain under debate and the molecular details are still not well understood; however, a growing body of evidence implicates reactive oxygen species (ROS) in contributing to Mt damage.(Vermulst, Wanagat, Kujoth, Bielas, Rabinovitch, Prolla, and Loeb 2008) In line with this, the mitochondrial theory of aging proposes that cumulative damage caused by the production of oxidants can alter MtDNA (e.g., point mutations and increase deletions). According to this theory, an overproduction of ROS from the electron transport chain (ETC) within the inner mitochondrial membrane are the driving force for the mitochondrial dysfunction associated with age-related muscle atrophy.(Harman 1972;Miquel, Economos, Fleming, and Johnson Jr 1980) The mitochondrial genome is particularly susceptible to free radical (oxidant) damage because of its close proximity to ROS generation and the lack of protective histones. In fact, there is substantial evidence showing increased ROS production and associated oxidative stress-induced damage to mitochondrial DNA (mtDNA) and ETC complexes in aged rodents and non-human primates (Figueiredo, Powers, Ferreira, Appell, and Duarte 2009;Lee, Choi, Birkenfeld, Alves, Jornayvaz, Jurczak, Zhang, Woo, Shadel, and Ladiges 2010;Lee, Wang, and Fanburg 1998;WANAGAT, CAO, PATHARE, and AIKEN 2001), as well as in the vastus lateralis muscle of humans.(Bua, Johnson, Herbst, Delong, McKenzie, Salamat, and AIKEN 2006) Increased damage to mtDNA can lead to abberrations in mtDNA-encoded ETC subunits affecting their assembly function and ultimately ATP production. Moreover, these impairments can further exacerbate the production of ROS leading to a vicious cycle. Additionally, damage to mitochondrial proteins and lipids may also contribute to mitochondrial dysfunction by not only affecting oxidative phosphorylation and ETC activity but also by altering the susceptibility of Mt to apoptosis.(Conley, Marcinek, and Villarin 2007;Dirks and Leeuwenburgh 2002;Gonzalvez and Gottlieb

2007;Paradies, Petrosillo, Pistolese, and Ruggiero 2002;Shidoji, Hayashi, Komura, Ohishi, and Yagi 1999) Recently, the use of a mitochondrial-targeted antioxidant peptide (SS-31) has been shown to inhibit ROS production and skeletal muscle atrophy in a variety of experimental animal models of inactivity (Min, Smuder, Kwon, Kavazis, Szeto, and Powers 2011;Powers, Hudson, Nelson, Talbert, Min, Szeto, Kavazis, and Smuder 2011) suggesting the importance of mitochondrially-produced ROS in skeletal muscle atrophy.

2.3.1 Mitochondrial Quality Control Processes; Dynamics and Autophagy—

Mitochondrial dynamics are another important determinant of organelle quality control and the maintenance of genome integrity by facilitating the renewal of healthy mitochondria and the removal of unhealthy/damaged organelles. (Busch, Kowald, and Spelbrink 2014) Mitochondrial morphology is governed by fusion and fission proteins including the dynamin-related GTPases mitofusin 1 and 2 (Mfn1 and Mfn2) and optic atrophy protein 1 (Opa1),as well as dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1) respectively. (Seo, Joseph, Dutta, Hwang, Aris, and Leeuwenburgh 2010) Fusion is responsible for the formation of an interconnected mitochondrial network and the distribution of metabolites, proteins, and mtDNA, while fission facilitates the removal of damaged organelles by lysosomal degradation pathways known as autophagy.(Twig, Elorza, Molina, Mohamed, Wikstrom, Walzer, Stiles, Haigh, Katz, and Las 2008) Muscle-specific deletion of Mfn1 and Mfn2 results in the accumulation of mtDNA mutations and deletions, reduced mtDNA content, as well as muscle atrophy.(Chen, Vermulst, Wang, Chomyn, Prolla, McCaffery, and Chan 2010) Moreover, enlarged mitochondria indicative of dyshomeostasis between fusion and fission (i.e. greater fusion and/or lower fission events) have previously been documented in aging muscles.(Tandler and Hoppel 1986) Similarly, increased fission via overexpression of fission proteins Drp1 and Fis1 leads to fragmented mitochondria and increased autophagy culminating in muscle atrophy.(Romanello, Guadagnin, Gomes, Roder, Sandri, Petersen, Milan, Masiero, Del, Foretz, Scorrano, Rudolf, and Sandri 2010)

Aging is characterized by a reduction in efficiency of cellular maintenance, repair, and turnover mechanisms resulting in the accumulation of lipids and damaged biomolecules and organelles.(Singh and Cuervo 2011;Weber and Reichert 2010;Wohlgemuth, Calvani, and Marzetti 2014;Yang, Li, Fu, Calay, and Hotamisligil 2010) The cellular quality control (QC) process of *autophagy* represents an important but underexplored biological process affecting age-related changes in muscle composition and functional decline.(Baumgartner 2000b;Blaum, Xue, Michelon, Semba, and Fried 2005a;Cesari, Kritchevsky, Baumgartner, Atkinson, Penninx, Lenchik, Palla, Ambrosius, Tracy, and Pahor 2005) It is generally accepted that ROS can trigger the induction of macroautophagy,(Scherz-Shouval and Elazar 2011) and the selective removal of damaged mitochondria, a major source and target of ROS, following oxidative stress has been reported.(Kim, Rodriguez-Enriquez, and Lemasters 2007) Impairments in autophagy can result in the accumulation of damaged mitochondria,(Brunk and Terman 2002;Terman and Brunk 2005) reductions in the bioenergetic status of the cell,(Marzetti, Lees, Wohlgemuth, and Leeuwenburgh 2009;Pyo, Yoo, and Jung 2013) and in myocyte apoptosis,(Wohlgemuth, Calvani, and Marzetti 2014) which may be reflected in decreased muscle strength(Buford, Anton, Judge, Marzetti, Wohlgemuth, Carter, Leeuwenburgh, Pahor, and Manini 2010b;Buford, Lott, Marzetti,

Wohlgemuth, Vandenborne, Pahor, Leeuwenburgh, and Manini 2012) and slower walking speed observed with aging.(Marzetti, Calvani, Bernabei, and Leeuwenburgh 2012;Nocera, Buford, Manini, Naugle, Leeuwenburgh, Pahor, Perri, and Anton 2011) Thus, evidence to date strongly implicates the mitochondria as having a pivotal role in the pathogenesis of age-related functional decline,(Coen, Jubrias, Distefano, Amati, Mackey, Glynn, Manini, Wohlgemuth, Leeuwenburgh, Cummings, Newman, Ferrucci, Toledo, Shankland, Conley, and Goodpaster 2013) and reductions in autophagy appear to be a critical biological mechanism affecting the collective function of the mitochondrial pool.(Weber and Reichert 2010;Zhu, Wang, and Chu 2013)

A growing body of evidence indicates DNA oxidative damage is also associated with impairments in bioenergetics and key defects in mitochondrial quality control processes including biogenesis, morphology, and autophagy.(Joseph, Adhihetty, Buford, Wohlgemuth, Lees, Nguyen, Aranda, Sandesara, Pahor, and Manini 2012;Short, Bigelow, Kahl, Singh, Coenen-Schimke, Raghavakaimal, and Nair 2005b) The majority of proteins required for mitochondrial biogenesis are encoded in the nucleus, targeted to mitochondria, and assembled into subcompartments where they form functional holoenzyme complexes. (Joseph, Pilegaard, Litvintsev, Leick, and Hood 2006) Improper gene expression, translation, import, and assembly can lead to the impaired assembly of ETC subunits and deficits in energy production. Of particular importance is PGC-1α, known as the master regulator of mitochondrial biogenesis because of its ability to coactivate and upregulate the coordinated expression of a number of genes required for substrate metabolism and biogenesis.(Handschin and Spiegelman 2006) PGC-1α protein and its downstream molecular targets are reduced in aging animals (Baker, Betik, Krause, and Hepple 2006) and humans.(Joseph, Adhihetty, Buford, Wohlgemuth, Lees, Nguyen, Aranda, Sandesara, Pahor, and Manini 2012;Safdar, Hamadeh, Kaczor, Raha, and Tarnopolsky 2010) In fact, forced overexpression of this gene in muscle attenuates mitochondrial dysfunction and the associated muscle atrophy in aging animals.(Wenz, Rossi, Rotundo, Spiegelman, and Moraes 2009) Thus, the ability of the cell to repair the damage and maintain genome stability may be impaired with age leading to a greater rate of damage formation than damage removal.

2.3.2 Mitochondrial DNA Mutations—The mammalian mitochondrial genome consists of 37 genes, encoding 13 proteins of the electron transport oxidative phosphorylation system.(Anderson, Bankier, Barrell, de Bruijn, Coulson, Drouin, Eperon, Nierlich, Roe, Sanger, Schreier, Smith, Staden, and Young 1981) Since mtDNA encoded proteins play a critical role in energy metabolism, mtDNA mutations have been hypothesized to accelerate the aging processes and contribute to age-related diseases. Indeed, specific mutations in mtDNA cause a number of mitochondrial disorders in humans including mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), and myoclonic epilepsy and ragged red fibers (MERRF). Noteworthy, more than 100 different deletions of mtDNA have been associated with mitochondrial disorders.(Chinnery, Elliott, Green, Rees, Coulthard, Turnbull, and Griffiths 2000;Kujoth, Bradshaw, Haroon, and Prolla 2007;Someya and Prolla 2010) Nuclear-encoded POLG is the only known DNA polymerase in mitochondria and has conserved polymerase and exonuclease domains, which repair

mtDNA mutations.(Kujoth, Bradshaw, Haroon, and Prolla 2007) There are over 80 pathogenic mutations in POLG in humans, including progressive external ophthalmoplegia (PEO), Alpers syndrome, and ataxia. Most reported mutations are recessive, commonly found in combination with other mutations in POLG, and associated with a variety of symptoms including ophthalmoplegia, cataracts, progressive muscle weakness, parkinsonism, premature ovarian failure, male infertility, hearing loss, and cardiac dysfunction.(Kujoth, Bradshaw, Haroon, and Prolla 2007;Mancuso, Filosto, Bellan, Liguori, Montagna, Baruzzi, DiMauro, and Carelli 2004) Taken together, these observations strongly suggest that accumulation of mtDNA mutations plays a key role in the development of a variety of age-related disorders and impairment.

2.3.3 Inflammation—A consistent observation of aging in humans and animals is a persistent low level increase in serum markers of inflammation, such as C-reactive protein and interleukin-6.(Chung, Cesari, Anton, Marzetti, Giovannini, Seo, Carter, Yu, and Leeuwenburgh 2009) Markers of inflammation in the blood and in specific tissues are associated with impaired motor and cognitive function (Blalock, Chen, Sharrow, Herman, Porter, Foster, and Landfield 2003;Speisman, Kumar, Rani, Foster, and Ormerod 2013;Zeier, Madorsky, Xu, Ogle, Notterpek, and Foster 2011) suggesting that the pro-inflammatory phenotype impairs the ability of older individuals to cope with age-related stressors and thus contributes to functional decline. Interestingly, anti-inflammatory treatments or behavioral therapies that reduce inflammatory markers in the blood are associated with improved cognitive performance and immune function.(Speisman, Kumar, Rani, Foster, and Ormerod 2013)

Growing evidence shows that low-grade chronic inflammation, characterized by elevations in plasma C-reactive protein (CRP), tumor necrosis factor Alpha (TNF-α), and particularly interleukin-6 (IL-6),(Brinkley, Leng, Miller, Kitzman, Pahor, Berry, Marsh, Kritchevsky, and Nicklas 2009;Cesari, Penninx, Pahor, Lauretani, Corsi, Guralnik, and Ferrucci 2004;Ferrucci, Harris, Guralnik, Wacholder, Tracy, Corti, Penninx, Pahor, Wallace, and Havlik 1999;Hsu, Kritchevsky, Liu, Kanaya, Newman, Perry, Visser, Pahor, Harris, and Nicklas 2009;Penninx, Kritchevsky, Newman, Nicklas, Simonsick, Rubin, Nevitt, Visser, Harris, and Pahor 2004;Sanders, Ding, Arnold, Kaplan, Cappola, Kizer, Boudreau, Cushman, and Newman 2014;Singh and Newman 2011) is an independent risk factor for disability, impaired mobility, and slow walking speed.(Brinkley, Leng, Miller, Kitzman, Pahor, Berry, Marsh, Kritchevsky, and Nicklas 2009;Cesari, Marzetti, Laudisio, Antonica, Pahor, Bernabei, and Zuccala 2010;Hsu, Kritchevsky, Liu, Kanaya, Newman, Perry, Visser, Pahor, Harris, and Nicklas 2009;McDermott, Liu, Ferrucci, Tian, Guralnik, Green, Tan, Liao, Pearce, Schneider, McCue, Ridker, Rifai, and Criqui 2008;Penninx, Abbas, Ambrosius, Nicklas, Davis, Messier, and Pahor 2004;Penninx, Kritchevsky, Newman, Nicklas, Simonsick, Rubin, Nevitt, Visser, Harris, and Pahor 2004;Verghese, Holtzer, Lipton, and Wang 2012) The age-related dysregulation of immune function may have direct adverse consequences on physical function and promote disability by causing fatigue and loss of muscle strength.(Brinkley, Leng, Miller, Kitzman, Pahor, Berry, Marsh, Kritchevsky, and Nicklas 2009;Ferrucci, Penninx, Volpato, Harris, Bandeen-Roche, Balfour, Leveille, Fried, and Md 2002;Schaap, Pluijm, Deeg, Harris, Kritchevsky, Newman, Colbert, Pahor,

Rubin, Tylavsky, and Visser 2009) The sources and consequences of chronic inflammation are important for identifying promising interventions (Figure 3.a.1.). Inflammation in older persons is affected by a numbers of factors including genes and their modifiers, the environment, and the *in situ* biochemical environment. Important exogenous environmental exposures include smoking, moderate (beneficial) and excessive alcohol consumption, and an anti-oxidative diet (beneficial). Pro-inflammatory endogenous factors include adiposity (especially visceral adiposity), subclinical disease burden, and oxidative stress, among others.

Regarding direct consequences, activation of NF-κB signaling increases muscle protein degradation and inhibits myogenesis,(Li, Malhotra, and Kumar 2008;Merritt, Stec, Thalacker-Mercer, Windham, Cross, Shelley, Craig, Kosek, Kim, and Bamman 2013) except in very late differentiation where it promotes homeostasis.(Li, Malhotra, and Kumar 2008) Low-grade chronic inflammation is a modifiable risk factor; however, it is unknown whether interventions that reduce the levels of inflammatory markers *per se* can improve mobility, or avert decline in mobility, in older adults.

2.3.4 Hormonal Factors—Successful aging is highly influenced by the interaction of genetic programming with endogenous and exogenous (i.e., hormonal replacement) hormonal changes.(Bean, Ianov, and Foster 2014;Foster 2012) In general, hormones are secreted from specific tissues in the body and the brain and transported in the blood to influence metabolic functions at close or distant sites. There is evidence that hormonal dysregulation during aging impacts multiple physiological systems including the muscle, brain, and immune system. This dysregulation includes an age-related decrease in some trophic hormones such as the gonadal steroids, estrogen and testosterone (Bean, Ianov, and Foster 2014), age-related increase in stress-related hormones such as cortisol(Bizon, Helm, Han, Chun, Pucilowska, Lund, and Gallagher 2001), and age-related changes in neuropeptides such as oxytocin.(Ebner, Maura, Macdonald, Westberg, and Fischer 2013) These hormones are crucially involved in the regulation of physiological and psychological processes related to aging.(Ebner, Kamin, Diaz, Cohen, and Macdonald 2014) For example, chronically high levels of cortisol have been shown to exert neurotoxic effects on muscles and the brain that contribute to age-related impairments. (Saleem 2011) In turn, estrogen and testosterone replacement may reduce risk for osteoporosis, cardiovascular disease, and Alzheimer's disease.(Nguyen, Dolomie-Fagour, Georges, and Corcuff 2008) More recent work has revealed that delivery of oxytocin can have beneficial effects on socio-affective functioning. (Bean, Ianov, and Foster 2014;Ebner, Horta, Lin, Feifel, Fisher, and Cohen 2015;Fekete, Seay, Antoni, Mendez, Fletcher, Szeto, and Schneiderman 2014;Scheele, Wille, Kendrick, Stoffel-Wagner, Becker, Gunturkun, Maier, and Hurlemann 2013;Schneiderman, Zagoory-Sharon, Leckman, and Feldman 2012) We therefore propose that hormonal changes represent an important contribution to the multi-factorial processes underlying functional decline during aging.

2.3.5 Cerebral Neurodegeneration—Accumulating evidence indicates that age-related loss of function is strongly linked to degeneration of cerebral structure and function.(Rosso, Studenski, Chen, Aizenstein, Alexander, Bennett, Black, Camicioli, Carlson, Ferrucci,

Guralnik, Hausdorff, Kaye, Launer, Lipsitz, Verghese, and Rosano 2013) Cerebral gray matter (primarily consisting of neuronal cell bodies) has been shown to atrophy with advancing age, (Hoffstaedter, Grefkes, Roski, Caspers, Zilles, and Eickhoff 2014) and gray matter volume has been linked to a variety of movement deficits. Bradykinesia has been shown to be associated with gray matter volume of the primary sensorimotor area.(Rosano, Bennett, Newman, Venkatraman, Yaffe, Harris, Kritchevsky, and Aizenstein 2012) Gait disturbances, such as slow speed, shorter steps and longer double support time, have been associated with reduced gray matter volume of the prefrontal, medial temporal, frontoparietal, and sensorimotor areas.(Rosano, Aizenstein, Brach, Longenberger, Studenski, and Newman 2008;Rosano, Aizenstein, Studenski, and Newman 2007;Rosano, Bennett, Newman, Venkatraman, Yaffe, Harris, Kritchevsky, and Aizenstein 2012) Cerebral white matter (i.e., myelinated axons) is also affected by aging. Most notably, an increase in size and intensity of white matter hyperintensities indicates the presence of demyelination and/or dilated perivascular spaces. White matter hyperintensity has been linked to mobility limitation, marked by slow walking speed,(Moscufo, Wolfson, Meier, Liguori, Hildenbrand, Wakefield, Schmidt, Pearlson, and Guttmann 2012;Rosano, Sigurdsson, Siggeirsdottir, Phillips, Garcia, Jonsson, Eiriksdottir, Newman, Harris, van Buchem, Gudnason, and Launer 2010;Viana-Baptista, Bugalho, Jordao, Ribeiro, Esperanca-Pina, and Ferro 2011;Wakefield, Moscufo, Guttmann, Kuchel, Kaplan, Pearlson, and Wolfson 2010;Willey, Scarmeas, Provenzano, Luchsinger, Mayeux, and Brickman 2013) and may attenuate the potential for rehabilitation induced gains in walking speed.(Nadkarni, Studenski, Perera, Rosano, Aizenstein, Brach, and Van Swearingen 2013) Altered connectivity in neuronal networks, as measured by transcranial magnetic stimulation, has also been associated with improvements in physical function in older adults.(McGinley, Hoffman, Russ, Thomas, and Clark 2010;Papegaaij, Taube, Baudry, Otten, and Hortobagyi 2014;Plow, Varnerin, Cunningham, Janini, Bonnett, Wyant, Hou, Siemionow, Wang, Machado, and Yue 2014) Emerging evidence suggests that chronic physical activity is a neuroprotective factor that may prevent or slow the course of cerebral neurodegeneration with advancing age.(Baezner, Blahak, Poggesi, Pantoni, Inzitari, Chabriat, Erkinjuntti, Fazekas, Ferro, Langhorne, O'Brien, Scheltens, Visser, Wahlund, Waldemar, Wallin, and Hennerici 2008;Gow, Bastin, Munoz, Valdes Hernandez, Morris, Murray, Royle, Starr, Deary, and Wardlaw 2012)

2.3.6 Peripheral Neurodegeneration—Weakness and functional decline have been linked to impairment of the peripheral nervous system including both motor (Resnick, Vinik, Schwartz, Leveille, Brancati, Balfour, and Guralnik 2000;Strotmeyer, de, Schwartz, Faulkner, Resnick, Goodpaster, Shorr, Vinik, Harris, and Newman 2008;Strotmeyer, de, Schwartz, Resnick, Goodpaster, Faulkner, Shorr, Vinik, Harris, and Newman 2009) and sensory (Buchman, Wilson, Leurgans, and Bennett 2009;Cruz-Almeida, Black, Christou, and Clark 2014;Deshpande, Ferrucci, Metter, Faulkner, Strotmeyer, Satterfield, Schwartz, and Simonsick 2008;Mold, Vesely, Keyl, Schenk, and Roberts 2004;Resnick, Vinik, Schwartz, Leveille, Brancati, Balfour, and Guralnik 2000) nerve function. A variety of factors can contribute to decline of nerve health in older adults including chronic inflammation, oxidative stress, diabetes, chronic infections, prolonged smoking, prolonged alcohol use, and prolonged vitamin deficiency.(Di, Cherubini, Volpato, Sparvieri, Lauretani, Franceschi, Senin, Abate, Paganelli, Martin, Andres-Lacueva, and Ferrucci 2006;Mallik and

Weir 2005;Manini, Hong, and Clark 2013) Motor neuron degeneration is evidenced by a decline in conduction velocity and in the amplitude of the maximum evoked compound muscle action potential.(Di, Cherubini, Volpato, Sparvieri, Lauretani, Franceschi, Senin, Abate, Paganelli, Martin, Andres-Lacueva, and Ferrucci 2006;Rivner, Swift, and Malik 2001) Another well-documented change with aging is increased rates of apoptosis of the large diameter, fast conducting motor neurons that innervate powerful Type II muscle fibers, (Kawamura, O'Brien, Okazaki, and Dyck 1977;Mittal and Logmani 1987) which can affect functional capacity. This process begins in middle-adulthood and accelerates with increasing age.(Larsson, Grimby, and Karlsson 1979;Mittal and Logmani 1987) Thus, peripheral neurodegeneration appears to represent an important factor underlying age-related decline in physical function.

Sensory nerve degeneration also contributes to mobility deficits. For example, impaired somatosensation in the lower extremities has been linked to the age-related decline of balance and walking speed.(Buchman, Wilson, Leurgans, and Bennett 2009;Cruz-Almeida, Black, Christou, and Clark 2014;Deshpande, Ferrucci, Metter, Faulkner, Strotmeyer, Satterfield, Schwartz, and Simonsick 2008;Mold, Vesely, Keyl, Schenk, and Roberts 2004;Resnick, Vinik, Schwartz, Leveille, Brancati, Balfour, and Guralnik 2000) In order to enhance somatosensory input to lower extremity somatosensory receptors, a number of researchers have investigated shoe insole devices that use vibration or augmented texture. The evidence shows that a vibrating insole can improve sway parameters during standing balance in older adults.(Priplata, Niemi, Harry, Lipsitz, and Collins 2003) Similarly, a textured insole improves sway parameters during walking and standing balance in older adult.(Palluel, Nougier, and Olivier 2008;Palluel, Olivier, and Nougier 2009) Recent evidence suggests that enhancing somatosensory feedback can restore a more normal motor control strategy during walking.(Clark, Christou, Ring, Williamson, and Doty 2014) Thus, peripheral neurodegeneration appears to represent an important factor underlying age-related decline in physical function.

2.4 Promising Interventions to Enhance Physical Function and Mobility

Few therapies have been identified to improve functional performance in human aging, and there are currently no FDA-approved medications for the treatment of functional decline in older adults. Empirically supported treatments are urgently needed to improve functional ability and prevent mobility disability in older adults. This section will review promising interventions for functional enhancement in older adults including lifestyle, smart and connected technologies, cognitive training, exergaming, non-invasive brain stimulation, pharmaceutical, nutraceutical, and hormone-based interventions.

2.4.1 Lifestyle (Diet)—Dietary restriction (DR) may confer significant functional benefits by reducing the structural and biological consequences of excess adiposity. Dietary weight loss can directly impact physical function by improving muscle quality and reducing intramuscular adipose tissue(Manini, Buford, Lott, Vandenborne, Daniels, Knaggs, Patel, Pahor, Perri, and Anton 2014) and decreasing joint load (Messier, Loeser, Miller, Morgan, Rejeski, Sevick, Ettinger, Pahor, and Williamson 2004). Weight reduction in overweight individuals can also impact physical function indirectly by reducing pain(McCarthy, Bigal,

Katz, Derby, and Lipton 2009) and fatigue.(Avlund 2010) In addition, DR can promote proper redox status (Hofer, Fontana, Anton, Weiss, Villareal, Malayappan, and Leeuwenburgh 2008;Ivanova and Yankova 2013), anti-inflammatory action(Chung, Cesari, Anton, Marzetti, Giovannini, Seo, Carter, Yu, and Leeuwenburgh 2009), and cellular quality control, as well as maintain a healthy population of mitochondria through biogenesis.(Aris, Alvers, Ferraiuolo, Fishwick, Hanvivatpong, Hu, Kirlew, Leonard, Losin, and Marraffini 2013;Dutta, Calvani, Bernabei, Leeuwenburgh, and Marzetti 2012) Furthermore, DR has been shown to be a potent stimulant of autophagy in preclinical models (Cavallini, Donati, Gori, Pollera, and Bergamini 2001;Donati, Cavallini, Paradiso, Vittorini, Pollera, Gori, and Bergamini 2001;Wohlgemuth, Julian, Akin, Fried, Toscano, Leeuwenburgh, and Dunn 2007), which may be a key mediator through which DR improves physical performance. (Jensen, Roy, Buchanan, and Berg 2004;Villareal, Chode, Parimi, Sinacore, Hilton, Armamento-Villareal, Napoli, Qualls, and Shah 2011)

Accumulating evidence indicates that DR leading to weight loss can improve physical function among obese older adults, independent of changes in physical activity.(Anton, Karabetian, Naugle, and Buford 2013) Yet, a concern associated with diet-induced weight loss is that it is comprised of reductions in both fat mass and fat free mass (Pourhassan, Bosy-Westphal, Schautz, Braun, Gluer, and Muller 2014;Wadstrom, Muller-Suur, and Backman 1991), and thus may exacerbate the progression of sarcopenia and further impair physical function. Therefore, a current challenge is finding ways to minimize the loss of fat-free mass that typically occurs during weight loss interventions targeting obese, older adults. Despite the promise of DR for improved physical function, few clinical trials have been conducted to support the efficacy of DR alone in obese, older adults. Jensen et al. examined changes in physical function after a three month dietary weight loss program for obese older women.(Jensen, Roy, Buchanan, and Berg 2004) At follow up, participants achieved a significant reduction in body weight and body composition parameters, in both fat and fat-free mass, and overall physical performance, as measured by a battery of physical tasks including 400-meter walk and stair climb, improved significantly. In line with these findings, self-reported physical functioning also improved significantly. In a one-year randomized controlled trial examining DR weight loss alone, exercise alone, and weight loss plus exercise compared to an educational control group, significant benefits related to physical function were found for all intervention groups.(Villareal, Chode, Parimi, Sinacore, Hilton, Armamento-Villareal, Napoli, Qualls, and Shah 2011) Although the weight loss plus exercise group showed the greatest improvements, the DR weight loss only group performed significantly better than the control group on measures of physical function.

Based on the findings of these studies, DR alone appears to be effective for improving physical functioning levels in obese older adults. More research is needed as the use of DR in older adult populations remains an area of significant debate due to concerns about lean muscle loss following DR. Limited evidence demonstrates that changes in fat mass following intentional weight loss may be more closely related to change in physical function compared to changes in lean mass.(Santanasto, Glynn, Newman, Taylor, Brooks, Goodpaster, and Newman 2010) Thus, reductions in body fat and change in body composition may be key physiological changes leading to improved physical function in this group. Importantly, little is known regarding the effects of DR on changes in physical

function among healthy or overweight older adults, thus DR should be limited to obese older adults until this is better understood.

2.4.2 Lifestyle (Exercise)—To date, physical exercise is the only intervention consistently demonstrated to attenuate functional decline among older adults.(Brown, Sinacore, Ehsani, Binder, Holloszy, and Kohrt 2000;Cress, Buchner, Questad, Esselman, deLateur, and Schwartz 1999;Miszko, Cress, Slade, Covey, Agrawal, and Doerr 2003;Nelson, Layne, Bernstein, Nuernberger, Castaneda, Kaliton, Hausdorff, Judge, Buchner, Roubenoff, and Fiatarone Singh 2004;Pahor, Blair, Espeland, Fielding, Gill, Guralnik, Hadley, King, Kritchevsky, Maraldi, Miller, Newman, Rejeski, Romashkan, and Studenski 2006) Regardless of dependent outcome, most studies in older adults show some degree of benefit to exercise when based on changes in the mean score of a given performance metric. However, these benefits are not observed in all individuals and the change in performance is quite variable.(Kohrt, Malley, Coggan, Spina, Ogawa, Ehsani, Bourey, Martin, III, and Holloszy 1991) A variety of participant-specific factors may limit gains in functional performance. For example, Manini et al. recently reported that obesity attenuated exercise-induced improvements in physical function among older adults in the Lifestyle Interventions for Independence Pilot Study.(Manini, Newman, Fielding, Blair, Perri, Anton, Goodpaster, Katula, Rejeski, Kritchevsky, Hsu, Pahor, and King 2010) In the same cohort, Buford et al. observed that participants who took ACE inhibitors derived greater physical benefit from the exercise than non-users, independent of obesity status. (Buford, Manini, Hsu, Cesari, Anton, Nayfield, Stafford, Church, Pahor, and Carter 2012) Importantly, each of these findings was independent of differences in confounding characteristics as well as the volume of exercise performed. Accordingly, phenotype (i.e. obesity) and medication use each had significant yet independent influences on the responsiveness of the participants to training. These findings suggest that exercise may be necessary, but insufficient, for preserving physical function and preventing disability among many older adults.(Keysor and Brembs 2011) Consequently, alternative or adjuvant strategies appear necessary to optimize the functional benefits of exercise. Table 1 summarizes the results of major lifestyle intervention trials for improving walking speed in mobility-limited older adults (defined by walking speed of < 1.0 m/s).

2.4.3 Smart and Connected Technologies—Long-term maintenance of lifestyle interventions can be difficult. The rapid pace of sensor and mobile technology along with recent advances in machine learning and intelligent system techniques have provided new opportunities for improving older adults' health and well-being through innovative smart and connected health solutions, such as real-time monitoring of mobility information, temperature and pulse information over time. (Rashidi and Mihailidis 2013;van, Kort, Rutten, and Duijnstee 2011) Today, even most smart phones are equipped with various sensors such as accelerometer, gyroscope, proximity sensor, and global positioning system (GPS), which can be used for detecting user activity and mobility. Additionally, recent advances in epidermal electronics and Micro-Electro-Mechanical Systems or MEMS technology promise a new era of health-related sensor technology that will allow for capturing temperature and pulse information. Furthermore, the Internet of things (IoT) (Hoy 2015) will allow for everyday objects to be sensed and controlled remotely, which will

provide many additional opportunities for healthy aging, e.g. by detecting and recognizing ADLs and IADLs (Bookman, Harrington, Pass, and Reisner E. 2007) in older adults as a daily measure of their cognitive and physical function. These technologies, when paired with lifestyle intervention hold great promise for informing older adults about their own adherence to recommended/prescribed lifestyle strategies in their daily lives.

Already the concept of “aging in place” has prompted interest in real time monitoring of physical and cognitive health of older adults via “smart homes.” (Rantz, Skubic, Koopman, Alexander, Phillips, Musterman, Back, Aud, Galambos, Guevara, and Miller 2012;Rashidi, Cook, Holder, and Schmitter-Edgecombe 2011) A smart home is a regular home that has been augmented with various sensors and actuators. For example, smart homes have been used for monitoring falls in older adults using ambient motion sensors, pressure sensors placed in floor tiles, as well as floor vibration detection through audio analysis (Alwan, Rajendran, Kell, Mack, Dalal S, Wolfe, and Felder 2006). Some researchers also have investigated providing interventions and means for overcoming physical limitations, e.g. by integrating assistive robots within the environments. (Graf, Heyer, Klein, and Wallhoff 2013)

Large data sets collected from smart and connected health solutions, often transmitted wirelessly, poses many unique data analysis challenges due to its inherent complexity and size. Advanced machine learning and other computational data analysis techniques (Bishop 2006) can be used to transform data into actionable knowledge. For example, abnormal mobility patterns can be extracted from longitudinal raw accelerometer data to identify current and potential future mobility complications. Additionally, it is possible to obtain valuable knowledge about the environment, one’s habits, activities, emotional well-being, as well as cognitive and physical health status over time.

This data from ambient and wearable sensors and analyzing it using advanced computational techniques (Bishop 2006) promises a new generation of health monitoring solutions for the older adults. The extracted knowledge will be used to inform the healthcare providers to enable them to provide better care and empower the elderly and their family members to interact with a wealth of knowledge in an interactive fashion using customizable interfaces. Ultimately, it will facilitate targeted initiation of intervention and preventive measures by using a cost effective and time saving method. (Rashidi and Mihailidis 2013)

2.4.4 Cognitive Training—While lifestyle interventions using physical exercise and diet have been found to attenuate declines in physical function and health, interventions aimed at slowing or preventing age-related decline in thinking and memory skills also hold promise for improving physical function.(Ball, Berch, Helmers, Jobe, Leveck, Marsiske, Morris, Rebok, Smith, Tennstedt, Unverzagt, and Willis 2002;Ball and Owsley 1993;Marsiske, Dzierzewski, Thomas, Kasten, Jones, Johnson, Willis, Whitfield, Ball, and Rebok 2013;Rebok, Ball, Guey, Jones, Kim, King, Marsiske, Morris, Tennstedt, Unverzagt, and Willis 2014) These cognitive abilities play an important role in functional decline in older adults, specifically related to fall injuries, loss of independence, and hospitalization. Cognitive training interventions typically involve computerized “games” aimed at progressively training specific cognitive skills (e.g., working memory, attentions, etc.) using

a series of challenging tasks. Recent years have seen a proliferation of marketed cognitive training tasks available to older adults. While the validity of many of the products remain untested, the science of cognitive training has proven effective in laboratory settings across a number of large clinical trials (e.g., NIA-funded ACTIVE study).(Rebok, Ball, Guey, Jones, Kim, King, Marsiske, Morris, Tennstedt, Unverzagt, and Willis 2014) The ACTIVE study showed significant improvement in driving performance and training measures lasting as long as ten years after the initial training targeting processing speed and attention in over 1500 older adults.(Rebok, Ball, Guey, Jones, Kim, King, Marsiske, Morris, Tennstedt, Unverzagt, and Willis 2014) Unfortunately, many other cognitive training measures have failed to demonstrate this level of transfer to real-world tasks, with effects limited to the specific training tasks.(Li, Li, Li, Li, Wang, and Zhou 2011;Papp, Walsh, and Snyder 2009;Reijnders, van, and van 2013) Thus, future work aimed at enhancing the effectiveness of cognitive training will be important for maximizing it effectiveness in preventing functional decline. Regardless, these methods hold great promise for enhancement of declining cognitive function in older adults. One area of emerging investigation is that of home-based cognitive training using gamified platforms (Edwards, Valdes, Peronto, Castora-Binkley, Alwerdt, Andel, and Lister 2015), which shows evidence of enhancing targeted cognitive functions and transferring to IADLs like driving (Ross, Edwards, O'Connor, Ball, Wadley, and Vance 2015). Such findings more broadly support the concept of deploying home based interventions, especially in computer-assisted and gamified forms.

2.4.5 Exergaming: Combining smart technologies, exercise, and cognitive stimulation—One area of intervention that may combine lifestyle/exercise and cognitive interventions is that of video games and exergames (i.e., video games in which the user engages the gaming interface through the use of physical activity). (Bamidis, Vivas, Styliadis, Frantzidis, Klados, Schlee, Siountas, and Papageorgiou 2014) Exergames hold appeal as an intervention delivery mechanism because they are widely available off-the-shelf, are relatively low cost (legacy/older systems can be deployed with an existing television, can obtained for under $200 US), and can be placed in home and congregate environments with essentially no redesign/retrofitting. In addition, there is clear evidence that older adults can adhere to long-term (e.g., 3 month) home-based interventions while maintaining and improving high levels of engagement. (Belchior, Marsiske, Sisco, Yam, and Mann 2012) Video games without exercise have been shown to improve executive and cognitive control, and selective attention in older adults. (Anguera, Boccanfuso, Rintoul, Al-Hashimi, Faraji, Janowich, Kong, Larraburo, Rolle, Johnston, and Gazzaley 2013;Basak, Boot, Voss, and Kramer 2008;Belchior, Marsiske, Sisco, Yam, and Mann 2012) Exergames are a broad category, and can range from simple seated tasks of dexterity and eye-hand coordination (e.g., tennis, golf, bowling, shooting) through full-body engagement using sensor/force plate/accelerometer technology (e.g., gamified “coaches” to encourage walking, running, stretching, yoga). There is evidence that, via engaging in exergames, middle aged and older adults can improve cardiovascular risk indices, energy expenditure, walk time, and balance. (Agmon, Perry, Phelan, Demiris, and Nguyen 2011;Guderian, Borreson, Sletten, Cable, Stecker, Probst, and Dalleck 2010;Studenski, Perera, Hile, Keller, Spadola-Bogard, and Garcia 2010) A secondary benefit of video games seems to be mood improvement (Rosenberg, Depp, Vahia, Reichstadt, Palmer, Kerr, Norman, and Jeste 2010;Studenski,

Perera, Hile, Keller, Spadola-Bogard, and Garcia 2010), with reduced levels of subsyndromal depression likely to further promote engagement in subsequent health behaviors. To date, benefits of exergaming for cognitive enhancement and/or reducing functional limitations have been relatively understudied, but initial evidence suggests both fitness and broad cognitive improvements with custom games. (Bamidis, Vivas, Styliadis, Frantzidis, Klados, Schlee, Siountas, and Papageorgiou 2014;Maillot, Perrot, and Hartley 2012) Thus, the exergaming environment holds great promise as a cost-effective implementation of widespread, community-based interventions to impact physical and cognitive health. Risks associated with unmonitored participation (e.g., increase probability of injury, social isolation) must also be studied.

2.4.5 Non-Invasive Brain Stimulation—While all human behaviors can be considered to require changes in brain activity (e.g., remembering a phone number, planning to walk across a room, etc.), a variety of intervention techniques specifically aim to modulate activity in the brains a means to enhance brain function. This general class of intervention can be referred to as “non-invasive brain stimulation,” and parsed further into direct and indirect stimulation methods. Transcranial direct current stimulation (tDCS) is one example of direct non-invasive brain stimulation with potential for impact on function in older adults. tDCS involves application of a weak electrical current through electrodes placed on the scalp.(Kessler, Minhas, Woods, Rosen, Gorman, and Bikson 2013;Minhas, Bikson, Woods, Rosen, and Kessler 2012;Woods, Hamilton, Kranjec, Minhaus, Bikson, Yu, and Chatterjee 2014) The resulting electrical field directly stimulates underlying cortical and subcortical tissue in the brain.(Bikson, Datta, and Elwassif 2009;Bikson, Name, and Rahman 2013) Using specific stimulation parameters, this technique can change the resting membrane potential of stimulated neurons, resulting in a net increase or decrease in the firing rate of these neurons.(Batsikadze, Moliadze, Paulus, Kuo, and Nitsche 2013;Nitsche, Muller-Dahlhaus, Paulus, and Ziemann 2012;Nitsche and Paulus 2011) Effects of stimulation last beyond the period of stimulation and facilitate neuroplastic response of the stimulated tissue. (Nitsche and Paulus 2000) When paired with neuro-behavioral interventions, such as motor skill training or cognitive training, tDCS can enhance the effectiveness and duration of paired interventions.(Berryhill and Jones 2012;Bolognini, Pascual-Leone, and Fregni 2009;Nitsche 2002;Nitsche, Schauenburg, Lang, Liebetanz, Exner, Paulus, and Tergau 2003;Rosen, Ramkumar, Nguyen, and Hoeft 2009) Furthermore, tDCS has shown effectiveness in reducing chronic pain and symptoms of depression, factors contributing to decreased mobility in older adults.(Kaye, Baluch, and Scott 2010) Thus, tDCS may serve as either an independent and/or adjunctive therapy that has the potential to alleviate factors limiting mobility and improve interventions aimed at enhancing physical and cognitive function in older adults.

2.4.6 Pharmaceutical—Pharmaceutical interventions represent another form of therapeutic strategy with significant promise for enhancing physical function and mobility in older adults. In recent years, studies have evaluated the use of pharmacologic agents for the prevention and treatment of age-related sarcopenia and functional decline. This approach has the benefit of requiring minimal effort on the part of patients, an important point given that the initial effort required to begin an intervention program is a primary barrier to

lifestyle-based treatments.(Lees, Clarkr, Nigg, and Newman 2005) Yet, evidence from studies evaluating the effects of mono-modal pharmacologic strategies on physical function have been mixed at best. Despite these equivocal findings, the potential use of pharmacotherapy for improving physical function in older adults should not be abandoned as the efficacy of such medications may be at least partially dependent on the lifestyle habits of the individual. For example, the popular drug metformin could potentially improve function and reduce frailty risk in older adults with type 2 diabetes.(Wang, Lorenzo, and Espinoza 2014) While the underlying mechanisms of metformin remain to be fully elucidated, biologically, it makes sense that one of the major proposed mechanism of metformin is to activate the enzyme AMP- activated protein kinase (AMPK), a key sensor of cellular energy status,(Zhou, Myers, Li, Chen, Shen, Fenyk-Melody, Wu, Ventre, Doebber, Fujii, Musi, Hirshman, Goodyear, and Moller 2001) which can further suppress m-TOR pathway. It has also been suggested that metformin recapitulates the effects of dietary restriction.(Onken and Driscoll 2010)

Others have proposed that exercise may stimulate adaptations to pharmaceuticals that are not observed in response to the drug alone.(Booth and Laye 2010) Findings from pre-clinical models provide initial support for this approach. For example, despite showing no effect when given to mice in isolation, an oral PPARδ agonist increased exercise tolerance when given in conjunction with an exercise-training regimen.(Narkar, Downes, Yu, Embler, Wang, Banayo, Mihaylova, Nelson, Zou, Juguilon, Kang, Shaw, and Evans 2008) Thus, the strategy of combining potentially beneficial medications with chronic exercise or other non-invasive interventions may be more efficacious than either intervention alone.

The use of some pharmaceutical agents as adjunctive therapies to exercise may enhance the effectiveness of each intervention. In particular, interest has been high regarding the potential utility of ACE inhibitors as therapeutic agents for preventing sarcopenia and functional decline.(Cranney 2007;Sumukadas, Struthers, and McMurdo 2006) Epidemiologic evidence from the Women's Health and Aging Study and the Systematic Assessment of Geriatric drug use via Epidemiology Study indicated that, compared to non-users, older adults using ACE inhibitors displayed attenuated declines in walking speed and fewer limitations in ADLs.(Gambassi, Lapane, Sgadari, Carbonin, Gatsonis, Lipsitz, Mor, and Bernabei 2000;Onder, Penninx, Balkrishnan, Fried, Chaves, Williamson, Carter, Di, Guralnik, and Pahor 2002) Other epidemiologic and animal evidence suggests that these outcomes may have been due to attenuated declines in skeletal muscle mass and strength. (Carter, Marzetti, Leeuwenburgh, Manini, Foster, Groban, Scarpace, and Morgan 2012;Di, van de Poll-Franse LV, Onder, Kritchevsky, Newman, Harris, Williamson, Marchionni, and Pahor 2004;Onder, Penninx, Balkrishnan, Fried, Chaves, Williamson, Carter, Di, Guralnik, and Pahor 2002) Despite these promising findings, the results of subsequent RCTs have been mixed regarding the impact of ACE inhibitor use on functional decline.(Cesari, Pedone, Incalzi, and Pahor 2010;Hutcheon, Gillespie, Crombie, Struthers, and McMurdo 2002;Sumukadas, Witham, Struthers, and McMurdo 2007;Zi, Carmichael, and Lye 2003) Thus, the benefits of ACE inhibitors on functional outcomes may be limited when utilized as an isolated treatment. However, Buford et al. recently reported that older adults (age > 70 years) who took ACE inhibitors displayed significant improvements in physical function in response to a 12-month exercise program compared to peers who did not take these

medications.(Buford, Manini, Hsu, Cesari, Anton, Nayfield, Stafford, Church, Pahor, and Carter 2012) These data demonstrate the potential impact of this adjunctive strategy in preserving function and mobility in older adults, and helps to highlight the value of adjunctive intervention strategies.

2.4.7 Nutraceutical—Natural compounds may also represent an important source of potential new interventions for older individuals. Similar to pharmaceutical agents, these compounds would likely be most effectively used as an adjunctive treatment with hypocaloric diets, behavioral self- management programs, physical exercise, or cognitive interventions. Estimates indicate that Americans spend over 12 billion dollars per year on nutritional supplements (Blanck, Khan, and Serdula 2001), and sales of these products are projected to continue to increase by approximately 10% per year. (Goldman 2001) Unfortunately, the vast majority of these products have little supportive data from well-designed randomized trials.(Bray 2008) Given the increasing popularity of these products among middle-age and older adults,(Mehlman, Binstock, Juengst, Ponsaran, and Whitehouse 2004) studies are needed to examine their safety and efficacy.

Among the various compounds, resveratrol, a polyphenol found in the skins of grapes and red wine, may have unique promise to improve age-related functional decline because it appears to activate similar pathways as DR without leading to muscle loss. These beneficial biological effects have been demonstrated across multiple species, and have been associated with improvements on a variety of functional tasks and health-span measures. In several species, resveratrol has even been found to extend healthy lifespan.(Baur, Pearson, Price, Jamieson, Lerin, Kalra, Prabhu, Allard, Lopez-Lluch, Lewis, Pistell, Poosala, Becker, Boss, Gwinn, Wang, Ramaswamy, Fishbein, Spencer, Lakatta, Le, Shaw, Navas, Puigserver, Ingram, de, and Sinclair 2006;Greer and Brunet 2009;Long, Gao, Sun, Liu, and Zhao-Wilson 2009) These findings are not unexpected given that resveratrol has been found to activate a wide variety of targets, and produces broad, systemic effects that are very similar to caloric restriction,(Marzetti, Wohlgemuth, Anton, Bernabei, Carter, and Leeuwenburgh 2009;Testa, Biasi, Poli, and Chiarpotto 2014) the only method to date that has been found to increase healthy lifespan in multiple species. The critical question of whether resveratrol works in humans and by what mechanisms, however, has not been answered, and very few studies have examined the effects of resveratrol in older adults.

2.4.8 Hormonal—There are a multiple hormonal approaches that may lead to improvements in physical function and mobility in at risk older adults, including testosterone, estrogen, oxytocin, DHEA, and growth hormone supplementation.

At present, there is not conclusive evidence to support one approach over another. Below we highlight recent studies related to novel administration of the hormone oxytocin to the administration of the hormone oxytocin, which can be delivered to the human brain by the use of nasal spray, tapping into central functions.(Born, Lange, Kern, McGregor, Bickel, and Fehm 2002) A number of experimental studies using acute or chronic oxytocin treatment have revealed intriguing effects on a wide spectrum of processes related to health, cognition, and psychosocial functioning.(Ebner, Maura, Macdonald, Westberg, and Fischer 2013) In particular, going beyond its classic role in labor and lactation (Pedersen 1997), the hormone

oxytocin has modulatory effects on higher-order cognitive processing (Meyer-Lindenberg, Domes, Kirsch, and Heinrichs 2011) and effects on the cardiovascular system in that it has been found to improve the vasculature, possibly in interaction with sex hormones (Gimpl and Fahrenholz 2001), and benefits weight control and insulin sensitivity.(Zhang, Wu, Chen, Chen, Xu, Wu, and Cai 2013) In addition, there is increasing evidence of pain amelioration, improved wound healing, and anti-inflammatory effects associated with oxytocin.(Clodi, Vila, Geyeregger, Riedl, Stulnig, Struck, Luger, and Luger 2008) The few existing studies on oxytocin administration in human aging provide first evidence that increased oxytocin levels ameliorate age-related physical decline and reduce fatigue (Barraza, Grewal, Ropacki, Perez, Gonzalez, and Zak 2013) as well as benefit psychosocial functioning.(Campbell, Ruffman, Murray, and Glue 2014;Ebner, Horta, Lin, Feifel, Fisher, and Cohen 2015) Thorough examination of oxytocin's cardiovascular and anti-inflammatory effects in aging constitutes a cutting-edge avenue for future research on interventions promoting physical function and mobility.

2.5 Statistical Considerations in Evaluating Interventions to Enhance Physical Function

Clinical trials are becoming increasingly expensive while the success rate remains low. (DiMasi, Hansen, and Grabowski 2003;Walker and Newell 2009) This is also true for evaluating interventions to enhance function in older adults. The success rate could be improved with more efficient clinical trial designs. Below we review the potential of adaptive designs to improve quality, speed and efficiency of decision making in clinical trials.

Group sequential designs became practical in the final quarter of the 20th century.(Jennison and Turnbull B.W. 2000) Such designs permit early termination of the study for efficacy or futility with flexibility to alter number and spacing of interim analyses. Group sequential designs with unblinded sample size re-estimation were introduced in the new millennium. (Cui, Hung, and Wang 1999;Lehmacher and Wassmer 1999;Proschan and Hunsberger 1995) Currently, many adaptive designs have been developed to use accumulating data to guide the subsequent modification of the study design without undermining the validity and integrity of the trial. Adaptions can include adding or dropping treatment arms/doses, modifying treatment allocation ratios, switching between non-inferiority and superiority hypothesis, changing in study population and trial phase. For example, an enrichment design attempts to reduce trial costs by targeting from the original heterogeneous study population a patient subpopulation that might optimally benefits from the treatment; (Wu, Tu, and He 2014) a seamless design combines the phase II trial and the confirmatory phase III trial, which improves efficiency through joint analysis of data and eliminates the gap between the two phases. (Wu, Wang, and Yang 2010)

Statistics will also play an important role in dealing with the challenges posed by two major changes in health care. The first one is *connected health*, a model for remote care or self-care through computer and cellular technologies, which allow patients to receive healthcare information electronically and enable clinicians to monitor patients' conditions remotely. Due to the increasingly widespread availability of Internet access and wellness devices, connected health has been flourishing into a multi-billion market. (Pai A 2014) The second

revolution is "*big data*", which refers to a massive volume of both structured and unstructured data that traditional database and software techniques are inadequate. Challenges include analysis, capture, curation, search, sharing, storage, transfer, visualization, and information privacy. Major factors driving this approach are the skyrocketing cost of medical care (17.9% of US GDP in 2012) and the increasing emphasis on evidence-based medicine. (Kayyali B, Knott D, and Van Kuiken S 2013) Modern digital and mobile technologies make it much easier to collect information from patients on a large-scale, which has resulted in a vast amount of medical data accumulating at numerous medical facilities throughout the world. Tremendous additional values can be uncovered if medical data from different sources, including individual patients, can be streamed together and made readily available. The resulting big data will give new, expanded meanings to connected health; it will serve as a nourishing base for new medical/ statistical/social technologies that connect patients, medical researchers, clinical practitioners, and health and pharmaceutical companies, in a concerted effort to lower medical cost, enable large-scale studies, and encourage preventive medicine at a community level.

3. Conclusions

In this review, we have highlighted the importance of developing a consensus definition of multi-faceted construct of "Successful Aging," in order to advance aging research and the development of strategies that promote independence in aging populations. Our theoretical reflections in this paper are in line with Bowling and Dieppe (2005), who argued that successful aging "needs to be viewed not only multidimensionally, but as an ideal state to be aimed for, and the concept itself should be placed on a continuum of achievement rather than subject to simplistic normative assessments of success and failure."

Despite the inherent difficulties in defining this multidimensional phenomenon, we believe that it is worth the effort to move toward this objective for the following reasons. First, in the absence of an accepted definition and commonly agreed on metrics, a diverse array of measures have been used to assess various dimensions of this construct. This has made it difficult to compare findings across studies. Second and perhaps most important, the adoption of a consensus definition that takes into account factors from multiple domains could provide much value for older adults themselves. Rather than classifying successful aging based on function within a single domain, a broader definition can provide critical information on level of function within and across multiple domains. As discussed in the current paper, interventional approaches can be targeted to improving function within domains in which an individual's functional level is lower relative to their functioning in other domains. Given the strong inter-relationship of functioning level across many domains (e.g., cognitive and physical function) that comprise this construct, an added benefit of the type of interventional approaches discussed in the current paper is that they are likely to lead to functional improvements in domains not specifically targeted.

To achieve the ambitious objective of developing a consensus definition of successful aging, an inter-disciplinary approach is needed, as adopted in the current paper, in which experts within each domain provide evidence-based recommendations regarding markers of successful aging within their domain. In this manner, scientists from multiple domains work

together towards a shared goal of having evidence-based markers of successful aging. Currently, there appears to be a sufficient body of evidence to move towards such a consensus definition on markers of successful aging within the physical domain. Evidence from multiple disciplines has converged on the use of common outcome measures, specifically walking speed (i.e., distance completed divided by time) and performance on a standardized measure of physical function (i.e., SPPB), as excellent surrogate markers of both functional ability and health status in older adults. By extension, we believe the evidence is now sufficient to propose that walking speed and performance on the SPPB should be considered surrogate markers of successful aging within the physical domain.

There remains a strong need, however, for clear and accepted criteria to assess functioning within other domains of successful aging. Once accepted definitions, metrics, and measures to evaluate such constructs are agreed upon, the effectiveness of treatment approaches targeting these outcomes can be better assessed. An increased understanding of the contribution of function within each of these domains would not only enhance our ability to define successful aging, but can also lead to the development of future interventions designed to improve mobility and physical function or attenuate declines in physical function in older adults.

To this end, we have provided an overview of specific health conditions, behavioral factors, and biological mechanisms that have been directly linked with physical function, and therefore appear to play an important role in contributing to declines in mobility and physical function during aging. We have also reviewed the role of promising interventions that can enhance mobility and physical function or attenuate functional decline in older adults. A continuing focus on interdisciplinary research is recommended to help move towards an accepted definition of successful aging that can be used to promote independence in the growing population of older adults.

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Highlights

- A consensus definition is needed for the multi-faceted construct of "Successful Aging" to advance the development of strategies that promote independence in an aging population.
- Once accepted definitions, metrics, and measures to evaluate dimensions of the construct of Successful Aging are agreed upon, the effectiveness of treatment approaches targeting these outcomes can be better assessed.
- A number of health conditions, behavioral factors, and biological mechanisms have been strongly linked to the pathogenesis of functional decline during aging.
- Few therapies have been identified to improve functional performance in human aging, and there are currently no FDA-approved medications for the treatment of functional decline in older adults.
- Empirically-supported treatments are urgently needed to improve mobility and prevent disability in older adults.

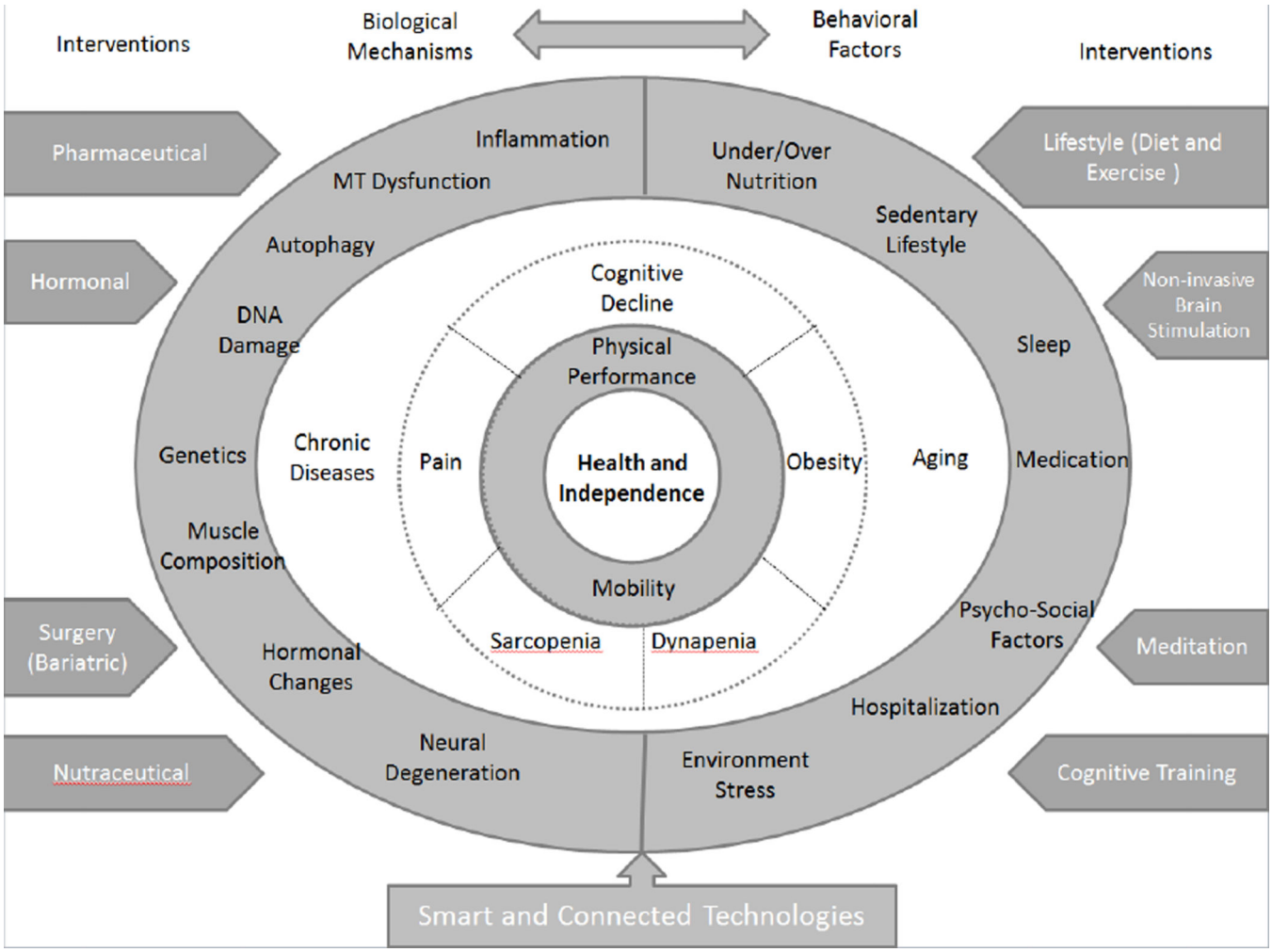

Figure 1.

The conceptual model illustrates important factors that can affect physical function during aging and ultimately maintenance of health and independence in older adults. Biological mechanisms and behavioral factors associated with reductions in physical function are illustrated in the outer ring. Specific health conditions that contribute to reductions in mobility and physical performance during aging are displayed in the middle ring. These conditions include but are not limited to cognitive decline, dynapenia, obesity, pain, and sarcopenia. Promising interventions for enhancing mobility and physical function, which target one or more biological mechanisms, behavioral factors, or health conditions contributing to functional decline, are shown in the outer edges. The ultimate goal is maintenance of health and independence, displayed in the inner most ring, through enhancement of mobility and/or physical function. This figure is not intended to be exhaustive but rather to highlight key biological mechanisms, behavioral factors, and health conditions that can contribute to functional decline in older adults, as well as promising interventions to attenuate declines in mobility and physical function during aging. MT: Mitochondria.

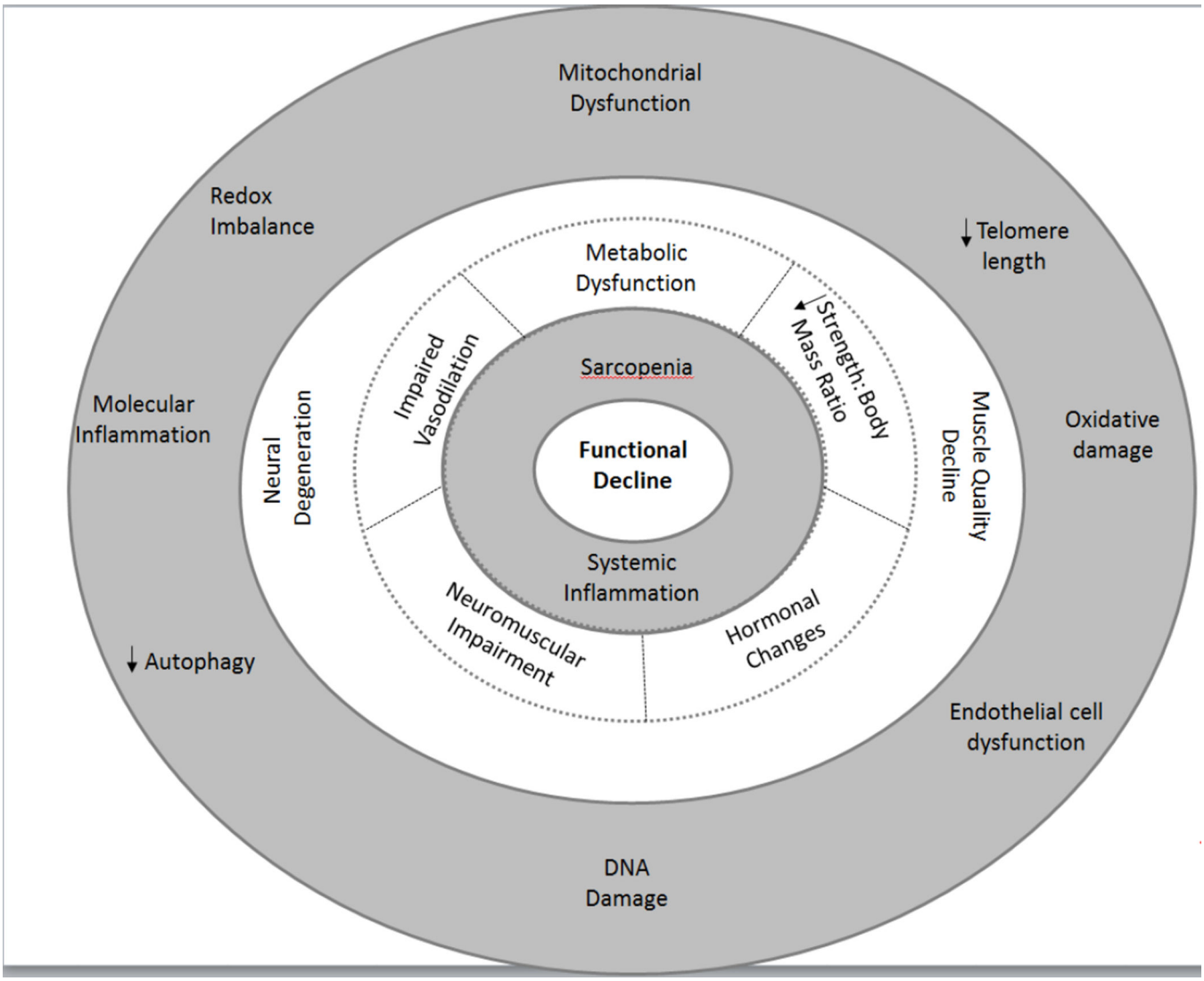

Figure 2.

The pathophysiology model illustrates key biological mechanisms that contribute to functional decline. Cellular mechanisms are displayed in the outer ring, tissue specific mechanisms are displayed in the next ring, and systemic mechanisms are displayed in the two inner rings.

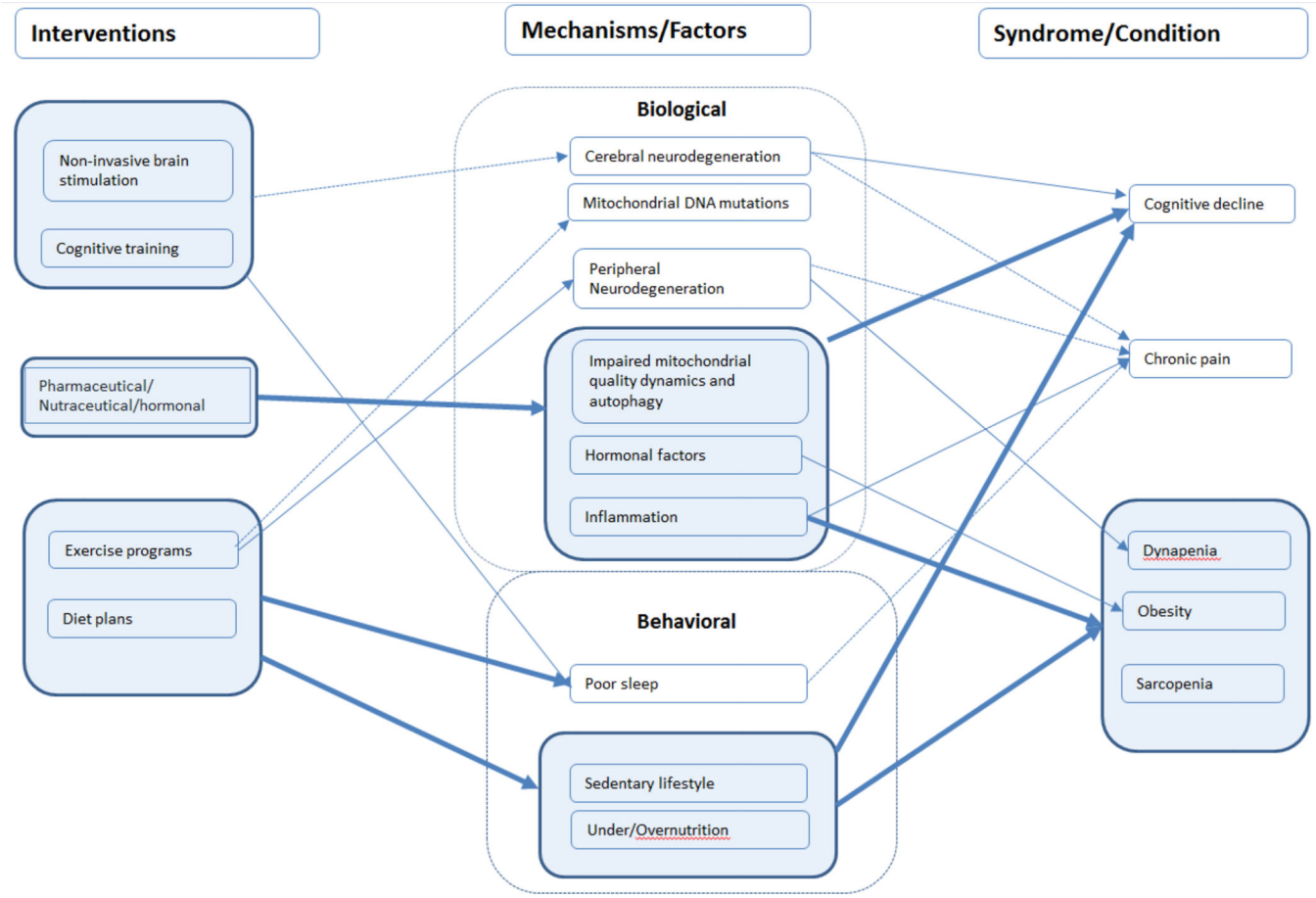

Figure 3.

The intervention model displays the effects different interventions have on biological and behavioral factors contributing to functional decline, as well as the interconnection between biological and behavioral factors with health conditions known to contribute to functional decline. Connections that have clear empirical support are displayed with a solid line, and theoretical connections are displayed with a dotted line.

Table 1

Effects of Lifestyle Interventions on Change in Walking Speed in Mobility-Limited Older Adults.

Study	N	Age Range (years)	Intervention Type	Length (weeks)	Walking Speed Measure	Baseline Walking Speed (m/s)	Δ in Walking Speed Pre-to Post-intervention (m/s)	P-value
Barnett et al. (2003)	83	≥60	PA	6	6-m Walk	0.95±0.3	0.03	n/a
Beling et al. (2009)	12	≥65	PA	12	GAITRite	0.88±0.2	0.07	n/a
Chmelo et al. (2015)	40	≥65	PA	20	400-m Walk	0.81±0.16	0.08	0.001
Fiatarone et al. (1994)	25	≥70	PA	10	6-m Walk	0.51±0.04	0.04	<0.01
Freiberger et al. (2012)	64	>70	PA	10	6-m Walk	0.98±0.18	0.02	n/a
Gine-Garriage et al. (2010)	26	70–90	PA	12	8-m Walk	0.82±0.04	0.12	n/a
Lazowski et al. (1999)	35	≥65	PA	16	7-m Walk	0.69±0.28	0.04	n/a
Manini et al. (2010)	424	70–88	PA	52	400-m Walk	0.88±0.18	0.04	n/a
Phillips et al. (2010)	213	≥65	PA	57	400-m Walk	0.86±0.18	0.08	0.03
Rosendahl et al. (2006)	45	≥65	PA	24	2.4-m Walk	0.35±0.17	0.05	0.02
Van Swearingen et al. (2011)	47	≥65	PA	12	4-m Walk	0.88±0.13	0.21	<0.001
Van Swearingen et al. (2009)	47	≥65	PA	12	4-m Walk	0.88±0.13	0.14	<0.001
Villareal et al. (2006)	27	≥65	CR+PA	26	25ft Walk	0.84±0.15	0.08	0.05
Villareal et al. (2011)	107	≥65	CR	52	25ft Walk	0.68±0.12	0.08	ns
			PA			0.79±0.19	0.14	ns
			CR+PA			0.82±0.17	0.28	0.01

CR= Caloric Restriction; PA= Physical Activity; m/s = meters per second; Δ= change; ft = feet. Change data are defined as the follow-up minus the baseline value.