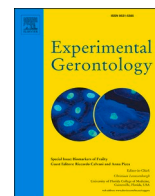




Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review



Innovations in Geroscience to enhance mobility in older adults

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ARTICLE INFO

Editor name: Cheryl Conover

Keywords:

Age
Mobility
Obesity
Sarcopenia
Healthspan
Longevity

ABSTRACT

Aging is the primary risk factor for functional decline; thus, understanding and preventing disability among older adults has emerged as an important public health challenge of the 21st century. The science of gerontology – or geroscience – has the practical purpose of “adding life to the years.” The overall goal of geroscience is to increase healthspan, which refers to extending the portion of the lifespan in which the individual experiences enjoyment, satisfaction, and wellness. An important facet of this goal is preserving mobility, defined as the ability to move independently. Despite this clear purpose, this has proven to be a challenging endeavor as mobility and function in later life are influenced by a complex interaction of factors across multiple domains. Moreover, findings over the past decade have highlighted the complexity of walking and how targeting multiple systems, including the brain and sensory organs, as well as the environment in which a person lives, can have a dramatic effect on an older person’s mobility and function. For these reasons, behavioral interventions that incorporate complex walking tasks and other activities of daily living appear to be especially helpful for improving mobility function. Other pharmaceutical interventions, such as oxytocin, and complementary and alternative interventions, such as massage therapy, may enhance physical function both through direct effects on biological mechanisms related to mobility, as well as indirectly through modulation of cognitive and socioemotional processes. Thus, the purpose of the present review is to describe evolving interventional approaches to enhance mobility and maintain healthspan in the growing population of older adults in the United States and countries throughout the world.

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<https://doi.org/10.1016/j.exger.2020.111123>

Received 17 July 2020; Received in revised form 15 October 2020; Accepted 16 October 2020

Available online 22 October 2020

0531-5565/© 2020 Published by Elsevier Inc.

Such interventions are likely to be greatly assisted by technological advances and the widespread adoption of virtual communications during and after the COVID-19 era.

1. Introduction

While prolongation of life remains an important public health goal, of even greater significance is that extended life should involve preservation of the capacity to live independently and to function well (Katz et al., 1983). The field of geroscience seeks to understand the genetic, molecular, and cellular mechanisms that make aging a major risk factor and driver of common chronic conditions and diseases of older people. Interventions targeting the fundamental biology of human aging have the potential to delay, if not prevent, the onset of aging-associated conditions (Kennedy et al., 2014; Ferrucci et al., 2016a; Seals et al., 2016; Seals and Melov, 2014; Justice et al., 2018). The unprecedented growth of the aging population and increasing prevalence of chronic disease has underscored an urgent need for such interventions. If the current trend in aging continues, the number of older persons (aged ≥ 60 years) will nearly triple in size globally, increasing from 673 million in 2005 to almost 2 billion by 2050 (United Nations World Populations Prospects, 2005).

Accordingly, the science of gerontology – or geroscience – has the practical purpose of understanding how aging processes enable diseases and to then apply this knowledge to reduce the emergence and progression of age-related diseases and disabilities. The ultimate goal is to develop feasible, practical, and safe interventions to delay the development of chronic diseases and conditions, while also increasing enjoyment, satisfaction, and quality of life, during the latter stages of an individual's lifespan. (Burch et al., 2014) Interventions that can achieve these objectives may also dramatically lower health care costs.

As we have previously described, (Anton et al., 2015; Nocera et al., 2011) a hallmark of successful aging is mobility, i.e. the ability to move without assistance, which is necessary for the maintenance of basic independent functioning (Katz et al., 1963; Rosow and Breslau, 1966). Additionally, mobility performance (i.e., walking speed) has emerged as a surrogate marker of overall health and functional ability among older adults. (Cesari, 2011) Improvements in usual gait speed predict better

survival and quality of life in older adults (Hardy et al., 2007). In contrast, mobility limitation is associated with more rapid functional decline, reduced quality of life (Forhan and Gill, 2013), as well as hospitalization, nursing home placement, and increased mortality (Hardy et al., 2011; Hoffman et al., 2007; Hoffman et al., 2010; Newman et al., 2006; Forman-Hoffman et al., 2015) (see Fig. 1). For these reasons, understanding and preventing mobility disability among older adults has emerged as one of the most important public health opportunities of the 21st century. Therefore, identification of promising interventions to preserve mobility that can be widely implemented in older adults is a major clinical and public health priority (Branch et al., 1991).

Since our previous review, (Anton et al., 2015) several advances in the field of geroscience have been achieved and are highlighted in this paper. For example, discoveries made in the past few years have illuminated the complex interactions between the brain and the body in affecting changes in mobility with aging. More specifically, the important role that the central and neuromuscular systems have in affecting mobility has spawned a host of new treatment options, such as use of neuro-modulatory adjuvants (e.g., transcranial direct stimulation) to enhance the beneficial effects of physical activity. In line with this, a growing body of research indicates that interventions designed to improve cognitive/emotional function (e.g., oxytocin) also have beneficial effects on mobility and physical function. Thus, it appears virtually impossible to influence an individual's cognitive/emotional function without affecting their physical function, and vice-versa. An increased understanding of biopsychosocial factors that may contribute to functional decline can aid in the development of future interventions designed to improve mobility and function in at-risk older adults. Aided by technological developments, the range of interventions now available has greatly increased in the past five years. Thus, we have expanded our conceptual model to incorporate technology, neural factors, and environmental factors.

Although there is a strong consensus on this goal, there are challenges to developing such interventions as an older adult's mobility and

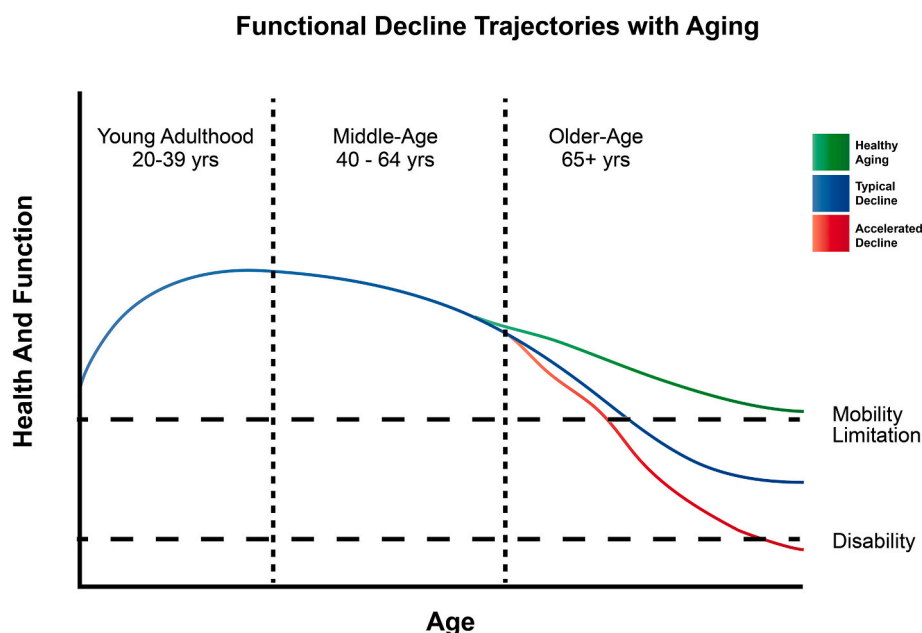


Fig. 1. Functional Decline Trajectories with Aging.

functional level are affected by factors across multiple domains. Moreover, the complex interactions between factors within biological, psychological, and social domains may increase the risk for functional decline and other age-related chronic disease conditions. As such, promising interventions will need to take into account these multifaceted interactions and also recognize that affecting change in one domain can lead to changes in other domains. With this goal in mind, we first review the role of specific biological contributors to functional decline. Next, we describe key behavioral and psychosocial factors that can affect physical function and risk for functional decline in older adults. We then discuss promising interventions from clinical trials that can enhance physical function and mobility, as well as the role of smart and connected technologies in the delivery of these interventions (see Fig. 2). In the final sections, we discuss the importance of preclinical models in guiding intervention selections, statistical considerations in aging research, as well as key strategies to effectively disseminate and implement efficacious interventions in clinical and community settings. (See Fig. 3.)

2. Role of specific biological systems in mobility decline and loss of independence

2.1. Metabolic contributors to mobility decline

The rising prevalence of metabolic syndrome in older adults, a condition diagnosed based on the presence of three or more metabolic risk factors, including abdominal obesity, high triglycerides (TG), low HDL-cholesterol (HDL-C), high blood pressure (BP), and impaired glucose tolerance, correlates with sedentary lifestyles, and poor nutrition habits (Bankoski et al., 2011; Ford et al., 2004; Ford, 2004; Edwardson et al., 2012). Approximately one-third of older adults in the USA are obese; however, nearly 55% of those aged 60 years or older are estimated to have metabolic syndrome (Shin et al., 2018a). Given the aging US population, the disproportionately high prevalence of the metabolic syndrome in older adults is a significant public health concern, as it substantially increases the risk for cardiovascular disease (CVD) (Wilson and Grundy, 2003; Gami et al., 2007; Isomaa et al., 2001; Xanthakis et al., 2015) and is associated with increased all-cause mortality, disability, CVD mortality, myocardial infarction, and stroke (Thomas et al., 2004). Additionally, the metabolic syndrome is associated with impairments in basic activities of daily living, social activities, and lower extremity mobility (United Nations World Populations Prospects, 2005; Baumgartner, 2000).

2.2. Muscular contributors to mobility decline

Aging typically promotes a loss of fat-free mass which parallels the reduction in metabolic rate and energy expenditure, particularly after the age of 50 (Baumgartner, 2000). This age-related muscle loss (i.e.,

sarcopenia) can diminish both the metabolic and mechanical functions of the skeletal muscle, (Bouchard et al., 2011; Sayer et al., 2005) a point of concern since skeletal muscle has the greatest contribution to an individual's metabolic rate (Blondin et al., 2015). In addition to the loss of total muscle mass, the muscle quality also declines with age due to increased fat infiltration within the muscle thus resulting in decreased muscle strength (Delmonico et al., 2009) and power (Tuttle et al., 2012).

After the age of 50, it is noteworthy that adults lose muscle strength (i.e., dynapenia) at a much faster rate, approximately 3–4% year, than they lose muscle mass, approximately 1–2% per year. Therefore, while muscle atrophy and weakness are certainly correlated, the former cannot fully explain lost muscle strength in late-life. Moreover, muscle weakness is a major independent contributor to maintaining physical independence in later life. (Larsson et al., 1979; Jette and Branch, 1981; Guralnik et al., 1995; Murray et al., 1980; Reed et al., 1991; Dannekiold-Samsøe et al., 1984)

2.3. Neuromuscular contributors to mobility decline

It was originally thought that the loss of skeletal muscle mass largely explained the muscle weakness observed in older adults; however, more recent findings suggest that other anatomical and physiological factors also play an important role in muscle weakness. The mechanisms determining loss of muscle strength or power output are related to both neurological and skeletal muscle properties, as it is well known that the output from these sources control muscle force and power production. Within the neuromuscular system, there are several potential mechanisms that may contribute to reductions in strength during aging, including reduced excitatory drive to the spinal motor neurons, reductions in motor neuron discharge rates, impairments in neuromuscular transmission, muscle cell death, muscle protein imbalance, reduced repair/regeneration of muscle cells and impairments in the excitation–contraction (E–C) coupling processes.

Aging in humans has been shown to be accompanied by robust reductions in the population of motor neurons and axon density (Rowan et al., 2012; Lexell, 1997; Tomlinson and Irving, 1977; Kawamura et al., 1977). Between the ages of 60 and 70 there is a ~30% reduction in the number of functional motor units (motor units = motoneuron and innervated muscle fibers) (Stalberg and Fawcett, 1982; Brown et al., 1988; Campbell et al., 1973; Doherty and Brown, 1993) and once the loss of motor units reaches a critical threshold, muscle strength begins to decline (McNeil et al., 2005). The exact underlying mechanisms of exhausted NMJ plasticity and motor neuron cell death remain obscure, but many factors such as deregulated inflammation, autophagy, reduced IGF-1 signaling, oxidative stress, and mitochondria dysfunction have been suggested to drive accelerated loss of muscle mass and function in late life (Aagaard et al., 2010; Hepple and Rice, 2016).

Many factors contribute to a loss of automaticity of walking in older adults. One likely factor is impairment of the communication between

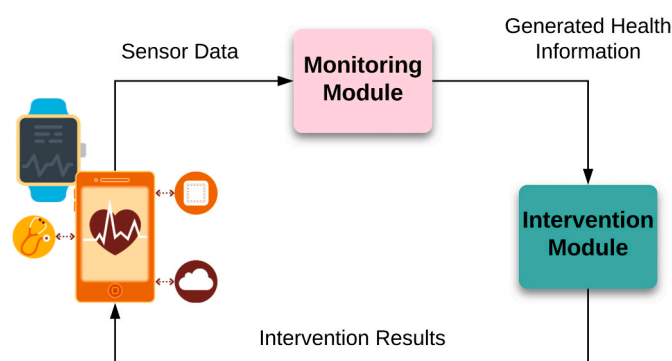


Fig. 2. Technological advancements to facilitate intervention delivery and track adherence.

the nervous system and muscle. Motor neurons innervate their axon terminals to the skeletal muscle fibers to form a neuromuscular junction (NMJ), which allows the presynaptic motor neurons to transmit chemical signals to the post-synaptic muscle fibers, leading to muscle contraction. During most of the adult life, there is considerable plasticity of the NMJ, where surviving motor units expand through collateral axonal sprouting to reinnervate any denervated NMJs (Hepple and Rice, 2016; Spendiff et al., 2016; Rowan et al., 2011). Exhaustion of this plasticity (persistent denervation and failed reinnervation) accelerates muscle atrophy during aging and is associated with movement impairment and functional decline (Rowan et al., 2012; Aare et al., 2016).

Accumulating evidence supports that models of cognitive brain aging may help us understand the decline in walking function in older adults (Clark et al., 2019; Chen et al., 2017; Reuter-Lorenz and Cappell, 2008). Changes in brain structure and function may also contribute directly to loss of automaticity, as well as reduce the capacity for recruiting additional resources to compensate for the loss of automaticity (Reuter-Lorenz and Cappell, 2008; Clark, 2015). Additional research is needed to better understand the major modifiable neural factors that influence control of walking with older age, so that targeted interventions can be designed (Clark et al., 2019).

2.4. Contribution of chronic pain to mobility decline

Chronic pain conditions represent three of the five leading causes of disability in the US, including low back pain, which is the leading cause of disability both in the US and worldwide (Blyth et al., 2019; Disease, G. B.D, et al., 2017). While pain affects individuals throughout the lifespan, older adults are disproportionately impacted (Verhaak et al., 1998). Another important contributor to mobility decline among older adults is movement-evoked pain (MEP). MEP refers to pain that is generated or exacerbated through physical movement or activity, and some evidence suggests that MEP may be driven by different mechanisms than pain at rest (Corbett et al., 2019). Recent findings in middle-aged and older adults with knee pain demonstrated a relationship between MEP and physical performance, highlighting the need to directly measure MEP when assessing functional performance in older adults (Cruz-Almeida

et al., 2017). Thus, one key mechanism through which pain may contribute to functional decline is through activity limitations among older adults (Ward et al., 2019; Rundell et al., 2019; Thakral et al., 2018; Fletcher et al., 2010; Pisters et al., 2012; Rossi et al., 2013; White et al., 2011).

Emerging evidence also suggests that pain may affect aging processes. Indeed, several recent studies suggest that pain is associated with cellular aging. Specifically, a combination of high psychosocial stress and high levels of knee pain were associated with shorter telomeres among middle-aged and older adults (Sibille et al., 2012), and subsequently these authors showed that more severe knee pain was associated with shorter telomeres (Sibille et al., 2017). More recently, chronic pain in older adults has been associated with brain aging (Cruz-Almeida et al., 2019a) and a validated epigenetic measure of aging (Cruz-Almeida et al., 2019b). Thus, the relationship between pain and aging appears to be bidirectional and complex, impacting multiple body systems.

2.5. Role of circadian rhythms in contributing to mobility decline

One area that is gaining recognition for the potential to impact aging processes is circadian rhythms, which are endogenously generated 24 h cycles that can be observed in behavior, physiology and metabolic processes. Driven by the circadian clock, circadian rhythms are found in virtually every cell in the body (Partch et al., 2014). Over the last ten years, research has uncovered that the circadian clock functions within cells to support daily tissue homeostasis, and disruption of the clocks leads to lowered resilience (Saeed et al., 2019). Studies in animal models support the decline in function of the circadian system with age, and this age-related decline appears to impact virtually all systems in the body including skeletal muscle and areas of the brain important for learning and memory (Nakamura et al., 2015; Logan et al., 2018; Vitale et al., 2019). In humans, studies have shown that circadian output changes with aging and affects body temperature and sleep-wake cycle (Maurer et al., 2015) (Hood and Amir, 2017). These observations raise the possibility that targeting circadian rhythms through timing lifestyle cues, such as meal timing, could be health promoting and may also reduce

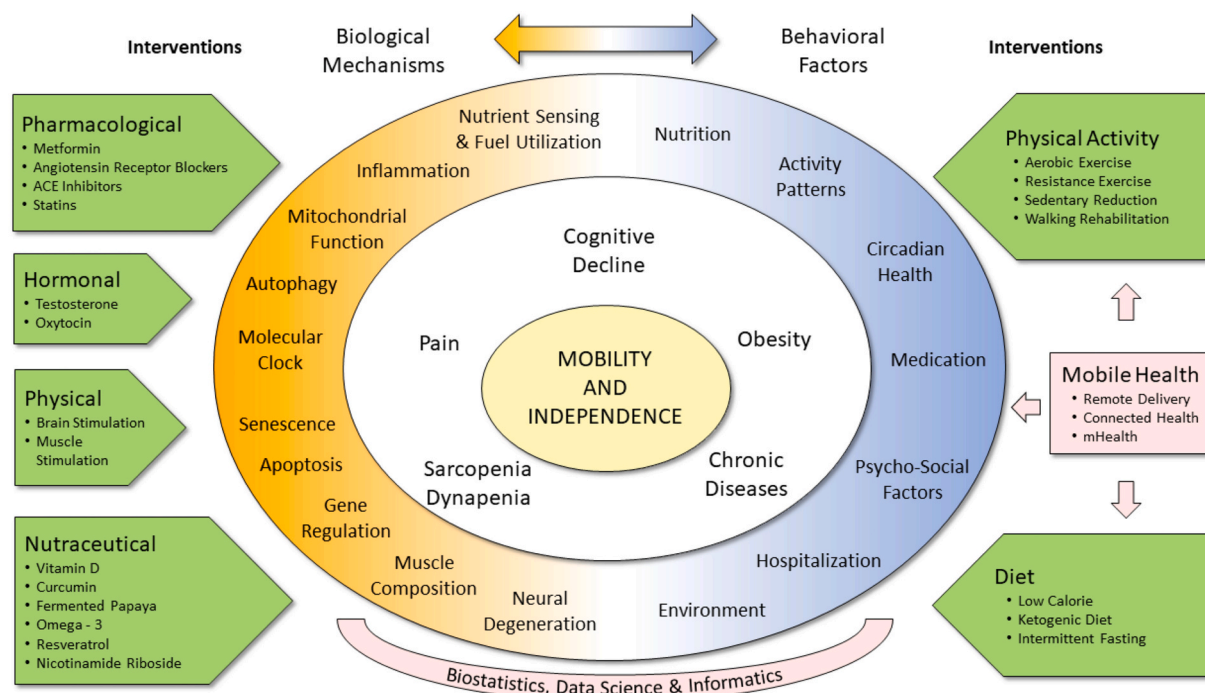


Fig. 3. Geroscience approach model to enhance mobility and independence.

age-related mobility decline.

2.6. Cellular and mitochondria contributors to mobility decline

Mitochondria play a key role in cellular function by regulating energy (ATP) generation, reactive oxygen species (ROS) homeostasis, and apoptotic signaling. The functional and morphological abnormalities in mitochondria are associated with all aspects of mobility and disability, including motor neuron death, destabilization of the neuromuscular junction, and loss of muscle mass and strength (Anagnostou and Hepple, 2020; Frontera et al., 1991; Hughes et al., 2001; Del Campo et al., 2018; Sebastian et al., 2016). Thus, the available evidence to date strongly implicates mitochondria as having a pivotal role in the pathogenesis of age-related functional decline, and it has been suggested that a substantial decrease in mitochondrial oxidative capacity in aging muscle might contribute to reduced exercise capacity in older adults (Peterson et al., 2012). Why there is a decrease in mitochondrial function with aging remains under debate, but emerging science indicates that there is a clear connection between mitochondrial biogenesis and function with fuel metabolism and circadian rhythms (Sardon Puig et al., 2018).

2.7. Role of the cardiovascular system in mobility decline

Cardiovascular disease (CVD) is a leading cause of death among older adults in the United States and the prevalence increases proportionally with age. In particular, 70% of older adults between 60 and 79 years old and 85% of older adults 80 years and older suffer from CVD (Writing Group, M, 2016). During aging, endothelial dysfunction induced by oxidative stress, inflammation and decline in bioavailability of nitric oxide (NO) leads to arterial stiffness, which overloads the heart leading to ventricular hypertrophy and myocardial fibrosis (Puntmann et al., 2014). Endothelial dysfunction and the overloaded heart reduce arterial-ventricular coupling, reflecting impaired global cardiovascular performance (Chantler and Lakatta, 2012). Recent evidence has demonstrated that subclinical declines in cardiovascular function contribute to functional decline by impaired peripheral tissue perfusion (Laurent et al., 2019).

2.8. Role of sepsis in mobility decline

Although sepsis can affect all ages, it is recognized to be the “quintessential disease of the elderly” (Prescott and Angus, 2018). Studies have shown that both the incidence of sepsis and hospital mortality increases exponentially beyond the age of 65 years, with more than 1 million US Medicare recipients hospitalized each year with sepsis. Numerous age-related factors increase the risk for developing sepsis including comorbidities (e.g., chronic lung disease and renal insufficiency), malnutrition, increased aspiration risk from altered mental status and decreased gag/cough reflex and immobility. The diagnosis of sepsis is commonly delayed in older patients because of a blunted systemic inflammatory response syndrome (SIRS) and the presence of comorbidities that can cause confounding symptoms. As a result, older patients present as septic later in the process. They are more likely to progress into septic shock due to limited cardiac reserve and have worsening of existing organ dysfunctions.

The principal cause of sepsis is a dysregulated systemic immune response, which is negatively affected by aging. In contrast to younger adults, older patients have difficulty returning to immunity homeostasis, increasing their risk for sepsis recidivism. Pre-existing sarcopenia, frailty and cognitive disabilities all adversely affect recovery. Additionally, ongoing SIRS induces profound catabolism with tremendous loss of vital lean body mass despite early nutritional support intervention. Moreover, care for sepsis in the ICU often involves bedrest and mechanical ventilation, exacerbating the ongoing loss of muscle mass and function. Once SIRS has resolved, older sarcopenic sepsis survivors have anabolic resistance that makes them non-responsive to nutritional and physical

therapy interventions.

2.9. Contribution of sensory loss in mobility decline

Our senses, hearing, vision, touch, smell, and taste play critical roles in survival throughout the course of life. Aging can affect all of these sensory systems, but the auditory system is thought to be especially vulnerable to age-related damages. Hearing loss is the third most prevalent chronic health condition affecting older adults and age-related hearing loss (AHL) is the most common form of hearing impairment (Ozmeral et al., 2016). The World Health Organization (WHO) estimates that one-third of persons over 65 years are affected by hearing loss (WHO, 2019). Worldwide, approximately 466 million people suffer from hearing impairment and this number is expected to rise to 630 million by 2030 and over 900 million by 2050. AHL is characterized by poor speech understanding (especially in noisy situations), central auditory processing deficits, and social isolation (Yamasoba et al., 2013).

2.10. Contribution of hormonal factors to mobility decline

As humans age, both males and females undergo various changes in hormone levels, leading to numerous long term and significant internal changes. Although some of these changes may be more detrimental than others, common and problematic alterations include loss of muscle mass (Lee et al., 2007), decreased bone mass (Garcia et al., 2019), and various cognitive impairments (Sonntag et al., 2005), which all increase risk for mobility loss and loss of independence.

In men, aging is often associated with decreased testosterone (Lee et al., 2007), which has been linked to bone loss (Jankowska et al., 2009) and decreased muscle mass (Shin et al., 2018b). With the loss of muscle and bone comes an increased risk of sarcopenia, oftentimes resulting in frailty, decreased functional mobility, and growing difficulties with independent living. In females, decreased estrogen levels post-menopause are often postulated to increase one's risk of sarcopenia and frailty (Lee et al., 2007). Loss of estrogen is accompanied by an increase of pro-inflammatory cytokine IL-6, which downregulates insulin-like growth factor-1 (IGF-1) (Lee et al., 2007). High IL-6/low IGF-1 levels have been shown to significantly limit walking and mobility tasks of daily living (Leng et al., 2004), increasing the risk for progressive disability in older females.

In addition to sex hormones, a decline in growth hormone (GH) has been observed with aging and is often associated with various changes in body composition, as well as physical and psychological functions (Garcia et al., 2019). As one approaches the fourth decade of life, there is a progressive decrease of GH secretion by ~15% each decade thereafter (Garcia et al., 2019). Age-related increases in body mass index (BMI) and diminished functional capacity tend to parallel the decline in GH secretion, although many other factors also likely contribute (Garcia et al., 2019).

2.11. Summary

In many cases, physical disability is directly caused or aggravated by acute events (stroke and hip fracture) and disease states (heart failure, coronary heart disease, diabetes, arthritis and peripheral artery disease) (Ferrucci et al., 1997; Fried and Guralnik, 1997). However, a large and growing number of older adults experience progressive declines in physical function over several years culminating in age-related physical disability with no clear connection to a single disease (Guralnik et al., 1991; Mor et al., 1994). Research over the past decade has highlighted the role of multiple body/biological/health systems in contributing to this decline. Moreover, many age-related conditions appear to affect other systems and may induce similar adverse changes at the cellular level.

3. Behavioral contributors to mobility and loss of independence

Among the behavioral factors, low levels of physical activity combined with excessive and unhealthy calorie intake appear to strongly contribute to functional decline among older adults (Goisser et al., 2015). In line with this, a recent review of trends in US health by the U.S. Burden of Disease Collaborators found that high body mass index (BMI), smoking, and high fasting plasma glucose are the three most important risk factors for disease and disability in the United States (Collaborators, U.S.B.o.D., 2018). Among these, only the prevalence of smoking is decreasing, while BMI and fasting plasma glucose levels are steadily increasing.

3.1. Role of over-nutrition in mobility decline

Chronic over-nutrition is also a key contributor to the development of lipotoxicity, as frequent consumption of calories results in an increase of carbohydrate utilization and a decrease of fatty acid oxidation. Over time, this can contribute to the accumulation of toxic fatty acids, as skeletal muscle loses the ability to switch between metabolizing lipids and carbohydrates. In addition to the role caloric excess can have in promoting metabolic inflexibility, there is also increasing evidence that the “Western-type” diet that is high in sugar, fat, and processed foods seems to be associated with less ideal aging phenotypes (Akbaraly et al., 2013).

3.2. Role of sedentary behavior in mobility decline

High levels of sedentary behavior (sitting) contributes to lipid accumulation (Smith et al., 2014; Larsen et al., 2014; Manini et al., 2007), metabolic impairments (Ford et al., 2005), and loss of muscle mass during aging (Atkins et al., 2014), all of which strongly contribute to functional decline (Landi et al., 2007a; Vincent et al., 2010; Vieira et al., 2013; Botoseanu et al., 2015). These findings are of concern as the majority of middle-age Americans spend over half their waking day (~8–9 h) engaged in sedentary pursuits (Cohen et al., 2013; Maher et al., 2013), with older adults spending an even greater proportion (75%) of their waking hours engaged in sedentary behavior (~11 h per day) (Mankowski et al., 2015). Moreover, each additional hour of sedentary behavior was associated with increased risk of the metabolic syndrome, whereas every additional hour of light intensity activity was associated with reduced risk.

3.3. Role of sleep in mobility decline

Perhaps the most common complaint older adults have is the lack of quality sleep. Sleep affects nearly every tissue and system in the body, from the brain, heart and muscle to metabolic, endocrine, cardiovascular and immune functions, as well as numerous cognitive processes such as learning and memory, emotion and motor control (Irwin, 2015). Similar to food and water, sleep is a basic human need, and sleep timing, duration, and quality are all essential to health. Despite this, sleep deficiency is prevalent in modern society, including an insufficient amount of sleep, low quality sleep, and sleep at the wrong time of day. According to a recent report from the Centers for Disease Control and Prevention (CDC), 30% of U.S. adults report some form of sleep deficiency (Prevention, C.f.D.C.a., 2020; Liu et al., 2016).

Sleep deficiency is more prevalent in older adults, exhibiting common nighttime sleep abnormalities, such as early bedtime and rise time, sleep fragmentation (i.e. less consolidated sleep with frequent awakenings), short sleep duration, less total sleep, and deep sleep (Mander et al., 2017); which is correlated with more frequent daytime naps. In fact, 1 in 4 older adults report severe daytime sleepiness that affects daytime mental and physical performance (Foley et al., 2007). These age-related sleep deficiencies have significant consequences for brain and body health, increasing the risk of chronic inflammatory and neuropsychiatric

diseases, metabolic and cardiovascular disease, as well as mental health problems and even pain. For example, poor sleep quality and chronic pain are both tied to significant reductions in quality of life in aging (Chen et al., 2019). Emerging evidence from our group suggests that sleep may negatively impact brain structure and function in older individuals, which may lead to worse self-reported pain (Montesino-Gicolea et al., 2020; Valdes-Hernandez and Cruz-Almeida, 2020).

3.4. Summary

An increased understanding of the behavioral factors that contribute to *functional decline in otherwise healthy older adults* can assist in both identifying at-risk older adults and designing targeted interventions for individuals in the later stages of life that maintain mobility and slow the rate of functional decline. It is recognized that there are many causes of functional decline and ultimately disability. While we believe behavioral factors, including over and under-nutrition, physical inactivity, and sleep, have a *central role* in maintaining mobility in later life, the pathways leading to physical disability in older adults are likely complex and involve consideration of a larger number of etiologic factors.

4. Social/environmental factors in mobility and loss of independence

4.1. Environment and social relationships

Environment and social relationships can serve as either risk or protective factors for aging adults. Environmental factors across the lifespan interact with biology and contribute towards health outcomes (Hill et al., 2015). Research shows that early life stressors can influence biological functioning, priming the stress system towards a level of heightened sensitivity increasing greater risk for later life health conditions and earlier mortality (Lupien et al., 2009). As individual age, environmental factors, life experiences, and personal and financial resources can buffer or exacerbate health-related conditions. Social relationships also influence health and well-being. Limitations in social relationships can be experienced as social isolation and loneliness (National Academies of Sciences, E. and Medicine, 2020). Of concern, approximately one fourth of adults, individuals aged 65 years and older meet social isolation criteria and among individuals aged 60 years and older, greater than 40% endorse loneliness (National Academies of Sciences, E. and Medicine, 2020).

Age-related life changes that increase susceptibility to social isolation and loneliness includes changes in health status limiting functioning and mobility; changes in family structure (divorce, childless); death of friends, family members, and spouse; auditory and visual changes reducing the ability to communicate and interact; and resource reductions including healthcare access and quality of care (National Academies of Sciences, E. and Medicine, 2020). There is also research evidence that socially isolated older adults are less physically active independent of any mobility limitations (Schrempft et al., 2019). However, whether or not declines in mobility mediate the well-established relationship between social isolation and all-cause mortality (Steptoe et al., 2013; Courtin and Knapp, 2017) remains unclear.

Minority older adults are at an even greater risk to the health consequences of environmental and social factors. Higher frequency of negative environmental exposures, limited environmental resources, possible language limitations, and experiences of stigma and discrimination might be further contributing to increased risk of morbidity and mortality (Hill et al., 2015). Despite this increased risk for poor health outcomes, access to medical care is often limited and the extended wait times to receive care may discourage healthcare utilization, particularly preventive health services among minority populations (van, 2002; Zogg et al., 2016; Towne Jr et al., 2014). Thus, environmental and social factors represent an area where research and evidence-based strategies can contribute to improved health outcomes (Hill et al., 2015; Myers,

2009; Lee et al., 2020).

4.2. Psychological factors

Older adults perceive mobility as essential to feeling whole and identify mobility assistance and adaptation as key to managing age-related changes (Goins et al., 2015). In fact, older adults who met just one of five established frailty phenotype criteria were more likely to also be depressed, suggesting frailty has both physical and psychological components (Batko-Szwaczka et al., 2020). Also noteworthy, psychological factors such as balance efficacy and falls efficacy have previously been found to be more important than physical factors (e.g., fall history, medical morbidity, and balance tests) in predicting future falls (Landers et al., 2016).

Theoretically, self-efficacy for specific tasks, mood, and behavior have a reciprocal influence on an older person's decision making and performance. For example, lower baseline self-efficacy for functional tasks predicted decreased walking performance and stair ascent among older women with osteoarthritis (Brisson et al., 2018). Falls efficacy, a measure of falls-specific self-efficacy, can be independently predicted by normal walking pace, anxiety, and depression (Tinetti et al., 1990). Dizziness, another common mobility-related complaint of older adults, has been associated with lower falls efficacy and slower walking speed (Lindell et al., 2020). These trends are consistent with other data showing fall history and female gender independently predict fear of falling (Friedman et al., 2002) and mobility device use (Gell et al., 2015).

5. Promising interventions to enhance physical function and mobility

Consistent with the data on the importance of psychosocial factors in mobility, a number of mobility-related clinical interventions are integrating falls-specific self-efficacy (Santos et al., 2017), balance-specific (Rose et al., 2018) and other psychological concepts into trials targeting frailty in older adults (Inzitari et al., 2018). Further, these trials are also targeting motivation for physical activity (Hyde et al., 2019), adherence to exercise programs (Arkkukangas et al., 2018), fall prevention (Okubo et al., 2016), and interventions to reduce the fear of falling and improve balance such as yoga (Nick et al., 2016). Protocols are emphasizing the need to tailor to older adult's preferences, personal choice, and providing social support (Koll et al., 2017). These factors should align with older adults' own attitudes and perceived needs (Maurer et al., 2019), as well as older adults' perceived enablers and barriers to participation in strength and balance activities (barriers = risk of cardiac events, death, and hyper muscularity; enablers = potential improvement in the ability to complete daily activities, prevent deterioration /disability, and decreased risk and fear of falling) (Cavill and Foster, 2018). In a 6-month integrated care program that included problem-solving psychotherapy reported improvements in frailty were sustained at one year follow up (Chan et al., 2017). Although these studies suggest promising results, the integrated biopsychosocial approach to mobility is still under-utilized.

5.1. Role of dietary interventions in physical function and mobility

Poor Nutrition may be a key factor that promotes metabolic syndrome and can exacerbate a decline in physical function and mobility. Given the link between metabolic syndrome or obesity with the musculoskeletal decline among the older population, it is no surprise that dietary interventions that reduce bodyweight also improve health outcomes in older adults. Dietary restriction (or caloric restriction), defined as a mild reduction of energy intake without malnutrition, delays aging in nearly all animal species tested so far (Weindruch, 1996). In addition to promoting longevity in various model organisms (e.g., yeast, worm, fly, mouse) (Weindruch, 1996; Kapahi et al., 2017), dietary

restriction had also been shown to be beneficial for enhancing physical function and mobility in older adults (Weerapong et al., 2005; Chaitow, 2018; Hornberger and Esser, 2004; Flynn et al., 2010). Furthermore, in overweight humans, caloric restriction has been shown to reduce several cardiac risk factors (Fontana et al., 2004; Fontana et al., 2007; Lefevre et al., 2009), improving insulin-sensitivity (Larson-Meyer et al., 2006), and enhancing mitochondrial function (Civitaresse et al., 2007).

Current challenges: Despite health-promoting biological changes, there are two important concerns related to calorie restriction interventions in older adults. First, weight loss could accelerate aging-associated muscle loss and thereby have adverse effects on physical function (Houston et al., 2009; Miller and Wolfe, 2008). Second, most individuals have difficulty engaging in caloric restriction over the long-term and frequently regain weight that was lost (Scheen, 2008). For these reasons, alternative innovative dietary approaches for reducing body weight, specifically body fat, in overweight, older adults at risk for functional decline are currently being explored.

Innovations from Geroscience: One alternative dietary approach that has been suggested to produce similar biological changes as calorie restriction that has received increasing interest from the scientific community is Intermittent Fasting or Time-Restricted Eating (TRE) (Anton et al., 2018). In contrast to traditional calorie restriction paradigms, there is typically no restriction to calorie consumption in TRE during designated eating periods (typically 8–12 h). In a recent review of the effects of intermittent fasting regimens, specifically TRE and alternate-day fasting, we found that TRE produced significant reductions in body fat without significant loss of lean tissue, suggesting it may be an effective intervention approach for overweight, older adults (Anton et al., 2018).

Another area of increasing scientific interest is understanding the role of dietary composition in impacting human physiology and physical performance. For example, the Mediterranean diet, which consists of healthy fats, fiber, fish, and minimally processed, plant-based foods, has been shown to provide health benefits including improving cardiovascular function, glucose control and decreasing body weight among older adults (Tosti et al., 2018; Struijk et al., 2018; Assmann et al., 2018). Also, noteworthy, in some preclinical studies conducted in rodent models, the ketogenic diet has been shown to extend longevity and healthspan, (Crane et al., 2012; Hallbook et al., 2012) improve memory and cognition, (Hallbook et al., 2012; Newman et al., 2017; Hernandez et al., 2018) and improve endurance athletic performance (Sefton et al., 2012; Harris and Richards, 2010). Based on such findings, the low-carbohydrate, high-fat ketogenic diet has attracted increasing attention as a potential dietary intervention to promote healthy aging.

Future directions: To date, the impact of diet interventions on physical function and mobility among seniors with aging-associated morbidities is unknown. Although some risk may be associated with lifestyle-based weight loss interventions in older adults, obesity, and sedentary lifestyle are known to predict the development of disability in otherwise healthy older adults (Vincent et al., 2010; Landi et al., 2007b). However, randomized controlled studies are needed to demonstrate whether the benefits of these interventions outweigh the risks before implementing these interventions on a broad scale. An important primary focus of these interventions should be enhancing and/or maintaining fat-free mass, as high-quality muscle is the primary driver of metabolism and also directly impacts mobility and physical function (Hardy et al., 2007; Purser et al., 2005). Notably, as multimorbidity is often a characteristic feature observed in older individuals with impairments in mobility, a Geroscience Approach will be instrumental in determining the long-term efficacy of nutrition-based interventions and addressing the potential challenges with aging-associated comorbidities.

5.2. Exercise interventions to improve mobility and physical function

Exercise provides benefits to all major body systems, including the nervous system. Aerobic exercise, in particular, can enhance brain

health by upregulating neurotrophic factors that improve nerve structure and function (Erickson and Kramer, 2009). To prevent functional decline, the American College of Sports Medicine (ACSM) guidelines for older adults recommend a regular exercise program that includes a combination of endurance and resistance training (Bonasio et al., 2010). In support of these recommendations, low-intensity aerobic activity such as walking 4–7 days per week (Clark, 1996) or going up and down a 10-stair staircase (Mor et al., 1989), have been shown to be protective against loss of mobility and functional decline (Clark, 1996; Mor et al., 1989; LaCroix et al., 1993).

Current challenges: While structured physical activity is a powerful tool to improve overall health in older adults, involvement in structured physical activity may be overwhelming for frail older adults who are home-bound and have poor physical performance. Older adults may not be capable of participating in structured, institution-based physical activity programs with multiple visits to research sites due to poor health status and distant living locations.

Innovations from Geroscience. Our group has shown that a structured, moderate-intensity physical activity program compared with a health education program reduced the incidence of major mobility disability over 2.6 years among older adults at risk for disability (Pahor et al., 2014). Other studies have found that resistance training can reduce and delay age-related changes in functional mobility (Papa et al., 2017), improves leg strength (Cho and An, 2014), and prevents falls by improving transfer of weight and swooping motions in the elderly (Chandler et al., 1998).

Future directions. While physical exercise conveys proven health benefits, the detailed molecular signals and responses to exercise are not fully understood. To advance science in this area, the Molecular Transducers of Physical Activity Consortium (MoTrPAC) is generating a molecular map of the effects of acute and chronic exercise (Sanford et al., 2020).

5.3. Sedentary behavior reduction to enhance mobility and physical function

Reduction of sedentary behavior may be an alternative way to deliver a home-based and remotely supervised intervention to improve the functional status of older adults who cannot engage in center-based physical activity programs. For example, an intervention to reduce sedentary time over 12-weeks improved scores on the short physical performance battery (SPPB) and self-reported moderate-to-vigorous physical activity (MVPA) levels in older men and women (Barone Gibbs et al., 2017). Such it could be a promising intervention to improve physical function in frail older adults in a home-based setting. Strong positive associations between breaks in sedentary time with physical function in older adults have also recently been reported (Sardinha et al., 2015).

Challenges: Remotely delivered interventions are more difficult to achieve long-term adherence to the intervention tasks. Additionally, considering heterogeneous levels of daily activity and sedentary time among individuals, it is challenging to set daily frequency of sedentary time reduction breaks and design the methods for prompting these breaks as well as an amount of steps to be reached daily. (Koltyn et al., 2019)

Innovations from Geroscience: Thanks to new developments of well-accepted wearable technology in older adults (Ashe et al., 2015), such as the Fitbit Alta device, activity and sedentary-behavior levels can be monitored and registered remotely, and importantly, users can be reminded automatically to transition from sitting to standing position and perform brief light-intensity activity such as leisurely walking (Manini et al., 2015). For example, participants using wearable technology aimed to achieve a minimum goal of 25% increase in daily posture breaks, and an additional 1000 steps a day to baseline, which is considered clinically meaningful in a geriatric rehabilitation population (Fisher et al., 2013). This novel and practical approach, is less physically

strenuous, does not require frequent visits to research sites, and can be operated and monitored remotely by a research team.

Future directions: Future randomized clinical trials are needed to test wearable technologies in a population of frail older adults with poor physical function, multi-morbidities, and live a far distance from research facilities.

5.4. Neuromuscular interventions to improve physical function and mobility

Given the importance of physical activity and exercise for healthy aging, it is important to consider how these can be optimized to promote neural control of walking. The mode of activity/exercise may be important, and there may be adjuvant interventions that promote neural plasticity.

Innovations from Geroscience. Task-specific aerobic exercise that incorporates complex walking tasks and other activities of daily living may be especially helpful for mobility function (Liu et al., 2014). An example of these interventions is the use of non-invasive neuromodulation such as transcranial direct current stimulation (tDCS), a mild form of electrical stimulation that is safely delivered via electrode sponges placed on the scalp. tDCS does not directly activate brain neurons, but rather alters the neuronal membrane potential, which is believed to alter the likelihood of eliciting neuron activity (either increased or decreased likelihood, depending on the stimulation parameters) (Woods et al., 2016). When paired with task practice, excitatory tDCS might reinforce task-specific neural circuits, enhance learning, retention of new skills, and has been shown to benefit walking tasks in preliminary studies (Hsu et al., 2015; Reis et al., 2015; Reis et al., 2009; Au et al., 2016).

Future directions. The use of neuro-modulatory adjuvants to enhance the beneficial effects of physical activity and exercise is a promising area of research. Future studies should investigate the safety and efficacy of exposure to neuromodulation. Interventions targeting neural control of walking have great potential to slow the age-related decline of mobility.

5.5. Cognitive interventions to improve physical function and mobility

Cognitive interventions refer to a broad set of methods designed to improve or maintain cognitive functioning (Stine-Morrow and Basack, 2011). Because many forms of cognition (e.g., memory, reasoning, speed, executive functioning, attention, working memory) are change with age, and are associated with functional losses in later adulthood (Stine-Morrow and Basack, 2011; Cohen et al., 2019; Aging, C.o.t.P.H.D. o.C, 2015), the field of cognitive intervention research has been rather broad. Methods of intervention have varied from cognitive training (e.g., providing elders with strategic instruction and practice/feedback in age-vulnerable cognitive domains), engagement (Stine-Morrow et al., 2014) (having elders engage in complex real-world or leisure activities, including video games) (Belchior et al., 2019), quilting and digital photography (Park et al., 2014), performing arts (Bugos et al., 2007; Chan et al., 2016) interacting with technology (Chan et al., 2016; Charness, 2020), to a wide variety of physical and nutritional strategies (e.g., cardiovascular and strength training, anti-inflammatory diets (Kane et al., 2017)). Most of this research has sought to investigate whether interventions can improve cognition and/or cognitively demanding activities of daily living.

Innovations from Geroscience. Useful field of view training progressively and adaptively trains older individuals to improve the speed with which they make accurate perceptual judgments about targets presented in the center of the field of view, while also correctly noting the location of peripheral objects presented on a display (Ball et al., 2002). Restrictions in useful field of view have been associated with problems of mobility (Wood and Owsley, 2014), balance (Reed-Jones and Dorgo, 2012) and increased risk of falling (Vance et al., 2006), although direct training benefits have not yet been widely reported. Of relevance to the mobility domain, older drivers who received useful field of view training

showed a roughly 50% reduction in five-year motor vehicle crash rates (Ball et al., 2010), presumably because of the improved ability to rapidly monitor a broad visual display and to divide attention between central and peripheral targets. The unifying feature of each of these domains of successful cognitive training is the focus on divided attention. In all cases, training included the feature of exposing elders to two tasks at once with one task usually representing a balance/gait or visual-perceptual challenge. Generalization of training to mobility tasks seems to be associated with the improved ability to attend to multiple tasks at once, or perhaps to be resistant to distracting tasks by having greater control over attentional prioritization (i.e., reducing the effects of distraction, or improving the ability to exert controlled attentional processing over mobility-relevant tasks).

The question of whether cognitive interventions might also improve mobility and physical functioning has received less attention, but a few areas of inquiry have yielded supportive findings. First, dual-task training has been shown to improve standing balance, gait, and to reduce fall risk (Kane et al., 2017; Li et al., 2010; Silsupadol et al., 2009; Hauer et al., 2020). The rationale for such studies is that balance and gait are thought to be under central (executive) control, and improving attentional capacity to concurrently conduct cognitive and motor challenges will improve the ability to maintain adequate mobility under distracting conditions, as distractions are thought to put elders at a high risk for falls.

5.6. Hormonal interventions in physical function and mobility

There are a number of hormonal interventions that have the potential to impact mobility and improve physical function. We focus on one promising compound, the neuropeptide oxytocin, which serves various adaptive and interrelated physiological, behavioral, and cognitive functions (Horta et al., 2020). As a hormone, oxytocin is released into the peripheral circulation and acts directly on multiple organ systems. For example, in humans, low plasma oxytocin levels were associated with increased prevalence of chronic pain, and acute (i.e., one-time) intranasal oxytocin administration decreased experimental pain sensitivity, increased pain inhibition, and improved mood and positive affect. In addition, there is increasing evidence of improved wound healing and anti-inflammatory effects associated with oxytocin (Clodi et al., 2008), promoting physical health.

Innovations from Geroscience: The ability to administer oxytocin centrally via nasal spray (Born et al., 2002; Quintana et al., 2018), with minimal and inconsistent side effects (MacDonald et al., 2011), has spurred research to explore the neuropeptide's therapeutic potential across functional domains, including physical health and in aging (Ebner et al., 2013; Ebner et al., 2015; Huffmeijer et al., 2013; Sannino et al., 2017). Going beyond its classic role in labor and lactation (Pedersen, 1997), oxytocin has been demonstrated to modulate higher-order cognitive processing (Meyer-Lindenberg et al., 2011), improve vasculature in the cardiovascular system, benefits weight control, and insulin sensitivity (Horta et al., 2020; Zhang et al., 2013). Oxytocin has also been shown to play a crucial role in endogenous analgesia and has recently been discussed as a promising treatment for pain in older individuals (Lussier et al., 2019). These analgesic mechanisms may be explained by oxytocin's role as both a neurotransmitter and a paracrine hormone and may be associated with brain-morphological processes. As a neurotransmitter, oxytocin may provide analgesia via widespread effects on the brain and spinal cord.

In humans, emerging evidence supports an association between plasma oxytocin levels and brain volumes (Andari et al., 2014; Mielke et al., 2018). Preliminary data from a 4-week intranasal oxytocin intervention in older men found increased regional gray matter volume following oxytocin but not placebo treatment, with this oxytocin-induced enlargement in brain volume was associated with improved processing speed (Ebner et al., 2019). Furthermore, animal models that administer repeated oxytocin treatment have documented brain changes driven by

cell proliferation, differentiation, and dendritic complexity of new-born neurons in the hippocampus (Sanchez-Vidana et al., 2016). Findings in both models offer promise for future investigations into the potential of intranasal delivery of oxytocin to counteract cognitive decline and positively affect physical health in aging. Additionally, data from an animal model that systematically administered oxytocin found that the administration enhanced muscle regeneration after injury through activation of stem cells and MAPK/ERK signaling (Elabd et al., 2014).

Future directions: Only one study to date has specifically examined the effects of intranasal oxytocin administration on physical health among older adults and found that 10-days of oxytocin spray was associated with less self-reported physical decline and reduced self-reported fatigue (Barraza et al., 2013). The promising findings from these diverse emerging fields call for more systematic research on both acute and chronic oxytocin intervention towards physical function among older adults. Examination of exogenous oxytocin's direct and mediated effects, and interaction with the endogenous oxytocin system (e.g., naturally circulating neuropeptide levels, oxytocin receptor gene polymorphisms and methylation levels (Ebner et al., 2015; Plasencia et al., 2019)), forms an interesting angle for future research on interventions promoting physical function and mobility in aging.

In addition, there is growing support in the literature of sex dimorphism in the oxytocin system (MacDonald et al., 2011), including in aging (Plasencia et al., 2019), and evidence of sex-dimorphic effects of intranasally administered oxytocin on both brain (Horta et al., 2020; Ebner et al., 2015) and behavior (Campbell et al., 1973; Horta et al., 2020; Ebner et al., 2015), including among older adults. In an age-heterogeneous sample of generally healthy women and men, plasma oxytocin levels were higher in women than men, with young women showing the numerically highest levels and older men showing the numerically lowest plasma oxytocin levels (Plasencia et al., 2019). Based on this emerging evidence, future research on the application of oxytocin's effects across different functional domains during aging will benefit from consideration of sex-by-age variations.

5.7. Pharmaceutical interventions to improve physical function and mobility

Pharmacological interventions targeted at underlying mechanisms of mobility decline may also lead to improvements in mobility and physical function in older adults. For example, cell senescence characterized by a loss of cell proliferative capacity, increased metabolic activity, and resistance to apoptosis is a major contributing factor to the development of various age-related conditions. Thus, targeting the removal of senescent cells or suppressing the senescence-associated secretory phenotype may be helpful in improving physical function (Ros and Carrasosa, 2020). Specifically, inhibition of cytoplasmic Hsp90 (a chaperone protein needed for proper protein folding) induced by Hsp90 inhibitors causes senescent cells to be more susceptible to apoptosis. Other pharmacological agents aimed to help proper protein folding or remove misfolded protein aggregates may also delay the onset of age-related diseases and subsequently prevent or ameliorate physical functional decline from these sources.

Innovations from Geroscience: The idea that aging itself may be modified through a pharmaceutical intervention will be tested in the Targeting Aging with Metformin (TAME) proposal, the first clinical trial to examine an intervention to slow aging rather than to treat a specific age-related chronic disease in humans pharmacologically (Barzilai et al., 2016). The impetus for this trial is that metformin has been demonstrated to have protective effects against several age-related diseases in humans. However, there does not appear to be a single biological mechanism targeted. Rather metformin appears to have broad systemic effects, which can enhance insulin sensitivity and upregulate stress responses at the cellular level.

Further, targeting cognition pharmacologically to improve mobility or prevent further decline may be possible, given the brain's

neurotransmitter systems shared between cognitive function and the circuits controlling gait. Specifically, drugs targeting the cholinergic, dopaminergic and glutamatergic systems have been reported with various degrees of success in individuals with Alzheimer's and Parkinson's Disease (Montero-Odasso, n.d.), but may be an additional option to explore in cognitively intact older adults with poor mobility.

Future directions: To date, there is very limited research focused on pharmacologically targeting aging for improving physical function. Given the mosaic of aging processes and potential multi-factorial underlying mechanisms, a Geroscience approach will be needed to test interventions with multi-functional properties that target the biopsychosocial contributors to aging processes.

5.8. Role of nutraceuticals in improving physical function and mobility

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 adjunct treatment with lifestyle interventions, behavioral self-management programs, physical exercise, or cognitive interventions.

Current challenges: For the vast majority of these compounds, the findings have primarily been shown in preclinical models and have not yet been translated to humans, and/or few clinical trials have shown positive effects on mobility in older adults when biologically based approaches are used alone and not in combination with a behavioral intervention (Glossmann and Lutz, 2019).

Innovations from Geroscience: Studies to date suggest some natural compounds may be effective adjuvants to lifestyle interventions. In this section, we will focus on one promising nutraceutical compound, nicotinamide riboside (NR), a form of vitamin B3 that stabilizes the NAD metabolome (NAD⁺, NADH, NADP⁺ and NADPH), which in a homeostatic state, mediates transformations from food into energy and repair processes (Bieganowski and Brenner, 2004; Belenky et al., 2007). Given the NAD metabolome destabilizes with age (Das et al., 2018), supplementation with NR has been shown to stabilize the NAD metabolome in a variety of tissues (Yoshino et al., 2018). Clinical studies have demonstrated excellent tolerability and safety of NR supplementation in middle-aged and older adults, and improved vascular function (Martens et al., 2018) and reduced fat tissue (Remie et al., 2020) following 6 weeks of supplementation.

Future directions: The effects of NR supplementation alone on physical performance in older humans are unclear, and therefore future studies warrant investigations of longer-duration NR supplementation on physical performance, weight loss and cardiovascular function in humans (Fluharty and Brenner, 2020; Custodero et al., 2020). Much will be learned about the promise of preclinical findings to translate to humans, as well as their compatibility with other interventions, in the coming years.

5.9. Complementary and alternative treatment modalities

There are many promising complementary and alternative treatment modalities, including biofeedback, hypnosis, meditation, mindful exercise, massage and other types of body-work, acupuncture, and music therapy, that have the potential to improve mobility and physical function in older adults. Here we will focus on the potential role of massage therapy (MT), which is a mind-body intervention that has been shown to improve muscle function and quality, preserve of neuromuscular function, improve sleep quality and psychological functioning (Huffmeijer et al., 2013; Weerapong et al., 2005; Chaitow, 2018; Hornberger and Esser, 2004; Flynn et al., 2010; Bove et al., 2016); (Oliveira et al., 2012); (Sharpe et al., 2007). Additionally, a growing body of literature supports the use of MT to treat chronic musculoskeletal pain associated with aging (Buckenmaier et al., 2016; Chou et al., 2017; Elibol, 2019; Skelly, 2018).

Current challenges: While MT shows significant promise for

improving factors associated with physical function and quality of life, there are important considerations for older adults, including access, attitudes, and approach. Attitudes towards complementary health approaches, specifically MT, are often biased towards a luxury service instead of an actual medical intervention. Also declines in mobility and independence may inhibit treatment seeking.

Innovations from Geroscience: Specific to biological processes in aging, MT has been shown to modify gene expression, protein synthesis, and inflammatory responses (Weerapong et al., 2005; Chaitow, 2018; Hornberger and Esser, 2004; Flynn et al., 2010), as well as improve peak isometric torque recovery following intense exercise (Haas et al., 2013), and protect against loss of strength and fibrotic nerve and connective tissue changes associated with repetitive motion injuries (Harvie and Howell, 2016). Massage therapy has also been demonstrated to modulate inflammatory processes that may be protective in aging (Rapaport et al., 2010; Rapaport et al., 2012). Of particular relevance, recent preclinical studies using rodent models, demonstrated MT induced immunomodulatory changes (e.g., increased satellite cell number) comparable to those seen in younger animals without damaging muscle tissues. (Unnikrishnan et al., 2019) The beneficial effects of massage therapy appear to take place quickly, as a single 10-minute massage therapy session following exercise-induced muscle damage was found to be beneficial for reducing inflammation and promoting mitochondrial biogenesis (Crane et al., 2012). Additionally, massage therapy is capable of altering proprioceptive feedback to the central nervous system (David et al., 2019; Shin and Sung, 2015), a critical component for maintaining mobility in aging.

Future directions. While the full benefits and mechanisms of massage therapy in older adults have yet to be fully elucidated, it is likely that massage therapy can serve a vital role in helping older adults maintain mobility by reducing pain, improving muscle functioning, maintaining proprioceptive abilities, and altering negative inflammatory processes, while improving psychological functioning (Oliveira et al., 2012; Sharpe et al., 2007; Ross et al., 2011; Sefton et al., 2012; Harris and Richards, 2010). Although MT may need to be modified to accommodate older adults' needs, it appears to be a safe and effective intervention. Given that MT acts upon multiple important pathways for mobility and independence, applying an integrated Geroscience approach will improve our understanding of MT in addressing age-related mobility and functional declines.

5.10. Summary

There is now evidence to support a wide variety of intervention approaches to improve mobility and attenuate functional decline in older adults. Both behavioral and biological interventions hold great promise for improving function and mobility and thereby extending healthspan and promoting wellness in functionally limited but healthy older adults. As noted previously, such interventions may enhance physical function directly, as well as indirectly through modulation of cognitive and socioemotional processes. These processes include depression, social stress, and anxiety, which all have high relevance in aging and may contribute to social isolation and reduced well-being among older adults.

The utility of such interventions to produce desired outcomes is directly impacted by participant adherence to prescribed treatments, and even the most efficacious intervention can be ineffective if the patient fails to follow treatment recommendations. Thus, it is very important to carefully evaluate the sustainability of such interventions, especially in light of research demonstrating that individuals who are not fully adherent to health interventions experience significantly fewer health benefits (Middleton et al., 2013). A variety of factors can affect long-term adherence to health promotion behaviors, including the complexity of the required changes, the number of decision points needed to carry out such changes on a daily basis, and a number of environmental, socio-cultural, and psychological influences (Middleton

et al., 2013). This suggests the need for two approaches to enhance the effectiveness of behavioral and biologically-based interventions: 1) continued refinement of strategies that can enhance the delivery of and adherence to such interventions, and 2) development of novel intervention approaches (e.g., intermittent fasting and intermittent activity bouts) that have the potential to produce similar health benefits as traditional lifestyle approaches and also may be easier to sustain over the long-term.

The role that technological advances may have in increasing the effectiveness of both traditional interventions, as well as more novel intervention approaches, is a topic of great interest. In the section below, we describe some of the key considerations in delivering digital and mobile health (mHealth) based interventions in older adults.

6. Role of smart and connected technologies

6.1. Digital interventions

Personally-held devices, such as smartphones, smartwatches and fitness trackers, provide a ubiquitous infrastructure for researchers and clinicians to passively collect a moment-by-moment quantification of individuals' behavior in their own environment, or recently referred to as digital phenotyping.

Smartphones are considered the most common electronically held devices. Pew Research Center (PRC) conducted a survey about the ownership of smartphones in 2019 showing that 81% of Americans and 53% of older adults own smartphones, usage doubling among Americans and nearly quadrupling among older adults since 2010 (*Tech Adoption Climbs among Older Americans, 2017; Demographics of Mobile Device Ownership and Adoption in the United States, n.d.*). Smartwatches are also growing rapidly. The International Data Corporation (IDC) Worldwide Quarterly Wearable Device Tracker published that smartwatches accounted for 44.2% of the wearable market in 2018 and is expected to rise to 47.1% by 2023 (*Framingham, 2019*). PRC has published recently a survey showing that one-in-five Americans (21%) wear a smartwatch or a fitness tracker (*Vogels, 2020*). A recent study by Manini and colleagues (*Manini et al., 2019*) about the perception of older adults (65+ years) towards the use of smartwatch technology for assessing pain showed an overall positive view.

Data collected using smart devices fall under two main categories: active and passive data. The essential difference between these two types is the involvement of participants in reporting data. The active data is described as questions or surveys that a participant has to self-report at specific times. This data is commonly used for ecological momentary assessment (e.g., pain, mood, or fatigue).

In contrast, passive data collection does not require participants to report any data. Participants are only required to carry the smart device to be able to continuously collect data through built-in sensors. The type of passively collected data and the quality depend on the availability and

modalities of sensors. The most common sensors available are: 1) global positioning sensor (GPS) that could be used to measure life-space mobility; which is a measure of the spatial size and frequency of interaction with the surrounding environment; 2) accelerometer that could be used to track physical activity pattern and energy expenditure; 3) microphone that could be used to collect voice samples to be used to extract vocal markers that can serve as a prognostic value for neurological disorders; and 4) call and text logs that can convey information about the size and reciprocity of a person's social network and can also serve as a prognostic value for neurological and psychological disorders.

The huge amount of data collected from personally held devices contain hidden, but useful knowledge about the behavior of an individual. Fortunately, the advancement of machine learning techniques allowed us to tap into this data and extract patterns.

6.2. Mobile health interventions

In recent years, sensors embedded into wearable and personal devices such as smartphones have made it possible to develop many mHealth apps, e.g. for tracking physical activity, monitoring blood pressure and heart rate, medication reminders, and many more (*Nouri et al., 2018; Larson, 2018*). Some mHealth apps additionally provide Just in Time (JIT) interventions (*Fig. 4*), such as prompting physical activity based on inferred levels of activity or daily steps.

A number of recent studies have utilized such mHealth tools in controlled trials to examine mHealth interventions, especially for chronic disease management (*Marcolino et al., 2018*). Several studies have used mHealth intervention tools in cardiovascular and diabetes patients, including the pilot mobile Atrial Fibrillation (mAF) (*et al., 2017*) Trial ($n = 113$, cluster randomized design pilot study). As the first mHealth trial of atrial fibrillation patients, mAF showed improved drug adherence and anticoagulant satisfaction versus the usual care. In a larger study, the Heart Failure II (TIM-HF2) trial (*Koehler et al., 2018*) ($n = 1571$, randomized parallel-groups), utilized remote monitoring and demonstrated that it could reduce the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality. In a remote monitoring study, Giacomelli et al. (*Olivari et al., 2018*) showed that remote monitoring after hospitalization for heart failure in older adults had no impact on the primary end-point but it significantly improved patients' quality of life.

Physical activity promotion also has been examined in several mHealth trials, including the mActive (*Kaerberlein et al., 2015*) trial which showed that tracking and texting intervention increased physical activity. Amorim and colleagues (*Amorim et al., 2019*) carried out a randomized controlled trial by integrating mHealth, health coaching, and physical activity for patients suffering from chronic low back pain, demonstrating feasibility and acceptance and a reduction in care-seeking after treatment discharge. Other studies have examined mHealth interventions for promoting mental health in clinical trials, including using smartphone cognitive behavioral therapy for refractory depression (*Mantani et al., 2017*) and smartphone-delivered intervention in patients with a serious and persistent mental health condition, with the improvement shown among patients from racial minority groups (*Thaiss et al., 2018*).

These recent intervention studies and especially controlled trials show promise for the potential scalability and acceptance of mHealth tools. An important but sometimes overlooked aspect of developing mHealth intervention tools is conducting formative usability evaluation research, besides evaluating efficacy in formal trials. Tools must be designed to effectively communicate the proper information by being interactive, interoperable, engaging, and accessible for diverse audiences (*Neuhauser and Kreps, 2008; Kreps, 2014*). Therefore, the following attributes should be considered during the development, adoption, and implementation of mHealth tools: 1) ease of use; 2) how the tool fits within the policies, practices, and technical infrastructure of existing health and social systems; and 3) whether intended users can

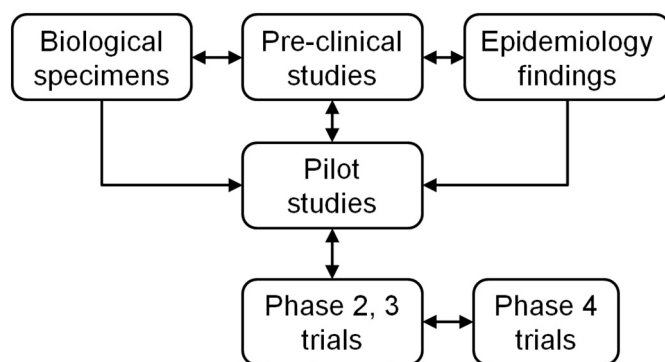


Fig. 4. Bench to bed pipeline model for developing geroscience based interventions.

understand and apply the health information provided. Performing needs analysis and audience analysis can help guide the design to achieve such objectives (Kreps, 2014).

In summary, while mHealth tools may enhance the delivery of some interventions, especially in chronic disease management, evidence regarding their effectiveness for geriatric conditions is still mixed (Marcolino et al., 2018; Dugas et al., 2020). Additionally, most controlled trials have been carried out in high-income countries, and evidence on the effectiveness of such tools in lower-income countries is missing (Marcolino et al., 2018). Finally, there are a lack of end-to-end systems for sharing JIT intervention results with providers through existing Electronic Health Record (EHR) systems.

7. Role of pre-clinical animal models

Both humans and animals exhibit an age-dependent progressive decline in mobility (Hosono et al., 1980a; Hsu et al., 2009; Jones and Grotewiel, 2011; Ferrucci et al., 2016b). Thus, mechanistic studies of age-related mobility impairment in pre-clinical models could advance our understanding of the fundamental mechanisms underlying disability. For example, there is much that can be learned from the study of the simple organism *C. elegans*. Despite its simple anatomy, *C. elegans* is capable of multifaceted behaviors in response to diverse environmental and intrinsic cues, and exhibits an age-associated decline in locomotion (Hsu et al., 2009; Hosono et al., 1980b). The multitude of genetic tools available also makes *C. elegans* an invaluable model system for the study of cellular and molecular mechanisms underlying aging-related locomotor and movement decline (Son et al., 2019). In *C. elegans*, the progressive deterioration of muscle occurs with age, which resembles human sarcopenia (Herndon et al., 2002). Importantly, the functional decline of motor neurons at the neural muscular junctions precedes the deterioration of muscle tissues during *C. elegans* aging (Liu et al., 2013), indicating an important role of motor neurons in the age-related mobility impairment.

Findings from pre-clinical models have led to the identification of important biological mechanisms related to the aging process including mitochondrial function and dynamics (Safdar et al., 2010; Garnier et al., 2005), autophagy (Singh and Cuervo, 2011; Wohlgemuth et al., 2010), oxidative stress (Lee et al., 2012), chronic inflammation (Chung et al., 2009), muscle composition (Manini et al., 2014), hormonal factors (Bizon et al., 2001), and neurodegeneration (Rosso et al., 2013). Moreover, preclinical studies have led to the transformative discovery that interventions targeting the fundamental biology of human aging have the potential to delay, if not prevent, the onset of aging-associated conditions (Kennedy et al., 2014; Ferrucci et al., 2016a; Seals et al., 2016; Seals and Melov, 2014; Justice et al., 2018). Ultimately a strong translational geroscience approach is needed to understand the disease-mediated pathways associated with functional decline and identify promising interventions to maintain mobility and physical function (see Fig. 4).

8. Statistical considerations

As aging research becomes more information-based, statistics plays a critical role in almost all research topics discussed in the previous sections. For any given aging research project, statistical support is needed at almost all stages starting with the formulation of a scientific hypothesis, study design, data collection, data management and analysis, and conclusion making and ending with manuscript writing. Often, the earlier a statistician is involved in an aging research project, the more productive the project will become.

Let us use a specific example to demonstrate how statistics can significantly help aging research. Assume that a research project aims to investigate whether an intervention (e.g., a nutritional supplement) can improve older adults' mobility. To make the hypothesis more specific, we first need to determine major mobility measurements. According to

Webber (Webber et al., 2010), mobility can be measured in five dimensions (i.e., cognitive, psychosocial, physical, environmental, and financial), and there are many different ways to measure mobility in each dimension. If we are interested in all five dimensions and would like to develop a single mobility index or choose some important ones from all possible mobility measures, then some preliminary studies to collect data on these measures are needed.

The data from these preliminary studies can be analyzed by statistical modeling and variable selection approaches, allowing us to come up with either a single mobility index or a relatively small number of mobility measures. These variables can then be used as the response variables of the original study. Second, the sample size for the study needs to be properly calculated. To do this, researchers need to specify the smallest meaningful difference between the intervention and control groups for each response variable. The next step is to check whether all model assumptions of the related sample size formula are valid. If not, then a new formula needs to be derived, which could be challenging.

For data collection, statisticians are vital in determining which study design is best, such as deciding between a double-blinded randomized study or other types of studies. These steps of study design are extremely important to make the collected data useful in testing the major scientific hypothesis. After data collection, much statistical expertise is required to analyze the data and make solid conclusions. During data analysis, proper statistical methods that clearly describe the observed data need to be chosen, all model assumptions should be verified, and develop new statistical methods when necessary.

9. Dissemination and implementation

Primary care physicians and geriatricians play an instrumental role in the identification of older adults who have or are at risk for impaired mobility. Unfortunately, healthcare providers encounter several barriers to the proper evaluation and treatment of mobility issues in older adults. Some of these barriers include insufficient knowledge of the latest research findings in the field of geroscience, time constraints in busy clinics, lack of needed resources for treatment interventions, weak patient support systems, and even language barriers in some minority communities. Despite these barriers, most patients can be quickly and efficiently screened for cognitive concerns and/or mobility issues with validated assessments, such as the "get up and go" test. When appropriate, providers should deliver succinct but impactful counseling on the importance of adopting a healthy diet, practicing regular physical exercises, and obtaining adequate sleep. The use of educational hand-outs can be very helpful for some patients. Clinicians should also use available resources for the enhancement of mobility, such as referrals to physical/occupational therapy, ophthalmology, audiology, and massage therapy.

There is a need for more educational programs for healthcare providers covering the latest research findings in the treatment of geriatric conditions including impaired mobility. Optimal communication between clinical researchers and clinicians might facilitate the prompt implementation of efficacious new treatments. Collaboration among academic investigators and community partners also has the potential to increase the relevance of the research and its potential for addressing public problems such as general health disparities (Jacquez et al., 2016) and health problems more specific to seniors, such as limited mobility. Such collaborations require (a) culturally sensitive, multidisciplinary academic research teams, (b) empowerment of community members through training them to assume leadership in implementing and disseminating research center-tested interventions and assisting in getting the institutional review board credentials for being equal research partners, (c) paying trained community member researchers as research professionals, (d) mobilizing community resources and partners (e.g., businesses and local officials) to make policy changes to reduce the social determinants of health (e.g., no/limited public transportation in target low-income Black communities) that impede implementation and

dissemination efforts.

Interventions shown to be efficacious in research centers are typically implemented and tested under controlled conditions with non-representative samples of motivated participants (Starfield, 1998). There is a need to implement and disseminate efficacious interventions in communities where uncontrollable social determinants of health (e.g., poverty, race and racism) and associated health disparities negatively influence the length and quality of community members' lives. These communities are where seniors, racial/ethnic minorities, the poor, and/or the medically underserved (i.e., health disparity groups) often live. Because of this, ideal implementation and dissemination sites in such communities are churches (et al., 2014; McNeill et al., 2018) and primary care centers (Tucker et al., 2020). It is these sites that commonly serve the aforementioned groups, are stable community structures with physical resources (e.g., meeting spaces), and have human resources (e.g., pastors and physicians) who can influence members of health disparity groups to participate in efforts to implement and disseminate health promotion interventions.

The empirically supported community-based participatory research (CBPR) approach (Belone et al., 2016) is useful in implementing and disseminating efficacious interventions in communities in general and in racial/ethnic minority, poor, and/or medically underserved communities in particular. CBPR creates a paradigm shift from traditional research practices that have characterized academics as experts towards a collaborative research process in which academics are also learners (Balazs and Morello-Frosch, 2013). Accordingly, the CBPR approach requires that community members be actively involved in all aspects of the research process, including the selection of the research topic and methodology, participant recruitment, research implementation, data collection, interpretation of study results, and dissemination of research findings (Balazs and Morello-Frosch, 2013; Horowitz et al., 2009).

The patient-centered culturally sensitive healthcare (PC-CSHC) model (Tucker et al., 2020), explains the linkages between provider cultural sensitivity and patients' health outcomes and is useful in guiding implementation and dissemination in community-based healthcare settings. Notably, cultural sensitivity extends beyond cultural competence and enables patients to feel comfortable with, trusting of, and respected by providers and researchers, and involves recognizing and overcoming biases and stereotypes that these groups have towards to each other (Tucker et al., 2020). The provider being culturally sensitive is one key aspect of the PC-CSHC model and is a major factor in health promotion. Further, patients must be allowed to determine what behaviors, methodologies, etc. enable them to feel comfort, trust and respect.

The other key aspect of this model is patient and community empowerment. In accordance with the PC-CSHC model, implementation and dissemination of research center-tested interventions in community primary care sites that serve health disparity groups requiring that patients and community health workers are active partners with academic researchers. For example, patients should ideally be involved in focus groups and/or interviews to identify culturally sensitive strategies for making these efforts successful. Community health workers, physicians, and other providers can then (a) implement these strategies and disseminate the target interventions, and (b) participate with researchers in town hall meetings to disseminate information to the community about the impact of these interventions. Culturally diverse, multidisciplinary academic research teams can provide the training needed for physicians/providers and patients to be empowered, equitable partners in implementing and disseminating target interventions. Such empowerment by academic researchers is particularly important for patients such as minority, senior, poor, and medically underserved patients with limited actual and/or perceived power to take charge of their health. Patient empowerment is the appropriate response to the increasing national calls for social, health, and healthcare justice.

10. Conclusions

Can we really slow the decline in mobility that occurs during aging? And can function improve as we age? The good news is that the answer to both questions appears to be an emphatic yes. Effective future interventions, however, will need to take into consideration factors across multiple domains, as well as the complex interaction among these factors. Findings over the past decade have highlighted the complexity of walking and how targeting multiple systems, including the brain and sensory organs, can have a dramatic effect on an older person's mobility and function. Additionally, several biological and behavioral factors have been identified as directly related to functional capacity.

These are exciting times within the field of Gerontology with novel discoveries happening across different fields of study that have direct implications for function and/or functional capacity. For example, the discoveries made within the biology of the aging realm have informed of the types of intervention targets that could truly make a difference in an older adult's functional capacity. Furthermore, COVID-19 has highlighted the importance of self-care and preventative medicine to promoting wellness and extend healthspan. COVID-19 has also highlighted the clear need to protect our older population, particularly minority older adults, as there are clear biological and metabolic factors that increase older adults' susceptibility to this condition. Additionally, COVID-19 has greatly increased the adoption of virtual communication; thus, the acceptability of technologically based future interventions is likely to be much greater than prior to COVID-19.

Before translating interventions on a broad scale, however, their suitability and effectiveness across a number of domains are needed to help inform decision making. Clearly, there is an important need to evaluate safety outcomes, first and foremost, with the next benchmark related to whether such interventions are sustainable. There is also the need to carefully determine the types of randomized clinical trials that are best suited to address particular questions, as well as the appropriate comparison groups.

Acknowledgements

Americans Independence Center (NIH/NIA P30AG028740), Science Institute (NIH/NCRR UL1TR000064).

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