Review

Successful Aging as a Continuum of Functional Independence: Lessons from Physical Disability Models of Aging

Kristin A. Lowry[1], Abbe N. Vallejo[2], Stephanie A. Studenski[1]

[1]Division of Geriatric Medicine, University of Pittsburgh, 3471 Fifth Avenue, Kaufmann Medical Building, Suite 500, Pittsburgh PA 15213, USA
[2]Children's Hospital of Pittsburgh, Departments of Pediatrics and Immunology, University of Pittsburgh, 4401 Penn Avenue, Rangos 9118, Pittsburgh, PA 15224, USA

ABSTRACT: Successful aging is a multidimensional construct that could be viewed as a continuum of achievement. Based on the disability model proposed by the WHO International Classification of Functioning, Disability and Health, successful aging includes not only the presence or absence of disease, but also aspects of mobility and social participation. Here we review definitions of successful aging and discuss relevance of the disability model in the evaluation of successful aging and frailty. In particular, we summarize evidences that highlight the importance of measures of mobility (ability to walk and perform activities of daily living), and social participation in identifying and locating older adults across the range of the successful aging continuum. Lastly, we discuss the role of inflammation in age-related decline and in frailty. Future research directions are proposed, including identifying causal pathways among inflammatory markers, disability, and frailty. A better understanding of immunological functioning in late life may help unlock novel ways to promote successful aging.

Key words: mobility; participation; frailty; inflammation

Over the past century, substantial increases in life expectancy and advances in health care and research, combined with escalating health care costs, have led to great interest in how to promote a healthier old age and how to age "successfully." The goal of aging successfully appears increasingly feasible, as evidence builds that interventions such as physical activity can reduce disability and promote better health in late life, and morbidity becomes compressed into a much shorter duration [1, 2]. With observations for increases in total life expectancy in recent years, there is considerable research interest in the measure of active life expectancy (ALE). ALE measures the number of years a person can expect to live without disability. Supporting the concept of morbidity compression, recent findings indicate that younger cohorts of older adults are living longer with less disability [3]. Recent work supports the premise that ALE provides valuable information to health care professionals and policy makers. For example, while neither obesity nor arthritis (alone or in combination) was related to length of life for older adults, the combination of the two was significantly related to decreased ALE, or higher levels of disability [4]. In another application, both men and women with Alzheimer's disease exhibited shortened life expectancy and spent a greater proportion of their remaining years with extensive disability compared to cognitively intact peers [5]. Thus, central to the tenet of ALE as a component of successful aging is the measurement of disability.

Nevertheless, there is little consensus on the optimal definition of successful aging and its measurement. There is also no consensus on what term would be used, with descriptors ranging from "healthy aging", "positive aging", "optimal aging" to "aging well". This review will discuss the definitions of successful aging, the use of the disability model in the measurement of successful aging, recent evidence linking disability, frailty, and

inflammation, and potential future directions for research.

Defining successful aging

The concept of successful aging was first introduced by Rowe and Kahn [6] and used in the MacArthur Research Network on Successful Aging [7]. They offered that those aging successfully would show minimal declines in physiologic function, while those aging 'usually' would show disease-related decrements and loss of reserve capacity, commonly interpreted as the effects of age. Specifically, they proposed three components of successful aging, namely: (a) absence or avoidance of disease and risk factors for disease, (b) retaining a high level of cognitive function, and (c) active engagement in life. Although this is an important model that separates the effects of disease from the aging process itself, it essentially excludes older adults with any degree of incapacity, and focuses on a smaller elite segment of the older population that may result in less interest in secondary and tertiary lines of prevention.

While Rowe and Kahn's biomedical model emphasizes the absence of disease as one of the keys to successful aging, Baltes and Baltes [8] defined successful aging from an ecological perspective. They viewed successful aging as the ability to function across physical/functional, cognitive, emotional, and social domains. They recognized that aging often leads to losses or limitation in one or more domains (allowing for the presence of chronic disease) and proposed that successful aging is the ability to optimize adaptation, i.e. making the most of one's remaining capacities and compensating for losses and limitations. Similarly, in their definition of successful aging, Vaillant and Mukamel [9] describe the importance of physical, social, and emotional health.

An operational definition of successful aging has been elusive. Self-perceived successful aging is much more common than Rowe and Kahn might suggest. About 50% of older adults in one study self-reported that they were aging successfully while only 19% were so classified using Rowe and Kahn criteria [10]. Self-perceived successful aging was nonetheless still related to health and function. The proportion who stated they were aging successfully declined as the number of prevalent medical conditions increased, and was lower in those with functional difficulties.

A recent review of 28 quantitative studies found 29 different operational definitions of successful aging [11]. The lack of a consensus definition presents uncertainty about the actual prevalence of successful aging. In the 28 studies, the mean proportion of successful agers was 36% but the range was 0.4% to 95%. The range was affected by the type of study population; the rates were inversely related to lowest eligible age. It was also affected by the complexity of the definition of successful aging; the rates decreased with the number of components in the definition.

Among the elements in the definition of successful aging, disability and/or physical functioning were the most frequently used (26 of 29) and were most commonly measured by self-reported activities of daily living (ADLs). Factors most frequently associated with any definition of successful aging included age, non-smoking, absence of disability, and absence of arthritis, diabetes, and hearing problems. While no satisfactory definition of successful aging has yet emerged, all evidences to date suggest that the presence of disability and level of physical functioning are key components of any definition.

Disability as a measurement of successful aging

The WHO International Classification of Functioning, Disability and Health (ICF) provides a framework to describe the impact of health conditions at both individual and societal levels [12]. From the ICF standpoint, disability is a result of an interaction between a person (with a health condition) and that person's contextual factors (environmental factors and personal factors)**.** Disability denotes all of the following: (a) impairments in body functions and structures; (b) limitations in activity (individual level); and (c) restriction in participation (societal level). Thus, disability = A + B + C, and the full picture of disability can only be acquired by measuring all three dimensions.

Impairment information: Anatomical impairment alone may not provide a complete picture of the situation of disability. Knowing that an individual has loss of vision or hearing does not reveal whether these impairments affect that person's ability to carry out day-to-day activities. Further, people with the same impairments may experience very different daily life restrictions. The converse is also true; people can experience the same restrictions even though they have different impairments.

Limitations in Activity: These are typically measured by assessing (a) mobility, and (b) both basic and instrumental ADLs. Mobility is defined as the ability to move one's own body through space, and includes activities such as walking, standing up, reaching, turning over in bed and climbing stairs [13]. These mobility tasks are the building blocks of both basic ADLs (e.g. bathing, dressing, eating) and instrumental ADLs (e.g. housework, preparing meals, shopping, managing

money). Walking, viewed as the fundamental mobility task for human life, is a complex neuromotor activity. Many variables influence walking speed, including musculoskeletal status [14, 15], sensory function [16], motor control [17], and cognitive status [18]. There is now rich empirical evidence that objective or self-reported measurement of walking ability in older adults is a powerful predictor of future health and mortality.

Walking ability is typically measured by determining: (a) usual walking speed, measured over a distance of 4 or 8 meters, (b) time to walk 400 meters (approximately 1/4 mile, or 2 to 3 city blocks), or (c) self-reported ability to walk 1/4 mile, rated on a scale ranging from no difficulty at all, to unable to walk the distance. The most common and practical objective measure of walking ability is usual walking speed, typically determined by the time to walk 4 or 8 meters, using a stopwatch or an instrumented walkway. Usual walking speed in healthy adults typically ranges from 1.2 to 1.4 m/s and begins to decline in the 5th and 6th decades of life [19].

In older adults, walking at speeds faster than 1.0 m/s has been associated with greater independence in ADLs and reduced likelihood of hospitalization and adverse events. Conversely, walking at speeds slower than 0.6 m/s has been associated with dependence in ADLs and increased likelihood of hospitalization [20]. Usual walking speed has been associated with survival in single cohorts [21-23] and a recent pooled analysis of 9 cohort studies revealed that faster walking speeds are associated with improved survival, with significant increments in survival per 0.1 m/s [24]. Further, the accuracy of predicted survival using only walking speed, age and gender has been found to be similar to more complex models including health-related factors or functional status [24]. These findings support the premise that walking speed is a general summary indicator that reflects the integrity of various underlying physiological processes.

Higher-level mobility includes the ability to go outside the home without help, the ability to walk longer distances such as 1/4 mile (400 meters), and the ability to climb stairs. Higher-level mobility disability has been defined as an inability or difficulty with walking 1/4 mile [13]. Slower 400-meter walk times have been associated with a higher risk of mortality [25, 26] and older adults who needed to stop and rest during the 400-meter walk were more likely to develop future mobility disability [27]. Similar to actual performance, self-reported limitations in walking 1/4 mile were associated with subsequent mortality, development of disability, and increased hospitalizations and health care costs [28].

Reports of limitations in functional abilities (activities of daily living or ADLs) are also associated with adverse outcomes. Older adults who were dependent on personal assistance for ADLs had the highest probability of admission to a skilled-nursing facility and highest probability of death, followed by those who reported being independent but had difficulty [29]. Older adults who reported no difficulty with ADLs exhibited the lowest probabilities of adverse outcomes. Similarly, ADL performance upon admission to a nursing home strongly predicted 3-year mortality [30].

Clearly, physical performance, and self-reported measures of mobility and ADL are simple, brief, and cost-effective methods that characterize an individual's limitations in activity. They provide estimates of future risk for hospitalization and mortality, and may be used to screen older adults in clinical settings.

Restriction in Participation: Participation restriction is defined as "problems an individual may experience in involvement in life situations"[12]. It refers to the negative personal and social consequences of health conditions. While it might be expected that limitations in activity are a major cause of participation restriction (e.g. difficulty in walking leads to restrictions in leaving the home), personal and environmental factors may worsen or lessen the effects of activity limitations, or cause restrictions in older adults who have no or minimal limitations [31]. For example, an older adult may initially walk faster than 1.0 m/s and be independent in ADLs. But with lack of transportation or finances, he/she may be restricted in leaving their home. This restriction could ultimately lead to a decline in mobility and health. Likewise, an older woman with minimal impairments and activity limitations who provides care to her dependent spouse could be restricted to her home. These types of issues have led to a growing interest in the investigation of participation restriction in older adults.

A cross-sectional survey revealed that that the health and disability factors most strongly associated with participation restriction were the number of health conditions, presence of pain, cognitive impairment, depression and activity limitation [31]. After adjusting for these factors, perceived adequacy of income, employment status, and occupational class were also strongly associated with participation restriction. Interestingly, 14% of responders classified at the highest level of activity limitation did not report any participation restriction. These findings suggest that while activity limitation and participation restriction are strongly related, participation restriction is a distinct concept influenced by a wide range of health and socio-economic factors.

Researchers investigating the natural history of participation restriction over 3 years in people aged 50 years and older found that overall participation was

unchanged in ~ 70% of the sample, and changed in 30% [32]. Nearly 30% of those free from restriction at baseline reported restriction in at least one aspect of life 3 years later, whereas 30% of those who had a restriction at baseline reported being free from restrictions 3 years later. The oldest age-group had both higher incidence and persistence of participation restriction. The most common form of restriction evident even in the young-old was restricted mobility outside the home. These findings indicate that participation restriction naturally fluctuates over time with periods of incidence and recovery, and that restrictions begin first with mobility outside the home.

Recently, the Late Life Function and Disability Instrument (LLFDI) [33, 34] was used to examine what variables contributed to self-reported frequency of involvement versus perceived restriction [35]. Participation frequency questions are phrased, "How often do you do...?", whereas perceived restriction questions are phrased "To what extent do you feel limited in doing…?". The authors found that age, fall history, and general physical activity levels were strongly associated with participation frequency, whereas mobility variables had the strongest associations with perceived restriction. Depressive symptoms were associated with both reduced frequency of involvement and more restrictions.

All the above findings highlight the complex relationships between health, mobility, and participation. Therefore, a definition of successful aging needs to consider a multidimensional construct, rather than a count of incident diseases or conditions. Rather than classifying an older adult as successful or unsuccessful, aging may be viewed as a continuum of achievement. Individuals with few activity limitations and participation restrictions may be on the "more successful" end of the continuum, whereas individuals with greater limitations and restrictions may be on the "less successful" end; that is, all the components of disability (impairments, limitations in activity, participation restriction) should be considered when locating an older adult on the continuum. Additionally, the findings from the participation restriction literature suggest that this continuum is not unidirectional. Rather, successful aging is dynamic, and individuals can move either way on the continuum. For example, a high-functioning older adult who undergoes a joint replacement or suffers a mild stroke may temporarily experience slow, painful gait, an inability to leave their home unassisted, and depression. But following rehabilitation and a recovery period, he/she may return to their previous status. While there is no current consensus on the critical parameters or minimal criteria for good or

bad physical function, usual walking speed and/or self-reported measures of walking ability and ADL status can be used to identify and locate older adults across the range of the continuum [20, 24, 28]. By monitoring these tasks over time, clinicians can detect change and initiate appropriate treatments to prevent decline or restore function. Thus, one important challenge to researchers and health care providers is to monitor and detect older adults at increased risk of disability. An important state that is distinct from normal aging and a strong risk factor for disability is the clinical syndrome of frailty [36].

Frailty

In clinical practice, the syndrome of frailty identifies the most vulnerable subset of older adults at increased risk for adverse outcomes and requiring enhanced care. In the United States, it is estimated that frailty affects 7% of the population age $\geq$ 65 years, and 25-40% of those $\geq$ 80 years [36], with a majority of nursing home residents identified as frail [37]. A recent Canadian study reported the percentage of deaths due to frailty was similar to percentages due to sudden death, terminal illness, or organ failure, and the health care costs for frailty in the last two years of life were similar to those for patients with cancer or organ failure [38]. Thus, the impact of frailty is significant for the individual, his/her immediate family, and the society at large.

Frail older adults are often assumed to be disabled, and have multiple chronic conditions or comorbidity. Recent research supports the premise that frailty, comorbidity, and disability are not synonymous terms, but describe distinct, yet interrelated entities. One-quarter of older patients show signs of frailty without multiple comorbidities or disability that makes them dependent on others or outside services [39]. It has also been demonstrated that there is not a linear path from comorbidity through disability to frailty; rather, frailty may either be the cause or the consequence of disability [40]. While frailty is a commonly used term in clinical practice, it remains an evolving concept that has neither consensus definition nor unique diagnostic criteria [41].

In general, frailty describes a subset of older adults who are at risk of adverse events due to reduced ability to respond to stress [41]. A research group led by Fried et al. [36, 42] described frailty as a state of global deficiency of physiological reserves and functional dysregulation involving multiple organ systems, resulting in poor homeostasis and increased vulnerability when faced with stressors. They defined a frailty phenotype as a clinical syndrome characterized by shrinking (unintentional weight loss and sarcopenia/muscle wasting), weakness, exhaustion or

poor endurance, slow walking speed, and reduced overall activity. Presence of three or more of the criteria was defined as positive for the frailty phenotype, whereas individuals with one or two of criteria are considered "pre-frail".

Based on data from the Cardiovascular Health Study (CHS), the frailty phenotype independently predicted incident falls, ADL disability, hospitalization and death, and prefrail status showed intermediate risk of adverse outcomes as well as increased risk of becoming frail [36]. Using this CHS frailty phenotype criteria, a recent study classified 48% of residents of assisted living facilities as frail, finding these individuals at greater risk for death (adjusted risk ratio 1.75) and hospitalization (adjusted risk ratio 1.54) [43]. Although research using this CHS frailty phenotype consistently supports its ability to predict poorer outcomes, one limitation is that items used to identify frailty are all measures of physical health without due consideration of cognitive performance or emotional status.

Another working group led by Rockwood et al. defined frailty as an at-risk state caused by the age-associated accumulation of deficits [44]. Deficits cover a whole range of health problems, and can be in the form of symptoms, signs, clinical laboratory abnormalities, and incident diseases or disabilities. Deficits are counted and combined in a "Frailty Index", determined from a comprehensive geriatric assessment of multiple domains including cognition, mood, motivation, communication, mobility, balance, ADL, bowel and bladder functions, nutrition, comorbidities, and social resources [45, 46]. The premise is that as older adults accumulate more deficits, they are at more risk and become more frail. Across studies, increasing values of the frailty index are highly associated with an increased risk of death. When both frailty index and age are combined in a multivariable model, frailty index has predicted mortality better than age [45, 47, 48].

From the ICF disability framework perspective, frailty is linked with both participation restriction and limitations in activity (mobility). In a study of community-dwelling adults who met the criteria for the CHS frailty phenotype, 80% reported participation restriction in at least one aspect of their lives [49]. And such participation restriction is independently associated with mobility, as 51% reported restricted community mobility.

Several recent studies have examined the relation between frailty status and mobility. Higher Frailty Index scores (more deficits) were associated with poorer performance on physical performance measures, including a timed walk test, but only at the very upper range of index scores did all participants demonstrate some mobility impairment [50]. In a cohort study of community-dwelling adults, those classified as having good baseline mobility (based on a timed fast walking test) had greater probability of improvement or stability of the Frailty Index over a 36 and 54 month follow up compared to those with poor baseline mobility [51]. These data suggest interactions between frailty, mobility, and participation restriction, supporting the premise that frail older adults are less mobile and more restricted [51].

Just as frailty is a syndrome reflecting the function of many systems, usual walking speed is also a general summary indicator reflective of the integrity of multiple underlying physiological processes. Given that slow walking speed is one of the five criteria for the CHS frailty phenotype, gait speed could be a useful single-item screening tool to identify frail older adults, with a proposed threshold speed of 0.8 m/s [52, 53]. While the pathophysiologic mechanisms underlying the frailty process are not yet fully understood, both the phenotypic and deficit accumulation definitions of frailty recognize the involvement of multiple systems. The most commonly suggested impairments involve dysregulation or loss of redundancy in neuromuscular, endocrine, and inflammatory systems.

Role of inflammation in age-related decline and in frailty

The serum levels of the inflammatory markers interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) have been found to increase with age. Although neither the sources of these molecules nor the cause for their systemic upregulation are known, higher quartiles of inflammatory markers have been associated with, and predict poorer outcomes in older adults, and are consistently associated with cardiovascular disease, diabetes, cancer, and all-cause mortality (see thorough review by Singh and Newman 2011)[54]. In addition to these associations with multiple chronic diseases, there is a growing body of research about the associations among inflammatory markers, mobility and disability.

Higher levels of IL-6 have been associated with poorer physical performance measures, including slower walking speeds, poorer standing balance, and longer times to complete repeated chair stands [55, 56]. In a large prospective study, circulating levels of IL-6 greater than 2.5 pg/mL predicted future mobility disability (walking 1/2 mile or climbing stairs) in older adults who had no disability at baseline [57]. Similarly, data from the Women's Health and Aging Study (WHAS) showed that older women in the highest IL-6 tertiles had higher

relative risks of mobility disability and severe limitations in walking compared with those in the lowest tertile, even after adjusting for age [58]. In the Health, Aging, and Body Composition (Health ABC) study, higher levels of IL-6, TNF-α and CRP predicted incident mobility limitation (difficulty or inability to walk 1/4 mile) over 30 months independent of disease and illness [59], and that individuals with elevated levels of all three markers had the highest incidence of mobility limitation. Further, the onset of disability is generally preceded by elevation of inflammatory markers [60, 61].

There is a growing body of evidence linking inflammation and frailty. Frail older adults exhibit higher levels of CRP [62] and IL-6 [63], and higher CRP levels are associated with an increased risk for development of frailty [64]. With increasing patient frailty (as defined by the CHS frailty phenotype and the Frailty Index of accumulated deficits), levels of TNF-α, IL-6, and CRP increase significantly, suggesting the association with inflammation does not depend on the specific definition of frailty [65].

One explanation for the associations among inflammation, mobility decline, and frailty is the effects that inflammatory markers have on muscles. CRP, IL-6 and TNF-α receptor-2 levels are negatively correlated with rate of skeletal muscle protein synthesis [66], indicating that inflammation participates in the development of sarcopenia, which is defined as a loss of muscle mass and strength leading to functional alterations [67]. Higher combined levels of IL-6 and TNF-α are associated with smaller muscle area, less muscle mass, and lower knee and grip strength [68]. In an InCHIANTI study, IL-6 independently predicted grip strength and muscle power [69], and in the Framingham Heart Study, IL-6 predicted loss of fat free mass [70]. In the previously mentioned WHAS study, when the hazard models for risk of mobility disability and severe limitations in walking were adjusted for change in knee strength over time, the association between high IL-6 and decline of physical function was substantially reduced, suggesting that one mechanism underlying the development of disability in these women with high IL-6 serum levels is the effect of IL-6 on muscle strength [58].

As sarcopenia is a major component of the CHS frailty phenotype, it has been proposed that inflammation in these individuals is related to sarcopenia rather than to frailty itself [65]. Further, sarcopenia may lead to changes in body composition and abdominal adiposity, which in turn is associated with insulin-resistance. Insulin-resistance is associated with an increased risk for the development of frailty [64].

However, causal relationships between IL-6, TNF-α, and other inflammatory markers, and muscle wasting, or frailty in general, have yet to be proven. While IL-6 appears a stronger predictor of muscle weakness, only TNF-α has been shown to elicit muscle cell cytolysis in vitro and in animal models [71, 72]. An important cautionary note is that during normal chronologic aging and in the setting of frailty, the levels of inflammatory markers found in serum are at low picogram-quantities, hence the term "low-grade inflammation" [73]. This is in stark contrast to much higher microgram/milligram-levels of systemic cytokines found in young patients with chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus [74, 75], yet such patients do not exhibit the clinical features of sarcopenia and frailty. Another important consideration is the pleiotropic effects of cytokines [76]. And although both IL-6 and TNF-α have clear inflammatory effects, they are also required for normal antibody-mediated and cell-mediated protective immune responses, respectively.

Therefore, an important question that has yet to be examined is the level at which IL-6 or TNF-α cause muscle wasting or sarcopenia. Alternatively, low levels of systemic IL-6 and TNF-α could simply be surrogate markers of ongoing age-related declines in various physiologic systems. And a counter intuitive but equally reasonable, possibility is that such low levels of systemic upregulation of cytokines might represent a unique physiologic environment wherein novel processes of homeostasis operate in old age. A case in point are centenarians who have been found to express more than twice the level of plasma IL-6 compared to 65-80 year olds, and yet such centenarians are functionally independent [77]. Clearly, there is much room for further investigation into the role of inflammatory molecules in the elaboration of the frailty phenotype in particular, and in health and performance outcomes in old age in general.

Gaps in knowledge and future directions for research

All the above findings indicate that successful aging is a multidimensional construct. Viewed from the ICF disability model [12] successful aging includes not only the presence or absence of disease, but also aspects of mobility and social participation. Thus, in order to pursue gaps in knowledge about underlying mechanisms and to translate insights into novel interventions, we suggest consideration of a spectrum of successful aging. Among more successfully aging older adults, a mechanistic research focus could be to identify factors which promote resilience from age-related frailty, while research in clinical translation could focus on

interventions that prevent, or substantially delay, functional decline. For the more frail, a mechanistic research focus could be on the dynamics of multiple system dysregulation, and a clinical research focus could be on novel interventions to promote recovery and increased tolerance to stress.

An important clinical translation study is a proposal for the development of standards for IL-6 serum levels that could be useful in medical practice [58], perhaps in the diagnosis of frailty and in prognosticating functional independence or dependence. Considering the consistent finding for the inverse relationship between IL-6, physical ability, incident disease, and mortality [54], a tantalizing idea is whether IL-6 neutralization might be clinically useful in improving health and function of older adults. Parenthetically, there currently are anti-IL-6 therapies that are clinically used in the treatment of inflammatory diseases such as rheumatoid arthritis and Castleman's disease [78, 79]. A research challenge is to determine whether such therapies would be safe for use among older adults who might otherwise have no inflammatory disease.

A key gap in knowledge is to clarify causal pathways among inflammatory markers, incident disease, disability, and frailty. One approach is to examine immunological responses to an intervention such as vaccination. Frail elders respond more poorly to vaccination compared to the less frail [80]. Thus, reduced vaccination responsiveness suggests that the frailty state might represent a distinctive immunosuppressed phenotype of aging.

An intervention that is known to promote health in aging is physical exercise. Resistance exercise training is known to improve muscle function and mobility in both healthy and frail older adults [81-83]. Multi-component exercise programs (usually focused on resistance, balance, aerobic, and flexibility training) have been shown to improve mobility [84], balance confidence [85], and blood lipid profiles [86]; they also reduce fall risk and fall rate [87], as well as improve quality of life [88].

One mechanism of benefit of physical exercise appears to be related to its effects in down modulating inflammatory markers. High levels of recreational activity have been associated with lower levels of inflammatory markers among high-functioning older adults [89]. In community-dwelling older men, those with self-reported light and moderate physical activity levels had lower levels of inflammatory markers than those who were sedentary [90]. More recently, the effect of exercise on inflammatory markers has been assessed in clinical trials. The Lifestyle Interventions and Independence for Elders (LIFE) Trial demonstrated that a 12-month structured physical activity program lowered IL-6 levels in community-dwelling older adults, and this effect was most pronounced in individuals with the greatest risk of disability [91].

Thus, both observational and clinical trial evidence shows strong association between physical activity and inflammatory state. Future research in this area could focus on the signaling pathways linking exercise to the control or attenuation of inflammation, and on the types of exercise that best promote healthy immune aging in successful agers and in frail older persons. A better understanding of immunological functioning in late life may help unlock novel ways to promote successful aging. This could be facilitated by building a shared vocabulary about the age-related states of health, functioning, and frailty and applying it consistently to studies of inflammation and immunity.

Acknowledgements

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