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Review

Frailty: Past, present, and future?

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ABSTRACT

The prevalence of frailty across the world in older adults is increasing dramatically and having frailty places a person at increased risk for many adverse health outcomes, including impaired mobility, falls, hospitalizations, and mortality. Globally, the concept of frailty is gaining attention and the scientific field has made great strides in identifying and conceptually defining frailty through consensus conferences, in advancing the overall science of frailty by drawing on basic science discoveries including concepts surrounding the hallmarks of aging, resilience, and intrinsic capacities, and in identifying the many challenges faced by professionals within diverse clinical settings. Currently, it is thought that frailty is preventable, thus the identification of a person's degree of frailty is vital. Identification of frailty is achievable through widely used frailty screening tools, which are valid, reliable, and easy to use. Following the identification of a person's degree of frailty, targeted intervention strategies, such as physical activity programs must be implemented. In this perspective, we provide a historical perspective of the frailty field since the last quarter of the 20th century to present. We identify the proposed underlying pathophysiology of multiple physiological systems, including compromised homeostasis and resilience. Next, we outline the available screening tools for frailty with a physical performance assessment and highlight specific benefits of physical activity. Lastly, we discuss current scientific evidence supporting the physical activity recommendations for the aging population and for older adults with frailty. The goal is to emphasize early detection of frailty and stress the value of physical activity.

Introduction

Across the world the older population is increasing rapidly. According to the United Nations, the population over aged 60 years is expected to reach 2.1 billion in 2050 and grow to 3.1 billion in 2100. Together with this increasing older population, the number of persons aged 80 or over is projected to increase threefold between 2017 and 2050, growing from 137 million to 425 million and to 909 million by 2100 as a result of the advances in healthcare and in public health that significantly impact life expectancy (United Nations, June 21, 2017; https://www.un.org/development/desa/en/news/population/world-population-prospects-2017.html; https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf). With this increasing population many serious health concerns emerge including increased risk of chronic diseases, such as diabetes, stroke, Alzheimer's disease and Parkinson's disease.[1] In fact, more than 80% of persons older than 65 years have at least one chronic disease, which increases to at least three by 75 years[2] resulting in global discussions concentrated on how societies will contend with the associated physical, psychological and health needs. For instance, the age-associated physical decline is associated with worldwide concerns of increased falls, hospitalizations, disabilities, and loss of independence.[3,4]

Regular physical activity and exercise play major roles in preventing muscle atrophy and weakness, maintaining cardiorespiratory fitness and cognitive function, boosting metabolic health, and improving or maintaining functional independence due to their influence on multiple physiological systems (e.g.[5]) They have the power to prevent or delay the onset of many diseases and to address the global concerns associated with age-related physical decline. As a matter of fact, Benjamin Franklin's timeless phase, “An ounce of prevention is worth a pound of cure” is of great relevance today. In order to highlight the value of prevention, this perspective is calling all exercise scientists and health professionals associated with adults (middle and older age) to consider placing their focus on identifying persons who are at risk for physical decline. Early detection of at-risk persons for physical decline provides an opportunity to step in and seize a leading role to guarantee these persons maintain a healthy lifestyle and avoid negative outcomes. Screening for physical frailty is a useful proactive first step in the early detection process of

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prevention. This perspective provides an overall summary of frailty from its historical perspective and potential contributing causes, the available screening tools, the specific benefits of physical activity supported by scientific evidence, and the current physical activity recommendations.

Historical perspective

Research focused on identifying frail persons has a long-standing history. Initially, the concept of frailty was published in the geriatric literature during the last quarter of the 20th century. The designation of frailty was synonymous with the concepts of institutionalization and failure to thrive (1970s and 1980s) (e.g.[6,7]) In the late 1980s, frailty was closely associated with the concepts of disability and comorbidity, and the frailty designation was used interchangeably to identify the group of older adults with physical vulnerabilities (e.g.[8–12]). At some point later on frailty, disability and comorbidity were recognized as separate conditions, although interrelated. In order to distinguish these conditions from each other, each condition required a set of criteria for its identification and a definition.[8,13–15] The call for discerning the criteria for identifying frail persons provided transforming direction and remarkable progress transpired.

The major breakthrough in developing the criteria for identifying frail persons was the grouping of multiple frailty manifestations or measures to form a composite score. In fact, the composite score from the multiple measures was found to be better in identifying frail persons than when a single measure was considered by itself.[16,17] This major discovery is clearly employed in the two well-established frailty assessment tools published at the dawn of the 21st century (Table 1, Physical Frailty Phenotype, Frailty Index of accumulative deficits), even though these two assessment tools have differences in methodology and underlying conceptual bases.

Briefly, Fried and colleagues defined physical frailty or phenotypic frailty "as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes."[18] Conceptually, a low level of molecular and cellular dysregulation is present within each physiological system (e.g., musculoskeletal, endocrine, cardiovascular). The summation of the low levels of dysregulation across the numerous physiological systems is revealed when five well-validated physical performance measures (phenotypic criteria) are determined: weakness (grip strength: lowest 20% by sex and body mass index), slowness (walking time/15 feet or 4.57 m: slowest 20% by sex and height), low physical activity (energy expenditure: lowest 20% by sex, <383 kcal/-week (men) and <270 kcal/week (female)), poor endurance/exhaustion (self-reported exhaustion on US Center for Epidemiological Studies depression scale, 3–4 days/week or most of the time) and weight loss (unintentional weight loss > 4.5 kg in prior year). Frailty is scored across a range from 0 (non-frail) to 5 (frail). Frailty is identified when 3 or more of the 5 phenotypic criteria are present, which indicates diminished energetics. Pre-frail is identified when 1 or 2 of the 5 criteria are present, which signifies a high risk of progressing to frailty.

Table 1
The landmark frailty assessment tools.

Physical Frailty Phenotype[18]
Criteria
- Weakness: weak grip strength, lowest quintile stratified by sex and body-mass index
- Slow gait speed: lowest quintile of gait speed (m/s) stratified by sex and height
- Low physical activity: low energy expenditure, based on physical activity questionnaire
- Exhaustion: self-reported, based on two items from the Center for Epidemiological Studies Depression scale
- Unintentional weight loss: self-reported weight loss of measured weight loss of ≥ 5% in past year

Frailty states: non-frail (0 criteria present), pre-frail (1–2 criteria present), and frail (≥3 criteria present)

Frailty Index of Accumulative Deficits[19,20]
Counts health deficits (at least 30), such as signs, symptoms, diseases, disabilities
Health deficits should meet these criteria:
- Represent multiple domains of functioning or multiple organ systems
- The prevalence must increase with age
- Not be too common before the age of 65
- The prevalence should not be lower than 1%

Frailty score: sum of health deficits present divided by total number of deficits measured
Continuous score between 0 and 1, higher scores indicate higher degree of frailty, with ≥ 0.25 indicating frailty

In contrast to the Physical Frailty Phenotype, Mitnitski and colleagues[19,20] defined frailty "as a continuous process characterized as a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability". Taking advantage of the elements within a comprehensive geriatric clinical assessment, a Frailty Index was designed by counting the number of health deficits with the idea that a greater number of deficits signified greater frailty (referred to as the accumulated deficits model.[19] The Frailty Index included health assessments of cognition, motivation, mood, communication, mobility, balance, activities of daily living, nutrition, bowel and bladder function, comorbidities, as well as social resources. The Frailty Index provides a score on a scale from 0 (no deficits) to 1 (all items exhibit deficits.) During the dawn of the 21st century, other frailty assessment tools were created[21]; however, the physical frailty phenotype and the Frailty Index are two frailty assessment tools extensively used today worldwide to predict adverse clinical outcomes.

Indeed, significant progress transpired between 1990 and 2010; yet, the field lacked a "gold standard" definition for frailty (a widely recognized, accepted and valid definition). To address the missing gold standard definition, in 2013 six major international, European, and United States societies (International Association of Gerontology and Geriatrics, European Union Geriatric Medicine Society, American Medical Directors Association, International Academy of Nutrition and Aging, American Federation for Aging Research, and Society on Sarcopenia, Cachexia, and Wasting Diseases) and 7 other experts in the field of frailty convened.[22] The major finding from the gathering of this esteemed international group was the recognition and agreement on the distinction between the broader definition of frailty and a more specific medical syndrome. The broad definition of frailty highlighted the general state or condition of an individual; whereas the specific medical syndrome focused on physical frailty. Physical frailty was defined as: "A medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death." Three years later in 2016, members of World Health Organization, experts working in the field of aging and frailty, and other stakeholders assembled at the "Clinical Consortium on Healthy Ageing" to discuss frailty and intrinsic capacity (https://www.who.int/ageing/health-systems/clinical-consortium-meeting/en/; https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf). This international group defined frailty conceptually as "a clinically recognizable state in which the ability of older people to cope with every day or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems." Interestingly, although consensus groups around the world have gathered together and agreements reached, the search for the gold standard definition of frailty continues (https://www.who.int/ageing/publications/world-report-2015/en/; https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf).

Importantly, the research field of frailty continues to make great strides since 2016. Currently in clinical practice there is intensified emphasis in defining the obstacles that hinder integration of frailty assessment and interventions. In parallel with identifying the barriers of integration there are increased efforts in establishing scientific proof supporting the value of performing frailty assessments and interventions in diverse clinical practice settings (e.g., nephrology, oncology, cardiology.) In order to drive the next generation of research the field of frailty is now capitalizing on the discoveries from basic science, preclinical and clinical studies (e.g., geroscience, animal models, RCT).[23–28] Lastly, there is increased interest in the concepts of physical resilience and intrinsic capacity. Physical resilience is defined as the ability to withstand or recover from functional decline after an acute or chronic health stressor.[29–32] The importance of physical resilience stems from the fact that resilience decreases with age while the risk of many stressors increases.[29,32–34] Physical resilience is not the opposite of frailty.[30] Briefly, the capacity to respond to a health stressor depends on the inherent physiological reserves across the numerous physiological systems (e.g., musculoskeletal, endocrine, cardiovascular). The processes associated with aging and disease result in the loss of physiological reserves, with the magnitude of reduction being unique to each physiological system or tissue.[35] When many of the physiological systems exhibit the presence of low physiological reserve, an individual's overall physiological potential is limited or compromised when a health stressor is imposed. Recently, it was suggested that the stages of frailty (non-frail, pre-frail, frail) reflect the amount of physiological potential available to react to the health stressors; whereas physical resilience is the actualization of the physiological potential.[30]

Consistent with an individual's overall physiological potential is the new concept of intrinsic capacity introduced by World Health Organization in 2015 (https://www.who.int/ageing/health-systems/first-CCHA-meeting-report.pdf?ua=1). The concept of intrinsic capacity includes an array of health characteristics as well as underlying age-associated physiological and psychosocial changes. Specifically, intrinsic capacity is defined as the combination of all the mental (including psychosocial) and physical capacities that an individual is able to use at any instance. With aging intrinsic capacity declines from a high-stable status to an impaired state with significant losses; however, the trajectories of internal capacity between individuals vary substantially. Indeed, there are older individuals who preserve a high-stable internal capacity status. Most importantly and pertinent to this perspective is the opportunity to increase intrinsic capacity throughout the lifespan of an individual. Enhancing intrinsic capacity, through various interventions, is a means of preventing frailty.

In summary, it can be argued the concept of frailty is constantly evolving; yet, over the past forty years several facts remain constant: frailty is multidimensional, the prevalence of frailty increases with age, frailty is dynamic, and frailty is potentially preventable. The current concepts of physical resilience and intrinsic capacity, the need to identify barriers in clinical practice settings, and the utilization of translational research paradigms underscore the complexity of frailty and the need to tackle this complexity by engaging experts across a multitude of professions.

Causes contributing to frailty

Risk Factors

There are numerous cellular and molecular aging processes, in combination with environmental, genetic, and chronic disease states, that act together to drive the development of frailty.[35–38] To date, several risk factors associated with frailty include sociodemographic, clinical, lifestyle-related, and biological (Table 2).[38] The significant sociodemographic and social risk factors focus on age, sex, ethnical background, education, low socioeconomic position, living alone and loneliness. The clinical risk factors span multimorbidity and chronic disease, obesity, malnutrition, impaired cognition, depressive symptoms, and polypharmacy. Physical inactivity, dietary patterns, smoking and alcohol consumption are identified within the lifestyle-related risk factors. The biological risk factors include compromised or altered immune function and neuroendocrine dysregulation (e.g., increased IL6, CRP, TNFα; androgen deficiency or IGF-1[39–42], micronutrient deficiencies (low carotenoids, vitamin B6, vitamin D or E),[39,42] sarcopenia and energy imbalances/oxidative stress.[42–44]

Table 2
Risk factors driving the development of frailty.[38]

Sociodemographic Factors	***Lifestyle Factors***
• Advanced age • Female sex • Ethnical background • Education • Low socioeconomic position • Living alone • Loneliness	• Physical inactivity • Dietary patterns • Smoking • Alcohol consumption
Clinical Factors	***Biological Factors***
• Multimorbidity and chronic diseases • Obesity • Malnutrition • Impaired cognition • Depressive symptoms • Polypharmacy	• Immune function • Neuroendocrine dysregulation • Micronutrient deficiencies • Sarcopenia • Energy imbalances/oxidative stress

Because the criteria within the physical frailty phenotype assessment tool discussed earlier (performance-based measures of grip strength and walking speed and self-reported measures of endurance and physical activity) reflect muscle health it is reasonable to conclude that sarcopenia (muscle loss, weakness and reduced muscle function with aging) is a major player in the identification of a frail person or a person at risk for frailty. Similar to frailty, the underlying biological mechanisms contributing to sarcopenia are complex and multifactorial (e.g., motor axonal degeneration, dysregulation of cell-signaling pathways, chronic low-grade inflammation, oxidative stress, endocrine dysfunction, stem cell dysfunction[45–47]).

Aging

Aging itself is associated with progressive homeostatic dysregulation across the multiple physiological systems, which compromise reserves, resilience, and internal capacities. Many of the well-known hallmarks of aging and the identified seven pillars of aging contribute to the physiological dysregulation (Fig. 1).[48,49] Briefly, the hallmarks of aging are divided into three categories: primary, antagonistic, and integrative. The primary hallmarks (genomic instability, epigenetic alterations, telomere attrition, loss of proteostasis) represent the triggers, which result in damage and are the drivers of the aging process. The antagonistic hallmarks (deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence) represent the protective compensatory mechanisms. It is important to note that although these compensatory mechanisms are at first protective, beyond a certain point or threshold and over extended time periods these compensatory mechanisms have severe detrimental outcomes. The integrative hallmarks (stem cell exhaustion, altered intercellular communication) represent the final outcome of the damage caused by both the primary and antagonistic hallmarks, which lead to dysfunction within the tissues and age-related chronic diseases. The seven pillars of aging are consistent with the hallmarks of aging and include adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, and stem cells and regeneration. Although the contribution of each of these hallmarks or pillars towards the onset and progression of frailty is unknown, the processes are certainly interwoven influencing an individual's physiological potential, physical resilience and intrinsic capacity.

As the field of frailty moves forward in the 21st century identifying the causes in the development of frailty appears to be a daunting endeavor. Currently, the hallmarks of aging and the pillars of aging have the potential to provide scientific roadmaps to drive new basic discoveries in the field of frailty. These results will impact early detection/diagnosis of frailty and the development of novel and appropriate

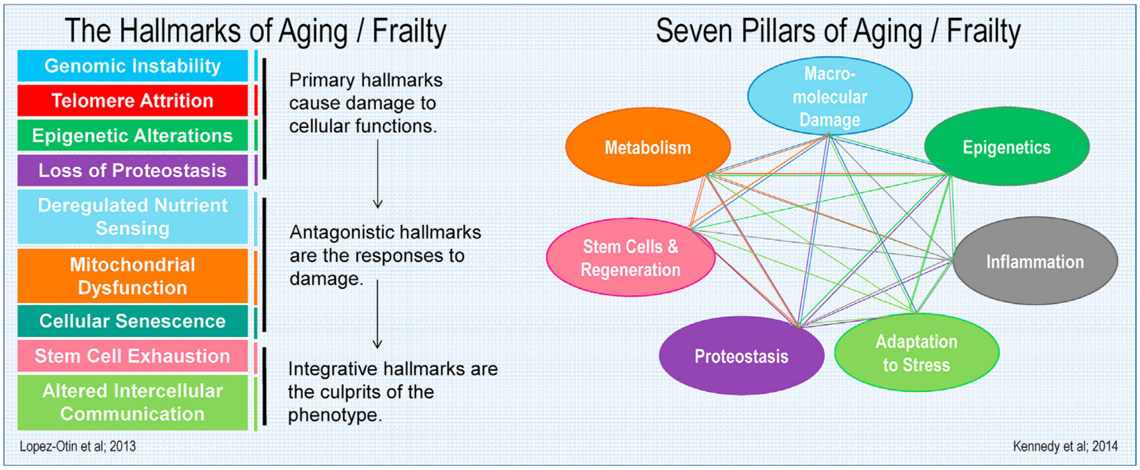

Fig. 1. The hallmarks of aging and the seven pillars of aging outlined a basic set of interconnecting biological mechanisms to understand the processes of aging. These hallmarks and the pillars provide a roadmap to understand the underpinnings of frailty development and progression. Understanding the molecular biology of aging and frailty could lead to increasing physiological potential, physical resilience and intrinsic capacity.

interventions. Furthermore, an understanding of how aging induces physiological system dysfunction may lead to the development of interventions for the prevention of frailty and its reversal through enhancing physiological potential, physiological reserve, and intrinsic capacity.

Frailty screening is coming of age

According to the World Health Organization the term "screening" refers to the use of simple tests across a healthy population in order to identify individuals who have risk factors or early stages of disease, but do not yet have symptoms (https://www.who.int/ageing/health-systems/clinical-consortium-meeting/en/; https://apps.who.int/iris/bitstream/handle/10665/272437/WHO-FWC-ALC-17.2-eng.pdf). With the goal to quickly differentiate individuals into those as frail, at risk of becoming frail or of being at risk of experiencing poor outcomes, the optimal screening tool would be short, yet sensitive in identifying those needing further attention. The optimal screening tool would also have good positive and negative predictive values.[50,51]

Similar to the missing "gold standard definition" for frailty, the field is lacking a "gold standard screening tool". In 2013 when the six major international societies convened to recognize and agree on the distinction between the broader definition of frailty and a more specific medical syndrome, this same international group also identified several quick and simple validated screening tools.[22] These screening tools include self-reports, direct measurements of performance and data extracted from assessments within clinical settings. Because many of the screening tools include an element of the physical frailty, they are valuable in identifying individuals who are at risk, who would benefit significantly from prevention activities, and who may need a more in-depth assessment. To date, two successful outcomes surrounding frailty screening stemmed from the Frailty Consensus: A Call to Action. First, the practice of routine screening for frailty has increased worldwide. Second, many professional groups are engaged in the screening process. Although the field has reported significant growth in frailty screening it is important to acknowledge the current challenges. The use of multiple frailty screening tools is identified as a major challenge for the field because the information evaluated from the multiple frailty screening tools is not interchangeable. Thus, the continued use of multiple frailty screening tools limits the potential to share information across the world and limits the potential to draw public health recommendations. Another challenge in the practice of routine screening for frailty is the lack of published, research evidence demonstrating its value and benefits. Anecdotally, it is reasonable to assume that screening for frailty would be a valuable activity to perform in various clinical practice settings and other environments; however, at this time, the data is not available. As partnerships and networks are built between the various professional groups in the 21st century, these challenges will likely be addressed.

Screening tools for frailty with an emphasis on physical function

Table 3 highlights screening tools for frailty with a focus on the physical function and they are briefly described below. The Physical Frailty Phenotype and the Frailty Index are described earlier in the perspective. A thorough review of the frailty assessment tools is beyond the scope of this perspective; however, several comprehensive reviews are available, which focus on their reliability, validity and their advantageous and disadvantages (e.g.,.[52–54])

Short physical performance battery

The short physical performance battery (SPPB) is an objective assessment tool for evaluating lower extremity functioning in older persons, offers a validated tool for determining mobility or physical fitness, and was developed by the National Institute on Aging (it is available for use without permission or royalty fees/https://www.nia.nih.gov/research/labs/leps/short-physical-performance-battery-sppb.) The SPPB is comprised of three objectives or timed physical assessments: standing balance, walking speed, and repeated chair stands, each with a score ranging from 0 to 4, for a summed composite score ranging from 0 to 12. The range of scores, from 0 (worst performance) to 12 (best performance) allows quantification of a person's level of frailty. The SPPB takes about 5–10 min to complete. For the balance portion, individuals are asked to stand and remain in three progressively more difficult positions (side-by-side, semi-, and full-tandem stances) for 10 s each. For

Table 3
Examples of screening tools for frailty.

- Frailty Physical Phenotype[18]
- Frailty Index[19,20]
- Short Physical Performance Battery[55–58]
- Study of Osteoporotic Fractures Scale[61–64]
- FRAIL Scale Questionaire[52,65–67]
- Groningen Frailty Indicator[68–71]
- Gérontopôle Frailty Screening Tool[72]
- Edmonton Frailty Scale[73–77]
- Clinical Frailty Scale[78]

the walking test, walking speed is measured over 8 feet. The chair stand requires the individuals to fold arms across their chest and rise from a chair five times as quickly as possible.[55,56] Two major strengths of the SPPB include a range of scores that can be monitored over time and normative values are available (e.g.,.[57]) Due to the relative ease of tasks assessed, many individuals may approach or achieve the maximum score. Because of this ceiling effect, the SPPB was modified (modified Physical Performance Test, MPPT) to include whole body skills, such as stair climbing, integrated tasks of gross, and fine motor, and upper extremity activities in order to identify global disability.[58] Lastly, the SPPB captures physical performance which has potential to provide a starting point for intervention and prevention strategies. It is important to note that if time is limited, gait speed (<0.8 m/s) and timed-up-and-go test (>10s) provide single screening measures.[59,60]

Study of Osteoporotic Fractures Scale

The Study of Osteoporotic Fractures Scale (SOF) screening tool is easy to use and has three items, with one item assessing physical function. The three items include: (1) intentional or unintentional weight loss >or equal 5% in the past 3 years, (2) inability to rise from a chair five consecutive times without using the arms, (3) self-perceived reduced energy level as described by a negative answer to the question “do you feel full of energy?” Frailty is scored across a range from 0 to 3, with frailty identified when two or more items are present, pre-frail when one item is present, and robust if no item is present.[61] The SOF has been validated in various settings (e.g.,.[62–64]) Because the SOF captures physical function it also has potential to provide a starting point for intervention and prevention strategies.

FRAIL scale questionnaire - fatigue, resistance, aerobic/ambulation, illnesses, loss of weight

The FRAIL is a self-reported screening tool of fatigue, mobility, strength, the number of co-morbidities and weight loss. Specifically, the five components include: Are you fatigued? (Fatigue), Cannot walk up 1 flight of stairs? (Resistance), Cannot walk 1 block? (Aerobic/ambulation), Do you have more than 5 illnesses? (Illnesses) and, Have you lost more than 5% of your weight in the past 6 months? (Loss of weight). Frailty is classified across a range of scores from 0 (no deficits) to 5 (frail.) When three or more of these deficits are present, a person is classified as frail; whereas the presence of one or two of these deficits the person is classified as prefrail. The FRAIL questionnaire is validated in several populations and is popular for its time-effectiveness.[52,65–67] Although the FRAIL does not objectively measure a physical performance parameter, the multiple questions spanning several domains of physical performance have potential to reflect difficulties, leading to further physical performance assessment.

Groningen frailty indicator

The Groningen frailty indicator (GFI) is also a self-report, multidimensional screening tool. The GFI consists of 15 questions including mobility (independence in shopping, walking outside, dressing, toileting); vision; hearing; nutrition (unintentional weight loss) and presence of co-morbidities (polypharmacy); cognition (complaints on memory); psychosocial factors (experience emptiness, missing others, feeling left alone; feeling depressed, feeling nervous or anxious) and overall physical fitness.[68,69] Frailty is identified across a range of scores from 0 (normal activity without restriction) to 15 (completely disabled), with frailty identified with scores $\geq$ 4. It has been suggested that this dichotomous scoring method may capture the dynamic state of frailty when used across several screenings and provide guidance in the direction for interventions.[52] The feasibility and reliability have been documented for the GFI, predominantly in the Netherlands.[31,68–71] Although this screening tool is multidimensional the focus on mobility independence and the rating of physical fitness provide information to facilitate further physical performance testing.

Gérontopôle frailty screening tool

The Gérontopôle Frailty Screening Tool (GFST) is an 8-item screening questionnaire intended to identify frailty in community-dwelling persons 65 years or older without functional disability or current acute disease.[72] The GFST comprises of two steps: a questionnaire is performed first, followed by a clinician's judgement of frailty status. The first 6 questions evaluate the individual's status: 1) whether the person lives alone; 2) whether the person has involuntary lost weight loss in the last 3 months; 3) whether the person has felt fatigue in the last 3 months; 4) whether the person has mobility difficulties in the last 3 months); 5) whether the person has memory problems and 6) whether the person has slow gait speed ($\geq$4 s to walk 4 m or <1 m/s). All questionnaire components having three potential answers: yes/no/unknown. If there is an answer of yes to any one of the six questions, the screening questionnaire requests the evaluator's opinion about the frailty status of the individual and the individual's willingness to be referred for further evaluation. Similar to the GFI and FRAIL, there is a focus on mobility with the addition of any presence of a mobility change over the past 3 months, which facilitates further objective physical performance testing.

Edmonton frail scale

The Edmonton Frail Scale (EFS) is a brief, user-friendly, valid and reliable assessment tool.[73] The EFS is multidimensional consisting of both performance-based testing and questionnaire (11 questions.) The EFS has nine domains: cognition, functional performance, functional independence, general health status, social support, medication use, nutrition, mood and continence. The domains of cognition, general health status, functional independence, social support, and functional performance are scored between 0 and 2 points with 0 points representing no errors or normal health, 1 point representing minor errors or mild/moderate impairment, and 2 points representing important errors or severely impaired. The domains of medication use, nutrition, mood, and continence are scored 0 point (always) and 1 point (sometimes). The final score is the sum of the points across the nine domains, ranging from 0 to 17. Frailty is classified along a continuum as no frailty (0–5 points), apparently vulnerable (6–7 points), mild frailty (8–9 points), moderate frailty (10–11 points), and severe frailty (12–17 points.) It is important to note that the EFS frailty classification and point system have been adapted since its inception in 2006 (e.g.,.[74,75]) Physical function is evaluated with the Timed Get Up and Go test (TUG), a test of basic mobility and balance consisting of a measurement of the time in seconds for a person to rise from sitting from a standard arm chair, walk 3 m, turn, walk back to the chair, and sit down. A cutoff score of $\geq$20 s was shown to predict falls in community dwelling frail elderly people.[60,76] In addition to the physical function assessment, the use of the EFS has been evaluated in specific populations and administered by individuals without formal medical training.[77] Thus, the EFS has potential to lead to further assessment or the initiation of interventions.

Clinical frailty scale

The clinical frailty scale (CSF) is considered a simple and practical frailty screening tool that assesses frailty and fitness.[78] The CSF summarizes health information with the use of written descriptors and pictographs (visual and written chart) which span the domains of mobility, energy, physical activity, function, and disability. The use of the CSF involves watching the person move and inquiring about their habitual physical activity and ability (independence in bathing, dressing, housework, going upstairs, going out alone, going shipping, taking care of finances, taking medications and preparing meals.) Frailty is identified across a range of scores from 1 to 9 (1, Very fit; 2, Well; 3, Managing well;

4, Vulnerable; 5, Mildly frail; 6, Moderately frail; 7, Severely frail; 8, Very severely frail; 9, Terminally ill.) The CSF is validated and the information may be obtained from the medical record.[78] The CFS requires clinical judgement in identifying the frailty classification. Because there is a focus on the level of independence this tool may be useful as an initial screening.

Indeed, there are many more screening tools available with a wide range in application. In summary, these screening for frailty tools provide exercise scientists and healthcare providers an opportunity for early detection of at-risk persons for physical decline. There is an opportunity to step in and seize a role in understanding the underpinnings contributing to the onset and progression of frailty and the development of appropriate intervention programs.

Physical activity- health promotion benefits specific to older adults and to frail adults

Physical inactivity is one of the major contributing risk factors for frailty. Whereas on the opposite side of the spectrum physical activity is known to preserve or improve the function of many of the identified physiological systems associated with frailty described earlier in this perspective (e.g., cardiovascular, musculoskeletal, neuromotor, metabolic and inflammation.[79]) In fact, physical activity plays an important role in healthy aging (e.g., optimal physical function and mobility) through the prevention and management of many of the common chronic diseases present in the older adult and in frail individuals.[80–82] A thorough review of the benefits of physical activity is beyond the scope of this perspective; however, major adaptations are briefly described. For instance, the cardiovascular adaptations associated with physical activity include hemodynamic adjustments (e.g., sustained reduction in blood pressure) and positive changes in numerous cardiovascular functions, such as contractility, maximal cardiac output, body fluid regulation, cardiac vagal tone (i.e., heart rate variability), and cardiac preconditioning.[83,84] These adaptations lead to lower risk of cardiovascular disease mortality and lower risk of cardiovascular disease and hypertension. Physical activity results in extensive remodeling of skeletal muscle at the cellular and molecular levels.[85] For example, there are positive adaptations within signaling pathways (e.g., insulin), mitochondrial respiratory capacity, substrate delivery, ROS production and inflammatory levels. As a result of these cellular and molecular changes, there is increased muscle strength and endurance, as well as reduced adipose deposition and body weight. Within the nervous system the adaptations to physical activity include remodeling (e.g., neurogenesis), attenuation of neurodegeneration, improved cognition (e.g., executive function, attention, memory) and decreased depressive symptoms.[86,87] The physical activity-induced metabolic benefits reach many of the organ systems and include increased resting metabolic rate, improved glucose metabolism and insulin sensitivity, efficient muscle protein synthesis/degradation and autophagy, increased fatty acid oxidation, upregulation of protective proteins as well as improved antioxidant activity. There are positive changes in mitochondrial function (e.g., biogenesis, bioenergetics, oxidative capacity) and circulating cholesterol and triglycerides levels. Based on the myriad of physical activity-induced benefits described above it is logical to propose the activity-induced cellular and molecular changes influence an individual's physiological potential, physical resilience and intrinsic capacity. Subsequently, it is possible to develop interventions that prevent, reverse, or slow the progression of frailty.

Physical Activity Guidelines

Recently, the 2018 Physical Activity Guidelines Advisory Committee (PAGAC) Scientific Report (Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report, 2018. Washington, DC; US Department of HSS: https://health.gov/our-work/physical-activity/current-guidelines/scientific-report) and the ensuring review by DiPietro et al.[88] stress the benefits of physical activity to improve physical function and mobility, in both the general aging population and in persons with specific chronic diseases, including frailty.

Collectively, this comprehensive report and review carefully examined a total of 146 published systematic reviews, meta-analyses, pool analysis, experimental reports, cohort and case-controlled studies between 2006 and 2018, to identify the scientific evidences supporting physical activity and health.[89] In particular, the PAGAC identified and prioritized 38 literature review questions and 104 subquestions and they subsequently graded the evidence as strong, moderate, limited, or not assignable based on the applicability, generalizability to the US population of interest, risk of bias or study limitations, quantity or consistency of results, and magnitude and precision of effect. Participants included in the studies reviewed for the general aging population were non-hospitalized, ambulatory, ages 50 years and older. In contrast, most participants included in the studies reviewed for the older adults with frailty were ages 65 years and older and all met at least one established criterion for frailty (e.g., slow walking speed, weakness, exhaustion.) For additional details on this body of evidence, https://health.gov/paguidelines/second-edition/report/supplementary-material.aspx for the Evidence Portfolio. The final outcome of this comprehensive endeavor was the development of recommendations identified as the Physical Activity Guidelines. Before describing the specific details of the scientific report focused on the physical activity for older adults and adults with frailty, the principal concept highlighted within the Physical Activity Guidelines is that *regular physical activity over months and years can produce long-term health benefits.*

Evidence supporting physical activity for the general aging population

The following describes the strong and consistent scientific evidence from the PAGAC Scientific Report for the general aging population (https://health.gov/our-work/physical-activity/current-guidelines/scientific-report). The scientific evidences include: (1) When older adults participate in multicomponent group or home-based fall prevention physical activity and exercise programs there is a reduction in the risk of injury severity from falls. The physical activity programs that stress training in the combinations of moderate-intensity balance, strength, endurance, gait, and physical function are the most effective in reducing the risk of fall-related injuries and fractures. (2) Physical activity improves physical function and reduces the risk of age-related loss of physical function in an inverse graded manner. (3) There is an inverse dose-response relationship between volume of aerobic physical activity and risk of physical functional limitations. (4) Aerobic, muscle-strengthening, and multicomponent physical activity programs appear to have the strongest relationship to improvements in physical function. “Multicomponent physical activity” refers to training that is comprised of more than one type of activity, such as aerobic, progressive muscle-strengthening, balance and functional training.

Evidence supporting physical activity for older adults with frailty

For older adults with frailty the 2018 PAGAC Scientific Report states that there is strong and consistent scientific evidence demonstrating: Physical activity improves physical function in frail older adults and contributes to improved walking and gait, balance, strength, self-reported measures of activities of daily living, and quality of life. Specifically, the report highlighted that multicomponent exercise training of at least moderate intensity, performed 3 or more times per week for a duration of 30–45min per session, over at least 3–5 months appears most effective to increase functional ability in frail older persons. Multicomponent physical activity programs are more effective than doing just a single type of physical activity. It is not surprising that a multicomponent exercise training program would be effective because it stimulates and facilitates positive adaptations of many physiological systems involved in the development of frailty, such as the neuromuscular and cardiovascular systems.

Key guidelines for older adults

Table 4 highlights the key guidelines for adults and older adults (https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf) developed from the 2018 PAGAC Scientific Report because regular physical activity effectively helps older adults improve or delay the loss of physical function and mobility. Older adults should aim to achieve the guidelines because greater amounts of physical activity provide additional and more extensive health benefits such as reduced risk of age-related loss of function and reduced risk of physical function limitations. The Guidelines strongly suggest: (1) As part of their weekly physical activity, older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities. (2) Older adults should determine their level of effort for physical activity relative to their level of fitness. (3) Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely. (4) When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow. It is also important to point out that adults 65 years and older gain substantial health benefits from regular physical activity, even if they do not meet the physical activity program guidelines stated above.

Highlighted measures of physical function and frailty

The measures of physical function within the systematic reviews and meta-analyses outlined in the 2018 PAGAC Scientific Report and in the subsequent review include: 6 min walk test, Timed Up and Go (TUG), 30s chair stands, gait, balance, strength or self-reported measures of ADL or quality of life. Although all of the scientific analyses included in the 2018 PAGAC Scientific Report note that physical activity improved some or all measures of physical function in older adults with frailty the following are several examples of the evidence cited:

One systematic review and meta-analysis by Gine-Garriga and colleagues[90] sought to determine the efficacy of exercise-based interventions on improving performance-based measures of physical function and markers of physical frailty in community-dwelling, frail older adults. Frailty was defined according to standardized criteria (e.g., Fried's, SPPB.) From comprehensive bibliographic searches in MEDLINE, the Cochrane Library, PEDro, and CINHAL databases (2013) data was extracted and analyzed from 19 RCTs. Physical activity showed a significant effect on gait speed and a significant benefit on gait test results, decreasing in 1.73 s the time required to walk 10 m. The gait test requires the individual to walk a short distance (e.g., 3 m), turn, and return to the initial position; hence, may also reflect general mobility. These findings were considered impactful because gait speed is a strong predictor of mortality risk and an improvement (as small as 0.1 $m \cdot s^{-1}$) significantly lowers the risk.[91]

A meta-analysis by Chou et al.,[92] sought to determine the effect of exercise (a single or comprehensive exercise training program) on physical function of frail older adults in the community or institutionalized. A broad definition of frailty, which may have included non-frail, pre-frail, and frail adults was used From bibliographic searches in PubMed, MEDLINE, EMBASE, the Chinese Electronic Periodical Service, CINAHL, and the Cochrane Library databases (2001–2010) data was extracted and analyzed from 8 RCTs involving 1068 frail older people between the ages of 75–87 years (mostly women). Compared with a non-physical activity control group, the physical activity groups increased gait speed by 0.07 m per second, improved scores on the Berg Balance Scale, and improved performance in ADLs. The impact of this meta-analysis lies in the benefits of exercise for this specific age group with a broad definition of frailty.

The systematic review by Lopez and colleagues[93] sought to determine the effect of resistance training alone or combined with multicomponent exercise intervention on muscle mass, maximal strength, power output, functional performance and risk of falls incidence in physically frail older adults. Frailty was defined by a large number of definitions such as according to standardized criteria (e.g., Fried criteria) or according to reduced physical function measured with physical performance scales (e.g., SPPB) or performance-based measures such as gait and mobility, or reduced physical function and status. From bibliographic searches in MEDLINE, Cochrane CENTRAL, PEDro, and SPORTDiscus (2005–2017) data was extracted and analyzed from 16 studies. Resistance training either alone or as part of multicomponent training significantly increased muscle strength (6.6%–37%), muscle mass (3.4%–7.5%), muscle power (8.2%), and functional capacity (4.7%–58.1%), gait speed (5.9%–14.5%) and the TUG score (5.5%–20.4%) in frail older adults.[93] The findings of this review suggest supervised and controlled resistance training (30%–70% 1-RM) is an effective intervention for individuals with frailty.

A systematic review by Cadore et al.,[94] sought to recommend training strategies to improve functional capacity in physically frail older adults (broad definition of frailty that included pre-frail, mild-to-moderate frail, and frail participants), focusing on supervised exercise programs that improve strength, fall risk, balance, and gait. From bibliographic searches in Scielo, Science Citation Index, MEDLINE, Scopus, Sport Discus, and ScienceDirect databases (1990–2012). Seven of 10 studies reported a lower incidence of falls among frail older adults (ages 70–90 years) in physical activity (multicomponent, muscle-strengthening training, combined endurance and yoga, or tai chi) groups, compared with those in control groups, with a reduction ranging from 22% to 58%. Improvements in gait speed (4%–50%), balance (5%–80%), and strength (6%−60%) were noted. The findings in this systematic review were considered impactful because the specific design of the exercise program must be tailored to provide a sufficient stimulus for improving the functional capacity of frail individuals.

Indeed, physical activity has positive effects in physical function of older adults with frailty; however, it is worth noting the definition and the degree of frailty in the cited studies within the 2018 PAGAC Scientific Report varied greatly. The inclusion of a well-defined frailty definition and a clear measurement of frailty are needed to facilitate comparisons between physical activity programs, which will lead to identification of the underlying molecular and cellular mechanisms contributing to the

Table 4
Key guidelines older adults.

These guidelines are the same for adults and older adults:
• Adults should move more and sit less throughout the day. Some physical activity is better than none. Adults who sit less and do any amount of moderate-to-vigorous physical activity gain some health benefits.
• For substantial health benefits, adults should do at least 150 min (2 h and 30 min) to 300 min (5 h) a week of moderate-intensity, or 75 min (1 h and 15 min) to 150 min (2 h and 30 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate-and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread through the week.
• Additional health benefits are gained by doing physical activity beyond the equivalent of 300 min (5 h) of moderate-intensity physical activity a week.
• Adults should also do muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these activities provide additional health benefits.
Additional guidelines just for older adults:
• As part of their weekly physical activity, older adults should do multicomponent physical activity that includes balance training as well as aerobic and muscle-strengthening activities.
• Older adults should determine their level of effort for physical activity relative to their level of fitness.
• Older adults with chronic conditions, such as frailty, should understand whether and how their conditions affect their ability to do regular physical activity safely.
• When older adults cannot do 150 min of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

positive effects (e.g., hallmarks and pillars of aging). Given a defined frailty definition and measurement communication will be enhanced between stakeholders and opportunities to address current concepts and to identify barriers in developing, testing, evaluating and implementing physical activity programs will increase.

Collectively, strong evidence demonstrates that regular physical activity has health benefits for everyone, regardless of age, sex, race, ethnicity, or body size. As the summary within the PAGAC states: "Nonetheless, evidence suggests that it is never too late in life to benefit from physical activity." The Physical Activity Guidelines provides information and guidance on the types and amounts of physical activity that provide benefits for the older adult and adults with frailty. The awareness of the guidelines by a wide range of professions has great potential to improve health and prevent the deleterious outcomes associated with frailty.

Conclusion

Frailty is recognized as a public priority with the increasing older population worldwide. Over the past 4 decades research efforts in defining frailty, assessing frailty, and identifying the biological underpinnings associated with frailty have made great discoveries, and the research field is poised to continue to make significant breakthroughs in the 21st century. Frailty screening across many professionals provides a valuable opportunity to identify persons at risk for frailty and to engage older adults and frail adults in evidenced-based physical activity programs. The prevention of frailty and chronic disease and the preservation of physical function and independence have worldwide public health implications. Lastly, a comprehensive review of the science shows that many evidence-based strategies can be used to promote and support physical activity in older adults and in frail adults.

Submission statement

The manuscript has not been published and is not under consideration for publication elsewhere.

Authors' contributions

LVT provided the conceptual bases for this manuscript and the first draft. DK added content, editing, and formatting.

Conflict of interest

The authors have no conflict of interest to report.

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