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Frailty

A Multidisciplinary Approach to Assessment, Management, and Prevention

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To the pillars of my life, my mother Laura and my wife Nieves, whose unwavering support, boundless love, and enduring strength have been the guiding lights on my journey.

—Jorge G. Ruiz, MD, FACP

To my yiayia, who at the age of 100 continues to be the biggest inspiration for my work on aging and frailty.

—Olga Theou, PhD

Preface

We take pride in presenting this groundbreaking, multiauthored book, *Frailty: A Multidisciplinary Approach to Assessment, Management, and Prevention*, as a testament to the collaborative expertise of an internationally renowned and diverse group of experts in the field of aging and frailty. This collective effort not only reflects a unique journey but also underscores the scientific foundation and clinical and educational implications embedded in the meticulous crafting of this work. As we stand on an era marked by an unprecedented demographic shift towards an aging population, the study of frailty emerges as a critical frontier in healthcare. Frailty, a complex and multifaceted condition, embodies the vulnerability and diminished physiological reserve that often accompanies the aging process. It transcends mere chronological age, encompassing a spectrum of physical, psychological, and social dimensions. In the context of this profound demographic transformation, the book *Frailty: A Multidisciplinary Approach to Assessment, Management, and Prevention* assumes heightened significance.

As we traverse the intricate landscape of frailty, it becomes apparent that a multidisciplinary perspective is not just valuable but indispensable. This book has been meticulously shaped to encapsulate the wealth of knowledge and nuanced insights of our esteemed contributors, who serve as prominent figures in their respective disciplines. Their routes of expertise converge from various corners of the globe, presenting readers with a panoramic view of frailty that transcends geographical and disciplinary boundaries.

Embarking on a comprehensive exploration, this book unfolds through curated parts, each encapsulating a unique facet of the intricate complexity that is frailty. In "Frailty and Related Concepts: An Overview," a robust foundation is laid, offering an in-depth understanding of the complexities inherent in frailty, emphasizing the scientific basis that underscores its multifaceted nature. In the "Mechanisms: Pathogenesis and Research" part, contributors' expertise converges to unveil the intricate mechanisms shaping our comprehension of frailty's origins, providing a deeper insight into the underpinnings of this multifaceted condition and its scientific underpinnings. The part on "Assessment" offers readers a comprehensive examination of assessment tools, methodologies, and advancements from diverse perspectives, showcasing the clinical implications for practitioners and educators alike. Moving onward, "Management: Treatment and Prevention" presents a valuable exploration of approaches to managing, treating, and preventing frailty, drawing on the well-traveled routes of expert contributors to enhance overall well-being. The "Settings of Care" part reflects contextual richness through contributors' varied experiences, addressing frailty in different care settings and providing a wealth of multidisciplinary insights crucial for clinical application. The "Other Conditions" part traverses interconnected landscapes of health, unraveling the intricate relationships between frailty and other healthcare conditions, thus presenting readers with a comprehensive view of complex health scenarios. Finally, "Social and Other Issues" transcends clinical boundaries as contributors navigate societal, contextual, and educational dimensions of frailty, providing a holistic understanding enriched by diverse perspectives with implications for clinical practice, educational, and healthcare policy endeavors. Together, these parts form a cohesive narrative, weaving together the broad range of expertise of contributors to present readers with a nuanced and multidimensional exploration of frailty across various dimensions of aging.

This collaborative endeavor is a testament to the collective wisdom and expertise of our contributors, who have embarked on a journey not only to advance the understanding of frailty but also to provide a scientific basis and offer invaluable clinical, educational, and policy insights. We envision this book as a beacon of knowledge, guiding healthcare professionals, researchers, and policymakers through the multidisciplinary routes that lead to a more comprehensive understanding of frailty, thereby enriching both scientific discourse and practical applications in clinical, educational, and healthcare policy settings.

Hollywood, FL, USA — Jorge G. Ruiz
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Part I

Frailty and Related Concepts: An Overview

The Frailty Phenotype

1

Jorge G. Ruiz and Sara Espinoza

Background

This chapter examines the frailty phenotype, an integral concept in geriatric healthcare introduced by Dr. Linda Fried and collaborators in 2001 [1]. This paradigm has transformed our approach to identifying and managing frailty in older adults, presenting a methodical framework for screening, evaluation and intervention. We begin by reviewing the operational definition of frailty according to the frailty phenotype, which is identified by meeting at least three out of five criteria: unintentional weight loss, self-reported exhaustion, muscular weakness, reduced gait speed, and low physical activity [1, 2]. This definition signifies a notable departure from the traditional view of aging as a mere time-related decline, instead acknowledging frailty as a specific medical condition and geriatric syndrome [3–5]. Progressing through the chapter, we will analyze how older adults are categorized as "frail" or "pre-frail," underscoring its clinical significance. We aim to elucidate how this classification facilitates early intervention, influences clinical decision-making, and directs the customization of therapeutic strategies for older adults.

The conceptualization and implementation of the frailty phenotype in the field of geriatric medicine is in constant flux. Later in this chapter, we address some of the criticisms aimed at this framework, including its focus on physical aspects, and the attendant omission of cognitive, psychological, and social dimensions of frailty. We will review research aimed at the frailty phenotype, providing a more encompassing viewpoint on an older individual's health. Additionally, we will attempt to address the challenges faced when implementing this framework in various clinical settings, stressing the need for a standardization of assessment techniques, a more holistic viewpoint of the frailty phenotype conceptualization, its significance in geriatric care, and the potential avenues for its future advancement.

The Concept of Frailty Before Fried

Prior to a more formal conceptualization of frailty using the frailty phenotype [1] and the deficit accumulation model [6], the notion of frailty in older adults was progressively becoming a key area of discussion in geriatric circles. During the 1950s and 1960s, the term "frailty" started receiving more attention and this movement only grew by the 1980s and 1990s [3, 5, 7, 8]. The Federal Council on Aging in the United States coined the terms "frail elderly [Sic]" in 1978, specifically referring to older adults, typically those above 75 years, who were usually high users of healthcare services due to the concurrence of medical and psychological multimorbidity [9]. These initial characterizations recognized frailty as a decrease in both physical and cognitive abilities, leading to increased vulnerability, but a critical interpretation was that frailty was not considered a necessary consequence of the aging process. The term was then broadly applied to describe a wide range of clinical conditions related to aging, including physical debility, susceptibility to illnesses, and a general decline in health, yet still lacking a cohesive, operational definition [4, 10].

In this early phase, the perception of frailty was seen as that of a multi-domain concept, representing the interplay of physical, mental, and social factors on an individual's health [11]. Key elements such as social withdrawal and

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mental health issues, including depression, were identified as contributing factors to frailty [12]. The prevailing clinical approach to frailty at this time was centered on the management of specific symptoms and health issues, rather than a comprehensive approach to the management of the frailty syndrome [3, 13]. Research in this period, although not as targeted as in later years, played a crucial role in shaping our understanding of frailty, with studies focusing on aging and susceptibility to health challenges. Comprehensive geriatric assessments were instrumental in the health evaluation of older adults during this time, but these assessments did not distinctly focus on frailty as a separate condition [14–16].

The Origins of the Frailty Phenotype: The Cardiovascular Health Study

Dr. Linda P. Fried's first formulation of the frailty phenotype concept occurred within the context of the Cardiovascular Health Study (CHS) marking a pivotal moment in the field of aging and geriatric medicine [1]. This study, a comprehensive and multicenter observational effort started in the late 1980s in the United States, was primarily designed at the identification of risk factors for cardiovascular diseases and strokes in older adults [17]. It was in this setting that Dr. Fried and her collaborators began pioneering research on frailty, using the CHS broad dataset from participants over 65 years old, encompassing detailed assessments, and various health indicators [1, 17, 18].

Dr. Fried and her team performed a broad analysis of CHS data, identifying specific, measurable characteristics that could consistently indicate frailty [1]. They identified five key criteria: unintentional weight loss, self-reported exhaustion, muscular weakness (assessed via handgrip strength), reduced walking speed, and decreased physical activity. The presence of these criterion in various combinations was associated with health outcomes relevant to older adults like falls, acute care hospitalizations, disabilities, and death [1, 2].

A pioneering aspect of Dr. Fried's approach was the formulation of an operational definition of frailty, classified as meeting at least three of these criteria. A related concept of "pre-frailty," defined by one or two criteria, was also formulated, allowing for an early identification and the possibility of the development and implementation of preventive measures to forestall the onset of frailty [1, 2]. This approach to frailty proved effective in predicting adverse health outcomes and quickly gained acceptance in geriatric medicine, providing clinicians a valuable tool to identify and aid frail older adults [19].

Biological Underpinnings of the Frailty Phenotype

The frailty phenotype, as conceptualized by Fried and colleagues, is underpinned by a complex biological and physiopathological framework, adding scientific substantiation to its five clinical criteria [20–23]. This phenotype emerges from a dysregulated complex dynamical system in the older adult, involving an array of modular systems and subsystems [23, 24]. These systems normally operate both autonomously and collectively, utilizing feedforward and feedback mechanisms to regulate allostasis and homeostasis [23, 25]. In cases of physical frailty, however, there's a collective failure in these core regulatory systems, leading to pronounced dysfunction under stress [26]. This results in a state of frailty characterized by reduced overall functionality, with a nonlinear relationship between the level of physiological dysfunction and the severity of frailty. A critical threshold exists, beyond which a reduced functional state is unsustainable [23].

Physically frail individuals exhibit dysfunction in crucial systems like metabolism, musculoskeletal structure, and stress response [23]. This manifests as disrupted energy metabolism, including altered glucose-insulin dynamics and hormonal imbalances [27, 28], as well as compromised musculoskeletal [29] and mitochondrial functions [30]. Additionally, the stress-response system is adversely affected, evidenced by heightened inflammation, autonomic nervous system dysregulation, and hypothalamic-pituitary-adrenal (HPA) axis imbalances [31, 32]. These dysregulated systems impair the ability of frail individuals to adequately respond to environmental challenges, underlining a set of pathophysiological traits central to physical frailty [23].

This concept is visually depicted in Fig. 1.1 [23], which illustrates physical frailty as a syndrome arising from a hierarchy of interconnected physiological and cellular systems. Key physiological systems critical to frailty are shown as gold circles, with their subcomponents as orange ovals. Cellular changes due to aging, represented by purple ovals, are thought to trigger dysfunction in these physiological systems. This dysfunction, indicated by a dark orange oval, is directly linked to the physical frailty phenotype, positioned at the apex of the model. This schema underscores the multilayered nature of frailty, emphasizing its roots in both cellular alterations and systemic interactions [23].

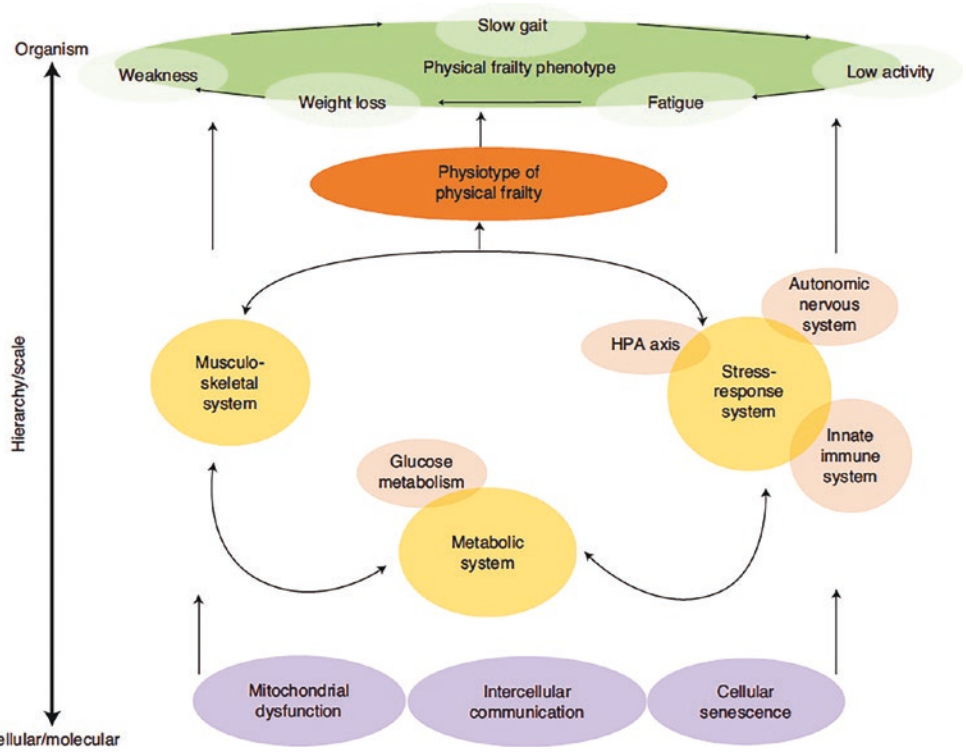

Fig. 1.1 A hierarchical, multiscale representation of the physiological dysregulation and likely biological drivers of physical frailty. Fried LP, Cohen AA, Xue QL, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nature aging. 2021 Jan;1 (1):36–46

Frailty Phenotype Criteria

Continuing from our introduction to the frailty phenotype framework, we will now explore the specific criteria that form its foundation (Fig. 1.2). These criteria are crucial for the identification and classification of older adults as "frail" or "pre-frail," offering a solid base for clinical evaluation and intervention [1, 2]. Unintended Weight Loss is identified when an individual experiences a loss of more than 4.5 kg (10 pounds) or over 5% of their body weight within a year, serving as a critical marker of frailty. This significant reduction highlights a decline in muscle mass and overall vigor, which are essential for the health and functionality of seniors. Self-Reported exhaustion is assessed through subjective evaluations of an individual's energy levels and motivation. Muscular Weakness is evaluated using handgrip strength as measured with a portable dynamometer. This assessment, adjusted for sex and body size, provides a measure of an individual's muscular strength. Slowness is observed through a reduction in gait speed, quantified by measuring walking speed over 4 m. This metric, adjusted for sex and stature, serves as a direct indicator of an individual's mobility and overall physical capabilities. Low physical activity is determined by self-reported levels of activity using the short version of Minnesota Leisure Time Activity, which estimates activity in kcal/kg, with adjustments made for sex to fairly compare an individual's activity against established benchmarks. These criteria help in assessing the extent of an individual's engagement in physical activities relative to normative standards.

An individual meeting three or more of these criteria is deemed "frail," displaying a heightened susceptibility to detrimental health outcomes such as falls, hospitalization, disability, and mortality [1]. Those matching one or two criteria fall into the "pre-frail" category, indicating a moderate risk and potential for developing significant frailty. It is essential to recognize that while this frailty definition is widely recognized, the frailty concept itself can differ in various research and clinical contexts [33]. Together, these indicators provide a comprehensive framework for identifying and addressing frailty in older adults, focusing on key areas of health and functionality to improve their quality of life.

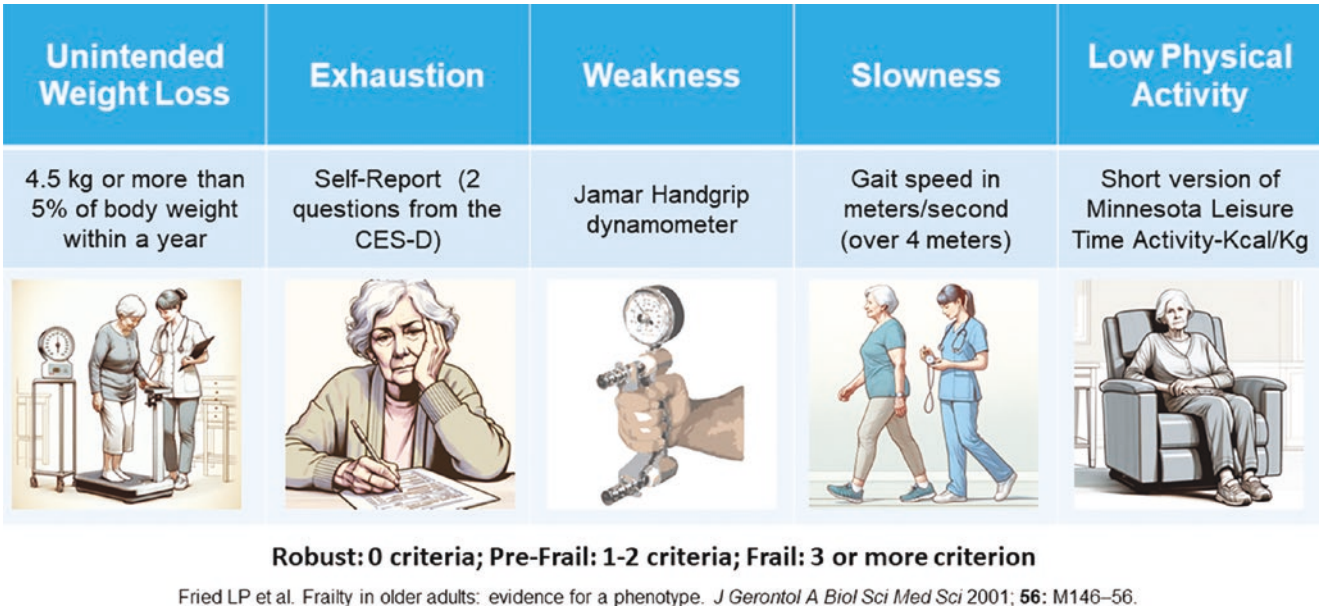

Fig. 1.2 The five frailty phenotype criteria

Application of the Frailty Phenotype in Research

Since its development by Dr. Fried and her team, the frailty phenotype has become a cornerstone in geriatric research, forming the basis of numerous studies on older adult health and well-being [1, 34]. Its clarity and operational criteria have allowed for a more uniform approach to frailty research across different populations and environments. Researchers have used this framework to examine the biological aspects of frailty and assess the impact of various interventions aimed at its prevention or mitigation [19].

In the field of epidemiology, the frailty phenotype has become a useful conceptual framework for the investigation of frailty-related risk factors and their progression [35]. These studies have shed light on the influence of lifestyle, health conditions, race, ethnicity, and other social-economic factors on frailty's development and course in older individuals [36–39]. The phenotype has also been integral in clinical trials testing both pharmacological and non-pharmacological strategies, ranging from exercise and nutrition programs to new medications, all aimed at enhancing outcomes for frail populations [40–43].

Moreover, the frailty phenotype has encouraged a broader perspective in geriatric research, highlighting the need to consider psychological, social, and environmental factors alongside physical aspects of aging [44, 45]. This comprehensive approach has deepened our understanding of aging and opened new pathways for intervention and policy formulation to improve older adults' quality of life [46].

Advantages and Disadvantages

The frailty phenotype model, known for its precise and pragmatic methodology, is particularly noteworthy in this regard. Its straightforwardness renders it highly effective in clinical and research environments [47]. These criteria are not chosen arbitrarily; they are solidly linked to negative health outcomes in older adults through empirical evidence [48, 49]. A strength of this model lies in its focus on observable physical dimensions of frailty, critical in the prediction of clinically relevant outcomes like falls, hospitalizations, physical disabilities, and death [47]. The frailty phenotype, applicable at first contact, effectively categorizes individuals as robust, pre-frail, or frail for an initial risk assessment [44]. The frailty phenotype indicators are invaluable in spotting individuals at risk, aiding in the prevention and management of age-related decline [50]. Additionally, the model's ability to identify "pre-frail" individuals allows for early intervention, potentially delaying or even reversing the future onset of frailty [47, 51]. This proactive approach can assist clinicians and researchers in the development, implementation, and evaluation of targeted measures aimed at improving quality of life, reduce the burden of multimorbidity and functional decline, reduce healthcare costs, and potentially prolong survival.

The frailty phenotype model, despite its solid grounding in research, presents several limitations. The frailty phenotype has seen limited uptake in routine clinical practice, due to several challenges [46]. The complexity and time constraints in clinical environments, especially in primary care and acute hospital settings, hinder its integration into daily practice [52,

53]. The requirement for specific measurements like grip strength and walking speed demands time commitments, training, and specialized equipment, which may limit its routine use in busy clinical practices [44, 46]. Another barrier is the varying levels of training and awareness among healthcare professionals [54, 55]. While the concept of frailty is widely recognized, comprehensive understanding and application of the frailty phenotype are not uniformly incorporated into medical training or professional development curricula [56]. Additionally, the emphasis on physical criteria in the frailty phenotype may cause clinicians to neglect other vital aspects of frailty, such as cognitive and psychosocial elements [57, 58]. This narrow scope may lead to an under-recognition of frailty in individuals who do not meet its stringent criteria. Compounding these issues is the reported variability in how the frailty phenotype is applied across different studies, resulting in marked inconsistencies in the reported prevalence of frailty, and the model's ability to predict clinical outcomes. The frequent adaptations or modifications of the original criteria as reported in the literature further impact the reliability and comparability of research outcomes [33].

Overall, the frailty phenotype model is helpful at identifying older adults at risk of falls, hospitalizations, disabilities, and death by categorizing them as robust, pre-frail, or frail. Its evidence-based, physical-focused criteria are critical for early, targeted interventions, potentially improving healthcare outcomes. However, its implementation in clinical practice faces challenges due to complexity, time constraints, the need for specific measurements and instrumentation, and training of healthcare professionals. The model's physical criteria emphasis may also overlook cognitive and psychosocial frailty aspects, limiting its comprehensive application.

Future Directions

Moving forward, the frailty phenotype model's role in geriatric care could be enhanced by addressing several areas:

Standardization of Criteria: The lack of standardization in the frailty phenotype criteria may lead to misclassification and the adjudication of incorrect clinical risks, leading to inappropriate management strategies for older individuals [59, 60]. To improve predictive accuracy and ensure the effectiveness of interventions, it is critical to tailor the criteria to the population's specific phenotypic traits. Addressing these challenges requires further research to refine assessment tools for broader applicability across various care settings.

Integration of Other Domains: The incorporation of cognitive and mental health domains into the frailty phenotype would provide a more comprehensive estimation to frailty. This holistic approach could lead to improved assessment and management outcomes for the older adult population [57].

Technological Advancements in Assessment: Employing emergent information technologies, like wearable devices, for example, widely available smart watches, could offer continuous monitoring of key indicators (gait speed, levels of physical activity and exercise), leading to more unobtrusive, efficient, accurate, and timely frailty detection and intervention [61, 62].

Education and Training: Enhancing healthcare professionals' understanding and use of the frailty phenotype through comprehensive training including the incorporation of the frailty phenotype into medical curricula could improve frailty identification and management, extending this training to interprofessional teams involved in the care of older adults [46, 63].

Policy and System Integration: Embedding the frailty phenotype into health policies and systems, including guidelines and protocols for assessment in various healthcare settings at the point of care or as part of population health, electronic health records, among others, could lead to better value-based care and better resource allocation for the growing aging population [46, 64].

Conclusions

In this chapter, we have reviewed the frailty phenotype, a transformative concept in geriatric healthcare introduced by Dr. Linda Fried and colleagues in 2001. This framework has revolutionized the way frailty is identified and managed in older adults, offering a clear operational definition based on five key criteria: unintentional weight loss, reported fatigue, muscle weakness, reduced gait velocity, and low physical activity. This approach represents a significant shift from traditional perceptions of aging as a mere time-related decline, highlighting frailty as a distinct geriatric syndrome. Despite its impact, the chapter also addresses the limitations of the frailty phenotype, particularly its focus on physical dimensions while often overlooking cognitive, psychological, and social factors. We discussed ongoing research efforts to expand the frailty concept and discussed the challenges faced in integrating this framework into clinical practice, emphasizing the importance of standardized assessment techniques and training for healthcare providers. Overall, this chapter provided a comprehensive overview of the frailty phenotype, underlining its pivotal role in the care of older adults.

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Deficit Accumulation

2

Samuel D. Searle and Kenneth Rockwood

Historical Background/Origins

With ageing, people and most species accumulate damage at molecular, cellular, and systems levels, which scale up to become clinically detectable [1, 2]. Although exactly which deficits accumulate in which people vary, in most people, at some age the number of deficits that they have matters more to their survival than exactly which ones they have [3]. This extends even to death from specific causes such as cardiovascular mortality [4, 5]. Such observations run counter to how most risk factors are related to a given disease/condition (i.e. 'what are the most critical risk factors for X condition'), to complement what is known about the scale of ageing. It also corresponds to the actuarial definition of frailty, as a lifelong ageing factor that results in people of the same age having variable risks of death [6]. In this it corresponds to the clinical approach to frailty based on deficit accumulation: with time, people accumulate deficits at varying rates.

The deficit accumulation approach views frailty as a general state of age-related risk of poor health outcomes; frailty can be graded by the extent to which individuals have accumulated deficits. Those with the greatest deficits at any age have higher risks for adverse outcomes than do their age peers. One of the ways that frailty exerts its effects in late life is to facilitate disease expression. Consider late-life dementia. As reviewed elsewhere, apparently disease-defining neuropathology and biomarkers [7] as well as polygenic risk [8] and neuropsychological test score performance [9] are more likely to be expressed as clinical dementia, the greater the degree of frailty. Indeed, for some people with high frailty scores, the relationship between even neuropathology and dementia is weak: frailty appears to be the chief risk factor [7]. Population studies identify genetics, social determinants, and environment to all play a role in deficit accumulation over the life course [7].

At the individual level, deficits accumulate, initially through well-known means, such as DNA methylation, telomere shortening, protein misfolding, inflammation, and problems in DNA repair [1, 2]. These small upstream changes become more prominent before causing cellular, tissue, organ, and clinical dysfunction.

Animal models of frailty have been supportive of these upstream changes and support the model's generalizability. In human studies, the doubling time of clinical health deficits appears to be 12–15 years [10]. In silico models for frailty have been able to replicate and further support the deficit accumulation theory [11]. Together, these should allow for rapid evaluation and the timely targeting of interventions along the spectrum of this process.

Frailty Index

Many frailty measurement tools count accumulated deficits, with the frailty index (FI) introduced in 2001 being representative [12]. With this approach, working from health records, or epidemiological or trials databases, candidate health variables are evaluated for their potential to be health deficits—in short, to be associated with age and to be related to adverse outcomes [13]. For each individual, the number of deficits is counted and then divided by the number of deficits that were considered, offering a number between 0 (no deficits present—i.e. fittest) and 1 (in theory, if all deficits were present). Given, however, that the degree of frailty is tied to the risk of death, in a properly constructed frailty index (see below) the usual maximum value is around 0.7. At that level of frailty/deficit accumulation, almost no one survives [7].

This tool is broadly used in research, clinical practice, and health policy and continues to be easily implemented in the digital health system [7]. Frailty indexes have been successfully created in animal models (mice/dogs/nonhuman pri-

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mates) [7, 14], disease-specific states [15–17], and subclinical frailty information (laboratory and biomarker measures) [18]. This deficit accumulation approach has also been used for non-frailty measurements such as social vulnerability [19].

The type of database a frailty index can be created from is broad, though for clinical feasibility, electronic data are likely best. These datasets include cohort studies, randomized controlled trials (primarily post hoc analysis), electronic health records, comprehensive geriatric assessments, and administrative data [20–26].

Frailty indices may differ broadly as to what is included in each index, though often attempts are made to have the same or similar indices in comparative populations. The validity of this tool is determined by how it is created and behaves, as opposed to the exact variables included. Unexpectedly, the number of items may mean more than each specific variable. Nevertheless, it has always been important that each frailty index covers a broad range of health deficits, including functional measures, comorbidities, and signs/symptoms, else the index may not be as informative [27]. Recently updated [28], the steps in making a frailty index from an existing (or new) study/population include:

1. Select all variables measuring a health problem.
2. Exclude variables with more than 5% missing values.
3. Recode all variables as '0' or '1', representing 'no deficit' and 'deficit'.
4. Exclude variables that are too rare (<1%) or common (>80%).
5. Ensure variables are associated with age.
6. Screen the variables for correlation with each other ($r >$ 0.95).
7. At least 30 variables should be included in the index.
8. Calculate the index scores by adding all the present deficits and dividing this sum by the number of deficits considered in each case/person.
9. Test the characteristics of the frailty index.

These steps cover most of the usual process. Further points require clarification for select cases. When using a frailty index longitudinally, the same variables should be included in each longitudinal measurement. At each measurement, the variables should satisfy other criteria (i.e. not be too rare or a saturating deficit). Partial deficits can be used (i.e. deficit scoring of '0', '0.5', '1'), and U-shaped variables can be coded as expected. Association with ageing requires attention because the steady-state prevalence can stabilize at later ages, likely due to mortality and new deficit development. Step 9 notes to test the characteristics of the index. This includes its correlation with age, a right-skewed distribution, higher mean FI in females, and 99% of the study sample being assigned scores less than 0.7. Laboratory or performance-based frailty indices tend not to be modified by sex, and some of these properties may not be apparent if using a narrow age range, a small population, or certain clinical samples.

There remain untested considerations, which mostly stem from a limitation to all frailty assessment tools; a single time-point frailty assessment will be less valid if ongoing recovery or health decline occurs at the clinical or subclinical level. Should those who have treated hypertension still be assigned a health deficit of hypertension? How frail is a patient when they are acutely ill? Similarly, the United Kingdom's primary care frailty index has been criticized for what appear to be immortal time health deficits, which likely should have some period of re-evaluation, after which they could be removed.

Frailty Assessment During Acute Illness

While on a population level the mean degree of frailty increases over time, individual frailty measurements, even in healthy community-dwelling samples, are dynamic and can show stability, decline, or improvement longitudinally. Expected and current frailty levels are least reliably measured when someone is acutely ill. The deficit accumulation theory for frailty reflects that during acute illness, an individual will have accumulated additional health issues (i.e. reflecting that at that time, they are 'sick') but is usually expected to have some health deficits removed or mitigated (i.e. by being treated). There are two key points here. Firstly, for any individual whose frailty was measured at a specific time during this illness, it would become outdated as soon as the measurement is completed. Secondly, recall that frailty indices need to be discriminative as per Step 4. Specifically, deficits need not be too rare, and not saturate. This needs to be satisfied at every measurement longitudinally. Hyperglycaemia/hypoglycaemia, hypotension/hypertension, arrhythmia, renal impairment, hypoxia, delirium, and immobility precluding the ability to perform functional tasks, among many others, can all be very common and fluctuate during acute illness hospitalizations. Naturally, in acute pain and pulse steroids, hypertension for a period does not mean that they have hypertension as a comorbidity.

The frailty level of a patient who is acutely sick in the hospital is best *approximated* by their pre-acute illness frailty status. However, the longer an individual requires hospitalization — the longer deficits remain and are therefore accumulated — the more likely they will have a higher degree of frailty when or if they leave the hospital. Initial treatment response, not dissimilar to the concept of autocorrelation in the general study of complex systems, is important in this setting to void further accumulation. Though this is expected within the deficit accumulation theory of frailty, and clinically a near tautology, these dynamics are not extensively studied.

The dynamic measurements of frailty during hospitalization are not well understood, and therefore, further work needs to be done. This will lead to clinically useful tools to help in prognostication, identify populations for intervention, and determine targets to be intervened upon with respect to further frailty development. Though untested, cognitive states (delirium) and functional mobility may be clinically measurable and meaningful markers of dynamic frailty change during acute illness [29, 30]. Frailty indices containing pre-clinical deficits, like the laboratory frailty index, could be dynamically measured in relatively brief time periods, forecasting — in near real time — frailty trajectory during acute illness.

Frailty in Relation to Social Vulnerability

As noted, social vulnerability—sometimes defined as the 'disadvantage conveyed by poor social conditions' [31]—can be quantified using a deficit accumulation approach [18]. It is analogous to the concept of frailty, to which it is related. Our group typically considers social vulnerability separately from frailty, and not include it within a frailty index. Instead, we evaluate the contribution of social vulnerability in a multivariable model. Considering the construct separately can be revealing. An illustrative example is found regarding the outcomes of the least frail older adults. Despite universal access to health care there, a Canadian study of outcomes by tercile of social vulnerability in older adults (aged 70+ years) with the lowest frailty scores (i.e. the least frail) was revealing [32]. Amongst the fitter (least frail people), the 5-year mortality rate for those with the least social vulnerability was 10.8%, compared with 32.5% for people living with the highest social vulnerability. This 22% absolute difference in mortality represented a significantly greater risk: the adjusted hazard ratio was 2.5, with the 95% confidence interval spanning 1.5–4.3.

In a causal model (e.g. with a directed acyclic graph) we see social vulnerability making frailty likely in two broad ways. First, if we consider that a deficit arises when damage goes unremoved, then social vulnerability makes damage more likely—in this sense, following the terminology of Ukraintseva and colleagues, it diminishes *robustness*—the ability to withstand a stress [33]. Consider, for example, people who live in a high-crime area. Greater social advantage is expressed in matters such as more frequent police or even private patrols, the deterrent effects of close monitoring (e.g. multiple closed-circuit cameras), the heft to make sure that street lighting is plenteous and well-maintained, and myriad other manoeuvres and social engagements that make injury or other forms of damage less likely. At the same time, should it occur, access to repair (medical care, physical rehabilitation, counselling, visible signs of community support) enhances *resilience*. As is evident, both assets operate at several levels, from the individual to the group, the community, and even government [34]. The influences are especially notable in hospital, where greater social vulnerability increases the risk of longer hospital stays and diminishes the chance of people living in their own homes, at all levels of frailty [35]. Similarly, access to home care is greatest for those with the least social vulnerability [36].

This approach appears to be generalizable across cultures, including across the life course [37–41]. The life course effects of social vulnerability are far-reaching. For example, in a Chinese report, childhood food deprivation increased the chance of late-life frailty [42]. This echoes work from the Survey of Health, Aging, and Retirement in Europe where older Europeans had accumulated about 20% more health deficits than did their age peers if they had experienced hunger as a child [43].

Conclusion

The deficit accumulation approach to frailty aims to tie the number of age-related health deficits together as a means of quantifying the degree of frailty. Its proponents argue that there are many ways to be frail, and that degrees of frailty are discernible clinically, with important consequences for prognosis and for care planning. Care plans must not just define risk: they must encourage practices in which risk might be mitigated.

The deficit accumulation approach has proved to be translatable across settings (population-based, clinical, and bench), countries, cultures, and species. In offering quantitative methods that are easy to understand, and that lend themselves to formal quantitative analysis and reasoning, this way of operationalizing frailty can enhance clinical practices and offer up opportunities for translation that embrace complexity. Even after two decades, there is much to be done, especially now that as of 2021, the leading edge of the Baby Boom is turning age 75, where deficit acceleration is most evident. This is a wave that will dominate much of health care for the professional lifetimes of most current practitioners. An organized way to tackle this challenge, and not just muddle through, is what is required now.

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Prevalence, Incidence, and Risk Factors of Frailty

3

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Introduction

Frailty is an age-related vulnerable state associated with increased risk of adverse health outcomes [1]. With an acceleration of population aging across the world, many countries will see an increase in the number of frail older adults. Given its significant impacts on healthcare systems and societies, frailty is now considered to be an emerging public health priority [2]. It is therefore vitally important for all stakeholders to better understand the epidemiology, etiology, and pathophysiology of frailty based on available evidence. This chapter focuses on the prevalence, incidence, and risk factors for frailty.

Prevalence of Frailty

Previous frailty research has accumulated epidemiological evidence of frailty [1, 2], and several studies have provided pooled prevalence data. One of the first published systematic reviews and meta-analyses of frailty authored by Collard and colleagues included 21 countries (mostly Western and high-income) and showed that the overall weighted prevalence of frailty is 10.7%, with prevalence recorded by individual studies ranging widely from 4.0% to 59.1% [3]. As part of the ADVANTAGE Joint Action, a European initiative to address frailty in older adults, the researchers used data from European countries and revealed that pooled prevalence of frailty in community settings was 12% [4]. Another study focused on frailty in low- and middle-income countries and found a higher pooled prevalence of 17.4% than that shown by the two studies above. Unsurprisingly, a similarly high pooled prevalence of 19.6% was provided by another meta-analysis study that examined mostly low- or middle-income countries in Latin America and the Caribbean [5]. Finally, the latest systematic review and meta-analysis study collected a large amount of data from 240 studies from 62 countries and showed that pooled frailty prevalence is around 18% [6].

Some characteristic findings were shared by these studies. Definitions of frailty appear to influence the prevalence of frailty; specifically, the pooled prevalence of frailty from studies using physical frailty was lower than that from studies using multidimensional frailty, such as a deficit accumulation model, for example, 9.9% vs. 13.6% [3], 12% vs. 16% [4], or 12% vs. 24% [6]. According to a study that examined frailty prevalence in the same cohort but using eight different scales, the prevalence of frailty varies considerably from 6.1% using the FRAIL scale to 43.9% with the Groningen Frailty Indicator [7]. Although any frailty tools are able to identify high risk groups, different tools capture different groups of individuals, thus providing different estimates of prevalence of frailty. Advanced age is a strong risk factors of frailty, and pooled estimate of frailty prevalence rises as populations become older [1]. The meta-analysis by Collard showed that the prevalence of frailty is less than 5% among individuals aged 65–69 years while rising to more than 25% among individuals aged 85 or older [3]. Another study further investigated the prevalence of frailty according to the minimum age cut-off at study entry (50–59, 60–69, 70–79, 80–89, and 90+), and showed that frailty becomes more prevalent from 11% up to 51% in a dose-response manner as the minimum age cut-off increases [6]. This study also showed a significant association between the mean age of participants and frailty prevalence by a meta-regression method [6]. Biological female sex is a well-known risk factor of frailty, and a few meta-analysis studies showed higher prevalence of frailty in women than in men (9.6% vs. 5.2%

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[3], 15% vs. 11% [6]). Given the various factors described above which can pose a significant impact on estimates of frailty prevalence, when assessing prevalence of frailty, it is important to take into consideration the frailty tools used, age distribution, sex proportion of the populations, and other related factors.

Incidence of Frailty

Compared with prevalence, less is known regarding the natural course or development of frailty [8–10]. It is important to understand how people develop frailty during their lifetime in order to deepen our knowledge of this issue and facilitate future research into the pathophysiology of frailty.

One systematic review focusing on the incidence of frailty was published in 2018 [10]. This review was done as part of a European research project on frailty and searched for original articles from both EU and non-EU countries providing incidence of frailty, defined as the number of new cases of frailty per population in a certain time period [10]. Of six included studies, the lowest incidence of frailty was 3.9% from 727 older adults aged 65 or greater in Germany who had been followed up for approximately 3 years. The highest incidence was 13.0% provided by a study including 6,306 Chinese people older than 55 years with a mean age of 70 years tracked over a period of 1 year [11]. The authors considered one study showing the incidence of 51.4% in 74 Aboriginal Australian people older than 45 years over 6.7 years [12] as an extreme outlier.

The other systematic review conducted a more comprehensive series of analyses on the incidence of frailty and prefrailty using data from 46 studies [9]. Among 100,313 nonfrail (robust or prefrail) older adults, 13.6% developed frailty over a median follow-up of 3 years, with the pooled incidence rate of 43.4 cases per 1000 person-years. The pooled incidence rate was significantly higher in prefrail than in robust people, at 62.7 vs. 12.0 cases per 1,000 person-years. This study also examined the development of prefrailty among 32,268 robust individuals, showing an incidence of prefrailty of 30.9% over a median follow-up of 2.5 years and a pooled incidence rate of 150.6 cases per 1,000 person-years. Another interesting finding was a significantly higher incidence and incidence rates of frailty and prefrailty in women than in men: frailty 15.6% vs. 9.2%, 44.8 vs. 24.3 cases per 1,000 person-years; prefrailty 40.1% vs. 32.6%, 173.2 vs. 129.0 cases per 1,000 person-years. The authors also conducted multivariable random-effects meta-regression analyses and found that four factors were associated with the incidence of frailty. First, measuring frailty using the frailty phenotype was associated with higher incidence than using the other tools (adjusted odds ratio = 1.48). Second, although the study location did not have significant impacts on the incidence of frailty, studies from high-income countries were associated with a significantly lower frailty incidence compared with studies from low- and middle-income countries (adjusted odds ratio = 0.563). Third, the male-only cohort studies were associated with significantly lower incidence of frailty than mixed cohort studies (adjusted odds ratio = 0.55). Fourth, more recent studies were significantly associated with lower incidence of frailty than earlier studies (adjusted odds ratios = 0.24 and 0.42 for studies published in 2010–2014 and 2015–2019, respectively, compared with studies published in 2009 or earlier).

Risk Factors of Frailty

Many studies have investigated risk factors for frailty [1], and their findings were collected and summarized by several systematic reviews [13–17]. Sociodemographic factors, such as age, sex, education, marital status, and living situation, have been frequently examined. Advanced age is almost always a risk factor of frailty, and a 1-year increase in age is associated with 5% higher frailty risk (pooled odds ratio = 1.05, 95% = 1.03–1.08, $p < 0.001$) [16]. It is well documented that women live longer than men, but paradoxically are likely to have higher prevalence and severity of frailty [18]. This sex difference is observed in different age groups and populations [19], and has been confirmed by meta-analyses [13, 14]. It seems that biological factors, in addition to social and behavioral ones, play some role in producing the sex difference, as earlier age at menopause [20, 21] and higher number of pregnancies [22] are associated with significantly higher risk of frailty. A U-shaped association was observed between body weight and frailty, and those who are underweight and overweight are at an increased risk of frailty. As compared with a normal BMI as the reference group, pooled relative risks of frailty are 1.45 (95%CI = 1.10–1.90, $p < 0.01$) for the underweight group (BMI < 18.5 kg/m^2), 0.93 (95%CI = 0.85–1.02, $p = 0.11$) for the overweight group (BMI = 25.1–30 kg/m^2), and 1.40 (95%CI = 1.17–1.67, $p < 0.01$) for the obese group (BMI > 30 kg/m^2) [23]. Poor education factors, such as fewer years of education or not having mandatory education, are associated with frailty risk [14]. Although educational level is mostly fixed during the period of young adulthood and remains stable afterwards, it can affect health through various related factors. For example, education can lead to more accurate health knowledge, and thus better lifestyle, including regular exercise and healthier diet, and to a better job and higher income, which will in turn enable access to healthier foods and better living environments. One longitudinal study explored explanatory factors mediating the associations between low educational levels and frailty and found that the strongest explanatory effect was income, followed by behavioral fac-

tors (smoking, alcohol use, obesity), mental factors (depressive symptoms, cognitive function, mastery, self-efficacy), and biomedical factors (number of chronic diseases, CRP, vitamin D level, IGF-1 level), and, interestingly, that social factors (having a partner, network size, emotional support) contributed little [24]. Low income itself has been shown to be associated with higher risk of frailty [25]. Multiple studies have examined living environments, such as neighborhood characteristics, marital status, and living situation, in association with frailty risk, and showed that living in a deprived neighborhood [26], not being married [27], and living alone [28] are associated with higher risk of frailty. A noticeable racial/ethnic disparity in frailty has been identified by previous research. For example, US studies have consistently shown that black race is associated with a higher risk of frailty, which could be attributable to low socioeconomic status, poor health status, or genetic polymorphisms [25]. Furthermore, several US studies stratified frailty risks according to race/ethnicity and found that racial and ethnic minority groups, particularly blacks and Hispanics, had excessively higher prevalence of frailty compared to non-Hispanic whites [29–31]. The underlying mechanisms for the disparity seem multifactorial [30]. Some studies attempted to explore the underlying causes further and demonstrated interesting findings. In one study, only socioeconomic status-related factors remained significant while race did not when mutually adjusted, suggesting the socioeconomic status may account for the racial disparity in frailty [32]. Another study showed that the higher frailty risk seen in Mexican Americans when compared with European Americans disappeared when ethnic-specific frailty criteria were used, which suggests that the frailty disparity may be largely due to the use of the frailty measurement tool, not underlying frailty per se [33].

Lifestyle and behavioral factors have also been well studied. Examples are diet, smoking, alcohol use, or exercise [25]. Poor diet and malnutrition are prevalent in older adults and are associated with frailty [34]. The Mediterranean diet is a well-known dietary pattern with health benefits [35] and is shown to be inversely associated with frailty [36]. Among different micro- and macro-nutrients that have been examined, protein is considered to be the most relevant and important factor for frailty, given that sarcopenia, age-related loss of muscle mass and functions, is the core feature of frailty [37, 38]. Multiple studies have shown that lower protein or amino acids are associated with higher risk of frailty and its related factors [34, 38]. Smoking and low level of exercise are shown to be associated with frailty [39, 40], while the association between alcohol use and frailty seems more complicated [41, 42]. Physical inactivity is recognized as one of the contributing risk factors for frailty [40], and physical activity/exercise is currently considered to be the most effective intervention against frailty [43].

Summary

This chapter focuses on the prevalence, incidence, and risk factors of frailty by referring to up-to-date systematic reviews and their meta-analyses. Understanding the prevalence, incidence, and risk factors of frailty will help us identify and stratify the risks of frailty, predict its development or progression, and provide appropriate interventions to reverse the severity of frailty or proactively prevent its related adverse outcomes. It will also contribute to more comprehensive health management of older adults.

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Integration: A Unified Frailty Framework

4

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Integration: A Unified Frailty Framework

Older people are burdened by the coexistence of multiple, often chronic conditions. In this context, psychological, socio-economic, and cultural issues may play a role by increasing the vulnerability of older persons to endogenous and exogenous stressors. Unfortunately, traditional models of care, largely built and focused on a disease-centered approach, are woefully unprepared to address the high biological, clinical, and social complexity of older people, especially the most vulnerable ones [1].

The development of the frailty concept has historically represented an opportunity to pay attention to neglected aspects of the older person's health with the aim of personalize care interventions. It has the potential for reshaping our obsolete care systems, driving them towards models that are more respectful of the individual's priorities, needs, and values. Indeed, frailty induces clinicians to look beyond the traditional nosological entities promoting a multidisciplinary and integrated approach focused on the older person's functions and capacities.

During the past couple of decades, the number of publications on frailty markedly increased, mainly because of the first attempts to operationalize this condition. Interestingly, an editorial published in 1968 in the *British Medical Journal* [2] explained the difference between "Old and Frail," stressing the inadequacy of the current models of care for addressing the evolving needs of the aging population. For many years, frailty has never been formally defined but used as a vague concept to generally indicate persons expressing a particularly high risk of adverse events due to their multiple clinical and disabling conditions.

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Starting at the beginning of this century, several groups of researchers and clinicians started to propose operational definitions of frailty, in the attempt to raise awareness about this critical condition and improve care for older persons. Such increasing interest was indeed very prolific. Just recently, Buta et al. [3] reported a total of 67 frailty instruments available in the literature, of which nine instruments were "highly cited" (i.e., with 200 or more citations), and these figures might be significantly higher today. In other words, the same concept (i.e., frailty) is measured using many different instruments. Unfortunately, although all these instruments were formally validated in the literature (mainly as predictive of adverse health-related outcomes), their agreement tends to be quite modest. In other words, each of these instruments seems to capture a different model of frailty [4, 5].

Of course, having so many (potentially conflicting) instruments to measure the same concept has frequently been the cause of debates, misleading messages, and different viewpoints in the field. The existence of several tools to measure frailty frequently resulted in a lack of agreement slowing the broad implementation of these instruments in the clinical practice [6]. The objective to provide adapted care to older persons for which frailty was there had become apparently (and paradoxically) secondary to the instruments used to measure it [1].

To standardize the emerging literature and practices, a panel of international experts in the field met in Orlando (FL, USA) in 2013 [7]. The resulting consensus paper provided an agreed theoretical definition of frailty, describing it as "a clinical state in which there is an increase in an individual's vulnerability for developing increased dependency and/or mortality when exposed to a stressor." It was clarified that frailty can result from a variety of illnesses and medical conditions and the need to adopt a multidimensional approach to manage it. Frailty was clearly differentiated from the concept of multimorbidity (i.e., the presence of two or more concomitant diseases), being diseases only a part, often marginal, of the frailty problem. The group did not endorse a specific instrument for measuring frailty and remained focused at standardizing its "higher level" theoretical concept.

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As soon as the theory of the concept is established, it makes more sense that frailty might then be perceived by different models (focusing on one or more specific aspects of the condition) and instruments (translating into numbers the clinical observation from the model) [8]. To date, as discussed in other chapters of the present book, the most commonly adopted models of frailty are the phenotypic model proposed by Fried and colleagues [9], the health deficit accumulation model developed by Rockwood and Mitniski [10], and the Tilburg Frailty Indicator proposed by Gobbens et al. [11]. The number of instruments is huge and exponentially increasing, considering that one single model may be translated and adapted in multiple ways (with different results) [12].

Despite frailty having its origins in geriatrics, it is today discussed and adopted by many specialties struggling to find solutions to the increasing complexity of their aging populations (i.e., neurology [13], orthopedics [14], cardiology [15], infectious disease medicine [16], and oncology [17]). Frailty is used in the evaluation of persons living with HIV [18] or Down's syndrome [19]. It is growingly measured in older persons with end-stage conditions (i.e., liver [20] or renal [21] diseases) to better allocate care interventions and identify needs for alternative approaches (e.g., palliation). Frailty is indeed increasingly used to measure "biological age" and overcome the paradigm of chronological age.

Interestingly, the multidimensional nature of frailty replacing the paradigm of chronological age may determine a different way of conducting research in older persons. It means relying on biology rather than on years of life in the estimate of the individual's complexity. The approach may allow to overcome some of the issues of current research that is still too rigidly focused on unidimensional variables and misses the heterogeneous complexity of the older person, resulting in a poor representativeness of the real life [22].

As soon as frailty is considered a biological measure of aging, it also becomes of special interest also for preclinical research. After all, different frailty models have demonstrated to possess a strong biological background and mirror the dynamic phenomenon of aging (Fig. 4.1). For example, the Frailty Index has shown to exponentially increase with aging up to a critical threshold of incompatibility between health deficit accumulation and life [23]. This behavior of the model has consistently been documented across species (e.g., *Caenorhabditis elegans* [24], mice [25], dogs [26]), becoming an interesting asset for promoting translational research on aging. Similarly, the phenotypic model of frailty has also shown important (and consistent) biological patterns again linking the frailty condition to aging [27]. In other words, working on frailty may mean acting on aging, capturing the heterogeneous clinical manifestations caused by the biological exhaustion of the systems.

As soon as frailty represents the dynamic process of aging, its detection might become the entry door to approach

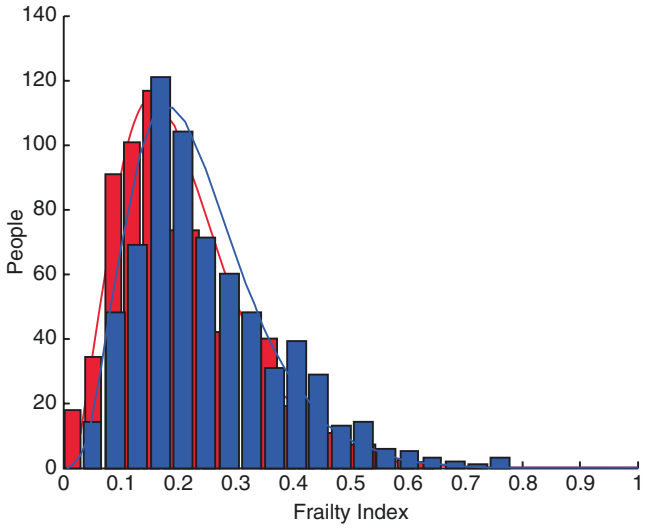

Fig. 4.1 Time-related modification of the Frailty Index from the baseline assessment (red histograms) to the 18-month follow-up visit (blue histograms) of the Yale Precipitating Events Project participants. The figure demonstrates the evolution of frailty over time (i.e., increase of health deficit accumulation) and the biological background of the model (i.e., incompatibility between excess accumulation of deficits and life beyond a certain [i.e., about 0.7] threshold). The figure is reproduced from Searle et al. [23] under the terms of the Creative Commons Attribution License

the age-related biology responsible for many clinical conditions of the older person. Given its multidimensional nature, the assessment and management of frailty requires a multidimensional approach [6, 28–30]. It cannot be based on the unidimensional model characterizing the traditional standalone disease approach because the underlying pathophysiological mechanism is not any more straightforward and organ-centered. It is necessary to be comprehensive and consider the wide spectrum of nosological and non-nosological features of frailty. The evaluation must consider the environment where the person lives because it plays a critical role in the design and implementation of the care plan.

To date, no pharmacological agent has been identified against frailty. Although several molecules are under investigation [31], the solution of a "magic pill" is likely far from being achieved. Some hope it might reside in geroscience and the research on the so-called "hallmarks of aging" [32]. The exploration of the aging process and the biological determinants of chronic conditions may help identify potential new targets of interventions and modify the inner mechanisms at the basis of the development of diseases.

However, strategies to prevent or improve frailty currently (and pragmatically) reside in the multidisciplinary and multidimensional approach depicted by the comprehensive geriatric assessment (CGA). The CGA is defined as "A multidimensional, multidisciplinary diagnostic and therapeutic process conducted to determine the medical, mental, and functional problems of older people with frailty" [33]. It

represents the gold standard intervention of geriatric medicine, which finds in its target population all those persons presenting the biological, clinical, and social expressions of increased vulnerability (i.e., frailty). The objective of the CGA is the development of a coordinated and integrated intervention plan (including diagnosis, treatment, and follow-up) to maximize the health status of the individual [33, 34]. Frailty can then be perceived as the cross-road in the clinical setting distinguishing persons who may have access to standard care (because biologically fit) from those who might better benefit from adapted geriatric interventions (because biologically aged or frail) [1].

Notwithstanding, it is widely agreed that frailty screening should be a necessary component of the clinical routine, especially in the community and primary care settings (in order to promote a preventive approach in the care provision) [35, 36]. Interestingly, the British Geriatrics Society proposed to screen for frailty at the primary care level without recommending a unique instrument but proposing a set of possible ones [37]. The document Fit for Frailty instead gave more relevance to the intervention to put in place after the detection of frailty, that is the CGA. In other words, (1) it is important to screen frailty, (2) it is marginally important how we do it (as soon as the instrument is validated and fits for the purpose), and (3) the CGA (the gold standard intervention) is the critical component of the process. After all, besides the fact that the systematic screening of frailty might not be cost-effective, it is important to consider that the detection and measurement of frailty make sense only if followed by an evidence-based intervention. Detecting frailty without a consequent, validated action may simply lead to overdiagnosis, malpractice, and ethical issues.

Last but not least, it is important to mention in this chapter how the frailty model has been inspiring the work conducted on healthy aging by the World Health Organization (WHO) over the past years [38]. The novel framework based on the interaction between intrinsic capacity (i.e., the composite of the physical and mental capacities) and environment in the definition of the older person's functional ability is aligned with the comprehensive approach traditionally followed by geriatricians in the management of frail individuals. Under the new framework, the WHO is recommending the re-orientation of services and policies for making them more responsive to the older person's needs, values, and priorities. The activities are based on the multidimensional assessment of the individual by a multidisciplinary team within an integrated care model for the development and implementation of a person-centered intervention. Indeed, the wording and the dynamics are strongly rooted in the frailty background cultivated over the years by geriatricians [39].

In conclusion, the condition of frailty can be used for levering the reshaping of the health and social care systems towards a person-centered, multidisciplinary, and integrated approach. In this context, it is important to consider frailty as a high-level concept, without confusing its meaning with the specific models or instruments used to measure it in the clinical and research practice.

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