The Journal of nutrition, health and aging 30 (2026) 100793

Contents lists available at ScienceDirect

The Journal of nutrition, health and aging

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

Review

Consensus document on frailty: conceptualization, detection, multidisciplinary management and future roadmap

Alejandro Álvarez-Bustos [a,b], Cristina Andres-Lacueva [a,c], Ignacio Ara [a,d,e], María Angeles Arévalo [a,f], Juan P. Bolaños [a,g], Ana Coto-Montes [a,h,i,j], José Antonio Enriquez [a,k], Germaine Escames [a,l], Francisco José García-García [a,e,m], María Carmen Gómez-Cabrera [a,n], Oriol Grau-Rivera [a,o], Mikel Izquierdo [a,p,2], Nicolás Martínez Velilla [a,q,2], Ander Matheu [a,r], Rocío Menéndez Colino [a,s], Manuel Muñoz Torres [a,t], Xavier Nogués [a,u], Juan Oliva [a,e,v], María Isabel Orts-Cortés [a,w,x], Ignacio Párraga Martínez [a,e,y,z], Feliciano Priego [a,A], Montserrat Rabassa-Bonet [a,c], María Ángeles Rol [a,B], José Antonio Serra-Rexach [a,C,D,E], Francisco José Tarazona-Santabalbina [a,F], Leocadio Rodríguez-Mañas [a,G,2], Pedro Abizanda [a,e,z,H,*], for the CIBERFES working group[1]

[a] *CIBER de Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, Madrid, Spain*
[b] *Department of Health, Universidad Villanueva, Madrid, Spain*
[c] *Biomarkers and Nutrimetabolomics Laboratory, Department of Nutrition, Food Sciences and Gastronomy, Nutrition and Food Safety Research Institute (INSA-UB), Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain*
[d] *GENUD Toledo Research Group, Faculty of Sport Sciences, University of Castilla-La Mancha, Toledo, Spain*
[e] *Instituto de Investigación de Castilla-La Mancha (IDISCAM), Toledo, Spain*
[f] *Cajal Institute, CSIC, 28002 Madrid and Cajal Neuroscience Center, CSIC, Campus de Alcalá de Henares, 28805 Madrid. Spain*
[g] *Institute of Functional Biology and Genomics, University of Salamanca, CSIC & Institute of Biomedical Research of Salamanca, Salamanca, Spain*
[h] *Department of Morphology and Cell Biology, University of Oviedo, Spain*
[i] *Research Group Oxidative Stress Knowledge and Advanced Research (OSKAR), Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*
[j] *Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain*
[k] *Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III. Madrid, Spain*
[l] *Departamento de Fisiología, Facultad de Medicina, Universidad de Granada, Granada, Spain*
[m] *Geriatrics Department, Hospital Virgen del Valle, Toledo, Spain*
[n] *Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia, Fundación Investigación Hospital Clínico Universitario/INCLIVA, Valencia, Spain*
[o] *Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain*
[p] *Navarrabiomed, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain*
[q] *Department of Geriatrics, Navarre Health Service (SNS-O), Navarre University Hospital (HUN), Navarrabiomed, Navarre Public University (UPNA), Navarra Institute for Health Research (IdiSNA), Pamplona, Spain*
[r] *Biogipuzkoa Health Research Institute, San Sebastian, Ikerbasque. Bilbao, Spain*
[s] *Geriatrics Department, Hospital Universitario La Paz, Research Institute la Paz (IdiPAZ), Madrid, Spain*
[t] *Instituto de Investigación Biosanitaria (Ibs), Departamento de Medicina, Universidad de Granada, Spain*
[u] *Hospital del Mar Resarch Institute, Universitat Pompeu Fabra, Barcelona, Spain*
[v] *Universidad de Castilla-La Mancha, Departamento de Análisis Económico y Finanzas, Toledo, Spain*
[w] *Department of Nursing, Alicante Institute for Health and Biomedical Research (ISABIAL), University of Alicante (BALMIS), 03690 Alicante, Spain*
[x] *Nursing and Healthcare Research Unit (Investén-Isciii), Instituto de Salud Carlos III, 28029 Madrid, Spain*
[y] *Centro de Salud Zona 8, Gerencia de Atención Integrada de Albacete, Spain*
[z] *Facultad de Medicina de Albacete, Universidad de Castilla-La Mancha, Albacete, Spain*
[A] *Fundación para la Investigación Biomédica de Córdoba (FIBICO), Spain*
[B] *Chronobiology and Sleep Laboratory, Department of Physiology, College of Biology, University of Murcia, Mare Nostrum Campus, IUIE, IMIB-Arrixaca, 30100 Murcia, Spain*
[C] *Geriatrics Service, Gregorio Marañón University Hospital, Madrid, Spain*
[D] *Health Research Institute Gregorio Marañón General University Hospital, Madrid, Spain*
[E] *Faculty of Medicine, Complutense University of Madrid, Spain*
[F] *Hospital Universitario de la Ribera, Alzira, Spain*

* Corresponding author.
E-mail address: pabizanda@sescam.jccm.es (P. Abizanda).

https://doi.org/10.1016/j.jnha.2026.100793
Received 30 November 2025; Received in revised form 15 January 2026; Accepted 16 January 2026
Available online 28 January 2026

[G] Geriatrics Department, Hospital Universitario de Getafe, Spain
[H] Geriatrics Department, Complejo Hospitalario Univesitario de Albacete, Spain

ARTICLE INFO

Keywords:
Frailty
Position statement
CIBERFES
Older adults
Aging.

ABSTRACT

Background: The lack of a universally accepted definition, a gold-standard assessment tool, and sufficient evidence-based interventions has hindered the integration of frailty into routine clinical practice, particularly outside geriatric medicine. For clinicians, health professionals, policymakers, and aging researchers, a unified framework based on robust evidence has become essential.
Objectives: To provide a consensus on relevant aspects of frailty, including definition, attributes, misunderstandings, pathophysiology, phenotypes, assessment, biomarkers, management, stigmas and future challenges, useful for epidemiological, clinical and research application across Europe.
Design: Consensus document.
Setting: 25 research centers on frailty and healthy aging.
Measurements: Relevant aspects on frailty.
Results: In this document we present a consensus regarding what frailty is, what frailty is not, what is aging, which are the most common misunderstandings related to frailty, which is the pathophysiology and which are the biomarkers of frailty, how should frailty be assessed and who should assess frailty, how should frailty be managed, the presence or absence of frailty subphenotypes or subtypes, how is the stigma of been considered frail, which are the gender considerations, and which are the current challenges and future directions. We support that frailty is the expression of an age-associated clinical phenotypic syndrome driven by the biology of aging, life-course environmental exposures, and disease burden. Its physiological basis lies in a heterogeneous decline of functional reserve across organ systems, accompanied by impaired homeostasis and reduced capacity to respond to stressors, ultimately predisposing to adverse health outcomes, mainly disability.
Conclusions: We present a consensus document on frailty, useful for epidemiological, clinical and research application across Europe.

1. Introduction

Over the past century, remarkable advances in medicine and public health have substantially extended life expectancy, driving both demographic and epidemiological transitions [1,2]. These changes have given rise to complex clinical, social, and economic challenges [3]. Health systems, historically designed to address acute and isolated conditions in younger populations, remain insufficiently adapted to the multidimensional needs of an aging population [3,4]. Within this scenario, there is an urgent imperative to redefine strategies of geriatric care that prioritize functional independence, enhance quality of life, and address the intricate interaction between aging, chronic disease, environmental influences, and their cumulative effects on functional capacity [3,5].

Geriatric Medicine has responded to this challenge by adopting a functional rather than a disease-centered perspective [6]. Initially focused on the management of disability, the discipline progressively evolved toward the prevention and early management of functional decline in older adults, thereby enabling the development of preventive approaches. Within this paradigm shift, the concept of "frailty" gained prominence in the late twentieth century and was consolidated at the beginning of the twenty-first century with the seminal work of Fried and colleagues [7].

Since that landmark, two major conceptual models have emerged to define and interpret frailty. Fried and colleagues described frailty as the phenotypic expression of a syndrome reflecting heightened vulnerability to minor stressors [7], whereas Rockwood and Mitnitski introduced a deficit accumulation model, shifted from functional age [8] to the cumulative burden of symptoms, signs, diseases, and disabilities [8–10]. While both frameworks are widely cited under the common label of "frailty," they conceptualize distinct constructs, fuelling a longstanding debate within geriatrics over the past two decades.

The lack of a universally accepted definition, a gold-standard assessment tool, and sufficient evidence-based interventions has hindered the integration of frailty into routine clinical practice, particularly outside geriatric medicine. Nonetheless, the frailty-related literature has grown exponentially over the past two decades, increasing from 42 PubMed-indexed references using "Frailty [title]" in 2004 to 2,664 in 2024. This rapid expansion, together with the inconsistent use of the term, underscores the pressing need for greater conceptual clarity [11,12]. For clinicians, health professionals, policymakers, and aging researchers, a unified framework based on robust evidence has become essential.

In this context, the Spanish Research Consortium on Frailty and Healthy Aging (CIBERFES), funded by the Instituto de Salud Carlos III (https://www.ciberfes.es/), has assumed the responsibility of providing a consensus document on frailty. CIBERFES constitutes the largest publicly funded Spanish initiative in this field, comprising 25 research groups: eleven clinical, nine basic science, two dedicated to physical activity and exercise, one focused on nursing care, one on nutrition, and one on health economics. This multidisciplinary and translational structure enables the integration of complementary expertise, facilitating the development of consensus documents that advance research and practice in frailty and healthy aging.

2. What is frailty?

Frailty is the expression of an age-associated clinical phenotypic syndrome driven by the biology of aging, life-course environmental exposures, and disease burden. Its physiological basis lies in a heterogeneous decline of functional reserve across organ systems, accompanied by impaired homeostasis and reduced capacity to respond to

[1] CIBERFES working group: GAITE (Albacete): Rafael García Molina,. Rubén Alcantud Córcoles, Almudena Avendaño Céspedes, Elena Gómez Jiménez; GENUD (Toledo): Luis M. Alegre, Julian Alcazar, Ivan Baltasar-Fernandez; Investén-isciii (Madrid) María Teresa Moreno Casbas; Hospital Gregorio Marañón (Madrid): Carlos Rodríguez López; FreshAge (Valencia): Gloria Olaso-Gonzalez, Juan Gambini, Consuelo Borras; Universidad de Barcelona: Miriam Martínez, Alex Sánchez, Anna Guadall, Tomás Meroño; Ibs (Granada): Beatriz Garcia Fontana; ISPA (Asturias): José Gutiérrez Rodríguez

[2] Given their role as editorial board member, Mikel Izquierdo, Nicolás Martínez Velilla and Leocadio Rodríguez-Mañas had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

stressors, ultimately predisposing to adverse health outcomes, mainly disability, as agreed by a group of experts using the Delphi method [11]. From this definition the main characteristics of frailty are as follows:

1 Frailty is a syndrome that not only precedes disability, but also is its main risk factor. In other words, it should be considered a pre-disability state [13].
2 Frailty falls within the functional continuum ranging from maximum functional autonomy and intrinsic capacity (robustness) to maximum disability and dependence [5].
3 Frailty is a progressive condition with a prodromal or preclinical phase commonly referred to as pre-frailty, which has been reported to affect up to 50% of community-dwelling older adults. Although pre-frailty has traditionally been defined by the presence of one or two frailty criteria, there remains no consensus regarding its operational definition, cut-off points, clinical relevance, or prognostic implications. Further research is therefore warranted to accurately characterize and identify this early stage of frailty.
4 The etiopathogenesis of frailty is multifactorial. Although the biology of aging plays a primary role, other factors, including diseases, other geriatric syndromes, lifestyle habits, genetic aspects, drugs, mental aspects (cognition, affect, anxiety) or psychosocial and economic aspects [14] among others, can trigger, accelerate, protect or modulate frailty. These factors may also contribute to the emergence of distinct clinical or biological sub-phenotypes [15–17], with greater predominance over strength, mobility, weight or fatigue (Fig. 1).
5 Its onset and progression can be prevented, delayed, slowed, or reversed with specific interventions targeting risk factors, some of which already have solid evidence [18–20]. In fact, treating frailty has been shown to be one of the main strategies for preventing or delaying disability and dependency [21–23]. Unfortunately, once the functional level of dependency has reached enough severity, reversibility is highly compromised and complex.

3. What is not frailty?

- Frailty cannot be dissociated from the aging process: As a consequence, if frailty is conceptualised as an age-associated syndrome, its assessment in populations where substantial age-related declines have not yet manifested (i.e., individuals younger than 50 years) may lack clinical relevance, particularly given that the primary target population comprises adults aged 65 years and older. To better understand this statement, a brief conceptualization of "what is aging" is presented below. Consequently, frailty cannot be attributed to declines in biological or functional capacities of organs or body systems occurring in younger populations as a result of diseases, health conditions, or environmental exposures, independent of the aging process, even if such changes share similarities and/or health outcomes.

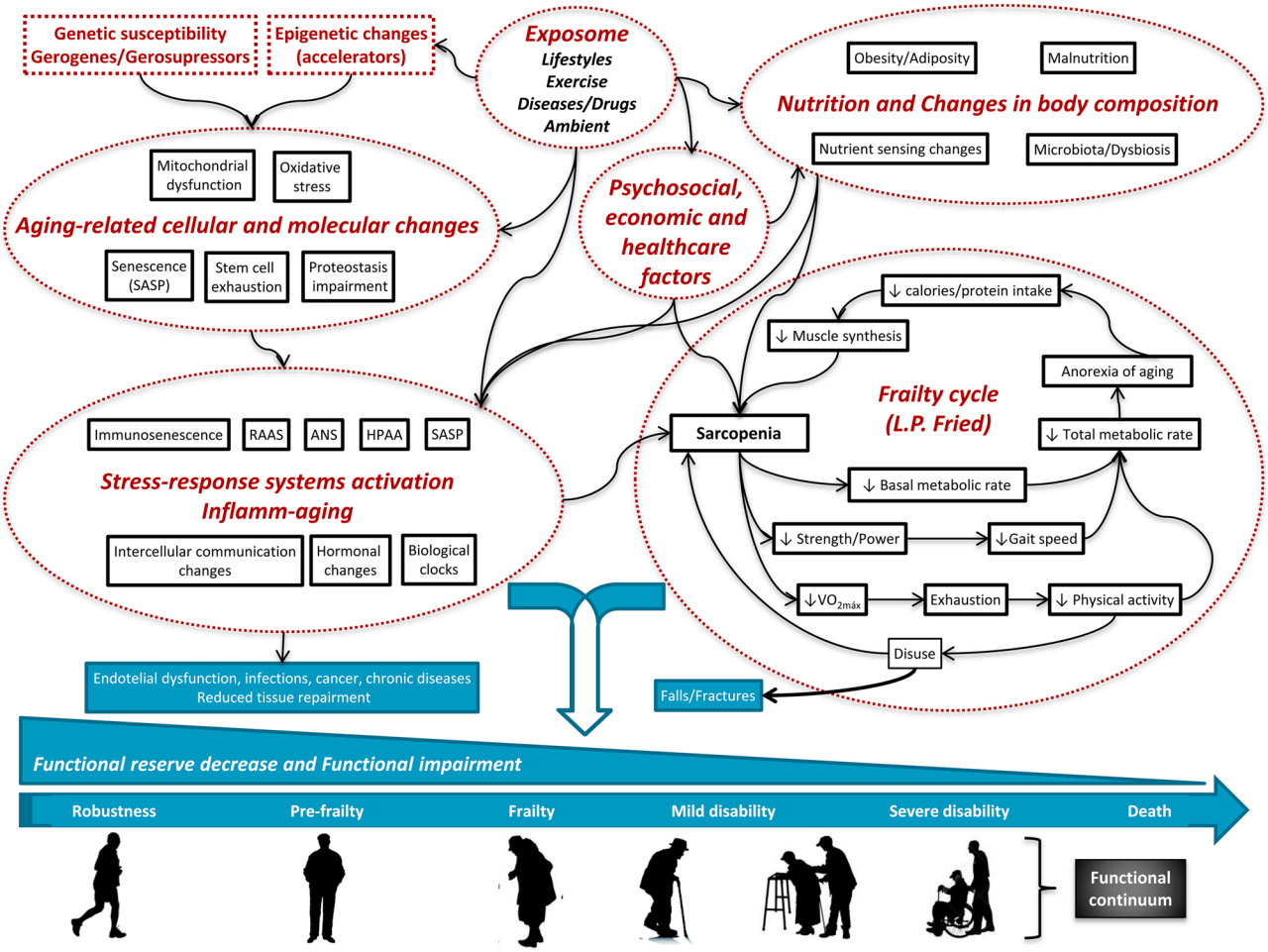

Fig. 1. Main pathways involved in the pathophysiology of frailty.
RAAS: Renin-angiotensin-aldosterone system; ANS: Autonomous nervous system. HPAA: Hypothalamic-pituitary-adrenal axis; SASP: Senescence-associated secretory phenotype.

- Frailty is not synonymous with aging: not every older adult is or will be frail. Although the biology of aging is a relevant contributor to the pathophysiology of frailty, frailty does not occur in all older people and can also appear at very different ages in older persons [24]. Even nonagenarians or centenarians may not be frail [25,26] and older people may die without ever having become frail.
- Frailty is not only a risk factor: While frailty predicts adverse events beyond disability, such as falls, reduced quality of life, hospitalisation, institutionalisation, and mortality, many other risk factors are also associated with these poor outcomes. Accordingly, not everything predisposing to these events is frailty. The definition of frailty should not be based on its outcomes but rather on its distinct pathogenesis linked to the aging process. One implication of this perspective is that although various diseases or health conditions, such as cancer or chronic kidney disease, among many others, may lead to health outcomes similar to those of frailty in older adults, they should not be considered frailty. At most, they may contribute to its pathogenesis by accelerating or modifying it. Second, not every scale associated with such adverse health outcomes in older adults can be regarded as a frailty scale. However, this approach has been used in the development of several tools, such as the Tilburg Frailty Indicator [27], the Groningen Frailty Indicator [28] or the electronic frailty index [29]. Likewise, not every scale showing to predict frailty-related outcomes is a frailty scale.
- Frailty is not comorbidity, multimorbidity or disability: frailty is an entity of its own, which can coexist with the presence of multiple conditions, such as sarcopenia [30,31], comorbidity [32], and disability [33,34]. This statement leads to a direct consequence: if frailty is distinct from disability, and frailty predicts the risk of disability, disability should not be part of the construct nor the measurement scales [10,35]. Similarly to hypertension regarding ischemic heart disease or cerebrovascular disease, where hypertension is more prevalent than in the whole population but it is not part of the disease.
- Frailty is not sarcopenia. Although frailty and sarcopenia are two conditions that can coexist [36,37], they are clearly two distinct conditions, and the existence of one does not guarantee the existence of the other [31,38]. Moreover, the inclusion of frailty in models showing an association between sarcopenia and some of its claimed adverse outcomes decrease significantly the strength of this association [30,31].
- Frailty should not be regarded as the opposite of intrinsic capacity, although there is considerable conceptual overlap among both entities, greater in the locomotor systems, and smaller in the cognitive/affective domains [39]. To promote a more comprehensive and clinically meaningful assessment of older adults with strong relevance in public health, the World Health Organization introduced the concept of intrinsic capacity, defined as the composite of all physical and mental abilities an individual can draw upon throughout life. Both constructs emerged from the shared need to overcome traditional biomedical paradigms that inadequately capture the complexity of aging, thereby hindering optimal clinical and research practices in geriatric populations [40]. From a biological standpoint, they also exhibit a comparable hierarchical and energy-dependent organisation, conceptualised as vitality in the case of intrinsic capacity and energy expenditure in the case of frailty [41]. Despite its potential relevance for epidemiological or gerontological applications, including public health, intrinsic capacity needs to improve its operationalisation, improving the clinical utility of the concept through a more robust validation of its measurement tools and the development of well-designed clinical trials showing the benefits of its measurement and interventions. In geriatric medicine, supported by CIBERFES, frailty, understood as a pre-disability state, remains more practical and advantageous, as it provides a pre-disability clinical framework enabling the implementation of targeted interventions that have been proven to succeed in large well-designed randomised clinical trials [42–45]. If concerns about stigma arise, strategies should focus on mitigating these issues rather than replacing the term with one derived from a purely "positivist" rationale.

4. What is aging?

Frailty cannot be fully understood without considering the biological process of aging. Aging is not a disease but a natural and universal process affecting all complex systems. It derives from the second law of thermodynamics, which states that entropy, a measure of disorder or randomness in a system, tends to increase over time. This provides a unifying physical principle linking biological aging to the universal laws of thermodynamics. Consequently, aging reflects the progressive accumulation of irreversible changes at molecular, cellular, organ, and integrative homeostatic levels, which gradually impair individual performance. It leads to a time-dependent decline in physiological functions essential for survival and reproduction, remaining distinct from any specific disease [46]. Nevertheless, this decline increases vulnerability to age-associated diseases and frailty. Very important, unlike age-associated diseases such as cancer or cardiovascular disease, the intrinsic features of aging universally affect all individuals of a species [46,47]. As highlighted by Ruden [48], "aging affects everyone, but it does not occur in the same way for every individual."

In the field of aging research, aging is defined as the progressive loss of physiological integrity, ultimately leading to functional impairment and increased mortality risk [49]. The concept of the "hallmarks of aging" has been proposed to describe common molecular alterations associated with the aging process. These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis [50]. More recently, changes in the extracellular matrix and psychosocial isolation have been recognised as additional hallmarks [51]. Although these hallmarks are of great conceptual value, it should be emphasised that many of them can also be observed individually or collectively in contexts unrelated to aging. Therefore, their assessment must be appropriately contextualized to avoid misinterpretation. Furthermore, as suggested by Tartière [52], future frameworks may need to incorporate additional elements that reflect higher levels of biological complexity, including tissue, organ, and whole-organism homeostatic processes. Importantly, the decline in the function of a specific organ due to disease should not be equated with the aging process itself [53], but rather with pathological multi-organ deficiency.

Despite the gains in life expectancy, recent evidence indicates that individuals now spend a greater proportion of their lives in poor health, as the duration lived with chronic diseases or frailty has disproportionately increased [54–56]. INotably, the contribution of disease accumulation to mortality risk appears to diminish with advancing age, likely because aging itself becomes the predominant determinant of survival [57,58]. Given this scenario, it is imperative to focus on strategies aimed at extending healthspan, rather than lifespan alone. Preventive interventions, both behavioural and pharmacological, targeted at decelerating the biological aging process hold promise for reducing the burden of frailty and chronic disease in older populations.

5. Frailty, a polysemic term leading to misunderstanding

The concept of frailty has been subjected to enormous terminological confusion from the outset in two ways. First, and as already mentioned, the struggle between the phenotype and the accumulation of deficits constructs has given rise to a broad, yet unresolved debate [59], although with the increasingly clear understanding that the two constructs do not measure the same thing and may be complementary. CIBERFES maintains that the frailty phenotype is the most clinically

useful construct, identifying a pre-disability state of vulnerability that can be addressed to prevent dependency.

The second confusion lies in the emergence of new terms that have appeared under the original construct of frailty. These include social frailty, oral frailty, cognitive frailty, and vascular frailty, among others. It is important to understand that although these terms may be valid in themselves, as it is the case with the word "insufficiency" that accompanies many others, they are not related to frailty as understood by CIBERFES. Nevertheless, in some aspects, they may present a certain association. Attempts have been made to rename frailty as understood by CIBERFES as "physical frailty" [60]. However, we believe that this term is not only unnecessary, but also inaccurate, since frailty transcends exclusively the physical aspects of older adults, although it is assessed primarily through physical function items.

6. Which is the pathophysiology of frailty?

Although substantial knowledge has been gained, many aspects of frailty remain unresolved. Since the seminal contributions of L.P. Fried [7,32], significant advances have further elaborated the concept of the "frailty cycle" originally proposed by the author [7]. It is out of the scope of this document to provide a complete review of the pathophysiology of frailty. However, it is increasingly recognised as a multifactorial syndrome arising from the interplay of diverse etiological mechanisms where changes due to the process of aging interact with processes linked to both subclinical and clinical diseases, which are phenotypically expressed as poor functional performance, that is, frailty. From our perspective, Fig. 1 schematically shows the main pathways involved in the pathophysiology of frailty (Fig. 1).

7. Frailty biomarkers: the search for the Holy grail?

Frailty is a complex construct where biological determinants, protective factors, triggers and accelerators interact, driving both its development and consequences (Fig. 2). Current research efforts focus on identifying biological and clinical drivers and biomarkers capable of accurately characterizing this condition and its mediators in an effort to improve its diagnosis and the monitoring of both its evolution and the response to interventions [61]. Nevertheless, due to its intricate and multisystemic origin, the presence of several clinical and subclinical conditions, and the lack of a consensus on a universally validated definition and way of assessment, identifying "the unique" biomarker or set of biomarkers remains challenging.

In this sense, markers related with inflammation (CXCL13, interleukin IL1A, IL-6, IL-8, IL-10, miR-125b-5p, homocysteine, C-reactive protein, fibrinogen, soluble intercellular adhesion molecule-1, tumor necrosis factor-alpha, and miR-21), oxidative stress (biological antioxidant potential, advanced glycation end-products, derivate of reactive oxygen metabolites, glutathione cycle, total thiol levels, malondialdehyde and protein carbonylation), mitochondrial dysfunction (growth differentiation factor-15), metabolism (homeostatic model assessment for insulin resistance, insulin-like growth factor-1, myostatin, adiponectin, sirtuin-1 and 3, klotho), muscle (pax7, myf5, myod, muf6, mstn), and endocrine (free and total testosterone, dihydrotestosterone, estradiol, sex hormone-binding globulin), have been related with frailty according to the frailty phenotype [61–67]. Furthermore, proteomic signatures of frailty across different pathways, such as innate immunity, cell growth/senescence, fibrosis/metabolism, and a host of proteins not widely described in human aging have been reported [68].

In this sense, we do promote and encourage researchers to strengthen the evidence on biomarkers and the prevalence, incidence and associated risks by using the frailty model we support. In addition, we advocate for the use of machine-learning models that integrate information from multiple physiological parameters to accurately discriminate frailty from other conditions that may similarly influence the same sets of biomarkers.

8. How should frailty be assessed?

A wide variety of frailty screening and diagnostic instruments have been developed and discussed in clinical, epidemiological, and academic contexts. Nevertheless, the feasibility and clinical utility of systematically screening older adults, particularly for the the early identification of individuals at heightened risk of adverse outcomes and their

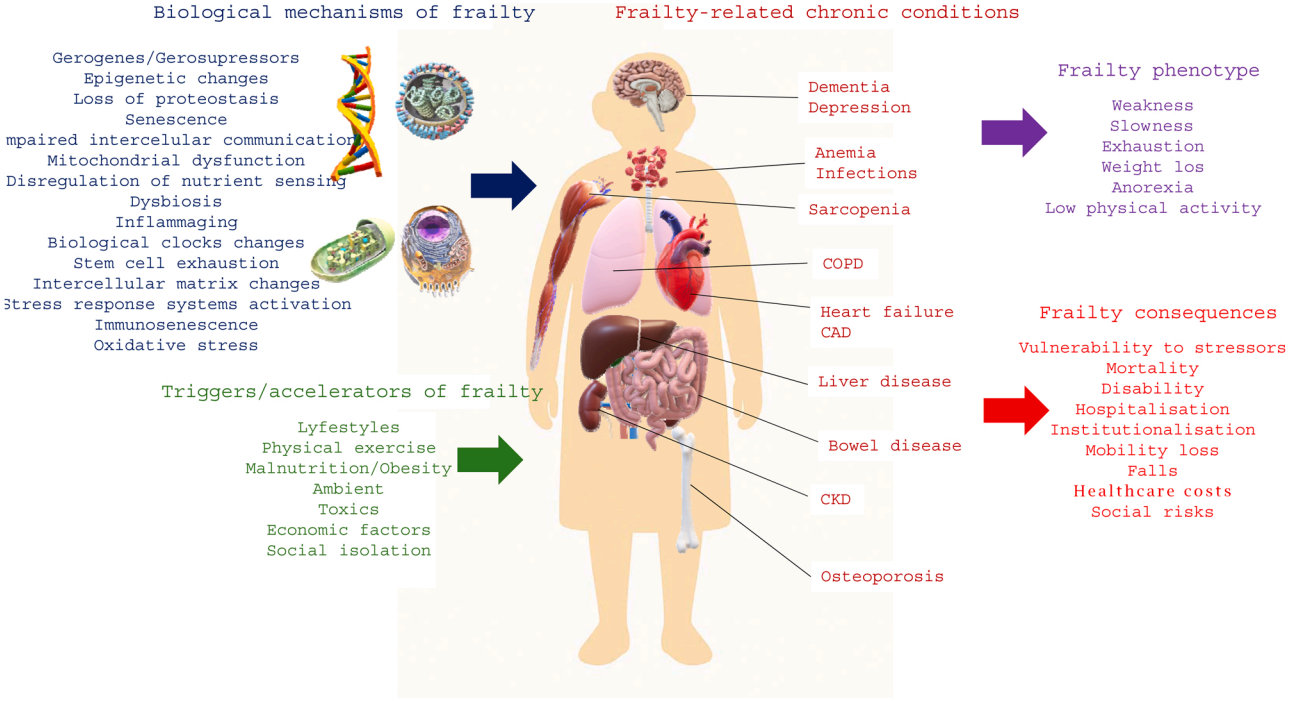

Fig. 2. Biological determinants, triggers, accelerators, related conditions and consequences of frailty.
COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CKD: Chronic kidney disease

subsequent referral for targeted interventions, remain insufficiently established [69,70].

To enable rapid, simple, sensitive, and standardised frailty screening, we recommend the use of the Short Physical Performance Battery (SPPB) [71], usual gait speed assessment [72], or the FRAIL Scale [73], in accordance with the recommendations of the ADVANTAGE Joint Action group [74] and the Frailty Working Group of the Spanish Ministry of Health [75]. Another promising marker of frailty is muscle power, measured using the sit-to-stand test [76] as age-related changes in maximal muscle power (powerpenia) occur earlier and progress more rapidly than reductions in muscle size and strength.

For diagnostic purposes, we propose the use of the Fried phenotype criteria [7], applying cut-off values adapted to the specific characteristics of the population under assessment. To address certain limitations of this tool, such as the dichotomous domain scoring, its limited sensitivity in detecting subtle but clinically relevant changes over time, and its suboptimal predictive accuracy, we additionally recommend the Frailty Trait Scale-5 (FTS5) [77].

9. Who should assess frailty? Training of professionals

All professionals involved in healthcare and social care for older adults should be familiar with and receive training in the assessment and management of frailty [78]. However, the curricula of many healthcare professionals still do not include them.

Undoubtedly, the best healthcare setting for conducting a baseline frailty assessment is Primary Care [79], but hospital settings (emergency rooms, inpatient departments, outpatient clinics, day hospitals), socio-sanitary facilities, and social services should be trained [69].

Nursing plays a pivotal role in this process: as the first point of contact for many older adults, nurses are uniquely positioned to conduct multidimensional assessments encompassing physical, psychological, social, and environmental domains. Alongside medical strategies, nursing care is also essential for comprehensive management: through monitoring, education, and caregiver support, nurses improve adherence to exercise and nutrition programmes. Nursing research has also generated person-centred and community-based interventions that can delay frailty progression and improve quality of life [80].

10. Once frailty is detected, what comes next?

Detecting frailty should prompt two sets of actions: diagnostic groundwork and therapeutic intervention. The diagnostic work must be oriented to characterise accompanying conditions that will modify the prognosis of the patients including existing comorbidities (cancer, heart failure, dementia, anaemia), but also associated conditions to frailty, mainly sarcopenia, which has been shown to modify the prognosis of frailty [30,81], along with psychological aspects like cognitive functioning and depressive mood. The best way to achieve these goals is to perform a Comprehensive Geriatric Assessment [75]. Interventions on frailty have been shown to be effective and cost-effective in promoting longer and healthier lives. The most effective interventions are those based on lifestyle changes, such as physical exercise and nutritional recommendations [82–84].

10.1. Physical exercise

Exercise prescriptions for older adults should be medically indicated, professionally implemented, and clinically monitored [85]. Exercise should be considered a first-line intervention when no effective pharmacological alternatives are available, such as in frailty, sarcopenia, and functional decline, or as a critical adjunct when medications blunt physiological adaptations [85,86]. The integration of exercise prescriptions with medication management offers a novel strategy to enhance health and functional capacity, optimising drug effectiveness, and reducing adverse drug reactions and polypharmacy in older adults [85,86].

Following the recommendations of the consensus on physical exercise in older adults by Izquierdo et al. [86], frail older adults should follow a multicomponent exercise program. In other words, exercise programs for frail and prefrail older adults should include strength and power training, balance and gait re-education, aerobic, and flexibility exercises [87], briefly:

- Strength and power: performed 2–3 sessions per week, performing 1–3 sets of 8–12 repetitions and combining low- and high-speed exercises (power training) at intensities of 40–80% of 1 repetition maximum (RM). This exercise simulates functional abilities, that is, standing from a chair.
- Balance and gait re-education: should be performed between 3 to 4 d/w, 1 to 2 sets of different exercises, emphasising in both static and dynamic postures which should progress in complexity,
- Aerobic exercise: performed 3–7 d/w which should start with durations of 5–10 min (or less) during the initial weeks of training and may extend to 20–30 min over time at a moderate intensity according to heart rate or perceived exertion.
- Flexibility exercises: are best utilised during the cooldown routine after every single exercise session, completing two sets of three repetitions, while maintaining in the same position for 10 s.

The VIVIFRAIL program (available at http://vivifrail.com/resources) is a simple, validated, and effective exercise program for prescribing physical activity based on the functional capacity [86,88]. Although the exercise program should ideally be maintained for 12 weeks, there is evidence of functional improvement over shorter periods in specific settings, such as nursing homes [89]. Upon completion of the training program, older adults should be re-evaluated to determine whether adjustments to the exercise prescription are needed. Notably, the benefits achieved through such exercise programs can persist for several months after training cessation [90]. Given its relevance, in addition to prescribing exercise, clinicians should maximise adherence to physical interventions in frail older adults [91,92]. The higher the adherence, the greater are the benefits.

Thus, it is not acceptable to omit the prescription of physical exercise in frail older adults [93] or to limit oneself to generating evidence only in comparison with usual care (without exercise). However, accurately determining the impact of different exercise parameters (i.e., intensity, type, frequency, and duration) would be a fundamental contribution to promoting the systematic and evidence-based implementation of these programs.

10.2. Nutritional interventions

According to the report from an ESPEN symposium published by Volkert et al. [94,95], frailty was highlighted as a major nutrition-related geriatric syndrome. In this regard, the authors themselves acknowledge the lack of evidence for specific nutritional requirements for frailty, particularly regarding protein and micronutrient requirements [96]. In epidemiological studies, entities like malnutrition, nutritional status evaluated through the body mass index (BMI), underweight, overweight and obesity, and low energy and protein intake, have all been associated with the onset or progression of frailty [95–97]. Micronutrient deficits (low carotenoid, alpha-tocopherol, albumin, low vitamin levels of B6, B12, C, D or E, total cholesterol, zinc, folate, and uric acid) have also been associated with frailty [98,99]. Other nutrition-related conditions like anorexia of aging [100] and poor oral health [101] have been related with the onset or progression of frailty. In addition, frail older adults consume less animal protein than do robust individuals [102]. Finally, among the dietary types, the Mediterranean diet has demonstrated a preventive effect against frailty, particularly in pre-frail individuals [103–105]. This effect could be supported on the capability of the Mediterranean diet to prevent or reduce oxidative stress

and inflammation, which have been strongly associated to the increase in the levels of advanced glycation end-products [106]. On the other hand, the role of nutrition in reversing or improving frailty is well supported by the literature when in combination with physical exercise programs [43,107,108]. However, the role of nutritional interventions in isolation are not well established and the identification of populations susceptible to benefit from them should be stressed, mainly those who are frail/prefrail and malnourished or at risk of malnutrition. Thus, we can extrapolate certain messages to apply in frail individuals [109]:

- An intake of at least 30 kcal/kg/day is recommended [94], with higher amounts in cases of malnutrition or the presence of disease.
- A minimum recommendation of protein intake (1.2–1.5 g/kg/day) from lean meats, fish, dairy, and plant-based proteins should be ensured for this population, with higher amounts if other geriatric syndromes such as malnutrition [94,110] or sarcopenia are present. It may be advisable to repart the proteins between meals, and with a mínimum amount of 25–30 gr at each one, to enhance muscle synthesis after each meal, avoiding anabolic resistance [111]. If a regular diet fails to meet these requirements, protein supplements may serve as an alternative [112,113].
- Daily amounts of 25 g of fibre should be considered adequate for normal laxation in absence of gastrointestinal disease.
- Adequate intake of Vitamin D and calcium is recommended to support bone health and muscle function. Supplementation to avoid 25 (OH) Vitamin D deficiency (<20 ng/mL) may be required [114].
- 1.6 L and 2.0 L of liquid should be offered for older women and men, respectively, except when fluid overload is present.
- The type, flavor, texture and time of consumption of food should be adapted to the individual's taste and eating capacities.
- When possible, adherence to healthy dietary patterns such as the Mediterranean diet should be prioritised, as it is based on a high intake of plant-based foods including fruits, vegetables, whole grains, legumes, and olive oil [103].

10.3. Technological interventions

A possible way to increase adherence to exercise and nutrition programs to prevent [115] and treat frailty [116] is through technology-based interventions. These interventions have shown promising results in the assessment, monitoring, and adaptation of care for older adults. However, their daily implementation in health services has yet to be confirmed, especially considering certain profiles of older adults in rural areas or with low socioeconomic status, where implementation might be limited.

10.4. Frailty and drugs

To date, there is no effective drug to treat frailty, and because of its multisystemic nature, such a drug may never be developed. However, numerous specific medications, such as anticholinergics, statins, and psychotropic drugs, are associated with worsening of frailty status [117,118]. Likewise, the appropriate or inappropriate combination of drugs has also been shown to be a factor associated with frailty [119]. In addition, because the pharmacokinetic and pharmacodynamic processes of drugs may be affected in frail older adults, it is necessary to conduct a thorough risk-benefit analysis of each drug and deprescribe as many drugs as possible in order to avoid undesirable interactions [120,121].

Deprescribing, the process of dose reduction or withdrawal of inappropriate medication that no longer has benefits, has been proposed as an intervention for frailty. However, there is currently limited evidence of strong benefits from such deprescribing services, such as reductions in the number of potentially inappropriate medications and medication costs [122]. There are no universal consensus criteria for deprescribing drugs owing to the lack of inclusion of the older population, and especially the frail one, in clinical trial studies [123]. However, a group of experts in geriatric pharmacology, led by O'Mahony, have proposed 190 criteria to optimise medication and minimise adverse events caused by drug interactions in the older people [124].

From this position statement, we call for an evaluation of the effect of drugs on the frail older population, with the goal of defining specific therapeutic objectives for this population, as is already the case in diabetes care [125,126].

11. Frailty phenotypes or frailty subtypes?

Several studies have proposed the existence of different frailty phenotypes, which could not only explain the discrepancies observed in the risk of adverse events, but also justify the need for differentiated clinical approaches for each phenotype. These different phenotypes, or subtypes within frailty, could be defined by specific biomarkers, domains exhibited by individuals, or by the presence of certain geriatric-related conditions, or even some diseases or multiple conditions. For instance, latent class analysis identified three distinct phenotypes showing differential rates of functional decline: non-mobility (weight loss and exhaustion), mobility (slowness and weakness), and low physical activity [127,128]. Another study identified three distinct frailty phenotypes, energy-based, sarcopenia-based, and hybrid-based, with an ability to predict various health consequences. [129]. Therefore, although this is a field that may be very upcoming, its importance cannot be corroborated.

A different approach is that of constructing mixed classes between multimorbidity and frailty. This approach has produced different frailty subclasses like minimal disease, cardiovascular disease, osteoarticular disease, neuropsychiatric disease, and high multisystem morbidity [130]. It is well known that frailty is associated with multiple chronic diseases (Fig. 2), probably being both cause and consequence, and this aspect may lead to different frailty phenotypes [131–140].

As it has been stated, frailty is a syndrome that can coexist with several different entities. Frailty can coexist in multiple entities. Below, we will detail those that we believe to be most important and the main aspects to consider in relation to each of them.

11.1. Sarcopenia and frailty

Various authors have used the terms sarcopenia and frailty interchangeably. However, in our opinion, these two terms are clearly differentiated. Similarly, although sarcopenia is a neuromusculoskeletal disease in which the main target organ (the muscle) shows a decrease in size and function, the pathophysiology of frailty is multisystemic. According to data from the Toledo Study of Healthy Aging, the presence of sarcopenia greatly increases the risk of developing frailty within three years [30], while the coexistence of frailty and sarcopenia in the same individual appears necessary to increase the risk of disability [81]. Frailty increases healthcare costs [141] and the risk of mortality in older adults with sarcopenia [81].

Emerging evidence suggests a link between the biological underpinnings of frailty and skeletal muscle mechanisms central to sarcopenia, including autophagy–mitochondria crosstalk and myogenic commitment. This interactome perspective may help explain trajectories from independence to dependence and support the development of mechanism-based biomarkers. [67,142].

This distinction in the risk of potential adverse events in older adults based on the prevalence of these two entities should be key when considering interventions.

11.2. Cognitive frailty

Since it was first used to identify individuals at high-risk for Alzheimer's disease in 2001 [143], the term cognitive frailty has mainly referred to the association between frailty and cognitive impairment [144]. However, the fact that frailty has been associated with brain

structural and functional abnormalities in neuroimaging studies [145], the lack of a clear definition of this syndrome (i.e., whether delirium and dementia would be included in cognitive impairment), and whether the combination of both entities provides added clinical value compared to either of them separately [146], indicate some hesitation about fully endorsing this position. Although the relevance of the gut-brain-muscle axis is well known [147], from CIBERFES, we encourage further research into the existence and clinical value of this possible subtype of frailty.

11.3. Social frailty or social vulnerability?

Frailty is partly determined by socioeconomic inequalities across the person's life course (i.e., loneliness and social isolation, perceived inadequacy of social support, and reduced social participation). Socioeconomic position is associated with higher frailty prevalence and incidence, with greater odds of transitioning towards a more severe frailty state and lower odds of frailty reversion [148].We recognise that social profiles have a significant impact on the quality of life of older adults and on frailty transitions, therefore, should be systematically assessed and incorporated into the design and implementation of multidimensional prevention and treatment programs at all levels of care, including primary care, hospital care, and long-term care. Social isolation and loneliness are potential outcomes of frailty.

Public health policies and health practitioners should prioritise interventions targeting social connections among older adults with pre-frailty or frailty [149,150]. This would require strategies that transcend the clinical setting and integrate the social dimension into interventions. Consequently, we consider it a priority to adopt multidisciplinary approaches aimed at the early identification and comprehensive management of frailty, complemented by policies that promote prevention, social inclusion, and community support. Thus, we recommend: (1) promoting personalised intervention programs, (2) strengthening the healthcare professionals' training in the comprehensive approach to frailty, and (3) establishing effective coordination mechanisms between the social and healthcare systems to ensure an integrated response [150,151].

Nevertheless, to avoid further confusion, we propose that the term used to refer to the scarce adequate social connections, support, or interaction should be "vulnerability" rather than "frailty" [150].

12. The stigma of being "frail"

There is an urgent need on how to address the stigma attached with being labelled 'frail' [59]. Older adults find frailty a difficult concept to accept and view the act of identifying themselves as frail as beginning a self-perpetuating cycle into decline [152]. Understanding older adults' perspectives on frailty is pertinent to developing an acceptable and appropriate patient-centred approach to frailty assessment and management. Words that promote negative stereotypes impact on health and promote paternalism and ageism, and negative self-perceptions of aging have been associated with detrimental effects on health outcomes [153]. Clinicians managing frailty need to be aware about the use of the term frailty, as a possible stigma with unintended harms including stereotyping and further isolation [154].

Two approaches may be used to reduce this stigma. The first one is the rewording of the term frailty, like what was done by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) renaming "dementia" as "major neurocognitive disorder", or the World Health Organisation approach promoting the term "intrinsic capacity", like a ying/yang construct [154,155]. This only leads to the concealment of a real problem as has been o served throughout this positioning. The second approach is based on strategies that facilitate the acceptance of frailty by health providers and patients, as has been done with other problems such as breast cancer or AIDS [156,157]. Strategies such as personal support, environmental interventions, advertising campaigns, objective information for patients, family members, and caregivers, training for healthcare professionals, campaigns led by celebrities, or the use of social media, among others, could be valuable, and CIBERFES adheres to this second approach.

13. Gender differences in frailty

Female sex is consistently associated with a higher prevalence of frailty across populations. Nonetheless, sex-related differences in frailty rates appear minimal at younger ages but become pronounced from approximately 65 to 70 years of age [158]. Moreover, significant gender-specific variations have been observed in frailty risk factors, transition rates, trajectories, and predictive models [159,160]. Gender also influences frailty-related outcomes: mortality rates tend to be higher among men, whereas women exhibit greater levels of disability and higher utilization of healthcare resources [161,162].

These observations underpin the so-called "sex–frailty paradox," which refers to the phenomenon whereby women, despite exhibiting higher levels of frailty and poorer health status, demonstrate lower mortality rates than men of comparable age [163].

Shared biological mechanisms that progress at different rates in men and women may underlie divergent aging and frailty trajectories. Consequently, a comprehensive and integrative approach to frailty research is urgently needed—one that incorporates a gender medicine perspective and addresses the biological underpinnings of the sex–frailty paradox [163].

14. Psychosocial, economic and healthcare factors of frailty

Psychosocial factors such as social isolation, loneliness, low health literacy, discrimination, depression, and cognitive impairment contribute to the onset and progression of frailty by negatively influencing health behaviors, stress responses, and functional reserve [164]. Economic constraints, including low income, financial insecurity, and limited access to social resources, further may exacerbate frailty by restricting adequate nutrition, housing stability, and timely utilization of preventive and therapeutic services. From a healthcare perspective, frail older adults often experience multiple barriers, including fragmented care, health inequity, lack of geriatric departments, long waiting lits, and increased dependence on informal caregivers, leading to higher rates of hospitalization, institutionalization, and adverse outcomes [165]. An integrated, person-centered care model that addresses social support, economic vulnerability, and coordinated healthcare delivery is therefore essential for the prevention, early identification, and effective management of frailty in older populations.

15. Frailty from the evidence to the clinical scenario: current challenges and future directions

Frailty has been established as a clinically relevant construct for predicting adverse outcomes in older adults, such as disability, falls, hospitalisation, institutionalisation and mortality [166]. In fact, some studies have shown this syndrome to be the main modifiable factor associated with mortality in older adults [167]. However, despite growing evidence supporting this practice, systematic frailty assessment is still not routinely performed in older adults, especially in primary care and non-geriatric settings. In addition, there is a clear lack of standardised protocols and integrated care pathways once frailty is detected.

Health policies and care model strategies for identifying frailty based on the scales proposed in this manuscript (screening and diagnosis), as well as the integration of multidimensional interventions involving physical exercise, nutritional optimisation, and medication

management, must be implemented and tailored to individual needs. In addition, the role of social vulnerability in frailty transitions should be considered.

The implementation of these programs will be essential to address population aging and reduce the burden on healthcare systems [168, 169].

16. Conclusions

In this consensus document, we present our understanding of frailty. Frailty is an age-related clinical phenotypic syndrome with a biological basis, whose cause is determined by the interaction of three factors: the aging process, environmental aspects and clinical and subclinical disease. It should be systematically assessed to prevent adverse events in older adults, mainly disability. Due to its dynamic and potentially reversible nature, interventions based on physical exercise, nutritional optimisation and pharmacological refinement should be implemented once frailty is detected. Nevertheless, despite current evidence supports the benefits of multidomain programs, several gaps remain in the systematic standardisation of criteria and clinical implementation.

Advancing translational research, incorporating technology-based interventions and evaluating social vulnerability, and designing age-adaptive care models are essential steps to improving the quality of life of older adults. Finally, specific professional training and the development of public policies aimed at preventing and comprehensively managing frailty are pillars for addressing this global challenge.

CRediT authorship contribution statement

PA was the coordinator of the complete work, AAB and LRM contributed with the drafting of the work, validation, visualization, methodology, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

CAL, IA, MAA, JPB, ACM, JAE, GE, FJGG, MCGC, OGR, MI, NMV, AM, RMC, MMT, XN, JO, MIOC, IPM, FP, MRB, MAR, JASR, FJTS, and the CIBERFES Working Group, participated in the investigation, validation, visualization, revision and final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors had a role in writing the final manuscript and approved the final version.

Ethics statement

The experiments comply with the current Spanish laws.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Perplexity in order to improve language editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding

The present study received funding from the projects CB16/10/00408, CB16/10/00269, CB16/10/00477, CB16/10/00383, CB16/10/00282, CB16/10/00289, CB16/10/00238, CB16/10/00456, CB16/10/00435, CB16/10/00417, CB16/10/00315, CB16/10/00496, CB16/10/00468, CB16/10/00475, CB16/10/00245, CB23/10/00037, CB16/10/00501, CB16/10/00464, CB16/10/00239, CB16/10/00314, Instituto de Salud Carlos III, Madrid, Spain.

Data statement

Data of the present manuscript are unsuitable to post, because they are opinions. There are no data available.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors sincerely thank Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES) for its invaluable assistance

References

[1] Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. Milbank Q. 2005;83:731–57.
[2] Crimmins EM. Lifespan and healthspan: past, present, and promise. Gerontologist. 2015;55:901–11.
[3] Rodriguez-Mañas L, Rodríguez-Artalejo F, Sinclair AJ. The third transition: the clinical evolution oriented to the contemporary older patient. J Am Med Dir Assoc 2017;18:8–9.
[4] Guo J, Huang X, Dou L, Yan M, Shen T, Tang W, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther. 2022;7:391.
[5] Hoogendijk EO, Romero L, Sánchez-Jurado PM, Flores Ruano T, Viña J, Rodríguez-Mañas L, et al. A new functional classification based on frailty and disability stratifies the risk for mortality among older adults: the FRADEA study. J Am Med Dir Assoc. 2019;20:1105–10.
[6] Warren MW. Care of the chronic aged sick. Lancet. 1946;1(6406):841–3.
[7] Cardiovascular Health Study Collaborative Research Group, Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146–56.
[8] Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr. 2002;2:1.
[9] Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173:489–95.
[10] Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722–7.
[11] FOD-CC group (Appendix 1), Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci 2013;68:62–7.
[12] Rodríguez-Mañas L, Sinclair AJ. Frailty: the quest for new domains, clinical definitions and subtypes. Is this justified on new evidence emerging? J Nutr Health Aging 2014;18:92–4.
[13] SPRINTT consortium, Cesari M, Marzetti E, Calvani R, Vellas B, Bernabei R, Bordes P, et al. The need of operational paradigms for frailty in older persons: the SPRINTT project. Aging Clin Exp Res. 2017;29:3–10.
[14] Deng Y, Yamauchi K, Song P, Karako T. Frailty in older adults: a systematic review of risk factors and early intervention pathways. Intractable Rare Dis Res. 2025;14:93–108.
[15] Ji F, Park JH, Rheem H, Kim JH. Overlapping and distinct physical and biological phenotypes in pure frailty and obese frailty. Biosci Rep. 2024;44:BSR20240784.
[16] Pujos-Guillot E, Pétéra M, Jacquemin J, Centeno D, Lyan B, Montoliu I, et al. Identification of pre-frailty sub-phenotypes in elderly using metabolomics. Front Physiol. 2019;9:1903.
[17] Singer JP, Calfee CS, Delucchi K, Diamond JM, Anderson MA, Benvenuto LA, et al. Subphenotypes of frailty in lung transplant candidates. Am J Transplant. 2023;23:531–9.
[18] Oliveira JS, Pinheiro MB, Fairhall N, Walsh S, Chesterfield Franks T, et al. Evidence on physical activity and the prevention of frailty and sarcopenia among older people: a systematic review to inform the world health organization physical activity guidelines. J Phys Act Health. 2020;17:1247–58.
[19] Money A, MacKenzie A, Parchment A, Norman G, Harris D, Ahmed S, et al. Evidence on non-pharmacological interventions for preventing or reversing physical frailty in community-dwelling older adults aged over 50 years: overview of systematic reviews. BMC Geriatr. 2025;25:183.
[20] Eidam A, Durga J, Bauer JM, Zimmermann S, Vey JA, Rapp K, et al. Interventions to prevent the onset of Frailty in adults aged 60 and older (PRAE-Frail): a systematic review and network meta-analysis. Eur Geriatr Med. 2024;15:1169–85.

[21] Abizanda P, Romero L, Sánchez-Jurado PM, Martínez-Reig M, Gómez-Arnedo L, Alfonso SA. Frailty and mortality, disability and mobility loss in a Spanish cohort of older adults: the FRADEA study. Maturitas. 2013;74:54–60.
[22] Liu HX, Ding G, Yu WJ, Liu TF, Yan AY, Chen HY, et al. Association between frailty and incident risk of disability in community-dwelling elder people: evidence from a meta-analysis. Public Health. 2019;175:90–100.
[23] Baltasar-Fernandez I, Soto-Paniagua H, Alcazar J, Uceta Espinosa MI, Alegre LM, Gracía-García FJ, et al. Long-term effects of a 6-week power-based resistance training and fast walking interval training program on physical function, muscle power, disability, and frailty in pre-frail and frail older adults. Gerontology. 2024; 70:701–14.
[24] O'Caoimh R, Galluzzo L, Rodríguez-Laso Á, Van der Heyden J, Ranhoff AH, Lamprini-Koula M, et al. Work Package 5 of the Joint Action ADVANTAGE. Prevalence of frailty at population level in European ADVANTAGE Joint Action Member States: a systematic review and meta-analysis. Ann Ist Super Sanita. 2018;54:226–38.
[25] Zhang J, Xu L. Frailty and associated factors among Chinese centenarians. J Nutr Health Aging. 2022;26:806–13.
[26] Skubiszewska A, Broczek K, Maruniak-Chudek I, Oledzka G, Jonas MI, Puzianowska-Kuznicka M, et al. Frailty and survivability of polish caucasian nonagenarians and centenarians. Geriatrics (Basel). 2024;9:14.
[27] Gobbens RJ, van Assen MA, Luijkx KG, Schols JM. The predictive validity of the Tilburg Frailty Indicator: disability, health ca re utilization, and quality of life in a population at risk. Gerontologist. 2012;52:619–31.
[28] Peters LL, Boter H, Buskens E, Slaets JP. Measurement properties of the Groningen Frailty Indicator in home-dwelling and institutionalized elderly people. J Am Med Dir Assoc. 2012;13:546–51.
[29] Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Aging. 2016;45:353–60.
[30] Álvarez-Bustos A, Carnicero-Carreño JA, Davies B, Garcia-Garcia FJ, Rodríguez-Artalejo F, Rodríguez-Mañas L, et al. Role of sarcopenia in the frailty transitions in older adults: a population-based cohort study. J Cachexia Sarcopenia Muscle. 2022;13:2352–60.
[31] Davies B, García F, Ara I, Artalejo FR, Rodriguez-Mañas L, Walter S. Relationship between sarcopenia and frailty in the toledo study of healthy aging: a population based cross-sectional study. J Am Med Dir Assoc. 2018;19:282–6.
[32] Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59:255–63.
[33] Abizanda P, Sánchez-Jurado PM, Romero L, Paterna G, Martínez-Sánchez E, Atienzar-Núñez P. Prevalence of frailty in a Spanish elderly population: the Frailty and Dependence in Albacete study. J Am Geriatr Soc. 2011;59:1356–9.
[34] Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Aging. Age Aging. 2015;44:162–5.
[35] Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Aging Res Rev. 2016;26:53–61.
[36] Cesari M, Landi F, Vellas B, Bernabei R, Marzetti E. Sarcopenia and physical frailty: two sides of the same coin. Front Aging Neurosci. 2014;6:192.
[37] Picca A, Calvani R, Cesari M, Landi F, Bernabei R, Coelho-Júnior HJ, et al. Biomarkers of physical frailty and sarcopenia: coming up to the place? Int J Mol Sci. 2020;21:5635.
[38] Mijnarends DM, Schols JM, Meijers JM, Tan FE, Verlaan S, Luiking YC, et al. Instruments to assess sarcopenia and physical frailty in older people living in a community (care) setting: similarities and discrepancies. J Am Med Dir Assoc. 2015;16:301–8.
[39] Rippl M, Polidori C, Drey M. Frailty at the interface of resilience and intrinsic capacity. Inn Med (Heidelb). 2025 Aug 22.
[40] Belloni G, Cesari M. Frailty and intrinsic capacity: two distinct but related constructs. Front Med (Lausanne). 2019;6:133.
[41] Yu Z, Lozupone M, Chen J, Bao Z, Ruan Q, Panza F. The biological rationale for integrating intrinsic capacity into frailty models. Clin Interv Aging. 2025;20: 273–86.
[42] European MID-Frail Consortium, Rodriguez-Mañas L, Laosa O, Vellas B, Paolisso G, Topinkova E, Oliva-Moreno J, et al. Effectiveness of a multimodal intervention in functionally impaired older people with type 2 diabetes mellitus. J Cachexia Sarcopenia Muscle 2019;10:721–33.
[43] SPRINTT consortium, Bernabei R, Landi F, Calvani R, Cesari M, Del Signore S, Anker SD, et al. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). BMJ. 2022 May 11;377:e068788.
[44] LIFE Study Group, Cesari M, Vellas B, Hsu FC, Newman AB, Doss H, King AC, et al. A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. J Gerontol A Biol Sci Med Sci. 2015;70: 216–22.
[45] Abizandsa Saro A., et al. 2016 FRAILMERIT.
[46] Hayflick L. Biological aging is no longer an unsolved problem. Ann N Y Acad Sci. 2007;1100:1–13.
[47] Gilbert SF. Developmental Biology. 6th ed. Sunderland (MA): Sinauer Associates; 2000.
[48] Ruden DM. The emerging role of multiomics in aging research. Epigenomics. 2025;17:897–904.
[49] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153:1194–217.
[50] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell. 2023;186:243–78.
[51] Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, et al. From geroscience to precision geromedicine: understanding and managing aging. Cell. 2025;188:2043–62.
[52] Tartiere AG, Freije JMP, López-Otín C. The hallmarks of aging as a conceptual framework for health and longevity research. Front Aging. 2024;5:1334261.
[53] Fraser HC, Kuan V, Johnen R, Zwierzyna M, Hingorani AD, Beyer A, et al. Biological mechanisms of aging predict age-related disease co-occurrence in patients. Aging Cell. 2022;21:e13524.
[54] Orrall A. As lifespan increases, people spend more years burdened by disease. JAMA. 2025;333:453.
[55] Choi M, Sempungu JK, Lee EH, Lee YH. Living longer but in poor health: healthcare system responses to aging populations in industrialised countries based on the Findings from the Global Burden of Disease Study 2019. BMC Public Health. 2024;24:576.
[56] Tazzeo C, Rizzuto D, Calderón-Larrañaga A, Dekhtyar S, Zucchelli A, Xia X, et al. Living longer but frailer? Temporal trends in life expectancy and frailty in older Swedish adults. J Gerontol A Biol Sci Med Sci. 2024;79:glad212.
[57] Sourial N, Bergman H, Karunananthan S, Wolfson C, Payette H, Gutierrez-Robledo LM, et al. Implementing frailty into clinical practice: a cautionary tale. J Gerontol A Biol Sci Med Sci. 2013;68:1505–11.
[58] Fabbri E, Candia J, Tanaka T, Moore AZ, Muratori P, Brugiavini A, et al. Dynamics of multimorbidity, health expectancy, and survival in middle aged and older individuals. J Gerontol A Biol Sci Med Sci. 2025;80:glaf164.
[59] Dent E, Clegg A, Roller-Wirnsberger R, Vetrano DL, Hoogendijk EO. Reorienting frailty in clinical practice, public health, and policy: the Lancet Commission on Frailty. Lancet. 2025;405(10497):2265–6.
[60] Pei B, Yu Y, Shen X, Jia Y, Wang J, Zhang Y, et al. Associations of physical frailty, social deficits, and cognitive impairment with risk of 45 incident non-communicable diseases: the mediating role of accelerated biological aging-a prospective cohort study. J Nutr Health Aging. 2025;29:100672.
[61] El Assar M, Rodríguez-Sánchez I, Álvarez-Bustos A, Rodríguez-Mañas L. Biomarkers of frailty. Mol Aspects Med. 2024;97:101271.
[62] de Jong JCBC, Caspers MPM, Dulos R, Snabel J, van der Hoek MD, van der Leij FR, et al. Blood-based biomarkers for early frailty are sex-specific: validation of a combined in silico prediction and data-driven approach. Geroscience. 2025; 47:3741–58.
[63] Landino K, Tanaka T, Fantoni G, Candia J, Bandinelli S, Ferrucci L. Characterization of the plasma proteomic profile of frailty phenotype. Geroscience. 2021;43:1029–37.
[64] FRAILOMIC initiative, Gomez-Cabrero D, Walter S, Abugessaisa I, Miñambres-Herraiz R, Palomares LB, Butcher L, et al. A robust machine learning framework to identify signatures for frailty: a nested case-control study in four aging European cohorts. Geroscience. 2021;43:1317–29.
[65] Álvarez-Satta M, Berna-Erro A, Carrasco-Garcia E, Alberro A, Saenz-Antoñanzas A, Vergara I, et al. Relevance of oxidative stress and inflammation in frailty based on human studies and mouse models. Aging (Albany NY). 2020;12: 9982–99.
[66] Kuiper LM, Picavet HSJ, Rietman ML, Dollé MET, Verschuren WMM. Advanced glycation end-products and metabolomics are independently associated with frailty: the longitudinal doetinchem cohort study. J Gerontol A Biol Sci Med Sci. 2025;80:glae272.
[67] Coto-Montes A, González-Blanco L, Antuña E, Menéndez-Valle I, Bermejo-Millo JC, Caballero B, et al. The interactome in the evolution from frailty to sarcopenic dependence. Front Cell Dev Biol. 2021;9:792825.
[68] Perry AS, Zhao S, Gajjar P, Murthy VL, Lehallier B, Miller P, et al. Proteomic architecture of frailty across the spectrum of cardiovascular disease. Aging Cell. 2023;22:e13978.
[69] Oviedo-Briones M, Rodríguez-Laso Á, Carnicero JA, Gryglewska B, Sinclair AJ, Landi F, et al. The ability of eight frailty instruments to identify adverse outcomes across different settings: the FRAILTOOLS project. J Cachexia Sarcopenia Muscle. 2022;13:1487–501.
[70] Checa-López M, Costa-Grille A, Álvarez-Bustos A, Carnicero-Carreño JA, Sinclair A, et al. Effectiveness of a randomized intervention by a geriatric team in frail hospital inpatients in non-geriatric settings: FRAILCLINIC project. J Cachexia Sarcopenia Muscle. 2024;15:361–9.
[71] Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49:M85–94.
[72] Lee L, Patel T, Costa A, Bryce E, Hillier LM, Slonim K, et al. Screening for frailty in primary care: accuracy of gait speed and hand-grip strength. Can Fam Physician. 2017;63:e51–7.
[73] Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012; 16:601–8.
[74] Rodríguez Mañas L, García-Sánchez I, Hendry A, Bernabei R, Roller-Wirnsberger R, Gabrovec B, et al. Key messages for a frailty prevention and management policy in Europe from the ADVANTAGE JOINT ACTION consortium. J Nutr Health Aging. 2018;22:892–7.
[75] Ministry of Health. Update of the consensus document on prevention of frailty in elderly people (2022). Madrid: Ministry of Health; 2022. Accesible at: https://www.sanidad.gob.es/areas/promocionPrevencion/envejecimientoSaludable/fragilidadCaidas/estrategiaSNS/docs/Update_of_the_consensus_document_on_prevention_of_frailty_in_elderly_people_2022_ACCESIBLE.pdf.

[76] Garcia-Aguirre M, Baltasar-Fernandez I, Alcazar J, Alfaro-Acha A, Bareiro-Quiñonez FA, Ara I, et al. Low relative sit-to-stand power is associated with the development of adverse health outcomes: a 5-year longitudinal study. J Cachexia Sarcopenia Muscle. 2025;16:e13852.
[77] García-García FJ, Carnicero JA, Losa-Reyna J, Alfaro-Acha A, Castillo-Gallego C, Rosado-Artalejo C, et al. Frailty trait scale-short form: a frailty instrument for clinical practice. J Am Med Dir Assoc. 2020;21:1260–1266.e2.
[78] Hammel IS, Chapman EN. Frailty training among healthcare professionals. J Nutr Health Aging. 2024;28:100258.
[79] Somagutta MR, Uday U, Bathula NR, Pendyala S, Mahadevaiah A, Jain MS, et al. Diagnosing frailty in primary care practice. Cureus. 2022;14:e23329.
[80] Flyum IR, Gjevjon ER, Eklund AJ, Borglin G. What do we know about nursing practice in relation to functional ability limitations, frailty and models of care among older people in home- and facility-based care: a scoping review. BMC Nurs. 2025;24:406.
[81] Davies B, Walter S, Rodríguez-Laso A, Carnicero Carreño JA, García-García FJ, Álvarez-Bustos A, et al. Differential association of frailty and sarcopenia with mortality and disability: insight supporting clinical subtypes of frailty. J Am Med Dir Assoc. 2022;23:1712–1716.e3.
[82] Negm AM, Kennedy CC, Thabane L, Veroniki AA, Adachi JD, Richardson J, et al. Management of frailty: a systematic review and network meta-analysis of randomized controlled trials. J Am Med Dir Assoc. 2019;20:1190–8.
[83] Sun X, Liu W, Gao Y, Qin L, Feng H, Tan H, et al. Comparative effectiveness of non-pharmacological interventions for frailty: a systematic review and network meta-analysis. Age Aging. 2023;52:afad004.
[84] Travers J, Romero-Ortuno R, Bailey J, Cooney MT. Delaying and reversing frailty: a systematic review of primary care interventions. Br J Gen Pract. 2019;69:e61–9.
[85] Izquierdo M, Ramírez-Vélez R, Fiatarone Singh MA. Integrating exercise and medication management in geriatric care: a holistic strategy to enhance health outcomes and reduce polypharmacy. Lancet Healthy Longev. 2025;6:100763.
[86] Izquierdo M, de Souto Barreto P, Arai H, Bischoff-Ferrari HA, Cadore EL, Cesari M, et al. Global consensus on optimal exercise recommendations for enhancing healthy longevity in older adults (ICFSR). J Nutr Health Aging. 2025;29:100401.
[87] Baltasar-Fernandez I, Soto-Paniagua H, Alcazar J, Uceta Espinosa MI, Alegre LM, Gracía-García FJ, et al. Long-term effects of a 6-week power-based resistance training and fast walking interval training program on physical function, muscle power, disability, and frailty in pre-frail and frail older adults. Gerontology. 2024;70:701–14.
[88] Izquierdo M, Rodriguez-Mañas L, Sinclair AJ. Editorial: what is new in exercise regimes for frail older people - how does the erasmus vivifrail project take us forward? J Nutr Health Aging 2016;20:736–7.
[89] Courel-Ibáñez J, Buendía-Romero Á, Pallarés JG, García-Conesa S, Martínez-Cava A, Izquierdo M. Impact of tailored multicomponent exercise for preventing weakness and falls on nursing home residents' functional capacity. J Am Med Dir Assoc. 2022;23:98–104.e3.
[90] Buendía-Romero Á, Vetrovsky T, Hernández-Belmonte A, Izquierdo M, Courel-Ibáñez J. Residual effects of physical exercise after periods of training cessation in older adults: a systematic review with meta-analysis and meta-regression. Scand J Med Sci Sports. 2025;35:e70010.
[91] Álvarez-Bustos A, Laosa O, Marzetti E, Carnicero JA, Castro-Rodriguez M, Landi F, et al. Response rates and associated factors after a multicomponent intervention in frail older adults with diabetes. Age Aging. 2024;53:afad253.
[92] Álvarez-Bustos A, Coelho-Junior HJ, Carnicero JA, García-García FJ, Marzetti E, Rodriguez-Mañas L. Adherence to the mediterranean diet and physical activity in relation to sarcopenia: a cross-sectional epidemiological cohort study. Aging Clin Exp Res. 2025;37:164.
[93] Izquierdo M, Rodriguez-Mañas L, Casas-Herrero A, Martinez-Velilla N, Cadore EL, Sinclair AJ. Is it ethical not to precribe physical activity for the elderly frail? J Am Med Dir Assoc. 2016;17:779–81.
[94] Volkert D, Delzenne N, Demirkan K, Schneider S, Abbasoglu O, Bahat G, et al. Nutrition for the older adult - Current concepts. Report from an ESPEN symposium. Clin Nutr 2024;43:1815–24.
[95] Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Hooper L, Kiesswetter E, et al. ESPEN practical guideline: clinical nutrition and hydration in geriatrics. Clin Nutr. 2022;41:958–89.
[96] Rodríguez-Mañas L, Rodríguez-Sánchez B, Carnicero JA, Rueda R, García-Garcia FJ, Pereira SL, et al. Impact of nutritional status according to GLIM criteria on the risk of incident frailty and mortality in community-dwelling older adults. Clin Nutr. 2021;40:1192–8.
[97] Raymond E, Reynolds CA, Dahl Aslan AK, Finkel D, Ericsson M, Hägg S, et al. Drivers of frailty from adulthood into old age: results from a 27-year longitudinal population-based study in Sweden. J Gerontol A Biol Sci Med Sci. 2020;75:1943–50.
[98] Semba RD, Bartali B, Zhou J, Blaum C, Ko CW, Fried LP. Low serum micronutrient concentrations predict frailty among older women living in the community. J Gerontol A Biol Sci Med Sci. 2006;61:594–9.
[99] O'Connor D, Molloy AM, Laird E, Kenny RA, O'Halloran AM. Sustaining an aging population: the role of micronutrients in frailty and cognitive impairment. Proc Nutr Soc. 2023;82:315–28.
[100] Rudzińska A, Piotrowicz K, Perera I, Gryglewska B, Gąsowski J. Poor appetite in frail older persons-a systematic review. Nutrients. 2023;15:2966.
[101] Dibello V, Lobbezoo F, Lozupone M, Sardone R, Ballini A, Berardino G, et al. Oral frailty indicators to target major adverse health-related outcomes in older age: a systematic review. Geroscience. 2023;45:663–706.
[102] Coelho-Júnior HJ, Rodrigues B, Uchida M, Marzetti E. Low protein intake is associated with frailty in older adults: a systematic review and meta-analysis of observational studies. Nutrients. 2018;10:1334.
[103] Poursalehi D, Lotfi K, Saneei P. Adherence to the Mediterranean diet and risk of frailty and pre-frailty in elderly adults: a systematic review and dose-response meta-analysis with GRADE assessment. Aging Res Rev. 2023;87:101903.
[104] Arroyo-Huidobro M, Amat M, Capdevila-Reniu A, Chavez A, Pellicé M, Ladino A, et al. The role of the Mediterranean diet in the prevention of sarcopenia and frailty in older adults: a narrative review. Nutrients. 2025;17:1743.
[105] Gross DC, Dahringer JC, Bramblett P, Sun C, Spangler HB, Lynch DH, et al. The relationship between a Mediterranean diet and frailty in older adults: NHANES 2007-2017. Nutrients. 2025;17:326.
[106] Capurso C, Bellanti F, Lo Buglio A, Vendemiale G. The Mediterranean diet slows down the progression of aging and helps to prevent the onset of frailty: a narrative review. Nutrients. 2019;12:35.
[107] Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330:1769–75.
[108] Wan X, Ma X, Yao G, Xu Y, Yang Y, Zheng L, et al. Effects of multi-component interventions on the lifestyle in pre-frail or frail older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr. 2025;139:106005.
[109] Cava E, Lombardo M. Narrative review: nutritional strategies for aging populations - focusing on dysphagia and geriatric nutritional needs. Eur J Clin Nutr. 2025;79:285–95.
[110] Lorbergs AL, Prorok JC, Holroyd-Leduc J, Bouchard DR, Giguere A, Gramlich L, et al. Nutrition and physical activity clinical practice guidelines for older adults living with frailty. J Frailty Aging. 2022;11:3–11.
[111] Marshall RN, Smeuninx B, Morgan PT, Breen L. Nutritional strategies to offset disuse-induced skeletal muscle atrophy and anabolic resistance in older adults: from whole-foods to isolated ingredients. Nutrients. 2020;12:1533.
[112] Coelho-Junior HJ, Marzetti E, Picca A, Cesari M, Uchida MC, Calvani R. Protein intake and frailty: a matter of quantity, quality, and timing. Nutrients. 2020;12:2915.
[113] Sirikul W, Buawangpong N, Pinyopornpanish K, Siviroj P. Impact of multicomponent exercise and nutritional supplement interventions for improving physical frailty in community-dwelling older adults: a systematic review and meta-analysis. BMC Geriatr. 2024;24:958.
[114] Gagesch M, Wieczorek M, Vellas B, Kressig RW, Rizzoli R, Kanis J, et al. Effects of vitamin D, omega-3 fatty acids and a home exercise program on prevention of pre-frailty in older adults: the DO-HEALTH randomized clinical trial. J Frailty Aging. 2023;12:71–7.
[115] Tohyama M, Momosaki R, Shirai Y, Ushida K, Kato Y, Shimizu M, et al. Digital health interventions for non-older individuals at risk of frailty: a systematic review and meta-analysis. Digit Health. 2025;11:20552076251328566.
[116] Valdés-Aragonés M, Pérez-Rodríguez R, Carnicero JA, Moreno-Sánchez PA, Oviedo-Briones M, Villalba-Mora E, et al. Effects of Monitoring Frailty Through a Mobile/Web-Based Application and a Sensor Kit to Prevent Functional Decline in Frail and Prefrail Older Adults: FACET (Frailty Care and Well Function) Pilot Randomized Controlled Trial. J Med Internet Res. 2024;26:e58312.
[117] Palmer K, Marengoni A, Russo P, Mammarella F, Onder G. Frailty and drug use. J Frailty Aging. 2016;5:100–3.
[118] Pazan F, Petrovic M, Cherubini A, Onder G, Cruz-Jentoft AJ, Denkinger M, et al. Current evidence on the impact of medication optimization or pharmacological interventions on frailty or aspects of frailty: a systematic review of randomized controlled trials. Eur J Clin Pharmacol. 2021;77:1–12.
[119] Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population. Eur J Clin Pharmacol. 2017;73:1165–72.
[120] Hilmer SN, Wu H, Zhang M. Biology of frailty: implications for clinical pharmacology and drug therapy in frail older people. Mech Aging Dev. 2019;181:22–8.
[121] Optimizing Geriatric Pharmacotherapy through Pharmacoepidemiology Network (OPPEN), Liau SJ, Lalic S, Sluggett JK, Cesari M, Onder G, Vetrano DL, et al. Medication management in frail older people: consensus principles for clinical practice, research, and education. J Am Med Dir Assoc. 2021;22:43–9.
[122] Alshatti D, Cox AR, Hirsch C, Cheng V, Aston J. Evaluation of deprescribing services in frail patients: a systematic review. Int J Pharm Pract. 2025;33:34–44.
[123] Florisson S, Aagesen EK, Bertelsen AS, Nielsen LP, Rosholm JU. Are older adults insufficiently included in clinical trials?-An umbrella review. Basic Clin Pharmacol Toxicol. 2021;128:213–23.
[124] O'Mahony D, Cherubini A, Guiteras AR, Denkinger M, Beuscart JB, Onder G, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 2023;14:625–32.
[125] Strain WD, Down S, Brown P, Puttanna A, Sinclair A. Diabetes and frailty: an expert consensus statement on the management of older adults with type 2 diabetes. Diabetes Ther. 2021;12:1227–47.
[126] Hanlon P, Butterly E, Wei L, Wightman H, Almazam SAM, Alsallumi K, et al. Age and sex differences in efficacy of treatments for type 2 diabetes: a network meta-analysis. JAMA. 2025;333:1062–73.
[127] Liu LK, Guo CY, Lee WJ, Chen LY, Hwang AC, Lin MH, et al. Subtypes of physical frailty: latent class analysis and associations with clinical characteristics and outcomes. Sci Rep. 2017;7:46417.
[128] Huang ST, Tange C, Otsuka R, Nishita Y, Peng LN, Hsiao FY, et al. Subtypes of physical frailty and their long-term outcomes: a longitudinal cohort study. J Cachexia Sarcopenia Muscle. 2020;11:1223–31.

[129] Lin YC, Yan HT. Frailty phenotypes and their association with health consequences: a comparison of different measures. Aging Clin Exp Res. 2024;36:233.
[130] Nguyen QD, Wu C, Odden MC, Kim DH. Multimorbidity patterns, frailty, and survival in community-dwelling older adults. J Gerontol A Biol Sci Med Sci. 2019;74:1265–70.
[131] Wu L, Liu S, Zhang M, Xiong X. Prevalence and associated factors of frailty in patients with chronic heart failure: a systematic review and meta-analysis. Rev Cardiovasc Med. 2025;26:26854.
[132] Wang L, Zhang X, Liu X. Prevalence and clinical impact of frailty in COPD: a systematic review and meta-analysis. BMC Pulm Med. 2023;23:164.
[133] Zhang F, Wang H, Bai Y, Zhang Y, Huang L, Zhang H. Prevalence of physical frailty and impact on survival in patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. 2023;24:258.
[134] Hu Y, Xu H, Ji W, Yang J, Li H, Li K, et al. Prevalence of frailty in senile osteoporosis: a systematic review and meta-analysis. Arch Gerontol Geriatr. 2025;130:105718.
[135] Slee A, Vignau MS, Bassett P, Jin X, Guo J, Smithard D. Investigation into the prevalence of malnutrition, sarcopenia and frailty in very old hospitalised patients and relationship with clinical outcomes. Clin Nutr ESPEN. 2025;70:129–37.
[136] Nguyen NH, Luong TT, Le TN, Nguyen HTT, Nguyen DV. Prevalence of frailty among older patients with acute ischemic stroke and its association with short-term functional outcome: a cohort study in Vietnam. BMC Geriatr. 2025;25:430.
[137] Li T, Shi W, Wang G, Jiang Y. Prevalence and risk factors of frailty in older patients with coronary heart disease: a systematic review and meta-analysis. Arch Gerontol Geriatr. 2025;130:105721.
[138] Nazir S, Abbas Z, Amjad S, Altaf A, Qadeer MA, Maqbool S, et al. Prevalence of osteosarcopenia and frailty in patients with chronic liver disease. Euroasian J Hepatogastroenterol. 2024;14:156–9.
[139] Ruiz-Grao MC, Sánchez-Jurado PM, Molina-Alarcón M, Garrido-Miguel M, Álvarez-Bueno C, Alcantud-Córcoles R, et al. Frailty, depression risk and 10-year hospitalization in older adults. The FRADEA study. Geriatr Nurs 2022;46:184–90.
[140] Carbery I, Todd O, Hale M, Black CJ, Clegg A, Selinger CP. Meta-analysis: prevalence of frailty and associated adverse events in inflammatory bowel diseases. Aliment Pharmacol Ther 2025;61:246–57.
[141] Álvarez-Bustos A, Rodríguez-Sánchez B, Carnicero-Carreño JA, Sepúlveda-Loyola W, Garcia-Garcia FJ, Rodríguez-Mañas L. Healthcare cost expenditures associated to frailty and sarcopenia. BMC Geriatr. 2022;22:747.
[142] Potes Y, Bermejo-Millo JC, Mendes C, Castelão-Baptista JP, Díaz-Luis A, Pérez-Martínez Z, et al. p66Shc signaling and autophagy impact on C2C12 myoblast differentiation during senescence. Cell Death Dis. 2024;15:200.
[143] Paganini-Hill A, Clark LJ, Henderson VW, Birge SJ. Clock drawing: analysis in a retirement community. J Am Geriatr Soc. 2001;49:941–7.
[144] IANA/IAGG, Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging. 2013;17:726–34.
[145] López-Sanz D, Suárez-Méndez I, Bernabé R, Pasquín N, Rodríguez-Mañas L, Maestú F, et al. Scoping review of neuroimaging studies investigating frailty and frailty components. Front Med (Lausanne). 2018;5:284.
[146] Timmons S, Faherty M, Curtin C, Ferrara MC, Bellelli G, Brunetti E, et al. Cognitive frailty: a useful concept or a source of confusion? Insights from a survey of European geriatricians. BMC Geriatr. 2025;25:280.
[147] Pan Y, Yang J, Jiang Y, Feng ZQ, Tang XY, Yuan Y, et al. Gut frailty: the core of reversing frailty. Ann Med. 2025;57:2527955.
[148] Hanlon P, Politis M, Wightman H, Kirkpatrick S, Jones C, Khan M, et al. Frailty and socioeconomic position: a systematic review of observational studies. Aging Res Rev. 2024;100:102420.
[149] Mehrabi F, Pomeroy ML, Cudjoe TKM, Jenkins E, Dent E, Hoogendijk EO. The temporal sequence and reciprocal relationships of frailty, social isolation and loneliness in older adults across 21 years. Age Aging. 2024;53:afae215.
[150] Hanlon P, Wightman H, Politis M, Kirkpatrick S, Jones C, Andrew MK, et al. The relationship between frailty and social vulnerability: a systematic review. Lancet Healthy Longev. 2024;5:e214–26.
[151] Bunt S, Steverink N, Olthof J, van der Schans CP, Hobbelen JSM. Social frailty in older adults: a scoping review. Eur J Aging. 2017;14:323–34.
[152] Archibald M, Lawless M, Ambagtsheer RC, Kitson A. Older adults' understandings and perspectives on frailty in community and residential aged care: an interpretive description. BMJ Open 2020;10:e035339.
[153] Wurm S, Benyamini Y. Optimism buffers the detrimental effect of negative self-perceptions of aging on physical and mental health. Psychol Health. 2014;29:832–48.
[154] Thillainadesan J, Scott IA, Le Couteur DG. Frailty, a multisystem aging syndrome. Age Aging. 2020;49:758–63.
[155] de Souto Barreto P, Rolland Y, Ferrucci L, Arai H, Bischoff-Ferrari H, Duque G, et al. Looking at frailty and intrinsic capacity through a Geroscience lens: the ICFSR & Geroscience Task Force. Nat Aging. 2023;3:1474–9.
[156] Wu J, Zeng N, Wang L, Yao L. The stigma in patients with breast cancer: a concept analysis. Asia Pac J Oncol Nurs. 2023;10:100293.
[157] Henny KD, McCree DH, Mermin J. Opening Editorial AIDS and Behavior Special Issue on Stigma. AIDS Behav. 2022;26(Suppl 1):1–4.
[158] Pitter JG, Zemplényi A, Babarczy B, Németh B, Kaló Z, Vokó Z. Frailty prevalence in 42 European countries by age and gender: development of the SHARE Frailty Atlas for Europe. Geroscience. 2024;46:1807–24.
[159] Mielke N, Schneider A, Huscher D, Ebert N, Schaeffner E. Gender differences in frailty transition and its prediction in community-dwelling old adults. Sci Rep. 2022;12:7341.
[160] Jang HY, Kim JH. Factors associated with frailty according to gender of older adults living alone. Healthcare (Basel). 2021;9:475.
[161] Corbi G, Cacciatore F, Komici K, Rengo G, Vitale DF, Furgi G, et al. Inter-relationships between gender, frailty and 10-year survival in Older Italian Adults: an observational longitudinal study. Sci Rep. 2019;9:18416.
[162] Zhang J, Xu L, Sun L, Li J, Qin W. Gender difference in the association of frailty and health care utilization among Chinese older adults: results from a population-based study. Aging Clin Exp Res. 2020;32:1985–91.
[163] Arosio B, Picca A. The biological roots of the sex-frailty paradox. Exp Gerontol. 2024;198:112619.
[164] Zhou J, Kou M, Tang R, Wang X, Li X, Heianza Y, et al. Joint physical-psychosocial frailty and risks of all-cause and cause-specific premature mortality. J Gen Intern Med. 2025;40:2207–17.
[165] Shakya S, Silva SG, McConnell ES, McLaughlin SJ, Cary Jr MP. Psychosocial stressors associated with frailty in community-dwelling older adults in the United States. J Am Geriatr Soc. 2024;72:1088–99.
[166] Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019;394(10206):1365–75.
[167] Yuan Y, Lin S, Lin W, Huang F, Zhu P. Modifiable predictive factors And all-cause mortality in the non-hospitalized elderly population: an umbrella review of meta-Analyses. Exp Gerontol. 2022;163:111792.
[168] García-Nogueras I, Aranda-Reneo I, Peña-Longobardo LM, Oliva-Moreno J, Abizanda P. Use of health resources and healthcare costs associated with frailty: the FRADEA study. J Nutr Health Aging. 2017;21:207–14.
[169] Chi J, Chen F, Zhang J, Niu X, Tao H, Ruan H, et al. Impacts of frailty on health care costs among community-dwelling older adults: a meta-analysis of cohort studies. Arch Gerontol Geriatr. 2021;94:104344.