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Frailty: pathophysiology, theoretical and operational definition(s), impact, prevalence, management and prevention, in an increasingly economically developed and ageing world

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Short title: Frailty in an increasingly economically developed and ageing world.

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Abstract

The world's population is ageing, and most older adults experience a later life burdened with disease and disability. Frailty is a multi-dimensional and dynamic condition characterised by declines in reserve and function across multiple physiologic systems, such that the ability to cope with every day or acute stressors becomes compromised. It is projected to become one of the most serious public health challenges economically developed societies will face in the coming century. This review provides a comprehensive overview of frailty, exploring its pathophysiology, theoretical and operational definition(s), impact, prevalence, management, and prevention, within the context of its emergence as a major public health challenge, in an increasingly economically developed and ageing world. Further, this review discusses the major limitations, deficiencies, and knowledge gaps presently within the field, and future research directions pertinent to the advancement of frailty research and the promotion of healthy longevity among the increasing global population of older adults.

Introduction

The twentieth, and presently twenty-first centuries have been characterised by accelerating medical, pharmacological, and technological advances [1-3]. In the context of population demographics, one of the most significant outcomes of these advances is the exponential increase in overall population, and the relatively rapid increase in life expectancy [4, 5]. These increases can be partially attributed to improvements in public health that have resulted in a profound reduction in global child mortality rates; with an increasing proportion of the population now living to sexual maturity [3, 6, 7]. However, increases in life expectancy has also occurred in the later part of life, albeit to a relatively lesser extent, in the increased population of older adults [4, 5] (Figure 1). *(Insert Figure 1)*

Closely succeeding these increases in life expectancy, another demographic phenomenon has been observed: a substantial reduction in global fertility rates, particularly in developed countries. With most of the developed world now below the population replacement rate of 2.1 births per female for several consecutive decades [9, 10]. The combination of these two demographic phenomena has resulted in a growing, yet increasingly ageing population throughout the developed world; and even in the developing world, the onset of these changes are beginning to be observed [9, 10].

In Europe, current demographic trends indicate that by the year 2030 almost one in six of the European population will be aged 60 years or older, and the number of older people will grow to 247 million by 2050; representing a 35% increase from 2017, with one in four older adults being over 85 by 2040 [11]. The social and economic impacts of this epidemiological transition have yet to be fully experienced, as dependency ratios remain relatively stable, as the increase in the older population is, to an extent, offset by the reduction in youth dependency [5, 12]. However, if present trends persist, over time, dependency ratios in developed countries may shift, as the absolute and relative number of those entering older age increases, while the absolute and relative number of those entering from youth dependency, to workforce participation, decreases [12]. When taken in conjunction with progressive declines in physical activity throughout all stages of the lifespan, this leaves this increasing population of older adults particularly susceptible to the development of disease and co-morbidities associated with a lack of physical activity and an increase in sedentary behaviour [13-15]. This alone, irrespective of future dependency ratios, will have substantial personal and economic impacts as life expectancy increases, while the proportion of the lifespan spent without disease and disability fails to keep pace, or potentially deceases; as has been observed with a number of lifestyle mediated non-communicable diseases in recent decades [16]. It is in this context that frailty, particularly in older age, has been described as *“without question, one of the most serious public health challenges we will face in this coming century”* [17 p. 1376].

Frailty

Frailty is a multi-dimensional and dynamic condition, theoretically defined as "*a state of increased vulnerability, resulting from age-associated declines in reserve and function across multiple physiologic systems, such that the ability to cope with every day or acute stressors is compromised*" [18 p. 1, 19] (Figure 2). *(Insert Figure 2)*

Although declines in physiological reserve are associated with senescence in the normal ageing process, frailty is an extreme consequence of this process, where this decline is accelerated and homeostatic responses begin to fail [21-23]. Frailty is a common and clinically significant condition among older adults [24]. This is predominantly due to its association with adverse health outcomes, such as hospitalisation, falls, disability, and mortality [19, 20, 25-29]. All older adults are susceptible to the risk of developing frailty, and even their younger counterparts [30, 31]. However, this risk is significantly increased with increases in chronological age, in the presence of comorbidities, low physical activity, poor dietary intake, and low-socioeconomic status, among a number of other factors (Figure 3) [19, 32-36]. *(Insert Figure 3)*

While frailty is a dynamic condition, with the possibility of bi-directional transition between frailty states [29, 38, 39], this transition is more commonly progressive [40]. This is largely due to the association of frailty with a plethora of adverse health outcomes, which can often lead to a spiral of decline. As frailty progresses, interventions to mitigate, manage, or reverse this decline become increasingly difficult to implement, both from practical and physiological perspectives [40, 41]. The relative prevalence of frailty in older adults may be reduced with future improvements in treatment, particularly those identified as effective at mitigating the onset of frailty [17]. However, irrespective of this, the absolute prevalence, and overall burden of frailty is projected to increase dramatically in the coming decades as the population ages [37]. Perhaps of most concern in this regard, is that several longitudinal birth cohort studies have reported increases in the relative prevalence of frailty among more contemporary generations of older adults, when compared to their generational predecessors [42-44].

Operational definitions of frailty

Although there is a general consensus regarding the theoretical definition of frailty as a multi-dimensional and dynamic condition characterised by a loss of reserve across multiple physiological systems which collectively result in a compromised resilience to cope with stressors [17-20, 37, 45-51]. Presently, there is no one universally utilised or accepted operational definition for the classification of frailty [28, 52, 53]. However, there are a number of valid operational definitions which exist i.e., definitions which take into consideration the multi-dimensional nature of the condition (face and content validity) and have been specifically validated for the assessment of frailty: either through their predictive validity regarding negative health outcomes associated with frailty, or their concurrent validity with existing validated frailty tools [54, 55]. The most commonly utilised and well-regarded of these operational definitions are the Fried frailty phenotype [19], and the Frailty Index (FI) [56-58]. The Fried frailty phenotype proposes that frailty be defined as a clinical syndrome in which three or more of the five following criteria are present: unintentional weight loss (≥ 10lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity (active kcals expended per week) [19] (Table 1). *(Insert Table 1)*

The FI proposes that frailty should be operationally defined on a spectrum utilising a mathematical model which considers frailty in regard to the accumulation of 'deficits'. In this model, deficits represent any symptom, sign, disability, or laboratory measurement regarded as 'abnormal'. The FI score is assessed as the accumulative proportion of these potential deficits that are present. Typically, the list of deficits ranges from approximately 30-70 items related to various aspects of health and well-being [46]. Although these are among the most commonly utilised operational definitions of frailty, there are also a number of other valid operational definitions which are frequently employed (Table 2). *(Insert Table 2)*

Further to these validated operational definitions, proxy indicators of frailty are also commonly utilised, such as unidimensional measures of physical function, e.g., the Short Physical Performance Battery (SPPB) [79], Timed-Up and Go (TUG) [80], Upper-Extremity Function (UEF) frailty index [81], gait speed [82], and hand grip strength [83]. These measures are associated with frailty and may even possess concurrent validity with existing frailty tools, or predictive validity regarding negative health outcomes associated with frailty. However, they lack the content validity regarding assessment of the multi-dimensional nature of the condition to be regarded themselves as valid operational definitions. Although strong arguments have been made regarding the pragmatic utility of these tools within various settings and circumstances [84].

Similarly, there are a number of other tools, such as the geriatric 8 questionnaire (G-8) [85], identification of seniors at risk (ISAR) [86], vulnerable elderly survey (VES-13) [87], frailty index for elders (FIFE) [88], frailty risk score [89], hospital frailty risk score [90], and PRISMA 7 [91], which serve as proxy indicators of frailty through identifying "frailty risk", often with the suggestion of further more comprehensive evaluation. However, they are not valid operational definitions which definitively distinguish between frail, pre-frail, or robust classification states.

Recently an alternative approach, separating itself from the phenotypic and accumulation of deficits models, has proposed a focus on intrinsic capacity, i.e., a composite measure of all physical and mental resources which an individual can draw from to overcome environmental, physical, and psychological challenges [92]. The development of this construct was initially supported by the World Health Organisation, however, remains to be empirically validated [92, 93]. While the construct of intrinsic capacity is in its theoretical and operational infancy, it may provide a new paradigm for future exploration, closely aligned with that of frailty research [94].

Presently, one of the major weaknesses in the frailty field is not only a lack of a single standardised operational definition, but also the common utilisation of non-validated iterations of the above definitions. This produces a detrimental effect on both the internal and external validity of such studies, resulting in a reduced capacity for accurate evaluation and comparison; even between studies which report to be utilising the same operational definition [95-97]. A recently published brief standard checklist for studies reporting frailty data has attempted to address this through outlining, and proposing solution to, some of these persistent issues within the literature, including: (1) studies often report participants as frail without a frailty assessment; (2) studies often claim to utilise validated operational definitions for the classification of frailty, however, adapt these definitions, or classification criteria, which resulted in the definitions becoming not only non-standardised, but also non-validated; (3) the use of the nomenclature for different operational definitions of frailty vary widely, even among studies utilising the same operational definition; (4) often, useful data regarding prevalence of frailty (such as pre-frailty, a sex breakdown of frailty, or occasionally the overall prevalence of frailty itself) is not reported. To address these issues the following checklist is proposed: (1) accurate citation of the validation study for the specific operational definition utilised for the classification of frailty; (2) accurate use of the nomenclature of the operational definition of frailty utilised in accordance with the initial validation study to maintain reliability and validity, or prominent subsequent study establishing the nomenclature; (3) reporting of the number of frail, pre-frail (if applicable), and robust participants; (4) a sex breakdown of the number of frail, pre-frail, and robust participants [98].

In this regard, the academic field of frailty is somewhat lacking a desired order and uniformity. This is likely the manifestation of the multi-dimensional and heterogenous nature of frailty as a combination of a multitude, and often different array, of phenomena which can result from many differential causes and pathways [20]. The breadth of proposed frailty definitions is a manifestation of this complexity. Ultimately what may be required regarding progress towards the establishment of a universally accepted operational definition, in addition to exploration of emerging constructs [92, 94, 99, 100], is mathematical modelling of large longitudinal datasets which can identify frailty through an abundance of potential multi-dimensional pathways over time, as it relates to the dynamic ability to cope with acute stressors over these periods. However, to date a universally accepted operational definition for the classification of frailty remains elusive, despite the utility this may provide in the future.

The prevalence of frailty

Although the exact prevalence of frailty within geriatric populations is poorly defined due to the lack of a single standardised operational definition, there are a number of systematic reviews and meta-analyses which have attempted to provide well-evidenced estimates of the prevalence of frailty among older adults within a variety of settings [101-109].

An enhanced understanding regarding the prevalence of a condition within a specific setting, has a number of important consequences; including the enhanced ability to contribute towards improvements in the planning and orientation of organisational structures and resources, to meet population needs. This is particularly true regarding the ability to tailor services within particular settings to the needs of service users. For example, specifically with regard to frailty, the potential implementation of exercise rehabilitation treatments within settings for this population; with physical activity and exercise being proposed as potentially offering the best form of treatment for frail older adults [110].

Community-dwelling older adults

Presently, there are several systematic reviews and meta-analyses which have examined the prevalence of frailty in various cohorts of community-dwelling older [102-105, 109] (Table 3). In the single review which examined the overall prevalence of frailty within this population, the pooled prevalence of frailty was 10.7%. However, the reported prevalence of frailty within the studies comprising this review ranged from 4.0-59.1%; largely due to inclusion of proxy indicators of frailty, and to a lesser degree the lack of a single standardised operation definition [109]. In the remaining four systematic reviews / meta-analyses of the prevalence frailty in various specific cohorts of community-dwelling older adults, the overall pooled prevalence of frailty ranged from 7.4% among community-dwelling older adults in Japan, to 68% among the overall population of undernourished community-dwelling older adults [104, 105]. Along a similar line of inquiry, a recent systematic review and meta-analysis found the global incidence of frailty, and pre-frailty, among community-dwelling older adults (≥ 60 years) to be 43.4, and 150.6 per 1,000 person-years respectively [111].
(Insert Table 3)

Older adults in residential care (assisted living facility, and nursing home residents)

Presently, there are no well-evidenced pooled estimates of the overall prevalence of frailty among older adults in assisted living facilities. Although, it could be postulated that this prevalence would likely be higher than that of community-dwelling older adults, given that older adults within assisted living facilities typically tend to be chronologically older, and often exhibit a greater number of comorbidities and a reduced functional capacity than their community-dwelling counterparts. However, these differences routinely become non-significant once standardised for age [112]. Additionally, the estimated prevalence of frailty, and pre-frailty in nursing homes (where qualified nursing care is required, in addition to care assistance) is approximately 52.3%, and 40.2% respectively [108]. As such, the prevalence of frailty in assisted living facilities likely lies somewhere in between that of community-dwelling older adults and nursing home residents; given the inherent nature of these respective settings, and the demographics of the individuals who occupy them. However, presently there appears a lack of individual studies which have examined the prevalence of frailty specifically within assisted living facilities.

Hospitalised older adults

A recently published systematic review and meta-analysis produced the first well-evidenced pooled estimates of the prevalence of frailty among geriatric hospital inpatients. This review found that approximately 47.4% (95% CI 43.7-51.1%) of all geriatric hospital inpatients are frail; and another 25.8% (95% CI 22.0-29.6%) pre-frail. This prevalence varied significantly based on prevalent morbidities, age, ward type, clinical population, and the operational definition utilised for the classification of frailty [101]. The overall pooled prevalence estimate of frailty of 47.4% reported within this review, places the prevalence of frailty among geriatric hospital inpatients between that reported for community-dwelling older adults at 10.7% [109], and older adults in nursing homes at 52.3% [108]; outlining an increase in the relative prevalence of frailty with progression through the healthcare system. The overall pooled prevalence of pre-frailty of 25.8% is lower than that reported for both community-dwelling older adults at 41.6% [109], and nursing home residents at 40.2% [108]; while the combined prevalence estimates of both frailty and pre-frailty increase from 52.3% among community-dwelling older adults, to 73.2% among geriatric hospital inpatients, and to 92.5% among nursing home residents. This underlines that differences in the relative prevalence of frailty status between community, and hospital inpatient settings, are the result of an increase in the relative prevalence of frailty, and similar reductions in the relative prevalence of both pre-frailty and robustness. However, differences in the relative prevalence of frailty status between hospital inpatient and nursing home settings appear primarily the result of a relative increase in the prevalence of pre-frailty, and reductions in the prevalence of robustness [101].

The overall pooled frailty, and pre-frailty, prevalence estimates of 47.4% (95% CI 43.7–51.1%), and 25.8% (95% CI 22.0–29.6%) reported within this review are relatively consistent with, though more precise than, estimates reported within another recent systematic review and meta-analysis which examined the prevalence of frailty and pre-frailty among hospitalised older adults in 11 studies which also assessed undernutrition risk, at 47% (95% CI 37–57%) and 36% (95% CI 29–44) respectively [113]. Similarly, the pooled prevalence estimates of frailty on acute wards of 51.1% (95% CI-35.9–66.2%), as well as among all acute hospital inpatients, of 47.3% (95% CI 42.8–51.8%) outlined in the review are relatively consistent with findings of a recent scoping review, which reported a median frailty prevalence of 49% (range 34–69%) in acute care hospital settings [114]. Further, no significant differences in the prevalence of frailty were observed in stratified analyses by sex in this review. This is in contrast to systematic reviews and meta-analysis of the prevalence of frailty among community-dwelling older adults [102, 103, 109]. However, consistent with the findings of systematic reviews and meta-analysis among other clinical populations of older adults such as nursing home residents [108]. These findings contribute to the literature illustrating sex differences in the prevalence of frailty among community dwelling older adults may dissipate among clinical geriatric populations [101, 108].

The impact of frailty

Frailty is associated with a myriad of adverse health outcomes, which have both personal and economic consequences. Among these adverse outcomes include the increased occurrence of falls, fractures, worsening mobility, disability, cognitive decline, dementia, depression, hospitalisation, institutionalisation, and mortality [70, 115-120]. Moreover, frailty has been consistently shown to be associated with increased healthcare cost and usage [121-123]. For example, a cross sectional analysis of approximately 2,600 older adults aged ≥ 60 years in Germany found that the mean three-month healthcare expenditure was almost six-fold higher among the frailest participants (five-positive Fried frailty phenotype criteria), at €3,659, compared to the least frail participants (no positive Fried frailty phenotype criteria), at €642 [124]. A subsequent three-year longitudinal analysis of over 1,600 older adults within the same cohort found that progression from a non-frail to a frail state was associated with an average of 54% to 101% increase in healthcare cost in those with 3, and 4 or 5 positive frailty criteria respectively; including a 200% increase in inpatient costs from those who transitioned from non-frail (no positive Fried frailty phenotype criteria) to low-levels of frailty (three positive Fried frailty phenotype criteria) [125]. Similarly, a recent analysis of 5,300 community-dwelling older adults aged ≥ 60 years in China, found frailty to be an independent predictor of increased health expenditure [121]. However, the impact of frailty on an individual's life extends further than the clinical manifestation or economic impact of these adverse health outcomes, with frailty additionally being associated with a reduced quality of life, and loneliness [126, 127].

The associations between frailty and socio-economic variables

While at the individual level there is evidence of the association between socio-economic status and frailty onset and progression [35], at the societal level the association between economic variables and frailty is less well evidenced. Preliminary research into this area has shown the prevalence of frailty in the community to be correlated with national economic indicators such as gross domestic product (GDP) per capita purchasing power parity (PPP), and health care expenditure per capita PPP. However, noted that more research is needed better understand the relationship between macro-economic indicators and the prevalence of frailty [128]. A recent systematic review and meta-analysis found no significant association between the prevalence of frailty among geriatric hospital inpatients and GDP per capita PPP, or health care expenditure per capita PPP [101]. The authors postulated it possible that these associations, while present in the community, are not present in inpatient hospital settings. Given the inherent nature of hospital inpatient settings, i.e., institutions for chronically or acutely unwell patients, such association may be more sensitive among the general population of community-dwelling older adults; however, more large-scale and comprehensive studies are required in a variety of settings. In this regard, a limitation of these analyses is that included studies were predominantly from economically developed countries, as there is presently limited evidence regarding the prevalence of frailty in low-income countries [103]. However, while it has been postulated that increases in economic prosperity may limit the prevalence and burden of frailty within national health systems [128], these findings bring this postulation into question; and as such reliance of non-direct intervention such as economic development, to improve the prevalence and burden of frailty on health systems alone, appears, at least partially, to be misplaced. As such these findings further suggest the need for more direct interventions to address the burden of frailty among this population.

The prevention, treatment, and management of frailty

Presently, care plans specifically for frail individuals have yet to be extensively developed or assessed. However, there are several proposed treatments and care pathways involved in the prevention, treatment, and management of frailty. Initial establishment of agreed goals of care may be assisted in clinical settings in particular by a comprehensive geriatric assessment, which can provide a framework from which to develop a management and intervention plan for frail individuals. Further, as frailty progresses patients will develop different care needs, and require different forms of care, often in different settings (Table 4). *(Insert Table 4)*

Regular physical activity and exercise has been shown to provide a degree of protection against multiple components of frailty in both sexes, at all stages of the condition, and all stages of the life cycle [129, 130]. Further, exercise interventions have been proposed as potentially offering the best form of treatment for frail older adults [110], with promising results in a variety of settings and geriatric populations [131, 132], and even shown to mediate the reversal of frailty in some cases [133, 134]. However, more research is needed to determine the feasibility and efficacy of exercise interventions in different settings and clinical populations [25, 134].

Exercise interventions for frail geriatric populations

Regular physical activity and exercise have been shown to consistently improve cognition, physical function, sarcopenia (low muscle quantity, strength, and performance), and mood in both non-frail and frail older adults [129]. While inactivity is a modifiable risk factor for frailty onset and progression, physical activity and exercise are known to improve function across multiple physiologic systems, including the muscle, heart, brain, endocrine system, and inflammation response [135]. In this regard, exercise can improve function in all physiological systems known to be dysregulated with the onset and progression of frailty [136]. However, while there is evidence of the benefits of exercise regarding the prevention, treatment, and potential reversal of frailty, it is universally noted that there needs to be more studies within this area to truly assess the feasibility and efficacy of exercise in frail geriatric populations within different settings, and particularly in clinical settings [25, 137]. Further, to increase external validity of such studies, particularly those among clinical cohorts, it is imperative that prospective studies attempt to recruit as representative a sample as possible, so that feasibility and efficacy assessments are extrapolatable to real world settings. In this regard for example, a recent systematic review examining exclusion rates in 305 randomised controlled trials involved in the treatment of 31 physical conditions, reported that a quarter of all trials excluded 89% of patients with the specific condition to be treated within that trial, while half excluded 77.1% of patients with the condition. Those excluded were primarily attributed to advanced age, and those with significant co-morbidity and co-prescription; characteristics which are ubiquitous among those treated in clinical practice [138]. Though it is often required to exclude certain cohorts to define the clinical population and control for confounding factors, particularly with regard to exercise interventions which pose a low likelihood of contra-indication, it is essential that representative samples are examined, which among frail older adults, and particularly in certain settings, invariably includes those with significant co-morbidities and polypharmacy.

Interventions among community-dwelling older adults

Exercise, or exercise and nutrition interventions combined, have been shown to be capable of reversing frailty [133, 134, 139], or limiting its progression [140, 141], among cohorts of community-dwelling older adults.

Interventions among older adults in residential care (assisted living and nursing home residents)

The implementation of exercise interventions in nursing home settings have been shown to be effective in improving strength, gait speed, and balance in older adults residing in these settings [142, 143]. Further, individualised and progressive multicomponent exercise interventions at a moderate intensity have been shown to be effective in the prevention of falls, and the reduction of frailty and mortality among older nursing home residents [132].

Interventions among hospitalised older adults

Acute hospital admission for older adults is associated with further loss of physical activity and represents a period of increased susceptibility to sarcopenia and frailty [144]. Frailty is associated with longer stay and increased rates of mortality in hospitalised older adults, as well as serving as a predictor of readmission [145, 146]. Therefore, there is an urgent need to examine the feasibility of such interventions within this setting, and whether these interventions can be employed to improve various aspects of health in frail older populations in inpatient hospital ward settings. Preliminary research has shown some success in the implementation of exercise interventions to reverse functional decline among general geriatric inpatient populations [147, 148], and walking during hospitalisation has been shown to be associated with a shorter length of stay [149]. However, to date, presently there are no studies which have attempted to assess the feasibility or efficacy of such an intervention in operationally defined frail participants with more significant initial impairments.

Future directions

There are several research directions which are pertinent to the advancement of the understanding of frailty and the promotion of healthy longevity among the increasing global population of older adults. More generally within the frailty field, further work towards a universally accepted operational definition of the construct, to practically complement the theoretical definition [18] is of paramount interest to the field. Additionally, the association between frailty and other related composite measures such as allostatic load [150-152] and intrinsic capacity [92, 94], and the potential utilisation of these constructs as inexpensive proxy measures for biological ageing (identified through associations with the pattern of DNA methylation at different cytosine-phospho-guanine (CpG) sites which correlate with mortality and time [153, 154], morbidity and lifespan [155-158], and the pace of ageing [159]) is of interest for future research. The initial validation of cost-effective assessments as valid proxy measures of biological ageing may allow for a better understanding of ageing, not only in economically developed nations, but throughout the globe, and especially among less economically developed areas of the world. The lack of data in these regions in particular will become increasingly important from a global perspective, given that these are the regions of the world projected to undergo the largest population growth in the coming century (e.g., the population of sub-Saharan Africa is projected to grow 298% from 2017-2100, from 1.03 to 3.07 billion), while conversely many economically developed regions are projected to experience marked population decline (e.g., Europe's population is projected to decline 19.2% from 2017-2100, from

758 to 613 million, and China's population is projected to decline 48% over the same period, from 1.41 billion to 732 million) [160].

Further, as frailty is a relatively new concept, particularly as an operationally defined one, with most studies cited within this review published in the past 20 years, the potential change in frailty over time, particularly as it relates to national policy directives, and economic indicators is of interest for future research. Although at the individual level, there is evidence of the association between socioeconomic status and frailty onset and progression [35], at the societal level the association between economic variables and frailty is less well evidenced. More large scale and comprehensive research is needed in this regard to better understand this relationship between macro-economic indicators and the prevalence of frailty in a variety of settings. Further, more comprehensive systematic analyses of this association between frailty and national economic indicators among community-dwelling older adults, older adults in residential care settings, and hospitalised older adults, may help to further elucidate this relationship within relevant settings.

Regarding the provision of well-evidenced estimates of the prevalence of frailty within various settings, presently there are no currently published well-evidenced pooled estimates of the prevalence of frailty among older adults residing in assisted living facilities. Further research is required to elucidate the prevalence of frailty among older adults in these settings. Further, adapted exercise interventions among frail hospital and intermediate care patients is also of interest for future research. Particularly, the continuation of these activities and assessments following patient discharge from hospital over a prolonged period, and the impact on these activities on measures of multi-dimensional health and other health-related outcomes, such as readmissions, and cost-effectiveness. Exercise interventions have been shown to be effective at reducing functional decline among general hospital inpatients during hospitalisation [147], however, to date no research has been conducted among specifically frail inpatients, or providing continuity of the interventions, post-inpatient discharge. Further, adapted exercise interventions may also be ideally suited within more stable clinical environments, such as those of intermediate care facilities, assisted living facilities, nursing homes, or 'hospital at home' settings.

Conclusion

Frailty and healthy longevity have become increasingly important fields of research, which, if present global demographic trends persist, will continue to grow in importance as the world's population ages. Further elucidation of frailty, and its exploration in the context of emerging constructs, is pertinent to the advancement of frailty research and the promotion of healthy longevity among the increasing population of older adults.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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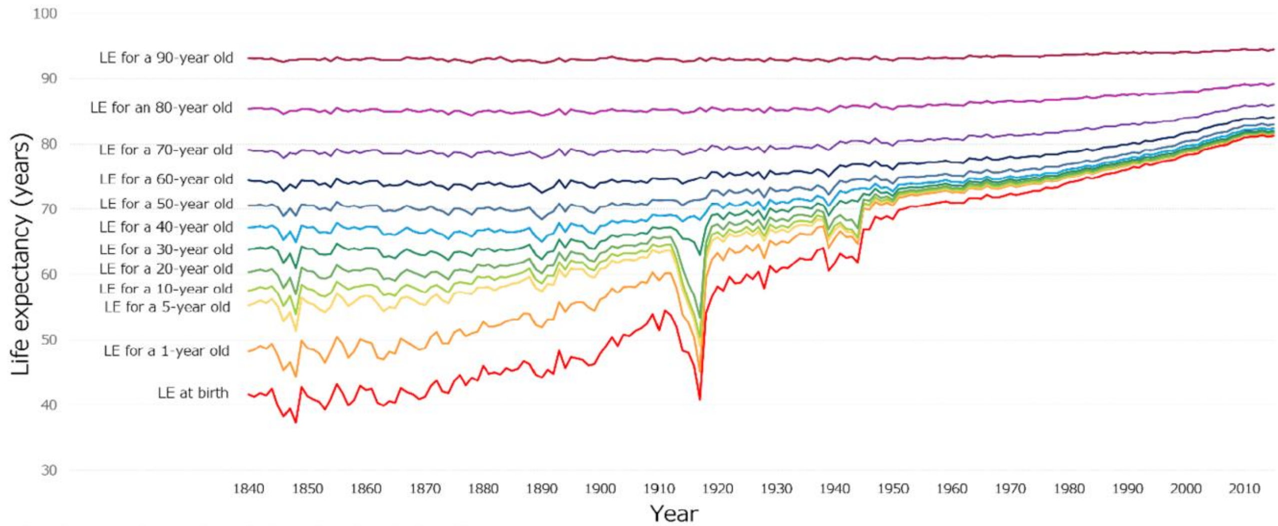
Figures

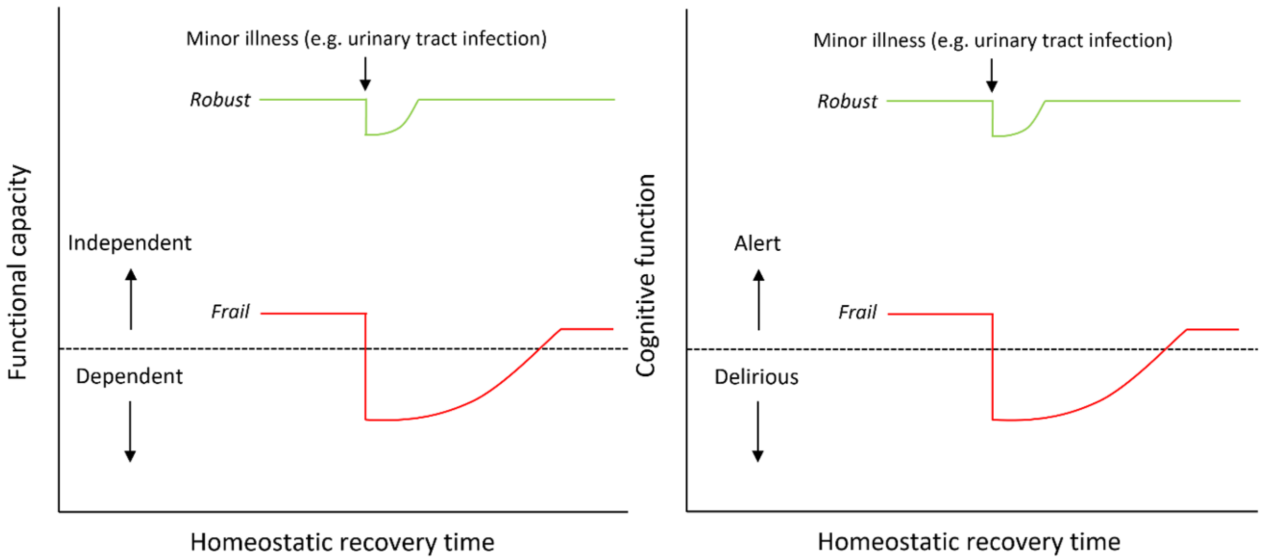
Figure 1. Estimated life expectancy (LE) by age in England and Wales (1841-2016). Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Data available at www.mortality.org, raw data downloaded on 22/02/2020. Adapted from [8].

Figure 2. An illustration of the multidimensional nature of frailty as a loss of physiological reserve across multiple systems, such that resilience, and homeostatic response to stressors becomes compromised (Adapted from [20]).

Figure 3. Risk factors associated with the development and progression of frailty. Derived and adapted from [19, 32-36], and [37] respectively.



100
90
80
70
60
50
40
30
LE for a 90-year old
LE for an 80-year old
LE for a 70-year old
LE for a 60-year old
LE for a 50-year old
LE for a 40-year old
LE for a 30-year old
LE for a 20-year old
LE for a 10-year old
LE for a 5-year old
LE for a 1-year old
LE at birth
Life expectancy (years)
1840 1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010
Year


Minor illness (e.g. urinary tract infection)
Robust
Functional capacity
Independent
Frail
Dependent
Homeostatic recovery time
Minor illness (e.g. urinary tract infection)
Robust
Cognitive function
Alert
Frail
Delirious
Homeostatic recovery time

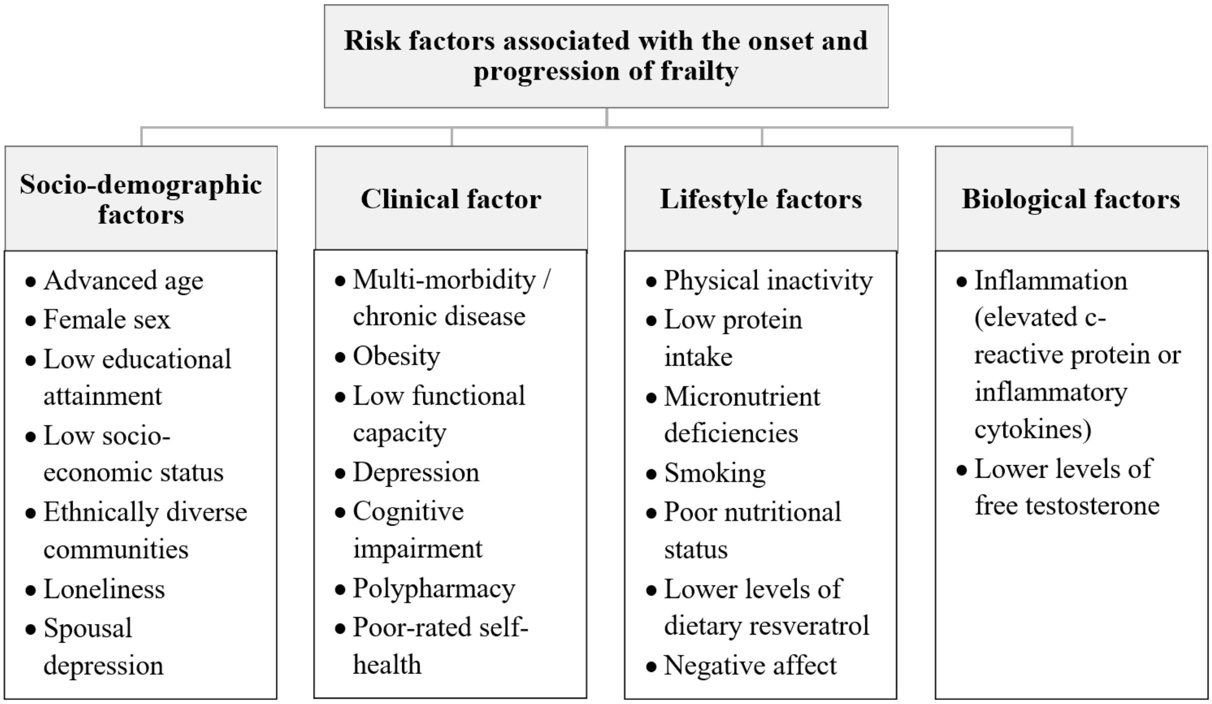

Risk factors associated with the onset and progression of frailty
Socio-demographic factors
• Advanced age
• Female sex
• Low educational attainment
• Low socio-economic status
• Ethnically diverse communities
• Loneliness
• Spousal depression
Clinical factor
• Multi-morbidity / chronic disease
• Obesity
• Low functional capacity
• Depression
• Cognitive impairment
• Polypharmacy
• Poor-rated self-health
Lifestyle factors
• Physical inactivity
• Low protein intake
• Micronutrient deficiencies
• Smoking
• Poor nutritional status
• Lower levels of dietary resveratrol
• Negative affect
Biological factors
• Inflammation (elevated c-reactive protein or inflammatory cytokines)
• Lower levels of free testosterone

Table 1. Components of the Fried frailty phenotype operational definition for the classification of frailty [19].

	Components	Method of assessment
1.	**Unintentional weight loss**	Self-reported unintentional weight loss of ≥10lbs in the last year
2.	**Self-reported exhaustion**	Centre of Epidemiological Studies – Depression scale: two subjective questions regarding endurance and energy, scored from 0-3 (a score > 1 on either of these questions signifies confirmation of the exhaustion criteria)
3.	**Weakness**	Grip strength measurement. Classification criteria relative to sex and body mass index (BMI)
4.	**Slow walking speed**	15-foot gait speed assessment. Classification criteria relative to sex and height
5.	**Low physical activity**	Short version of the Minnesota leisure time activity questionnaire utilised to estimated active calories expended per week. Classification criteria relative to sex.

Table 2. Valid operational definitions for the classification of frailty.

Operational definition	Number of items	Components	Classification criteria
Fried frailty phenotype criteria [19]	5	○ Unintentional weight loss (≥10lbs in the last year) ○ Self-reported exhaustion ○ Weakness (grip strength) ○ Slow gait speed ○ Low levels of physical activity	0 = Robust (non-frail) 1-2 = Pre-frail ≥ 3 = Frail
Frailty Index (of cumulative deficits) [56]	~ 30-70	Accumulative health deficits (typically 30 or more), with scoring ranging from 0 (absence of all deficits), to 1 (presence of all deficits).	Typically reported as a continuous variable; cut-off of > 0.25 suggested for frailty
Frailty Index (from comprehensive geriatric assessment (CGA)) [57]	14-52	Accumulative health deficits, with scoring ranging from 0-1, derived from the CGA. 10 domains: ○ Cognition ○ Emotion ○ Communication ○ Mobility ○ Balance ○ Bladder ○ Bowel ○ Nutrition ○ Activities of daily living ○ Social	Typically reported as a continuous variable; cut-off of > 0.25 suggested for frailty
Edmonton Frailty Scale [59]	11	○ Cognition ○ Hospital admission ○ General health ○ Functional capacity (x2) ○ Social support ○ Medication usage (x2)* ○ Nutrition* ○ Mood* ○ Continence*	0-5 = Non-frail 6-7 = Vulnerable 8-9 = Mild frailty 10-11 = Moderate frailty 12-17 = Severe frailty
Reported Edmonton Frailty Scale [60]	11	○ Cognition ○ Hospital admission ○ General health ○ Functional capacity ○ Social support ○ Medication usage (x2)* ○ Nutrition* ○ Mood*	0-5 = Non-frail 6-7 = Vulnerable 8-9 = Mild frailty 10-11 = Moderate frailty 12-18 = Severe frailty

		○ Continence* ○ Self-reported performance	
Clinical Frailty Scale [61]	1	Visual and written chart scoring frailty on a continuous scale between 1 (very fit) - 9 (terminally ill)	1-3 = Non-frail 4 = Vulnerable 5-9 = Frail
Canadian Study on Health and Ageing (CSHA) Clinical Frailty Scale [61]	1	Visual and written chart scoring frailty on a continuous scale between 1 (very fit) - 7 (severely frail)	1-3 = Non-frail 4 = Vulnerable 5-7 = Frail
FRAIL Scale [62]	5	○ Fatigue ○ Resistance (ability to climb stairs) ○ Ambulation (ability to walk one block) ○ Illnesses ○ Loss of weight	0 = Robust (non-frail) 1-2 = Pre-frail ≥ 3 = Frail
Survey of Health, Ageing and Retirement in Europe-Frailty Instrument (SHARE-FI) [63]	5	○ Walking difficulties ○ Weakness (grip strength) ○ Exhaustion ○ Loss of appetite ○ Low physical activity	Typically reported as a continuous variable; the following cut-offs are suggested: < 0.08 = Non-frail ≤ 0.08-< 0.25 = Pre-frail ≥ 0.25 = Frail
Groningen Frailty Indicator [64]	15	4 domains: ○ Physical (x9) ○ Cognitive ○ Social (x3) ○ Psychological (x2)	≥ 4 = Frail
modified Frailty Index (mFI) [65]	11	○ Functional status ○ Diabetes mellitus ○ Lung problems ○ Congestive heart failure ○ Myocardial infarction ○ Cardiac problems ○ Hypertension ○ Impaired sensorium ○ Prior transient ischemic attack ○ History of stroke ○ Peripheral vascular disease	0 = Robust (non-frail) > 0-< 0.21 = Pre-frail ≥ 0.21 = Frail
Tilburg Frailty Indicator [66]	15	3 domains: ○ Physical (x8) ○ Psychological (x5) ○ Social (x3)	≥ 5 = Frail

Study of Osteoporotic Fractures (SOF) Index [67]	3	○ Weight loss ○ Exhaustion ○ Chair rise	0 = Robust 1-2 = Pre-frail ≥ 2 = Frail
Multi-dimensional Prognostic Index [68]	8	○ Comorbidity ○ Nutrition ○ Polypharmacy ○ Pressure sore risk ○ Living status ○ Activities of daily living ○ Instrumental activities of daily living	< 0.34 = Robust (non-frail) 0.34-0.66 = Pre-frail > 0.66 = Frail
Trauma Specific Frailty Index [69]	15	5 categories: ○ Co-morbidities (x3) ○ Daily activities (x5) ○ Health attitude (x5) ○ Function (x1) ○ Nutrition (x1)	≤ 0.12 = Robust 0.13-0.25 = Pre-frail > 0.25 = Frail
Emergency General Surgery Specific Frailty Index [70]	15	5 categories: ○ Co-morbidities (x4) ○ Daily activities (x5) ○ Health attitude (x5) ○ Nutrition (x1)	≥ 0.25 = Frail
Rockwood frailty assessment [71]	4	○ Activities of daily living ○ Bladder function ○ Bowel function ○ Cognition	≥ 2 = Frail
Kihon checklist [72, 73]	25	7 categories: ○ Physical strength ○ Nutrition ○ Oral function ○ Socialisation ○ Memory ○ Mood ○ Lifestyle	Dichotomous scoring of all items as per the frailty index. Cut-off of > 0.25 suggested for classification of frailty
preoperative Frailty Index (pFI) [74]	30	Accumulative health deficits with scoring ranging from 0 (absence of all deficits), to 1 (presence of all deficits).	> 0.21 = Frail
Comprehensive Assessment of Frailty (CAF) [75]	14	4 domains: Laboratory assessment ○ Serum albumin ○ Forced expiratory volume ○ Serum creatine Phenotype assessment ○ Exhaustion ○ Physical activity levels ○ Gait speed	1-10 = Non-frail 11-25 = Moderately frail 26-35 = Severely frail

		○ Weakness (grip strength) Modified physical performance assessment** ○ Balance ○ Chair rise ○ Timed ability to put on and remove jacket ○ Timed ability to pick a pen from the floor ○ 360-degree turn CSHA clinical frailty scale (CFS) assessment**	
Frailty predicts death One yeaR after CArdiac Surgery Test (FORECAST) [76]	5	○ Chair rise*** ○ Weakness ○ Stair climb ○ CSHA CFS assessment*** ○ Serum creatine	0-4 = Non-frail 5-7 = Moderately frail 8-14 = Severely frail
Robinson criteria [77]	7	○ Timed up and go ○ Katz index of activities of daily living ○ Cognition ○ Charleston index ○ Anemia ○ Nutrition ○ Falls	0-1 = Non-frail 2-3 = Pre-frail 4-7 = Frail
National Surgical Quality Improvement Program Frailty Index (NSQIP-FI) [78]	11	○ History of: - Diabetes - Obstructive pulmonary disease, or pneumonia - Cognitive heart failure - Myocardial infarction within 6 months of surgery - Percutaneous coronary intervention cardiac surgery or angina ○ Impaired functional status ○ Hypertensive medications ○ Peripheral vascular disease or rest pain ○ Impaired sensorium ○ Transient ischaemic attach or cardiovascular accident ○ History of cardiovascular attack with persistent residual dysfunction	> 0.25 = Frail

= All criteria on the EFS are scored from 0-2, with the exception of these items which are scored 0-1; **= All criteria on the CAF are score 0-1, with the exception of the modified physical performance assessment, and the CSHA CFS, for* *which each component is scored 0-4, and 0-7 respectively; * = All criteria on the FORECAST are scores 0-1, with the exception of the chair rise, and CSHA CFS assessments, which are scored 0-4, and 0-7 respectively.*

Table 3. Systematic reviews and meta-analyses examining the prevalence of frailty among community-dwelling older adults.

Author(s)	Study design	Population	Minimum age (years)	Included studies	Pooled sample	Pooled prevalence of frailty (95% CI) (%)	Pooled prevalence of pre-frailty (95% CI) (%)	Range of reported frailty prevalence (%)	Range of reported pre-frailty prevalence (%)
He et al., 2019 [102]	Systematic review and meta-analysis	Community-dwelling older adults in China	≥ 65	14	81,258	10 (8.0 - 12.0)	43 (37 - 50)	5.9 - 17.4	26.8 - 52.4
Siriwardhana et al., 2018 [103]	Systematic review and meta-analysis	Community-dwelling older adults in low-, and middle-income countries	≥ 60	47	75,133	17.4 (14.4 - 20.7)	49.3* (46.4 - 52.2)	3.9 - 51.4	13.4 - 71.6*
Kojima et al., 2017 [104]	Systematic review and meta-analysis	Community-dwelling older adults in Japan	≥ 65	5	11,414	7.4 (6.1 - 9.0)	48.1 (41.6 - 54.8)	4.6 - 9.5	38.0 - 65.2
Verlaan et al., 2017 [105]	Systematic review and meta-analysis	Malnourished community-dwelling older adults	≥ 50	10	128	68 (59.9 - 76.1)**	25.8 (18.2 - 33.4)**	n/a	n/a
Collard et al., 2012 [109]	Systematic review	Community-dwelling older adults	≥ 65	21	61,500	10.7 (10.5 - 10.9)	41.6*	4 - 59.1	18.7 - 53.1***

= data only available for 42/47 studies (47,302/75,133 participants); **= Not reported in original paper, derived from available data; *= data only available for 15/21 studies (53,727/61,500 participants).*

Table 4. Trajectory of care for frail individuals (Adapted from [37]).

Primary care	Advanced age older adult	**Primary prevention**
	Adoption / continuation of unhealthy lifestyle behaviours	
	Accumulation of frailty deficits and risk factors for disease	
	Diagnosis of chronic disease	**Secondary prevention**
Acute care	Acute decompensation of disease	
	Cycle of stabilisation and destabilisation	
Specialist care	Progression of disease to advanced stage	
	Intensive medical or surgical therapy	
	Iatrogenic complication from therapy	**Tertiary prevention**
	Prolonged hospitalisation	
Post-acute care	Functional decline	
	Institutionalisation	
Palliative care	Readmission to hospital	
	Death	